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^{1}H chemical shift differences of Prelog-Djerassi lactone derivatives: DFT and NMR conformational studies.

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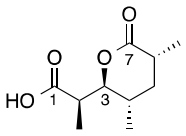
This work reports an experimental and theoretical study of the conformational preferences of several Prelog-Djerassi lactone derivatives, to elucidate the ^{1}H NMR chemical shift differences in the lactonic core that are associated with the relative stereochemistry of these derivatives. The boat-like conformation of **2** explains the anomalous ^{1}H chemical shift between H-5a and H-5b, in which the two methyl groups (C-8 and C-9) face H-5b, leading to its higher shielding effect.

Introduction

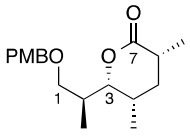
Studies involving the conformational preferences of carbon cyclic compounds have introduced valuable information to several fields of modern chemistry, allowing the understanding of molecular proprieties such as chemical reactivity and catalytic and biological activities, as well as the determination of relative stereochemistry of carbocyclic chiral units.[1] For this purpose, the combination of NMR and computational chemistry techniques has emerged as a powerful tool to determine the connectivity, conformation and stereochemistry of particularly challenging systems.[2]

Lactones, which constitute one of the most important classes of compounds in organic chemistry, highlight the six-membered ring, a common structural subunit present in many natural products, and display a wide range of biological activities.[3]

The commonly branded Prelog-Djerassi lactone (**1**) was first isolated by Prelog and Djerassi as an oxidative degradation product during the structural investigation of several antibiotic natural products (Fig. 1).[4] Its stereochemistry was fully elucidated by Rickards and Smith in 1970 using NMR spectroscopy.[5] Because its stereochemical pattern is also found in many natural products, a variety of strategies have been used to synthesise **1**, as well as its lactonic epimeric analogues.[6] As part of similar synthetic efforts, the Dias group disclosed the synthesis of the C11–C23 fragment of dictyostatin employing the 3-*epi*-Prelog-Djerassi lactone derivative (**2**) as a key intermediate.[7] It was observed that the H-5 methylene of compound **2** presented an anomalous ^{1}H chemical shift difference (1.02 and 2.54 ppm, $\Delta\delta$ = 1.52 ppm). In general, the chemical shifts of diastereotopic H-5 protons for the Prelog-Djerassi lactone (**1**) and its derivatives are in the range of 1.2 to 2.0 ppm ($\Delta\delta$ = 0.8 ppm).[5,6]



Prelog-Djerassi Lactone (**1**)



3-*epi*-Prelog-Djerassi Lactone derivative (**2**)

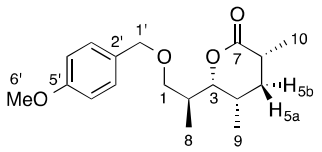
Fig 1. Prelog-Djerassi lactone (**1**) and lactone derivative (**2**).

Herein, a theoretical conformational analysis of **2**, along with some lactonic diastereoisomeric derivatives, is reported, followed by NMR chemical shift calculations to rationalise the ^{1}H NMR chemical shift differences in the lactonic core associated with the relative stereochemistry of these derivatives.

Results and discussion

NMR Spectroscopic Data for Lactone 2. A complete set of NMR spectra in $CDCl_3$ (^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY) were collected for lactone **2**. The chemical shift assignment of ^{1}H and ^{13}C NMR spectra is shown in Table 1.

Table 1. Experimental ^{1}H (500 MHz) and ^{13}C NMR (125 Hz) chemical shifts and selected coupling constants of lactone **2**. Data in $CDCl_3$.



position	δ (H)	mult	δ (C)
1	3.56 3.59	dd (3.0, 8.9) dd (5.1, 8.9)	71.3
2	2.01	m	34.7
3	4.15	dd (2.7, 10.4)	79.9
4	2.20	m	27.5
5a	2.41	dt (9.5, 13.7)	35.4
5b	1.02	ddd (3.2, 11.4, 13.7)	
6	2.54	m	32.1
7	-	-	176.5
8	0.98	d (6.9)	13.2
9	0.90	d (7.2)	14.8
10	1.17	d (6.6)	15.8
1'	4.41 4.43	d (11.7 Hz) d (11.7 Hz)	72.9
2'	-	-	130.8
3'	7.23	d (8.7 Hz)	129.2
4'	6.87	d (8.7 Hz)	113.8
5'	-	-	159.2
6'	3.80	s	55.3
$^{2}J_{H5a-H5b}$	13.7 Hz		
$^{3}J_{H5a-H4}$	9.7 Hz		
$^{3}J_{H5a-H6}$	9.7 Hz		
$^{3}J_{H5b-H4}$	3.2		
$^{3}J_{H5b-H6}$	11.5		

A 2D-NOESY spectrum was also recorded to corroborate the assignments and spatial relationship for certain methylene protons of lactone **2**. The NOE increments were determined by analysing the slices of the H-3 chemical shift (4.15 ppm), followed by integrating the areas of the peaks within the slice. The most important NOE intensities are depicted in Fig 2a. The highest NOE increments resulting from the cross relaxation between H-3 and H-6 (4.15 and 2.54 ppm, respectively), suggest a boat-like conformation as the most stable conformer, in which H-3 and H-6 remain relatively close (Fig 2b). This conformation also helps to explain the anomalous ^{1}H chemical shift between H-5a and H-5b; the two methyl groups (C-9 and C-10) face towards H-5b, which leads to its higher shielding effect (0.90 ppm).

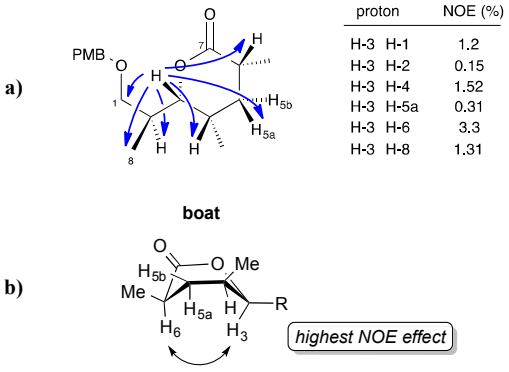


Fig 2. NOEs observed for lactone **2** (**a**) and its probable conformer (**b**).

Theoretical Conformational Analysis and NMR Calculations for Lactone 2'. A full conformational analysis was performed covering the conformational space of the simple model of lactone **2** (**2',** substituting the methoxy group with a hydrogen atom on the aromatic ring) by Monte Carlo Molecular Mechanics (MCMM) as implemented in Macromodel 10.0. The calculations found 302 different conformers possessing energies within 5 kcal mol^{-1} of the lowest-energy minimum. The next step was to employ the cluster analysis according to the atomic distances of the heavy-atoms and eliminating the redundant conformers, resulting in 28 groups. Representative structures of the low-energy clustered conformers were selected and fully optimized at the M06-2X/6-31+G(d,p) [IEF-PCM – $CHCl_3$] level of theory, seeking a low cost theoretical method in order to describe the conformational behavior of our lactones. The non-covalent interactions, very well described by this functional, can play an important role on the tri-substituted lactonic ring. The relative Gibbs energies and Boltzmann population at 25 ºC in $CDCl_3$ are shown in the SI (see Tables S1 and S2 of the SI for further details).

The most stable conformers (91.7% according to the Boltzmann distribution) for lactone **2'** presented a boat-like geometry (Fig 3a). The three lowest energy conformers (representing 71.5% of the population) are shown in Fig 3b. These results corroborate the boat-like geometry proposed by the NOEs experiments.

The analysis of the calculated NMR parameters (Tables 2 and 3) also confirmed that a boat-like geometry is the most stable, and that the two methyl groups on the lactonic ring are responsible for the chemical shift difference experienced by H-5a and H-5b. ^{1}H NMR scaled chemical shifts (δ) were evaluated for each conformer by calculation of the isotropic shielding values determined at mPW1PW91/6-311+G(2d,p) [SMD-$CHCl_3$]//M062X/6-31+G(d,p) [IEF-PCM-$CHCl_3$] level of theory (Table 2). The calculated Boltzmann weighting average NMR parameters for selected structures are shown in Table 2. The difference in the calculated ^{1}H chemical shift between H-5a and H-5b (0.89 and 2.31 ppm, respectively) was $\Delta\delta$ = 1.42 ppm, which was also in fine agreement with the experimental data.

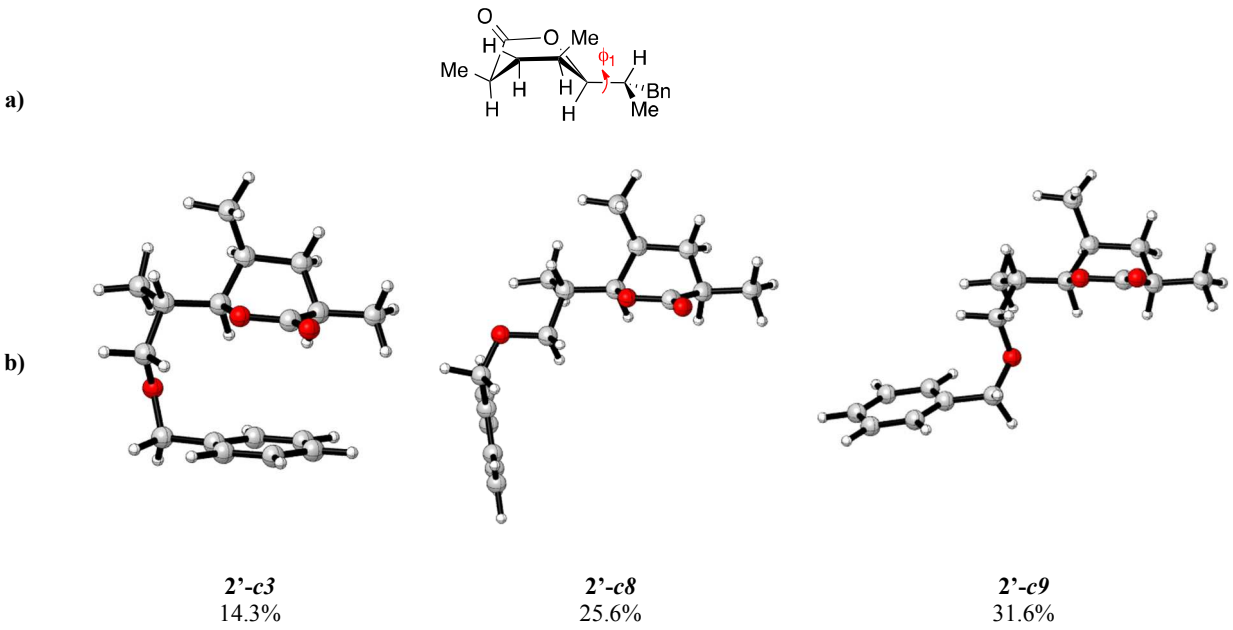


Figure 2. Preferential conformations for lactone **2'** and their Boltzmann population.

Table 2. Calculated ^{1}H scaled NMR chemical shifts of selected low-energy conformers of lactone **2'** at mPW1PW91/6-311+G(2d,p)[SMD-$CHCl_3$]//M062X/6-31+G(d,p) [IEF-PCM-$CHCl_3$] level of theory.

	2'-c1	*2'-c3*	*2'-c6*	*2'-c8*	*2'-c9*	*2'-c19*	*2'-c28*	*av*
1	3.29	3.29	3.81	3.56	2.97	3.63	3.91	3.37
	3.50	3.46	2.66	2.98	3.48	3.04	3.01	3.23
2	1.52	1.41	2.11	2.04	1.84	0.16	2.32	1.85
3	3.88	3.75	3.68	3.53	4.55	3.33	3.91	3.96
4	1.80	1.74	2.11	2.14	2.17	1.74	2.31	2.07
5a	2.15	2.08	2.27	2.29	2.44	2.10	2.44	2.31
5b	0.67	0.66	0.88	1.01	0.93	0.72	1.02	0.89
6	2.27	2.24	2.35	2.44	2.59	2.41	2.42	2.44
8	0.94	0.88	1.16	1.15	1.09	0.58	1.26	1.08
9	0.75	0.72	0.86	0.83	0.85	0.30	0.95	0.82
10	0.90	0.85	0.97	1.00	1.06	0.98	1.02	0.99
1'	4.39	4.48	4.15	4.62	4.26	4.07	4.69	4.43
	3.83	3.96	4.89	4.11	4.64	4.69	4.57	4.35
Ar	7.17	7.16	7.23	7.26	7.25	7.24	7.21	7.22
	7.27	7.31	7.41	7.26	7.20	7.29	7.33	7.27
	7.14	7.06	7.45	7.21	7.16	7.48	7.44	7.21
	7.48	7.56	7.22	7.67	7.50	7.38	7.07	7.48
	7.16	7.18	7.24	7.36	7.34	7.31	7.16	7.28

Additionally, the selected coupling constants (*J*) involving H-4, H-5a, H-5b, and H-6 were calculated at the B3LYP/6-31+G(d,p)//M06-2X/6-31+G(d,p) level in $CDCl_3$ (Table 3). A very strong correlation was found between the experimental values (Table 1) and the calculated ones (Table 3). *According to the results listed in Table 3, there is no significant variation in the coupling constants among the studied conformers.*

Theoretical Conformational Analysis of Prelog-Djerassi Lactone derivatives: To rationalise how the relative stereochemistry of the lactonic stereocentres influence the conformational preference of the ring, and therefore its chemical shifts, a theoretical conformational analysis was explored, followed by chemical shift calculations for the simpler systems, **3**, **4**, **5** and **6** (Fig 4). We removed the supposed negligible functional groups in determining the preferred conformation, –CO_2H and –OPMB of **1** and **2**, respectively. The first approach was to replace the side chain with an *i*-Pr group, thus removing the outer asymmetry while maintaining its steric volume.

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Table 3. Free Energies (G),[a] Boltzmann population (pop),[a] coupling constants (J)[b] and geometrical parameters calculated for lactone **2'**.

	2'-c1	***2'-c3***	***2'-c6***	***2'-c8***	***2'-c9***	***2'-c19***	***2'-c28***	***av***
G (au)	-887.279576	-887.280044	-887.279493	-887.280596	-887.280795	-887.277822	-887.279765	-
ΔG_{rel} (kcal mol^{-1})	0.76	0.47	0.82	0.12	0.00	1.87	0.65	-
pop (%)	8.7	14.3	8.0	25.6	31.6	1.4	10.6	-
$^2J_{H5a-H5b}$	14.8	14.8	15.0	15.0	15.0	15.0	15.0	15.0
$^3J_{H5a-H4}$	10.6	10.6	10.6	10.7	10.7	10.7	10.7	10.7
$^3J_{H5a-H6}$	8.1	8.3	8.6	8.3	7.9	7.9	8.0	8.1
$^3J_{H5b-H4}$	2.3	2.2	2.0	2.3	2.7	2.8	2.6	2.4
$^3J_{H5b-H6}$	11.3	11.2	10.7	10.9	11.1	11.1	11.1	11.0
ϕ [H_{5a}-C-C-H_4]	1.3	0.5	1.3	1.1	3.6	3.9	3.3	-
ϕ [H_{5a}-C-C-H_6]	55.1	54.4	52.0	53.4	55.3	55.5	54.9	-
ϕ [H_{5b}-C-C-H_4]	118.7	117.9	116.1	118.3	120.9	121.2	120.5	-
ϕ [H_{5b}-C-C-H_6]	170.2	169.5	166.9	168.2	170.1	170.4	169.7	-

[a] Calculated at M06-2X/6-31+G(d,p) [IEF-PCM – $CHCl_3$] and 25° C. [b]Calculated at B3LYP/6-31+G(d,p) [IEF-PCM – $CHCl_3$] //M06-2X/6-31+G(d,p) [IEF-PCM – $CHCl_3$].

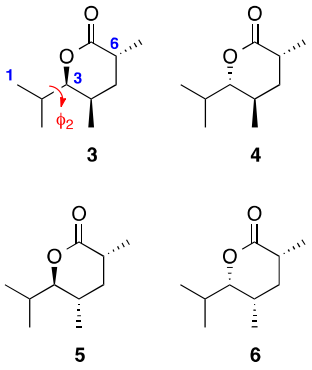

Fig 4. Stereoisomers explored in the theoretical conformational analysis.

A systematic conformational search was performed on these systems, exploring both the boat-like and chair-like initial geometries, by varying the dihedral ϕ_2 and the pseudo-axial/pseudo-equatorial orientation of substituents (see Tables S3 to S10 in the SI for all obtained structures). The calculated lowest energy conformations, populations, and selected ^{1}H NMR chemical shifts of each system are shown in Fig 5 and Table 4.

The current results suggest that the conformational preferences of lactones **3**-**6** are primarily based on the relationship between C3 and C5 stereocenters. Initially, we observe that the bulky substituent at C3 remains in the pseudo-equatorial position. The lactones **3** and **5** with a 3,6-*anti* stereochemical relationship presented half-chair-like geometries as the most stable conformers, keeping C3 and C6 substituents on the pseudo-equatorial position, even when the stereocenter at C-4 occupies a pseudo-axial position, as shown for lactone **3** (**3e**, Figure 5).

On the other hand, the 3,6-*syn* relationship of lactones **4** and **6** imposes a boat-like conformation as the preferred lowest energy state, keeping these groups as far as possible from each other. In this case, the C4 stereocenter plays an important role. While the 3,4-*anti* relative stereochemistry of **4** lead to a conformational equilibrium of 48.7% as boat-like (**4d**) and 34.8% as half-chair-like (**4f,** SI), the 3,4-*syn* stereochemistry of **6** amplifies to 97% the boat-like population (**6g**). The half-chair-like conformation of lactone **6** (see structure **6i**, SI) leads to a strong 1,2-diaxial repulsion between the 3,4-*syn* dimethyl substituents.

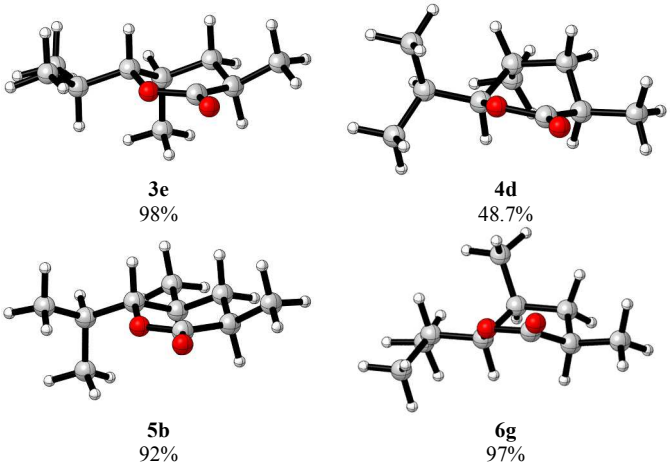

Fig 5. Preferential conformation for lactones **3-6** and their Boltzmann populations.

In addition, a new conformational search involving the Prelog-Djerassi lactone **1** and the acid derivative of **2** (named **6''**) were

performed (see SI, Tables S16 to S19). A half-chair-like and boat-like has presented as the preferential conformations for **1** and **6''**, respectively, in consonance with results obtained for **5** and **6**. This scenario suggest that the carboxylic group don`t play a role in determining the preferred conformations of these lactonic rings.

The most relevant information obtained from these results suggests that the difference in shielding constants of isomers **5** and **6** (containing both identical 4,6-*cis* relative stereochemistry) are related to the conformation of their rings. Table 4 shows a more pronounced shielding effect on only one of the methylene hydrogens on the boat conformation of isomer **6** ($\Delta\delta$ = 1.37 ppm), whereas the other isomers have typical methylene chemical shift differences ($\Delta\delta$ = 0.04 to 0.39). This scenario can be extrapolated to the Prelog-Djerassi lactone derivatives mentioned before, and are in accordance with reported ^{1}H NMR experimental spectra.[5,6]

To confirm the shielding effect of the methyl group, we performed a ^{1}H NMR theoretical calculation replacing the two methyl groups in position C4 and C6 with hydrogen atoms (selecting $r_{C\text{-}H}$ = 1.09 Å) while keeping the other geometrical parameters fixed in the original boat-like conformation of lactone **6** (named lactone **6'**). The difference of $\Delta\delta$ = 0.27 ppm in the calculated ^{1}H chemical shift between H-5a and H-5b (1.97 and 1.70 ppm, respectively) corroborated our hypothesis (see Table S15 in the SI).

Table 4. Free Energies (*G*), Boltzmann population (*pop*), ^{1}H NMR chemical shifts and dipole (μ) calculated for lactones **3-6**.

		G (au)	ΔG_{rel} (kcal mol^{-1})	*pop* (%)	δ H_{5a}	δ H_{5b}	Δδ	μ (debye)
3	***3e***	-541.935864	-	100	***1.80***	***1.62***	***0.18***	*5.86*
	4a	-541.934786	0.78	13.0	1.58	1.75		5.87
	4b	-541.933585	1.54	3.6	1.45	1.54		5.84
4	***4d***	-541.936033	0.00	48.7	1.48	1.58		5.84
	4f	-541.935713	0.20	34.8	1.70	1.49		5.93
	4-av				***1.55***	***1.59***	***0.04***	
	5a	-541.934328	2.12	2.6	1.71	1.30		5.91
	5b	-541.937699	0.00	92.2	1.78	1.32		5.86
5	***5j***	-541.934575	1.96	3.4	1.70	1.34		5.91
	5k	-541.934009	2.32	1.9	1.69	1.37		5.85
	5-av				***1.72***	***1.33***	***0.39***	
6	***6g***	-541.9359860	-	100	***2.27***	***0.90***	***1.37***	**5.86**

Experimental

Computational details: The conformation search for **1**, **2'** and and **6''** were performed in the gas phase, including all rotatable single bonds, using the Monte Carlo (MCMM) method with the Polak-Ribiere Conjugate Gradient (PRCG),[8] the MMFF force field,[9] dielectric constant-dependent electrostatics (ε=1), and normal cut-off points to model the non-bonded interactions, as implemented in MacroModel (Version 10).[10] All heavy atoms were included in the test for redundant conformers, using the default cut off (maximum atom deviation) of 0.5 Å. The energy window for saving new structures was 5 kcal mol^{-1} relative to the current global minimum with a maximum number of steps of 30000 or 1000 steps per rotatable bond. Each search continued until the global energy minima were found at least 10-20 times, thus ensuring that all of the relevant conformers had been found. The cluster analyses of **2'** was performed using a python script, "Clustering of Conformers", interfaced with the Maestro (Version 9.4) program.[11] Several works have exhibited this cluster analysis for the precise description of organic molecules in solution.[12] To generate the RMS matrix, all heavy atoms were included. The average method was used to calculate the best number of clusters in all cases. All conformers were clustered and graphically represented. The low-energy structures of each cluster were selected and submitted to a full geometric optimisation using a Quantum Mechanics calculation through the Gaussian09 program.[13] The representative structures (low energy) of each cluster of **2'**, as well as the conformers of **1**, **3-6**, **6'**, and **6''** were fully optimised using Truhlar M06-2X[14] density functional in conjunction with the 6-31+G(d,p) basis set, and the default PCM model for inclusion of the solvent effect for all optimisations. Frequency calculations at 295.15 K (1 atm) ensured that the stationary points represented either minima (no imaginary frequency) on the potential-energy surface, thus furnishing the Gibbs free energies. ^{1}H and chemical shift values were computed using the default gauge-independent atomic orbital (GIAO) method.[15] The calculated ^{1}H chemical shifts (δ) were determined at the mPW1PW91/6-311+G(2d,p)[SMD-$CHCl_3$]//M062X/6-31+G(d,p) [IEF-PCM-$CHCl_3$] level of theory, and were empirically scaled in order to remove systematic error, following the recommendation of Rablen, Tantillo and co-workers.[2a,2f,16] The scaling factor used in this work were generated utilizing the database and slight modified shell scripts available on the web site at http://cheshirenmr.info. The best fit line from the theoretical and experimental ^{1}H NMR data provided the intercept (m = -1.0957) and slope (b = 31.8718) and are applied to the computed chemical shifts (δ) by the equation: $\delta = (b - \sigma)/-m$, in which σ is the computed isotropic shielding constant conformationally-averaged using the M062X/6-31+G(d,p) [IEF-PCM – $CHCl_3$] energies. The computed coupling constants (J) were calculated at the

B3LYP/6-31+G(d,p)[IEF-PCM – $CHCl_3$]//M062X/6-31+G(d,p)[IEF-PCM – $CHCl_3$] level of theory, and then conformationally-averaged using the M062X/6-31+G(d,p) [IEF-PCM – $CHCl_3$] energies. Only the conformers with population higher than 1% was considered for calculation of NMR parameters.

The conformational search of lactones **3-6** was performed systematically, exploring both the initial boat-like and chair-like geometries, by varying the dihedral ϕ_2 (see Figure 3 in the main text) and the pseudo-axial/pseudo-equatorial orientation of substituents. The same chemical model employed for lactone **2'** was used for these systems.

All of the Cartesian coordinates and additional information are supplied in the SI.

NMR details: NMR spectra were recorded on a spectrometer operating at 500 and 600 MHz for ^{1}H and 125 and 150 MHz for ^{13}C. Measurements were carried out at a probe temperature of 25°C, using solutions of *ca.* 5 mg cm^{-3} in $CDCl_3$. The ^{1}H spectra were based on a TMS reference. Compound **2** was fully characterised using 1D ^{1}H and ^{13}C spectra, 2D HSQC with multiplicity editing, and HMBC and NOESY contour plots. For NOESY, the mixing time was set as 1 sec.

Synthesis: The Lactone **2** used in the NMR studies was an authentic sample synthesised according to the method described in reference 7. Data of **2**: Rf 0.12, (15% EtOAc/hexane); $[\alpha]^{20}_D = -60$ (c = 1.6, $CHCl_3$); For ^{1}H and ^{13}C NMR spectra see Table 1. IR vmax (film): 992, 1028, 1084, 1206, 1265, 1380, 1463, 1514, 1612, 1740, 2876, 2935, 2972, 3055.

Conclusions

In conclusion, the present experimental and theoretical study demonstrated that the anomalous H-5 methylene ^{1}H chemical shift difference presented for compound **2** is related to its boat-like conformation, in which the two methyl groups (C-8 and C-9) face towards H-5b, leading to its higher shielding effect. In addition, this study was extended to other diastereoisomeric lactonic analogues, showing the influence of the relative stereochemistry on the conformational preferences, and their ^{1}H NMR chemical shifts.

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Notes and references

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