Highly Diastereoselective Hydrogenations Leading to β-Hydroxy δ-Lactones in Hydroxy-Protected Form. A Modified View of δ-Lactone Conformations

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Abstract: Enol MEM ethers **4** and **15** and the corresponding enol acetates were hydrogenated over Pd/C with very high (>99%) diastereoselectivity to saturated δ-lactones. A stereochemical generalization can be formulated thus: *trans*-5,6-disubstituted 1-oxa-3-cyclohexen-2-ones (e.g. **14** and **15**) are hydrogenated over Pd with high selectivity from the side trans to the C(6)-substituent. A mechanistic rationalization of the stereochemical outcome in the Pd-catalyzed hydrogenation of this as well as other types of substituted α,β-unsaturated δ-lactones is presented. An analysis of X-ray crystallographic data for 67 compounds demonstrated a great conformational diversity of the saturated δ-lactone ring. Besides, ab initio calculations (HF/6-31G*) indicated a very high conformational mobility. Thus, the lowest calculated transition state for the conversion of the half-chair, most stable, conformer of δ-valerolactone to the boat-type conformer lies only 1.93 kcal/mol above the former. Beside these two conformers, also chair, envelope and skew conformations are accessible; all lie less than 2 kcal/mol above the half-chair. The previous conformational paradigm comprising only boat and half-chair types is incomplete.

Introduction

A high degree of stereocontrol is a necessity in the synthesis of compounds containing many stereocenters. Several efficient methods have been developed during the past decades and used for instance in the synthesis of macrolides[1,2] or other compounds of biological interest.[3] 1-Oxacyclohexane-2,4-diones (β-keto δ-lactones) have an oxygen function in every second position in the carbon chain and are thus structurally related to polyketides. Such lactones are therefore potentially useful intermediates for the synthesis of polyketides. The compounds are in tautomeric equilibrium[4a,b] with the corresponding enol forms, for example **1**, **2**, and **13**. Our objective was to achieve stereoselective reductions of alkylated β-keto δ-lactones, either in the keto or the enol form. The desired products were β-hydroxy δ-lactones, either hydroxy-protected or unprotected. Compounds such as **1**, **2**, and **13** (as well as its cis isomer) have been prepared in high enantiomeric purity by intramolecular chain elongations in two steps from β-hydroxy esters or imides.[4] Combined with a diastereoselective reduction of the β-keto, or enol, function, these chain elongations would constitute a synthetic sequence which bears some resemblance to biosynthetic processes leading to polyketides. In the first part of this publication, we describe some catalytic hydrogenations leading to saturated δ-lactones containing one or two new stereocenters formed with high or very high (>99%) diastereoselectivity. A reaction model which predicts the stereochemical outcome of the Pd-catalyzed heterogeneous hydrogenation of differently substituted α,β-unsaturated δ-lactones is presented.

In the work with the above hydrogenation reactions, there were indications that saturated δ-lactone rings possess a larger conformational freedom than had previously been indicated in the literature. This aspect was then elucidated by analysis of 67 published X-ray crystallographic structures of saturated δ-lactones and by quantum mechanical calculations (HF/6-31G*)
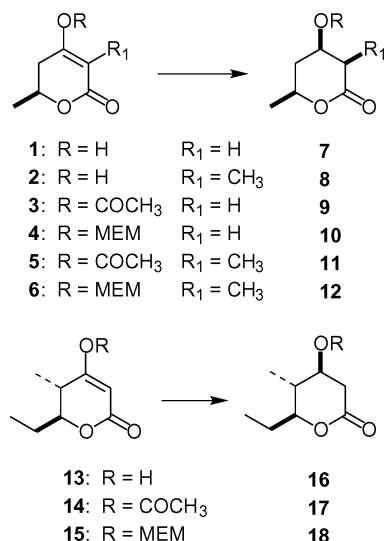
† Stockholm University.

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(1) For selected reviews, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624. (b) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055−5072. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114. (d) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200. (e) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9,* 357−389. (f) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054−2070. (g) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947.

(2) (a) For a recent synthetic work in the epothilone series which contains references to initial reports from several research groups, see: Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T.-C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124, 9825−9832.* (b) For two reviews on epothilone biology and synthesis, see: Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014−2045. Nicolaou, K. C.; Ritzén, A.; Namoto, K. *J. Chem. Soc., Chem. Commun.* **2001**, 1523−1535.

(3) For general reviews, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29,* 1320−1367. (b) Nicolaou, K. C.; Sorensen, E. J.; Winssinger, N. *J. Chem. Educ.* **1998**, *75*, 1226−1258. (c) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44−122.

(4) (a) Brandänge, S.; Leijonmarck, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1097−1098 and references therein. (b) Brandänge, S.; Leijonmarck, H.; Ölund, J. *Acta Chem. Scand.* **1989**, *43*, 193−195 and references therein (correction on p 713). (c) Brandänge, S.; Leijonmarck, H. *Tetrahedron Lett.* **1992**, *33*, 3025−3028. (d) Hinterding, K.; Singhanat, S.; Oberer, L. *Tetrahedron Lett.* **2001**, *42*, 8463−8465. (e) Hinterding et al.[4d] reduced **13**, probably as its keto tautomer, with *t*-BuNH₂−BH₃ to obtain **16** with a 13:1 stereoselectivity; a similar reduction of the cis isomer of **13** gave a 4:1 stereoselectivity. (f) Landi, J. J., Jr.; Garofalo, L. M.; Ramig, K. *Tetrahedron Lett.* **1993**, *34*, 277−280.

on δ-valerolactone and some of its simple analogues. In the second part of this publication, we describe the results of these investigations which led to a modified view of δ-lactone conformations.

Scheme 1 [a,b]

1: R = H   R₁ = H   7
2: R = H   R₁ = CH₃   8
3: R = COCH₃   R₁ = H   9
4: R = MEM   R₁ = H   10
5: R = COCH₃   R₁ = CH₃   11
6: R = MEM   R₁ = CH₃   12

13: R = H   16
14: R = COCH₃   17
15: R = MEM   18

[a] All compounds are racemic. [b]MEM: 2-methoxyethoxymethyl.

Catalytic Hydrogenations. Initial experiments showed that Raney-Ni-catalyzed hydrogenation of **1**, **2**, and **13** produced β-hydroxy δ-lactones **7**, **8**, and **16** in good yields but with moderate to poor stereoselectivity (78, 82, and 6% de, respectively). Use of PtO₂ leads to reductions which are influenced by the α-substituent. With hydrogen in the α-position, the main reaction pathway involves hydrogenolysis[5] which produces δ-lactones deoxygenated in the β-position. Thus compound **1** is converted to 5-hexanolide in almost 100% yield;[6] our hydrogenation of **13** gave the hydrogenolysis product and the β-hydroxy δ-lactone in the ratio 65:35 (^{1}H NMR). On the other hand, hydrogenation of the α-alkylated lactone **2** using PtO₂ is known to give the β-hydroxy δ-lactone; the yield and stereoselectivity were not specified.[6] We obtained less than 3% of the hydrogenolysis product in this reduction, but the formation of β-hydroxy δ-lactone **8** proceeded with only 54% stereoselectivity (isomer ratios 54:44:1:1). A homologue of **2** bearing hexyl and undecyl groups reacted more uniformly and gave the all-cis isomer (homologue of **8**) in an 84% yield.[7]

Concurrent reduction of keto and enol tautomers could have contributed to the low stereoselectivities presented above. To eliminate this possibility, we prepared various enol derivatives of **1**, **2**, and **13** and investigated the hydrogenation of these. Since the *tert*-butyldimethylsilyl enol ether of **2** proved somewhat unstable, we turned to other enol derivatives (but not to other silyl ethers). The best results were obtained with the enol MEM ethers **4**, **6**, and **15**. Hydrogenation over Pd/C (1−5 atm H₂, diethyl ether) led to the dihydro derivatives **10**, **12**, and **18** in high isomeric purities (99.3, 91.0, and 99.1% respectively),

Table 1. Stereoselectivities (%) in the Pd- or Rh-Catalyzed Hydrogenations of Enol Acetates and Enol MEM Ethers[a]

Starting compound	catalyst	
	Pd	Rh
3: R=COCH₃	> 99	
4: R=MEM	> 99	
5: R=COCH₃	97.7[b]	81.0[c]
6: R=MEM	91.0	
14: R=COCH₃	> 99	87.6
15: R=MEM	> 99	

[a] Values from a single hydrogenation run unless otherwise stated. [b] Top value from six runs; mean value, 92.7%. [c] Top value from three runs; mean value, 79.2%.

in good yields (81−95%), and with hardly detectable hydrogenolysis. The corresponding enol acetates (**3**, **5**, and **14**) were hydrogenated over Pd/C with equal or even better stereoselectivities (Table 1, 97.7% for the conversion of **5** to **11**), but the yields of the saturated acetates were in the 40−79% range due to extensive hydrogenolysis.[8] Rhodium/C has been used by Rozzell[9] for the hydrogenation of β-acyloxy-α,β-unsaturated esters with negligible hydrogenolysis (yields of dihydro derivatives were 90−100%). but this catalyst gave extensive hydrogenolysis of our enol acetates. Enol acetate **5** gave 43% hydrogenolysis with Rh and 50% with Pd catalyst (^{1}H NMR); enol acetate **14** gave 70% hydrogenolysis with Rh and 44% with Pd catalyst. Moreover, use of Rh led to inferior stereoselectivities (Table 1). Wilkinson's catalyst has been used with varying success for the hydrogenation of β-acyloxy-α,β-unsaturated esters.[9,10] On attempted hydrogenations of **5** with this catalyst, no or little reaction occurred (180 atm H₂, 22 °C, 7 days).

Since it appeared obvious that hydrogenation of the enol derivatives of the cis isomer[4a,c−e] of **13** would show very high diastereoselectivities, we made a preliminary investigation only. ^{1}H NMR analysis of the crude reduced enol acetate (H₂, Pd/C) indicated >95% isomeric purity of the saturated acetate (no GLC reference mixture was used). Within all probability, the product is the all-cis-substituted δ-lactone; the amount of hydrogenolysis product was less than 10%.

Häusler[11] deduced the configurations of **7** and its trans isomer from ^{1}H NMR spectra, and later workers agreed.[12] The configuration of the acetate **9** and MEM ether **10** follow from their preparation from **7**. The structures of products **17** and **18** were assigned as shown since the ^{1}H NMR signals from the
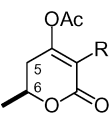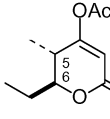
(5) (a) Michael, A.; Ross, J. *J. Am. Chem. Soc.* **1931**, *53*, 2394−2414. (b) Roll, L. J.; Adams, R. *J. Am. Chem. Soc.* **1931**, *53*, 3469−3476. (c) Belmont, J. A.; Soto, J.; King, R. E., III.; Donaldson, A. J.; Hewes, J. D.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1989**, *111*, 7475−7486. (d) Hudlicky, M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 910.
(6) Bacardit, R.; Moreno-Mañas, M. *Tetrahedron Lett.* **1980**, *21*, 551−554.
(7) Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218−1221.

(8) Platinum(IV) oxide gives hydrogenolysis exclusively; see ref 5a and b and Brandänge, S.; Jansbo, K.; Minassie, T. *Acta Chem. Scand.* **1987**, *B41*, 736−739.
(9) Rozzell, J. D. *Tetrahedron Lett.* **1982**, *23*, 1767−1770.
(10) Mohrig, J. R.; Dabora, S. L.; Foster, T. F.; Schultz, S. C. *J. Org. Chem.* **1984**, *49*, 5179−5182.
(11) Häusler, J. *Liebigs Ann. Chem.* **1983**, 982−992.
(12) (a) Bennett, F.; Knight, D. W.; Fenton, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 133−140. (b) Fehr, M. J.; Consiglio, G.; Scalone, M.; Schmid, R. *J. Org. Chem.* **1999**, *64*, 5768−5776.

hydrogens at C(3) were similar (chemical shifts and coupling constants) to those of **9** (Table A, Supporting Information) but clearly different from those of the trans isomer of **9** (Experimental, Supporting Information). Furthermore, the H(4) hydrogen in **17** appears as an NMR quartet (*J* 6.5 Hz) which corresponds well with the dq splitting seen for the same hydrogen in **9** (*J* 8.6 and 6.4 Hz, respectively). There are also great similarities between the ^{1}H NMR spectra of **17** and its 6-isopropyl analogue.[13] Hydrogenation of **5** and **6** afforded major products (**11** and **12**, respectively) which showed closely similar ^{1}H NMR signals from the ring protons (Table A). This means that the two products have the same configuration and the same major conformation. Using the Karplus-type dependence[14] of the ^{1}H NMR [3]*J* couplings, it can be seen that one of the two H(5) hydrogens in compound **11** is trans-diaxial to H(6) (*J* 11.6 Hz) but not to H(4) (*J* 3.7 Hz). The latter, small value of *J* excludes a half-chair major conformation in which the acetoxy group is equatorial. The other H(5) hydrogen shows an 8.5 Hz splitting due to H(4). This is not compatible with a half-chair major conformation in which the acetoxy group is axial. An all-cis configuration and a predominant boat or boatlike conformation of **11** and **12** was inferred. The similarities between the ^{1}H NMR signals from the ring protons in **11** and **12** and some analogous compounds (see below) support this conclusion.

The high or very high (>99%) stereoselectivities obtained in the hydrogenations of the α,β-unsaturated lactones **3**−**6** and **14** and **15** are due to the 6-methyl group in **3**−**6** and the two trans-disposed 5,6-substituents in **14** and **15** (Table 1). Trans-disposed substituents are usually expected to exert opposite directing effects which may partially cancel out. Yet stereoselectivities exceeding 99% were obtained with **14** and **15**, too. The stereostructures of the products (**17** and **18**, respectively) show that the 6-alkyl group can be said to be dominant; the hydrogens are added to the C(3) and C(4) carbons from the side of the ring which is trans to the 6-alkyl group. A search for analogous reactions provided five different hydrogenations of 5,6-trans-substituted analogues of **14** and **15** which together demonstrate a general stereochemical effect.[15−19] These analogues have a substituent at C(3) instead of C(4). The first example, described by de Lederkremer et al. in 1974 and four later ones all display the same stereochemical course as found here for **14** and **15**. The catalyst in these reactions was Pd/C, and the solvent was EtOH or EtOAc; we used Et₂O. Our hydrogenations of **14** and **15** are the first for which a high value of the stereoselectivity is reported. Apart from a 6:1 ratio,[18] the stereoselectivities were not specified; they were probably high.[15−17,19] The stereochemical effect is independent of the nature of the substituent on the 3,4-double bond (C−, O−, or N−) and also independent of the nature of the substituents in the 5- and 6-positions (C− or O−). Compounds have been

(13) Bindseil, K. U.; Zeeck, A. *Helv. Chim. Acta*, **1993**, *76*, 150−157.
(14) Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.
(15) De Lederkremer, R. M.; Litter, M. I.; Sala, L. F. *Carbohydr. Res.* **1974**, *36*, 185−187.
(16) (a) Varela, O. J.; Cirelli, A. F.; de Lederkremer, R. M. *Carbohydr. Res.* **1979**, *70*, 27−35. (b) Han, O.; Liu, H. *Tetrahedron Lett.* **1987**, *28*, 1073−1076.
(17) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360−362.
(18) Pilli, R. A.; Murta, M. M. *J. Org. Chem.* **1993**, *58*, 338−342.
(19) Varela, O. J.; Nin, A. P.; de Lederkremer, R. M. *Tetrahedron Lett.* **1994**, *35*, 9359−9362.

Table 2. Boltzmann-Averaged Coupling Constants (J_{found} and J_{calc}) and Calculated Pyramidalities (HF/6-31G*) in the Unsaturated Lactones **3**, **5**, and **14**

Compound		Coupling protons	J_{found}	J_{calc}	Pyramidalities (Å)[a]
OAc structure	**3**	3-5α	1.0	-0.8	C(3): 0.033
		3-5β	2.2	-2.3	C(4): 0.038
		5α-6α	4.2	3.4	
		5β-6α	11.2	10.2	
3: R=H **5**: R=Me	**5**	5α-6α	4.0	3.1	C(3): 0.037
		5β-6α	11.5	11.1	C(4): 0.044
OAc structure	**14**	3-5β	1.3	-1.6	C(3): 0.019
		5β-6α	≈6.6	4.6	C(4): 0.043

[a] Pyramidalities calculated for the most stable conformer, given as the distance (Å) from the trigonal carbon *down* to the plane defined by the three atoms bonded to the carbon.

assumed, without explanation, to react in their [6]H₁ (our numbering) half-chair conformation.[15,16,19] A rationalization of the stereochemical effect is given below.

Three groups have reported on the hydrogenation of enol derivatives of β-keto δ-lactones. The tetraacetylated β-glucoside of **1** was claimed[20] to give a trans-substituted δ-lactone (Pd/C), but serious doubts can be raised against this assignment since (a) it would require a hydrogenation stereochemistry which is opposite to that found in the hydrogenation of **3** and **4**, (b) the published ^{1}H NMR data of the product show much better agreement with our cis acetate **9** than with its corresponding trans isomer (see Experimental), and (c) the melting point of the obtained product was 7° lower than that of tetraacetylparasorboside, the presumed product. The second example is a hydrogenation of 6-benzyloxymethyl-4-methoxy-1-oxa-3-cyclohexene-2-one over Rh which gave a cis product with a diastereoselection higher than 95%.[21a] The third example is the recent work by Baiker et al. in which achiral 2-pyrones were hydrogenated using Pd/TiO₂ as catalyst and cinchonine as chiral inductor.[21b,c] The product most similar to ours is *cis*-4-methoxy-6-methyl-δ-valerolactone. At yields below 20%, this product was obtained with an 86−89% ee and a 98−99% de.[21b,c]

As a first step in the analysis of the stereochemistry of the hydrogenations of **3**−**6** and **14** and **15**, we carried out a combined molecular mechanics (MM) and ab initio quantum mechanics (QM) study (HF/6-31G*) conformational search on the unsaturated acetates **3**, **5**, and **14**. The most stable conformers of each compound are characterized in Table B (Supporting Information). Coupling constants for the ring hydrogens were calculated from the QM results in Table B and showed a good agreement with the measured values of *J* (Table 2). For both **3** and **5**, the four most stable conformers are envelopes in which C(6) is out of plane.

For each compound, the two low-energy conformers have the 6-methyl group equatorial and the acetyl moiety on different

(20) Nagumo, S.; Toyonaga, T.; Inoue, T.; Nagai, M. *Chem. Pharm. Bull.* **1989**, *37*, 2621−2623.
(21) (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. (b) Huck, W.-R.; Mallat, T.; Baiker, A. *New J. Chem.* **2002**, *26*, 6−8. (c) Huck, W.-R.; Mallat, T.; Baiker, A. *Catal. Lett.* **2002**, *80*, 87−92.
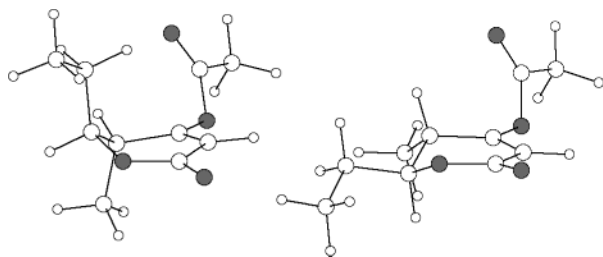
Figure 1. Calculated (HF/6-31G*) two most stable conformers, **14**-01 (left) and **14**-06 (right), of enol acetate **14**. Filled circles are oxygen atoms.

sides of the ring plane. The two high-energy conformers, which lie roughly 1.5−2 kcal/mol above, have the 6-methyl group axial and the acetyl moiety on different sides of the ring plane. In agreement with these results, the *J* values for the couplings between H(6) and the two H(5) protons indicate that H(6) is predominantly axial: *J* 11.2 and 4.2 Hz for **3** and *J* 11.5 and 4.0 Hz for **5**. The most stable conformer of **3**, and **5** as well, has C(6) and the acetyl group on the same side of the ring; the opposite side is therefore maximally unhindered. Addition of hydrogen from the latter side would give a trans product. In practice, however, the hydrogenations afford cis products with very high stereoselectivities. A similar conformational study of the acetate **14** afforded six conformers (Table B, Supporting Information). All six have an envelope ring conformation with C(6) lying out of plane. The two low-energy conformers **14**-01 and **14**-06 are depicted in Figure 1. Four conformers (**14**-01 to **14**-04) have the trans-disposed 5-methyl and 6-ethyl groups diaxial; there are two ethyl rotamers and, as for **3** and **5**, two positions of the acetyl group. Conformers **14**-05 and **14**-06 have both alkyl groups equatorial and differ only in the position of the acetyl group. Conformers with axial alkyl groups are slightly lower in energy than their diequatorial counterparts. The $J_{5,6}$ coupling constant for **14** is close to or in the 6.4−7.0 Hz range; a decoupling performed on the MEM analogue **15** gave the value 7.2 Hz. This is what is expected for a conformational equilibrium between approximately equally populated diaxial and diequatorial states. Although the double bond to be hydrogenated may seem more easily accessible in the diequatorial conformers, as in **14**-06, it is evident that the conformer search provides no basis for an unequivocal stereochemical interpretation of the hydrogenation results.

Seebach and co-workers analyzed addition reactions of some unsaturated systems fairly similar to ours and found a correlation between the facial selectivity and the direction of a pyramidality at the starting carbon−carbon double bond.[22] Although a few exceptions were found later,[23] the correlation seems to hold in the majority of cases. Evidence for pyramidal configurations at C(3) and C(4) in **3**, **5**, and **14** was found in the energy-minimized structures (Table 2). The direction of the calculated pyramidality is the same as in Seebach's compounds; that is, the pyramid apex is on the C(6) side of the ring. According to the theory, this is the preferred reaction side. Additional evidence in favor of a pyramidality in **14** was gained from the two 5,6-trans-substituted 5,6-dihydropyran-2-ones which were found in the Cambridge Structural Database (CIHPUE,[24a] WESHOR[24b]). The

pyramidalities at C(3) in these compounds are in the same direction as those calculated for **14**. The Seebach correlation predicts the two low-energy conformers **14**-01 and **14**-06 to undergo preferential addition to the carbon−carbon double bond from opposite sides of the ring. The steric hindrance from the alkyl groups in **14**-01 should favor reaction with **14**-06. Formation of **17** ensues. However, the significance of this type of analysis is highly questionable. Heterogeneous catalytic hydrogenations of alkenes are multistep processes in which all steps except the last one are believed to be reversible under the conventional reaction conditions.[25] Only the first step, the formation of the olefin-metal π-complex, should be directly affected by the pyramidality of the olefin. The stereochemical outcome of catalytic hydrogenations should thus be determined by other factors, later in the multistep processes.

A hypothetical rationalization of the exceedingly high facial selectivities in the heterogeneous hydrogenations of **3**, **4**, **14**, and **15** may be advanced on the basis of mechanistic studies of homogeneous hydrogenations[26] and on the conformational preferences of saturated δ-lactones described below. We assume the TS energy of the rate-determining step of a competing reaction pathway to be related to the energy content of the last intermediate. The latter is believed to be formed in a reaction step similar to the insertion of an olefin into an H−Pd$_{cat}$ bond. Such insertions are normally cis additions to the double bond. The most likely regiochemistry is the addition of hydrogen to C(4) and Pd$_{cat}$ to C(3), possibly assisted by a bonding between the carbonyl group and the catalyst, that is, a haptophilicity effect.[25a] Such a bonding seems to be important not only in homogeneous but also in heterogeneous hydrogenations.[25d,e] This regioselectivity is possibly reinforced by the matching polarities of the Pd−H bond and the α,β double bond.[25d,e] To account for the facial selectivity, we note that the ab initio calculations on δ-valerolactone described below show an only 0.12 kcal/mol difference in energy between the ideal chair $^2C_5$ conformation and the global energy minimum half-chair. The substituted $^2C_5$ ring is thus likely to be a good model for the olefin insertion product. Addition of the H−Pd$_{cat}$ unit at the bottom face of the carbon−carbon double bond in **14** or **15** (viewing lactones as in Scheme 1) would produce a $^2C_5$ chair with its four substituents, including Pd$_{cat}$, in equatorial positions. The alternative addition, from the top face, would produce a lactone having two equatorial and two axial substituents. Addition of H−Pd$_{cat}$ from the bottom face thus seems to be the favored route to the last intermediate. The final step forming **17** and **18** is assumed to be of the reductive elimination type in which the Pd$_{cat}$ substituent is replaced with hydrogen with retention of configuration. A similar bottom face addition to the carbon−carbon

(22) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763−4772.

(23) (a) Gandolfi, R.; Tonoletti, G.; Rastelli, A.; Bagatti, M. *J. Org. Chem.* **1993**, *58*, 6038−6048. (b) Sato, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Am. Chem. Soc.* **1995**, *117*, 4279−4287. (c) Uehara, F.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1999**, *47*, 293−294.

(24) (a) Garson, M. J.; Staunton, J.; Jones, P. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1021−1026. (b) Lichtenthaler, F. W.; Lindner, H. J.; Rönninger, S.; Paulus, H. *Z. Kristallogr.* **1994**, *209*, 274−277.

(25) (a) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 417−442. (b) Zaera, F. *Chem. Rev.* **1995**, *95*, 2651−2693. (c) Cremer, P. S.; Su, X.; Shen, Y. R.; Somorjai, G. A. *J. Am. Chem. Soc.* **1996**, *118*, 2942−2949. (d) Yu, J.; Spencer, J. B. *Tetrahedron* **1998**, *54*, 15821−15832. (e) Yu, J.; Whitney, P.-S.; Spencer, J. B. *J. Mol. Catal. A* **1999**, *146*, 199−210. (f) Ceyer, S. T. *Acc. Chem. Res.* **2001**, *34*, 737−744. (g) Zaera, F. *J. Phys. Chem. B* **2002**, *106*, 4043−4052.

(26) (a) Birch, A. J.; Williamson, D. H. *Org. React.* **1976**, *24*, 1−186. (b) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, pp 41−69. (c) Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 443−469. (d) Brown, J. M. *Chem. Soc. Rev.* **1993**, *22*, 25−41. (e) Torrent, M.; Solà, M.; Frenking, G. *Chem. Rev.* **2000**, *100*, 439−493.
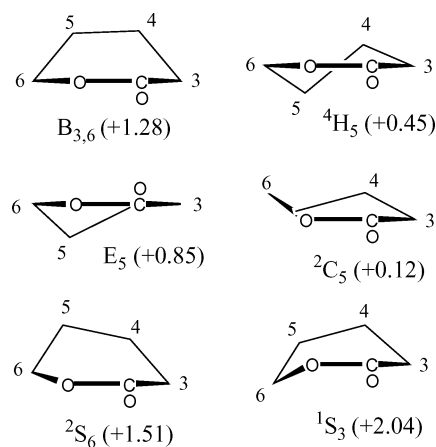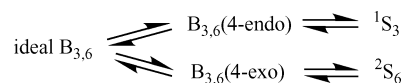
Figure 2. Some energy-minimized, *ideal* conformations of δ-valerolactone, seen with O(1)−C(2)−C(3) in the horizontal plane. All structures show τ_2 < 0. In parentheses: ab initio energies (kcal/mol) relative to the calculated global energy minimum half-chair.

double bond in **3** or **4** would lead to a lactone in which all three substituents, including Pd$_{cat}$, are equatorial; this process eventually leads to **9** and **10**. In the literature analogues[15−19] of our reductions the starting lactones have a substituent at C(3) instead of C(4). Reaction of these analogues with the same regio- and stereochemistry as above would lead to intermediates having three ring substituents, including Pd$_{cat}$, in equatorial position; the C(3)-substituent present in the substrate then being axial. This facial selectivity, which eventually leads to the products found, should be favored since the effective size of the Pd$_{cat}$ substituent is likely to exceed that of the initial C(3)-substituent. Thus, our model is valid for the hydrogenation of all three groups of differently substituted α,β-unsaturated δ-lactones.

Conformations of Saturated δ-Lactones. The basic conformations of nonplanar six-membered rings in general are the boat (B), chair (C), envelope (E), half-chair (H), and skew (S) forms.[27] For δ-lactones, there are conformational restrictions which are due to the strong preference of the C(6)−O(1)−C(2)−C(3) unit to be close to planar and thus preserve the resonance energy of the ester group.[28] Pure chair and skew forms are not compatible with this planarity. We introduce *ideal* δ-lactone conformations (Figure 2) as a means of exploring the conformational space and also for use as reference structures in assigning a main type conformation to δ-lactones. These ideal conformations were created by locking a proper part of the δ-valerolactone structure, followed by an energy minimization (HF/6-31G*). Conformations were specified by six intraannular dihedral angles τ, defined as $\tau_1 = $ O(1)−C(2)−C(3)−C(4), and so forth. In the ideal boat, envelope, and half-chair types, the ester unit C(6)−O(1)−C(2)−C(3) is locked in a plane, thus $\tau_6 \approx 0°$. In addition, the ideal boat has atoms C(3)−C(4)−C(5)−

(27) We use the IUPAC conformational nomenclature of carbohydrates but not the ring numbering; the latter follows the systematic name. See: *Pure Appl. Chem.* **1996**, *68*, 1919−2008. *Carbohydr. Res.* **1997**, *297*, 1−92. In the cyclohexane series, the skew is called twist. See ref 5e and *IUPAC Compendium of Chemical Terminology*; McNaught, A. D., Wilkinson, A., Eds.; Blackwell Science: Oxford, 1997; for an online version, see http://www.chemsoc.org/chembytes/goldbook/C00964.pdf.

(28) For summaries of X-ray crystallographic results, see: (a) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1547−1554. (b) Nørskov-Lauritsen, L.; Bürgi, H.-B.; Hofmann, P.; Schmidt, H. R. *Helv. Chim. Acta* **1985**, *68*, 76−82. (c) The Z (s-trans) conformers of esters are 5−6 kcal/mol more stable than the E conformers; the energy barriers are typically 10−13 kcal/mol.[55d] (d) From matrix IR spectra of methyl acetate, the E/Z difference was estimated as 8.5 ± 1.0 kcal/mol. Blom, C. E.; Gunthard, H. H. *Chem. Phys. Lett.* **1981**, *84*, 267−271.

C(6) in another plane ($\tau_3 \approx 0°$). In the ideal envelopes ^4E and E_5, a fifth atom, C(5) and C(4), respectively, has joined the C(6)−O(1)−C(2)−C(3) plane. As shown below, a boat-type δ-lactone can be similar to the ideal boat ($\tau_3 \approx 0°$) or twisted ($\tau_3 > 0°$). Two types of twist-boats can be discerned, distinguished by their relative signs of τ_3 and τ_4 (or τ_3 and τ_2). Opposite signs mean that the ideal boat has been twisted so as to move C(5) closer to the ester unit and C(4) away from it, that is in the exo direction. When instead τ_3 and τ_4 show the same sign, then the twist has brought C(4) closer to the ester unit, in the endo direction. We describe these two conformations as $B_{3,6}$(4exo) and $B_{3,6}$(4endo), respectively. These denotations are independent of which enantiomer is inspected.

As shown below, skew types are not uncommon among δ-lactones and clearly defined ideal skew conformations therefore constitute useful reference structures. An ideal skew form in the cyclohexane series has ring atoms 1, 2, 3, and 5 in one plane and atoms 4, 5, 6, and 2 in another. Such a locking of ring atoms in δ-valerolactone gives three different skew forms, all of which show energy contents far above the calculated global energy minimum half-chair (planes 1−2−3−5 and 4−5−6−2, +2.36 kcal/mol; planes 2−3−4−6 and 5−6−1−3, +5.21 kcal/mol; planes 3−4−5−1 and 6−1−2−4, +2.69 kcal/mol). Nonplanar ester groups contribute to the instabilities: $\tau_6 = 29.8°$, 57.7°, and 26.6°, respectively. If instead the ideal skew forms are defined by a *single* plane containing ring atoms 1−2−3−5 (arbitrary numbering) and with atoms 4 and 6 on different sides of that plane, then there are six possible ideal skew conformations of δ-valerolactone. This approach led to results of a larger practical value. On energy minimization of the six input structures, three of them lost their skew character and were transformed into other types of conformations. Skew form $^4S_2$ was converted into a structure closely similar to the envelope type ^4E and with the same relative energy, +1.63 kcal/mol. From $^1S_5$ was obtained a structure (+0.71 kcal/mol; τ_1 −5.6°; τ_2 28.8°; τ_3 −54.6°; τ_4 60.3°; τ_5 −38.7°; τ_6 10.6°) which is similar to the envelope E_5. Finally, skew $^3S_5$ was minimized to a structure closely similar to the $^4H_5$ half-chair global energy minimum (+0.13 kcal/mol). The remaining three structures retained their skew character on energy minimization. In these single-plane skew forms, the ester group is more planar and the relative energies lower than in the double-plane skew types. An exception is the single-locked skew form $^4S_6$ which is almost identical with its double-locked analogue; the calculated energies are the same and the values of $\tau_1-\tau_6$ differ by less than 0.5°. Skew form $^1S_3$ which is related to the same double-locked analogue deviates a little bit more from it. Since the $^1S_3$ and $^4S_6$ are structurally closely related (via the double-locked structure) and $^1S_3$ is the more stable, it is unlikely that the $^4S_6$ type will be common. The relative energies and dihedral angles of the remaining skew forms, $^1S_3$ and $^2S_6$, are given in Table 5. These skew forms are related to the ideal boat $B_{3,6}$ since they can be formed from it by imposing a 4-endo or 4-exo twist, respectively, which is accompanied by a loss of ester planarity.

In the conversion of ideal boat to skew, the numerical value of τ_3 increases from 0° to ca. 30°. Values in the vicinity of 15°

Table 3. Calculated Main Conformers of δ-Valerolactone, Its Ideal Conformations, Transition States, and Simple Derivatives[a,b]

derivative of δ-valerolactone (substituent position)	conformation type	relative QM energy[c] (kcal/mol)	dihedral angles[d] (degrees)					
			$\tau 1$	$\tau 2$	$\tau 3$	$\tau 4$	$\tau 5$	$\tau 6$
parent lactone	$^4H_5-^2C_5$	0.00	26.3	−44.9	58.0	−53.9	36.6	−22.1
	$B_{3,6}(4exo)$	1.16	47.1	−39.0	−9.6	55.4	−52.8	0.3
	ideal $^2C_5$	0.12	24.7	−40.5	55.9	−57.2	43.1	−26.0
	ideal $^4H_5$	0.45	12.6	−42.8	60.9	−50.4	19.9	−0.2
	ideal E_5	0.85	0.3	−29.5	56.9	−58.1	29.7	0.0
	ideal $B_{3,6}$	1.28	50.3	−47.1	−0.1	48.9	−51.6	0.2
	ideal $^2S_6$	1.51	41.9	−19.5	−29.6	63.8	−45.1	−7.9
	ideal ^4E	1.63	29.0	−57.1	57.6	−30.6	0.5	0.4
	ideal $^1S_3$	2.04	37.0	−61.6	30.1	24.1	−54.5	21.2
	TS 1	1.93	25.0	−0.1	−41.5	64.4	−42.3	−2.8
	TS 2	2.99	32.3	−61.5	44.4	0.0	−34.0	16.6
3-methyl								
(eq)[e]	$^2C_5$	0.00[e]	30.3	−46.8	58.2	−53.1	38.6	−26.7
(bowsprit)	$B_{3,6}(4exo)$	0.70	49.0	−41.7	−6.7	53.6	−52.1	−1.0
(pseudo-ax)	$^4H_5-^2C_5$	1.47	23.2	−42.0	57.4	−54.3	37.4	−21.2
6-methyl								
(pseudo-eq)[e]	$^4H_5-^2C_5$	0.00[e]	26.9	−44.8	58.2	−53.6	37.0	−23.2
(bowsprit)	$B_{3,6}(4exo)$	1.15	47.0	−40.6	−7.7	53.7	−53.0	1.5
(pseudo-ax)	$^4H_5-^2C_5$	1.71	27.4	−45.9	57.3	−49.5	31.3	−20.2
cis-3,6-dimethyl								
(3eq,6ax)	$^2C_5$	0.98	31.6	−47.8	57.3	−48.8	33.9	−25.5
(3ax, 6eq)	$^4H_5-^2C_5$	0.76	23.4	−41.9	57.7	−54.1	37.7	−22.1
(both as bowsprits)	$B_{3,6}(4exo)$	0.00	48.7	−40.7	−8.0	53.6	−51.4	−1.2
3-tert. butyl								
(bowsprit)	$B_{3,6}-^2S_6$	0.00	51.8	−34.2	−17.7	59.5	−46.9	−9.9
(eq)	$^2C_5$	0.13	29.0	−46.2	59.0	−53.5	38.7	−26.2
3-methoxy								
(eq)[f]	$^2C_5$	0.00	38.9	−50.1	57.4	−52.7	43.8	−36.4
(pseudo-ax)[f]	$^4H_5-^2C_5$	0.17	31.7	−49.5	59.5	−51.3	34.7	−24.4
(flagpole!)	$B_{3,6}(4exo)$	0.57	48.3	−42.4	−4.4	51.0	−50.7	−0.3
(bowsprit)	$B_{3,6}(4exo)$	0.86	52.0	−42.0	−7.9	54.0	−49.4	−4.8
4-methoxy								
(ax)[g]	$^2C_5$	0.00[h]	30.5	−47.4	58.4	−53.1	36.8	−25.0
(eq)[g]	$^4H_5-^2C_5$	0.81	26.2	−44.3	57.8	−54.7	37.2	−22.4
(pseudo-eq)	$^2S_6$	1.74	45.3	−25.9	−24.6	63.0	47.5	6.4
(ax)	$B_{3,6}(4endo)$	2.44	47.0	−56.3	14.0	39.4	−54.8	9.4
5-methoxy								
(ax)[i]	$^4H_5$	0.00[h]	23.8	−45.1	58.7	−53.1	33.3	−17.8
(eq)[j]	$^4H_5-^2C_5$	0.06	27.1	−45.1	57.8	−54.3	38.0	−23.5
(pseudo-eq)	$B_{3,6}-^1S_3$	0.65	43.4	−55.1	13.7	40.3	−58.1	13.2
(pseudo-ax)	$^1S_3$	1.84	41.9	−57.5	19.0	35.1	−56.6	14.7

[a] Only the most stable of the substituent rotamers is presented. [b] The ideal conformations are defined in the text and shown in Figure 2. [c] HF/6-31G*. [d] Endocyclic dihedral angles are defined as $\tau 1 = O(1)-C(2)-C(3)-C(4)$, etc. [e] The most stable conformation of 3-methyl-δ-valerolactone is 3.02 kcal/mol less stable than that of the 6-methyl isomer. [f] Trans conformation of $C(4)-C(3)-O-CH_3$. [g] Trans conformation of $C(5)-C(4)-O-CH_3$. [h] The most stable conformation of 4-methoxy-δ-valerolactone is 1.32 kcal/mol more stable than that of the 5-methoxy isomer. [i] Trans conformation of $C(4)-C(5)-O-CH_3$. [j] Trans conformation of $C(6)-C(5)-O-CH_3$.

indicate conformations which are intermediate between ideal boat and skew, but the value of τ_6 is also decisive. A compound with a low value of τ_6 (near planar ester group) is more easily associated with a twisted boat than with a skew form.

Ideal chair forms of δ-valerolactone may be defined along the lines presented above. Thus, the ideal $^2C_5$ chair form (Table 3) is an energy-minimized structure which has ring atoms 1−3−4−6 locked in a plane; atom 2 is above the plane, and atom 5 below. It shows a considerable structural similarity with the calculated global energy minimum half-chair and lies only 0.12 kcal/mol above it in energy; the $O(1)-C(3)-C(4)-C(6)$ dihedral angle is 0° in the chair and −5.4° in the half-chair. The other conceivable ideal chair forms, $^1C_4$ and $^3C_6$, are less stable, +0.91 ($\tau_6 = 32.6°$) and +1.46 kcal/mol ($\tau_6 = 50.8°$), respectively. This bias should be due to the preferred bond

lengths and bond angles of the ester group which differ markedly from those of the cycloalkane-type portion of the δ-valerolactone ring.[28]

Molecular Modeling. Computational studies of δ-valerolactone have involved ab initio quantum mechanical[29] as well as molecular mechanics[29a,30] techniques. Two low-energy conformers have been found, the half-chair $^4H_5$ and the boat $B_{3,6}$. Analysis by various spectral techniques has shown the half-chair to be 0.6−1.0 kcal/mol more stable than the boat.[29b,30a,31] More than 20 years ago, Allinger et al. calculated (MM2) the

(29) (a) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697−7705. (b) Abraham, R. J.; Ghersi, A.; Petrillo, G.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1279−1286.
(30) (a) Philip, T.; Cook, R. L.; Malloy, T. B., Jr.; Allinger, N. L.; Chang, S.; Yuh, Y. *J. Am. Chem. Soc.* **1981**, *103*, 2151−2156. (b) Allinger, N. L.; Zhu, Z. S.; Chen, K. *J. Am. Chem. Soc.* **1992**, *114*, 6120−6133.
(31) Lambert, J. B.; TeVrucht, M. L. E. *Org. Magn. Reson.* **1984**, *22*, 613−615.
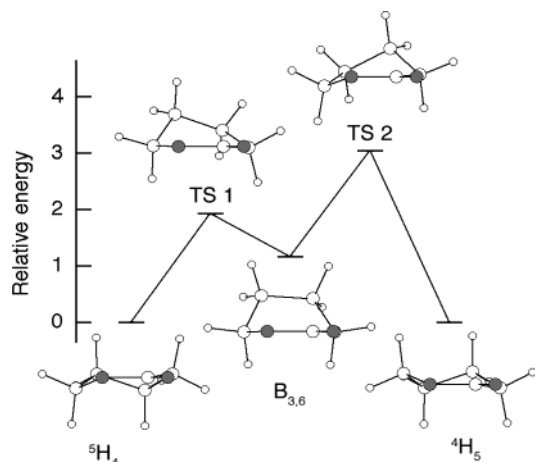
Figure 3. Ab initio optimized boat (B) and half-chair (H) conformers of δ-valerolactone together with two conformational transition states. Relative energies are in kcal/mol.

molecular structure of both conformers and an energy difference of 0.54 kcal/mol in favor of the half-chair.[30a] A more recent publication gave the value 1.16 kcal/mol (HF/6-31G*) and a structure of the half-chair.[29b] We repeated the latter results and in addition characterized the boat-type conformer (Table 3). It belongs to the $B_{3,6}$(4exo) type, as seen by its different signs of τ_3 and τ_4. Also the MP2/6-31G* calculations by Wiberg and Waldron led to a $B_{3,6}$(4exo) boat variant of δ-valerolactone, as judged from the depicted conformer.[29e] The same applies to the MM3 boat of Allinger et al..[30b]

The relative energies and ring structures found in our ab initio calculations (HF/6-31G*) on δ-valerolactone are summarized in Table 3 and Figure 3. The striking feature is the low relative energies of all ideal conformations. Two conformational transition states, TS 1 and TS 2, were found (Figure 3). Even these are low-lying, less than 3 kcal/mol above the global energy minimum half-chair type. In essence, TS 1 and TS 2 are characterized by zero values of τ_2 and τ_4, respectively. There is some similarity between TS 1 and the $^2S_6$ ideal skew form; the latter is 0.42 kcal/mol lower in energy. There is also some similarity between TS 2 and the ideal $^1S_3$ skew; the latter being 0.95 kcal/mol more stable.

A combined molecular mechanics (MM) and ab initio quantum mechanics (QM) study (HF/6-31G*) of the hydrogenation products **9**, **11**, and **17** was performed in order to, if possible, find support for the proposed stereostructures and the predominance of a boat or boatlike conformation of **11** and **12**. The conformational space of each lactone was explored employing the MM2*, MM3*, and MMFF force fields in Monte Carlo Multiple Minimum searches. As seen in Table C (Supporting Information), the three MM force fields produce clearly different sets of conformers of lactones **9**, **11**, and **17**. The MM structures served as starting geometries for HF/6-31G* optimizations. In all calculations on these compounds, conformers with a relative energy exceeding +3.0 kcal/mol were discarded. For lactones **9**, **11**, and **17**, we obtained six, four, and eleven unique QM conformers, respectively. Disregarding substituent rotamers, the numbers become four, three, and four; these are characterized in Table C. Boltzmann-weighted endocyclic coupling constants ^3J were calculated from the sets of MM conformers as well as from all QM conformers (Table 4). The best agreements with the J values recorded by NMR were obtained with the MMFF

**Table 4.** Coupling Constants ^3J Calculated for δ-Lactones **9**, **11**, and **17**

	coupl. ^{1}H nuclei	J found (NMR)	MM2* (10)[a]	MM3* (6)[a]	MMFF (9)[a]	QM (6)[a]
9	3α−4α	6.2	5.3	5.8	5.5	5.8
	3β−4α	6.6	4.5	9.9	6.2	9.4
	4α−5α	6.2	7.0	3.3	6.1	5.0
	4α−5β	8.6	7.9	11.1	8.7	10.3
	5α−6α	2.9	2.5	3.5	2.5	2.6
	5β−6α	11.7	10.9	10.9	10.9	11.4
rms[b]		0.0	1.1	2.1	0.5	1.4

	coupl. ^{1}H nuclei	J found (NMR)	MM2* (5)[a]	MM3* (5)[a]	MMFF (4)[a]	QM (4)[a]
11	3α-4α	4.7	4.2	4.6	4.2	2.5
	4α-5α	8.5	8.4	8.9	7.6	7.2
	4α-5β	3.7	6.3	3.2	6.4	3.6
	5α-6α	4.0	2.6	4.8	2.8	4.2
	5β-6α	11.6	10.8	8.0	10.7	10.6
rms[b]		0.0	1.4	1.7	1.5	1.2

	coupl. ^{1}H nuclei	J found (NMR)	MM2* (24)[a]	MM3* (9)[a]	MMFF (18)[a]	QM (11)[a]
17	3α−4α	5.8	4.6	5.6	5.5	4.3
	3β−4α	6.2	3.9	10.0	4.6	6.4
	4α−5β		5.4	10.2	7.0	5.8
	5β−6α	10.3	9.6	9.9	8.9	10.0
rms[b]		0.0	1.5	2.2	1.2	0.9

[a] Number of conformers. [b] Root-mean-square values of the deviations in Hz from the J values found.

and the QM conformer sets; MM3* gave the poorest correlation. All calculated values refer to gas phase. The results are in accord with the conclusion drawn from ^{1}H NMR spectra that only compound **9** (and its MEM analogue **10**) shows a clear half-chair preference. This is reflected in the 3α−5α long-range W type coupling[32] which is seen only for **9** and **10** (Table A, Supporting Information). The calculations also support the conclusion drawn from NMR spectra that a boat-type conformation prevails for **11**.

To approach an understanding why the *cis*-3,4,6-substituted δ-lactones **11** and **12** prefer boatlike conformations, we carried out a computational study of some simple methyl derivatives of δ-valerolactone. The ab initio (HF/6-31G*) results for 3-methyl- and 6-methyl-δ-valerolactone are shown in Table 3 together with those for *cis*-3,6-dimethyl-δ-valerolactone. The latter shows a preference for the boat-type conformation; the lowest lying half-chair type was 0.76 kcal/mol higher in energy. In a half-chair conformation, one of the methyl groups has to be in an unfavorable pseudoaxial position. The bond to this methyl group is then involved in a gauche interaction with the C(4)−C(5) bond. In the boat-type conformation having both methyl groups in bowsprit position, which is by far the most stable boat, there is instead an anti arrangement of these bonds. *cis*-3,6-Dimethyl-δ-valerolactone is known as the "carpenter bee pheromone".[33,4b] It is the major component of the sex pheromone

(32) (a) Carroll, F. I.; Blackwell, J. T. *Tetrahedron Lett.* **1970**, 4173−4176. (b) Tschesche, R.; Hoppe, H.-J.; Snatzke, G.; Wulff, G.; Fehlhaber, H.-W. *Chem. Ber.* **1971**, *104*, 1420−1428. (c) Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335−3346. (d) Schröder, H.; Haslinger, E. *Magn. Reson. Chem.* **1994**, *32*, 12−15 and references therein.
(33) Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, *17*, 4029−4032.
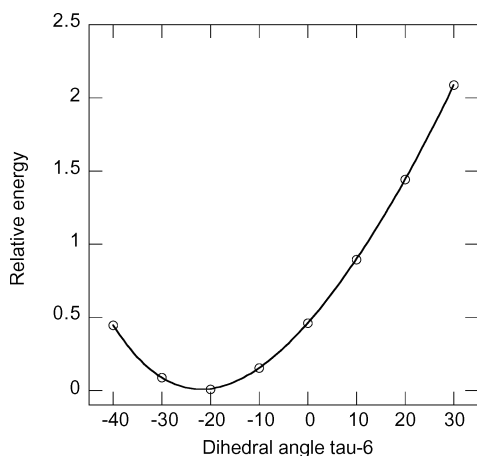
Figure 4. Calculated relative energy (kcal/mol) of chair/half-chair/skew conformations of δ-valerolactone as a function of dihedral angle τ_6.

excreted from the mandibular gland of the male carpenter bee (*Xylocopa hirutissima*). There are no published ^{1}H NMR ^3J couplings from which a conformation can be deduced. However, the calculated data in Table 3 indicate a preferred $B_{3,6}$(4exo) conformation of the pheromone.

A noteworthy feature of the calculated chair/half-chair-type conformers of δ-valerolactone and its simple derivatives (Table 3) is the large deviation from planarity of the C(6)−O(1)−C(2)−C(3) unit; the corresponding dihedral angle τ_6 lies typically in the 18−27° region. This is at variance with acyclic esters which generally show a strong preference for the planar, transoid conformation.[28] The (HF/6-31G*) energy dependence on τ_6 calculated with the Jaguar program for δ-valerolactone is seen in Figure 4; the minimum is found at τ_6 −22.1° (Table 3). Torsion of the ester group in the opposite, positive direction leads to unstable conformations. Thus, τ_6 +20° represents a skew-type molecule which lies some 1.5 kcal/mol above the minimum. A hypothetical conversion of our calculated ideal half-chair, with its planar ester group, to the calculated global energy minimum half-chair releases 0.45 kcal/mol and makes the ring more chairlike. Such a transformation of the ester group may be somewhat unfavorable but is evidently more than compensated for by a torsional strain reduction which is due to an increase of the dihedral angles τ_1, τ_5, and τ_6. A presumably unfavorable effect of the puckering is the reduction from 42.6° to 32.6° of the dihedral angle between the carbonyl double bond and the closest C(3)−H(3) bond. To alleviate this increase in torsional strain and possibly also compensate for a presumed minor loss of resonance energy due to the puckering, there is a slight pyramidality of the carbonyl unit; the carbonyl oxygen is situated 0.083 Å below the O(1)−C(2)−C(3) plane when the molecule is seen as in Figure 2. In the δ-valerolactone ideal half-chair, the carbonyl oxygen atom is only 0.016 Å below this plane.

Conformations of Saturated δ-Lactones Determined by X-ray Crystallography. Brief summaries of the early literature on the conformational aspects of saturated δ-lactones can be found in two publications.[34] There is also an analysis of 20 saturated δ-lactone structures determined by X-ray crystallography.[34a] However, all but one of these compounds have a

δ-lactone ring being bridged or fused to one or more other rings. Such lactone rings have a restricted conformational freedom and may adopt forced upon conformations which are not representative for solitary (nonfused and nonbridged) δ-lactone rings. We therefore made a survey to elucidate the conformational variability of solitary δ-lactone rings. The results are based on our ab initio calculations and an analysis of X-ray structures available in the Cambridge Structural Database (CSD). After also leaving out spiro compounds, the analysis was based on 67 compounds containing a solitary δ-lactone ring (December 2002 version of CSD). No selection regarding X-ray crystallographic precision was made.

For the nonplanar six-membered ring compounds which deviate from the ideal conformational types B, C, E, H, and S described above, there is a need for a characterization system using quantitative terms. That of Cremer and Pople[35] has found widespread use since its introduction. Recently, Bérces, Whitfield, and Nukada (BWN) developed a modified system[36] which can be operated on the Internet.[37] Input of endocyclic dihedral angles gives the conformation as a linear combination of three ideal conformations together with values of the Cremer−Pople parameters. The BWN ideal conformations have standardized dihedral angles and differ therefore from ours which are computationally energy-minimized structures.

With our initial focus on boat-type conformations, we used the C(3)−C(4)−C(5)−C(6) dihedral angle, that is τ_3, to get a quick identification of such conformations. This particular angle is the one showing the largest numerical variation. In the ideal conformations, it equals 0° in the boat, shows values in the vicinity of 30° in the skew forms in Table 3, and reaches maximum values around 55−60° in the half-chair and envelope conformations ^4E and ^5E. When the solitary δ-lactones found in the CSD were listed after their value of τ_3 (Table 5), they formed two groups. In the first group, the angle τ_3 is between 0° and 35°, and in the second, it is between 50° and 66°. Only two out of 67 lactones show a τ_3 value in the range 35°−50°. We find the boat-type and skew forms in the former group, and the chair, envelope, and half-chair forms in the latter.

Boat and Skew Types. The finding that lactones **11** and **12** prefer boat-type conformations raised the question of its generality. Eight examples of all-*cis*-3,4,6-trisubstituted δ-lactones, that is, analogues of **8**, **11**, and **12**, were found in the literature.[38] Two of these have been subjected to X-ray crystallographic analysis (Table 5, entries 9 and 21) which revealed boat or boatlike conformation in both cases.

(35) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354−1358.
(36) Bérces, A.; Whitfield, D. M.; Nukada, T. *Tetrahedron* **2001**, *57*, 477−491.
(37) (a) http://www.nrc.ca/ibs/6ring.html. (b) This web interface sometimes erroneously uses the third characterization line. Thus, two of the four most typical boats in Table 5 (entries 2 and 5) are described as predominantly skew forms on the third characterization line. Compounds in entries 3 and 4 are correctly described as boats.
(38) (a) Lavie, D.; Kirson, I.; Glotter, E.; Snatzke, G. *Tetrahedron* **1970**, *26*, 2221−2228. (b) DeShong, P.; Simpson, D. M.; Lin, M.-T. *Tetrahedron Lett.* **1989**, *30*, 2885−2888. Ammon, H. L.; DeShong, P.; Simpson, D. *Acta Crystallogr., Sect. C* **1991**, *47*, 2482−2484. (c) Hanessian, S.; Di Fabio, R.; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436−3438. Hanessian, S.; Bennani, Y. L.; Di Fabio, R. *Acta Crystallogr., Sect. C* **1990**, *46*, 939−941. (d) Stalder, H.; Oesterhelt, G.; Borgström, B. *Helv. Chim. Acta* **1992**, *75*, 1593−1603. (e) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978−8979. (f) Kiyooka, S.; Shahid, K. A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1485−1495. (g) Jurczak, M.; Rabiczko, J.; Socha, D.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2015−2022. (h) Hanaki, N.; Ishihara, K.; Kaino, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron* **1996**, *52*, 7297−7320.

(34) (a) Thomas, S. A. *J. Crystallogr. Spectrosc. Res.* **1985**, *15*, 115−131. (b) Stanley, J.; Matallana, A.; Kingsbury, C. A. *J. Phys. Org. Chem.* **1990**, *3*, 419−427.

Table 5. Conformations of Solitary Saturated δ-Lactones Analyzed by X-ray Crystallography[a–e]

entry	Cambridge Crystallogr. Code[reference]	substituent positions	conform. type	dihedral angles[c] (degrees)					
				$\tau 1$	$\tau 2$	$\tau 3$	$\tau 4$	$\tau 5$	$\tau 6$
1	ideal boat		$B_{3,6}$	50.3	−47.1	−0.1	48.9	−51.6	0.2
2	FUJJID10[44a]	4, 4, 5β, 6β	$B_{3,6}$(4endo)	52.0	−51.2	0.7	52.7	−58.1	4.4
3	XIXREB[44b]	4β, 6α	$B_{3,6}$(4endo)	48.6	−46.7	2.2	44.5	−47.1	−1.6
4	FUJJAV10[44a]	4, 4, 5β	$B_{3,6}$(4endo)	50.0	−52.2	4.5	47.8	−56.1	5.4
5	HIKJIU[44c]	3β	$B_{3,6}$(4exo)	50.4	−44.5	−4.6	52.5	−51.5	−1.5
6	PEQGEX[44d]	4β, 5α, 6β	$B_{3,6}$(4endo)	43.6	−48.3	4.6	43.6	−53.5	8.5
7	VINTAN[44e]	3β, 4α, 5α, 6β	$B_{3,6}$(4endo)	46.1	−50.0	4.7	47.3	−56.7	7.7
8	BESVIE[40]	3β, 4α, 6β	$B_{3,6}$(4exo)	53.9	−46.3	−4.9	53.9	−51.4	−3.4
9	VOBTIP[38b]	3β, 4β, 6β	$B_{3,6}$(4endo)	49.7	−52.7	4.9	47.9	−55.9	5.4
10	VISQET[44f]	3β	$B_{3,6}$(4exo)	46.4	−41.9	−6.9	54.5	−54.7	2.7
11	YILFEE[44g]	3β	$B_{3,6}$(4endo)	43.1	−50.9	7.2	44.9	−56.6	9.7
12	YOBQIP[41]	3β, 4α, 6β	$B_{3,6}$(4exo)	45.6	−41.1	−7.6	55.4	−55.9	−4.1
13	FEVXIN[44h]	4β, 6β	$B_{3,6}$(4exo)	48.2	−42.8	−7.8	54.4	−53.3	2.2
14	KESXEL[44i]	4, 4, 6, 6	$B_{3,6}$(4exo)	49.3	−41.1	−8.4	51.8	−48.2	−1.3
15	TAPZAL[44j]	4β, 6β	$B_{3,6}$(4exo)	46.8	−42.0	−9.2	55.8	−53.2	2.2
16	QIMRAF(1)[44k]	3β, 4α, 5β, 6β	$B_{3,6}$(4exo)	55.1	−41.7	−9.3	53.7	−45.0	−9.6
17	JIZJAD[44l]	3β, 4β, 5α, 6β	$B_{3,6}$(4endo)	47.7	−55.8	10.7	43.7	−56.9	8.5
18	VEQTUG(1)[21a]	3β, 4β, 5α, 6β	$B_{3,6}$(4endo)	48.9	−56.1	11.2	41.3	−53.0	5.8
19	FUJJEZ10(1)[44a]	4, 4, 5α, 6β	$B_{3,6}$(4exo)	44.0	−35.9	−15.0	59.7	−56.3	5.1
20	FUJJEZ10(2)	4, 4, 5α, 6β	$B_{3,6}$(4exo)	45.7	−34.8	−15.1	60.9	−55.0	1.9
21	VEJDUJ[38c]	3β, 4β, 6β	$B_{3,6}-^1S_3$	47.3	−58.2	15.5	38.4	−54.8	10.2
22	QIMRAF(2)	3β, 4α, 5β, 6β	$^2S_6-B_{3,6}$	55.9	−37.4	−16.0	59.1	−44.5	−11.9
23	KATQOL[44m]	3β, 4β	$B_{3,6}-^2S_6$	48.4	−33.8	−19.5	63.3	−52.6	−4.1
24	FUJJEZ10(3)	4, 4, 5α, 6β	$B_{3,6}-^2S_6$	48.9	−31.8	−20.3	62.9	−50.6	−5.0
25	LINDIV[44n]	3β, 4α	$^2S_6$	52.8	−33.7	−20.7	64.2	−49.2	−9.1
26	VEQTUG(2)	3β, 4β, 5α, 6β	$^1S_3$	49.6	−65.7	25.4	30.8	−50.8	7.9
27	TAMSOP[44o]	4α, 5β	$^1S_3$	43.0	−65.5	28.6	27.9	−55.8	17.4
28	ZIDCIY[42]	3β, 4α, 6β	$^2S_6$	38.0	−19.3	−28.8	63.2	−48.2	−2.8
29	ideal skew		$^2S_6$	41.9	−19.5	−29.6	63.8	−45.1	−7.9
30	ideal skew		$^1S_3$	37.0	−61.6	30.1	24.1	−54.5	21.2
31	YISSOI[43]	3β, 4α, 6β	$^2S_6$	43.3	−19.7	−30.4	63.0	−44.2	−8.8
32	JIQTEI[44p]	5, 5, 6β	$^2S_6$	31.7	−10.7	−33.4	60.4	−45.3	−2.5
33	ZIDCEU[42]	3α, 4β, 6β	$^2S_6$	32.7	−11.0	−34.8	63.1	−44.7	−3.9
34	EFAKAX[44q]	3β, 4α	$^6S_2-^2C_5$	−27.2	−0.3	44.8	−67.6	42.8	5.3
35	EFAJUQ[44q]	3β, 4α	$^6H_5-^6S_2$	−15.2	−11.2	49.1	−65.4	40.7	0.1
36	EFAKOL[44q]	3β, 4α	$^6H_5$	−10.2	−14.5	50.1	−64.4	40.9	−3.1
37	EFAKEB[44q]	3β, 4α	$^6S_2-^2C_5$	−24.9	−8.1	50.2	−64.6	33.1	12.3
38	TIVHAH[44r]	3α, 6, 6	$^2C_5$	42.5	−52.2	51.4	−34.5	23.6	−29.1
39	GIKVOL[44s]	4α, 5α, 6β	$^4H_5$	18.2	−36.1	52.4	−52.8	34.0	−16.6
40	EFALAY[44q]	3β, 4α	E_5	−2.9	−23.0	53.9	−60.8	35.4	−3.3
41	HOSNAE[44t]	5, 5, 6α	E_5	1.1	−26.3	54.1	−60.5	40.2	−8.3
42	SUNKOB[44u]	3β	E_5	−1.0	−26.2	55.9	−61.2	35.3	−3.1
43	ideal chair		$^2C_5$	24.7	−40.5	55.9	−57.2	43.1	−26.0
44	ideal envelope		E_5	0.3	−29.5	56.9	−58.1	29.7	0.0
45	FUJJOJ10[44a]	4β, 5α, 6α	$^4H_5-E_5$	9.8	−32.2	57.5	−62.7	41.4	−14.4
46	FUJHOH10[44a]	4, 4, 6α	$^2C_5$	34.4	−49.9	58.6	−49.9	33.3	−25.4
47	BAFTAE[44v]	4α, 5β, 6α	$^4H_5$	14.8	−38.6	58.7	−55.8	32.3	−11.2
48	PATCUI[44x]	5α, 6α	$^4H_5$	16.9	−41.8	58.7	−50.5	25.6	−8.4
49	QIYYUS01[44y]	3α, 4β, 5β, 6α	$^4H_5$	33.8	−55.0	58.7	−40.1	20.0	−16.6
50	ZIRMUI[44z]	3, 3, 4β, 5β, 6α	$^4H_5$	21.5	−41.9	59.3	−54.6	33.5	−17.5
51	PEFXED[45a]	6α	$^4H_5$	19.3	−42.0	59.1	−53.7	31.5	−13.8
52	FIPCIQ[45b]	4β, 5β, 6α	$^4H_5-^2C_5$	32.4	−50.8	59.2	−46.8	29.4	−22.5
53	TAPYUE(1)[44j]	4β, 6α	$^4H_5-^2C_5$	26.7	−44.9	59.4	−54.2	36.0	−22.3
54	TAPYUE(2)	4β, 6α	$^4H_5$	21.3	−45.0	59.7	−49.5	25.2	−11.0
55	DOKNEW(1)[45c]	4β, 6α	$^4H_5$	18.4	−41.7	59.7	−55.2	31.0	−12.3
56	DUHMUO[45d]	4β, 6α	$^4H_5$	26.4	−48.1	59.8	−49.1	27.2	−15.7
57	COMPAC[45e]	4β, 6α	$^4H_5$	30.0	−50.7	59.8	−47.7	27.4	−18.1
58	CEXVAC[45f]	4α, 5β, 6α	$^4H_5$	26.1	−45.3	60.0	−54.7	33.1	−19.7
59	CEKBEZ[45g]	4β, 6α	E_5	9.6	−38.2	60.0	−53.8	25.4	−3.0
60	BUKPAY[45h]	3β, 5β, 6α	$^2C_5$	33.2	−50.0	60.2	−53.3	38.8	−28.2
61	HOSMUX[44t]	5, 5, 6β	$^4H_5$	19.2	−44.4	60.5	−53.6	30.7	−12.4
62	JOCDAG[44a]	4, 4, 5α	$^4H_5$	12.4	−41.4	60.5	−52.0	21.2	0.8
63	RACKUB[45i]	3, 3	$^4H_5$	17.1	−41.4	60.6	−53.9	30.8	−11.8
64	CAPLOU(1)[45j]	4, 4, 6α	$^4H_5$	23.6	−47.5	60.7	−49.2	23.5	−10.7
65	NOYVOM[45k]	4β, 6α	$^4H_5$	27.7	−52.1	60.8	−44.1	19.1	−10.8
66	JOCCEJ(1)[44a]	4α, 6, 6	$^4H_5$	14.8	−39.8	60.8	−55.8	29.7	−9.6
67	ideal half−chair		$^4H_5$	12.6	−42.8	60.9	−50.4	19.9	−0.2

Table 5. (Continued)

entry	Cambridge Crystallogr. Code[reference]	substituent positions	conform. type	dihedral angles[c] (degrees)					
				$\tau 1$	$\tau 2$	$\tau 3$	$\tau 4$	$\tau 5$	$\tau 6$
68	TEHGES[45l]	3, 3, 5β, 6β	⁴H₅	18.7	−45.6	61.1	−46.5	19.5	−5.9
69	FUJHUN10[44a]	4, 4, 6α	⁴H₅	14.1	−42.1	61.3	−51.6	20.9	−2.3
70	CAPLOU(2)	4, 4, 6α	⁴H₅	22.8	−47.0	61.3	−49.7	24.4	−11.3
71	LYSLAC[45m]	3β, 6α	⁴H₅	21.2	−45.8	61.4	−52.1	28.2	−12.3
72	COYHON10[45n]	3β, 6, 6	⁴H₅	24.8	−46.3	61.4	−52.4	31.7	−17.9
73	KATQUR[44m]	3β, 4α	⁴H₅	16.4	−41.7	61.4	−54.6	27.4	−8.2
74	VIFQOQ[45o]	3β, 4α, 5α	⁴H₅–²C₅	24.0	−44.0	61.6	−59.9	41.5	−22.9
75	FUJJUP10[44a]	4β, 5β, 6α	⁴H₅	21.3	−48.4	61.7	−47.3	19.8	−6.1
76	GLULAC1[45p]	3β, 4α, 5β, 6α	⁴H₅	24.8	−47.3	61.7	−50.9	28.2	−15.2
77	QEHVII[45q]	3β, 5β, 6α	⁴H₅	27.9	−50.8	61.8	−48.4	27.9	−17.3
78	XIXRAX[44b]	4β, 6α	⁴H₅	20.1	−49.1	61.9	−47.3	17.9	−3.6
79	NISMIL[45r]	3β, 4α, 6α	⁴H₅	20.5	−49.1	61.9	−44.1	13.0	−1.2
80	JOCCEJ(2)	4α, 6, 6	⁴H₅	22.3	−45.9	62.1	−53.1	28.9	−13.6
81	DOKNEW(2)	4β, 6α	⁴H₅	20.5	−45.4	62.5	−54.3	29.4	−11.6
82	SUPRAW[45s]	3β, 4β, 5β, 6α	⁴H₅	13.3	−40.0	65.8	−65.0	39.6	−13.1

[a] The order of listing is the increasing absolute value of τ_3. [b] The results are normalized to show, as in Figure 2, the enantiomer with $\tau_2 < 0$. [c] Ring dihedral angles are defined as $\tau_1 = O(1)-C(2)-C(3)-C(4)$, etc. [d] Values calculated for some energy-minimized ideal conformations of δ-valerolactone are included for comparison. [e] Different conformations in the unit cell are numbered as in entries 19, 20, and 24.

Compound VOBTIP[38b,39] (entry 9) and a third δ-lactone[38e] have been characterized by recording the key ¹H NMR ³*J* couplings. These coupling data are similar to those of our compounds **11** and **12** (Table A, Supporting Information) and indicate that boat-type conformations are predominating in the solutions of these lactones. There are four 3,4,6-trisubstituted δ-lactones in which the 3- and 6-substituents are cis and the 4-substituent is trans. Two of them[40,41] (Table 5, entries 8 and 12) crystallize in a boat conformation, while the other two[42,43] appear as conformationally related ²S₆ skew forms (entries 28 and 31).

A conformational dichotomy related to the ring substitution pattern emerges from the X-ray crystallographic results. There are eleven compounds in Table 5 in which the positions 3 and 6 are monosubstituted in a cis manner. Ten of these are either a boat or a skew type and show $|\tau_3| \leq 30.4°$. This is in line with the above ab initio calculation on *cis*-3,6-dimethyl-δ-valerolactone (Table 3). Compound QIYYUS01 (entry 49) is an exception; its lactone ring forms a half-chair which bears a 3-methyl group in the unfavorable pseudoaxial position (Table 3). On the other hand, its silyloxy substituent in the pseudoaxial 4-position is probably a stabilizing factor (see below). Intermolecular forces in the crystal may favor the half-chair but are not easily evaluated.

The second half of the conformational dichotomy consists of the six compounds in Table 5 in which positions 3 and 6 are monosubstituted in a trans manner. All six except ZIDCEU (entry 33)[42] are either chairs or half-chairs. Studies of compounds in solution show the same pattern. Thus, CD spectra of steroidal solitary 3,4,6-trisubstituted δ-lactones[38a] were interpreted as indicating "half-boats" when the 3- and 6-substituents were cis irrespective of the position of a 4-methyl group. A 3,6-trans isomer was instead considered to be a half-chair. In

the carbohydrate series, results from NMR[15,46] studies of δ-lactones agree with those of X-ray investigations (entries 16, 22, and 76) and show that the conformational equilibria are shifted far toward the half-chair for glucono-1,5-lactone which is 3,6-trans-substituted but toward the boat for the 3,6-cis-substituted δ-lactones.

Besides the solid state examples QIYYUS01 and ZIDCEU, we found two examples of δ-lactones in solution which at first glance seem not to comply with the conformational dichotomy. In the first example, isomeric 3-methyl-6-alkyl-substituted δ-lactones were studied by ¹H NMR and both cis and trans isomers were assumed to exist as half-chairs.[47] However, a reinterpretation of the NMR data in the cis series seems appropriate. Besides the quartet splitting due to the 3-methyl substituent, the H(3) showed a triplet splitting due to the two H(4) hydrogens (*J* 6.6 and 7.2 Hz in the two compounds studied). A conformational equilibrium between skew and boat forms similar to what is described below for compound

(39) Selected ¹H NMR data for VOBTIP[38b] (CDCl₃, 400 MHz): δ 4.38 (ddq, *J* = 12.4, 6.2, 4.0 Hz, H-6), 4.31 (dt, *J* = 8.2, 3.6 Hz, H-4), 3.09 (m, *J* = 8.2, 5.5, 4.4 Hz, H-3), 2.35 (ddd, *J* = 14.2, 8.2, 4.0 Hz, H-5), 1.54 (ddd, *J* = 14.2, 11.2, 3.3 Hz, H-5). We thank Prof. Philip DeShong, University of Maryland, for kindly communicating these and other unpublished data.

(40) Axiotis, S.; Dreux, J.; Perrin, M.; Royer, J. *Tetrahedron* **1982**, *38*, 499–504.

(41) Fuller-Stanley, J. A.; Loehlin, J. H.; Bolin, K. A.; Fairbrother, G.; Nazaire, F. *J. Org. Chem.* **2002**, *67*, 27–31.

(42) Tinant, B.; Touillaux, R.; Declercq, J. P.; Miserque, O. *J. Phys. Org. Chem.* **1995**, *8*, 747–752.

(43) Alfonso, D.; Bernardinelli, G.; Kapetanidis, I. *Phytochemistry* **1993**, *34*, 517–521.

(44) (a) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036–80. (b) Buckley, S. L. J.; Drew, M. G. B.; Harwood, L. M.; Macías-Sanchez, A. J. *Tetrahedron Lett.* **2002**, *43*, 3593–3596. (c) Enders, D.; Teschner, P.; Gröbner, R.; Raabe, G. *Synthesis* **1999**, 237–242. (d) Greeves, N.; Lee, W.-M.; Barkley, J. V. *Tetrahedron Lett.* **1997**, *38*, 6453–6456. (e) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912–4915. (f) Otto, A.; Liebscher, J. J. *Heterocyclic Chem.* **2000**, *37*, 891–894. (g) Morikawa, T.; Washio, Y.; Harada, S.; Hanai, R.; Kayashita, T.; Nemoto, H.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 271–281. (h) Stokker, G. E.; Rooney, C. S.; Wiggins, J. M.; Hirshfield, J. *J. Org. Chem.* **1986**, *51*, 4931–4934. (i) Novotny, J.; Ondracek, J.; Schwarz, M.; Kratochvil, B. *Collect. Czech. Chem. Commun.* **1989**, *54*, 1661–1665. (j) Ammon, H. L.; Prasad, S. M.; Kumar, N. *Acta Crystallogr., Sect. C* **1992**, *48*, 669–675. (k) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995–. (l) Ammon, H. L.; DeShong, P.; Simpson, D. *Acta Crystallogr., Sect. C* **1991**, *47*, 2693–2695. (m) Enders, D.; Vázquez, J.; Raabe, G. *Eur. J. Org. Chem.* **2000**, 893–901. (n) Nierlich, M.; Lance, M.; Thuéry, P.; Vigner, J. D.; Roux, M. C.; Wartski, L. *Acta Crystallogr., Sect. C* **1995**, *51*, 673–674. (o) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C.-G.; Boulanger, T.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729–5733. (p) Haque, M. B.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881–2889. (q) Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4763–4765. (r) Rochfort, S. J.; Gable, R. W.; Capon, R. J. *Aust. J. Chem.* **1996**, *49*, 715–718. (s) Panfil, I.; Urba'nczyk-Lipkowska, Z.; Chmielewski, M. *Carbohydr. Res.* **1998**, *306*, 505–515. (t) Dang, H.-S.; Elsegood, M. R. J.; Kim, K.-M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061–2068. (u) Csuk, R.; Schaade, M.; Schmidt, A. *Tetrahedron* **1994**, *50*, 11885–11892. (v) Panfil, I.; Urba'nczyk-Lipkowska, Z.; Suwínska, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1199–1212. (x) Tochtermann, W.; Scholz, G.; Bunte, G.; Wolff, C.; Peters, E.-M.; Peters, K.; von Schering, H. G. *Liebigs Ann. Chem.* **1992**, 1069–1080. (y) Smith, A. B., III.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664. (z) Di Nardo, C.; Varela, O.; de Lederkremer, R. M.; Baggio, R. F.; Vega, D. R.; Garland, M. T. *Carbohydr. Res.* **1995**, *269*, 99–109.

SUNKOB seems more likely than the single half-chair invoked by the authors.

The second example is that of Morimoto et al..[48] In their study of compound **19** three vicinal endocyclic ^{1}H NMR *J* couplings were recorded which were believed to indicate a half-chair conformation in which the 5- and 6-substituents are trans diaxial and the 3-methyl group equatorial. The axial position of the 5-methoxy group was mainly accounted for by the gauche effect cooperating with an effect analogous to that causing the known axial preference in 4-methoxycyclohexanone.[49] MM2 and PM3 calculations were performed on **19**, but no full conformational search was reported.[48] A single energy minimum was depicted, but no angles relating to it were specified.[48] Our attempt (PM3) to reproduce Morimoto's optimized PM3 (and MM2) structure of **19** led to a minimum with a half-chair lactone moiety which is virtually indistinguishable from that in Morimoto's picture. There were, however, some small differences in the positions of the substituents on silicon. The dihedral angle H(5)/H(6) in our structure was −80.9°, from which a *J* coupling of 0.9 Hz was calculated. The measured value of 5.1 Hz is markedly different.[48] We also carried out ab initio calculations (HF/6-31G*) on the 6-methoxymethyl analogue **20**. In agreement

19   **20**
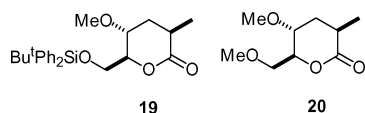
with Morimoto's conclusions regarding **19** we found the 5,6-trans-diaxially substituted half-chair of **20** to be more stable than its 5,6-trans-diequatorial counterpart (Table 6). The lactone ring of the former, most stable half-chair is very similar to that in our PM3 structure of **19**. For instance, the useful dihedral angle H(5)/H(6) is 81.1°, again showing the discrepancy between found and calculated values. Even more important was the

(45) (a) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970−2971. (b) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464−3466. (c) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Hirschfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170−181. (d) Haruyama, H.; Kuwano, H.; Kinoshita, T.; Terahara, A.; Nishigaki, T.; Tamura, C. *Chem. Pharm. Bull.* **1986**, *34*, 1459−1467. (e) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165−1170. (f) Davies, S. G.; Smyth, G. D.; Chippindale, A. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3089−3104. (g) Sato, S.; Hata, T.; Tsujita, Y.; Terahara, A.; Tamura, C. *Acta Crystallogr., Sect. C* **1984**, *40*, 195−198. (h) Adams, R. D.; Segmuller, B. E. *Acta Crystallogr., Sect. C* **1983**, *39*, 780−782. (i) Node, M.; Nishide, K.; Imazato, H.; Kurosaki, R.; Inoue, T.; Ikariya, T. *J. Chem. Soc., Chem. Commun.* **1996**, 2559−2560. (j) Ferres, H.; Hatton, I. K.; Jennings, L. J. A.; Tyrrell, A. W. R.; Williams, D. J. *Tetrahedron Lett.* **1983**, *24*, 3769−3772. (k) Weinges, K.; Schick, H.; Schilling, G.; Irngartinger, H.; Oeser, T. *Eur. J. Org. Chem.* **1998**, 189−192. (l) Fallon, G. D.; Lawrence, R. M.; Perlmutter, P. *Acta Crystallogr., Sect. C* **1996**, *52*, 2067−2069. (m) de Kok, A. J.; Romers, C. *Cryst. Struct. Commun.* **1981**, *10*, 745−750. (n) Di Maio, G.; Portalone, G.; Spagna, R.; Vecchi, E.; Zeuli, E. *Z. Kristallogr.* **1986**, *175*, 131−138. (o) Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623−5631. (p) Hackert, M. L.; Jacobson, R. A. *Acta Crystallogr., Sect. B* **1971**, *27*, 203−209. (q) Hao, J.; Aiguade, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 821−824. (r) Valente, E. J.; Fuller, J. F.; Ball, J. D. *Acta Crystallogr., Sect. B* **1998**, *54*, 162−173. (s) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardinelli, G. *Tetrahedron Lett.* **1995**, *36*, 4413−4416.

(46) (a) Walaszek, Z.; Horton, D.; Ekiel, I. *Carbohydr. Res.* **1982**, *106*, 193−201. (b) Nelson, C. R. *Carbohydr. Res.* **1987**, *163*, 275−278 and references therein.

(47) Fujimoto, Y.; Iwadate, H.; Ikekawa, N.; Kihira, K.; Hoshita, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2701−2704.

(48) (a) Morimoto, Y.; Mikami, A.; Shirahama, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1376−1378. (b) Morimoto, Y.; Shirahama, H. *Tetrahedron* **1997**, *53*, 2013−2024.

(49) Stolow, R. D.; Giants, T. W. *J. Chem. Soc., Chem. Commun.* **1971**, 528−529.

Table 6. Low-Energy Conformers of Model Compound **20**

conformer type	ΔE^a	dihedral angles (degrees)					
		τ1	τ2	τ3	τ4	τ5	τ6
$^1S_3$-$B_{3,6}$	0.00	43	−59	20	34	−56	14
$^4H_5$ (ax)^b	0.57	37	−50	54	−43	31	−28
$^5H_4$ (eq)^b	1.10	−24	45	−58	50	−31	17

*^{a} ΔE in kcal/mol, HF/6-31G*. ^{b} Position of the 5-methoxy group.*

finding that a boatlike $^1S_3$ skew form, not mentioned by Morimoto et al., was the most stable conformer of **20**. In fact, a skew form was also found in our PM3 study of **19**, but it was not possible to find an energy minimum with a reasonable structure since the PM3 program showed the previously known improper handling of short distance hydrogen−hydrogen interactions.[50] A set of Boltzmann-averaged ^3J couplings was then calculated from those three conformers of **20** presented in Table 6; a high energy axial methoxy rotamer was omitted. A good agreement with the published *J* values (in parentheses) was found: $J_{3/4ax}$ 11.2 Hz (12.8); $J_{4ax/5}$ 6.1 Hz (5.1); $J_{5/6}$ 6.2 Hz (5.1). Thus the model compound **20**, and possibly also **19**, seems to comply with the conformational dichotomy. The two literature examples[47,48] are therefore by no means any obvious exceptions to our conformational generalization.

To elucidate the alleged stabilizing effect of an axial 5-methoxy group, we performed ab initio calculations on 5-methoxy-δ-valerolactone as well as its 4-methoxy analogue. We obtained boat and half-chair conformers which are substituted either equatorially or axially, and for each of these four combinations, there were two methoxy rotamers. This makes a total of eight conformers of each compound; only the most stable methoxy rotamer in each pair is presented in Table 3. For 5-methoxy-δ-valerolactone, the energy difference between the axially and the equatorially substituted half-chairs is negligible. For 4-methoxy-δ-valerolactone, the situation is quite different. The most stable conformer of the 4-isomer lies 1.32 kcal/mol lower than that of the 5-isomer, and there is a clear preference for the 4-axially substituted chair/half-chair type (Table 3). Thus, the assumed stabilizing effect of an axial 5-methoxy group[48] is calculated to be substantial only when the axial methoxy group is in the 4-position. In the axially substituted half-chair of 4-methoxy-δ-valerolactone, the spatial relation between the methoxy group and the carbonyl group is fairly similar to that in the axially substituted chair conformation of 3-methoxycyclohexanone, and there may be stabilizing effects of similar origin. Various explanations have been put forward to account for the stabilizing effect in the cyclohexanones bearing strongly electronegative substituents in the axial position at C(3).[51]

Four monosubstituted solitary δ-lactones in the CSD (Table 5, entries 5, 10, 11, 42) have a large group in the 3-position. Three of them are typical boats in the crystal. From the ab initio analyses presented in Table 3, it is seen that the calculation on 3-*tert*-butyl-δ-valerolactone gives a better agreement with the solid-state structures of these lactones than does that on 3-methyl-δ-valerolactone. However, the calculated values of the ^{1}H NMR $J_{3/4}$ couplings provide no conformational guidance

(50) Csonka, G. I.; Ángyán, J. G. *J. Mol. Struct.* **1997**, *393*, 31−38.
(51) (a) Lu, Y.; Barth, G.; Kieslich, K.; Strong, P. D.; Duax, W. L.; Djerassi, C. *J. Org. Chem.* **1983**, *48*, 4549−4554. (b) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173−4182. (c) Bowen, J. P.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 1830−1834. (d) Nagao, Y.; Goto, M. *Heterocycles* **1995**, *41*, 883−888.
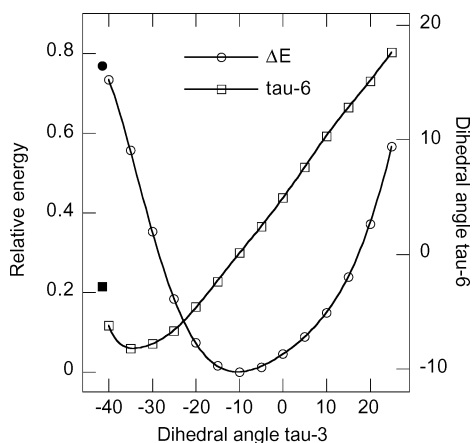
Figure 5. Calculated energies (kcal/mol) relative to the $B_{3,6}$ conformer and τ_6 of boat/skew conformations of δ-valerolactone as a function of τ_3 (degrees). Filled symbols (left) refer to transition state TS 1.

since the H(3)/H(4) dihedral angles differ only little between the boat and the half-chair types. From the conformers in Table 3, we calculated Boltzmann-weighted $J_{3/4}$ values of 11.4 Hz (trans) and 4.2 Hz (cis) for 3-methyl-δ-valerolactone and 11.7 and 4.9 Hz, respectively, for 3-*tert*-butyl-δ-valerolactone.

About as many $B_{3,6}(4exo)$ as $B_{3,6}(4endo)$ boat types (defined above) were found among the δ-lactones examined by X-ray crystallography (Table 5). Fortuitous or not, this even distribution is in agreement with the small energy differences between these conformations which were indicated in calculations on δ-valerolactone using the Jaguar program (Figure 5). Although the $B_{3,6}(4exo)$ type ($\tau_3 < 0$) is predicted to be favored over the $B_{3,6}(4endo)$ type ($\tau_3 > 0$), the energy differences are small. Within a modest energy gap of 0.4 kcal/mol above the minimum point, the dihedral angle τ_3 can vary between ca. −30° and +20°. The ideal biplanar boat, with its many eclipsed interactions, is not represented by any δ-lactone in Table 5, but compounds FUJJID10 and XIXREB (entries 2 and 3) come rather close.

Skew conformations in the solid state are represented in Table 5 by two $^1S_3$ forms (entries 26 and 27), five $^2S_6$ forms (entries 25−33 part), a few compounds which are intermediate between boat and skew, and lactones EFAKAX and EFAKEB which form a group of their own (entries 34 and 37). The fact that there are more $^2S_6$ than $^1S_3$ skews is probably not purely accidental since the ab initio calculations on δ-valerolactone (Table 3) show a ca. 0.5 kcal/mol lower energy content for the $^2S_6$ skew type. A contributing factor is certainly the more planar ester group in the latter ($\tau_6 = 7.9°$ vs 21.2° in the energy-minimized ideal structures of δ-valerolactone). The τ angles in the diastereomers EFAKAX and EFAKEB show a sequence of signs which differs from those of all other compounds in Table 5. These two lactones cannot be satisfactorily described by using the ideal conformations described above. The BWN system[36,37] characterizes them as predominantly $^6S_2$ but with a substantial contribution of the chair $^2C_5$. Such a combination of two very different conformations is not easily visualized but underscores the deviating character of these two lactones. The close resemblance between the ring structures of EFAKAX (entry 34) and the conformational transition state TS 1 of δ-valerolactone (Table 3) is indeed remarkable.

There seems to be only two solitary δ-lactones which explicitly have been assigned a skew conformation in solution.[38g,52]
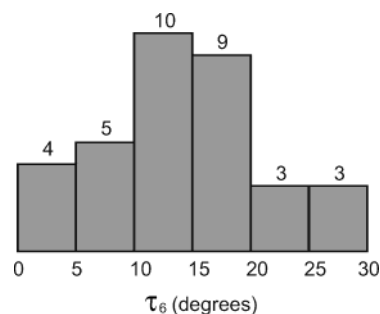
Figure 6. Distribution of dihedral angles τ_6 in the solid state of 34 δ-lactones of the chair/half-chair types $^2C_5/^4H_5$.

A $^2S_6$ conformation of *cis*-3,5-dimethoxy-δ-valerolactone was inferred from its ^1H NMR $^3J_{3/4}$ couplings of 10.6 Hz (trans) and 8.1 Hz (cis).[52] For comparison, we calculated the Boltzmann-weighted $^3J_{3/4}$ values of 3-methoxy-δ-valerolactone from its conformational data in Table 3 (only the most stable methoxy rotamer of each of the four conformers was used). The resulting values were 6.9 and 4.3 Hz, respectively, suggesting that 3-methoxy-δ-valerolactone and *cis*-3,5-dimethoxy-δ-valerolactone may be conformationally unrelated.

Chair, Envelope, and Half-Chair Types. There is a clear predominance of the half-chair type in Table 5, and this is in agreement with both the experimental and the computational results for δ-valerolactone.[24−26] δ-Lactone half-chair conformations distorted either in the envelope direction (entry 45) or in the chair direction (entries 52, 53, and 74) were found. There are four compounds in Table 5 which are E_5 envelopes (entries 36, 40−42, 59) but none of the ^4E type. The absence of the latter type is in line with the calculations on δ-valerolactone (Table 3) which showed the E_5 envelope type to be ca. 0.8 kcal/mol more stable than the ^4E type.

A common feature of the $^4H_5$ half-chairs in the crystalline state is the pronounced nonplanarity of the ester unit C(6)−O(1)−C(2)−C(3). The variation in angle τ_6 within the group of 34 lactones which belong to the $^4H_5/^2C_5$ main type group is shown in Figure 6 (only the first listed conformation of each compound is included). The geometric mean value of τ_6 is 13.9°. Three lactone rings are so strongly puckered that they are best characterized as chair forms: TIVHAH, FUJHOH10, and BUKPAY (entries 38, 46, 60). We used an H/C borderline arbitrarily set at $\tau_6 = 25°$. The BWN system[36,37] is more prone to use the chair label and classifies for instance the calculated global energy minimum half-chair of δ-valerolactone (Table 3) as being predominantly a $^2C_5$ chair. Except for the entry 62 lactone in which the ester group is practically planar, all analyzed $^4H_5$ half-chairs are puckered in the same direction; the ring approaches a chair rather than a skew form. This is seen as a difference in sign between τ_5 and τ_6. Our ab initio calculations (Tables 3 and C (Supporting Information)), which apply to vacuum, showed the ester units in the chair/half-chair conformers to be far from planar; $\tau_6 \approx 18−27°$. Lower values of τ_6 were found for the chair/half-chair conformations in the solid state (Figure 6). There is a fairly symmetrical distribution around the mean value of 13.9°. The ab initio method used here gives values of τ_6 which are roughly 8° larger. It should be remembered, however, that this angle difference corresponds to a calculated difference in energy for δ-valerolactone which

(52) Zamora, F.; Galbis, J. A. *Carbohydr. Res.* **1996**, *293*, 251−258.

is very small, <0.1 kcal/mol. The common drawing of δ-lactone $^4H_5$ half-chairs with $\tau_6 = 0°$ is not representative and is to be regarded as either a misconception or an oversimplification.

Remarkably, a variant of the previously unknown half-chair type $^6H_5$ is represented in Table 5 (entries 35−36). Compounds EFAJUQ and EFAKOL are characterized by the BWN system[36,37] as $^6H_5$ with a minor contribution of the skew $^6S_2$. This is another example of the great conformational diversity of the δ-lactone ring.

There are eight compounds in Table 5 which show the $4\beta,6\alpha$ substitution pattern. All of them have an oxygen substituent at C(4), and most of them are of biological origin. Six of the lactone rings are of the half-chair type (entry 53 and below), one is a boat (entry 3), and one is an envelope (entry 59). Irrespective of the ring conformation, all eight compounds have the 4-substituent in an axial or pseudoaxial position. Turning to the cis analogues $(4\beta,6\beta)$ we find two compounds (entries 13 and 15) which crystallize as typical boats, again with the 4-oxy substituent axial. Although crystal packing forces may have contributed, it is likely that the predominance of the axial position for the oxygen substituents reflects the stabilization effect described above.

As to the studies of δ-lactones in solution, half-chair-type conformations have been inferred from ^1H NMR spectra of, for instance, **7** and its trans isomer,[11] a corresponding glucoside,[32b] and the cis and trans isomers[32a,53a] of 4,6-dimethyl-1-oxacyclohexane-2-one. Supported by a CD analysis of the latter isomer, a "slightly flattened form" was ascribed to it.[53b] An analysis based on MM2 and ^1H NMR ^3J couplings in both cis and trans isomers of 5-methyl-4-(3-oxobutyl)-1-oxacyclohexan-2-one led to the conclusion that a half-chair predominated (63%) in the cis isomer, whereas a half-chair and two boat forms were roughly equally populated in the trans isomer.[54]

It was shown above that a half-chair conformation is favored when the δ-lactone has trans-disposed substituents in positions 3 and 6; a double substitution in either of these positions should have the same effect. A reason for this is that the boat-type conformation becomes disfavored since one of the substituents must be sterically congested in a "flagpole" position.[55a] However, a phenyl substituent seems able to avoid severe interactions in this position. Compound KESXEL (Table 5, entry 14), which is 4,4-dimethyl-6,6-diphenyl-1-oxacyclohexane-2-one, adopts a moderately twisted $B_{3,6}$(4exo) conformation ($\tau_3 = 8.4°$) with one of the phenyl groups in the flagpole position. To minimize its interaction with the H(3) hydrogen, this phenyl group turns its flat side toward H(3). This phenomenon is reminiscent of the preferred orientation of the axial phenyl group in the most stable chair conformation of 1-methyl-1-phenylcyclohexane in solution.[55b,56] There is also in Table 5 one example of a boat form having a 6-alkoxy group in the flagpole position (entry 3).

Compound SUNKOB (Table 5, entry 42) appears as an almost perfect E_5 envelope in the solid state. In the ^1H NMR

Scheme 2. Formal Route to 3,4-*trans*-Substituted δ-Lactones

e. g. **7** or **16**
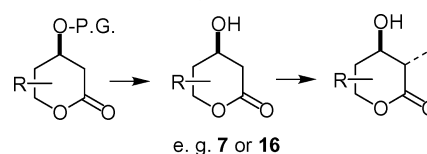
spectrum (CDCl$_3$) of the compound, the H(3) hydrogen shows an 8 Hz triplet due to coupling with the two H(4) hydrogens. This triplet is incompatible with an envelope conformation. A calculation of $J_{3/4}$ values based on the bond angles found in the ideal envelope E_5 of δ-valerolactone gave J 12.3 Hz (trans) and 3.8 Hz (cis). Unless there is an unexpected effect from any oxygen atom in the SUNKOB molecule, the 8 Hz triplet found for it should be due to an equilibrium which includes a substantial proportion of conformations in which the dihedral angle H(3)-α/H(4)-α is small. The conformations which fulfill this requirement are of the $^2S_6$ type.

Concluding Remarks

Racemic compounds were hydrogenated in this work, but equally high diastereomeric purities of the products are to be expected when using starting materials of high enantiopurity.[4b−d] Outlined above is a reaction model which accounts not only for the stereoselectivities displayed in our hydrogenations but also for five similar hydrogenations described in the literature. Beside the hydrogenation reactions leading to α,β cis-substituted δ-lactones, a route to the corresponding trans isomers can be envisaged by taking a known methylation reaction[57] into account (Scheme 2). After a hydrogenation yielding a δ-lactone unsubstituted in the α-position, for instance **10** or **18**, a deprotection[58] would afford the corresponding β-hydroxy lactones, that is **7** or **16** or their analogues. Subsequent dilithiation and α-methylation with methyl iodide introduces an α-methyl group trans to the β-hydroxy group with stereoselectivities of about 20:1 or better irrespective of the positions of other substituents in the δ-lactone ring.[57] This synthetic sequence thus increases the versatility of the hydrogenation type described in here by expanding the group of possible target stereostructures.

Many δ-lactones of biological origin are monosubstituted in positions 3 and 6. We found that an overwhelming majority of solitary δ-lactones in which these substituents are cis-disposed prefer boat-type or skew conformations in the solid state, whereas the trans isomers prefer the half-chair type. Biosynthetically formed δ-lactone rings also often bear a hydroxy group at C(4). In Table 5, there are 29 compounds containing either a free or a derivatized hydroxy group at C(4); not all of them are of natural origin. In 24 of these compounds, the oxygen substituent is axial, in a boat, envelope, or half-chair main type conformation. Although several factors may lie behind this bias, it seems likely that it also is due to the stabilizing effect which was found in the ab initio calculations on the methoxy derivatives of δ-valerolactone.

Solitary δ-lactone rings show a great conformational diversity in the crystalline state. The well-known $^3B_6$ boat and $^4H_5$ half-

(53) (a) Carroll, F. I.; Mitchell, G. N.; Blackwell, J. T.; Sobti, A.; Meck, R. *J. Org. Chem.* **1974**, *39*, 3890−3896. (b) The trans isomer was ascribed a "slightly flattened" half-chair conformation, but in our opinion the drawing shows a strongly twisted boat (possibly a skew).
(54) Ronchetti, F.; Toma, L. *Tetrahedron* **1986**, *42*, 6535−6540.
(55) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994; pp 686 and 1199. (b) *Ibid*., pp 698 and 706. (c) *Ibid*., p 688. (d) *Ibid*., p 619. (e) *Ibid*., pp 688−689 and 1210.
(56) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959−1962.

(57) (a) Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmerman, J. *Liebigs Ann. Chem.* **1986**, 1281−1308. (b) Fukui, M.; Okamoto, S.; Sano, T.; Nakata, T.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 2890−2892. (c) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 8225−8228. (d) Tholander, J.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 613−622.
(58) (a) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *17*, 809−812. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley: New York, 1999; pp 41−44.

chair types are in the majority in Table 5, but $^2C_5$ chairs, E_5 envelopes, and $^1S_3$ and $^2S_6$ skew conformations are also represented, as well as intermediary forms. According to the BWN classification method,[36,37] two recently analyzed δ-lactones (entries 35 and 36) are variants of a new type of half-chair ($^6H_5$). There are also several examples of conformational variation within a single crystal. Six compounds in Table 5 display two conformations in the solid state; compound FUJJEZ10 (entries 19−24) even shows three. The great conformational diversity should be due to small energy differences between the various δ-lactone ring conformations. Accordingly, ab initio quantum mechanical calculations on the HF/6-31G* level showed small energy differences between various conformations of δ-valerolactone itself and of some of its simple derivatives (Table 3). Moreover, the calculated low-lying conformational transition states indicate a high mobility. A highly remarkable finding is the great similarity between the δ-lactone ring structures of compound EFAKAX (Table 5, entry 34) and the conformational transition state TS 1 of δ-valerolactone (Table 3). The lowest barrier for the half-chair to half-chair interconversion of δ-valerolactone is only 2.99 kcal/mol (Figure 3). This value is lower than those of other simple six-membered ring compounds. Thus, for cyclohexanone (in kcal/mol), the following was observed: experimentally found[59] 4.0 ± 0.1, calcd 4.85 (MM4),[60] 5.17 (HF−6-31G*);[61] for cyclohexene, found 7.95 (upper limit),[62] calcd 6.56 (HF−6-31G*);[62] for cyclohexane,[55c] found 10−11 kcal/mol.

In most previous studies of the conformation of saturated δ-lactones in solution, only half-chair and/or boat main types have been considered.[15,16a,32a−c,34b,38a,40,46a,b,47,48,53a,54,63] It may be of interest in this context to note that our ab initio calculations on δ-valerolactone showed that the E_5 ideal envelope and the $^2C_5$ ideal chair, although not energy minima, are more stable than the boat type. This excluding boat/half-chair dualism has previously been questioned by Kingsbury et al. but on a relatively weak basis.[34b] We have in here presented more compelling results which lead to the conclusion that the previous view of δ-lactone conformations should be modified to include also chair, envelope, and skew forms.

Supporting Information Available: Experimental section including computational results; Tables A, B, and C. This material is available free of charge via the Internet at http://pubs.acs.org.

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(59) Anet, F. A. L.; Chmurny, G. N.; Krane, J. *J. Am. Chem. Soc.* **1973**, *95*, 4423−4424.
(60) Langley, C. H.; Lii, J.-H.; Allinger, N. L. *J. Comput. Chem.* **2001**, *22*, 1451−1475.
(61) We found this TS which probably is the lowest barrier.
(62) Anet, F. A. L.; Freedberg, D. I.; Storer, J. W.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10969−10971.
(63) (a) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1988**, *29*, 37−40. (b) Bravo, P.; Resnati, G.; Viani, F.; Arnone, A. *Tetrahedron* **1987**, *43*, 4635−4647. (c) Pasquet, G.; Boucherot, D.; Pilgrim, W. R. *Tetrahedron Lett.* **1980**, *21*, 931−934. (d) Kefurt, K.; Snatzke, G.; Snatzke, F.; Trska, P.; Jary, J. *Collect. Czech. Chem. Commun.* **1974**, *41*, 3324−3334.