Synthesis and ^{13}C NMR Spectral Data of 4α,5α- and 4β,5β-Epoxyeudesmanolides. Configuration and γ Effect of the Oxirane Ring†,[1]

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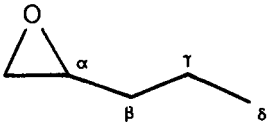
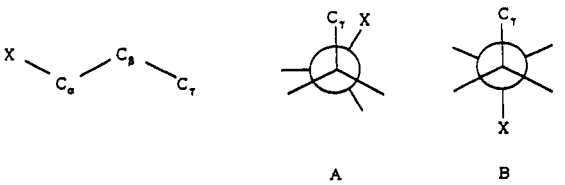
The epoxide eudesmanolides 14-21, which constitute epimeric pairs with respect to the configuration of the oxirane ring, have been synthesized in a stereochemically unambiguous way. Comparison of their ^{13}C NMR spectra with those of the parent olefins 10-13 does not, however, reveal any significant correlation between the configuration of the oxirane ring and the shifts undergone by the signals of the γ carbon atoms C-1/C-2/C-7/C-9/C-14.

Introduction

In the course of our current investigation on terpene natural products, we have been confronted with the problem of assigning a configuration to an epoxide ring condensed with a cyclic system.[3] Aside from chemical methods, NMR spectroscopy constitutes the most convenient method of solving such problems. In most instances ^1H NMR is used for the structural analysis of oxiranes,[4-9] but NMR spectroscopy of other nuclei also provides useful information. While ^{17}O NMR studies[10] on this class of compounds are still scarce, ^{13}C NMR spectroscopic research on epoxides has given rise to a considerable number of publications.[7,9,10b,11-25] The interest has focused not only on the NMR signals of the epoxide carbons themselves (α, counting from the oxygen atom), but also on the influence of the heterocyclic ring on the ^{13}C NMR signals of the spatially proximate β, γ, and δ carbon atoms.



For stereochemical assignments, the emphasis until now has been on the γ effect of the epoxide ring, i.e. the effect produced by the three-membered heterocycle on the NMR signal of the γ carbon atom. While much has been published concerning the origins and mechanisms of the γ effect,[26-34] no definitive conclusions of a general structural application have been reached. The core of the problem lies in the fact that the γ effect is not intrinsically homogeneous. As a matter of fact, conceptual differences have been established between the so-called γ-syn (γ gauche) effect and the γ-anti effect, these names being related to the dihedral angles in the fragment $X-C_\alpha-C_\beta-C_\gamma$ (see illustration). The γ-syn effect is usually shielding and is observed in conformational gauche dispositions, such as that depicted in A (dihedral angle from 0 to ca. 60°), where X may be either a carbon or a heteroatom. Interestingly, a hydrogen atom must be present on the γ carbon atom in order for an upfield (shielding) γ-syn effect to be observed, otherwise downfield (deshielding) shifts occur. Different explanations have been offered to account for this spectral behavior.[30,33] As for the γ-anti effect, which may also be both shielding and deshielding, it is associated with conformational, antiperiplanar orientations such as B (dihedral angle ca. 180°). This effect has also been the object of various theoretical approaches.[29,31-33]



As mentioned above, no general agreement has been

† Dedicated to the memory of the late Prof. F. Gaviña, deceased May 1990.

(1) Part 3 of a series on ^{13}C NMR spectroscopy of sesquiterpenes. For parts 1 and 2, see: (a) Marco, J. A.; Carda, M. *Magn. Reson. Chem.* **1987**, *25*, 628-634. (b) Marco, J. A.; Carda, M. *Magn. Reson. Chem.* **1987**, *25*, 1087-1090.

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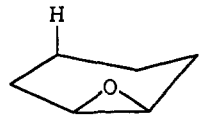
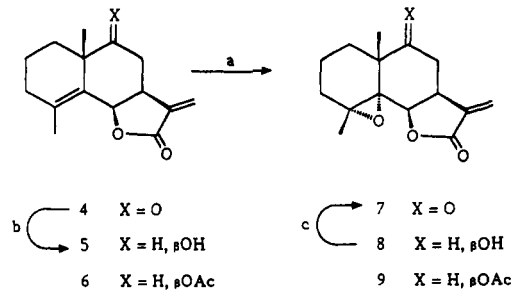
reached as yet regarding the exact nature of the factors which contribute to the γ effect; nevertheless, it has become clear that, aside from the dihedral angle X-$-C_\alpha-C_\beta-C_\gamma$, many other molecular features may play an important role in determining both the size and sign (upfield or downfield) of the observed overall effect. These features include the nature of the atom X,[29] the bond angles and lengths[30b,32] in the carbon chain which connects X and C_γ, the degree of substitution[31] within this carbon chain, linear electric field effects,[33] and n^*_X-$\sigma_{H(\gamma)}$ orbital overlap.[33] The extreme diversity of these factors advises against the indiscriminate application of γ effects to stereochemical assignments.[31]

The γ effect has also been used in the structural analysis of epoxides. It has been claimed that the shifts of the ^{13}C NMR signals produced by the introduction of the oxirane moiety into mono- or polycyclic frameworks can be used to determine configurational assignments unambiguously. One example of this is the shift of the NMR signal of the bridge carbon atom in norbornane derivatives[12,14,20,35] and structurally related compounds[7,8b,9,22] after the introduction of the epoxide oxygen. A similar effect had been previously observed in cyclopropane analogues.[36] In polycyclic compounds containing six-membered rings, like steroid[11,18b] and diterpene epoxides,[19,25] characteristic upfield shifts with respect to the parent olefin are observed in the NMR signals of those γ carbons having an axial hydrogen syn relative to the epoxide oxygen. In contrast, the signals of γ carbon atoms lacking this feature do not undergo significant shifts.



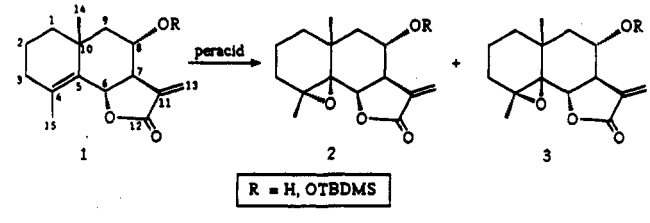
Several years ago we synthesized[37] and measured the ^{13}C NMR spectra[1] of a number of sesquiterpene lactones with eudesmane framework. Among these were the pairs of

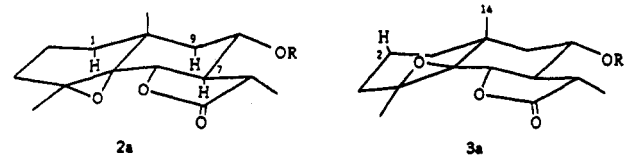
Scheme I. Synthesis of the α-Epoxides 7–9[a]



[a] (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) $NaBH_4$, MeOH, −50 °C; (c) PCC, NaOAc, CH_2Cl_2, rt.

epoxide eudesmanolides **2** and **3** (R = H, OTBDMS), which were obtained by peracid epoxidation of **1** (R = H, OTBDMS). In the absence of other stereochemical criteria, the α-epoxide configuration was assigned in each case to the major lactone **2** formed during the epoxidation reaction[37a] (preferential attack from the less hindered side of the double bond). After measuring the ^{13}C NMR spectra, it became evident that the signals of the carbon atoms C-1, C-2, C-7, C-9, and C-14 (γ with respect to the oxirane ring) did not show the expected systematic shifts in relation to the corresponding signals in the parent olefin **1**. According to the aforementioned syn axial γ hydrogen rule,[11] the epoxides **2** should have shown upfield shifts in the NMR signals of C-1, C-7, and C-9, taking lactone **1** as a reference. In the case of **3**, however, such upfield shifts should have occurred only in the signals of C-2 and perhaps C-14.





Surprisingly, appreciable upfield shifts (from ca. −1.5 to −6.5 ppm) in the signals of C-1, C-2, C-7, C-9, and C-14 were observed for *both* **2** and **3**.[1a] Moreover, as the size of these shifts did not significantly differ from the α- to the β-epoxides, they could not be accurately correlated with the configuration of the oxirane ring. The question of whether this was a single case or if these observations could be extended to other pairs of diastereoisomeric epoxides presented itself, for should the latter prove to be the case, it would clearly show that the syn axial γ hydrogen rule cannot be universally applied to configurational assignments. We therefore decided to synthesize other pairs of diastereoisomeric epoxy lactones with *unambiguously* defined stereochemistry in the oxirane ring. The four epimeric pairs of lactone epoxides **14–21** (see below) were chosen for synthesis due to the ready availability of the natural eudesmanolide **4**.[38] Subsequent examination of

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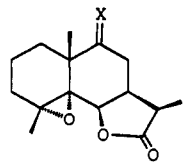
Table I. ^{13}C NMR Data of Lactones 10–21[a]

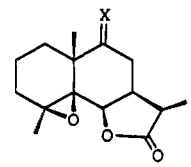
carbon	10[b]	11	12	13	14	15	16	17	18	19	20	21
1	33.95	35.50	35.09	36.06	27.33	29.62	29.39	30.05	34.11	33.30	33.33	33.21
2	17.74	17.85	17.55	18.06	14.69	14.88	14.63	15.12	16.10	16.00	16.03	16.34
3	32.57	33.12	32.98	33.34	26.35	27.63	27.38	27.92[c]	32.27	31.70	31.58	31.84
4	128.29[c]	128.24[c]	127.45[c]	128.80[c]	63.91	63.04	63.06	63.12	61.85	64.29	63.87[c]	64.10
5	140.11[c]	140.45[c]	140.85[c]	140.09[c]	66.90	65.09	64.68	65.26	65.11	64.29	64.00[c]	64.10
6	75.66	75.98	75.60	76.00	77.42	78.59	78.35	78.72	80.73	79.19	78.83	78.84
7	41.43	39.65	39.37	39.52	39.13	37.58	37.37	37.47	36.73	37.91	37.64	37.92
8	31.78	26.85	23.76	27.73	34.02	27.06	23.83	27.81[c]	32.98	26.21	23.38	27.43
9	213.40	76.96	78.38	77.29	211.31	73.69	75.65	74.12	210.37	72.39	74.09	73.10
10	48.37	38.76	37.54	39.30	47.09	37.85	36.83	38.34	47.90	38.52	37.49	39.29
11	40.71	41.02	40.87	41.02	40.21	40.19	40.10	40.21	38.09	41.02	40.83	41.16
12	178.33	179.26	178.91	179.28	177.81	178.51	178.20	178.59	176.91	178.70	177.79	177.95
13	9.71	9.41	9.30	9.40	9.42	9.15	9.09	9.18	10.13	9.19	9.39	9.36
14	26.21	18.12	19.46	18.48	20.87	13.45	14.63	13.73	18.62	16.25	17.65	16.73
15	20.00	20.05	19.95	20.04	19.99	20.03	19.92	20.14	19.95	21.42	21.54	21.88
OR			170.65	6.97			170.44	6.95			170.65	6.92
			21.08 (OAc)	5.26 ($OSiR_3$)			20.99 (OAc)	5.16 ($OSiR_3$)			21.00 (OAc)	5.23 ($OSiR_3$)

[a] At 50 MHz in $CDCl_3$ (25 °C). The δ values (parts per million downfield from Me_4Si) are referenced to the center signal of the solvent triplet at δ 77.00 ppm. [b] Data from ref 38a. [c] The signals with this superscript may be interchanged within the same column.

the ^{13}C NMR spectra of these epoxides should then allow us to assess the utility of the oxirane γ effect for configurational assignments.



14 X = O
15 X = H, βOH
16 X = H, βOAc
17 X = H, βOSiEt$_3$



18 X = O
19 X = H, βOH
20 X = H, βOAc
21 X = H, βOSiEt$_3$

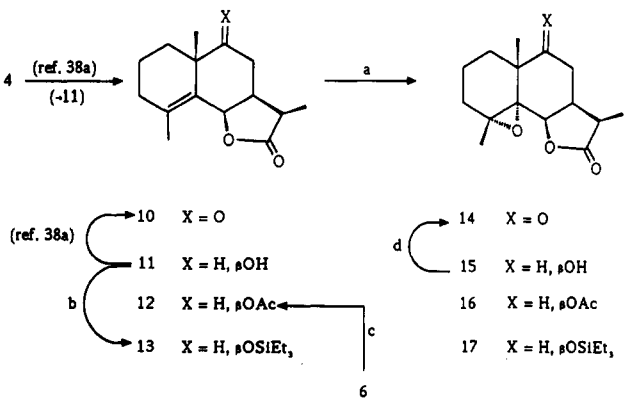
Synthesis of Epoxy Lactones

In contrast to 1,[37a] lactone 4 yielded only one epoxide 7 by peracid epoxidation, with no trace of the formation of a second isomer. The hydroxy and acetoxy lactones 5 and 6, obtained by isolation from the plant source[38] and/or by chemical transformation of 4 (Scheme I), displayed similar behavior and each gave a single epoxide 8 and 9, respectively, after peracid treatment. All three epoxides were initially thought to belong to the α series, as inspection of molecular models indicated that the α side of the double bond was much less hindered.

Since the direct preparation of the β-epoxides from the parent compounds 4–6 did not appear to be feasible,[39] it was reasoned that epoxidation from the upper side of the double bond would occur if the axially oriented 6_β oxygen atom (eudesmane numbering) could assist the required oxygen transfer from the appropriate reagent by means of chelation. This was not expected to happen in lactones 4–6 themselves, but rather in the corresponding hemiacetals or diols, derived from the lactones by reductive opening. Since any reductive treatment of compounds 4–6 would most likely affect the conjugated double bond $\Delta^{11,13}$, the synthesis of the two epimeric series of epoxides was not performed with the natural lactones 4–6, but with the respective 11,13-dihydro derivatives 10–12, obtained as depicted in Scheme II. Like their precursors 4–6, lactones 10–12 gave rise to single epoxides 14–16 by peracid treatment (Scheme II). For the same reason as mentioned above, they were assumed to be the α-epoxides.

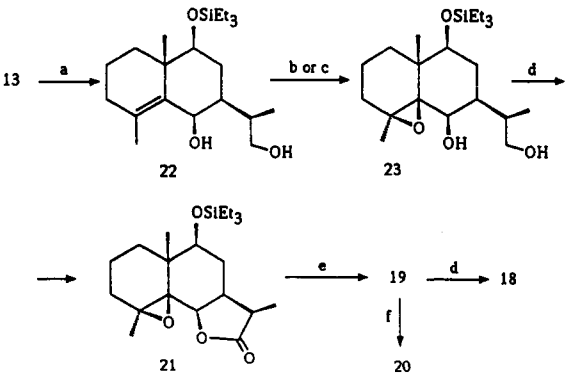
(39) Attempts to add BrOH to the tetrasubstituted double bond were unsuccessful.

Scheme II. Synthesis of the α-Epoxides 14–17[a]



[a] (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) Et_3SiCl, Et_3N, DMAP, CH_2Cl_2, rt; (c) $NaBH_4$, MeOH, −20 °C; (d) PCC, NaOAc, CH_2Cl_2, rt.

Scheme III. Synthesis of the β-Epoxides 18–21[a]



[a] (a) $LiAlH_4$, THF, rt; (b) *m*-CPBA, CH_2Cl_2, 0 °C; (c) *t*-BuO_2H, $VO(acac)_2$, benzene, rt; (d) PCC, CH_2Cl_2, rt; (e) aqueous HOAc/THF, 45 °C; (f) Ac_2O, pyridine, DMAP, rt.

Scheme III displays the synthesis of the required β-epoxides. The free hydroxyl function of lactone 11 was first protected[40,41] as the triethylsilyl derivative 13 (Scheme II). Attempts to reduce it to the corresponding hemiacetal[42]

(40) The silylation was intended to protect the 9-OH group in the latter oxidation step 23 → 21, as well as to improve the solubility of the substrate for the Sharpless reaction 22 → 23.

(41) While the more labile trimethylsilyl group did not survive the subsequent reaction conditions, the TBDMS group could not be introduced, as lactone 11 did not react with either TBDMSCl or TBDMSOTf.

Table II. Compared Chemical Shift Differences in Some ^1H and ^{13}C NMR Signals for Epoxide/Olefin Pairs[a]

	α-epoxides				β-epoxides			
atom	14–10	15–11	16–12	17–13	18–10	19–11	20–12	21–13
H-7	0.22	0.23	0.22	0.25	0.21	0.02	0.08	0.01
H-9	–	0.29	0.24	0.30	–	0.27	0.38	0.36
H-14	0.03	0.05	0.05	0.05	−0.04	−0.03	0.05	0.03
C-1	−6.62	−5.88	−5.70	−6.01	0.16	−2.20	−1.76	−2.85
C-2	−3.05	−2.97	−2.92	−2.94	−1.64	−1.85	−1.52	−1.72
C-7	−2.30	−2.07	−2.00	−2.05	−4.70	−1.74	−1.73	−1.60
C-9	−2.09	−3.27	−2.73	−3.17	−3.03	−4.57	−4.29	−4.19
C-14	−5.34	−4.67	−4.83	−4.75	−7.59	−1.87	−1.81	−1.75

[a] $\delta_{epoxide} - \delta_{olefin}$ (ppm): positive (negative) values denote downfield (upfield) shifts.

were unsuccessful, but lithium aluminum hydride reduction gave the diol **22** in fairly good yield. Sharpless reaction gave a single epoxide **23**, which was assigned the β configuration.[43] Not unexpectedly,[44] peracid epoxidation of **22** yielded the same epoxide. PCC oxidation of **23** gave lactone **21** in 49% yield. This lactone proved to be different from compound **17**, obtained by *m*-CPBA oxidation of **13** (Scheme II), thus confirming the idea that the latter reagent gives rise to α-epoxides. Deprotection with aqueous acid[45] yielded hydroxy lactone **19**, which was then transformed into **18** and **20**.

Results and Discussion

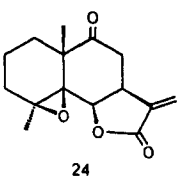
Table I summarizes the ^{13}C NMR spectral data of lactones **10–21** (those of lactones **4–9** and of compounds **22–23** are given in the Experimental Section). The ^1H signals were first assigned through their characteristic chemical shifts and coupling patterns (the signal of H-15 was unambiguously differentiated from that of H-14 because of the NOE observed between H-15 and H-6). The ^{13}C signals were then assigned with the aid of two-dimensional one-bond heteronuclear correlations. In two cases (compounds **16** and **18**) a heteronuclear correlation modulated by long-range couplings (COLOC[46]) was also performed. This enabled the assignment of the quaternary epoxide signals (C-4 and C-5) since only the latter carbon showed correlations with both H-6 and H-14. Other long-range correlations (C-9/H-14, C-10/H-14, C-4/H-15) further served to confirm the assignments of the signals from H-14 and H-15. Table II shows the chemical shift differences for the γ carbons (C-1, C-2, C-7, C-9, and C-14) between the respective epoxides (α or β) and the parent olefins, as well as the chemical shift differences for some hydrogen atoms (H-7, H-9, and H-14). It is worth noting that all of the aforementioned carbon atoms underwent appreciable upfield shifts after the introduction of the oxygen atom, regardless of the stereochemistry of the oxirane ring. This situation, which closely resembles that observed in our previous examples,[1a] differs from the literature predictions specified above. It is also significant that the epoxidation shifts of some ^1H signals do not coincide with what might be expected due to the steric compression effect of the oxirane ring. The signal of the angular methyl H-14, for instance, remains practically unaffected by the presence (and the configuration) of the epoxide. Furthermore, the signal of H-9 (α axial) undergoes even greater downfield shifts in some β-epoxides than in their epimeric counterparts (Table II).

Table III. Distances (in Angstroms) between the Epoxide Oxygen and the Indicated Hydrogen Atoms[a]

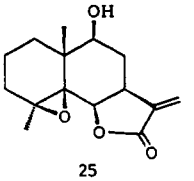
	O–$H_{1\alpha}$	O–$H_{2\beta}$	O–H_7	O–H_9
		α-Epoxides		
7	2.639	3.825	3.676	–
8	2.676	3.838	3.302	2.749
14	2.656	3.825	3.120	–
15	2.664	3.836	3.170	2.773
		β-Epoxides		
18	3.790	2.782	4.300	–
19	3.780	2.708	4.337	4.123
24[b]	3.784	2.771	4.417	–
25[b]	3.765	2.799	4.336	4.623

[a] Calculated with MACROMODEL. [b] Not synthesized (see text).

Due to the importance of the aforementioned geometric aspects (bond lengths and distances, dihedral angles, etc.) in determining the magnitude of these chemical shifts, it seemed appropriate to have an approximate knowledge of the actual shape in solution of the molecules under study. The coupling constants of the hydrogen atoms H-6 to H-9 and H-11 are easily measurable in their respective ^1H NMR spectra (Experimental Section). Their values give a partial view of the molecular conformation, at least that of the right-hand cyclohexane ring. Because there is a great deal of overlapping among the hydrogen signals of the left-hand ring, however, a conclusion about the shape of this ring could not be obtained from the spectral data. We thus resorted to a computer-assisted conformational analysis of several of the molecules in question via Still's MACROMODEL program.[47] Aside from compounds **7**, **8**, **14**, **15**, **18**, and **19**, we also carried out calculations for the as yet unsynthesized β epoxides **24** and **25**. The results are summarized in Tables III and IV, which contain the calculated values for some selected dihedral angles and interatomic distances corresponding to the lowest energy conformer obtained. The vicinal $J_{H,H}$ values given by the program[47,48] are, for the most part, in agreement with those



24



25

(42) For the use of a hemiacetal to control the steric course of a Sharpless oxidation, see: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Shuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020–7031.

(43) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63–74.

(44) Kishi, Y. *Aldrichimica Acta* **1980**, *13*, 23–30.

(45) Desilylation with tetra-*n*-butylammonium fluoride produced partial epimerization at C-11. Side reactions during desilylations with *n*-Bu_4NF due to the basicity of the reagent are well precedented: Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(46) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: Oxford, 1987; Chapter 9.

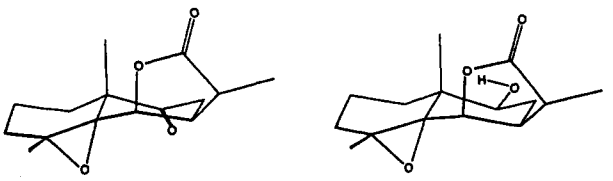
(47) MACROMODEL version 3.0, W. C. Still, Columbia University. Coupling constants were calculated in the NMR Analysis submode of the program (ref 48). Energy minimizations were performed with the BATCHMIN program (version 3.1c), using the Monte Carlo multiconformer search (MCMM).

Table IV. Dihedral Angles (in Degrees) in the Fragment $O-C_\alpha-C_\beta-C_\gamma$[a]

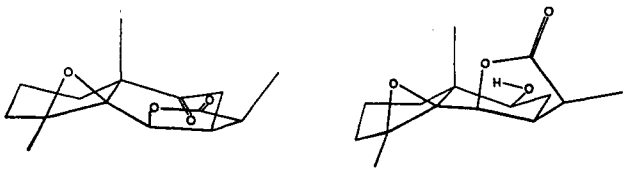
	$O-C_5-C_{10}-C_1$	$O-C_4-C_3-C_2$	$O-C_5-C_6-C_7$	$O-C_5-C_{10}-C_9$	$O-C_5-C_{10}-C_{14}$
			α-Epoxides		
7	40.7	-77.5	86.5	-80.3	162.6
8	43.9	-78.8	88.6	-76.3	163.6
14	43.7	-78.0	82.6	-77.4	165.3
15	43.2	-78.2	85.6	-76.9	162.8
			β-Epoxides		
18	-79.7	49.1	171.2	164.3	45.8
19	-74.0	45.9	-164.6	168.6	48.0
24	-78.9	48.8	177.2	165.2	46.7
25	-78.9	50.1	171.9	163.7	42.3

[a] Calculated with MACROMODEL. For the meanings of the signs, see the diagram.

measured from the spectra, a circumstance which supports the validity of the calculated conformations. The chair form is predicted for the right-hand six-membered ring of each of compounds **8**, **14**, **15**, and **19**. The left-hand ring displays the expected half-chair form. In contrast, a boat form is predicted for the right-hand ring in lactones **7**, **18**, **24**, and **25**.[49] In fact, this boat conformation had already been proposed for the parent lactone **4** and one of its 11,13-dihydro derivatives from a consideration of the coupling constant values.[38] The lowest energy conformations of the epoxide lactone pairs **14**, **15**, **18**, and **19** are represented in the following diagram.



14 **15**



18 **19**

It is worth noting that the distances between the oxirane oxygen and the axial hydrogen atoms H-1_α, H-2_β, H-7 (α), and H-9 (α) differ considerably between the α and the β series of epoxides (Table III). As expected, the oxygen atom is much closer to H-1α, H-7, and H-9 in the former (**7**, **8**, **14**, and **15**) than in the latter (**18**, **19**, **24**, and **25**). H-2_β, however, is nearer to the oxirane oxygen in the β-epoxides. This is not easily reconciled with the aforementioned fact that H-9 is slightly more deshielded in the β-epoxide **19** than in the α-epoxide **15**. Neither does it account for the upfield shifts observed in the ^{13}C signals of all γ carbon atoms. Thus the interatomic distance between the epoxide oxygen and the axial H_γ does not seem to be a decisive factor in determining the size and sign of the oxirane γ effect on the corresponding carbon. This clearly contrasts with the syn axial hydrogen rule,[11] in which this distance plays the principal role.

A second factor to be considered is the dihedral angle $O-C_\alpha-C_\beta-C_\gamma$. Table IV shows the results of the angle calculations for the same molecules mentioned in the preceding paragraphs. The meaning of the signs is explained in the adjoining diagram, but for the present discussion, only the absolute values are relevant. In the case of the α-epoxides, for instance, the epoxide oxygen is in a gauche relationship, within a certain degree of tolerance (dihedral angle 64 ± 24°), to C-1, C-2, C-7, and C-9. The same can be said of C-1, C-2, and C-14 in the β epoxides (Table IV). Should the dihedral angle be the most relevant factor, shielding of these carbon atoms in the corresponding epoxides would thus be expected. On the contrary, C-7 and C-9 are practically anti coplanar (dihedral angle 170 ± 8°) to the oxirane oxygen in the β-epoxides, as is C-14 in the α-epoxides. Either downfield or upfield epoxidation shifts should be observed in these cases, depending on whether the interconnecting atom chain consists of quaternary or less substituted carbon atoms, respectively.[31,50] This leads to the prediction of downfield shifts for C-9 in the β-epoxides and C-14 in the α-epoxides, whereas upfield shifts for C-7 should be observed in both series.

In fact, as mentioned at the beginning of the discussion, *upfield* epoxidation shifts are observed for *all* γ carbon atoms C-1, C-2, C-7, C-9, and C-14 in *both* epimeric series. This shows that the dihedral angle alone cannot explain the epoxide γ effect. It should also be pointed out that the values for the carbonyl carbon C-9 in the keto derivatives **14** and **18** show the same upfield trend, even though this carbon does not bear hydrogen atoms. It thus remains uncertain whether or not these values should be given the same relevance as the other shift values. Furthermore, the

(48) Calculations are based on an extended Karplus equation. For a discussion on the accuracy of the obtained values, see: (a) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Bull. Soc. Chim. Belg.* **1980**, *89*, 125–131. (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792. (c) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Org. Magn. Reson.* **1981**, *15*, 43–52.

(49) Besides the lowest energy conformer, the program also found for lactone **25** a second conformer, very close in energy content (ΔE ca. 0.6 kcal·mol^{-1}), which displayed a chair conformation in the right-hand six-membered ring.

(50) A possible contribution from compression in the atomic arrangement $O-C_\alpha-C_\beta-C_\gamma$ is not expected here (ref 32) since we are only comparing diastereoisomeric compounds.

shift value of C-1 in compound 18 deviates from the general trend in that it shows a small downfield effect (Table II). This may, however, reflect some specific conformational differences (see above).

These facts taken together clearly show that the syn axial hydrogen rule does not hold for all possible cases. The complex nature of the γ effect has already been examined (see Introduction), as has the great difficulty of making a rigourous dissection of this effect into its components.[29-33] It is no less difficult to determine whether one of these components, if any, plays the main role in controlling both the size and sign of the effect. In the present paper we have made an independent theoretical calculation of two of these components, the interatomic O–γH_{ax} distance and the dihedral angle O–$C_α$–$C_β$–$C_γ$, but no reliable correlation could be made between the calculated values of these two magnitudes and the observed epoxidation shifts. Inclusion of other previously mentioned structural factors (orbital overlap, electric field effects, etc.) into the calculations is beyond our computation possibilities. Of course, the number of structural cases we have presented in this study is limited. It would thus be desirable to investigate the epoxide γ effect in other structural types with various carbon frameworks and different relative dispositions of the epoxide ring. Unfortunately, few publications[11,18b,19] on ^{13}C NMR of alicyclic epoxides contain the data for both components of an epimeric pair, and none of these include detailed conformational analyses of the molecules under study. It should therefore be emphasized that, in view of the influence which even subtle structural factors may exert in determining the magnitude of effects at the molecular level, such conformational studies should always accompany any prediction of NMR spectroscopic properties.

Experimental Section

General. ^1H NMR spectra were measured at 200 MHz and ^{13}C NMR spectra at 50 MHz. Multiplicity assignments (DEPT) and two-dimensional correlation experiments were performed with standard Bruker software. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Electron impact MS were run at 70 eV. Samples for IR spectral measurements were prepared as KBr pellets. Melting points are not corrected. Column chromatography was made on silica gel, Merck (40–63 μm). Experiments which required an inert atmosphere were carried out under dry argon in a flame-dried glass system. THF and benzene were freshly distilled from sodium/benzophenone ketyl and sodium wire, respectively, and were transferred via syringe. Methylene chloride was distilled from P_2O_5 and stored over 4-Å molecular sieves. Triethylamine was distilled from CaH_2. PCC, DMAP, $NaBH_4$, $LiAlH_4$, $VO(acac)_2$, and Et_3SiCl are commercially available and were used as received. Benzene solutions of t-BuO_2H were prepared as described[43] from the commercially available 70% aqueous solution. "Usual workup" of the organic layer means washing with brine, drying on anhyd $MgSO_4$, and evaporating in vacuo with a rotary evaporator at aspirator pressure.

Keto lactone 4: obtained from the plant source as white needles; mp 163–166 °C (lit.[38b] mp 165 °C); IR, MS, and ^1H NMR (400 MHz) in ref 38b; ^{13}C NMR δ (from C-1 to C-15) 34.15, 17.77, 32.35, 128.25*, 139.95*, 75.17, 37.44, 40.86, 213.41, 47.19, 137.88, 169.54, 124.15, 24.65, 19.62 (the assignments of the starred signals are interchangeable). This spectral assignment differs from the published one[38b] in that the signals from the pairs C-4 (or C-5)/C-13 and C-14/C-15 have been reversed.

Hydroxy lactone 5 occurs in the plant source,[38b] but in low yields. Its synthesis from the more abundant keto compound 4 is thus preferable.

$NaBH_4$ Reduction of Keto Lactone 4 to 5. A solution of lactone 4 (61.5 mg, 0.25 mmol) and $NaBH_4$ (47.5 mg, 1.25 mmol) in MeOH (3 mL) was stirred at −50 °C for 45 min. The reaction mixture was then diluted with water and extracted three times with CH_2Cl_2. The combined organic layers were worked up as usual, and the residue was chromatographed on silica gel (50% ethyl acetate in hexane), affording 56.5 mg (91%) of hydroxy lactone 5 as an amorphous solid. Recrystallization from hexane yielded colorless cubes: mp 110–111 °C (lit.[38b] oil); IR, MS, and ^1H NMR (400 MHz) in ref 38b; ^{13}C NMR δ (from C-1 to C-15) 35.06, 17.79, 33.06, 127.91*, 141.40*, 74.94, 39.51, 32.44, 75.77, 38.35, 141.40, 170.62, 120.37, 18.05, 20.07 (the assignments of the starred signals are interchangeable).

Acetoxy lactone 6: obtained from the plant source as an oil (lit.[38b] oil); IR, MS, and ^1H NMR (400 MHz) in ref 38b; ^{13}C NMR δ (from C-1 to C-15) 34.73, 17.52, 32.91, 127.13*, 141.82*, 74.60, 39.15, 29.23, 77.31, 37.18, 140.98, 170.32, 120.68, 19.50, 20.00, 170.68 (acetate C=O), 21.02 (acetate Me) (the assignments of the starred signals are interchangeable).

Epoxidation of 4 to Keto α-Epoxide 7. Keto lactone 4 (49 mg, 0.2 mmol) and 85% m-CPBA (49 mg, 0.24 mmol) were dissolved in CH_2Cl_2 (3 mL) and stirred at 0 °C for 6 h. The reaction was quenched with aqueous Na_2SO_3 and diluted with CH_2Cl_2. The organic layer was then separated, washed once with 5% aqueous $NaHCO_3$, and worked up as usual. Column chromatography of the residue on silica gel (50% ethyl acetate in hexane) yielded first unreacted 4 (16 mg) and then 33 mg of 7 (63% yield, 94% based on recovered 4) as a white solid (longer reaction times led to diminished yields). Recrystallization from ethyl acetate gave colorless prisms: mp 207–208 °C, IR 1755, 1708, 1329, 1259, 1144, 999, 811 cm^{-1}; ^1H NMR δ 6.40 (d, J = 3.3 Hz, H-13′), 5.73 (d, J = 3 Hz, H-13), 4.73 (d, J = 9.6 Hz, H-6), 3.7 (ddddd, J = 9.6, 6.8, 3.3, 3, 2.7 Hz, H-7), 3.01 (dd, J = 15.5, 6.8 Hz, H-8α), 2.62 (dd, J = 15.5, 2.7 Hz, H-8β), 1.49 (s, H-15), 2.00–1.30 (m, H-1 to H-3), 1.11 (s, H-14); ^{13}C NMR δ (from C-1 to C-15) 29.48, 14.96, 27.51, 63.61, 65.57, 77.12, 39.87, 211.58, 45.74, 136.79, 169.33, 124.81, 20.27 (x 2); MS m/z (relative intensity) 262 (M^+, 27), 247 (M^+ – Me, 13), 244 (M^+ –H_2O, 22), 229 (12), 219 (62), 204 (100), 201 (75), 192 (48), 163 (72), 159 (69), 81 (81), 53 (88); HRMS m/z calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1210.

Epoxidation of 5 to α-Epoxide Lactone 8. Hydroxy lactone 5 (37 mg, 0.15 mmol) and 85% m-CPBA (45 mg, 0.22 mmol) were dissolved in CH_2Cl_2 (2 mL) and stirred at 0 °C for 7 h. The reaction was worked up as described above (4 → 7). Column chromatography of the residue on silica gel (60% ethyl acetate in hexane) yielded 30 mg (76%) of 8 as a white solid. Recrystallization from hexane–ethyl acetate gave colorless needles: mp 177–178 °C; IR 3340 (OH), 1755 (C=O), 1257, 1148, 950 cm^{-1}; ^1H NMR δ 6.16 (d, J = 1.1 Hz, H-13′), 5.63 (d, J = 1 Hz, H-13), 4.03 (d, J = 5.7 Hz, H-6), 3.66 (dd, J = 12, 4.3 Hz, H-9), 3.24 (ddddd, J = 12, 7.7, 5.7, 1.1, 1 Hz, H-7), 2.00 (ddd, J = 12, 7.7, 4.3 Hz, H-8α), 1.64 (ddd, J = 12, 12, 12 Hz, H-8β), 1.37 (s, H-15), 2.00–1.40 (m, H-1 to H-3), 1.06 (s, H-14); ^{13}C NMR δ (from C-1 to C-15) 29.34, 14.93, 27.70, 63.06, 64.95, 77.94, 37.61, 32.66, 72.74, 37.52, 139.92, 169.77, 121.54, 13.30, 20.21; MS m/z (relative intensity) 264 (M^+, 32), 249 (M^+ – Me, 8), 246 (M^+ – H_2O, 18), 221 (38), 207 (42), 203 (73), 188 (59), 153 (100), 129 (84), 81 (82), 55 (85); HRMS m/z calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1365.

Oxidation of 8 to Keto Epoxide 7. PCC (39 mg, 0.18 mmol) and anhyd NaOAc (1.5 mg, 0.018 mmol) were added to a solution of lactone 8 (16 mg, 0.06 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred at rt for 3 h, quenched with water, and diluted with CH_2Cl_2. The organic layer was then separated, washed once with 5% aqueous $NaHCO_3$, and worked up as usual. Column chromatography of the residue on silica gel (70% ethyl acetate in hexane) gave 12.5 mg (81%) of 7.

Epoxidation of 6 to 9 was performed under the same conditions as before (4 → 7), with similar molar amounts and a reaction time of 10 h. Column chromatography on silica gel (30% ethyl acetate in hexane) afforded 9 in 74% yield as a white solid. Recrystallization from hexane–diethyl ether gave colorless needles: mp 148–149 °C; IR 1764, 1728, 1650, 1236 cm^{-1}; ^1H NMR δ 6.15 (d, J = 1.2 Hz, H-13′), 5.62 (d, J = 1 Hz, H-13), 4.80 (dd, J = 12, 4.2 Hz, H-9), 4.06 (d, J = 5.8 Hz, H-6), 3.30 (ddddd, J = 12, 7.7, 5.8, 1.2, 1 Hz, H-7), 2.08 (ddd, J = 12, 7.7, 4.2 Hz, H-8α), 2.00 (s, OAc), 1.65 (ddd, J = 12, 12, 12 Hz, H-8β), 1.37 (s, H-15), 2.00–1.40 (m, H-1 to H-3), 1.14 (s, H-14); ^{13}C NMR δ (from C-1 to C-15) 29.23, 14.68, 27.45, 63.12, 64.53, 77.68, 37.32, 29.15, 74.70, 36.49, 139.55, 169.44, 121.73, 14.52, 20.07, 170.38 (acetate C=O), 20.90

(acetate Me); MS m/z (relative intensity) 306 (M^+, 20), 263 ($M^+ - COCH_3$, 50), 246 ($M^+ - HOAc$, 48), 221 (40), 203 (49), 188 (42), 161 (45), 153 (41), 129 (100), 55 (97); HRMS m/z calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1467.

$NaBH_4$ Reduction of 4 to Hydroxy Lactone 11. This reduction was performed as previously described:[38a] a solution of lactone 4 (740 mg, ca 3 mmol) and $NaBH_4$ (570 mg, ca 15 mmol) in MeOH (35 mL) was stirred at −50 °C for 30 min and then for 90 min more at −20 °C. Workup as for 4 → 5 and column chromatography on silica gel (60% ethyl acetate in hexane) yielded 706 mg (94%) of hydroxy lactone 11 as an amorphous solid. Crystallization from hexane–ethyl acetate gave colorless needles: mp 157–158 °C; IR 3460, 1740, 1185, 1160, 905 cm^{-1}; ^1H NMR δ 5.15 (d, J = 4.5 Hz, H-6), 3.34 (dd, J = 12.5, 4 Hz, H-9), 2.82 (dq, J = 7.2, 7.2 Hz, H-11), 2.43 (dddd, J = 12.5, 7.2, 6.3, 4.5 Hz, H-7), 2.10 (m, H-3), 1.78 (s, H-15), 1.75 (m, H-8$_\alpha$), 1.45 (ddd, J = 12.5, 12.5, 12.5 Hz, H-8$_\beta$), 1.90–1.40 (m, H-1 to H-2), 1.18 (d, J = 7.2 Hz, H-13), 1.00 (s, H-14); ^{13}C NMR, Table I; MS m/z (relative intensity) 250 (M^+, 55), 235 (M^+ − Me, 38), 232 ($M^+ - H_2O$, 35), 217 (20), 206 (48), 189 (29), 139 (100), 133 (40), 84 (52), 55 (47); HRMS m/z calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1571.

Epoxidation of 11 to 15. Performed under the same conditions as for the reaction 5 → 8 and with similar molar amounts and reaction time. Column chromatography of the residue on silica gel (60% ethyl acetate in hexane) afforded 15 in 92% as a white solid. Recrystallization from hexane–ethyl acetate gave colorless prisms: mp 198–199 °C; IR 3400, 1763, 1268, 1153, 1023, 972, 953, 920 cm^{-1}; ^1H NMR δ 3.99 (d, J = 4.2 Hz, H-6), 3.64 (dd, J = 12, 4 Hz, H-9), 2.74 (dq, J = 7, 7 Hz, H-11), 2.66 (dddd, J = 11, 7, 5.8, 4.2 Hz, H-7), 1.90 (m, H-3), 1.76 (ddd, J = 13.3, 5.8, 4 Hz, H-8$_\alpha$), 1.50 (ddd, J = 13.3, 12, 11 Hz, H-8$_\beta$), 1.70–1.40 (m, H-1, H-2), 1.36 (s, H-15), 1.19 (d, J = 7 Hz, H-13), 1.05 (s, H-14); ^{13}C NMR, see Table I; MS m/z (relative intensity) 266 (M^+, 82), 251 (M^+ − Me, 8), 248 ($M^+ - H_2O$, 9), 238 (6), 233 (M^+ − Me − H_2O, 9), 223 (97), 222 (41), 209 (43), 205 (71), 175 (59), 153 (77), 135 (81), 133 (83), 109 (84), 55 (100); HRMS m/z calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1526.

Oxidation of 15 to Keto Epoxide 14. Performed under the same reaction conditions as for 8 → 7. Column chromatography of the residue on silica gel (50% ethyl acetate in hexane) afforded 14 in 48% yield as a white solid. Recrystallization from ethyl acetate gave colorless prisms: mp 215–216 °C; IR 1768, 1707, 1244, 1185, 1160, 1050, 971, 924 cm^{-1}; ^1H NMR δ 4.26 (d, J = 5 Hz, H-6), 3.05 (dddd, J = 10, 7.7, 7, 5 Hz, H-7), 2.88 (dq, J = 7, 7 Hz, H-11), 2.53 (dd, J = 14.7, 10 Hz, H-8$_\beta$), 2.41 (dd, J = 14.7, 7.7 Hz, H-8$_\alpha$), 1.90 (m, H-3), 1.80–1.40 (m, H-1, H-2), 1.43 (s, H-15), 1.37 (s, H-14), 1.21 (d, J = 7 Hz, H-13); ^{13}C NMR, see Table I; MS m/z (relative intensity) 264 (M^+, 2), 249 (M^+ − Me, 3), 246 ($M^+ - H_2O$, 2), 236 (3), 231 (3), 206 (41), 203 (18), 191 (20), 133 (69), 109 (31), 55 (100); HRMS m/z calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1361.

$NaBH_4$ Reduction of 6 to Acetoxy Lactone 12. Lactone 6 (58 mg, 0.2 mmol) and $NaBH_4$ (38 mg, 1 mmol) were allowed to react in MeOH (3 mL) at −20 °C for 1 h. Workup as for 4 → 5 and column chromatography of the residue on silica gel (50% ethyl acetate in hexane) yielded 48.5 mg (83%) of 12 as a white solid. Recrystallization from hexane–diethyl ether gave colorless prisms: mp 172–173 °C; IR 1750, 1725, 1281, 1231, 1177, 1152, 1015, 980, 905, 790, 745 cm^{-1}; ^1H NMR δ 5.17 (d, J = 4.5 Hz, H-6), 4.54 (dd, J = 12, 4 Hz, H-9), 2.82 (dq, J = 7.2, 7.2 Hz, H-11), 2.49 (dddd, J = 12.5, 7.2, 6.3, 4.5 Hz, H-7), 2.10 (m, H-3), 2.02 (s, OAc), 1.76 (s, H-15), 1.75 (m, H-8$_\alpha$), 1.49 (ddd, J = 12.5, 12.5, 12.5 Hz, H-8$_\beta$), 1.90–1.40 (m, H-1 to H-2), 1.14 (d, J = 7.2 Hz, H-13), 1.06 (s, H-14); ^{13}C NMR, see Table I; MS m/z (relative intensity) 292 (M^+, 33), 277 (M^+ − Me, 19), 250 (15), 232 (36), 217 (34), 189 (23), 137 (51), 87 (100), 55 (90); HRMS m/z calcd for $C_{17}H_{24}O_4$ 292.1675, found 292.1679.

Epoxidation of 12 to 16 was performed under the same conditions as the reaction 5 → 8, with similar molar amounts and a reaction time of 10 h. Column chromatography of the residue on silica gel (30% ethyl acetate in hexane) afforded 16 in 89% yield as a white solid. Recrystallization from hexane–diethyl ether gave colorless prisms: mp 190–191 °C; IR 1777, 1721, 1235, 1152, 1022, 980, 954, 929, 797 cm^{-1}; ^1H NMR δ 4.78 (dd, J = 12, 4 Hz, H-9), 3.99 (d, J = 4 Hz, H-6), 2.75 (dq, J = 7, 7 Hz, H-11), 2.71 (dddd, J = 11, 7, 5.8, 4 Hz, H-7), 1.99 (s, OAc), 1.90 (m, H-3), 1.82 (ddd, J = 13.3, 5.8, 4 Hz, H-8$_\alpha$), 1.49 (ddd, J = 13.3, 12, 11 Hz, H-8$_\beta$), 1.70–1.40 (m, H-1, H-2), 1.35 (s, H-15), 1.14 (d, J = 7 Hz, H-13), 1.11 (s, H-14); ^{13}C NMR, see Table I; MS m/z (relative intensity) 308 (M^+, 62), 265 ($M^+ - COCH_3$, 100), 248 (33), 233 (21), 223 (81), 205 (82), 175 (55), 131 (80), 119 (78), 55 (78); HRMS m/z calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1627.

Silylation of Hydroxy Lactone 11 to 13. Triethylsilyl chloride (0.6 mL, 3.6 mmol) was added to a solution of lactone 11 (626 mg, 2.5 mmol), triethylamine (0.7 mL, 5 mmol), and DMAP (31 mg, 0.25 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred under an inert atmosphere at rt for 8 h and then quenched with water and diluted with CH_2Cl_2. The supernatant aqueous layer was extracted twice more with CH_2Cl_2. The combined organic layers were then worked up as usual. Column chromatography of the residue on silica gel (20% ethyl acetate in hexane) yielded 903 mg (99%) of 13 as a colorless oil, which solidified on standing. Recrystallization from hexane gave colorless needles: mp 96–97 °C; IR 1774, 1250, 1185, 1160, 1103, 1080, 861, 834, 772 cm^{-1}; ^1H NMR δ 5.13 (d, J = 4.4 Hz, H-6), 3.33 (dd, J = 8.5, 6.8 Hz, H-9), 2.81 (dq, J = 7, 7 Hz, H-11), 2.38 (dddd, J = 12, 7, 6.5, 4.4 Hz, H-7), 2.10 (m, H-3), 1.77 (s, H-15), 1.90–1.40 (m, H-1, H-2, H-8), 1.19 (d, J = 7 Hz, H-13), 0.99 (s, H-14), 0.95 (t, J = 7.5 Hz, Si-C-CH_3), 0.57 (q, J = 7.5 Hz, Si-CH_2); ^{13}C NMR, see Table I. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.17; H, 9.95. Found: C, 69.26; H, 10.09.

Epoxidation of 13 to Silylated Epoxide 17. The reaction conditions were as for the reaction 5 → 8, with similar molar amounts and a reaction time of 4 h. Column chromatography of the residue on silica gel (30% ethyl acetate in hexane) yielded 17 in 89% as a colorless oil. Recrystallization from hexane gave colorless prisms: mp 75–76 °C; IR 1787, 1264, 1235, 1156, 1107, 1007, 981, 929, 837, 741 cm^{-1}; ^1H NMR δ 3.98 (d, J = 4.4 Hz, H-6), 3.64 (dd, J = 11, 4.6 Hz, H-9), 2.74 (dq, J = 7, 7 Hz, H-11), 2.63 (dddd, J = 11, 7, 6, 4.4 Hz, H-7), 1.90 (m, H-3), 1.70–1.40 (m, H-1, H-2, H-8), 1.37 (s, H-15), 1.20 (d, J = 7 Hz, H-13), 1.03 (s, H-14), 0.94 (t, J = 7.5, $SiCCH_3$), 0.58 (q, J = 7.5, $SiCH_2$); ^{13}C NMR, see Table I. Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 66.39; H, 9.71.

$LiAlH_4$ Reduction of 13 to Diol 22. Lactone 13 (583 mg, 1.6 mmol), dissolved in dry THF (15 mL), was added via syringe under an inert atmosphere to a suspension of $LiAlH_4$ (106 mg, 2.8 mmol) in dry THF (8 mL). The reaction mixture was stirred for 4 h at rt and then quenched by careful addition of water (250 μL) and 10% aqueous NaOH (170 μL). Stirring was continued under the inert atmosphere for 30 min more. The crude reaction mixture was then diluted with THF and filtered through a pad of anhyd Na_2SO_4. The solid cake was washed twice with additional THF, and the combined organic layers were evaporated in vacuo. Column chromatography of the residue on silica gel (50% ethyl acetate in hexane) yielded 496 mg (84%) of 22 as a white solid. Recrystallization from hexane–diethyl ether gave colorless needles: mp 145–146 °C; IR 3400, 1450, 1370, 1280, 1232, 1100, 1065, 1016, 949, 863, 740, 724 cm^{-1}; ^1H NMR δ 3.60–3.20 (m, H-6, H-9, H-12), 1.72 (s, H-15), 2.00–1.30 (m, H-1, H-2, H-3, H-7, H-8, H-11), 1.16 (s, H-14), 0.95 (m, H-13, CH_3CSi), 0.57 (q, J = 7.5 Hz, CH_2Si); ^{13}C NMR δ (from C-1 to C-15) 37.51, 18.40, 33.43, 132.65, 135.88, 69.54, 44.67, 26.13, 80.45, 40.07, 38.44, 64.49, 17.74, 19.71, 20.66, 7.00 (CCSi), 5.24 (CCSi). Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94. Found: C, 68.56; H, 11.03.

Epoxidation of 22 to Diol Epoxide 23. (A) By Sharpless procedure: At rt t-BuO_2H (0.53 mL of a 3.8 M solution in benzene, 2 mmol) was added by drops to a solution of diol 22 (442 mg, 1.2 mmol) in dry benzene (25 mL) containing $VO(acac)_2$ (27 mg, 0.1 mmol). The resulting dark red solution was stirred at rt for 90 min, diluted with CH_2Cl_2, and quenched with aqueous Na_2SO_3. After the layers were decanted in a separatory funnel, the aqueous layer was washed once more with CH_2Cl_2. The combined organic layers were then worked up as usual. Column chromatography of the residue on silica gel (50% ethyl acetate in hexane) yielded 443 mg (96%) of 23 as a white solid. Recrystallization from hexane gave colorless prisms: mp 76–77 °C; IR 3435, 3350, 1445, 1366, 1269, 1168, 1098, 1073, 1032, 969, 906, 745, 719 cm^{-1}; ^1H NMR δ 3.70–3.30 (m, H-6, H-9, H-12), 2.00–1.30 (m, H-1, H-2, H-3, H-7, H-8, H-11), 1.35 (s, H-15), 1.13 (s, H-14), 0.95 (m, H-13, CH_3CSi), 0.57 (q, J = 7.5 Hz, CH_2Si); ^{13}C NMR δ (from C-1 to C-15) 34.17, 16.70, 32.37, 66.63, 69.07, 71.77, 26.07, 75.88, 39.92, 37.98, 64.57, 17.24, 18.10, 21.63, 6.94 (CCSi), 5.18 (CCSi). Anal. Calcd for

$C_{21}H_{40}O_4Si$: C, 65.57; H, 10.48. Found: C, 65.73; H, 10.64. (B) By reaction with *m*-CPBA: Reaction conditions as in the peracid epoxidations described above. Reaction time: 3 h. Yield: 92%.

Oxidation of 23 to Silyl β-Epoxide Lactone 21. PCC (475 mg, 2.2 mmol) was added to a solution of lactone **23** (423 mg, 1.1 mmol) in dry CH_2Cl_2 (30 mL). The reaction mixture was stirred at rt for 30 min. More PCC (475 mg) was then added, and stirring was continued for 3 h. Quenching and usual workup (8 → 7), followed by column chromatography of the residue on silica gel (30% ethyl acetate in hexane), yielded 205 mg (49%) of **21** as a white solid. Recrystallization from hexane–diethyl ether gave colorless needles: mp 119–120 °C; IR 1767, 1279, 1231, 1153, 1105, 1086, 956, 920, 757 cm^{-1}; ^1H NMR δ 4.19 (d, J = 4 Hz, H-6), 3.70 (dd, J = 11.2, 4.3 Hz, H-9), 2.77 (dq, J = 7, 7 Hz, H-11), 2.39 (dddd, J = 10.5, 7, 6.5, 4 Hz, H-7), 1.90 (m, H-3), 1.70–1.40 (m, H-1, H-2, H-8), 1.40 (s, H-15), 1.19 (d, J = 7 Hz, H-13), 1.02 (s, H-14), 0.94 (t, J = 7.5, $SiCCH_3$), 0.58 (q, J = 7.5, $SiCH_2$); ^{13}C NMR, see Table I. Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 66.39; H, 9.69.

Desilylation of 21 to Hydroxy β-Epoxide Lactone 19. A solution of silylated lactone **21** (190 mg, 0.5 mmol) in HOAc/THF/H_2O, 6:1:3 (20 mL), was stirred at 45 °C for 3 h. The reaction mixture was then diluted with water and extracted twice with CH_2Cl_2. The combined organic layers were then washed once with 5% aqueous NaOH and worked up as usual. Column chromatography of the residue on silica gel (75% ethyl acetate in hexane) yielded 94 mg (71%) of **19** as a white solid. Recrystallization from ethyl acetate gave colorless platelets: mp 226–227 °C; IR 3300, 1766, 1188, 1157, 1021, 953, 906 cm^{-1}; ^1H NMR δ 4.18 (d, J = 4.2 Hz, H-6), 3.62 (dd, J = 11.5, 3.8 Hz, H-9), 2.75 (dq, J = 7, 7 Hz, H-11), 2.45 (dddd, J = 11, 7, 6.5, 4.2 Hz, H-7), 1.90 (m, H-3), 1.70–1.40 (m, H-1, H-2), 1.70 (ddd, J = 13.5, 6.5, 3.8 Hz, H-8$_\alpha$), 1.42 (ddd, J = 13.5, 11.5, 11 Hz, H-8$_\beta$), 1.35 (s, H-15), 1.13 (d, J = 7 Hz, H-13), 0.99 (s, H-14); ^{13}C NMR, see Table I; MS m/z (relative intensity) 266 (M^+, 40), 251 (M^+ – Me, 8), 248 (M^+ – H_2O, 10), 238 (9), 233 (7), 223 (98), 209 (53), 205 (80), 193 (45), 175 (66), 153 (82), 135 (92), 131 (100), 123 (83), 109 (96), 95 (95), 55 (99); HRMS m/z calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1519.

Oxidation of 19 to Keto β-Epoxide 18. Reaction conditions were virtually as described above for 8 → 7. Reaction time: 5 h. Column chromatography on silica gel (10% MeOH in diethyl ether) afforded **18** in 70% as a white solid. Recrystallization from hexane–diethyl ether gave colorless platelets: mp 175–176 °C; IR 1771, 1704, 1250, 1214, 1168, 1115, 1096, 1010, 965, 726 cm^{-1}; ^1H NMR δ 4.49 (d, J = 5.7 Hz, H-6), 3.04 (br ddd, J = 9.5, 7, 5.7 Hz, H-7), 2.86 (dq, J = 7, 7 Hz, H-11), 2.75 (dd, J = 13.6, 9.5 Hz, H-8$_\alpha$), 2.33 (br d, J = 13.6 Hz, H-8$_\beta$), 2.05 (m, H-3), 1.80–1.40 (m, H-1, H-2), 1.47 (s, H-15), 1.30 (s, H-14), 1.23 (d, J = 7 Hz, H-13); ^{13}C NMR, see Table I; MS m/z (relative intensity) 264 (M^+, 6), 249 (M^+ – Me, 6), 246 (M^+ – H_2O, 5), 236 (8), 231 (3), 221 (28), 206 (91), 203 (68), 191 (70), 147 (55), 133 (100), 109 (51), 55 (92); HRMS m/z calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1361.

Acetylation of 19 to 20 was performed under the standard conditions (Ac_2O–pyridine–DMAP, rt, 12 h). Quenching with water and usual workup yielded an oily residue which was chromatographed on silica gel (50% ethyl acetate in hexane). This gave **20** in 78% yield as a white solid. Recrystallization from hexane–diethyl ether gave colorless cubes: mp 202–203 °C; IR 1753, 1718, 1278, 1238, 1158, 1147, 1096, 1021, 975, 950, 914, 742 cm^{-1}; ^1H NMR δ 4.92 (dd, J = 11, 3.8 Hz, H-9), 4.26 (d, J = 4.3 Hz, H-6), 2.81 (dq, J = 7, 7 Hz, H-11), 2.57 (dddd, J = 11, 7, 6.5, 4.3 Hz, H-7), 2.05 (s, OAc), 1.90 (m, H-3), 1.80–1.40 (m, H-1, H-2, H-8$_\alpha$), 1.51 (ddd, J = 13.4, 11.2, 11 Hz, H-8$_\beta$), 1.40 (s, H-15), 1.16 (d, J = 7 Hz, H-13), 1.11 (s, H-14); ^{13}C NMR, see Table I; MS m/z (relative intensity) 308 (M^+, 14), 265 (M^+ – $COCH_3$, 100), 248 (16), 233 (9), 223 (51), 209 (79), 205 (62), 175 (35), 131 (59), 119 (54), 55 (38); HRMS m/z calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1624.

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Supplementary Material Available: ^1H NMR spectra of compounds **7**, **8**, **9**, **11**, **12**, **14**, **15**, **16**, **18**, **19**, and **20** (22 pages). Ordering information is given on any current masthead page.

Synthesis and Testing of Sugar Phosphofluoridates and Cyclic Phosphates as Inhibitors of Phosphoglucomutase

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Three aldose phosphofluoridates, D-glucose 6-phosphofluoridate, α-D-mannopyranosyl phosphofluoridate, and 2-deoxy-2-fluoro-α-D-glucopyranosyl phosphofluoridate, have been synthesized from the parent phosphate and 2,4-dinitrofluorobenzene, and the mechanism of fluorination has been investigated. Another modified aldose phosphate, α-D-glucopyranosyl 4,6-cyclic phosphate [phosphate] has also been synthesized as an analogue of 6-phospho-α-D-glucopyranosyl phosphate. These compounds were tested as possible mechanism-based inactivators of rabbit muscle phosphoglucomutase, but no time-dependent inactivation was observed. They were, however, found to be reversible inhibitors of phosphoglucomutase, and comparison of their dissociation constants with those of the parent phosphates revealed that the removal of a single negative charge weakens ground-state binding by approximately 11 kJ/mol. Further, the absence of any detectable phosphorylation of these analogues reveals that this second charge is even more important for transition-state interactions, contributing at least 40 kJ/mol to transition-state stability. This suggests that the parent substrates bind to the enzyme and react in their dianionic forms, and it provides a measure of the value of charge–charge interactions at the active site of this key metabolic enzyme.

A complete understanding of the specificities and mechanisms of enzymes that utilize substrates or cofactors containing ionizable groups requires a knowledge of the charge state of the enzyme-bound species. In the cases of enzymes utilizing phosphate monoesters for example, both monoanions and dianions are present in solution at physiological pH and in principle either could be the active species. Studies on the reaction's pH dependence[1] and, in the case of phosphate-containing ligands, the ^{31}P NMR

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