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CIS AND TRANS β,γ-DISUBSTITUTED δ-VALEROLACTONES: CONFORMATIONAL STUDIES AND CONFIGURATIONAL ASSIGNMENTS BY MOLECULAR MECHANICS

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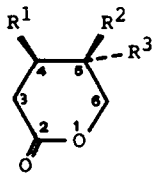
Abstract - Two β,γ-disubstituted δ-valerolactones 2 and 3 were synthesized starting from (R)-(+)-limonene. The most significant conformations for each lactone were determined by molecular mechanics calculations; then the ^{1}H-NMR coupling constants for each pair of vicinal hydrogen atoms of the lactone rings were calculated through suitable Karplus equations. Comparison of experimental and calculated coupling constants allowed the assignment of the vicinal stereorelationship between the β and the γ substituents in 2 and 3.

Conformational analysis of δ-valerolactone systems is a peculiarly difficult problem[1-3] owing to the small energy difference between the boat and chair conformations of the lactone ring; in fact, δ-valerolactone itself 1 shows an energy difference of only about 0.5 Kcal/mol in favour of the chair conformation.[2] Even when the molecule has two substituents at the C-4 and C-5 positions (e.g. 2 and 3), its flexibility makes it difficult to detect one conformation as the most stable. The relative configuration of the two stereocenters cannot be assigned simply by the measurement of the vicinal coupling constants in the ^{1}H-NMR spectra, as is the case for rings which have a fixed conformation. A careful conformational analysis through empirical calculations can be of help to make the above assignment; an application of molecular mechanics to this purpose is reported here.



1: $R^1=R^2=R^3=H$

2: $R^1=\overset{7}{C}H_2\overset{8}{C}H_2\overset{9}{C}\overset{10}{O}CH_3$, $R^2=H$, $R^3=\overset{11}{C}H_3$

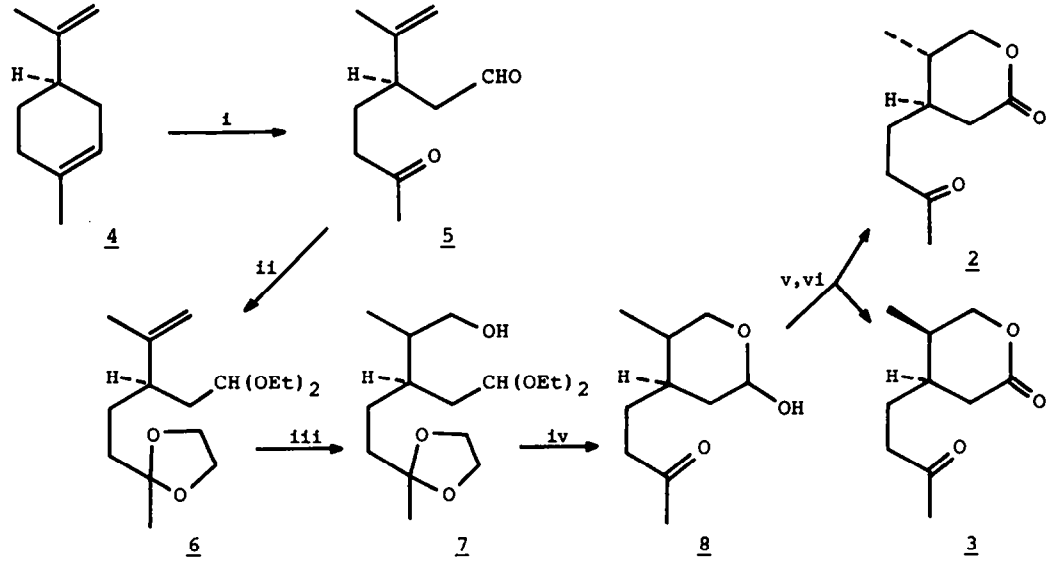
3: $R^1=CH_2CH_2COCH_3$, $R^2=CH_3$, $R^3=H$

RESULTS AND DISCUSSION

While concerned with the synthesis of functionalized phytosterol side chains starting from R-(+)-limonene 4, we obtained, through to the sequence illustrated in scheme 1, two diastereomeric δ-valerolactones 2 and 3. In both compounds the 4-carbon atom had the R configuration as a consequence of the synthetic pathway; the two stereoisomers differed at the C-5 stereocenter, the configuration of which had therefore to be established.

As shown in table 1 the less polar lactone 2 and the more polar 3 exhibited different sets of vicinal coupling constants for the ring hydrogen atoms; for example, the H(4)-H(5) coupling constant was 8 Hz for 2 and 4 Hz for 3. However, if one draws the most significant conformations for each lactone (see figure 1, I-IV for the trans 2 and V-VIII for the cis isomer 3), one can see that the 8 Hz coupling constant can either be attributed to the trans isomer, provided that one of its preferred conformations is (I), or to the cis isomer, if its preferred conformations are (VI) and/or (VII).

So we effected molecular mechanics calculations utilizing Allinger's MM2 program:[4,5] taking into consideration the rotamers (a, b, and c) originating from the rotation of the oxobutyl side-chain around the C4-C7 bond, we calculated for both the diastereoisomers the minima of the potential energy surface which corresponded to the conformations depicted in figure 1. In table 2 the data obtained for the trans isomer are reported; eleven conformers were identified in a range of 2 Kcal/mol above the lowest energy one. Table 3 reports the data of the six conformers which were significant for the cis stereoisomer. The distribution of the populations for each set of conformers was calculated from their relative energies by the Boltzmann equation.



Scheme 1. Reagents: i, O_3 then Zn,AcOH; ii, $HOCH_2CH_2OH$,$HC(OEt)_3$,pTSA,THF; iii, BH_3·THF then H_2O_2,aqNaOH, iv, CH_3COCH_3,aqHCl; v, PCC,CH_2Cl_2; vi, SiO_2 column, hexane-AcOEt 35:65

Table 1. ^{1}H-NMR data of compounds 2 and 3 (200 MHz).

compound	chemical shifts (ppm) H-3a	H-3b	H-4	H-5	H-6a	H-6b	H-7a	H-7b	H-8a	H-8b	H-10	H-11
2	2.12	2.63	1.56	1.68	3.86	4.24	1.41	1.89	2.40	2.48	2.14	1.00
3	2.23	2.57	1.96	2.02	4.15	4.29	1.50	1.67	2.44		2.14	0.97

compound		coupling constants (Hz) $J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{5,11}$
2	exp	17.0	8.5	6.0	8.0	9.0	4.5	11.5	6.5
	calc[6]		8.8	5.4	8.2	8.8	3.9		
	calc[7]		8.7	5.4	8.6	8.6	3.8		
3	exp	18.0	10.0	6.5	4.0	4.0	3.5	11.5	7.0
	calc[6]		10.5	5.8	3.5	4.6	2.9		
	calc[7]		10.1	5.6	4.1	5.0	3.4		

The results turn out to be quite different in the two cases. The trans isomer has a population of 35% in the chair conformation (I) with the two substituents equatorial and of 2% in the inverted chair conformation (IV). The remaining population is almost equally distributed between the two boat conformations: 30% in conformation (II) having the pseudo-axial methyl and the pseudo-equatorial oxobutyl group and 33% in conformation (III). The cis isomer shows a cleaner situation with a great predominance of one conformer: 63% of the molecules are in

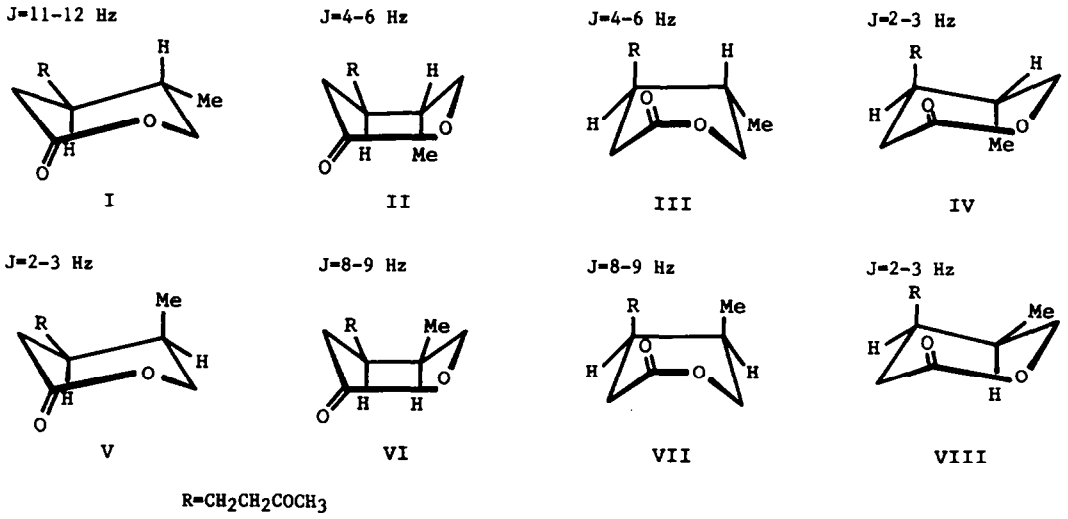


Figure 1. Conformations of lactones 2 (I-IV) and 3 (V-VII).

Table 2. Calculated conformations, energies, torsional angles of compound 2.

conf.	rel energy (Kcal/mol)	%	torsional angles 3a-4	3b-4	4-5	5-6a	5-6b	C5-C4-C7-C8
Ia	0.00	24.9	-167	-50	-172	-174	-56	-177
Ib	0.67	8.0	-174	-57	-171	-171	-54	-57
Ic	1.38	2.4	-170	-53	-171	-174	-56	94
IIa	0.24	16.6	-168	-51	125	-70	48	67
IIb	0.47	11.2	-157	-39	106	-62	57	176
IIc	1.59	1.7	-168	-50	120	-66	52	-67
IIIa	0.28	15.5	-77	39	137	-175	-56	62
IIIb	0.45	11.6	-83	33	145	180	-60	165
IIIc	0.84	6.0	-86	31	147	-179	-60	-72
IVa	1.84	1.1	-73	42	64	-70	46	58
IVb	1.91	1.0	-72	43	65	-72	44	165

Table 3. Calculated conformations, energies, torsional angles of compound 3.

conf.	rel energy (Kcal/mol)	%	torsional angles 3a-4	3b-4	4-5	5-6a	5-6b	C5-C4-C7-C8
Va	0.00	33.4	-163	-46	61	66	-51	172
Vb	0.08	29.2	-164	-48	60	66	-51	59
VIa	0.37	17.8	-153	-36	-27	-175	65	178
VIIa	1.58	2.3	-109	7	40	57	-62	62
VIIb	1.61	2.2	-104	13	36	57	-62	164
VIIIa	0.47	15.1	-68	48	-61	168	51	-168

the chair conformation (V) with the oxobutyl side chain equatorial and the methyl axial. The remaining 37% is divided among the other three conformations: 15% in the inverted chair (VIII) and 18% and 4% in the two boats (VI) and (VII).

Table 2 and 3 also report the torsional angles for each couple of vicinal hydrogen atoms of the lactone ring. In order to calculate the ^1H coupling constants for the above hydrogens we applied two different Karplus equations[6,7] which work for substituted ethanes. The constants reported in table 1 are the weighted averages of the constants obtained for each conformation.

The fairly close correlation between the experimental and the calculated constants that is observed whichever Karplus equation was utilized allows to assign to the higher R_f lactone 2 the relative trans configuration and to the

lower R_f lactone 3 the relative cis arrangement.

The molecular mechanics approach is therefore shown to be a valuable method for determining the vicinal stereorelationship of substituents in compounds such as δ-valerolactones which, though alicyclic, have a great molecular flexibility preventing a sure recognition of the preferred conformation by mere handling of molecular models.

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EXPERIMENTAL

General methods.

^{1}H-NMR spectra were recorded with a Brüker WP-80 or with a Varian XL-200 spectrometer in deuteriochloroform solutions containing Me_4Si as an internal standard. Optical rotations were measured with a Perkin Elmer 241 polarimeter. Analytical TLC was carried out on Merck 60 F_{254} silica gel plates (0.25 mm thickness) and the spots were detected by spraying with 50% aqueous H_2SO_4 and heating at 110°C. Column chromatography was performed with Merck 60 silica gel (70-230 mesh) and elution with mixtures of hexane-ethyl acetate of varying composition. Work up refers to dilution with water, extraction with an organic solvent, washing to neutrality, drying over Na_2SO_4, filtration, and evaporation under reduced pressure.

(R)-3-(1-methylethenyl)-6-oxoheptanal 5.

(R)-(+)-Limonene 4 (10.1 g, 74.3 mmoles) was dissolved into 220 ml of dry methylene chloride and ozone (1 mol eq) was flushed into the solution at -78°C. Zinc powder (7.3 g) and acetic acid (13 ml) were added and the mixture was stirred at -78°C for 15 min, then allowed to reach room temperature and stirred overnight. After filtration the solution was washed with 5% aq. $NaHCO_3$ and worked up. Compound 5 (9.0 g, 72%) was obtained as an oily product.

$[\alpha]_D$ +14° (c=1.1 $CHCl_3$).

^{1}H-NMR (80 MHz) δ: 1.4-1.8 (2H, m), 1.61 (3H, t, J=1 Hz, $C\underline{H}_3C$=C), 2.08 (3H, s, $C\underline{H}_3CO$), 2.1-2.7 (5H, m, $C\underline{H}_2CO$, $C\underline{H}_2CHO$ and $C\underline{H}C$=), 4.75 (2H, m, $\underline{H}_2C$=), and 9.65 (1H, t, J=2 Hz, $C\underline{H}O$).

(R)-6,6-Ethylenedioxy-3-(2,2-diethyloxyethyl)-2-methylhept-1-ene 6.

Compound 5 (6.0 g, 35.7 mmoles) was dissolved into 30 ml of dry THF, 0.15 g of p-toluenesulfonic acid were added, followed by 15 ml of ethylene glycol and 5 ml of triethyl orthoformate. After 1.5 h the mixture was poured into 50 ml of saturated aq. $NaHCO_3$ and worked up. Column chromatography yielded 8.5 g (83%) of compound 6 as an oil.

$[\alpha]_D$ +2° (c=2.1, $CHCl_3$).

^{1}H-NMR (80 Mhz) δ: 1.15 and 1.16 (6H, 2t, J=7 Hz, $CH_2C\underline{H}_3$), 1.27 (3H, s, $C\underline{H}_3C$-O), 1.4-1.8 (6H, m), 1.60 (3H, bs, $C\underline{H}_3C$=), 2.0-2.3 (1H, m, $C\underline{H}C$=), 3.2-3.8 (4H, m, $OC\underline{H}_2CH_3$), 3.90 (4H, bs, $OC\underline{H}_2C\underline{H}_2O$), 4.41 (1H, t, J=6 Hz, $C\underline{H}(OEt)_2$), 4.6-4.8 (2H, m, $=C\underline{H}_2$).

(2RS,3R)-6,6-Ethylenedioxy-3-(2,2-diethyloxyethyl)-2-methylheptan-1-ol 7.

Compound 6 (1.32 g, 4.6 mmoles) was dissolved into 25 ml of dry THF, the solution was cooled to 0°C and 1.6 ml of 1 M BH_3 in THF were added in 0.5 h under nitrogen. After stirring for 2 at r.t., water was carefully added followed by 2.5 ml of 0.5 N NaOH and 0.72 ml of 30% H_2O_2. The mixture was stirred for 0.5 h, then worked up. The oily compound 7 (1.36 g, 97%) was obtained as a 1:1 mixture of two stereoisomers.

^{1}H-NMR (80 Mhz) δ: 0.70 and 0.86 (3H, 2d, J=6.5 Hz, $CHC\underline{H}_3$), 1.18 (6H, bt, J=7 Hz, $CH_2C\underline{H}_3$), 1.24 (3H, bs, $C\underline{H}_3C$), 1.4-1.8 (8H, m), 2.6 (1H, bs, $O\underline{H}$), 3.3-3.8 (6H, m, $OC\underline{H}_2CH_3$ and $C\underline{H}_2OH$), 3.91 (4H, bs, $OC\underline{H}_2C\underline{H}_2O$), 4.4-4.6 (1H, m, $C\underline{H}(OEt)_2$).

(2RS,4R,5RS))-5-methyl-4-(3-oxobutyl)-tetrahydropyran-2-ol 8.

Compound 7 (1.31 g, 4.3 mmoles) was dissolved into 60 ml of 1:1 acetone-water and 0.3 ml of concentrated aq. HCl were added. After 2 h saturated aq. $NaHCO_3$ was added and the mixture was worked up. The oily compound 8 was obtained (0.78 g, 97%) as a mixture of four stereoisomers.

^{1}H-NMR (80 Mhz) δ: 0.75-1.00 (3H, cluster of doublets, $CHC\underline{H}_3$), 1.1-2.0 (6H, m), 2.13 (3H, s, $C\underline{H}_3CO$), 2.43 (2H, bt, J=7 Hz, $C\underline{H}_2CO$), 2.9-4.2 (2H, m, $C\underline{H}_2O$), 4.5-4.8 (0.5H, m, $OC\underline{H}OH$), and 5.15-5.35 (0.5 H, m, $OC\underline{H}OH$).

(4R,5S)- and (4R,5R)-5-methyl-4-(3-oxobutyl)tetrahydropyran-2-one 2 and 3.

Compound 8 (0.75 g, 4.0 mmoles) was dissolved in 40 ml of dry methylene chloride and 1.8 g of pyridinium chlorochromate were added. The mixture was stirred for 18 h, then diluted with ethyl ether and filtered through a short silica gel bed. The crude product (0.73 g) obtained was chromatographed using hexane-ethyl acetate 35:65 as eluant yielding the higher R_f product 2 (0.30 g, 40%) and the lower R_f product 3 (0.27 g, 36%) as oily products.

2: $[\alpha]_D$ -36° (c=1.0, $CHCl_3$).

3: $[\alpha]_D$ +15° (c=1.0, $CHCl_3$).

For the ^{1}H-NMR spectra see table 1.

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