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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 effect³ etc.

 $z \xrightarrow{Y} y = x$ x Y



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^tOK-Bu^tOH, 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 : $\alpha = 6:1$, 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) fragment⁸ 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. Oxidation¹⁰ 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, CHCl₃). Finally the lithium enolate formed by treatment of 10 with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C was methylated¹¹ 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, Bu⁴Ph₂SiCl, dimethylaminopyridine, Et₃N, CH₂Cl₂, 97%; ii, KI, Zn–Cu, DMF, reflux, 90%; iii, NaH, MeI, THF, 90%; iv, MCPBA, BF₃·OEt₂, molecular sieve 4 Å, CH₂Cl₂, -15 °C, 92%; v, H₂, 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 ¹³C (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, CHCl₃), and 11b, m.p. 104–106 °C; $[\alpha]_D^{24}$ $+59.0^{\circ}$ (c 1.00, CHCl₃), 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 $(J_{a,b'} 12.8, J_{b',c} 5.1, J_{c,d} 5.1 \text{ Hz})$ and high field shifts at C-2 (δ -2.8), C-3 (-0.9) and C-5 (-2.2) in its ¹³C 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,CH₂OR 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 CH₂OR 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 attraction¹⁶ and/or n, π^* 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.

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

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- 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.
- 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.