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Unexpected Stability of δ-Lactones with Axial Substituents rather than Equatorial Ones. Conformational Evaluation by Molecular Mechanics and Molecular Orbital Calculations

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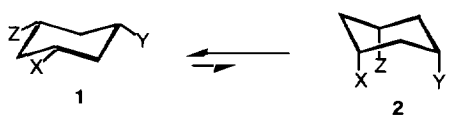
Abstract: A 1:1 mixture of the trisubstituted δ-lactones **5a** and **5b** was subjected to thermodynamically equilibrated conditions to give predominantly **5b** with axial substituents rather than **5a** with all equatorial ones, in contrast to the Prelog-Djerassi lactone derivatives **3a** and **3b**. Further surprisingly, it has been found that the disubstituted lactone **15** also adopts a half-chair conformation with axial substituents. The conformational analyses of these compounds by molecular mechanics and molecular orbital calculations have emphasized *gauche* effects and electrostatic interactions as a cause of the preference for axial conformers.

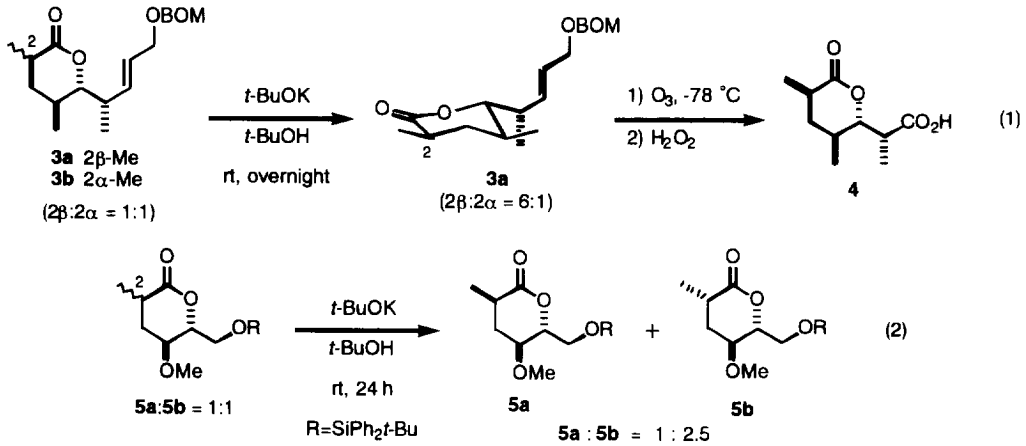
INTRODUCTION

The axial and equatorial concept on six-membered rings is one of the most fundamental and important ones in organic chemistry.[1] Considering the conformational stability of substituted six-membered rings, it has been generally accepted as common recognition that the conformer **1** with equatorial X, Y, and Z substituents is thermodynamically more stable than the conformer **2** with axial ones because of nonbonded steric repulsion, 1,3-diaxial interaction,[2] except for the anomeric effect[3] *etc.*



1 **2**

Thus, it is possible to control the stereochemistry on six-membered rings by exploiting the difference of such a thermodynamic stability. For example, Suzuki *et al.* have reported that a 1:1 mixture of lactones **3a** and **3b** subjected to thermodynamically equilibrated conditions predominantly gives the lactone **3a**, bearing 2β-Me with a ratio of β:α = 6:1, which is converted to the Prelog-Djerassi lactone (**4**)[4] by ozonolysis (equation 1).[5] However, when a 1:1 mixture of the analogous lactones **5a** and **5b** was exposed to the same condition as equation 1, surprisingly, it has been found that **5b** with axial substituents predominates over **5a** with all equatorial ones in contrast to the above example (equation 2). In this article we report the unexpected but stimulating results of the thermodynamic equilibration and conformational inspection by molecular mechanics and molecular orbital calculations concerning di and trisubstituted δ-lactones.[6]



RESULTS AND DISCUSSION

During the course of our synthetic studies[7] on the immunosuppressant FK 506 (**6**),[8] we planned the thermodynamic control of the 11-Me configuration on the δ-lactone **8**, to obtain the lactone **9** with all equatorial substituents, corresponding to the C10-C15 substructure[9] of FK 506 (**6**) (Fig. 1). The actual synthesis of δ-lactone **5** is depicted in Scheme 1. After protection of the primary alcohol in the diol **10**[10] readily prepared from commercially available methyl α-D-glucopyranoside (**7**) as a *tert*-butyldiphenylsilyl ether,[11] reductive elimination of the dimesylate **11** in refluxing *N*,*N*-dimethylformamide provided the allylic alcohol **12** which was converted to the methyl ether **13**. Oxidation[12] of **13** to the α,β-unsaturated lactone **14** was carried out by treatment with *m*-chloroperbenzoic acid in the presence of boron trifluoride etherate and subsequent hydrogenation afforded the lactone **15**. Finally, the lithium enolate formed by treatment of **15** with lithium diisopropylamide in tetrahydrofuran at -78 °C was methylated[13] with iodomethane to give the predictable 1:1 mixture of **5a** and **5b**, which were then subjected to equilibration conditions.[14]

The results are summarized in Table 1. The equilibration of a 1:1 mixture of **5a** and **5b** in the presence of a variety of bases such as pyridine, triethylamine, *N*-ethylpiperidine, and *N*,*N*-diisopropylethylamine (entries 1-

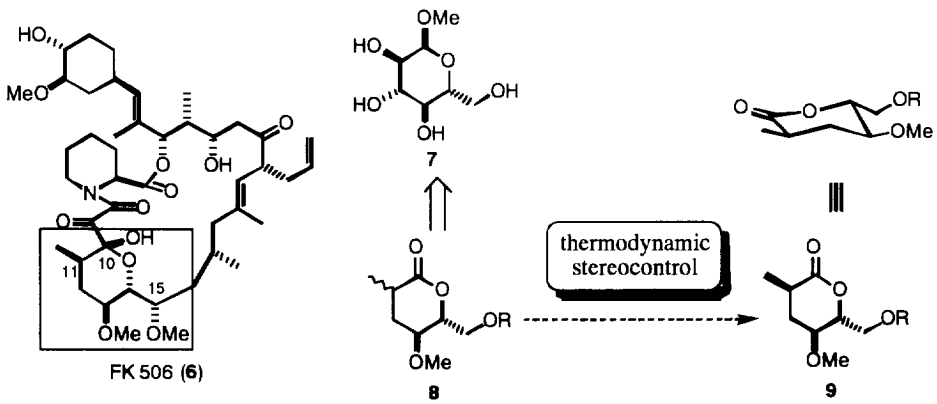
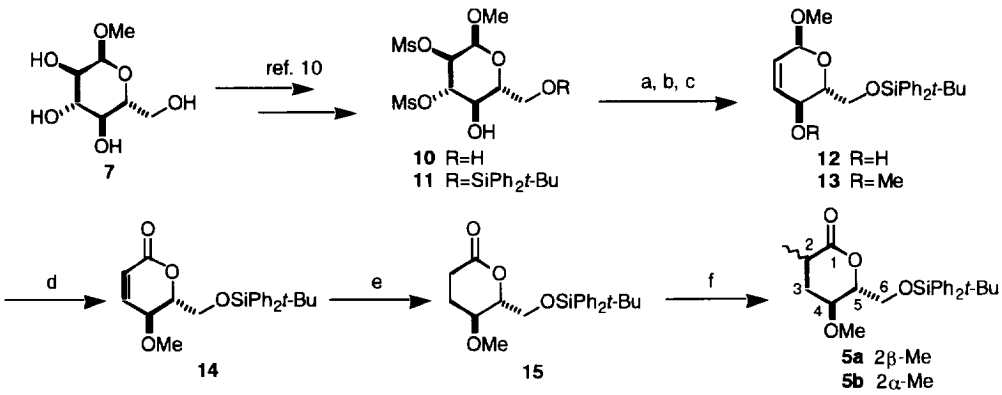


Fig. 1. Synthetic plan for the C10-C15 fragment **9** of FK 506 (**6**).



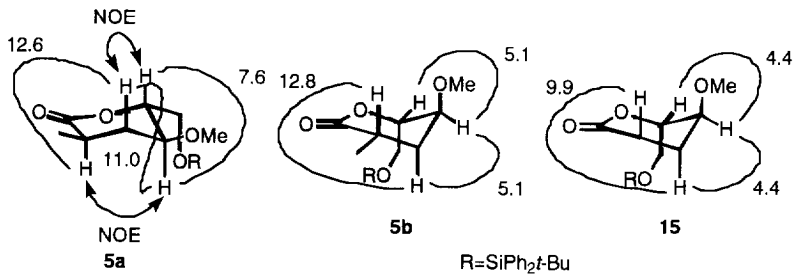
Scheme 1. Reagents and conditions: (a) *t*-BuPh$_2$SiCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, rt, 2 h, 97%; (b) KI, Zn-Cu, DMF, reflux, 4 h, 90%; (c) NaH, MeI, THF, rt, 30 min, 90%; (d) *m*-CPBA, BF$_3$•OEt$_2$, MS 4A, CH$_2$Cl$_2$, -15 °C, 1 h, 92%; (e) H$_2$, 10% Pd/C, EtOH, rt, 3 h, 95%; (f) LDA, THF, -78 °C, then MeI, HMPA, -78 °C, 1 h, 80% (**5a**:**5b** = 1:1).

4) has only recovered the starting material (**5a**:**5b** = 1:1). Though utilization of 1,8-diazabicyclo[5.4.0]undec-7-ene and potassium *tert*-butoxide as a base observed a different ratio of **5a** and **5b** (entries 5-7), the major isomer was unexpectedly **5b**. As shown in Fig. 2, coupling constants ($J_{2\text{-}3ax}$=12.6 Hz, $J_{3ax\text{-}4}$=11.0 Hz, $J_{4\text{-}5}$=7.6 Hz) in the minor component **5a** indicated the *trans*-diaxial relationship between vicinal protons and nuclear Overhauser effect (NOEs) observed for H2-H4 and H3ax-H5 clarified that **5a** adopts the half-chair conformation with all equatorial substituents. It has been found that the major component **5b** possesses a half-chair conformation with one equatorial and two axial substituents as shown from the coupling constants ($J_{2\text{-}3ax}$=12.8 Hz, $J_{3ax\text{-}4}$=5.1 Hz, $J_{4\text{-}5}$=5.1 Hz) and high field shifts at C2 (2.8 ppm), C3 (0.9 ppm), and C5 (2.2 ppm) in its ^{13}C NMR in comparison with **5a**, due to the steric compression effect.[15] Furthermore, the lactone **15** also revealed coupling constants ($J_{2ax\text{-}3ax}$=9.9 Hz, $J_{3ax\text{-}4}$=4.4 Hz, $J_{4\text{-}5}$=4.4 Hz) showing a half-chair conformation with two axial substituents at the C4 and C5 positions.

Why was a stability of the δ-lactones **5a** and **5b** against our expectation ? It seems to be worth while giving consideration to the anomalous preference for the conformation bearing axial substituents in the lactones **5b** and **15** in contrast to the Prelog-Djerassi lactone derivatives **3a** and **3b**. There we have performed an inspection about thermodynamic stability and conformational behavior of the δ-lactones **5a** and **5b** by molecular

Table 1. Equilibration of 1:1 Mixture of **5a** and **5b** in the Presence of Various Bases

entry	base	solvent	temp	time (h)	ratio (**5a**:**5b**)
1	Py	benzene	reflux	24	1 : 1
2	Et$_3$N	benzene	reflux	24	1 : 1
3	*N*-ethylpiperidine	benzene	reflux	24	1 : 1
4	*i*-Pr$_2$NEt	benzene	reflux	24	1 : 1
5	DBU	benzene	reflux	24	1 : 2
6	DBU	toluene	reflux	24	1 : 2.5
7	*t*-BuOK	*t*-BuOH	rt	24	1 : 2.5



	5a	5b
C2	33.4	30.6
C3	32.0	31.1
C4	72.7	72.8
C5	83.0	80.8

Fig. 2. Half-chair conformations of δ-lactones **5a**, **5b**, and **15** supported from diagnostic ^{1}H (coupling constants in Hz) and ^{13}C (chemical shifts in ppm) NMR.

mechanics and semi-empirical molecular orbital calculations. The results calculated by MM2 and PM3 are shown in Fig. 3.[16] Although the thermodynamic stability of **5a** was much the same as **5b** in MM2[17] calculations, the results calculated by PM3[18] have revealed that in the trisubstituted δ-lactones **5b** with axial substituents is more stable than **5a** with all equatorial ones by 0.61752 kcal/mol, which is well consistent with experimental facts. In the disubstituted δ-lactones comparison of the half-chair conformer **15** with hypothetical *flipped*-**15** by PM3 calculations invoked a conformational preference for **15** with axial substituents over *flipped*-**15** with equatorial ones as well. In **5b** and **15** the presence of C=O and O in the ring removes two potentially unfavorable 1,3-diaxial interactions, leaving only one 1,3-H,OMe and one 1,3-H,CH_2OSiPh_2t-Bu interaction in contrast to

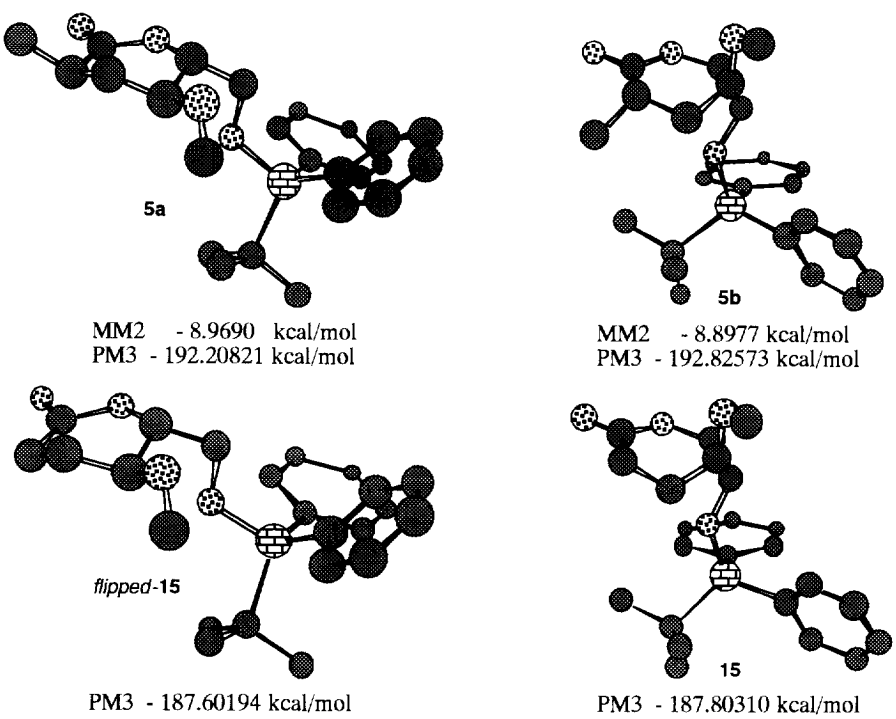


Fig. 3. The optimized structures and minimun steric energies of tri and disubstituted δ-lactones **5a**, **5b**, **15**, and *flipped*-**15** calculated by MM2 and PM3. Hydrogens have been omitted for clarity.

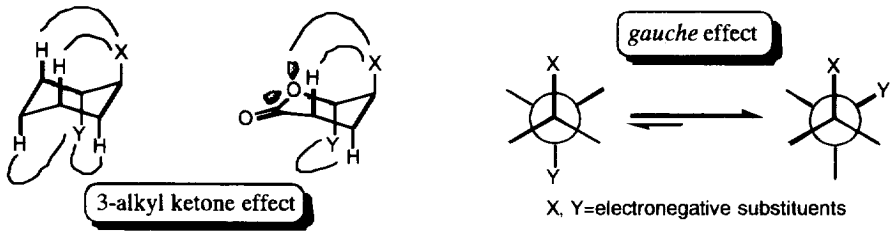


Fig. 4. Reduction of 1,3-diaxial interaction by the 3-alkyl ketone effect biased in favor of axial conformation in certain extent and *gauche* effect favored for axial conformer.

cyclohexanes, which have two such interactions (3-alkyl ketone effect[19] in Fig. 4). However, as the 3-alkyl ketone effect is also the case for the Prelog-Djerassi lactone derivatives **3a** and **3b**, the effect alone can not explain the preference for axial conformer.

It is known that OMe has an axial preference when *para* to C=O.[20] Since the relative configuration at C4 and C5 is fixed by the synthesis, this will assist CH_2OSiPh_2t-Bu also to be axial . A detailed inspection of the C4-C5 and C5-C6 bonds in **5b** and **15** by ^{1}H NMR showed *gauche* conformations for not only C4-O and C5-O bonds on their lactone rings but also C5-O and C6-O bonds out of the rings (**5b**, $J_{5\text{-}6}$=4.0 Hz, $J_{5\text{-}6'}$=4.0 Hz; **15**, $J_{5\text{-}6}$=3.5 Hz, $J_{5\text{-}6'}$=4.3 Hz) (Fig. 5). Thus the unusual bis-axial geometry here may result from a fortuitous combination of this *gauche* interaction,[21] the so-called *gauche* effect[22] (Fig. 4), and the above two factors. Although it can be understood that the *gauche* effect plays an important role in a preference for the axial conformer, $J_{5\text{-}6}$ and $J_{5\text{-}6'}$ values in ^{1}H NMR shows that the conformer **A** predominates over the conformer **B** sterically preferred of the two possible *gauche* conformers around C5-C6 bond out of the rings (Fig. 5). In order to explore a relationship between a stable conformation and the dihedral angle O-C5-C6-O in **5b** and **15**, MM2 calculations[16] were carried out again.

The results are indicated in Fig. 6. When the dihedral angle O-C5-C6-O is rotated from 0° to 360°, it has been shown that there is three local minimal conformers **B**, **C**, and **A**, the *gauche* conformers **B** and **A** of which are more stable than the *anti* conformer **C** as rationalized by the *gauche* effect. Furthermore, it has been also found that of the two *gauche* conformers an inner conformer **A** is more stable than an outer conformer **B** as if these calculations imply our experimental results. Indeed, a validity of these conformational analyses is reflected to some extent by the vicinal coupling constants Ha-Hb and Ha-Hc estimated by the modified Karplus equation[23] on the basis of the dihedral angles and population at 300 K in respective conformers (Fig. 6).

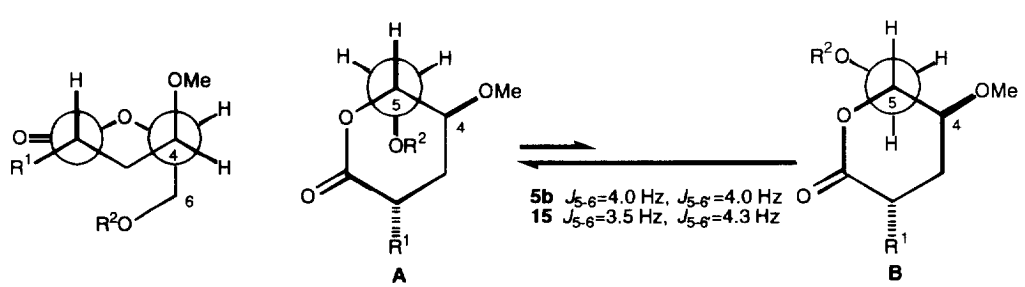
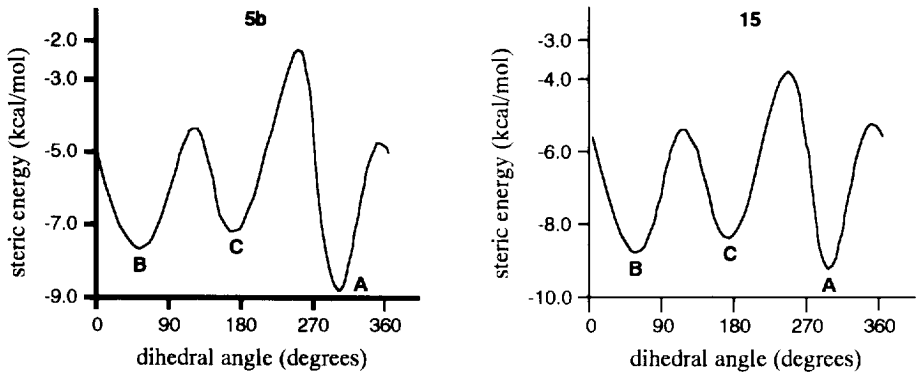
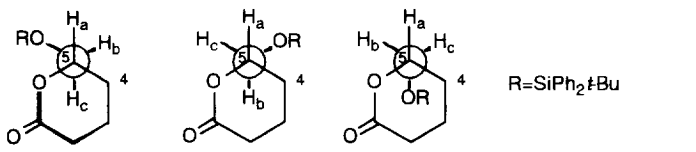


Fig. 5. *Gauche* conformation around C4-C5 and C5-C6 bonds in **5b** (R^1=Me, R^2=$SiPh_2t$-Bu) and **15** (R^1=H, R^2=$SiPh_2t$-Bu).





B C A

		B	C	A	estimated J value
5b	local minimun (kcal/mol)	-7.5729	-7.2183	-8.8977	$J_{a\text{-}b}$=4.0 Hz
	population (%)	9.25	5.13	85.6	$J_{a\text{-}c}$=1.6 Hz
15	local minimun (kcal/mol)	-8.5553	-8.1536	-9.2927	$J_{a\text{-}b}$=4.2 Hz
	population (%)	20.2	10.3	69.5	$J_{a\text{-}c}$=2.9 Hz

Fig. 6. Dihedral angle O-C5-C6-O dependence of the conformational stability, local minima (kcal/mol), population (300 K), and the estimated coupling constants around C5-C6 bond in **5b** and **15**.

Molecular orbital calculations (Extended Hückel) were next performed to gain an incentive of the preference for the inner conformer **A** over the outer conformer **B**.

Some principal partial charges by the Extended Hückel MO[16] and PM3 calculations are listed in Table 2. We then focused on the coulombic intercharge interactions between positive charge on C1 in the δ-lactone and negative charges on O9 and O11 in the side-chains which have relatively large mobility (Fig. 7). Though in a comparison of the conformer **A** with **B** of the two possible *gauche* conformers around C5-C6 bond in **5b** and **15** the distances C1-O9 are almost the same in these respective conformers optimized by MM2, the distances C1-O11 in the inner conformer **A** are shorter than in the outer conformer **B** by at least 0.602 Å, which the preference for the inner conformer **A** over the outer conformer **B** may be attributed to. In the case of the axial versus equatorial problem, the distances C1-O11 and C1-O9 in the axial conformers **5b**-**A** and **15**-**A** optimized by PM3 are also shorter than in the equatorial conformers **5a** and *flipped*-**15** by at least 0.273 and 0.797 Å, respectively. Thus, the unexpected preference for the axial conformers over the equatorial ones may be explained by not only the above mentioned *gauche* effect but also these electrostatic attraction.

In conclusion, in the course of our synthetic studies on the immunosuppressant FK 506 (**6**) we tried thermodynamically stereocontrolling the 2-Me configuration of δ-lactone **5**, corresponding to the C10-C15 substructure of **6**, to give predominantly **5b** with axial substituents rather than **5a** with all equatorial ones. It has been found that the disubstituted lactone **15** also adopts a half-chair conformation with axial substituents. The

Table 2. Partial Charges (au) of the Atoms Possessing |partial charge|>0.5 Calculated by Extended Hückel MO (basis set : STO-3G) in the Conformers **5b-B,A** and **15-B,A** Optimized by MM2 and |partial charge|> 0.25 Obtained by PM3 in the Conformers **5b-A**, **5a**, **15-A**, and *flipped*-**15** Optimized by PM3

	partial charge (au)						
atom	**5b-B**	**5b-A**		**5a**	**15-B**	**15-A**	*flipped*-**15**
		Hückel	PM3			Hückel PM3	
C1	+1.2169	+1.2151	+0.3751	+0.3593	+1.2266	+1.2249 +0.3709	+0.3604
O7	- 0.5909	- 0.5892			- 0.5869	- 0.5852	
C4	+0.5186	+0.5178			+0.5228	+0.5221	
O8	- 1.0602	- 1.0618	- 0.3591	- 0.3498	- 1.0549	- 1.0567 - 0.3617	- 0.3527
O9	- 0.7941	- 0.7936	- 0.2624	- 0.2531	- 0.7940	- 0.7936 - 0.2635	- 0.2537
C10	+0.5343	+0.5337			+0.5343	+0.5339	
O11	- 1.1039	- 1.0966	- 0.4037	- 0.4008	- 1.1050	- 1.0965 - 0.4053	- 0.4015
Si	+2.2159	+2.2179	+0.6952	+0.6961	+2.2198	+2.2174 +0.6976	+0.6974

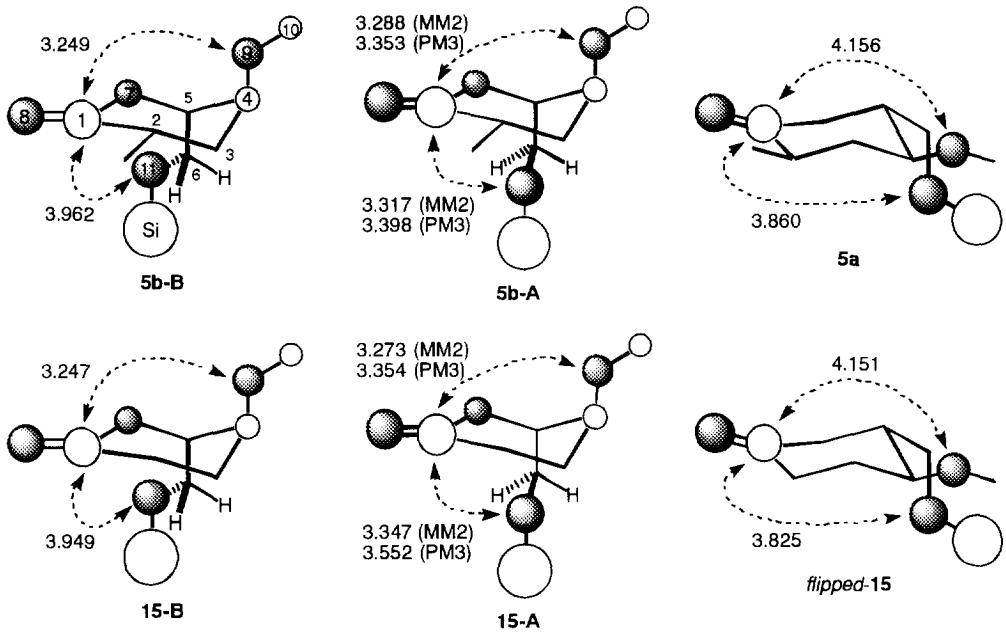


Fig. 7. Interatomic distances (Å) of C1-O9 and C1-O11 in conformers optimized by MM2 (inner **A** versus outer **B**) and PM3 (axial versus equatorial) between attractive positive and negative charges which the preferred conformations may be attributed to.

conformational analyses of these unusual compounds by molecular mechanics and molecular orbital calculations have suggested an importance of the *gauche* effects and electrostatic interactions between the neighboring polar substituents for this unexpected phenomenon.

EXPERIMENTAL SECTION

General Procedures

Melting points are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform on Hitachi R-90H (90 MHz), JEOL model JNM-GX 270 (270 MHz), and Bruker AM-400 (400 MHz) spectrometers. ^{13}C NMR spectra were measured in deuteriochloroform on JEOL model FX-500 (125 MHz) spectrometer. Chemical shifts were reported in ppm down field from the peak of tetramethylsilane as an internal standard. The data are reported as follows: chemical shift, number of proton, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broadened), and coupling constants. Infrared (IR) spectra were recorded on a JASCO IR-S spectrophotometer. Optical rotations were determined on a JASCO DIP-360 digital polarimeter using the sodium D line (λ=589 nm) at the temperature indicated and are reported as follows: $[\alpha]_D^{temp}$, concentration (c=g/100 mL), and solvent. Low (EI and FD) and high (EI) resolution mass spectra were determined on JEOL model JMS-DX 303 and JMS-HX 110 spectrometers.

Analytical thin layer chromatography was carried out by precoated silica gel (Macherey-Nagel DC-Fertigplatten SIL G-25 UV_{254} and Merck DC-Fertigplatten Kieselgel 60 F_{254}). Silica gels used for column chromatographies were Merck kieselgel 60 Art 7734 and Amicon Matrex® silica Si chromatography medium. Medium pressured column chromatography was performed employing Lobar® Größe B (310-25) LiChroprep® Si 60 (40-63 μm) (Merck) equipped with a FMI LAB POMP MODEL RP SY. All reactions were performed in oven-dried glassware.

Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine, and pyridine (Py) were distilled from calcium hydride. Ethanol (EtOH) was distilled from magnesium ethoxide. *tert*-Butyl alcohol (*t*-BuOH) was distilled from magnesium activated with iodine. *N*,*N*-Dimethylformamide (DMF), *N*-ethylpiperidine, *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt), hexamethylphosphoric triamide (HMPA), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled from calcium hydride at reduced pressure. Activation of powdered 4A molecular sieves (MS 4A) involved heating in a vacuum oven at 160 °C and 0.05 mmHg pressure for at least 3 h. Methyl 2,3-di-*O*-methanesulfonyl-α-D-glucopyranoside (**10**), mp 150-151 °C; $[\alpha]_D^{25}$ +89.6° (*c* 1.00, MeOH) [lit.[10] mp 150-151 °C; $[\alpha]_D^{25}$ +82.4° (*c* 1.06, MeOH)], was prepared according to literature method.

Methyl 6-*O*-*tert*-butyldiphenylsilyl-2,3-di-*O*-methanesulfonyl-α-D-glucopyranoside (11)

To a solution of methyl 2,3-di-*O*-methanesulfonyl-α-D-glucopyranoside (**10**)[10] (10.8 g, 30.9 mmol) and 1.89 g (15.5 mmol) of 4-dimethylaminopyridine in 110 mL of CH_2Cl_2 at room temperature under Ar was added 6.46 mL (46.4 mmol) of triethylamine. To the solution was added dropwise 9.64 mL (37.1 mmol) of *t*-butylchlorodiphenylsilane and the resulting mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into 100 mL of water and the organic layer was separated. The aqueous layer was extracted with ether (50 mL × 2). The combined organic layer was washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/benzene) on 324 g of silica gel to give silyl ether **11** (17.6 g, 97% yield): mp 88-90 °C; $[\alpha]_D^{19}$ +44.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.71-7.12 (10H, m), 5.02-4.76 (2H, m), 4.48 (1H, dd, *J*=10, 4 Hz), 3.97-3.55 (4H, m), 3.33 (3H, s), 3.14 (3H, s), 3.11 (3H, s), 1.08 (9H, s); IR ($CHCl_3$) 3530, 3030, 2950, 2870, 1365,

1179, 1115, 1050, 1003, 960, 916, 848, 762, 705 cm^{-1}; FD-MS *m/z* (relative intensity) 588 (M^+, 1.2); EI-MS *m/z* (relative intensity) 531 (M^+—*t*-Bu, 3.6), 403 (30), 307 (35), 277 (78), 241 (100), 199 (52), 163 (74), 135 (45), 99 (71), 81 (39); EI-HRMS calcd for $C_{21}H_{27}O_{10}S_2Si$ (M^+—*t*-Bu) 531.0815, found 531.0809.

Methyl 6-*O*-*tert*-butyldiphenylsilyl-α-D-*erythro*-hex-2-enopyranoside (12)

To a solution of dimesylate **11** (10.4 g, 17.7 mmol) and 6.94 g (0.106 mol) of zinc-copper couple in 140 mL of DMF at room temperature was added a portion of potassium iodide (17.6 g, 0.106 mol) and the resulting mixture was vigorously stirred at reflux for 4 h under Ar. An oil bath was removed and the mixture was cooled to room temperature. To the reaction vessel was added 50 mL of saturated aqueous NH_4Cl and the mixture was poured into 300 mL of 10% aqueous $Na_2S_2O_3$, followed by extracting with ether (300 mL × 3). The ethereal layer was washed with 500 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/benzene) on 312 g of silica gel to provide alcohol **12** (6.35 g, 90% yield) as an oil: $[\alpha]_D^{26}$ +28.8° (*c* 0.500, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.79-7.15 (10H, m), 5.90 (1H, br d, *J*=10 Hz), 5.68 (1H, dt, *J*=10, 2 Hz), 4.78 (1H, br s), 4.31-4.03 (1H, m), 3.96-3.55 (3H, m), 3.33 (3H, s), 2.48 (1H, d, *J*=5 Hz), 1.07 (9H, s); IR (neat) 3410, 3020, 2910, 2865, 1589, 1472, 1429, 1391, 1360, 1185, 1110, 1051, 1010, 963, 867, 824, 798, 744, 700 cm^{-1}; EI-MS *m/z* (relative intensity) 398 (M^+, 0.02), 341 (M^+—*t*-Bu, 1.3), 242 (24), 241 (100), 199 (31), 163 (62), 100 (35), 81 (22), 71 (24); EI-HRMS calcd for $C_{19}H_{21}O_4Si$ (M^+—*t*-Bu) 341.1209, found 341.1194.

Methyl 6-*O*-*tert*-butyldiphenylsilyl-4-*O*-methyl-α-D-*erythro*-hex-2-enopyranoside (13)

To a solution of sodium hydride (744 mg, 31.0 mmol, washed with hexane) in 25 mL of THF at room temperature was added dropwise a solution of alcohol **12** (4.95 g, 12.4 mmol) in 25 mL of THF and the solution was stirred at reflux for 30 min under Ar. After the temperature was cooled to room temperature, 3.86 mL (62.0 mmol) of freshly distilled methyl iodide was added to the solution and the resulting mixtures were stirred at the same temperature for additional 30 min. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 50 mL of water, followed by extracting with ether (50 mL × 3). The combined ethereal layers were washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography (1.5% EtOAc/benzene) on 149 g of silica gel to give methyl ether **13** (4.59 g, 90% yield) as an oil: $[\alpha]_D^{21}$ +71.9° (*c* 1.00, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.82-7.50 (4H, m), 7.50-7.15 (6H, m), 6.03 (1H, d, *J*=10 Hz), 5.73 (1H, dd, *J*=10, 2 Hz), 4.86 (1H, d, *J*=2 Hz), 4.00-3.67 (4H, m), 3.40 (3H, s), 3.30 (3H, s), 1.07 (9H, s); IR (neat) 2930, 2885, 1475, 1431, 1398, 1189, 1101, 1050, 1018, 999, 964, 828, 745, 701 cm^{-1}; FD-MS *m/z* (relative intensity) 412 (M^+, 0.95); EI-MS *m/z* (relative intensity) 355 (M^+—*t*-Bu, 4.6), 323 (22), 242 (24), 241 (100), 213 (24), 163 (60), 114 (39), 99 (20), 71 (21); EI-HRMS calcd for $C_{20}H_{23}O_4Si$ (M^+—*t*-Bu) 355.1366, found 355.1352.

(4*S*,5*R*)-6-(*tert*-Butyldiphenylsilyl)oxy-4-methoxy-2-hexen-5-olide (14)

To a solution of methyl ether **13** (4.59 g, 11.1 mmol) and 4.00 g of activated 4A molecular sieves in 45 mL of CH_2Cl_2 at -15 °C under Ar were added dropwise *m*-chloroperbenzoic acid (80% purity, 2.63 g, 12.2 mmol) dissolved in 20 mL of CH_2Cl_2 and 1.50 mL (12.2 mmol) of freshly distilled boron trifluoride etherate and the solution was stirred at the same temperature for 1 h. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ and the resulting mixture was filtered through a pad of Celite *in suction*. The filtrates were

poured into 100 mL of water and extracted with ether (80 mL × 3). The organic layer was washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/hexane) on 138 g of silica gel to afford α,β-unsaturated lactone **14** (4.05 g, 92% yield): $[\alpha]_D^{20}$ +56.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.75-7.18 (10H, m), 6.84 (1H, d, *J*=10 Hz), 5.98 (1H, d, *J*=10 Hz), 4.31 (2H, br s), 3.89 (2H, br s), 3.42 (3H, s), 1.08 (9H, s); IR (neat) 3040, 2920, 2840, 1739, 1474, 1430, 1393, 1259, 1230, 1195, 1170, 1132, 1110, 1029, 828, 745, 701 cm^{-1}; EI-MS *m/z* (relative intensity) 397 (M^++H, 0.03), 339 (M^+—*t*-Bu, 39), 242 (25), 241 (100), 223 (24), 213 (18), 199 (22), 183 (16), 163 (71), 109 (15), 98 (17); EI-HRMS calcd for $C_{19}H_{19}O_4Si$ (M^+—*t*-Bu) 339.1052, found 339.1040.

(4*S*,5*R*)-6-(*tert*-Butyldiphenylsilyl)oxy-4-methoxy-5-hexanolide (15)

To a solution of α,β-unsaturated lactone **14** (3.91 g, 9.86 mmol) in 40 mL of EtOH was added a portion of 196 mg of 10% palladium on carbon and the mixture was stirred at room temperature for 3 h under 1 atm of hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite *in suction* and concentrated under reduced pressure. The residue was subjected to column chromatography (15% EtOAc/hexane) on 117 g of silica gel to furnish lactone **15** (3.73 g, 95% yield): mp 50-53 °C; $[\alpha]_D^{23}$ +42.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.61 (4H, m), 7.49-7.35 (6H, m), 4.34 (1H, dt, *J*=3.4, 4.4 Hz), 3.86 (1H, dd, *J*=11.2, 3.4 Hz), 3.81 (1H, dd, *J*=11.2, 4.4 Hz), 3.74 (1H, dt, *J*=5.9, 4.4 Hz), 3.37 (3H, s), 2.68 (1H, ddd, *J*=17.6, 9.9, 5.9 Hz), 2.46 (1H, dt, *J*=17.6, 5.9 Hz), 2.09 (1H, dddd, *J*=13.8, 9.9, 5.9, 4.4 Hz), 1.95 (1H, dq, *J*=13.8, 5.9 Hz), 1.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 135.5, 135.4, 132.8, 132.5, 129.8, 127.7, 81.6, 72.3, 63.3, 56.4, 26.7, 26.4, 22.3, 19.1; IR ($CHCl_3$) 2880, 1730, 1466, 1421, 1231, 1181, 1155, 1097, 1047, 993, 814, 735, 688 cm^{-1}; FD-MS *m/z* (relative intensity) 399 (M^++H, 2.7); EI-MS *m/z* (relative intensity) 341 (M^+—*t*-Bu, 46), 267 (32), 213 (83), 199 (100), 183 (33), 129 (52), 117 (33), 111 (64), 55 (34); EI-HRMS calcd for $C_{19}H_{21}O_4Si$ (M^+—*t*-Bu) 341.1209, found 341.1227.

(2*R*,4*S*,5*R*)-6-(*tert*-Butyldiphenylsilyl)oxy-4-methoxy-2-methyl-5-hexanolide (5a) and (2*S*,4*S*,5*R*)-6-(*tert*-butyldiphenylsilyl)oxy-4-methoxy-2-methyl-5-hexanolide (5b)

To a solution of diisopropylamine (1.50 mL, 10.7 mmol) in 15 mL of THF at 0 °C under Ar was added dropwise 6.73 mL (10.7 mmol) of *n*-butyllithium (1.59 M in hexane) and the mixture was stirred for 30 min at the same temperature followed by cooling to -78 °C. To the solution was added dropwise lactone **15** (3.88 g, 9.74 mmol) dissolved in 15 mL of THF and the mixture was stirred at -78 °C for additional 30 min. To the solution were added successively 1.35 mL (21.8 mmol) of freshly distilled iodomethane and 3.80 mL (21.8 mmol) of hexamethylphosphoric triamide and the resulting mixture was stirred at the same temperature for 1 h. After quenching with 5 mL of saturated aqueous NH_4Cl at -78 °C, the reaction mixture was allowed to warm to room temperature, poured into 60 mL of water, and extracted with ether (40 mL × 3). The combined organic layers were washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography on 194 g of silica gel yielded 1:1 mixture of 2β-Me **5a** and 2α-Me **5b** (3.22 g, 80% yield) eluted with 9% EtOAc/hexane and the recovered lactone **15** (241 mg, 6.2% yield) eluted with 20% EtOAc/hexane. The 1:1 mixture of **5a** and **5b** was subjected to the next equilibration conditions.

The equilibration of a 1:1 mixture of 5a and 5b with various bases.

A procedure utilizing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is described as a representative.

To a solution of 1:1 mixture of **5a** and **5b** (200 mg, 0.485 mmol) in 5 mL of toluene at room temperature under Ar was added 0.218 mL (1.46 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene and the mixture was stirred at reflux for 24 h. An oil bath was removed and the mixture was cooled to room temperature. The organic solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9% EtOAc/hexane) on 6 g of silica gel to give a mixture of **5a** and **5b** (182 mg, 91% yield). The mixture of **5a** and **5b** (182 mg) was further subjected to medium pressured column chromatography (9% EtOAc/hexane) to provide pure 2β-Me **5a** (52.0 mg, 26% yield) and 2α-Me **5b** (130 mg, 65% yield).

2β-Me **5a**: $[\alpha]_D^{23}$ +23.7° (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74-7.61 (4H, m), 7.48-7.33 (6H, m), 4.18 (1H, dt, *J*=7.6, 2.6 Hz), 3.89 (1H, dd, *J*=11.5, 2.6 Hz), 3.86 (1H, dd, *J*=11.5, 2.6 Hz), 3.84 (1H, ddd, *J*=11.0, 7.6, 4.8 Hz), 3.37 (3H, s), 2.52 (1H, ddq, *J*=12.6, 4.8, 6.8 Hz), 2.32 (1H, dt, *J*=12.6, 4.8 Hz), 1.58 (1H, dt, *J*=11.0, 12.6 Hz), 1.33 (3H, d, *J*=6.8 Hz), 1.05 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 135.6, 135.4, 133.1, 132.5, 129.74, 129.70, 127.7, 83.0, 72.7, 62.9, 56.8, 33.4, 32.0, 26.7, 19.2, 17.1; IR (neat) 2950, 1748, 1465, 1433, 1384, 1365, 1187, 1112, 1040, 1010, 971, 830, 750, 710 cm^{-1}; EI-MS *m/z* (relative intensity) 413 (M^++H, 0.21), 267 (38), 213 (64), 199 (100), 183 (30), 85 (45); EI-HRMS calcd for $C_{24}H_{33}O_4Si$ (M^++H) 413.2148, found 413.2120.

2α-Me **5b**: mp 104-106 °C; $[\alpha]_D^{24}$ +59.0° (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74-7.58 (4H, m), 7.50-7.32 (6H, m), 4.29 (1H, dt, *J*=5.1, 4.0 Hz), 3.86 (1H, dd, *J*=11.0, 4.0 Hz), 3.83 (1H, dd, *J*=11.0, 4.0 Hz), 3.75 (1H, dt, *J*=3.1, 5.1 Hz), 3.34 (3H, s), 2.73 (1H, ddq, *J*=12.8, 5.9, 6.8 Hz), 2.06 (1H, ddd, *J*=14.1, 5.9, 3.1 Hz), 1.77 (1H, ddd, *J*=14.1, 12.8, 5.1 Hz), 1.24 (1H, d, *J*=6.8 Hz), 1.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 135.5, 135.4, 132.9, 132.6, 129.7, 127.6, 80.8, 72.8, 63.4, 56.4, 31.1, 30.6, 26.7, 19.1, 15.7; IR (nujol) 2940, 1760, 1462, 1381, 1190, 1149, 1102, 1079, 984, 955, 827, 806, 747, 707 cm^{-1}; FD-MS *m/z* (relative intensity) 413 (M^++H, 0.19); EI-MS *m/z* (relative intensity) 355 (M^+—*t*-Bu, 54), 267 (54), 213 (79), 199 (100), 163 (56), 129 (72), 125 (61), 97 (64), 71 (53), 45 (61), 41 (77); EI-HRMS calcd for $C_{20}H_{23}O_4Si$ (M^+—*t*-Bu) 355.1366, found 355.1360.

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