Torsional, Rotor, and Electronic Effects in 4-*tert*-Butylmethylenecyclohexane Epoxidations and Osmylations

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Abstract: The axial epoxidation preference for 2-substituted 4-*tert*-butylmethylenecyclohexanes is attributed to a combination of small effects, including existing bond torsion and rotor effects. Contributions from developing bond torsion are smaller and may be negligible. Cieplak ($\sigma-\sigma^*$) effects are too small to identify in most of the epoxidations, but a marginal effect could be present according to comparisons of isosteric systems **11a** and **15a** or **19a** and **19b**. Dimethyldioxirane epoxidations and osmylations are more sensitive to steric factors, resulting in a trend for equatorial attack.

Introduction

Allylic heteroatom directing effects are useful in synthetic strategies that rely upon acyclic stereocontrol. The largest effects usually involve covalent interactions between substrate heteroatoms and the reagent,[1] but other factors may also control alkene addition reactions.[2−6] Earlier work from our laboratory found no dominant stereoelectronic effects in epoxidations or osmylations of 4-substituted 2-pentenes,[5b] but conformational issues in these flexible substrates could have complicated the interpretation. Evidence in more rigid analogs was desired.

The goal of the present work was to probe stereoelectronic, steric, and torsional factors in the epoxidation and osmylation of 4-*tert*-butylmethylenecyclohexane derivatives. This system was chosen for several reasons. First, the bonds at C_2 and C_6 have a clear stereoelectronic bias. Thus, the axial bonds at C_2 and C_6 are antiperiplanar to developing axial bonds at C_1 while the ring C_2-C_3 and C_5-C_6 bonds are antiperiplanar to developing equatorial bonds. Second, the system contains reasonably well-understood steric bias and provides a realistic analogy for more flexible acyclic systems. Third, the methylenecyclohexane family has been instrumental over the history of attempts to understand stereoelectronic and torsional factors, and the literature contains many examples of epoxidation experiments,[3,7−9] as well as some osmylations.[3] Starting from this information base, we hoped to clarify the origins of the axial epoxidation preference of 4-*tert*-butylmethylenecyclohexane that has stimulated controversy since the report by Carlson and Behn in 1967.[7,10]

Background

Selected epoxidation results from prior studies are summarized in Table 1. Cieplak, Tait, and Johnson showed that the increase in percent axial epoxidation from entry 15 to entry 18 correlates with a decrease in the σ-electron donor ability of the substituent at C_3.[3] Because the C_2-C_3 ring bond is antiperiplanar to the developing σ^* orbitals for equatorial C−O bond formation at C_1, electron-withdrawing substituents at C_3 should retard the rate of equatorial attack (Cieplak effect). This would favor increased axial selectivity from entry 15 to entry 18. Most of the other results in Table 1 were reported earlier by Sevin and Cense along with an explanation based on torsional effects.[8]

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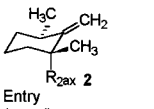
Table 1. Epoxidations with $XC_6H_4CO_3H$ (CH_2Cl_2)[a]

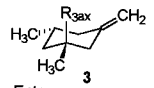
1

Entry (cmpd)	R_{2eq}	R_4	% O Axial	RATE (L mol^{-1} sec^{-1}) ax+eq	ax	eq	X	Ref.
1 (a)	H	H	---	0.190			*p*-NO_2	8
2 (b)	H	*t*-Bu	70	0.222	0.156	0.067	*p*-NO_2	8
3 (b)	H	*t*-Bu	69				*m*-Cl[a]	7
4 (c)	H	CH_3	65				*p*-NO_2	8
5 (d)	CH_3	H	54	0.199	0.107	0.092	*p*-NO_2	8
6 (e)	*i*-Pr	CH_3	43	0.118	0.051	0.067	*p*-NO_2	8
7 (f)	*i*-Pr	H	49	0.121	0.059	0.062	*p*-NO_2	8
8 (g)	CH_3	CH_3	54				*p*-NO_2	8
9 (h)	CH_3	*t*-Bu	58	0.219	0.127	0.092	*p*-NO_2	8



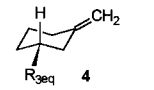
2

Entry (cmpd)	R_{2ax}	% O Axial	RATE (L mol^{-1} sec^{-1}) ax+eq	ax	eq	X	Ref.
10 (a)	H	45	0.209	0.094	0.115	*p*-NO_2	8
11 (b)	CH_3	57	0.185	0.105	0.080	*p*-NO_2	8



3

Entry (cmpd)	R_{3ax}	% O Axial	RATE (L mol^{-1} sec^{-1}) ax+eq	ax	eq	X	Ref.
12 (a)	H	64	0.190	0.122	0.068	*p*-NO_2	8
13 (b)	CH_3	17	0.092	0.017	0.075	*p*-NO_2	8



4

Entry (cmpd)	R_{3eq}	% O Axial	X	Ref.
14 (a)	$SnMe_3$	50	*m*-Cl[a]	9f
15 (b)	$SiMe_3$	52	*m*-Cl[a]	3
16 (c)	*t*-Bu	60	*p*-NO_2	8
17 (d)	C_6H_5	70	*m*-Cl[a]	3
18 (e)	*p*-$CF_3C_6H_5$	75	*m*-Cl[a]	3

[a] Reaction at 0 °C.

Torsional strain is related to the barrier for rotation around single bonds.[11−13] In the Pitzer interpretation,[11] torsional strain in ethane is attributed to destabilization between filled orbitals in the eclipsed conformation. This view has been widely accepted by organic chemists, resulting in the generalization that all eclipsing interactions along sp^3-sp^3 bonds are destabilizing. However, increasingly sophisticated theoretical treatments are reaching a rather different consensus. The filled orbital interactions in the eclipsed rotamer of ethane cannot cause a barrier to rotation *because they have been shown to be stabilizing in nature*.[12,13d] One recent interpretation associates the ethane barrier with C−C bond lengthening in the eclipsed rotamer and a corresponding decrease in attractive interactions.[13d] An alternative approach (Weinhold *et al.*)[12] uses natural bond orbital (NBO) analysis of high-level calculations and attributes the barrier to stabilizing hyperconjugative σ-CH, σ^*-CH interactions in the staggered rotamer.[12] Similarly, the torsional barrier in propane is largely hyperconjugative, but in butane a composite of hyperconjugative and filled orbital (steric) effects is involved. Torsional barriers involving the sp^2-sp^3 bond of propene are smaller than in ethane, and an eclipsed geometry is preferred.[13]

Both existing and developing bonds may influence torsional energy as rehybridization occurs from the ground state to the transition state. Changes in *existing bond torsion* were proposed for diimide reduction,[14a] for the *endo* vs *exo* deprotonation of norbornanone,[14b] and for 1,6-dimethylcyclohexene epoxidation.[14c] The often-cited torsional argument of Felkin *et al.* (1968) has a different emphasis, and specifically invokes destabilizing interactions between *partial* (developing) bonds and adjacent C−H bonds.[15] Changes in other torsional interactions were not explicitly treated, but staggered transition state geometries were emphasized. In the case of ketone addition reactions, torsion between the developing nucleophile- - -C_1 bond and the axial C−H bonds at cyclohexanone C_2 and C_6 was given as the reason why compact reagents prefer to attack from the axial direction. The developing axial bond was drawn assuming a 90° bond angle with respect to the carbonyl plane, and a dihedral angle of ca. 10° was shown between the developing nucleophile- - -C_1 bond and the adjacent axial C_2-H and C_6-H bonds. This would be close to an eclipsed geometry between the developing bond and the existing axial C_2-H and C_6-H bonds. Klein and Lichtenberger later suggested that release of torsional strain between equatorial C_2-H and C_6-H bonds and the adjacent C=O bond may also favor axial attack.[16] Felkin *et al.* commented on methylenecyclohexane epoxidations in a brief footnote,[15b] but did not indicate whether the same torsional effects were intended for epoxidations as for ketone additions.

Sevin and Cense discussed methylenecyclohexane epoxidations in greater detail.[8] They noted that an axial C_2 methyl group should affect epoxidation stereochemistry if developing bond torsion between axial C_2-H and C_1- - -O is the reason for axial selectivity in the parent compound as proposed by Felkin *et al.*[15b] Only a small difference was found (Table 1; compare entries 10 and 11) and the authors concluded that torsional interactions between the developing equatorial C_1- - -O bond and the axial C_2 and C_6 hydrogens are unimportant. Advanced bonding was invoked between peracid oxygen and the primary (methylene) carbon compared to the tertiary (C_1) carbon (asynchronous transition state).[17] Decreased axial selectivity was expected in a more nearly synchronous transition state due to increased reagent interactions with axial C_3 and C_5 hydrogens. Supporting evidence was found in the epoxidation of 4-*tert*-butyl-1-isopropylidenecyclohexane (57% axial epoxide vs 70% axial in the methylene analog).[8]

Houk *et al.* have developed a general treatment of addition reactions at sp^2-hybridized carbon that recognizes torsional, stereoelectronic, and electrostatic factors.[2] Nucleophilic addition reactions of ketones were analyzed using *ab initio* methods and MM2 models were developed where the torsional contributions from developing bonds as well as from existing bonds depend on the choice of MM2 parameters. In a related study of epoxidations, Martinelli, Houk *et al.* correlated transition state preferences using a developing bond torsional argument.[4a] They also referred to the *ab initio* transition state geometry calculated

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by Bach *et al.*[4b] for ethylene + performic acid, but neither group optimized the geometry for more complicated substrates.

Several groups have reported experiments designed to separate steric, torsional, and stereoelectronic variables using substrates with minimal bias close to the reacting sp^2 carbon.[18] Trends in the epoxidation of the unbiased 4-substituted methyleneadamantanes are consistent with the Cieplak effect.[18a] Similarly, changes in the equatorial 3-substituent in methylenecyclohexanes should not affect steric or torsional variables. Selectivity trends (Table 1; entries 14−18) should therefore reflect the electronic (not steric or torsional) properties of the substituents.[3]

Allylic oxygen-containing systems of interest to synthetic chemists are inherently biased, but analogs designed within the methylenecyclohexane skeleton allow bias to be tested in a well-studied environment.[19,20] Methylcyclohexane inversion occurs via a half-chair TS with nearly coplanar C_6, C_1, C_2, and C_3 (inversion barriers, parent:[20a] $\Delta G^* = 8.4$ kcal/mol; 2-methyl,[19a] $\Delta G^* = 9.0$ kcal/mol; 2-methoxy,[19a] $\Delta G^* = 9.0$ kcal/mol; 2,2-dimethyl,[20b] $\Delta G^* = 8.1$ kcal/mol). Thus, ground state torsional contributions from the existing bonds should vary by less than 1 kcal/mol as the 2-H, 2-methyl, and 2-methoxy substituents are interchanged. However, torsional contributions in the transition state might depend on the extent of rehybridization. This is because the torsional energy minimum for an alkene usually has an eclipsed allylic bond, while the minimum for sp^3-hybridized bonds is likely to be a staggered geometry.[13] Replacement of C_2−H or C_2−alkyl groups by electron-withdrawing substituents could lead to relatively late transition states that would be increasingly destabilized by eclipsed bonds compared to early transition states.

To address the role of torsional variables, a study of the epoxidations and osmylations of 4-*tert*-butylmethylenecyclohexane and the 2-methyl-, 2-methoxy-, and 2-methyl-2-methoxy derivatives was initiated. Rigid analogs that constrain the C_2 oxygen and carbon substituents to a spiro-fused tetrahydrofuran ring were also studied to evaluate rotor effects. Finally, the 2-methyl-2-ethyl (hydrocarbon) analog was investigated. This alkene is isosteric with the 2-methyl-2-methoxy derivatives but it contains no allylic oxygen and has minimal electronic bias.

Preparation of Starting Materials

Alkylation of 4-*tert*-butylcyclohexanone[21] produced a mixture of the known 2-methyl-4-*tert*-butylcyclohexanones[22] **5a** and **5b** in a ratio of ca. 1:3 equatorial−axial methyl after hydrolysis.[21] Conversion of **5a** into the methylene derivative **6a** proceeded smoothly under conventional Wittig conditions, but the axial methyl isomer **6b** was partly isomerized using this procedure. Lombardo olefination proved more reliable and gave **6b** in 68% yield.

The 2-methyl-2-methoxy-4-*tert*-butylcyclohexanones were obtained from the mixture of **5a** + **5b** via enol silane **7a**.[23] Attempts to prepare **7a** using the method of Krafft and Holton[24a] gave a 3:1 mixture of **7a** and **8a**. However, the procedure of Miller and McKean (Me_3SiI; $[Me_3Si]_2NH$)[24b] worked well and afforded **7a** with less than 5% **8a** (NMR assay). Oxidation of **7a** with dimethyldioxirane (DMD)[25,26] then gave the separable acyloins **9a** and **9b**, 1.0:1.5 ratio (85% yield), and Wittig methylenation afforded **10a** and **10b** (>90% yield). The stereochemistry was established by NOE studies. A 10% NOE enhancement was observed between the equatorial methyl and adjacent methylene protons in **10a**, but no analogous effect was seen in the axial methyl isomer **10b**. Both isomers **10a** and **10b** were then methylated (NaH, MeI) to afford the methyl ethers **11a** and **11b**. A similar methylation procedure converted the known 2-hydroxy-4-*tert*-butylmethylenecyclohexanes **12a** and **12b**[9e] into the methyl ethers **13a** and **13b**.

An analogous sequence was used to prepare the isomeric 2-ethyl-2-methyl-4-*tert*-butylmethylenecyclohexanes. Thus, treatment of **7a** with methyllithium at 0 °C followed by ethyl iodide afforded a 3:1 ratio of **14a** and **14b**. Wittig olefination gave the corresponding ratio of alkenes **15a** and **15b**. However, neither the alkenes **15** nor ketones **14** could be separated into individual isomers. The sequence was therefore repeated with a reversal in the order of alkylation steps. Thus, the ethyl ketone **16a,b** was converted into enol silane **7b**, and enolate generation followed by methylation gave a mixture of ketones **14a** and **14b** in a ratio of 1:3. The yield of **14** was poor, but Wittig methylenation was uneventful and afforded a 1:3 ratio of **15a:15b**, 80% yield. Thus, two different mixtures of the isomers **15a,b** were available, and the stereoselectivity of epoxidations or osmylations could be deduced by comparing product ratios with the ratio of starting materials in two sets of parallel experiments.

The stereochemistry assigned to **14a** and **14b** was determined using lanthanide shift reagents. The ^{1}H NMR chemical shift of the equatorial 2-methyl signal of **14a** was shifted from δ 0.98 ppm [$CDCl_3$] to δ 1.79 ppm [$CDCl_3$ + $Eu(fod)_3$] under conditions where the axial 2-methyl isomer **14b** gave chemical shifts of δ 1.12 ppm (no shift reagent) and 1.73 ppm [$Eu(fod)_3$ added]. Thus, the relative chemical shifts of the 2-methyl groups were inverted by the lanthanide reagent. The equatorial methyl should be influenced more strongly because it is in the plane of the carbonyl oxygen. The shift reagent-based assignment is consistent with preferred axial enolate alkylation in both sequences leading to **14a** and **14b**, as expected from literature analogies.[22]

The same techniques were applied to the synthesis of alkenes **19a** and **19b** starting from the dimethylhydrazone of 4-*tert*-butylcyclohexanone. The mixture of alkylated ketones **17a,b** starting from the dimethylhydrazone of 4-*tert*-butylcyclohexanone. The mixture of alkylated ketones **17a,b** was taken directly to enol silane **7c**, and treatment with MCPBA gave a

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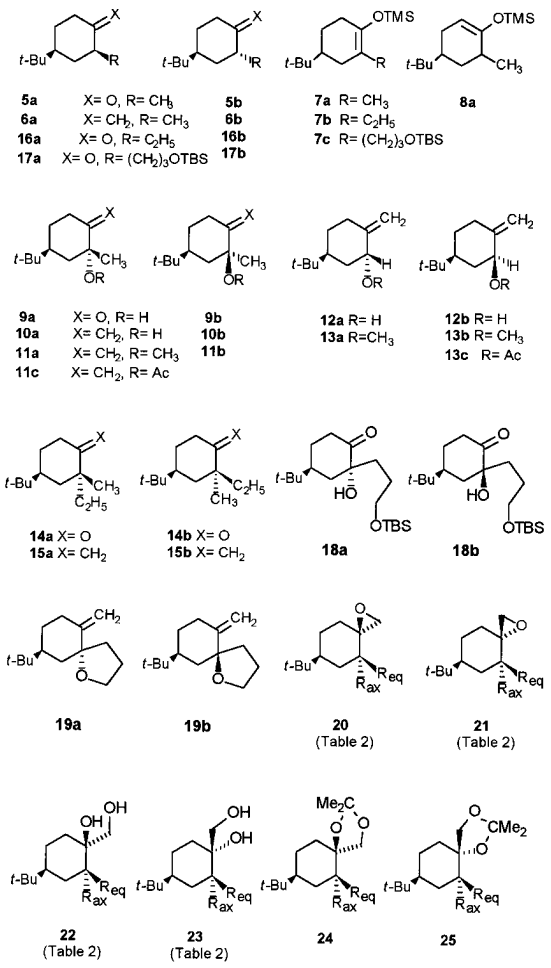
Chart 1



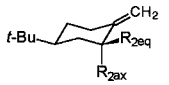
mixture of hydroxy ketones **18a:18b**. Wittig methylenation, deprotection (Bu_4NF), and Mitsunobu cyclization then produced **19a** and **19b**. The stereochemical assignment was based on ^{13}C analysis at the stage of **19a,b** using the characteristic deshielding effect of equatorial oxygen at the γ-carbon.[27] Thus, a comparison of ^{13}C chemical shifts for the C_4 methine carbon signals gave values of δ 43.7 for **19a** (axial C_2-O) and 46.8 for **19b** (equatorial C_2-O). Similar differences were seen in the ^{13}C spectra of products obtained from **19a,b** by epoxidation or osmylation (see Experimental Section, Table 4).

Methylenecyclohexane Epoxidations

Conversion of the alkenes into epoxides followed one of two protocols. In the first, the alkene was treated with 1.5 equiv of *m*-$ClC_6H_4CO_3H$ (MCPBA) in dichloromethane at 0 °C (3 h) followed by warming to room temperature. The second procedure employed dimethyldioxirane as the oxidant.[25,26] The reagent was prepared in acetone (ca. 0.1 M)[25] and a large excess (15 equiv) was added to the alkene in dichloromethane at 0 °C. The mixture was then allowed to warm to room temperature. The dioxirane reagent was applied to a limited subset of alkenes because the reactions proved to be relatively nonselective and not very sensitive to substituent effects. Also, the presence of acetone and water in the dioxirane distillate caused problems with sensitive substrates. Thus, **19a** and **19b** gave mixtures upon attempted DMD epoxidation and the diastereoselectivity could not be determined.

(27) (a) Senda, Y.; Ishiyama, J.; Imaizumi, S. *Tetrahedron* **1975**, *31*, 1601. (b) Davis, R.; Kluge, A. F.; Maddox, M. L.; Sparacino, M. L. *J. Org. Chem.* **1983**, *48*, 255.

Table 2. Oxidations with MCPBA, Dimethyldioxirane (DMD), and OsO_4



					% O Axial (**20**)		% O Axial (**22**)
Entry	Alkene	R_{2ax}	R_{2eq}	Product	MCPBA	DMD	OsO_4
1	**1b**	H	H	**a**	69	31	**14**
2	**6a**	H	CH_3	**b**	62	23	<5
3	**12b**	H	OH	**c**	60		<5
4	**13b**	H	OCH_3	**d**	60		<5
5	**19**	H	OAc	**e**	75		8
6	**6b**	CH_3	H	**f**	65	55	65
7	**11b**	CH_3	OCH_3	**g**	88	31	24
8	**15b**	CH_3	CH_2CH_3	**h**	59	29	57
9	**13a**	OCH_3	H	**i**	83		88
10	**18**	OAc	CH_3	**j**	83[a]		67
11	**11a**	OCH_3	CH_3	**k**	83	62	93
12	**15a**	CH_2CH_3	CH_3	**l**	92	70	>95
13	**19a**	$OCH_2CH_2CH_2$		**m**	73	b	55
14	**19b**	$CH_2CH_2CH_2O$		**n**	81	b	20
15	**12a**	OH	H	**o**	11		33
16	**10a**	OH	CH_3	**p**	13	17	14

[a] Initial product ratios through ca. 50% conversion; decomposition was detected using longer reaction times that allowed higher conversion. [b] The ratio could not be determined because of partial product decomposition.

Isomer ratios and assignments were established using ^1H and ^{13}C NMR methods on the initial product mixture, prior to separation. Epoxides having an axial CH_2 group have characteristic long-range coupling involving one of the epoxide CH_2 protons and a ring methylene proton (J = ca. 1.5−2.5 Hz).[9c] Furthermore, the same isomers experience characteristic downfield ^{13}C shifts for the C_5 ring methylene carbon, due to deshielding by equatorial epoxide oxygen at C_1.[27] The difference is not large (1−2 ppm), but the ^{13}C chemical shifts for C_5 are very consistent (δ 24−25 ppm for the epoxides with axial C_1 oxygen and 26−27 ppm for the isomers having equatorial C_2 oxygen; see Table 4). Both the ^1H and ^{13}C criteria gave self-consistent assignments of stereochemistry.

Methylenecyclohexane Osmylations

Hydroxylation experiments were performed using the catalytic osmylation method of Van Rheenen *et al.* (room temperature, acetone solution).[28] As before, product stereochemistry was assigned by ^{13}C NMR spectroscopy based on the characteristic deshielding effect of equatorial C_1 oxygen on the ring methylene carbon at C_5.[27] This signal appears as the highest field methylene carbon in all of the diols **22** and **23** or the derived acetonides **24** and **25** (obtained by treatment of the diols with 2,2-dimethoxypropane and TsOH) reported in Table 2. Thus, **23** or **25** having equatorial oxygen were characterized by C_5 chemical shifts in the range of δ 23.2−24.5 ppm while the axial oxygen isomers **22** or **24** were assigned based on C_5 δ values of 21−22 ppm. Several of these assignments were confirmed by chemical correlation with the epoxides. Thus, epoxides obtained from Table 2, entries 4, 5, 9, and 11, were converted stereospecifically into the diols using aqueous NaOH in *tert*-butyl alcohol at 70° (entries 4, 5, 9) or aqueous $NaHCO_3$ in *N*-methylpyrrolidinone at 130 °C (entry 11). The results were consistent with the ^{13}C chemical shift assignments.

(28) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.

Selectivity Patterns

The oxidations summarized in Table 2 follow a unique pattern of selectivity for each specific reagent. The well-known Henbest effect of axial OH is responsible for the observed equatorial selectivity in the MCPBA reactions of entries 15 and 16.[1a] The situation is less clear for the dimethyldioxirane (DMD) and osmylation experiments because several of the reactions (entries 1−5) proceed with similar equatorial selectivity. However, some evidence for a Henbest-like effect was obtained from solvent studies. The osmylation of entry 16 was repeated in dichloromethane (stoichiometric osmylation conditions; pyridine as the activating ligand). This gave only 5% axial attack, corresponding to increasingly favored bonding syn to hydroxyl oxygen. Since the catalytic osmylation experiments of Table 1 are performed in the presence of hydroxylic species, the solvent effect suggests a modest contribution from hydrogen bonding in the dichloromethane experiment. The standard DMD oxidation conditions are relatively free of hydroxylic agents (acetone−dichloromethane solution; traces of water), so the oxidation (entry 16) was repeated in a mixture of acetone and methanol as the cosolvent to suppress intramolecular hydrogen bonding. The selectivity changed from 17% axial (acetone−methylene chloride) to 33% axial (acetone−methanol), consistent with a moderate Henbest effect in the first example. A similar solvent effect for the dimethyldioxirane epoxidation of 2-cyclohexenol has been attributed to hydroxyl participation.[26f] Thus, the axial OH entries for each of the three reagents probably include at least some component of hydrogen bonding that favors oxidation syn to the OH group. However, the remaining data points indicate substantial selectivity differences among the reagents and will be discussed according to the reagent. The MCPBA reactions will be considered in detail to establish a basis for comparing electronic, torsional, and steric factors.

The most striking feature of the MCPBA results for entries 1−14, Table 2, is their similarity. All of these reactions afford the axial epoxide as the major product, as do most of the earlier epoxidation examples reported in Table 1. In the absence of substantial opposing steric effects, the axial epoxidation pathway is preferred by $\Delta\Delta G^* = 0.8 \pm 0.6$ kcal/mol. A clear equatorial preference is seen only in the case of substrates that contain an axial substituent at C_3 or C_5 (for example, entry 13, Table 1), and in the Henbest examples already discussed. Substituents at C_2 (and/or C_6) cause relatively modest changes in selectivity. The most dramatic "effect" is observed with the relatively mundane C_2 ethyl substituent (entry 12; $\Delta\Delta G^* = 1.4$ kcal/mol; compare to parent $\Delta\Delta G^* = 0.5$ kcal/mol, entry 1).

Cieplak's explanation for the axial epoxidation preference of the parent 4-*tert*-butylmethylenecyclohexane (Table 1, entries 2 and 3) is that the axial C-2 and C-6 hydrogens are better σ donors than are the equatorial C_2-C_3 and C_5-C_6 carbon bonds. If this is correct, then the axial pathway would have a rate advantage because of better $\sigma-\sigma^*$ overlap. In addition, the concept predicts that a molecule containing axial C_2-H and C_6-H bonds should react faster than an analog having axial C_2-alkyl substituents. Thus, an axial methyl group at C_2 should decrease the rate of the axial epoxidation pathway. A comparison of Table 1, entries 10 and 11, shows a small trend in the opposite direction.[8] Axial C_2 methyl decreases the rate of the *equatorial* pathway, probably from a small steric effect, but it slightly accelerates the axial epoxidation. The results are not consistent with stabilization of the axial epoxidation transition state by axial C_2-H or C_6-H bonds.

A similar conclusion follows from facial selectivity comparisons for the hydrocarbon entries of Table 2. Epoxidation selectivity is virtually unaffected by the presence of a 2-methyl substituent in the 4-*tert*-butylmethylenecyclohexane skeleton (compare MCPBA entries 1, 2, 6; 62−69% axial attack). The equatorial 2-ethyl, axial 2-methyl example (entry 8; 59% axial attack) also gives essentially identical results. Only the axial 2-ethyl, equatorial 2-methyl substrate (entry 12) stands out in epoxidation selectivity (92% axial) among the examples that contain alkyl (not oxygen) substituents at C_2. No significant difference in σ-donor properties is expected for axial methyl vs axial ethyl, so the contrast between entries 8 and 12 must have a different origin. Axial epoxidation in entry 12 (axial 2-ethyl) is probably favored because equatorial attack destabilizes one of the ethyl rotamers, resulting in an entropic penalty. The rotor effect is less important for equatorial ethyl because unfavorable rotamer interactions with the peracid occur in both the equatorial and the axial pathways. The other hydrocarbon entries in Table 2 are unexceptional, and there is no indication that the presence of axial C_2-H vs C_2-alkyl bonds is a factor in epoxidation selectivity.

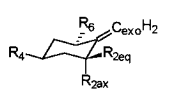
The hyperconjugative rationale of Cieplak, Tait, and Johnson for 3-substituted methylenecyclohexanes (Table 1, entries 15−18) is independent of the C−H vs C−C σ-donor issue discussed above. On the other hand, the differences in selectivity for entries 15−18 are modest, and such small effects are difficult to evaluate. A more decisive interpretation should be possible for variable substituents placed at C_2, one bond closer to the reacting center, provided that other factors can be held constant. An axial C_2 σ-bond has the geometry required for interaction with the σ^* orbital for a developing axial C- - -O bond at C_1, and axial acceptor groups at C_2 should retard axial epoxidation if the σ,σ^* effect is significant.

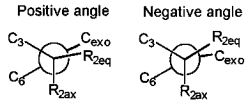
Entries 10, 11, and 12 in Table 2 (MCPBA epoxidations) allow comparisons between rotor groups that are similar in size and shape, but that differ predictably in acceptor properties according to Taft σ_I values: ethyl, $\sigma_I = -0.01$; acetoxy, $\sigma_I = +0.38$; methoxy, $\sigma_I = +0.30$).[29] The difference in epoxidation selectivity between C_2-ethyl (entry 12, 92% axial) and the C_2 oxygen substituents (entry 10, OAc, 83% axial; entry 11, OMe, 83% axial) is qualitatively in the direction predicted by the Cieplak effect, but the difference between the C_2-ethyl and the C_2-oxygen substituents is surprisingly modest. The selectivity in the methoxy and acetoxy vs ethyl examples could also be attributed to differences in steric effects (filled orbital interactions) or dipole effects, or to a combination of small, opposing steric and Cieplak effects. The rigid, spiro-fused tetrahydrofurans of entry 13 (axial oxygen at C_2; 73% axial attack) and entry 14 (axial CH_2CH_2 and equatorial oxygen at C_2; 81% axial attack) follow the same trend. Some of the other oxygen-substituted examples in Table 2 (entries 4, 5, and 9) cannot be compared with confidence because the isosteric 2-alkyl analogs were not studied. However, there is no clear indication that σ,σ^* effects are important, and the similarity between entries 9 and 11 suggests that the rotor effect of an unsymmetrical substituent (methoxy) in the axial position dominates in both cases.

One of the largest differences among the isosteric examples in Table 2 involves the equatorial ethyl vs equatorial methoxy examples (entry 8 vs entry 7; both with axial C_2 methyl). Since the equatorial C_2-C or C_2-O substituent is roughly orthogonal to the developing epoxide bond at C_1, the σ,σ^* effects are not responsible for this difference. More likely, the difference between equatorial ethyl and methoxy groups arises because developing bonds in both the axial and the equatorial epoxidation transition states can feel the steric effect of an unsym-

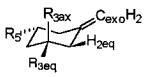
(29) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119.

Table 3. Dihedral Angles (R_{2eq}-C-C-C_{exo}) in Alkenes and Epoxides (MM2)





Entry (cmpd)		R_{2ax}	R_{2eq}	R_4	R_6	Dihedral Angle (R_{2eq}-C-C-C_{exo}) Alkene	Ax Epox	Eq Epox	% Axial
1	(**15a**)	C_2H_5	CH_3	*t*-Bu	H	-11.8°[a]	-31.3°[b]	+11.2°[c]	92
						-15.0°[d]	-36.5°[e]	-0.8°[f]	
2	(**1b**)	H	H	*t*-Bu	H	-1.5°	-21.4°	+6.4°	69
3	(**1c**)	H	H	CH_3	H	-1.6°	-21.6°	+6.4°	65
4	(**6b**)	CH_3	H	*t*-Bu	H	-11.5°	-30.4°	+3.3°	65
5	(**6a**)	H	CH_3	*t*-Bu	H	+2.2°	-18.3°	+8.3°	62
6	(**15b**)	CH_3	C_2H_5	*t*-Bu	H	-14.0°[g]	-38.2°[h]	-0.9°[i]	59
						-17.2°[j]	-40.5°[k]	-4.1°[l]	
7	(**2b**)	CH_3	CH_3	H	CH_3	-9.9°	-34.4°	+1.4°	57
8	(**1d**)	H	CH_3	H	H	+1.9°	-19.0°	+8.2°	54
9	(**1g**)	H	CH_3	CH_3	H	+2.0°	-18.8°	+8.3°	54
10	(**2a**)	H	CH_3	H	CH_3	+4.3°	-15.3°	+9.2°	45



Entry (cmpd)		R_{3eq}	R_{3ax}	R_5	Dihedral Angle (H_{2eq}-C-C-C_{exo}) Alkene	Ax Epox	Eq Epox	% Axial
11	**11**	CH_3	H	CH_3	-1.2°	-21.6°	+7.1°	64
12	**12**	*t*-Bu	H	H	+0.5°	-21.1°	+7.7°	60
13	**13**	$SiMe_3$	H	H	-0.8°	-21.2°	+7.2°	52
14	**14**	CH_3	CH_3	CH_3	+0.9°	-25.2°	+9.7°	17

Steric energies (kcal/mol): lowest energy rotamer (a) 19.77 (b) 27.87) (c) 27.37; next lowest energy rotamer: (d) 20.21 (e) 27.73 (f) 28.28; highest energy rotamer not tabulated, alkene steric energy 23.34. Lowest energy rotamer: (g) 20.83 (h) 28.44 (i) 28.76; next lowest energy rotamer: (j) 20.95 (k) 29.37 (l) 29.62; highest energy rotamer not tabulated, alkene steric energy 21.64.

metrical rotor substituent in the equatorial position. The ethyl and methoxy rotamers will experience similar torsional and steric interactions, but the equatorial methoxy rotamers will also encounter dipole and electron pair interactions in the competing transition states. We do not raise these issues in an attempt to rationalize entries 7 and 8, but to argue that the σ,σ^* effects are small compared to other variables. This is also clear in the rigid spiro-fused tetrahydrofurans of entries 13 and 14 where no rotor effect is possible. As in the axial C_2 ethyl vs axial C_2 methoxy comparison, the modest increase in axial MCPBA epoxidation from entry 13 (73%) to entry 14 (81%) probably reflects the sum of small Cieplak, dipole, and steric effects, all of which are expected to favor axial attack. It is apparent that none of these factors is dominant since their sum amounts to a $\Delta\Delta G^*$ in the range of 0.3−0.5 kcal/mol.

Torsional Effects in Epoxidations

Qualitative torsional energy comparisons require some knowledge of molecular geometry along the reaction coordinate and of the associated change in hybridization. Several of the hydrocarbon substrates and derived epoxides were therefore analyzed using the MM2 force field as implemented in MACROMODEL.[30] Little change was found in the preferred geometry along the C_3-C_5 ring segment or in the ring bond angles, but the dihedral angles calculated between equatorial substituents at C_2 (C_2-R_{2eq}) and the methylene bond (C_1-C_{exo}) were sensitive to the nature of C_2 substituents (Table 3). All of the methylenecyclohexanes with R_{2ax} = H have the R_{2eq} substituent within a ca. 4° dihedral angle of the $C_2-C_1-C_{exo}$ plane. This is the eclipsed geometry that corresponds to the energy minimum for unconstrained alkenes.[13] The epoxide entries show larger variations and the dihedral angles range from −15 to −41° for the products of axial epoxidation (equatorial C_{exo}) and from −4 to +11° for the equatorial epoxides (axial C_{exo}). According to the convention, R_{2eq} is below the plane as drawn for $C_2-C_1-C_{exo}$ when the $R_{2eq}-C_2-C_1-C_{exo}$ dihedral angles are positive, and above the plane when the angles are negative. In the parent 4-*tert*-butylmethylenecyclohexane system, the epoxide $R_{2eq}-C_2-C_1-C_{exo}$ dihedral angle is −21.4° for the axial epoxidation product **20** and +6.4° for the equatorial isomer **21** (R_{2eq} = R_{2ax} = H). Therefore, intermediate values between these limits and the −1.5° dihedral angle of the starting alkene **1b** are expected in the competing transition states for epoxidation. It follows that there must be substantial eclipsing between existing bonds ($R_{2eq}-C_2$ and C_1-C_{exo}) in the equatorial epoxidation transition state. On the other hand, the axial epoxidation pathway involves a decrease in eclipsing as bonding proceeds. Unfavorable torsional interactions in the alkene substrate will therefore develop gradually (if at all) in the axial pathway, and the torsional contribution to ΔG^* from existing bonds will be lower than in the equatorial pathway. The argument assumes that staggered carbon−carbon bonds will be preferred in epoxides, as in other sp^3-hybridized structures.[13] If this is correct, then the partially rehybridized equatorial transition state will encounter a larger fraction of the increase in torsional energy along the reaction coordinate, and the result will be an advantage for axial epoxidation. In its essential features, this is the same torsional argument that was advanced by Sevin and Cense in 1974.[8]

No other useful correlations emerged from the MM2 comparisons. For example, the change in sign from positive dihedral angles in a few of the alkenes (entries 5, 8, 9, and 10) to negative angles in the axial epoxides could not be associated with distinct selectivity behavior. The sign change requires that R_{2eq} must slip past the C_1-C_{exo} bond, but the resulting eclipsing interaction apparently occurs early along the reaction coordinate where eclipsed geometries still correspond to the torsional energy minimum.

The magnitude of transition state torsional energy contributions to $\Delta\Delta G^*$ from substrate bonds can be estimated by comparing ground state CH_3-C torsional barriers for methyl-substituted alkenes with the barriers of the corresponding epoxides:[31] propylene oxide, 2.56 kcal/mol;[31c] 1-propene, 1.95 kcal/mol;[31a] *trans*-2-butene oxide, 2.44 kcal/mol;[31d] *trans*-2-butene 1.95 kcal/mol;[31a] *cis*-2-butene oxide, 1.61 kcal/mol;[31e] *cis*-2-butene, 0.75 kcal/mol.[31b] According to these examples, the torsional component of ground state energy will increase by ca. 0.5−1.0 kcal/mol as the alkene undergoes the bonding and hybridization changes required to form the corresponding epoxide. Some fraction of this increase in torsional energy will be felt in the epoxidation transition states, depending on the degree of rehybridization. The dependence of torsional energies vs bond angles is not known in the methylenecyclohexane series, but a similar range in the torsional energy difference between alkenes and the corresponding epoxides is plausible.

The magnitude of the increase in existing bond torsional interactions is in the range of epoxidation $\Delta\Delta G^*$ values. According to the arguments presented earlier, the axial epoxi-

(30) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(31) (a) Kilpatrick, J. E.; Pitzer, K. S. *J. Res. Natl. Bur. Stand.* **1946**, *37*, 163. (b) Sarachman, T. N. *J. Chem. Phys.* **1968**, *49*, 3146. Kondo, S.; Sakurai, Y.; Hirota, E.; Morino, Y. *J. Mol. Spectrosc.* **1970**, *34*, 231. (c) Herschbach, D. R.; Swalen, J. D. *J. Chem. Phys.* **1958**, *29*, 761. (d) Emptage, M. R. *J. Chem. Phys.* **1967**, *47*, 1293. (e) Sage, M. L. *J. Chem. Phys.* **1962**, *35*, 142.

dation transition state should experience little if any increase in existing bond torsion compared to the equatorial transition state. Thus, it is possible that most if not all of the 0.5 kcal/mol ΔG^* advantage for axial epoxidation in the parent 4-*tert*-butylmethylenecyclohexane can be obtained from changes in existing bond torsion from the alkene to the equatorial epoxide. No torsional contribution to $\Delta\Delta G^*$ from the developing C−O bonds would be necessary according to this analysis and the question must now be asked whether developing bond torsion plays any role in epoxidations.

The subsequent discussion is intended to unify and to clarify the often divergent torsional arguments of different groups where possible, and to establish criteria that may be useful for evaluating torsional rationales. First, we note that the evidence does not require that the magnitude of developing bond torsional energy is negligible, nor does the argument depend on any specific range of dihedral angle values. The data of Sevin and Cense[8] as well as our own would be consistent with the scenario where the ΔG^* component due to developing bond torsion is significant, but happens to be similar for both diastereomeric transition states (i.e., the developing bond contribution to $\Delta\Delta G^*$ is negligible).

Since the torsional barrier is the difference between a composite of steric and steroelectronic factors,[12] it is not easy to evaluate this energy term by intuition nor to dissect it into its component parts. Nevertheless, the concept has a clear experimental basis as long as the issue is torsion among existing bonds. On the other hand, the extension of this concept to developing bonds encounters formidable difficulties. In the ground state, the torsional effect is defined by the measurement of a torsional barrier, an energy that usually represents the difference in free energies of the eclipsed and the staggered geometries of the same substance. The torsional contribution to ground state energy can be represented by parameters in empirical force fields without having to know exactly what causes torsional barriers. For simple molecules such as ethane, the absolute energies can also be computed by *ab initio* methods with sufficient accuracy to reproduce the torsional barrier and to separate these energies into recognizable components.[12,13]

Is there an analogous way to dissect transition state torsional energies? Where ground state (existing bond) torsion represents the difference in energies of eclipsed and staggered rotamers, the transition state analog would need to evaluate the free energy of diastereomers and conformers of the transition structures. To do this by computation, it would be necessary to locate different saddle points on the energy surface, each of which would need to be evaluated in terms of total energy and dissected into components. This does not appear to be a realistic prospect if transition state torsional effects are to be described by the same component variables that define the ground state version. It is already difficult to calculate absolute values for ground state torsion for non-trivial molecules, and the transition state analog must deal with additional variations in bond lengths, bond angles, hyperconjugative contributions, and so on. Only the filled orbital repulsive component of developing bond torsion appears to be accessible to intuition. Fundamentally, this would be no different than to invoke a qualitative overall steric effect. In the region of the reaction coordinate where internuclear distances are ca. 2−3 Å, this component of transition state energy will likely increase with the bulk of interacting groups and with decreasing distance between them. For reactions with relatively late transition states and shorter (extensively rehybridized) bonds, "developing bond" torsion might be identified as a distinct energy term because the new bond would be mostly formed and would be subject to the factors that contribute to torsion in the product. However, in the general case (especially for early transition states) it may be best to merge the concepts of developing bond torsion and traditional steric effects because neither can be independently measured or evaluated in the transition state. In the remaining discussion, we will focus on *existing bond* torsional effects, extrapolated from the ground state to the transition state, and in some examples we will also refer to developing bond steric (not torsional) effects.

Dioxirane Epoxidations, Osmylations

Both the dimethyldioxirane and osmium tetroxide reagents are sufficiently bulky that the transition state differences in existing bond torsion are small compared to steric differences in reagent−substrate interactions that favor equatorial attack. With the dioxirane, an equatorial C_2 methyl group reinforces the trend for equatorial epoxidation to a small extent (Table 2, entries 1 vs 2), while an axial C_2 methyl (entry 6) is enough to cancel the equatorial preference, resulting in a nonselective reaction. The presence of an unsymmetrical rotor in the equatorial position (C_2−methoxy; C_2−ethyl) in addition to the axial C_2 methyl group restores the equatorial preference (entries 7 and 8). However, axial methoxy or ethyl rotors (entries 11 and 12) are dominant over the small effect of equatorial C_2 methyl, resulting in axial selectivity. This simple picture shows that dimethyldioxirane has moderately increased steric demand compared to MCPBA, a result that can be attributed to the *gem*-dimethyl groups. Significant sensitivity to substrate steric effects can also be deduced from other reported diastereoselective epoxidations using dimethyldioxirane.[26]

The osmylations show an increased trend toward equatorial products in the parent alkene **1b** (Table 2, entry 1), and the trend is reinforced by equatorial substituents at C_2 (entries 2−5). An axial methyl group at C_2 inverts the normal equatorial preference and promotes axial osmylation (entry 6), and the axial ethyl rotor of entry 12 has a similar, but larger effect. The most striking trend among the osmylations is the tendency for bond formation to occur away from unconstrained ether or ester oxygen substituents (Kishi effect).[32] This effect dominates all others, and a combination of lone pair repulsions and the rotor effect of unsymmetrical substituents appears to be responsible. The lone pair component is suggested by the large effect from axial methoxy vs axial acetate (compare entries 4 and 5, or 10 and 11). However, the contrast between entries 11 and 13 suggests that the rotor and lone pair effects are interconnected. The constrained axial alkoxy group (entry 13) is not nearly as effective in promoting axial osmylation as is the axial methoxy analog (entry 11). Since the lone pair density of the tetrahydrofuran **19a** is directed toward the cyclohexane ring, not toward the incoming osmium reagent, this is the expected result.

As already mentioned, axial OH appears to exert a Henbest effect, presumably involving transition state stabilization via hydrogen bonding. Other examples of hydroxyl directing effects in osmylations are known.[33] However, a comparison of entries 1 and 3 or 1 and 15 shows that hydroxylation *syn* to axial C_2−OH is less favored than attack *syn* to axial C_2−H. Thus, the Henbest effect is opposed by the lone pair repulsion or steric effects of hydroxyl. In other respects, the osmylations resemble the epoxidations in that all three reagents respond to the unsymmetrical rotor groups. The selectivity pattern of the axial acetate and methoxy derivatives could be rationalized by invoking a small Cieplak effect, but the behavior of the

(32) (a) Kishi, Y.; Christ, W. J.; Cha, J. K. *Tetrahedron* **1984**, *40*, 2247. (b) Review: Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

(33) Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399. Smith, A. B.; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217. Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495.

equatorial analogs (entries 4 and 5) is more compatible with the lone pair repulsion argument. Entries 9, 10, 11, and 13 show a preference for the non-Cieplak product. Steric interactions between the substrate and the developing bonds, together with the Kishi effect, play the most important role while contributions from the Cieplak effect and from existing bond torsion are too small to clearly identify.

Our results do not help to clarify the mechanistic picture for the osmylation reactions.[34] Either the 2 + 3 cycloaddition or the 2 + 2 cycloaddition pathways are consistent with substantial steric effects, lone pair avoidance by the reagent, and sensitivity to unsymmetrical rotor groups. In the context of methylene cyclohexane facial selectivity, the two pathways are not much different. If the rate-determining event is the ligand-promoted conversion of a 2 + 2 adduct into the cyclic osmate ester,[34a] then the stereochemistry-determining transition state could have (but need not have) a fully formed C−O bond at the primary carbon (C_{exo}), and partially formed C_1−Os and C_1−O bonds. If the mechanism involves some variation of the 2 + 3 cycloaddition process,[34b] then both osmate C−O bonds would be partially formed. Asynchronous bonding with the unsymmetrical methylenecyclohexane derivatives is expected in any case, and the difference in transition state geometries between the two mechanisms is too subtle for any comment based on our data.

Asynchronous Bonding in Methylenecyclohexane Epoxidations

Peracid epoxidation mechanisms are well-understood.[1,9a,b,35,36] Asynchronous bonding is expected by analogy to the styrene epoxidations,[30] and the Bartlett butterfly arrangement as modified by Beak *et al*. appears secure.[36a] The competing transition states in the methylenecyclohexane series can therefore be represented by structures **26** and **27**. The preferred geometry **26** is consistent with relatively small developing bond steric interactions, and also with the observation that epoxidation selectivity is opposite to the axial/equatorial preference of the product epoxides.[8] There is relatively little rehybridization at ring carbon C_1, and the magnitude of 1,3-diaxial interactions is therefore small. Sevin and Cense proposed a similar transition state geometry.[8] They also investigated solvent effects on diastereoselectivity in the reaction of 4-*tert*-butylmethylenecyclohexene with *p*-nitroperbenzoic acid. Only small differences in percent axial epoxidation were found: dichloromethane, 70%; methanol, 73%; ether, 80%. Similar axial selectivities were observed in the present study with *m*-chloroperbenzoic acid: $CDCl_3$, 72%; methanol, 75%; benzene, 78%; acetonitrile, 78%; THF, 80%. Thus, the competing transition states do not differ much in terms of charge separation or dipole moment. The relative insensitivity to solvent effects suggests that the peroxide oxygen electron pairs provide effective internal stabilization for the partial positive charge at C_1, as also deduced in earlier mechanistic studies.[9a] Hanzlik and Shearer found that rehybridization at the benzylic carbon in styrene epoxidations is too small to detect from the ^{13}C kinetic isotope effect.[30] However, peracid epoxidations of β-substituted styrenes are stereospecific and the reactions tend to be fastest in nonpolar solvents.[9a,30] This rules out ionic intermediates having a lifetime sufficient for bond rotation and indicates a relatively nonpolar transition state. There must be a strong electrostatic interaction or a weak bond between the partially negative peracid fragment and the partially positive olefinic carbon, presumably expressed via the electron pairs at the peroxidic oxygen.

Asynchronous Bonding and Torsion in Cyclohexene Epoxidations

Jerina *et al*. have reported that the cyclic styrene **28** reacts with MCPBA to give a single epoxide **29** (NMR assay; 92% isolated).[37] Related examples have been studied by Martinelli *et al*. and the epoxidation selectivities are accurately known.[4a] Thus, **30** produces **31** with remarkable 99:1 selectivity (MCPBA conditions). Several analogous dihydronaphthalene derivatives afford epoxides with selectivities ranging from 85:15 to 99:1, but an indene analog of **30** (5-methyl-1,2-benzocyclopentadiene) gives a 1:1 mixture of epoxides. However, cyclohexenes **32** and **33** react nonselectively with *p*-nitroperbenzoic acid (45:55 and 50:50, respectively).[38] Martinelli, Houk *et al*. invoked interactions between developing C- - -O bonds and adjacent axial C−H bonds to explain these contrasts as follows.[4a] Formation of the eclipsed bond in a half-chair **34** might be destabilized by a developing bond interaction relative to the staggered bond. Such an effect would be magnified in an asynchronous transition state with relatively advanced bonding at the styrene β-carbon because the peracid subunit would be closer to the axial allylic C−H bond.[4a] In cyclohexenes **32** and **33**, containing two allylic axial C−H bonds, there is an equal number of interactions for bonding at either face of the double bond, similar to the model **35**, and there would be no selectivity if developing bond interactions are dominant.[4a]

The cyclohexene examples differ from the methylene cyclohexane system discussed earlier in at least one important way. In the exocyclic alkenes, the geometric consequences of an asynchronous transition state place the most highly developed C−O bond far from the sp^3-hybridized allylic ring carbons (C_2 and C_6, methylenecyclohexane numbering). The situation is reversed for the dihydronaphathalenes **28** or **30** where bond formation occurs near the allylic C−H bonds. Depending on the extent of rehybridization, interactions between the developing C- - -O bond and the axial allylic hydrogen could contribute to the stability difference between the competing transition states as proposed by Martinelli, Houk, *et al*.[4a] However, a transition state analysis based primarily on existing bond interactions can also account for the cyclohexene examples.

Simple cyclohexenes (for example, **32**) may react with peracids via nearly synchronous transition states with both olefinic carbons partially rehybridized. The six-membered ring resembles a half-chair cyclohexene regardless of which face of the double bond is attacked and the minimal steric requirement of the peracid results in a nonselective reaction. In contrast, structures such as **30** that contain a dihydronaphthalene subunit prefer highly asynchronous transition states with substantial benzylic cation character due to the extended delocalization enforced by ring constraints. Three families of asynchronous transition structures can be considered, represented by the limiting cases **36**, **37**, and **38**. Geometries **36** and **37** have the more developed C_β- - -O σ bond in the plane of the benzylic p-orbital to maximize the stabilizing interaction between the peroxidic oxygen electron pairs and the benzylic π-system. Staggered geometries similar to **38** have a nearly orthogonal

(34) (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1994**, *116*, 1278. Veldkamp, A.; Frenking, G. *J. Am. Chem. Soc*. **1994**, *116*, 4937. (b) Houk, K. N.; Wu, Y.-D.; Wang, Y. *J. Org. Chem*. **1992**, *57*, 1362. Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc*. **1993**, *115*, 12579.

(35) Review: Schroder, M. *Chem. Rev*. **1980**, *80*, 187.

(36) (a) Beak, P.; Woods, K. W. *J. Am. Chem. Soc*. **1991**, *113*, 6281. (b) Rebek, J., Jr.; Marshall, L.; McManis, J.; Wolak, R. *J. Org. Chem*. **1986**, *51*, 1649.

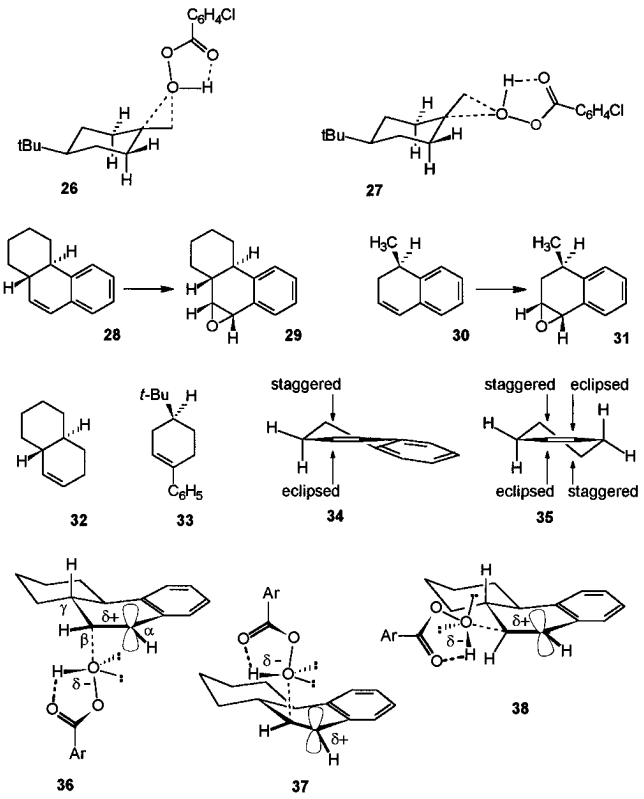
(37) Sayer, J. M.; Yagi, H.; Silverton, J. V.; Friedman, S. L.; Whalen, D. L.; Jerina, D. M. *J. Am. Chem. Soc*. **1982**, *104*, 1972.

(38) Casadevall, A.; Casadevall, E.; Mion, M. *Bull. Soc. Chim. Fr*. **1968**, 4498. Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron* **1968**, *24*, 1755.

σ,p orbital arrangement and can be discounted on stereoelectronic grounds. The transition structure **37** allows better proximity of oxygen electron pairs and the benzylic orbital, but this comes at the cost of a geometry that resembles a half-boat cyclohexene and that also twists the benzylic p-orbital relative to the benzene orbitals. The alternative envelope structure **36** allows ideal overlap between the aromatic ring and the benzylic p-orbital and also maintains close proximity between peroxidic electron pairs and the partially positive benzylic carbon. There is better staggering of *all of the sp³ or partly sp³ bonds* (not only of the developing bonds) compared to the situation in **37**. Some fraction of the 5−6 kcal/mol energy difference between half-boat and half-chair cyclohexenes[39] should stabilize **36** relative to **37**.[40] The observed $\Delta\Delta G^*$ values for the epoxidation of **28**, **30**, and related dihydronaphthalenes (1.5−2.7 kcal/mol) are within the available energy range.

The above discussion is not intended to rule out a contribution by developing bond steric effects in the epoxidations of **28** or **30**. The indicated transition state geometries are not fundamentally different from those considered by Martinelli, Houk, *et al*., and there are no substantial differences in the interpretations if the transition state is relatively advanced. Extensive rehybridization at the styrene β-carbon would surely encounter a torsional contribution to $\Delta\Delta G^*$ because the environment at C_β and C_γ would have to select between staggered and eclipsed geometries of sp^3 or sp^3-like bonds. Differences in the rationales are more substantial for reactions having early transition states, and for this scenario it is expected that existing bond torsional factors will dominate over developing bond steric effects.

Chart 2



Summary

The larger effects in the methylenecyclohexane epoxidations of Table 2 arise from the steric influence of unsymmetrical rotor substituents. A similar trend has been observed for Diels−Alder reactions where allylic methoxy is large compared to methyl,[41] and in addition reactions of α-methoxyacetaldehyde.[6b] In the absence of unsymmetrical rotors, there is a small, but consistent trend for axial epoxidation that can be understood by invoking torsional effects among existing bonds in the asynchronous equatorial epoxidation transition state.[8] We cannot say that these factors are responsible for all of the axial preference of the parent 4-*tert*-butylmethylenecyclohexane,[6] but they are in the correct range of energies. Small $\sigma-\sigma^*$ effects may be responsible for the trends observed with some of the 3-substituted examples (Table 1, entries 14−18), but such effects are minimal in the examples of Table 2 where isosteric substituents can be compared. The 3-silyl- or 3-stannylmethylenecyclohexanes are epoxidized nonselectively (Table 1, entries 14 and 15), corresponding to $\Delta\Delta G^* =$ ca. 0.5 kcal/mol toward equatorial epoxidation compared to the parent alkene. The other (equatorially) 3-substituted examples of Table 1 differ so little from the parent that they require no further rationale. The effect of silicon or tin substituents at C_3 could be hyperconjugative, but alternative explanations may need to be considered. In view of the long history of the methylenecyclohexene problem, further discussion of elusive phenomena must await the discovery of substrates where the effects are dominant over the torsional, hyperconjugative, or FMO factors that have been featured in existing explanations.[3,4,6,8]

Ground state torsional interactions have complicated origins, but they are defined by experimental data (rotational barriers) and the torsional energies of *existing bonds* can often be extrapolated to transition structures if the extent of rehybridization can be estimated. There is currently no way to estimate the torsional effects for *developing bonds*, short of including all possible 1,2-interactions (all permutations of the filled, unfilled, and partially filled orbital 1,2-interactions) in competing transition states. This approach appears to be too unwieldy for the evaluation of transition states. However, qualitative comparisons are possible for relatively late transition states where the developing bonds resemble product bonds in hybridization. Attempts to separate steric (filled orbital) factors and electronic (including unfilled and partially filled orbital interactions) factors have been helpful,[3,18] but our data suggest that a distinct combination of variables is needed for each specific reagent−substrate family. Disappointingly, the torsional effects, steric effects, rotor effects, Cieplak effects, FMO effects, electrostatic effects, etc., do not cleanly "separate" by definition, and they do not work in the same way in a sufficiently large number of systems to justify their extrapolation from one system to another without detailed study.

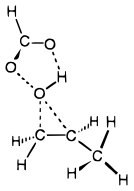
Note Added in Proof: Yamabe *et al.* have recently reported that an asynchronous transition state for the $CH_2{=}CH_2 + HCO_3H$ reaction has lower energy than the symmetrical transition structure found by Bach *et al.* using similar *ab initio* methods.[4b] The former authors also found an asynchronous transition structure for the reaction of propene + HCO_3H as shown below (Yamabe, S.; Kondou, C.; Minato, T. *J. Org. Chem.* **1996**, *61*, 616). The $C-C-CH_3$ geometry resembles the torsional minimum of propene (methyl C−H eclipsed with nearly planar C_2), and is consistent with the dihedral angles

(39) Anet, F. A. L.; Freedberg, D. I.; Storer, J. N.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10969. See also: *Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; VCH, New York, 1989; pp 1−45.

(40) The non-selective epoxidation of **33** can be explained by arguing that the unconstrained phenyl substituent is not effective in providing benzylic delocalization due to steric interactions between the benzene ring and equatorial C−H bonds at C_2 and C_6 in the necessary rotamer. This would result in relatively synchronous half-chair epoxidation transition states for attack from either olefin face.

(41) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472.

suggested for the peracid atoms relative to the alkene in **36** or **37** and with asynchronous bonding in methylenecyclohexane epoxidations (see **26** and **27**).



Experimental Section

Ketones. The dimethylhydrazone anion technique of Corey *et al*.[21] was used to prepare 2-methyl-4-*tert*-butylmethylenecyclohexanones **5a** and **5b**,[22a] the 2-ethyl analogs **16,b**,[22b] and the 2-(3-*tert*-butyldimethylsiloxy)propyl analogs **17a,b** (inseparable mixture).

2-Hydroxy-2-methyl-4-*tert*-butylcyclohexanones (9a and 9b). To 1-(trimethylsiloxy)-2-methyl-4-*tert*-butyl-1-cyclohexene[23,24b] (1.57g, 6.5 mmol) was added dimethyldioxirane solution in acetone (70 mL of a 0.1 M solution, 7.0 mmol)[25] at 0 °C and the reaction was stirred at 0 °C for 3 h, dried ($MgSO_4$), and concentrated (aspirator) to yield a yellow oil. Isomers were separated by flash chromatography on silica gel (80 mm column, 15% EtOAc/hexane). The equatorial alcohol **9b** eluted first. Pure material was obtained by crystallization from 4:1:1 hexane−Et_2O−CH_2Cl_2. This product 673 mg (56% yield) of white crystals of **9b**: mp 47−48 °C; analytical TLC on silica gel, 15% EtOAc/hexane, R_f = 0.27. Molecular ion calcd for $C_{11}H_{20}C_2$: 184.14630; found *m/e* 184.1463. Error = 0 ppm. Base peak = 127 amu; IR (neat, cm^{-1}) 1710, C=O; 3497, O−H. 200-MHz NMR ($CDCl_3$, ppm) δ 3.94 (1 H, s), 2.65−2.48 (2 H, m), 2.22−2.08 (3 H, m), 1.63−1.42 (2 H, m), 1.41 (3 H, s), 0.92 (9 H, s).

Later fractions produced **9a**. Pure material was obtained by crystallization from 4:1:1 hexane/Et_2O/CH_2Cl_2: 350 mg white crystals (29% yield); mp 70−71 °C; analytical TLC on silica gel, 15% EtOAc/hexane; R_f = 0.20. Molecular ion calcd for $C_{11}H_{20}O_2$: 184.14630; found *m/e* 184.1463. Error = 0 ppm. Base peak = 127.07 amu. IR (neat, cm^{-1}) 3594, O−H; 1709, C=O. 200-MHz NMR ($CDCl_3$, ppm) δ 2.91−2.74 (1 H, m), 2.41−2.29 (1 H, m), 2.12−1.99 (2 H, m), 1.81−1.72 (1 H, m), 1.54−1.38 (2 H, m), 1.31 (3 H, s), 0.90 (9 H, s).

2-Ethyl-2-methyl-4-*tert*-butylcyclohexanones (14a and 14b). The enol silanes **7** and **17** were prepared from 2-methyl-4-*tert*-butylcyclohexanones **5a,b**[22a] and 2-ethyl-4-*tert*-butylcyclohexanones **16a,b**[22b] using the procedure of Miller and McKean.[24b] In the preparation of **17**, the reaction was performed using 3.06 g (16.8 mmol) of ketone **16a,b** to give 3.52 g (38% yield) of product as a pale oil after distillation (bulb-to-bulb; 70 °C pot temperature; −78 °C receiving flask temperature; 0.5 mmHg). The distilled product **17** was assayed by NMR, which indicated a >95:<5 ratio of thermodynamic to kinetic isomers.

To a stirred solution of 1-(trimethylsiloxy)-2-methyl-4-*tert*-butyl-1-cyclohexene (**7**) (82 mg, 0.34 mmol) in 3 mL of THF at 0 °C was added MeLi (0.45 mL of a 1.36 M solution, 0.61 mmol) via syringe and the mixture was stirred for 45 min. Iodoethane (0.052 mL, 0.65 mmol) was then added via syringe and the reaction was stirred an additional 7 h at 0 °C before being warmed to room temperature. The reaction was poured onto 10 mL of 1 M $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (aspirator) to yield an oil composed of a 15:5:1 ratio of axial alkylated product to equatorial alkylated product to 2-ethyl-4-*tert*-butylcyclohexanone according to ^1H NMR assay. Also present were polyalkylated products. The undesired byproducts were removed via preparative plate chromatography (20 cm × 20 cm × 0.01 cm; 1:19 EtOAc/hexane, two developments) to yield 16 mg (24% yield) of a clear, colorless oil composed of an inseparable 3:1 mixture of isomers **14a**−**14b**: analytical TLC on silica gel, 1:19 EtOAc/hexane, R_f = 0.21. Molecular ion calcd for $C_{13}H_{24}O$: 196.18271; found *m/e* = 196.1830. Error = 1 ppm. IR (neat, cm^{-1}) 1707, C=O. 200 MHz NMR ($CDCl_3$, ppm) δ 2.60−2.42 (1 H, m), 2.34−2.23 (1 H, m), 2.08−1.95 (1 H, m), 1.89−1.20 (3 H, m), 1.88−1.26 (3 H, m), 1.12 (0.6 H, s), 0.91 (1.8 H, s), 0.90 (7.2 H, s), 0.98 (2.4 H, s), 0.84 (0.6 H, t, J = 7.5 Hz), 0.78 (2.4 H, t, J = 7.5 Hz). The complementary mixture of diastereomers was prepared as follows: To a stirred solution or 1-(trimethylsiloxy)-2-ethyl-2-*tert*-butyl-1-cyclohexene (**17**) (2.09 g, 8.23 mmol) in THF at 0 °C was added MeLi (9.0 mL of a 1.36 M solution, 12.3 mmol) via syringe and the reaction was stirred for 45 min. The reaction was cooled to −40 °C, iodomethane (0.62 mL, 9.9 mmol) was added via syringe, and the reaction was stirred at −40 °C for an additional 7 h and then allowed to warm to room temperature overnight. The same workup and purification was employed as was described above. This procedure yielded 304 mg (19% yield) consisting of a 3:1 ratio of axial methyl (**14b**) to equatorial methyl (**14a**) diastereomers. The same NMR signals were observed, but the integral ratios were inverted compared to those described above.

General Procedure for Wittig Methylenation. To a thick suspension of methyltriphenylphosphonium bromide (6 equiv) and potassium *tert*-butoxide (6 equiv) in the minimum amount of THF at room temperature was added the ketone in minimum THF and the reaction was stirred at room temperature until TLC analysis indicated complete conversion to olefin. Following the Fitjer method,[42] hindered ketone reactions were heated (reflux) and the amount of solvent was reduced in order to increase the ylide concentration. All reactions were quenched onto aqueous NH_4Cl and extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated (aspirator) to yield crude products. Pure materials were obtained by flash chromatography or by preparative TLC using the solvent system recorded for individual examples.

Alkenes. The following alkenes have been described previously: 4-*tert*-butylmethylenecyclohexane (**1b**),[7] *cis*-2-methyl-4-*tert*-butylmethylenecyclohexane (**6a**),[8] and 2-hydroxy-4-*tert*-butylmethylenecyclohexanes **12a** and **12b**.[43]

***trans*-2-Methyl-4-*tert*-butylmethylenecyclohexane (6b).** To a stirred solution of the *trans*-2-methyl-4-*tert*-butylcyclohexanone[22] (52.4 mg, 0.31 mmol) in CH_2Cl_2 at 0 °C were added 10-mL aliquots of the preformed Lombardo reagent[44] via a large diameter cannula at 0 °C until the reaction was complete by TLC analysis. After each addition the reaction was sonicated for 1 h. The reaction was then quenched with 2:1 saturated $NaHCO_3/H_2O$ (2 × 30 mL), dried (Na_2SO_4), and filtered through a plug of coarse silica gel and then the solvent was removed (aspirator). The residue was purified by flash chromatography, (10 mm column: 10% EtOAc/hexane) to give 35.7 mg (68% yield) of a clear, colorless oil: analytical TLC on silica gel, 10% EtOAc/hexane, R_f = 0.81. 200-MNz NMR ($CDCl_3$, ppm) δ 4.62−4.6 (1 H, m), 4.54 (1 H, t, J = 2.1 Hz), 2.7−2.5 (1 H, m), 2.31−2.08 (2 H, m), 1.9−1.75 (1 H, m), 1.67−1.55 (1 H, dq, J = 11.6, 1.8 Hz), 1.48−1.12 (2 H, m), 1.08 (3 H, d, J = 7.2 Hz), 1.04−0.89 (1 H, m), 0.84 (9 H, s).

2-Hydroxy-2-methyl-4-*tert*-butylmethylenecyclohexane (10a). The standard Wittig procedure from **9a** (228 mg, 1.24 mmol), 24 h reflux, gave 221 mg (96% yield) of a clear, colorless oil: analytical TLC on silica gel, 1:6 EtOAc/hexane, R_f = 0.22. Molecular ion calcd for $C_{12}H_{22}O$: 182.16705; found *m/e* 182.1671. Error = 0 ppm. Base peak = 149 amu. IR (neat, cm^{-1}) 3594, O−H; 3077, =C−H. 200-MHz NMR ($CDCl_3$, ppm) δ 4.85 (1 H, s), 4.74 (1 H, t, J = 1.6 Hz), 2.47−2.39 (1 H, m), 2.27−2.17 (1 H, m), 1.92−1.83 (2 H, m), 1.71−1.55 (1 H, m), 1.41 (3 H, s), 1.28−0.88 (3 H, m), 0.86 (9 H, s). ^{13}C NMR (500 MHz, $CDCl_3$, ppm) δ 153.0, 106.6, 71.9, 42.8, 42.0, 32.8, 32.2, 29.0, 28.3, 27.8.

2-Hydroxy-2-methyl-4-*tert*-butylmethylenecyclohexane (10b). The standard Wittig procedure from **9b** (140 mg, 0.76 mmol), 24 h at reflux, gave 128 mg (93%) of white crystals: analytical TLC on silica gel, 1:6 EtOAc/hexane, R_f = 0.17. Pure materials (451 mg, 80% yield) was obtained by crystallization from hexane, mp 78−79 °C. Molecular ion calcd for $C_{12}H_{22}O$: 182.16705; found *m/e* 182.1671. Error = 0 ppm. Base peak = 125 amu. IR (neat, cm^{-1}) 3594, O−H; 1646, C=C; 200 MHz NMR ($CDCl_3$, ppm) δ 4.97 (1 H, dd, J = 1.7, 1.7 Hz), 4.71 (1 H, dd, J = 1.7, 1.7 Hz), 2.37−2.34 (1 H, m), 2.22−2.02 (1 H, m), 1.93−1.79 (2 H, m), 1.52 (1 H, s), 1.33 (3 H, s), 1.29−0.95 (3 H, m), 0.86 (9 H, s).

2-Methoxy-2-methyl-4-*tert*-butylmethylenecyclohexane (11b). To a stirred heterogeneous solution of NaH (744 mg, 31.0 mmol, washed

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with Et_2O and dried by N_2) in 35 mL of THF was added **10b** (112 mg, 0.61 mmol) in 10 mL of THF and the mixture was refluxed for 3 h. The mixture was then cooled to room temperature, iodomethane (2.1 mL, 34.0 mmol) was added, and the reaction was stirred for an additional 2 h. Saturated NH_4Cl was added SLOWLY until bubbling stopped. After separation of layers the aqueous layer was extracted with Et_2O (3 × 60 mL), and the combined organic layers were dried ($MgSO_4$) and concentrted (aspirator). Bulb-to-bulb distillation (pot temperature 92 °C; collection vessel temperature −78 °C; 0.5 mmHg) yielded 110 mg (92% yield) of a clear, colorless chromatographically pure oil, **11b**: analytical TLC on silica gel, 1:19 EtOAc/hexane, R_f = 0.35. Molecular ion calcd for $C_{13}H_{24}O$: 196.18271; found *m/e* 196.1826. Error = 1 ppm. Base peak = 149 amu. IR (neat, cm^{-1}) 2950, C−H; 1150. 200-MHz NMR ($CDCl_3$, ppm) δ 4.9 (1 H, dd, J = 2.1, 2.1 Hz), 4.73 (1 H, dd, J = 2.1, 2.1 Hz), 3.3 (3 H, s), 2.34 (1 H, ddd, J = 14.0, 4.4, 2.8 Hz), 2.2−2.0 (1 H, m), 1.9−1.7 (2 H, m), 1.4−0.9 (3 H, m), 1.29 (3 H, s), 0.85 (9 H, s). ^{13}C NMR (500 MHz, $CDCl_3$, ppm) δ 150.95, 105.93, 49.48, 45.42, 37.8, 33.5, 32.0, 29.7, 28.6, 27.6, 24.6, 22.7, 14.1.

2-Methoxy-2-methyl-4-*tert*-butylmethylenecyclohexane (11a). The same procedure as for **11b** was used starting with 285 mg (1.43 mmol) of **10a**. The residue was purified using basic Al_2O_3 (hexane) to yield 239 mg (80% yield) of **11a**: colorless oil; analytical TLC on silica gel, 1:19 EtOAc/hexane, R_f = 0.4. Molecular ion calcd for $C_{13}H_{24}O$: 196.18271; found *m/e* 196.1827. Error = 8 ppm. Base peak = 107 amu. IR (neat, cm^{-1}) 1640, C═C; 1070, C−O; 200-MHz NMR ($CDCl_3$, ppm) δ 4.91 (1 H, s), 4.8 (1 H, s), 3.03 (3 H, s), 2.2−2.1 (2 H, m), 2.0−1.8 (2 H, m), 1.65 (1 h, dddd, J = 12.3, 12.3, 3.4, 3.4 Hz), 1.2−0.9 (2 H, m), 1.22 (3 H, s), 0.81 (9 H, s).

2-Acetoxy-2-methyl-4-*tert*-Butylmethylenecyclohexane (11c). The title compound was prepared by treatment of alcohol **10a** with excess acetic anhydride/(dimethylamino)pyridine; analytical TLC (silica gel F254), 5% EtOAc/hexane, R_f = 0.30. MS. Base peak = 107. Exact mass calcd for $C_{14}H_{24}O_2$ 224.1776; found 224.1773. Error = 1.4 ppm. IR (neat, cm^{-1}): C−H, 2970; C═O, 1750; C−O, 1250. 200-MHz NMR ($CDCl_3$) δ 4.92 (1H, s), 4.86 (1H, s), 2.34 (1H, dt, J = 13.4, 3.8 Hz), 2.23−2.13 (2H, m), 1.99 (3H, s), 1.90−1.80 (1H, m), 1.63 (3H, s), 1.47 (1H, dt, J = 12.4, 3.3 Hz), 1.24−0.86 (2H, m), 0.84 (9H, s).

***trans*-2-Methoxy-4-*tert*-butylmethylenecyclohexane (13a).** To a solution containing *cis*-2-hydroxy-4-*tert*-butylmethylenecyclohexane (**12a**)[43] (500 mg; 2.98 mmol) and methyl iodide (0.26 mL; 4.12 mmol) in 5 mL of anydrous DME was added 78 mg (3.23 mmol) of sodium hydride in four portions over 15 min. After the heat had evolved an additional 0.1 mL of methyl iodide was added and the reaction was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the crude residue was taken up in ether. The sodium iodide was removed by filtration and the filtrate washed with ether. The combined ether layers were concentrated under reduced pressure to yield the crude ether (503 mg, 92%): oil, analytical TLC (silica gel F254), 1% ether/hexane, R_f = 0.1. MS, base peak = 93. Exact mass calcd for $C_{12}H_{22}O$ 182.1671; found 182.1678. Error = 4.1 ppm. IR (neat, cm^{-1}): C−H, 2950; C═C, 1650; C−O, 1000. 200-MHz NMR ($CDCl_3$) δ 4.85−4.80 (1H, m); 4.80−4.75 (1H, m); 3.71 (1H, t, J = 2.9 Hz); 3.20 (3H, s); 2.30−2.10 (2H, m); 2.06 (1H, dq, J = 13.4, 2.9 Hz); 1.90−1.70 (1H, m); 1.58 (1H, tt, J = 12.5, 3.1 Hz); 1.24 (1H, dt, J = 13.0, 2.9 Hz); 1.03 (1H, dd, J = 12.3, 5.7 Hz); 0.83 (9H, s).

***cis*-2-Methoxy-4-*tert*-butylmethylenecyclohexane (13b).** The same procedure as described for **13a** was used, starting from **12b**:[43] oil, analytical TLC (silica gel F254), 1% EtOAc/hexane, R_f = 0.1. MS, base peak = 125. Exact mass calcd for $C_{12}H_{22}O$ 182.1671; found 182.1673. Error = 1.3 ppm. IR (neat, cm^{-1}): C−H, 2950; C═C, 1650; C−O, 1110. 200-MHz NMR ($CDCl_3$) δ 4.90−4.85 (1H, m), 4.75−4.70 (1H, m), 3.55−3.50 (1H, m), 3.44 (3H, s), 2.50−2.30 (1H, m), 2.30−2.10 (1H, m), 2.00−1.70 (2H, m), 1.26 (1H, tt, J = 12.0, 2.9 Hz), 1.10−0.90 (2H, m), 0.85 (9H, s).

***trans*-2-Acetoxy-4-*tert*-butylmethylenecyclohexane (13c).** The title compound was prepared from **12a**[43] (0.48 g), excess acetic anhydride (1.1 mL), *p*-(dimethylamino)pyridine (0.1 g), and triethylamine (2.4 mL) in CH_2Cl_2 (30 mL), 3 h at room temperature. After routine aqueous workup, the product was purified by flash chromatography to afford 0.54 g **13c** (98%): oil, analytical TLC (silica gel F254), 5% EtOAc/hexane, R_f = 0.30. MS, base peak = 168. Exact mass calcd for $C_{13}H_{22}O_2$ 210.162; found 210.1627. Error = 3.6 ppm. IR (neat, cm^{-1}): C−H, 2970; C═O, 1750; C−O, 1230. 200-MHz NMR ($CDCl_3$) δ 5.20−5.10 (1H, m), 4.70 (2H, t, J = 1.6 Hz), 2.42 (1H, dt, J = 13.4, 2.8 Hz), 2.10 (3H, s), 2.10−2.00 (1H, m), 1.90−1.70 (1H, m), 1.42−0.95 (4H, m), 0.83 (9H, s).

2-Ethyl-2-methyl-4-*tert*-butylmethylenecyclohexane (15a,b). The standard Wittig procedure from a 3:1 mixture of **14b**−**14a** (170 mg, 0.87 mmole) was used, 24-h reflux. This produced 159 mg (94% yield) of a clear, colorless oil after chromatography, inseparable 3:1 mixture of isomers **15b:15a**: analytical TLC on silica gel, hexane, R_f = 0.69. Molecular ion calcd for $C_{14}H_{26}$ 194.20344; found *m/e* 194.2017. Error = 9 ppm. Base peak = 109 amu. IR (neat, cm^{-1}) 3083, ═C−H. 200-MHz NMR ($CDCl_3$, ppm) δ 4.70 (0.7 H, s), 4.60 (0.3 H, s), 4.59−4.55 (1 H, m), 2.34−2.1 (2 H, m), 1.9−0.89 (7.9 H, m), 1.0 (0.9 H, s), 0.99 (2.1 H, s), 0.84 (9 H, s), 0.70 (2.1 H, t, J = 7.4 Hz). The complementary mixture was prepared similarly from the 3:1 mixture of **14a**−**14b**.

Tetrahydrofuran Derivatives 19a and 19b. The silyl enol ether **7c** was prepared from a mixture of **16a,b** using the TMSCl/NaI/HN-$[SiMe_3]_2$ procedure,[24b] >9:1 isomer ratio according to NMR assay. To the crude **7c** (200 mg; 0.51 mmol) in hexane (4 mL) at 0 °C was added mCPBA (0.12 g; 0.571 mmol). After 3 h, the suspension was filtered, the hexane filtrate was evaporated, and the crude residue was taken up in 5 mL of CH_2Cl_2. Triethylamine hydrofluoride (93 mg; 1.02 mmol) was added dropwise. The reaction was stirred for 2 h and diluted with CH_2Cl_2. The mixture was washed successively with aqueous $NaHCO_3$, 1 N HCl, and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. Separation by flash chromatography (5% EtOAc/hexane) gave the axial and equatorial hydroxy ketones **18a** (59 mg) and **18b** (23 mg), 47% yield, as clear oils.

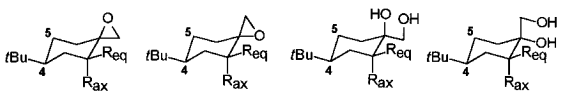
Each isomer was subjected to a modified Wittig procedure. Thus, to a stirred solution containing methyltriphenylphosphonium bromide (0.33 mmol; 0.12 g) in 2 mL of THF was added 0.83 mL (0.33 mmol) of a 0.4 M solution of potassium *tert*-butoxide in THF dropwise. The reaction was stirred for 10 min and a solution containing **18a** (56 mg; 0.16 mmol) in 2 mL of THF was added dropwise. The reaction was heated at 60 °C for 1 h. The cooled reaction was quenched by addition of saturated NH_4Cl and the mixture was extracted with ether. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to give the crude allylic alcohol which was purified via flash chromatography (5% EtOAc/hexane) to given an oil (45 mg; 82%).

To a stirred solution containing the above allylic alcohol (29 mg; 0.09 mmol) in 2 mL of THF was added 0.19 mL (0.19 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in THF. The reaction was stirred for 10 min, followed by addition of brine and extraction with ether. The ether layer was washed with water and brine, dried over $MgSO_4$, and evaporated. Purification via flash chromatography (5% MeOH/$CHCl_3$) afforded the expected diol (17 mg; 84%) as an oil.

To a stirred solution containing diethyldiazodicarboxylate (0.012 mL; 0.075 mmol) in 1 mL of Et_2O was added a solution containing the above diol (17 mg, 0.075 mmol) and triphenylphosphine (0.075 mmol; 20 mg) in 2 mL of Et_2O dropwise over 1 h. The reaction was then stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (5% EtOAc/hexane) to afford **19a** (13 mg; 82%): oil, analytical TLC (silica gel F254), 5% EtOAc/hexane, R_f = 0.35. MS, base peak = 151. Exact mass calcd for $C_{14}H_{24}O$ 208.1827; found 208.1831. Error = 1.9 ppm. IR (neat, cm^{-1}): C−H, 2920; C═C, 1630; C−O, 1120. 200-MHz NMR ($CDCl_3$) δ 4.76 (1H, s), 4.71 (1H, s), 3.83 (1H, q, J = 7.5 Hz), 3.66 (1H, q, J = 7.5 Hz), 2.50−2.10 (3H, m), 2.00−1.80 (4H, m), 1.80−1.40 (2H, m), 1.30−1.00 (2H, m), 0.83 (9H, s). ^{13}C NMR ($CDCl_3$) δ 150.19, 106.10, 83.65, 65.77, 43.68, 39.90, 33.31, 32.99, 32.01, 28.84, 27.44, 24.94.

The same sequence was performed with the minor hydroxy ketone **18b** to afford **19b**: oil, analytical TLC (silica gel F254), 5% EtOAc/hexane, R_f = 0.35. MS, base peak = 151. Exact mass calcd for $C_{14}H_{24}O$ 208.1827; found 208.1824. Error = 1.5 ppm. IR (neat, cm^{-1}): C−H, 2990; C═C, 1640; C−O, 1000. 200-MHz NMR ($CDCl_3$) δ 4.90−4.85 (1H, m), 4.70−4.60 (1H, m), 4.00−3.80 (2H, m), 2.45−2.35 (1H, m), 2.10−1.60 (6H, m), 1.25−0.90 (4H, m), 0.83 (9H, s).

Table 4. ^{13}C NMR Chemical Shifts (ppm) for C_5; Diastereomeric Epoxides and Diols or Acetonides



R_{ax}/R_{eq}	C_5	C_4	C_5	C_4	C_5	C_4	C_5	C_4
H/H	24.9[a]	47.3[a]	26.7[a]	47.3[a]	21.9	48.1	24.3	47.4
H/CH_3	24.9[a]	48.0[a]	27.0[a]	47.7[a]	b	b	24.5	47.6
CH_3/H	25.0	40.3	26.8	40.3[c]	21.9	41.0	24.1	40.1
CH_3/OCH_3	24.3	44.9	26.1	44.8	22.0[d]	44.8[d]	24.9[d]	43.8[d]
OCH_3/CH_3	24.3	41.8	26.7	41.5	22.6[d]	41.6[d]	24.8[d]	41.1[d]
OAc/CH_3	23.9	42.2	26.2	42.6	22.5[d]	42.4[d]	NA	NA
CH_3/CH_2CH_3	24.8	42.7	26.6	42.4	21.9	42.3	24.3	42.1
CH_2CH_3/CH_3	24.8	42.4	27.1	42.1	22.0	42.1	b	b
$CH_2CH_2CH_2O$	23.9	46.2	26.0	46.3	22.9[d]	45.7[d]	24.7[d]	45.2[d]
$OCH_2CH_2CH_2$	23.9	43.1	25.7	42.6	22.6[d]	42.1[d]	24.6[d]	41.6[d]

[a] Data from ref 27b. [b] Diastereomer not detected. [c] Tentative assignment; overlapping signals. [d] Value given is for the acetonide.

^{13}C NMR ($CDCl_3$) δ 152.33, 104.62, 85.72, 67.54, 46.82, 1.33, 35.73, 33.80, 32.26, 28.58, 27.57, 25.63.

General Procedure for MCPBA Epoxidations. To a stirred solution of the olefin (1 equiv, approximately 0.1−0.2 mmol) in methylene chloride (10 mL) was added 80−85% MCPBA (1.5 equiv) in 5−10 mL of methylene chloride via cannula at 0 °C. The reaction was stirred at 0 °C for 3 h and then allowed to warm to room temperature overnight. The reaction was then washed with 10% Na_2SO_3 (1 × 10 mL), 1 M $NaHCO_3$ (1 × 10 mL), and brine (2 × 10 mL) and dried ($MgSO_4$) and then the solvent was removed (aspirator). Pure materials were obtained via flash chromatography according to the Still method employing the solvent system listed for TLC analysis.

General Procedure for Dimethyldioxirane Epoxidations.[25] To a stirred solution of the olefin (1 equiv, approximately 0.2 mmol) in methylene chloride (30 mL) at 0 °C was added an excess of the dimethyldioxirane solution (in acetone 0.01−0.1 M) via syringe (normally 15−30 equiv to ensure complete conversion). The reaction was stirred at 0 °C for approximately 1 h and was then warmed to room temperature overnight, dried ($MgSO_4$), and concentrated (aspirator). Pure materials were obtained via flash chromatography (Still method) employing the solvent systems listed for TLC analysis.

Epoxides **20a** and **21a**,[7] **20b** and **21b**,[8,27b] **20c** and **21c**,[9e] and **20o** and **21o**[9e] are described in the literature. The other epoxides of Table 2 are characterized in the supporting information.

Osmylation Procedure. The procedure of Van Rheenen *et al*. was employed.[28] To a stirred solution of 4-methylmorpholine *N*-oxide (1.5 equiv) in acetone (3−6 mL) containing 5 drops of water was added a small crystal of OsO_4 (ca. 17 mg, 0.07 mmol) resulting in a yellow solution. To this solution was added the olefin (30−50 mg; 1 equiv) in acetone (2−5 mL) via cannula. The reaction was stirred at room temperature of 18−36 h after which time 2 drops of 3-mercaptopropionic acid was added and the resulting black solution was stirred at room temperature for an additional hour. The mixture was partitioned between 1 M $NaHCO_3$ and EtOAc and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine (1 × 15 mL), and dried ($MgSO_4$) and the solvent was removed (aspirator). All compounds were purified by flash chromatography using the same solvent system reported for analytic TLC unless otherwise noted. The diastereomer ratios were established by ^1H NMR assay of the product, and the composition of mixtures was confirmed after separation where possible, and at the stage of the acetonides in several cases.

Acetonide Formation. Alcohols that were difficult to purify by chromatography were converted directly into the acetonides for characterization. To a stirred solution of the diol (1 equiv) and 2,2-dimethoxypropane (1 equiv) in 3 mL of anhydrous CH_2Cl_2 was added a spatula tip of camphorsulfonic acid and the reaction was stirred for 3 h at room temperature. The reaction was diluted with Et_2O and several drops of $NaHCO_3$ were added. The solution was washed with brine, dried ($MgSO_4$), and concentrated (aspirator). All acetonides were purified via flash chromatography.

Diols/Acetonides. The diastereomeric 4-*tert*-butylmethylenecyclohexane diols (**22a** and **23a**) are described in the literature.[45] The other osmylation products are characterized in the supporting information.

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Supporting Information Available: Characterization data for epoxides and diols described in Table 2 (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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