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Substituted γ-Lactones with Vicinal Hydrogen Atoms. Conformational Study by MM2 Calculations and Coupling Constant Analysis

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The conformational analysis of substituted γ-lactones with vicinal hydrogen atoms is carried out by the MM2/3JHH tandem. The agreement between experimentally available and calculated data is globally correct (rms = 1.16 Hz). A general preference for a hydroxyl group to occupy the equatorial position if it is on C-2 or the axial position if it is on C-3 or C-4 is observed as a consequence of the presence of H bond or of the gauche effect, respectively.

One of the modern synthetic strategies consists of using tunable chiral synthons.[1] Among them, probably sugar γ-lactones are the most widely used due to their availability and economy. Successful syntheses of a variety of homochiral compounds have been achieved by using γ-lactones as starting materials.[1-2] The presence in nature of many products having the γ-butyrolactone skeleton reinforces the interest in their conformational analysis and configurational assignment. Traditionally, ^{1}H-NMR techniques are used by organic chemists to assign the relative configuration to vicinal chiral centers as a consequence of the close interrelation between vicinal coupling constant values and dihedral angles. It has already been shown that this correlation is governed not by the configuration but by the conformation of the fragment in study, at least for some di- and trisubstituted γ-lactones.[3]

In this paper, we continue our work on the conformational study of substituted γ-lactones by combining theoretical calculations and experimental results. Since dimethyl-γ-butyrolactones were already studied,[3] the target molecules (Table I) are now as follows: (i) the mono-, tri-, and tetramethyl-γ-lactones containing vicinal hydrogen atoms as models for alkyl-substituted γ-butyrolactones and (ii) the mono-, di-, and trimethylhydroxy-γ-lactones with vicinal hydrogen atoms as models for alkoxyalkyl-γ-butyrolactones.

The conformational analysis of γ-butyrolactone has been extensively studied by different computational methods;[3-6] only two degenerate envelope conformations should be considered for this system, i.e., conformations A and B. The introduction of substituents leads to two unequally populated conformers. The experimental coupling constants will be thus a weighted average between the contribution of each conformer. The inadequacy of extracting conformational information from J values has been repeatedly shown. In this paper we intend to report reliable theoretical coupling constants for an unequivocal configurational assignment in substituted γ-butyrolactones.

Results and Discussion

Computational Details. Program MM2(91),[7] an improved version of the MM2(77) force field,[8] was used throughout all this work for the computation of the geometry and the energy of each conformer. Due to the absence of torsional parameters for the C(O)OCOH unit a provisional set ($V_1 = V_2 = V_3 = 0.0$) was used. Only two envelope conformations for the γ-butyrolactone ring were considered, and the three possible rotamers around the C–OH bond (whenever present) were taken into account. The default value for the dielectric constant ($\epsilon = 1.5$) was used in spite of comparing NMR data registered in different solvents. No need to change this parameter was found since the obtained agreement between calculated and experimental coupling constants was globally satisfactory. The computation of the averaged coupling constants was done by the 3JHH program[9] which is based on Altona's generalized Karplus equation.[10] The results of the calculations and the available experimental coupling constants are shown in Table II.

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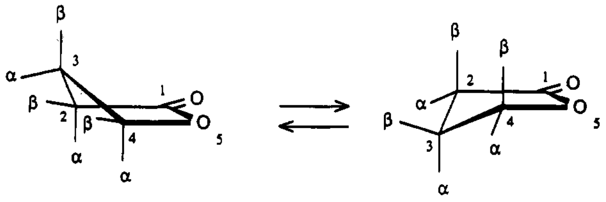
Table I



A B

	C-2		C-3		C-4			C-2		C-3		C-4	
compd	α	β	α	β	α	β	compd	α	β	α	β	α	β
1	H	Me	H	H	H	H	35	H	Me	H	Me	OH	H
2	H	H	H	Me	H	H	36	Me	OH	H	Me	H	H
3	H	H	H	H	H	Me	37	Me	H	H	Me	H	OH
4	Me	Me	H	Me	H	H	38	Me	H	H	Me	OH	H
5	Me	Me	H	H	H	Me	39	OH	Me	H	H	H	Me
6	H	Me	H	H	Me	Me	40	H	Me	H	OH	H	Me
7	H	H	H	Me	Me	Me	41	H	Me	OH	H	H	Me
8	Me	Me	H	Me	H	Me	42	H	Me	H	H	OH	Me
9	Me	Me	H	Me	Me	H	43	OH	Me	H	H	Me	H
10	H	Me	H	Me	Me	Me	44	H	Me	H	OH	Me	H
11	Me	H	H	Me	Me	Me	45	H	Me	OH	H	Me	H
12	H	OH	H	H	H	H	46	H	Me	H	H	Me	OH
13	H	H	H	OH	H	H	47	H	OH	H	Me	H	Me
14	H	H	H	H	H	OH	48	OH	H	H	Me	H	Me
15	OH	Me	H	H	H	H	49	H	H	H	Me	OH	Me
16	H	Me	H	OH	H	H	50	H	OH	H	Me	Me	H
17	H	Me	OH	H	H	H	51	OH	H	H	Me	Me	H
18	H	Me	H	H	H	OH	52	H	H	H	Me	Me	OH
19	H	Me	H	H	OH	H	53	OH	Me	H	Me	H	Me
20	H	OH	H	Me	H	H	54	OH	Me	H	Me	Me	H
21	OH	H	H	Me	H	H	55	Me	OH	H	Me	H	Me
22	H	H	H	Me	H	OH	56	Me	OH	H	Me	Me	H
23	H	H	H	Me	OH	H	57	H	Me	H	Me	OH	Me
24	H	OH	H	H	H	Me	58	H	Me	H	Me	Me	OH
25	OH	H	H	H	H	Me	59	Me	H	H	Me	OH	Me
26	H	H	H	OH	H	Me	60	Me	H	H	Me	Me	OH
27	H	H	OH	H	H	Me	61	Me	Me	H	Me	H	OH
28	H	H	H	H	OH	Me	62	Me	Me	Me	H	H	OH
29	Me	Me	H	OH	H	H	63	Me	Me	H	OH	H	Me
30	Me	Me	H	H	H	OH	64	Me	Me	OH	H	H	Me
31	H	OH	H	H	Me	Me	65	H	Me	H	OH	Me	Me
32	H	H	H	OH	Me	Me	66	H	Me	OH	H	Me	Me
33	OH	Me	H	Me	H	H	67	H	OH	H	Me	Me	Me
34	H	Me	H	Me	H	OH	68	H	OH	Me	H	Me	Me

Methyl-γ-butyrolactones 1–11 with Vicinal Hydrogen Atoms. Only three possible monomethyl derivatives 1–3, four trimethyl- 4–7, and four tetramethyl-γ-butyrolactones 8–11 are considered.

The methyl-γ-butyrolactones 1–3 mainly adopt envelope conformations with equatorial methyl groups. Calculations suggest that compound 3 exists with 31% in the conformation with the methyl in axial position. This percentage is confirmed by the agreement between the experimental (8.1 Hz) and calculated (7.7 Hz) $J_{3\beta,4\alpha}$. In conformer A this calculated coupling constant is 10.4 Hz while in conformer B it is only 1.8 Hz.

The trimethyl derivatives 4–7 also present the same tendency (equatorial methyl groups), and the agreement between the calculated and the available experimental coupling constants reinforces the validity of the calculations. The calculated values of $J_{2,3}$ in 6 are remarkably smaller than the experimental values (by 2–3 Hz). Probably, some inadequacy in Altona's equation may explain this phenomenon because the largest calculated values are about 10 and 8 Hz for the same pairs of protons in conformer A. The tetramethyl derivatives 8–11 do not present 1,3-diaxial interactions in their more stable conformations. However, compound 8 exists in a roughly A:B = 35:65 mixture of the two conformers because conformer A has two almost eclipsed gauche interactions and two methyl groups in the 1,2-diaxial position while B has the same two gauche interactions and one methyl/methyl 1,3-diaxial interaction. Experimental coupling constants could only be found for products 8 and 9, and the values are interchanged with the data calculated herein.[28]

Hydroxy- and Hydroxymethyl-γ-butyrolactones 12–28 with Vicinal Hydrogen Atoms. The 2-hydroxy-γ-butyrolactone 12 adopts conformation A with an equa-

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(28) Since the configurational assignment was originally made exclusively on the basis of $J_{cis} > J_{trans}$ in a five-membered ring (rule which has been proved to be non applicable to γ-lactones) and in view of the good agreement between experimental and calculated coupling constants found in this and other articles dealing with the same class of compounds,[3] the assignment of configuration for products 8 and 9 in ref 13 should be revised.

Table II. Calculated Vicinal Coupling Constants (in Hz) for the Individual Conformations A and B as Well as the Population-Weighted Values for Compounds 1–68 and the Experimentally Available Data (in Hz)

	conformer A[a]			conformer B[b]			calcd J's		expl J's	
compd	%[b]	$J_{2,3}$[c]	$J_{3,4}$[c]	%[b]	$J_{2,3}$[c]	$J_{3,4}$[c]	$J_{2,3}$[c]	$J_{3,4}$[c]	$J_{2,3}$[c]	$J_{3,4}$[c]
1	80.1	10.5, 7.6	8.7, 10.4, 1.3, 6.9	19.9	1.4, 8.6	7.3, 1.5, 10.1, 9.0	8.7, 7.8	8.4, 8.7, 3.0, 7.3	*d*	*d*
2	22.9	1.2, 8.2	1.5, 6.8	77.1	10.6, 7.5	10.7, 8.0	8.5, 7.7	8.6, 7.7	?, 7[d]	8, 6[d]
3	68.6	10.1, −0.1, 11.8, 10.3	10.4, 6.5	31.4	10.7, 11.3, 0.0, 10.6	1.8, 8.7	10.3, 3.5, 8.1, 10.4	7.7, 7.2	10.0, 6.5, 7.0, 10.0[e]	8.1, 5.8[e]
4	15.6		1.6, 6.9	84.4		10.8, 7.9		9.4, 7.7		*f*
5	83.7		10.3, 6.6	16.3		3.1, 9.5		9.1, 7.1		9, 7[g]
6	88.5	10.3, 7.9		11.5	2.4, 9.8		9.4, 8.1		12, 9[h]	
7	16.5	1.2, 8.4		83.5	10.7, 7.4		9.1, 7.6		*f*	
8	35.9		5.8	64.1		7.8		7.1		10.3[i]
9	3.2		2.8	96.8		9.5		9.3		7.2[i]
10	49.6	8.0		50.4	9.2		8.6		*f*	
11	2.5	2.2		97.5	11.2		11.0		*f*	
12	100.0	9.5, 7.8	8.9, 10.9, 1.0, 7.1	0.0	1.2, 6.4	7.3, 1.1, 10.7, 9.1	9.5, 7.8	8.9, 10.9, 1.0, 7.1	*f*	*f*
13	83.5	1.2, 6.4	1.5, 5.0	15.5	8.4, 8.5	8.6, 8.8	2.4, 6.6	2.6, 5.4	1.8, 5.5[j]	1.6, 4.1[j]
14	19.0	11.3, −0.1, 11.2, 11.4	7.5, 7.9	81.0	11.3, 11.3, −0.1, 11.2	1.4, 6.5	11.3, 9.1, 2.0, 11.2	2.6, 6.8	*f*	*f*
15	0.8		9.6, 10.3, 1.2, 7.9	99.2		7.5, 1.0, 10.8, 9.2		7.5, 1.0, 10.8, 9.2		
16	95.6	5.5	1.4, 4.8	4.4	8.2	8.7, 8.8	5.5	1.7, 4.8	5.4[k]	1.0, 3.4[k]
17	42.4	8.8	8.8, 8.8	57.6	0.5	5.2, 1.5	4.0	6.6, 4.6	5.5[l]	6.0, 5.0[l]
18	50.8	10.2, 8.0	7.7, 7.8	49.2	2.0, 9.4	1.6, 7.1	6.1, 8.7	4.7, 7.5	*f*	*f*
19	93.9	10.1, 8.1	6.5, 1.4	6.1	1.6, 9.0	8.0, 7.2	9.6, 8.1	6.6, 1.8	*f*	*f*
20	99.0	7.4	1.4, 6.7	1.0	6.6	10.4, 8.3	7.4	1.5, 6.7	7.3[m]	
21	0.0	0.5	1.5, 6.7	100.0	9.7	10.8, 7.8	9.7	10.8, 7.8	10.5[m]	
22	1.3	1.3, 8.6	6.2	98.7	10.4, 7.7	4.6	10.3, 7.7	4.6	11.0, ?[n]	5.0[n]
23	64.2	1.3, 8.6	1.1	35.8	10.2, 7.9	6.6	4.5, 8.3	3.0		
24	100.0	9.5, 7.8	10.6, 6.3	0.0	*p*	*p*	9.5, 7.8	10.6, 6.3	9, 9[f,o]	7, 8.5[f,o]
25	0.7	7.7, 1.4	9.5, 7.4	99.3	8.0, 9.2	1.7, 8.5	8.0, 9.2	1.7, 8.5	9.5, 9[f,o]	2.2, 8.5[f,o]
26	9.17	1.2, 6.3	3.6	8.3	8.5, 8.5	7.0	1.8, 6.3	3.7	1.5, 5.3[q]	3.6[q]
27	28.5	8.4, 8.5	7.2	71.5	6.5, 1.2	1.1	7.0, 3.2	2.8	6.5, 3.6[r]	2.8[r]
28	89.4	11.2, −0.3, 11.6, 11.2		10.6	11.6, 11.1, −0.2, 11.6		11.2, 0.9, 10.4, 11.3		*f*	*f*
29	79.7		1.5, 5.0	20.3		8.8, 8.8		2.9, 5.7		
30	28.4		7.5, 7.8	71.6		1.7, 7.2		3.3, 7.4		*f*
31	100.0	9.2, 8.0		0.0	*p*	*p*	9.2, 8.0		9.8, 8.7[s]	
32	80.4	1.2, 6.5		19.6	8.5, 8.4		2.6, 6.8		3.2, 5.9[t]	
33	0.1		1.6, 6.9	99.9		10.9, 7.8		10.9, 7.8		9.3, 8.3[u]
34	6.4	8.1	6.2	93.6	9.0	4.9	9.0	5.0	*f*	*f*
35	84.4	8.2	1.0	15.6	8.4	6.9	8.3	1.9		
36	97.7		1.6, 6.9	2.3		10.5, 8.1		1.8, 6.9		10.0, 6.9[u]
37	0.8	0.8	6.4	99.2	11.1	4.7	11.0	4.7		
38	35.2	1.3	1.2	64.8	10.9	6.6	7.5	4.7		
39	6.7		10.1, 6.9	93.3		2.8, 9.4		3.3, 9.2		5.8, 9.0[v]
40	98.6	5.4	3.5	1.4	9.1	7.4	5.4	3.4	4.7[w]	3.3[w]
41	75.3	8.9	7.3	24.7	0.9	1.6	6.9	5.9	9.2[r]	7.4[r]
42	96.4	10.2, 8.0		3.6	2.7, 9.9		10.0, 8.0			
43	0.2		9.3, 2.5	99.8		6.5, 10.4		6.5, 10.4		5.5, 9.5[v]
44	90.6	5.7	1.1	9.4	8.3	7.3	5.9	1.7	5.6[w]	1.1[w]
45	26.6	8.9	7.1	73.4	0.5	3.8	2.7	4.5	5.0[x]	5.0[x]
46	36.2	10.0, 8.1		63.8	1.9, 9.4		4.9, 8.9			
47	99.7	7.4	5.7	0.3	6.8	7.7	7.4	5.7		
48	0.1	0.5	6.1	99.9	9.9	7.1	9.8	7.1	10.9[y]	8.5[y]
49	81.3	1.3, 8.5		18.7	10.5, 7.6		3.0, 8.3			
50	98.3	7.6	1.2	1.7	6.7	9.2	7.6	1.4		
51	0.0	*p*	*p*	100.0	9.7	9.6	9.7	9.6	10.5[y]	9[y]
52	1.4	1.4, 8.7		98.6	10.4, 7.7		10.3, 7.7			
53	0.7		5.8	99.3		8.0		8.0		
54	0.0		1.8	100.0		9.8		9.8		
55	99.6		6.0	0.4		7.7		6.0		
56	84.1		2.4	15.9		9.5		3.5		
57	94.1	8.2		5.9	9.2		8.3			
58	4.1	8.4		95.9	9.1		9.1			
59	51.2	1.3		48.8	11.4		6.3			
60	0.1	1.8		99.9	11.2		11.2			
61	3.4		6.4	96.6		5.1		5.2		
62	38.2		7.1	61.8		5.2		5.9		
63	94.5		3.8	5.5		7.6		3.9		
64	70.3		7.4	29.7		1.7		5.7		
65	96.6	5.8		3.3	9.3		5.9			
66	76.9	9.0		23.1	1.0		7.1			
67	99.0	7.8		1.0	7.1		7.8		7.5[g]	
68	100.0	9.9		0.0	*p*	*p*	9.9		11.6[g]	

[a] See structures A and B for explanation. [b] Populations according to Boltzman distribution. Energy values taken from MM2 results. Rotamers around to C–OH bond (if any) were also considered. [c] Values are given in the following order: $n\beta(n+1)\beta$, $n\beta(n+1)\alpha$, $n\alpha(n+1)\beta$, $n\alpha(n+1)\alpha$. See structures A and B for explanation. Example: the $J_{2,3}$ for product 1 should be $J_{2\beta,3\beta}$, $J_{2\beta,3\alpha}$, $J_{2\alpha,3\beta}$, and $J_{2\alpha,3\alpha}$, but one Me group is present in the 2β position 1, thus couplings are only $J_{2\alpha,3\beta}$ and $J_{2\alpha,3\alpha}$. [d] NMR spectrum not resolved at 220 MHz, ref 11. [e] Values for the 4-[(trityloxy)methyl] derivative, ref 1. [f] Product described but its NMR spectrum is not analyzed. [g] Values for the 2-ethyl-2-methyl-4-[(trityloxy)methyl]-γ-butyrolactone, ref 1. [h] Reference 12. [i] Reference 13. [j] Reference 14. [k] References 15. [l] Reference 16. [m] Reference 17. [n] Values for the 5-menthyloxy derivative, ref 18. [o] Values for the α-hydroxy-γ-(ethoxycarbonyl)-γ-butyrolactone, ref 19. [p] This conformer does not exist with MM2(91) force field. [q] Reference 20. [r] Reference 21. [s] Reference 22. [t] Reference 23. [u] Values for the 3-phenyl derivative, ref 14a. [v] Values for the 4-isobutyl derivative, ref 24. [w] Values for the 2-butyl derivative, ref 25. [x] Reference 26. [y] Values for the *O*-*tert*-butyldiphenylsilyl derivative, ref 27.

torial hydroxyl group due to a strong H bond with the carbonyl oxygen. However, the 3- and 4-hydroxy-γ-butyrolactones **13–14** seem to prefer conformations with axial hydroxyl groups. The experimental data for **13** agrees with this observation. This must be due to the known Tendency of the O–C–C–O arrangement to adopt gauche conformations.[29]

The conformational equilibria for hydroxy 2-methyl-γ-butyrolactones **15–19** are mainly controlled by the hydroxyl group. Compounds **15** and **16** mainly adopt conformations B and A where the hydroxyl group is in equatorial and axial positions, respectively. Compounds **17** and **18** exist in a 1/1 ratio for A/B conformations, while **19** again adopts the conformation presenting the methyl and hydroxyl groups in equatorial and axial positions, respectively. The preference of an OH group on C-3 or C-4 to be in the axial position seems to be large enough as to overcome the destabilization coming from an axial methyl group.

In 3-methyl-γ-butyrolactones containing one hydroxyl group, **20–23**, a similar situation is observed. The case of product **21** is worth mentioning: this compound exists exclusively in conformation B. The computational results for the behavior of **22** and **23** follow the same trend: preference of the hydroxyl group for occupying an axial position whenever they are on C-3 or C-4.

The behavior of the hydroxy-4-methyl-γ-butyrolactones **24–28** also reinforces this hypothesis. All the compounds prefer the conformation with the hydroxyl group in the axial position except **24**. In this compound, conformation B does not exist in the MM2(91) force field. It has one axial hydroxyl group and also presents one 1,3-diaxial Me/OH interaction.

The good general agreement between calculated and experimentally available coupling constants indicates the correctness of the calculations.

Dimethylhydroxy-γ-butyrolactones 29–52 with Vicinal Hydrogen Atoms. The γ-butyrolactones **29–32** with one hydroxyl and one *gem*-dimethyl group and the hydroxy-*cis*-2,3-dimethyl-γ-butyrolactones **33–35** always present one axial and one equatorial methyl groups. The conformational equilibria will thus be controlled by the OH group. Again, the calculated preference is always for equatorial OH on C-2 (**31** and **33**) and for axial OH group on C-3 or C-4.

In the hydroxy *trans*-2,3-dimethyl-γ-butyrolactones **36–38** a predominance of the conformation with equatorial methyl groups could be expected by steric reasons. However, the calculations for compound **36** indicate it exists only in conformation A with the hydroxyl group on C-2 in equatorial position strongly H-bonded to the carbonyl group. Its experimental coupling constants[13] suggest the exclusive existence of conformation B, in clear contradiction with the theoretical data. Nevertheless, experimental data are obtained in C_5H_5N as solvent instead of in $CDCl_3$, fact that may alter the conformational equilibrium due to intermolecular H-bonds, favoring conformation B with two equatorial methyl groups. Calculations on compounds **37** and **38** agree with the hypothesis of predominance of equatorial methyl groups, but **38** shows an increase in the population of conformer A (with two axial methyl groups) due to the tendency of having a hydroxyl group in axial position on C-4.

The hydroxy-*cis*-2,4-dimethyl-γ-butyrolactones **39–42** always prefer conformer A (with two equatorial methyl groups and one axial OH group in all cases) except in **39** where the H-bond with the carbonyl group makes the molecule adopt conformation B and in **41** where B is slightly stabilized. In the trans-isomers **43–46**, one axial and one equatorial methyl group are present and again the hydroxyl group should control the equilibria. Compound **44** prefers conformation A but **45–46** prefer conformation B with the hydroxyl group in axial position, while **43** adopts only conformation B with equatorial OH group on C-2. Again comparison of calculated and experimental *J*'s suggests that the results of the MM2 calculations are correct.

The hydroxy-*cis*-3,4-dimethyl-γ-butyrolactones **47–49** also are dominated by the OH group. Compounds **47** and **48** exist in conformations A and B, respectively, with the OH group on C-2 H-bonded to the carbonyl group. The experimental *J*'s also suggest the predominance of these conformations almost exclusively. A similar situation is found in the trans isomers **50–52**. Compounds **50** and **51** adopt conformations with equatorial OH groups while **52** prefers to have the hydroxyl group in the axial position. The experimental data for **51** suggest the exclusive existence of conformation B in good agreement with our calculations.

Trimethylhydroxy-γ-butyrolactones 53–68 with Vicinal Hydrogen Atoms. The lack of available experimental data precludes us from extracting reasonable conclusions from this section. Only experimental coupling constants for **67** and **68** are found, and both agree well with calculations. Only comments on the MM2 calculations will be made in this paragraph.

The hydroxy-2,3,4-trimethyl-γ-butyrolactones **53–60** present a clear predominance of only one single conformation. Compounds **54**, **58**, and **60** prefer conformation B while **55–57** exist in conformation A and **59** shows no clear preference. The reason for the predominance of conformation B for **53** and **54** and of conformation A for **55** and **56** is clear: hydrogen bonding with the carbonyl group. The situation is not clear in **59**. While the axial hydroxyl group on C-4 stabilizes conformation A, the two equatorial methyl groups stabilize conformation B. In **60**, conformer B is preferred due to the absence of axial methyl groups and to the presence of the hydroxyl group in axial position on C-4.

The 2,2,3-trimethyl-4-hydroxy-γ-butyrolactones **61–62** and the 2,2,4-trimethyl-3-hydroxy-γ-butyrolactones **63–64** always prefer the conformation having an axial hydroxyl group. However, in the case of the 2,4,4- and of the 3,4,4-trimethyl derivatives **65–66** and **67–68**, respectively, the situation is not so clear. While in **65** the preferred conformation has an axial hydroxyl group, in **66–68** the favored conformation has the maximum number of equatorial groups (the OH being one of them). The good agreement of the calculated *J*'s with the scarce experimental data reinforces the validity of the calculations.

Conclusions

The MM2(91) calculations combined with 3JHH program correctly reproduce all available experimental coupling constants for the compounds studied in this paper. No large differences are observed for this class of molecules with the γ-butyrolactone skeleton.

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[29] Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51.

The hydroxyl group shows a general preference for being in the equatorial position when it is on C-2 and in the axial position if it is on C-3 or C-4 in spite of having axial methyl groups. These tendencies are understandable considering the hydrogen bond with the carbonyl on C-1 when the hydroxyl group is on C-2 and the so-called "gauche effect" when the hydroxyl group is on C-3 or C-4, as a consequence of considering the ester oxygen equal to the ether oxygen in the MM2 scheme.

Without considering the J values for products **8**, **9**, and **36**, the root mean square (rms) deviation is 1.16 Hz.[30] The inclusion of polar groups, as the OH, on the C-2 of the γ-butyrolactone ring diminishes the agreement between calculated and experimental coupling constants.[3]

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[30] A total of 64 J values are considered. The rms deviations for calculated J's of each individual bond are as follows: $J_{2,3} = 1.22$ Hz and $J_{3,4} = 1.10$ Hz.