# Unprecedented Stability of δ-Lactones with Axial Substituents rather than Equatorial ones; Comparison with the Prelog–Djerassi Lactone Derivative

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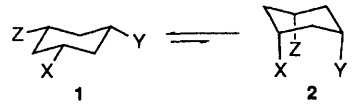
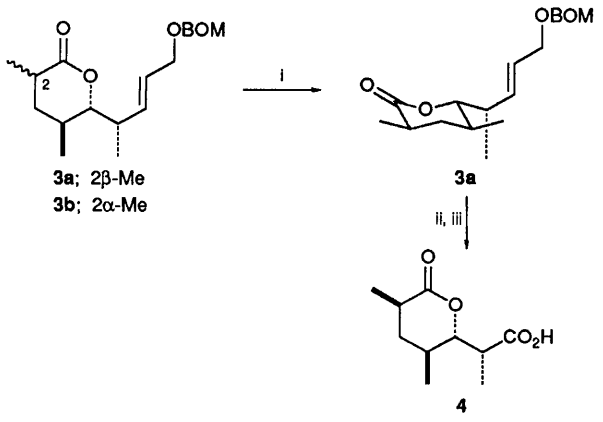
A 1 : 1 mixture of the trisubstituted δ-lactones **11a** and **11b** was subjected to thermodynamically equilibrated conditions to give predominantly **11b** with axial substituents rather than **11a** with all equatorial ones, in contrast to the Prelog–Djerassi lactone derivatives **3a** and **3b**, and, further surprisingly, it has been found that the disubstituted lactone **10** also adopts a chair conformation with axial substituents.

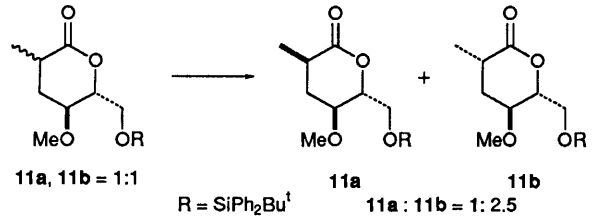
The axial and equatorial concept on six-membered rings is one of the most fundamental and important ones in organic chemistry.[1] Considering the conformational stability of substituted six-membered rings, it has been generally accepted as common recognition that the conformer **1** with equatorial X,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




**1** **2**




**Scheme 1** *Reagents and conditions*: i, Bu$^t$OK–Bu$^t$OH, room temp., overnight; ii, $O_3$; iii, $H_2O_2$, (BOM = benzyloxymethoxy)

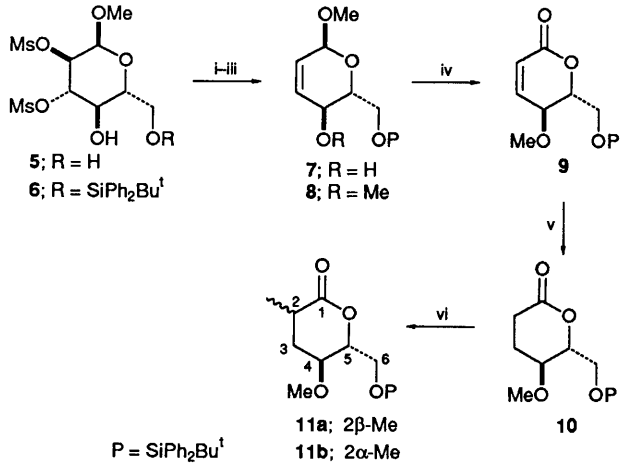



**Scheme 2** *Reagents and conditions*: Bu$^t$OK–Bu$^t$OH, room temp. or DBU–toluene, reflux

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 gives predominantly 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 (Scheme 1).[5] However, when a 1 : 1 mixture of the analogous lactones **11a** and **11b** was exposed to the same conditions, surprisingly, it has been found that **11b** with axial substituents predominates over **11a** with equatorial ones (Scheme 2) in contrast to the above example. In this communication we report the unexpected but interesting results of the thermodynamic equilibrium concerning di- and tri-substituted δ-lactones.

During the course of our synthetic studies on the immunosuppressant FK 506,[6,7] we planned the thermodynamic control of the 2-Me configuration on the δ-lactone **11**, easily derived from diol **5**,† to obtain the lactone **11a** with all equatorial substituents, corresponding to the C(10)–C(15) fragment[8] of FK 506 (Scheme 3). After protection of the primary alcohol in **5** as a *tert*-butyldiphenylsilyl ether,[9] reductive elimination of the dimesylate **6**, m.p. 88–90 °C, in refluxing *N,N*-dimethylformamide (DMF) provided the allylic alcohol **7** which was converted to the methyl ether **8**. Oxidation[10] of **8** to the α,β-unsaturated lactone **9** was carried out by treatment with *m*-chloroperbenzoic (MCPBA) acid in the presence of boron trifluoride–ether and subsequent hydrogenation afforded the lactone **10**, m.p. 50–53 °C; $[\alpha]_D^{23}$ +42.3° (*c* 1.00, $CHCl_3$). Finally the lithium enolate formed by treatment of **10** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C was methylated[11] with iodomethane to give the predictable 1 : 1 mixture of **11a** and **11b**, which were then subjected to equilibration conditions.

† Diol **5**, m.p. 150–151 °C; $[\alpha]_D^{25}$ +89.6° (*c* 1.00, MeOH) {lit. m.p.150–151 °C; $[\alpha]_D^{25}$ +82.4° (*c* 1.06, MeOH)}, was prepared according to the following literature: B. Fraser-Reid and B. Boctor, *Can. J. Chem.*, 1969, **47**, 393.




**Scheme 3** *Reagents and conditions*: i, Bu$^t$Ph$_2$SiCl, dimethylaminopyridine, $Et_3N$, $CH_2Cl_2$, 97%; ii, KI, Zn–Cu, DMF, reflux, 90%; iii, NaH, MeI, THF, 90%; iv, MCPBA, $BF_3$·$OEt_2$, molecular sieve 4 Å, $CH_2Cl_2$, −15 °C, 92%; v, $H_2$, Pd/C, EtOH, 95%; vi, LDA, THF, −78 °C, then MeI, 80%, **11a : 11b** = 1 : 1

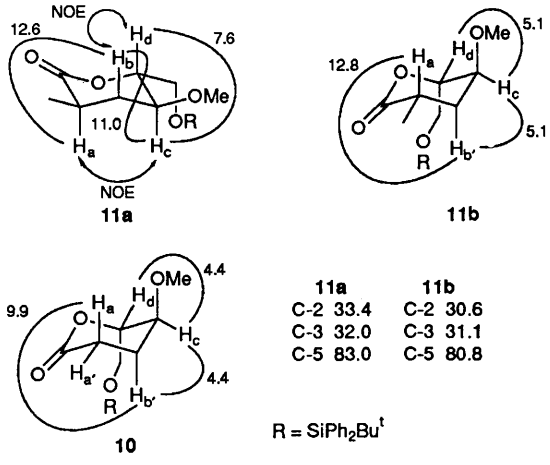
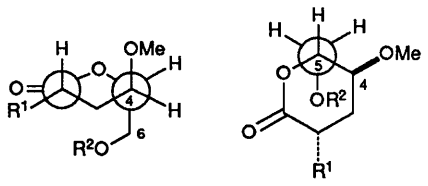



**Fig. 1** Conformations of δ-lactones **10**, **11a** and **11b** supported from $^1H$ (coupling constants, Hz) and $^{13}C$ (chemical shifts, δ) NMR

The equilibration of a 1 : 1 mixture of **11a** and **11b** with either one equivalent of potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature[5a,b] or three equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene unexpectedly led to the 1 : 2.5 mixture of **11a**, $[\alpha]_D^{23}$ +23.7° (*c* 1.00, $CHCl_3$), and **11b**, m.p. 104–106 °C; $[\alpha]_D^{24}$ +59.0° (*c* 1.00, $CHCl_3$), which could be separated by medium pressure column chromatography (hexane–EtOAc = 91 : 9) (Scheme 2). As shown in Fig. 1, coupling constants ($J_{a,b}$ 12.6, $J_{b,c}$ 11.0, $J_{c,d}$ 7.6 Hz) indicated the *trans*-diaxial relationship between vicinal protons and nuclear Overhauser effect (NOEs) observed for $H_a$-$H_c$ and $H_b$-$H_d$ in the minor component **11a** clarified that **11a** adopted the chair conformation with all equatorial substituents; it was found that the major component **11b** possessed a chair conformation with one equatorial and two axial substituents as shown from the coupling constants ($J_{a,b'}$ 12.8, $J_{b',c}$ 5.1, $J_{c,d}$ 5.1 Hz) and high field shifts at C-2 (δ-2.8), C-3 (−0.9) and C-5 (−2.2) in its $^{13}C$ NMR in comparison with **11a**, due to the steric compression effect.[12] Furthermore, the lactone **10** also revealed coupling constants ($J_{a,b'}$ 9.9, $J_{b',c}$ 4.4, $J_{c,d}$ 4.4 Hz) showing a chair conformation with two axial substituents at the C-4 and C-5 positions.

It seems to be worth while giving consideration to the anomalous preference for the conformation bearing axial



**10** $R^1$ = H, $R^2$ = $SiPh_2Bu^t$; **11b** $R^1$ = Me, $R^2$ = $SiPh_2Bu^t$

**Fig. 2** *Gauche* conformation around C(4)–C(5) and C(5)–C(6) bonds in **10** and **11b**

substituents in the lactones **10** and **11b** in contrast to the Prelog-Djerassi lactone derivatives **3a** and **3b**. In **10** and **11b** the presence of C=O and O in the ring removes two potentially unfavourable 1,3-diaxial interactions, leaving only one 1,3-H,OMe and one 1,3-H,$CH_2OR$ interaction in contrast to cyclohexanes, which have two such interactions. It is known that OMe has an axial preference when *para* to C=O.[13] Since the relative configuration at C-4 and C-5 is fixed by the synthesis, this will assist $CH_2OR$ also to be axial. An inspection of the C(4)–C(5) and C(5)–C(6) bonds in **10** and **11b** by $^1H$ NMR showed *gauche* conformations for not only C(4)–O and C(5)–O bonds on their lactone rings but also C(5)–O and C(6)–O bonds out of the rings (**10**, $J_{5,6}$ 3.5, $J_{5,6}$ 4.3 Hz; **11b**, $J_{5,6}$ 4.0, $J_{5,6}$ 4.0 Hz)‡ (Fig. 2). Thus the unusual bis-axial geometry here may result from a fortuitous combination of this *gauche* interaction,[14] the so-called *gauche* effect,[16] and the above two factors. Furthermore, this preference for the axial substituent at the C-5 position may also be understood in terms of through-space interaction[15a] such as an electrostatic attraction[16] and/or n, $\pi^*$ orbital overlap between the C-6-oxygen atom and the carbonyl group.[13] Quantitative treatment of this phenomenon by molecular orbital and molecular mechanics calculations is under investigation and will be reported in due course.

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## References

1 D. H. R. Barton, *Experientia*, 1950, **6**, 316.
2 N. L. Allinger and E. L. Eliel, *Topics in Stereochemistry*, Wiley, New York, 1971, vol. 6, p. 1; *Topics in Stereochemistry*, Wiley, New York, 1967, vol. 1, p. 199.
3 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983, p. 4.
4 R. Anliker, D. Dvornik, K. Gubler, H. Heusser and V. Prelog, *Helv. Chim. Acta*, 1956, **39**, 1785; C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, 1956, **78**, 6390.
5 (*a*) K. Suzuki, K. Tomooka, T. Matsumoto, E. Katayama and G. Tsuchihashi, *Tetrahedron Lett.*, 1985, **26**, 3711; (*b*) *J. Am. Chem. Soc.*, 1986, **108**, 5221. For other examples related to the thermodynamic control of α-methyl groups on δ-lactones, see: (*c*) S. Hacini and M. Santelli, *Tetrahedron*, 1990, **46**, 7787; (*d*) F. Matsuda, N. Tomiyoshi, M. Yanagiya and T. Matsumoto, *Chem. Lett.*, 1987, 2097.
6 H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto and T. Taga, *J. Am. Chem. Soc.*, 1987, **109**, 5031.
7 For the total syntheses of FK 506, see: T. K. Jones, R. A. Reamer, R. Desmond and S. G. Mills, *J. Am. Chem. Soc.*, 1990, **112**, 2998; M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling and S. L. Schreiber, *J. Am. Chem. Soc.*, 1990, **112**, 5583; A. B. Jones, A. Villalobos, R. G. Linde II and S. J. Danishefsky, *J. Org. Chem.*, 1990, **55**, 2786; R. Gu and C. J. Sih, *Tetrahedron Lett.*, 1990, **31**, 3287.
8 For the synthesis of the C(10)–C(15) fragment of FK 506 employing sugars as a starting material, see: P. Kocienski, M. Stocks, D. Donald, M. Cooper and A. Manners, *Tetrahedron Lett.*, 1988, **29**, 4481; R. E. Ireland and P. Wipf, *Tetrahedron Lett.*, 1989, **30**, 919; A. B. Smith III and K. J. Hale, *Tetrahedron Lett.*, 1989, **30**, 1037; A. V. R. Rao, T. K. Chakraborty and K. L. Reddy, *Tetrahedron Lett.*, 1990, **31**, 1439.
9 S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99.
10 P. Jarglis and F. W. Lichtenthaler, *Tetrahedron Lett.*, 1982, **23**, 3781.
11 J. L. Herrmann and R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 1973, 711.
12 H. Kalinowski, S. Berger and S. Braun, *Carbon-13 NMR Spectroscopy*, Wiley, Chichester, 1988, p. 258.
13 Y. Nagao, M. Goto, M. Ochiai and M. Shiro, *Chem. Lett.*, 1990, 1503; R. D. Stolow and T. W. Giants, *J. Chem. Soc., Chem. Commun.*, 1971, 528.
14 K. Tomioka, T. Suenaga and K. Koga, *Tetrahedron Lett.*, 1986, **27**, 369; M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia and E. L. Eliel, *J. Am. Chem. Soc.*, 1976, **98**, 956; L. Phillips and V. Wray, *J. Chem. Soc., Chem. Commun.*, 1973, 90; R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer and M. K. Kaloustian, *J. Am. Chem. Soc.*, 1972, **94**, 1913; E. L. Eliel and M. K. Kaloustian, *J. Chem. Soc., Chem. Commun.*, 1970, 290.
15 (*a*) N. S. Zefirov, *Tetrahedron*, 1977, **33**, 3193; (*b*) S. Wolfe, *Acc. Chem. Res.*, 1972, **5**, 102.
16 W. B. Schweizer, G. Procter, M. Kaftory and J. D. Dunitz, *Helv. Chim. Acta*, 1978, **61**, 2783.

‡ These vicinal *J*-values were determined by a detailed calculation (Bruker, PANIC, VERSION 850501.0).