JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 3, 419–427 (1990)

CORRELATION OF MOLECULAR MECHANICS AND NMR DATA: CONFORMATION AND CONFIGURATION OF THE MEERWEIN LACTONES

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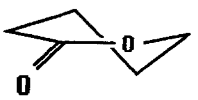
A method for relating averaged NMR parameters with point-by-point geometries for MM2 calculations is given for mobile molecules, e.g. δ-lactones. This method permits the identification of *cis/trans* geometry in cases where a complete set of isomers is not available. 2-Oxa-3*r*,4*c*,5*t*-triphenylcyclohexanone is prepared by condensation of 1,2-diphenylethanone with 3-phenylpropenal. The initially formed biscarbonyl adduct undergoes an internal Cannizzaro reaction forming a hydroxy ester, which lactonizes during work-up. The stereochemistry of the hydride transfer in the Cannizzaro reaction is consistent with the Felkin rule for asymmetric induction. The configurations of this and related lactones were studied through observation of NMR coupling constants, reductions to hemiacetals and molecular mechanics calculations. The most stable conformations are found to be a boat form for the parent lactone and a half-chair form for two isomers. The half-chair and boat forms lie near in energy for all isomers. The calculation techniques outlined illustrate that it is incorrect to consider only chair and boat forms; many intermediate conformations exist. Difficulties with previous IR methods of analysis are discussed.

It is difficult to relate NMR data (an average over all conformations) to the results of molecular mechanics calculations on specific conformations. The problem is exacerbated in molecules with shallow energy minima, such as the Meerwein lactones studied here. This study covers initial results in the correlation of 'averaged' NMR data with 'point-by-point' MM2 calculations. This correlation method, when fully developed, may have several applications: (1) identification of *cis/trans* isomerism (especially in cases where a full set of isomers is not available); (2) evaluation of force-field constants; and (3) determination of whether all low energy conformations have been located.[1,2]

δ-Lactones seldom if ever occupy a classical chair conformation.[3] Allinger and co-workers[3] consider the conformation of lactones to be the result of interplay between two factors: the tendency for the ester group to maintain coplanarity and the torsional and steric demands of the hydrocarbon part of the molecule, giving a staggered shape.

In other work, infrared, UV, ORD/CD and NMR methods have been used to study the conformation of δ-lactones.[4-9] Literature results generally have been interpreted in terms of two conformations, the half-chair (1) or the half-boat form (2).[4,6-15] In many studies, the data indicated a preference for the half-chair form,[8-11] although the boat form was considered to be dominant in a few instances.[4,12,13] ORD/CD data seem to give different results than other experimental data.[14,15]



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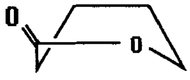

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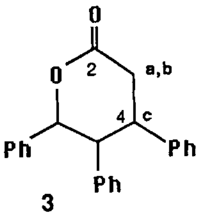

3

PRESENT WORK

Meerwein[16] prepared the lactones of interest (cf. **3**) by condensation of ketones, i.e. 1,2-diphenylethanone (**4**), with 3-phenyl-2-propenal (**5**) yielding a biscarbonyl compound (**6**), which then undergoes an internal Cannizzaro reaction involving hydride transfer from the aldehyde to the ketone group. Under work-up conditions, the hydroxy ester **7** lactonizes to form **3**.

The structure of the major product **3a** (*trans–cis*) is

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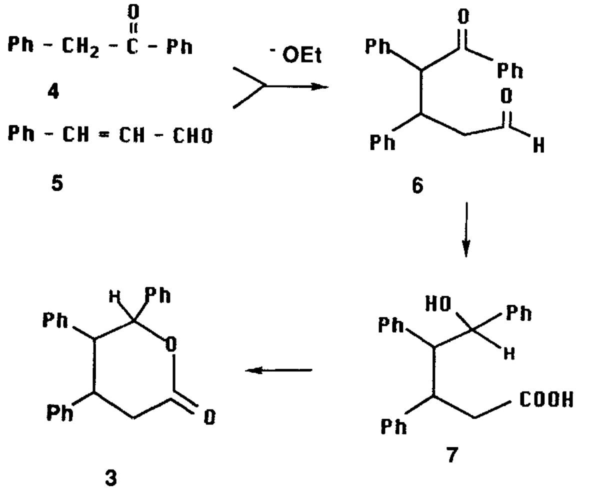
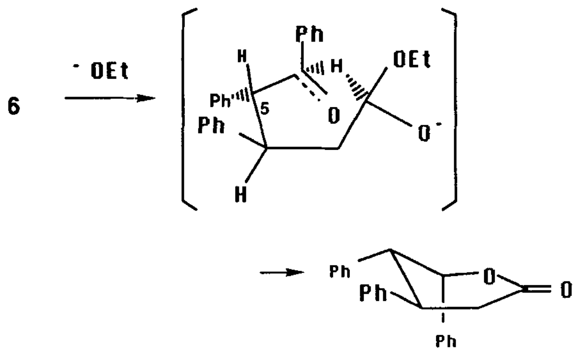
0894–3230/90/070419–09$05.00

Received 28 April 1988
Revised 3 October 1989



consistent with the Felkin–Anh predictions of asymmetric induction.[17] The phenyl group at C-5 is *anti* to the hydride being transferred in the transition state of the Cannizzaro reaction. This observation suggests that the asymmetric induction predictions are independent of the possible ion-pairing effects of counter ions. Ion pairing or aggregation is a concern in other studies establishing stereochemistry, i.e. Grignard reactions or hydride reductions.[18]

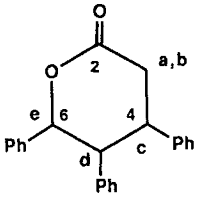


CONFIGURATION OF LACTONES

Tables 1 and 2 list the NMR data for the lactones (**3a–c**) and the hemiacetals (**8a,b**) derived from **3a,b** by reduction. As expected, the observed NMR coupling constants of **3a,b** did not provide a clear indication of configuration. However, the hemiacetals were considered likely to occupy relatively pure chair forms, and thus *cis–trans* relationships are more clearly indicated.

In the ^{13}C spectrum (cf. Table 2), the axial group at C-6 of **8a** gives rise to an upfield shift at this carbon. The axial Ph at C-5 in **8b** gives an upfield shift at this carbon and C-3. Skew forms may also be important in **8a**, as C-4 undergoes no upfield shift.[19]

Table 1. ^{1}H chemical shifts (ppm) for the lactones and hemiacetals[a]



	Lactones			Hemiacetals	
Proton	**3a**	**3b**[c]	**3c**	**8a**[b]	**8b**[b]
Ha(eq)[d]	3·03	2·92	3·23	2·19	2·21
Hb(ax)[d]	3·03	3·06	2·95	2·31	2·71
Hc	3·56	3·94	3·70	3·20	3·73
Hd	3·61	3·68	3·25	3·44	3·56
He	5·81	6·09	5·51	5·74	5·37

[a] Spectra for **3a–c** were taken in CDCl$_3$ solution at 360 MHz. For **8a,b** the solvent was pyridine-d_5 (300 MHz).

[b] For **8a** and **8b**, the anomeric hydrogen is at 5·75 and 5·59 ppm respectively.

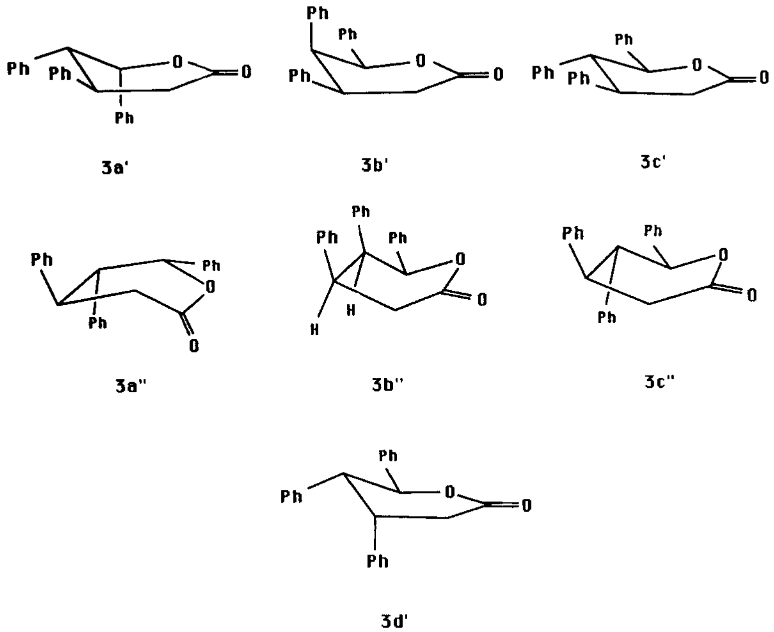
[c] A $^4J_{ad}$ of ca 0·8 Hz is found for the 1,3-pseudoequatorial hydrogens.

[d] Ax. and eq. refers to the half-chair hydrogens.

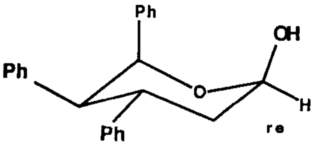
Table 2. ^{13}C chemical shifts (ppm) for the lactones and hemiacetals

	Lactones			Hemiacetals[c]	
Carbon	**3a**	**3b**	**3c**	**8a**	**8b**
C-2	171·4	170·5	170·4	92·8	96·6
C-3	37·0	31·6	37·9	36·3	32·2
C-4	42·1	43·3	44·3	45·1	44·3
C-5	52·5	50·8	54·7	53·8	50·4
C-6	81·9	84·4	86·3	71·4	78·3

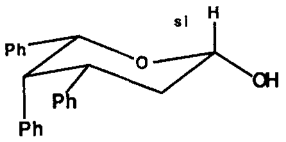
The data for the hemiacetals are consistent with geometry of the phenyl substituents as shown in Scheme 1. For **8a**, the axial hydroxyl results from the axial C-6–Ph group blocking *si* approach of hydride in the reduction step. In **8b**, the normal *si* approach of hydride has occurred, aided somewhat by blockage of *re* approach by the axial C-5–Ph. The low ^3J values (Table 4) are indicative of gauche hydrogens at C-4, C-5 and C-6, and are in agreement with this structure. The ^3J values for **8a** are similarly corroborative, despite the probable lack of complete conformational purity. Since **3c** is the minor product in the formation of **3a**, the C-6 epimeric structure shown is indicated.



Scheme 1. Low-energy conformers of **3a–d**



8a



8b

CALCULATION METHODS

The results of molecular mechanics calculations on the lactones are given in Table 3. In order to relate MM2 calculations to the average NMR parameters,[20] the dihedal driver option of MM2 was used. Beginning from previously determined half-chair and boat minima of energy, rotations on either side of the minimum were carried out using the dihedral driver option of MM2. In practice, conformations of 1·5 kcal above the overall minimum had negligible weights, and later calculations ignored structures of ca 2 kcal above the minimum.

At each point of the array of structures, ^3J was calculated using the technique of Altona and co-workers [equation (1)][21] or of Gandour and co-workers [equation (2)],[22] and weighted according to the MM2 steric energy. These two methods provided similar data. The summation over all MM2 structures [equation (3)] provided an expectation value for the coupling constant.[22]

$$^3J_{\mathrm{HH}} = P_1 \cos^2 \Phi + P_2 \cos \Phi + P_3 + \Sigma\Delta\chi_i[P_4 + P_5 \cos^2(\xi\Phi + P_6|\Delta\chi_i|)] \quad (1)$$

$$^3J(\mathrm{HCCH}) = A + B \cos \theta + C \cos 2\theta + \sum_{i=1}^{4} \Delta S_i \cos \theta \cos \Phi_{\mathrm{HX}_i} \quad (2)$$

$$J_{\mathrm{T}} = \frac{\Sigma J_{\mathrm{HH}} \exp(-SE/RT)}{\Sigma \exp(-SE/RT)} \quad (3)$$

With regard to possible difficulties, the 'lagging' phenomenon reported by Allinger *et al.*[23] should be noted. If a given dihedral angle is rotated and the energy minimized in all other degrees of freedom, it is found that a complementary full rotation does not occur elsewhere in the molecule. However, the energy may still be fairly accurate. By rotating on either side of a predetermined minimum, it was hoped that the effects of 'lagging' would be minimized. Lagging proved to be most serious at low energies, however. Near the energy minimum, a 5° rotation of the main angle gave a much smaller rotation (e.g. 2°) of adjacent angles, but at higher energies, a larger (e.g. 3·5°) corresponding change in adjacent angles occurred.

MM2 essentially provides relative internal energies of the conformers, not free energy. Therefore, entropy is

Table 3. Molecular mechanics data for **3a–c**

	3a′			3a″			3b′			3b″			3c′			3c″		
	Orig.^{a}	TG^{b}	MM2(87)^{c}	Orig.^{a}	TG^{b}	MM2(87)	Orig.^{a}	TG^{b}	MM2(87)	Orig.^{a}	TG^{b}	MM2(87)	Orig.^{a}	TG^{b}	MM2(87)	Orig.^{a}	TG^{b}	MM2(87)
Steric energy:	10·3^{d}	10·8	10·7	9.8	10·6	10·1	11·8	12·2	12·0	12·2	13·6	12·8	8·2	8·5	8·4	8·7	9·3	9·0
Compression	1.4	1.6	1.3	1.5	1.7	1.4	1.4	1.7	1.3	1.5	1.8	1.5	1.5	1.5	1.5	1.2	1.5	1.2
Bending	7.7	5.9	7.9	3.7	2.9	3.9	9.0	7.2	9.0	5.3	4.1	5.3	6.7	4.8	5.3	3.7	2.4	3.7
Van der Waals																		
1,4-Interactions	17.4	19.0	17.9	18.5	20.1	19.1	17.4	18.9	17.8	18.7	20.3	19.2	17.6	19.0	18.0	18.4	20.0	19.0
Other interactions	−6.1	−6.1	−6.2	−5.5	−6.1	−6.0	−5.6	−5.7	−5.7	−6.5	−6.6	−6.6	−6.7	−6.8	−6.8	−6.1	−6.8	−6.8
Torsional interactions	−16.4	−16.2	−16.5	−14.6	−14.5	−14.6	−16.7	−16.4	−16.7	−13.2	−12.6	−13.1	−16.8	−16.5	−17.0	−14.8	−14.2	−14.5
Dipolar interactions	5.8	6.2	5.8	5.9	6.2	5.9	5.8	6.2	5.8	6.0	6.3	6.0	5.9	6.2	5.9	5.9	6.3	6.0

[a] original parameterization, adjusted for 'hard phenyls' (see Experimental).

[b] 10th generation parameters (see Experimental)

[c] MM2(87) with a π-minimization

[d] kcal/mole

not considered. If a given ring conformer permits facile rotation of a side-chain group, and another conformation does not. The present procedure has no easy way of incorporating the entropic advantage of the first conformer.[24]

RESULTS

For the parent lactone, **3a**, the boat forms generally had lower energies than the half-chair forms. In agreement, a strong NOESY interaction was observed for H_c and H_d, which are *trans*-diaxial in the half-chair form, but closer in space in the boat form. The chair form with two axial phenyls and one equatorial phenyl, although of surprisingly low steric energy (ca 11–12 kcal), is a minor contributor.

Summing over 31 conformations gave a calculated J_{cd} of 6·8 Hz [equation (1)] or 6·2 Hz [equation (2)], in fair agreement with the observed $^3J_{cd}$ of 7·9 Hz (cf. Table 4). Rotation of 2–3–4–5 provided values of 11·8 and 4·9 Hz for $^3J_{ac}$ and $^3J_{bc}$ (observed, 12·7 and 5·2 Hz). Variation of 1–6–5–4 gave $^3J_{de}$ = 4·7 Hz (observed, 5·1).

For **3b**, the half-chair form is calculated to be slightly more stable than the boat form (by ca 0·4 kcal). Summing over 17 conformations, the calculated $^3J_{cd}$ of 5·2 Hz was greater than the observed $^3J_{cd}$ of 4·2 Hz. A 'Barfield correction', as recommended by Altona, is included in the calculation (cf. Experimental).[21,25] The boat forms have a high contribution to J as their weights are fairly high. Further, the hydrogens are nearly eclipsed (cf. **3b**″, Scheme 1) and the instrinsic coupling constant is large.

The calculations disclosed a family of fairly stable conformations in between the pure boat and half-chair forms. The calculations showed that rotations of the C-3—C-4 bond is the most likely path for half-chair to boat interconversion, with a barrier of ca 2 kcal. The alternative chair form, i.e. with two axial and one equatorial phenyl groups, was also investigated but was found to have a high steric energy. The alternative boat form having a bowsprit phenyl group is also strongly disfavored.

On rotating the 1–6–5–4 angles, good agreement of the calculated $^3J_{de}$ of 3·6 Hz with the observed value of 3·5 Hz was found. However, on rotating 2–3–4–5, the calculated $^3J_{ac}$ and $^3J_{bc}$ of 4·4 and 9·4 Hz were not in good agreement (observed, 5·2 and 13·9 Hz). The difficulty in the latter case may not lie entirely with MM2, as $^3J_{bc}$ = 13·9 Hz is near the maximum afforded by equation (1) for a single optimum dihedral angle.

The small **3b**′ – **3b**″ energy difference (0·4 kcal) seems extraordinary, as eclipsed phenyl groups are present in the boat forms. Toward the end of this study, calculations using MM2 (87) became possible. This version gives a larger energy difference (**3b**′ – **3b**″, 0·8 kcal). However, since the energy difference seemed very low, and since the correlation of calculated vs observed coupling constants showed substantial deviations, a search for improved bending, torsional, etc., parameters was instituted.

Although isomer **3c** occupies a seemingly stable half-chair conformation with equatorial phenyl substituents, the half-boat forms were calculated to lie only ca 0·5 kcal higher than the half-chair form (cf.**3c**′ vs **3c**″ in Table 3). However, a NOESY interaction was found for protons H_b and H_e, which form a 'bowsprit' interaction in the boat form, but are distant in the half-chair form, thus corroborating the importance of the boat form. Summation over 21 structures gave a calculated $^3J_{cd}$ of 11·7 Hz [equation (1)] (observed 10·3 Hz). As in the case of **3b**′ vs **3b**″, the improved bending energy in the half-boat forms counteracts the higher torsional energy giving roughly isoenergetic half-chair and boat forms.[2] The calculation data for other couplings for **3c**, listed in Table 4, show better agreement.

The calculated coupling constants are critically dependent on the relative energies of the chair vs boat forms. Thus, an increase of 0·3 kcal in the boat vs half-chair energies causes a sizable change in the calculated

Table 4. Calculated vs observed coupling constants (Hz)

Coupling constant	**3a**			**3b**			**3c**		
	Obs.	Orig.[a]	TG$_b$	Obs.	Orig.[a]	TG[b]	Obs.	Orig.[a]	TG[b]
$^3J_{ac}$[d]	5·2	4·9	4·6	5·2	4·4	4·2	6·5	5·2	5·5
$^3J_{bc}$	12·7	11·8	11·6	13·9	9·4	11·5	9·8	9·2	9·6
$^3J_{cd}$	7·9	6·8	7·9	4·2	5·2	4·2	10·3	11·7	11·6
$^3J_{de}$	5·1	4·7	4·1	3·5	3·6	3·4	10·9	10·6	10·5

[a] Calculated using original MM2 parameterization adjusted for 'hard phenyls' (see Experimental).

[b] '10th generation' parameters (see Experimental).

[c] The observed coupling constants for **8a** are $^3J_{ac} = 3·3$ Hz, $_3J_{bc} = 13·7$, $^3J_{cd} = 9·2$, $^3J_{de} = 5·8$, $^3J_{ef} = 6·3$ and $^3J_{bf} = 5·9$ (the last two of the anomeric hydrogen). For **8b**, $^3J_{ac} = 2·3$ Hz, $^3J_{bc} = 13·9$, $^3J_{cd} = 4·4$, $^3J_{de} = 2·3$, $^3J_{af} = 2·0$, $^3J_{bf} = 9·4$.

[d] All values were determined using equation (1).

^3J (e.g. ca 1 Hz in some cases). In an attempt to find MM2 parameters that would provide a better fit of the ^3J data, a series of adjusted bending parameters were investigated. The energy of the half-chair vs the boat form is critically dependent on the C—O—C(O) bond angle. This angle is ca. 120° in all chairs forms, which is substantially above the optimum value of 109°. The boat forms are less strained [C—O—C(O) angles ca. 114°). Thus, most of the initial parameter changes involved this angle. Even so, an improved fit of ^3J did not evolve. The best data occurred where slightly increased van der Waals constants were used for phenyl, thus increasing the energy of the boat form **3b**″, *which* has eclipsed phenyls. Slightly increased torsional parameters were also used for the eclipsed case. These '10th generation constants' led to a ca 1·4 kcal energy difference (**3b**′ vs **3b**″).

The predicted coupling constants using the '10th generation' parameters (Table 4) are indeed in better agreement with the observed data for **3b**, although the agreement for **3a,c** is not improved.

Infrared data

A review of the infrared absorptions of **3a** showed a broad absorption with a major peak at 1745 cm^{-1} and a shoulder at 1757 cm^{-1}. For **3b**, there is a major peak at 1730 cm^{-1} and a better defined shoulder at 1737 cm^{-1}. For **3c**, the main peak occurs at 1731 and a well defined shoulder at 1740 cm^{-1}. It seems that these shoulders may result from the boat form. The broadness of the **3a** absorption may result from many conformations. However, as the boat form has been assigned an absorption range of 1758–1765 cm^{-1} (half-chair, 1730–1750 cm^{-1}),[4,9,11,15] none of these peaks, except the shoulder on **3a** absorption, clearly lay in the half-boat region. If only infrared data were available, the conformations would have been assigned as half-chair.

CONCLUSIONS

The Boltzmann summation technique using MM2 steric energies is useful in establishing *cis/trans* relationships in mobile molecules, where observed NMR coupling constants are unrevealing. Although the agreement between calculated and observed conformers is inexact, the method is sufficiently accurate to resolve the identity of the isomers. The data in Table 4 differ markedly from the predicted coupling constants of the fourth lactone **3d** (which was not isolated) (cf. Scheme 1). The predicted coupling constants are $^3J_{ac} = 3{\cdot}9$, $^3J_{bc} = 3{\cdot}1$, $^3J_{cd} = 3{\cdot}2$ and $^3J_{de} = 7{\cdot}3$ Hz, clearly much different than those observed for **3a–c** (Table 4). This technique is currently being tested with some success on five-membered rings, where NMR coupling constants are completely untrustworthy as a guide to geometry. However, more exact predictions of coupling constants await the evolution of improvements in the utilization of equation (1) and in such factors as the MM2 dihedral driver.

This technique present strong evidence that the lactones in this study occupy both half-chair and boat conformers with many low-energy states in between, not one conformation or the other, as often suggested in early work on similar compounds.

EXPERIMENTAL

5-Oxo-3,4,5-triphenylpentanal. (**6**). Prepared by the method of Meerwein,[16] m.p. 176–177 °C (lit.[16] m.p., 176·5–177 °C); IR ($CHCl_3$), 1730 (CHO) and 1690 cm^{-1} (ketone C=O); NMR, δ9·3 (m, 1, CHO), 2·55 (m, 2, CH_2), 4·23 (m, 1, PhC*H*) and 4·9 (dd, 1, PhC*H*).

1-Oxa-4r,5t,6t-triphenylcyclohexan-2-one (**3a**). Prepared by the method of Meerwein,[16] m.p. 141–142 °C (lit.[16] m.p., 140–141 °C); IR, 1745 cm^{-1} (lactone C=O); NMR data are given in Tables 1 and 2.

1-Oxa-4r,5t,6c-triphenylcyclohexan-2-one (**3c**). Prepared by the method of Meerwein,[16] m.p. 171–172 °C (lit.[16] m.p., 171–172 °C); IR (thin film, NaCl), 1731 cm^{-1} (lactone C=O).

1-Oxa-4r,5c,6c-triphenylcyclohexan-2-one (**3b**). Prepared via hydrolysis, oxidation to the keto acid and reduction, by the method of Meerwein,[16] m.p. 171–172 °C (lit.[16] m.p., 168–170 °C); IR (thin film, NaCl), 1730 cm^{-1} (C=O).

1-Oxa-4r,5c,6c-triphenylcyclohexan-2-ol (**8b**). The lactone **3b** was dissolved in the minimum volume of hot dimethyl sulfoxide, then ethanol was added up to the point of insolubility. $NaBH_4$ was added in small increments to the stirred solution. When an excess of borohydride was apparent, the mixture was stirred overnight. After ca 24 h, fine white crystals appeared; water was added, and the crystals were filtered and recrystallized from ethanol. The crude hemiacetal was purified by flash chromatography, giving product of m.p. 181–183 °C; IR ($CHCl_3$), 3590 (free OH), 965 cm^{-1} (eq. OH); mass spectrum (CI) for $C_{23}H_{22}O_2$, 330 g mol^{-1}, *m/z* (relative intensity) 331(1·7), 313(9·6), 295(11), 270(23), 269(100), 133(28·7), 127(10·8) and 105(28·8).

1-Oxa-4r,5t,6t-triphenylcyclohexan-2-ol (**8a**). The lactone **3a** (2·0 g, 6 mmol) was dissolved in 20 ml of dry tetrahydrofuran and cooled to ca −70 °C with dry-ice–propan-2-ol. The solution was equilibrated at this temperature for ca 5 min, then an excess of 20% diisobutylaluminum hydride (DIBAL) (9·0 ml) in hexane was added dropwise over 4 min, and the resulting mixture stirred at −70 °C for 1 h. The solution was then slowly added to 5 ml of acetic acid in 12 g of ice. The aqueous layer was extracted with dichloromethane and the solvent reduced in volume with rotary evaporation, whereupon crystals appeared (crude yield, 1·6 g). The product was purified by flash chromatography (10:1 light petroleum ether–ethyl acetate), giving a product of m.p. 131–133 °C; IR ($CHCl_3$), 3685 (free OH) and 1010 cm^{-1} (ax. OH); mass spectrum (CI) for $C_{23}H_{22}O_2$, 330 g mol^{-1}, *m/z* (relative intensity) 331(95·5), 313(100), 270(8·2), 269(36·5), 180(14·8), 135(31), 133(12·3) and 105(15·5).

Spectral data. All IR spectra were taken on a Perkin-Elmer 283 instrument. Most spectra were run as solution spectra in $CHCl_3$ (alcohol removed), although some few were run in CH_2Cl_2 or CCl_4 or as thin films. The carbonyl absorptions mentioned under Conclusions were variable in position ±5 cm^{-1}, depending on concentration.

In a typical ^{13}C NMR determination, usually run on a Varian XL100 (or later on a VXR200) instrument, a 5-kHz spectral width was used with an approximate 45° tip angle; approximately 7000 transients were collected at a pulse repetition time of 1 s. The transformed peaks were referenced to $CDCl_3$ taken as 76·9 ppm. An 8K data table gave an intrisic accuracy of ±0·05 ppm.

In a typical ^1H NMR determination, a Nicolet WP360 or Varian VXR200 instrument was used, operating at 360·1 or 200 MHz. A 10 ppm window was observed using a 32K data table, giving an intrinsic accuracy of $\pm 6 \times 10^{-4}$ ppm. The spectra were simulated with various versions of LAOCON, principally the IBM PC version of LAOCON/3.[26] Trouble was encountered in the iterative mode of operation of this program in the version accompanying the NMR instrument; the best results were **3a**, rms error 0·064; **3b**, 0·153; and **3c**, 0·124. The hemiacetal data were not fitted well and the entries in Table 1 (best fit by individual peak matching) should not be taken as highly accurate. One problem was the growth of the anomeric form. The very large $^3J_{ac}$ of 13·9 Hz for **3b** was duplicated by LAOCON simulation of both 360 MHz and by manual calculation of the ABX part of a 100 MHz spectrum.

The coupling constants for **3a** were determined from a spectrum run in acetone-d_6, as the $CDCl_3$ spectrum gave extensive superposition of peaks. The chemical shifts are from the $CDCl_3$ spectrum, however and owing to extremely close separation of resonances these are fairly rough.

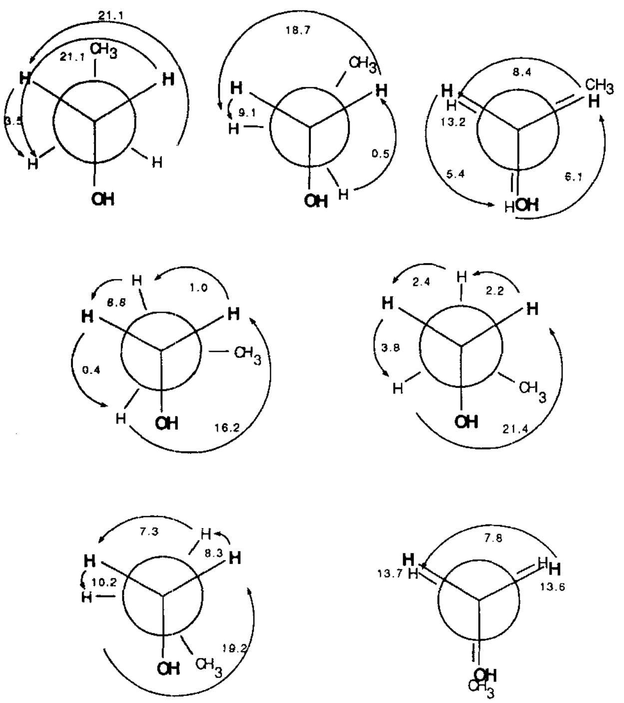
The NOESY samples were deoxygenated by entrainment (by passing nitrogen through the NMR sample until half the original volume of $CDCl_3$ was evaporated). The spectra were run on a Varian VXR200 instrument using the parameterization set-up by the instrument computer. In a typical run, an 1100-Hz window was used with the phase-sensitive mode of operation of NOESY. A total of 32 transients were collected per each of 64 increments using 512 data points in each domain and a 'mix' time of 0·1 s. COSY and homonuclear *J* correlation experiments were also run, which were not additionally informative.

Calculation techniques. Calculations were done using MM2(77) on an IBM 4381 mainframe. Selected low-energy conformations were checked by using MM2(87) on a VAX 785, using full π minimization, and on a AT version of MM2(85). The differences in the two programs seemed to involve the treatment of phenyl groups. The critical parameterization of the lactone function appeared to be the same in the two programs.

In order to ensure identification of the minimum energy conformation for the half-chair and the boat forms, extensive rotation of the side-chain phenyl groups using the dihedral driver option was carried out. The phenyls were rotated singly and in groups. This did lead to significant improvements in the steric energies, especially for **3b**. The resulting new minimum was reminimized without constraint. This provided the basis for the dihedral driver rotation of the internal ring bonds.

In order to provide the input data for the program LACA, which calculates the expected coupling constants, MM2 was used to rotate each internal bond on either side of the pre-determined minimum a set number of degrees (5°). Using a smaller increment (2·5°) did not appear to improve the final results. Thus, to calculate $^3J_{ac}$ or $^3J_{bc}$ the carbons 2–3–4–5 were rotated. It was considered inappropriate to rotate hydrogens *per se*, as the carbons underwent almost no change accompanying a rather large change in the H—C—C—H dihedral angle. Thus the energy changes reflected a twisting of hydrogens, rather than a basic change in conformation of the δ-lactone ring.

In the application of equation (1), the term was explicitly defined only for dihedral angles of 60° or 180° (for the coupled proton vs an electronegative group). In order to assess the effect of electronegativity of other conformations, calculations of the effect of electronegativity on ^3J were performed using the program FINITE (QCPE 224), giving the information shown in Scheme 2.[27] Although the couplings are obviously too large in some cases, the effect of the electronegative OH function was clear. The salient features are that OH reduces *J* not only when it is *anti* to one H, but when it is eclipsed with H. Therefore, ξ was taken as 1 for angles of 30° to 150°, but as −1 for angles above 150° and −1·2 for angles of 0–30°. More complex assignment of parameters improved the calculated coupling constants marginally. The original calculations used of 0·8 for $\theta < 30°$, 1 for $\theta = 30$–$80°$ and −1 for $\theta > 150°$. In practice, the ξ factor caused a



Scheme 2. Coupling constants calculated by FINITE

0·7 Hz variation in couplings in some cases, but usually the differences were ±0·2 Hz.

The original parameterization for the carbonyl function contained a disturbing element, namely that the sum of the intrinsic angles around C=O is not 360°. Therefore, an optimization of the calculated ^3J values was attempted by varying these bond angles, and the C—O—C(O) bond angle by trial-and-error. It turned out that the carbonyl angles did not affect ^3J very much, although the C—O—C(O) angle was crucial. Eventually, the time-consuming trial-and-error approach was replaced by estimation of the bond angle bending constants based on MNDO calculations. The best technique, in our hands, seemed to be a very small change in the angle in question (2° or 5°) and observation of the increase in energy. Care was taken that van der Waals interactions or other parameters changed minimally. A set of simultaneous equations gave values for each carbonyl angle. The final data used (cf. 'TG' data, Table 3) involved atom types 1–3–6, $K(\mathrm{b}) = 1{\cdot}05$, $\theta = 117{\cdot}9°$; 1–3–7, $K(\mathrm{b}) = 1{\cdot}0$, $\theta = 125{\cdot}3°$; 6–3–7, $K(\mathrm{b}) = 1{\cdot}1$, $\theta = 116{\cdot}8°$; and 1–6–3, $K(\mathrm{b}) = 0{\cdot}95$, $\theta = 110{\cdot}0°$. The MNDO calculations were done on molecules such as *cis*-formic acid and *cis*-methyl formate. Even with formic acid, the intrinsic angle for C—O—C(O) did not appear to be correct from MNDO (114°). Only values near 110° gave a reasonable fit to ^3J, and this was used.

The final '10th generation' constants used to bring the ^3J values for **3b** into more reasonable agreement involved slightly increased van der Waals parameters for the sp^2 carbon (eps $= 0{\cdot}044$, $R^* = 1{\cdot}96$), and a more stringent torsional interaction for eclipsed phenyls, i.e. for 2–1–1–2, $V_1 = 2{\cdot}3$, $V_2 = 0{\cdot}17$ and $V_3 = 0{\cdot}19$.

At the time the original calculations were made, a 'hard phenyl' was used in order to reduce the calculation time. Thus, the 2–2 stretching parameter was taken as 10·0, with a natural length of 1·397 Å. The out-of-plane bending parameter for 0–2–2 was taken as 4·0; the in-plane 2–2–2 bending constant was taken as 4·0 with a natural angle of 120°. Later, the predicted coupling constants for **3a** were checked against the predictions using the native MM2 parameterization. The differences were of the order of 0·1 Hz.

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