Totally Stereoselective Additions to 2,6-Disubstituted 1,3-Dioxin-4-ones (Chiral Acetoacetic Acid Derivatives). Synthetic and Mechanistic Aspects of Remote Stereoselectivity§

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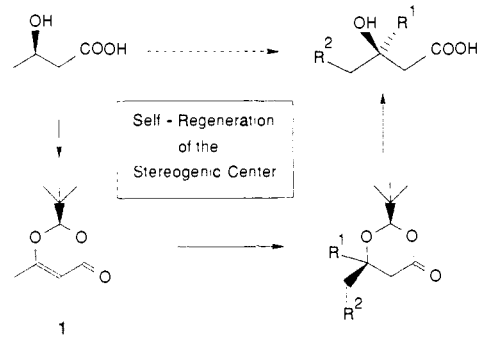
Abstract: Cuprates, Grignard reagents doped with CuI, and hydrogen activated by Pd/C add to dioxinones (**1–4**) containing a stereogenic acetal center exclusively with relative topicity *ul*. Bonding parameters of the X-ray structures of a dioxanone (**11**) and of dioxinones (**12–16**) are used to explain the different reactivities of these heterocycles (S_N2 substitution vs Michael addition) toward the same type of reagent. The observed stereoselectivity of addition to the dioxinone double bond is shown not to be due to steric effects (van der Waals forces) by molecular modeling, with the coordinates from structure analyses. A kinetic stereoelectronic effect [n → $(\sigma^*)^*$ interaction] is proposed to cause the preponderance of axial attack on the rather flat dioxinone molecule. The trigonal centers of the dioxinones are pyramidalized in the same direction from which reaction occurs. Pyramidalization of the same kind is found in almost 40 structures with sofa-type conformation of six-membered rings in the Cambridge data base. The pyramidalization and the bond lengths and angles of dioxinones are reproduced for the parent system by ab initio calculations, which also give structural data of the triplet excited state. The stereoselectivities of thermal and photochemical additions to dioxinones and other systems are correlated with pyramidalizations of the reacting centers. It is suggested that experimentally and/or computationally determined pyramidalization may be used by synthetic chemists for predicting the steric course of reactions with due care.

In the course of our work on the use of (*R*)-3-hydroxybutanoic acid[5] as a chiral synthetic building block, we also addressed the problem of replacing hydrogens at the 3- and 4-positions by other groups stereoselectively. To this end, we developed a three-step method of converting the acid to the dioxinone **1** of *R* configuration: acid-catalyzed acetalization of pivalaldehyde with the hydroxy acid, dehydrogenative bromination of the resulting *cis*-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one with *N*-bromosuccinimide, and reductive debromination (H_2–Pd/C).[6] The chiral acetoacetic acid derivative **1** thus obtained has a reactive double bond between carbons 2 and 3, as well as allylic activation at carbon 4 of the butanoic acid moiety, so that the desired overall transformations become feasible (Scheme I).[7] In a preliminary paper[8] we have mentioned that Michael addition to and catalytic hydrogenation[9] of the dioxinone **1** are highly stereoselective. It is the purpose of this paper to describe Cu(I)-induced additions to **1** in full detail and to discuss the effects that may cause the exclusive[10] formation of single diastereoisomers in reactions of the double bond in **1**, including ab initio calculations of its ground and triplet excited states.[11]

Scheme I



Preparative Results

Dialkyl, -allyl, and -phenyllithium cuprates (Gilman reagents) combine with the dioxinone **1** to give the products **5a–h** in the yields shown in Table I. Grignard reagents modified by addition of small amounts of copper(I) salts give comparable results. The ethyl (**2**) and the TBDMS-protected (hydroxymethyl)dioxinone (**3**), and, most notably, the dimethyl derivative *rac*-**4** react in the same way, see Scheme II and Table I, products **5i**, **5k**, and **7**, respectively. Thiophenol can be added to **1** under base catalysis (Et_3N), see **6**. In all cases a single diastereoisomer is formed.[10] Acid-catalyzed equilibration of **5e** ($CHCl_3$/HCl) to a ca. 1:1 mixture with its C2 epimer clearly shows that we would have detected the second stereoisomer by NMR.[12,13] The configuration of the products **5–7** was determined by nuclear Overhauser effect (NOE) measurements and by chemical correlations, see Scheme III.

As indicated in A–C, we double checked the steric relationship between cis-disposed groups by the NMR method. The dioxanones

Table I. Products of Type **5** by Addition of Cuprates or Grignard Reagents (in the Presence of ~20 mol % CuCl) to **1–3**

	product **5**		% yield with	
	R^1	R^2	$R^2{}_2CuLi$	R^2MgX/CuCl
a	CH_3	CH_3	93	
b	CH_3	CD_3	93	
c	CH_3	C_2H_5		71
d	CH_3	C_3H_7	79	91
e	CH_3	C_4H_9	71	
f	CH_3	C_8H_{17}	57	71
g	CH_3	C_6H_5	73	
h	CH_3	$CH_2CH{=}CH_2$	62	
i	C_2H_5	CH_3	90	
k	$CH_2OTBDMS$	C_4H_9	70	

5c and **5i** were hydrolyzed to the enantiomeric β-hydroxy acids **8** with quaternary carbinol centers, formally derived from an aldol

§ Dedicated to Prof. Dr. E. J. Corey on the occasion of his 60th birthday.

(1) Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, CH-8092 Zürich, Switzerland.
(2) Part of the Ph.D. Thesis of J. Zimmermann, ETH Diss. No. 8518, 1988.
(3) Part of the Master's Thesis of U. Gysel and R. Ziegler, ETH Zürich, 1987.
(4) Laboratorium für Physikalische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, CH-8092 Zürich, Switzerland.

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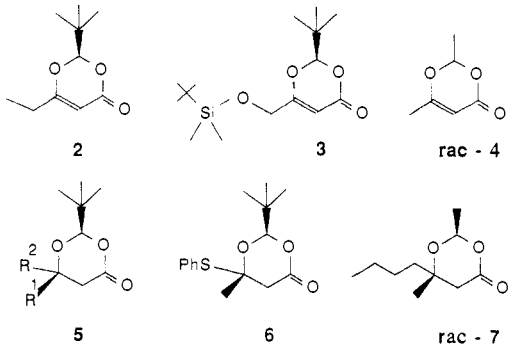
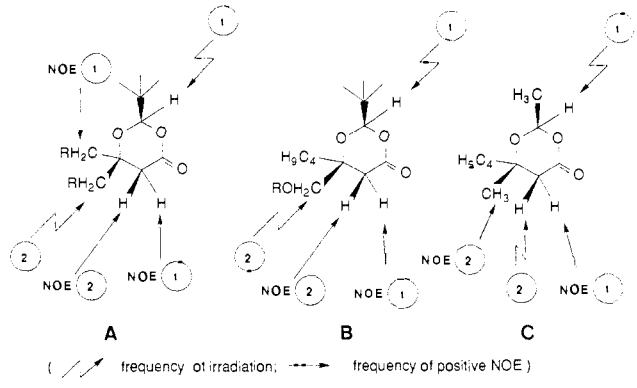
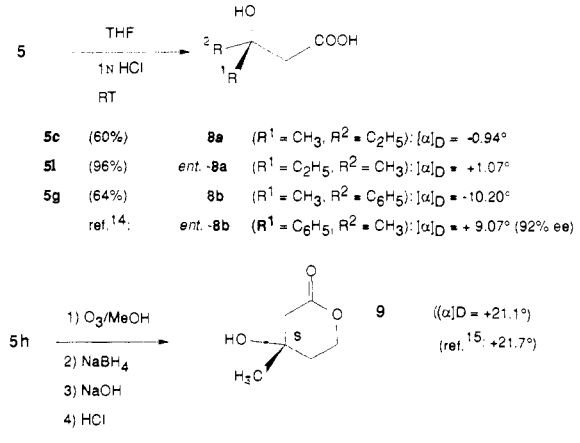
Scheme II



Scheme III





addition of acetic acid to methyl ethyl ketone,[16] The phenyldioxanone **5g** was cleaved to (*R*)-3-phenylbutanoic acid (**8b**) whose

Scheme IV

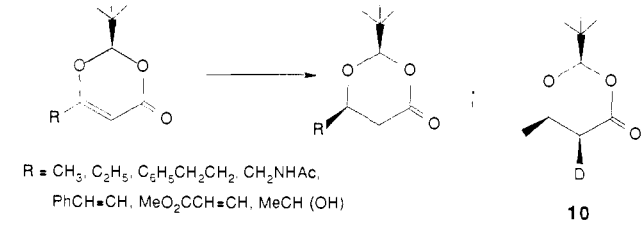
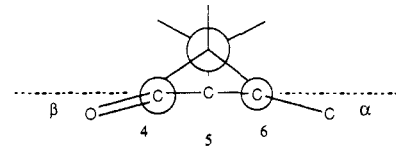


Table II, Deviations of the Trigonal Centers in the 4- and 6-Positions of Dioxinones **12–16** (For the Definition of Pyramidality Δ, See Ref 33)



	α, deg	β, deg	Δ_6, Å
bromodioxinone **12**	0.9	3.0	0.008
trimeric diketene **13**	2.0	5.0	0.014
methanone derivative **14**	2.0	2.9	0.016
salicylic acid derivative **15**	2.6	5.3	0.064
salicylic acid derivative **16**	2.5	3.8	0.061

sense and value of optical rotation was compared with those of the known *S* isomer. Finally, the allylated product **5h** was converted to (*S*)-(+)-mevalolactone (**9**), see Scheme III. Thus, the nucleophilic additions[17] have taken place from the face of the ring on which the acetal center carries the hydrogen. This is entirely analogous to the steric course of the catalytic hydrogenations of dioxinones; as shown in Scheme IV, a cis addition of the two hydrogens is observed (5-deuterio-**1** → **10**). Again, the approach of the molecules to the catalyst surface[18] occurs with the face remote from the *tert*-butyl substituent on the acetal center. In addition to the parent systems **1** and **2**, we have demonstrated this with a number of derivatives bearing various groups in the 6-position of the dioxinone.[9]

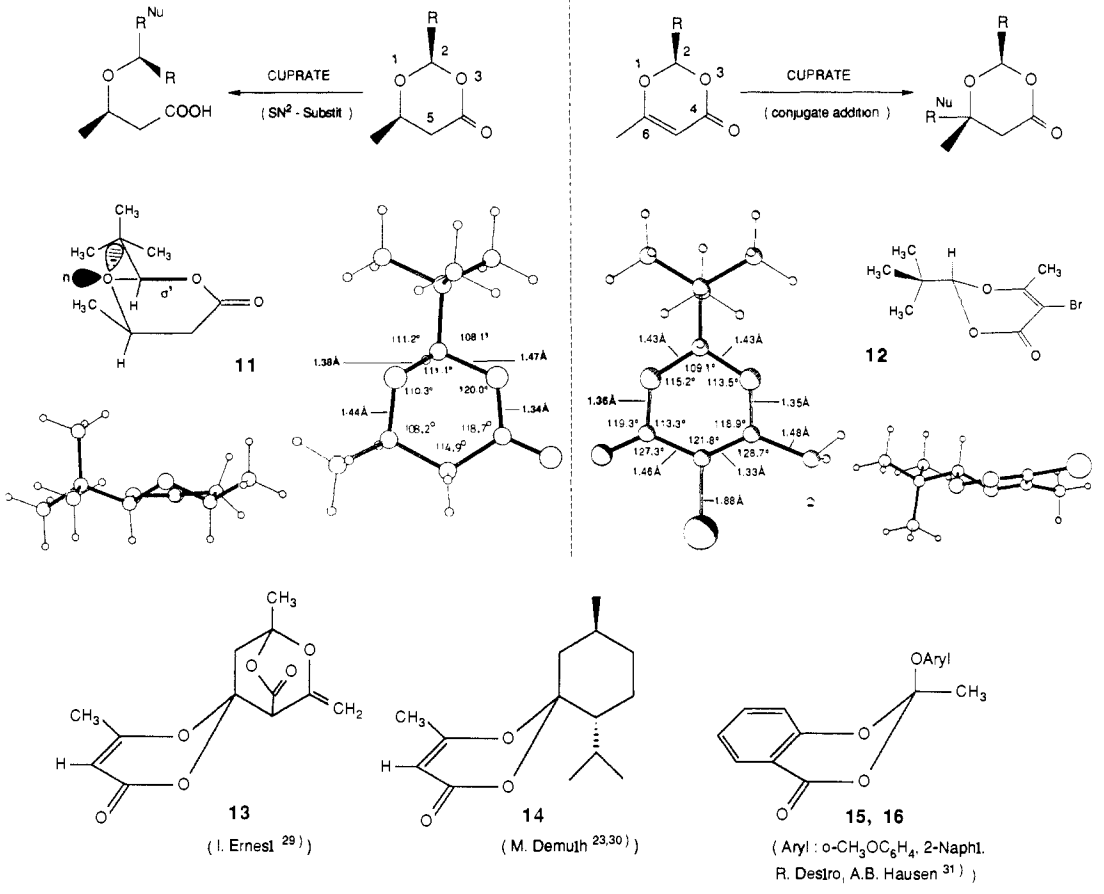
Structures, Reactivity, and Modeling

The reactions described here were surprising to us for several reasons: (i) Cuprates and other nucleophiles open up dioxanones in an S_N2 reaction occurring at the acetal carbon,[19,20] a reaction that we did not notice to compete with the conjugate additions to dioxinones, see top line of Scheme V. (ii) The high stereo-

(5) Seebach, D.; Roggo, S.; Zimmermann, J. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Verlagsgesellschaft: Weinheim, 1987; pp 85–126.
(6) Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104.
(7) Cf. the corresponding reactions of the achiral acetonide of acetoacetic acid enol: Smith, A. B. III; Scarborough, R. *Tetrahedron Lett.* **1978**, 4193. Boeckmann, R. K.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823.
(8) Seebach, D.; Zimmermann, *J. Helv. Chim. Acta* **1986**, *69*, 1147.
(9) Full paper on reactions of brominated derivatives of **1** and on hydrogenations of dioxinones: Noda, Y.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 2137.
(10) With exclusive or complete we indicate throughout this paper, that no other diastereoisomer was detected by 300-MHz ^{1}H NMR spectroscopy of the corresponding crude products.
(11) Reactions of 5-alkyliden-2-*tert*-butyl-6-methyldioxanones and of the dienolate from **1** will be described separately (Amberg, W.; Misslitz, U.; Zimmermann, J. ETH Zürich, 1986–1988).
(12) The chemical shifts of the acetal hydrogens of **5e** and its C2 epimer are 4.93 and 4.96 ppm, respectively.
(13) 5-Bromo-6-methyl- and 5-bromo-6-(bromomethyl)-1,3-dioxin-4-ones[6] are debrominated by R_2CuLi reagents and thus are no suitable Michael acceptors for cuprates.[2,9]
(14) Mitsui, K.; Konno, K.; Onuma, I.; Shimizu, K. *Nippon Kagaku Zasshi* **1964**, *85*, 437 and 497.
(15) Frye, S. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402.
(16) For a review on chiral acetic acid enolate derivatives, see: Braun, M. *Angew. Chem.* **1987**, *99*, 24; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.
(17) The yields given in Table I are obtained only if the reaction temperature of the cuprate addition is carefully controlled (see the Experimental Section): the intermediate enolates (i) can undergo fragmentation (or retro-Diels–Alder reaction?) to aldehyde and crotonates.

Compare with cuprate additions to open chain enol derivatives of acetoacetic ester and to other cyclic β-alkoxy-α,β-unsaturated carbonyl compounds: Casey, Ch. P.; Marten, D. F.; Baggs, R. A. *Tetrahedron Lett.* **1973**, 2071. Smith, A. B. III, Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Workulid, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501 and references cited therein.
(18) For recent results that may require at least a modification of our views about the mechanism of heterogeneous catalytic hydrogenation, see: Lebrilla, C. B.; Maier, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 1606. Cogen, J. M.; Maier, W. F. *Ibid.* **1986**, *108*, 7752. McEwen, A. B.; Etzkorn, F. A.; Maier, W. F. *Chimia* **1987**, *41*, 293.
(19) Seebach, D.; Imwinkelried, R.; Stucky, G. *Angew. Chem.* **1986**, *98*, 182; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 178. Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.
(20) Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, *27*, 2945.

Scheme V



selectivity of cuprate addition and hydrogenation of the dioxinones—even with a methyl group on the acetal carbon—was not expected,[21] considering that there is only one tetrahedral center in the six-membered ring of these heterocycles. (iii) Photochemical cycloadditions to dioxinones of type **1–4** tend to occur from the opposite face and with lower selectivity[22-24] (Scheme VI). We therefore sought detailed structural information from X-ray analysis, The dioxanone **11** and the bromodioxinone **12** formed suitable crystals with which the structures shown in the middle of Scheme V were determined.

The dioxanone **11** is rather flat and has a sofa conformation with five of the six atoms approximately in a plane, and the "ether" oxygen (O1) out of plane. The two oxygens in the ring are also very different with respect to their bonding parameters: O1 forms a COC bond angle of 110° (sp^3), the "ester" oxygen (O3) of 120° (sp^2); the two acetal bonds have very different bond lengths (O1–C2 1.38 and O3–C2 1.47 Å), which is a consequence of a large stereoelectronic effect,[25,26] Thus, the molecules of **11** are ideally set up for an S_N2 reaction with stereoelectronic assistance; the carboxylate anion is already on its way as a leaving group, even in the absence of a nucleophile and of an activating Lewis acid.[27] The dioxinone **12** is an even flatter molecule also present in a sofa conformation but with the acetal carbon out of plane. Both ring oxygens are now in conjugation with the carbonyl group (vinylogous carbonate structure), and their bonding is very similar.[28] We found four more structures **13–16** containing dioxinones,[29-31] two of them (**15, 16**) derived from salicylic acid and all having the same ring conformation as our bromodioxinone **12** (Scheme V). With this information in hand, it became obvious that the high diastereoselectivity of the additions to the dioxinone double bond is not caused by steric, i.e. van der Waals, effects. The *Si* attack on the *tert*-butylmethyldioxinone **1** is clearly more hindered by the 1,3-diaxial-type neighborhood of the hydrogen on the acetal center than is the *Re* attack by the methyl hydrogen on the *tert*-butyl group [1.5-disposition; also remember that replacement of *tert*-butyl by methyl did not decrease the selectivity (**4** → **7**)]. This was confirmed by molecule modeling,[32] see bottom part of Scheme VI: The coordinates of **12** were used to mimic the approach of a nucleophile from the *Re* or *Si* face, which clearly showed that there was more hindrance, especially in the early

(21) The enolates derived from dioxanones, see (i) in footnote I7, above, may react preferentially from the face cis or trans to the R group on the acetal center: Zimmermann, J.; Seebach, D. *Helv. Chim. Acta*, in press.

(22) Winkler, J. D.; Hey, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6425. Winkler, J. D.; Hey, J. P.; Hannon, F. J. *Heterocycles* **1987**, *25*, 55.

(23) Demuth, M.; Palomer, A.; Sluma, H. D.; Dey, A. K.; Kruger, C.; Tsay, Y. H. *Angew. Chem.* **1986**, *98*, 1093; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1117.

(24) Sato, M.; Sekiguchi, K.; Kaneko, Ch. *Chem. Lett.* **1985**, 1057 and earlier papers by this group, cited therein. Sato, M.; Takyama, K.; Furuya, T.; Inukai, N.; Kaneko, Ch. *Chem. Pharm. Bull. Jpn.* **1987**, *35*, 3971.

(25) Reviews: Kirby, A. J. *Reactivity and Structure Concepts in Organic Chemistry*; Springer-Verlag: Berlin, 1983; Vol. 15. Deslongchamps, P. In *Stereoelectronic Effect in Organic Chemistry*; Pergamon: Oxford, 1983.

(26) Jones, P. G.; Kirby, A. J. *J. Chem. Soc., Chem. Commun.* **1979**, 288.

(27) The radical bromination[6] of **11** and of the 2-methyl analogue appears to occur preferentially on C6. If the conformation found in the crystal is relevant for this reaction, it is only HC2 and HC6 that can be removed with stereoelectronic assistance.[25] It seems that HC2 is deactivated, rather than activated by the second oxygen.

(28) The coordinates and thermal parameters of the structures described here (**11, 12**) are available as supplementary material and have been deposited in the Cambridge Crystallographic Data File. Some information about the structure analyses is given in the Experimental Section.

(29) Ernest, I.; Fritz, H.; Rihs, G. *Helv. Chim. Acta* **1987**, *70*, 203.

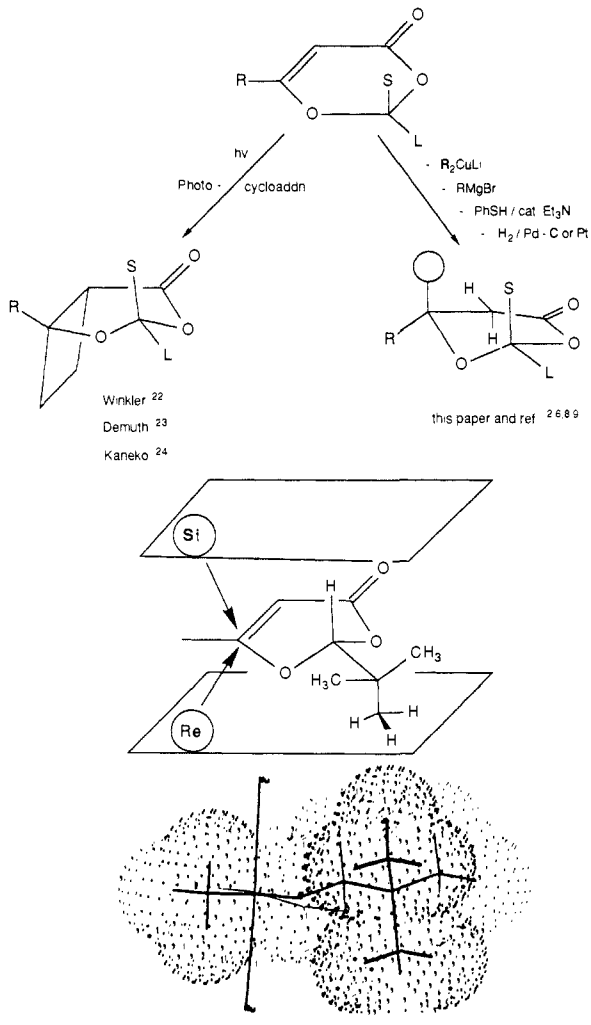
(30) Demuth, M., personal communication, 1987.

(31) Jørgensen, J. E.; Hansen, A. B. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1982**, *B38*, 991. Destro, R.; Saccarello, M. L. *Tetrahedron* **1983**, *39*, 3151.

(32) Evans Sutherland, PS 300.

(33) Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783.

Scheme VI



stages, by the axial hydrogen on the acetal center.

Closer inspection of the five dioxinone structures revealed another fascinating common feature: all the trigonal carbon atoms are pyramidalized in the direction of the acetal center, the out-of-plane bow. The actual values on carbons 4 and 6 are given in Table II, the deviations from planarity are small (0.9–5.3°, notably largest on the aromatic carbons), but significant and consistent in their direction. A search in the Cambridge crystallographic data base[34] furnished another 40 structures[35] (D, E, G, H) that fulfilled the requirements that they contain at least three adjacent trigonal centers, have at least one enol ether oxygen (or enamine nitrogen) in the ring, and exist in a sofa conformation with a tetrahedral carbon atom outside of an approximately coplanar assembly of the other five atoms. The result is shown in Scheme VII and confirms what we found in the dioxinones F. With high fidelity (percentage values in the small tables underneath each structural type), the trigonal centers are pyramidalized in the direction of the bow, the average values α lying between 0.8 and 4.2°. In systems not containing the enamine or enol ether structural moiety and in five-ring analogues of D–H, pyramidalizations were found to be smaller and/or erratic with respect to the folding of the ring.

Computations

In order to find out whether the pyramidalization effect found in the crystalline state is reproduced by theory, we took the unsubstituted model dioxinone **17** all the way to the gas phase, which would also allow us to gain information about the excited state(s) of this molecule. The quantum-chemical calculations were carried out with the GAUSSIAN 82 program system.[36] A complete geometry optimization of the ground and the lowest lying excited triplet states $[(n\pi^*)^3]$ with respect to all 27 internal coordinates was performed with ab initio self-consistent field (SCF) gradients. The split-valence 3-21 G basis set[37] was employed throughout. For the $(n\pi^*)^3$ state the spin-unrestricted Hartree–Fock method was employed. The results are shown in Scheme VIII. All salient features of the crystal structures of dioxinones are reproduced by the calculation of the parent system **17**: the quasi-symmetry of the binding of the two ring oxygens and the degree as well as the direction of pyramidalization of the three trigonal centers. The energy required to push the carbonyl oxygen into the plane of the carbon atoms is, however, calculated to be extremely small (0.12 kcal/mol, with complete relaxation of the entire molecule). The triplet geometry is very interesting; as with simple carbonyl compounds,[38] there is strong pyramidalization in the excited state. The lowest lying triplet of **17** that we found has a dramatic pyramidalization at C6 in the same direction as the ground state. There are two more triplet states only 1.9 and 3.2 kcal/mol higher in energy than the most stable one, and these are both pyramidalized at C6 in opposite direction. The carbonyl carbon (C4) and C5 are essentially planar in all three triplet states.[39]

Discussion and Conclusions

At the outset of a discussion about a reaction mechanism we must be sure whether the observed reaction is subject to kinetic or thermodynamic control. In the first case, transition state, in the second case product stabilities matter. The acid-catalyzed equilibration of our products (cf. **5e**) with their epimers indicates kinetic control of the overall reaction.[40] On the other hand, Corey[41] has shown that the primary cuprate addition to an enone to form a Cu(III) adduct prior to C–C bond formation may be reversible. While we can not exclude that this might also happen in cuprate additions to the dioxinones, their catalytic cis hydrogenation (Scheme IV) can not be the result of such a preequilibration.[42] Since both reactions follow the same steric course, we may assume that both are under kinetic control.

How, then, can the higher reactivity of that diastereotopic face of dioxinones be rationalized, which appears to be more hindered in the conformation we find to be present both in the solid state and in the gas phase? The stereoselectivity of acceptor and donor double bonds bearing an allylic stereogenic center or a center with diastereotopic substituents (I in Scheme IX) has been studied extensively. These transformations involve the reactivity of allylic and α-carbonyl centers (a), direct and conjugate nucleophilic additions to carbonyl, imine, and nitro groups, radical, electrophilic, and pericyclic additions to double bonds (b/c), as well as $S_{N'}$ and $S_{E'}$ reactions (c). The additions to dioxinone double bonds described here belong to another group of transformations in which diastereoface selectivity is caused by remote groups,[43] in particular

(34) Cambridge Structural Data Base (CS), 4.9.1987.

(35) Structures in the Cambridge File with a bond to the sp^3 carbon as part of a further ring and with heteroatoms at the double bond were excluded. The pyramidalization was not calculated for structures containing a hydrogen at the trigonal center. The symbols of the Cambridge File structures we included are the following. D ($R < 6\%$, $\sigma_{C-C} < 0.01$ Å): BEJBUN, BETGAI, BEXLOF, BEXLUL, BEZZIP, BIGSAL, BIYSIL, BIYSOR, CEBKID 10, CEGREL, CIXFOE 10, COPHIY, CURHUS, DARYUQ, DEBPOP, ERSTNA, ERSTND, MHNPYO, PENMEB, PMFPSH, SPIPYR. E ($R < 7\%$, $\sigma_{C-C} < 0.01$ Å): BAMHEC, BRFLAYP 20, CEMBAX, DECYEP, DELYIC, DOLRIF, IPBPNM. F: BEGTIQ, CANXUK, ref 29–31. G: BASBAY, BFRNDX, CUNWEN, DIWSOR, DOBTET, STREPB 10, CIKSIY. H: BUGDEM, CPXHQM, PMHQZC 10, PCXQCO, PICQCD.

(36) Binkley, J. S.; Frisch, M. J.; De Frees, D. J.; Raghavachari, K.; Whitehead, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A. GAUSSIAN 82, Carnegie-Mellon University, Pittsburgh, PA, 1983.

(37) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(38) Robinson, G. W.; Erdmanis Di Giorgio, V. *Can. J. Chem.* **1958**, *36*, 31.

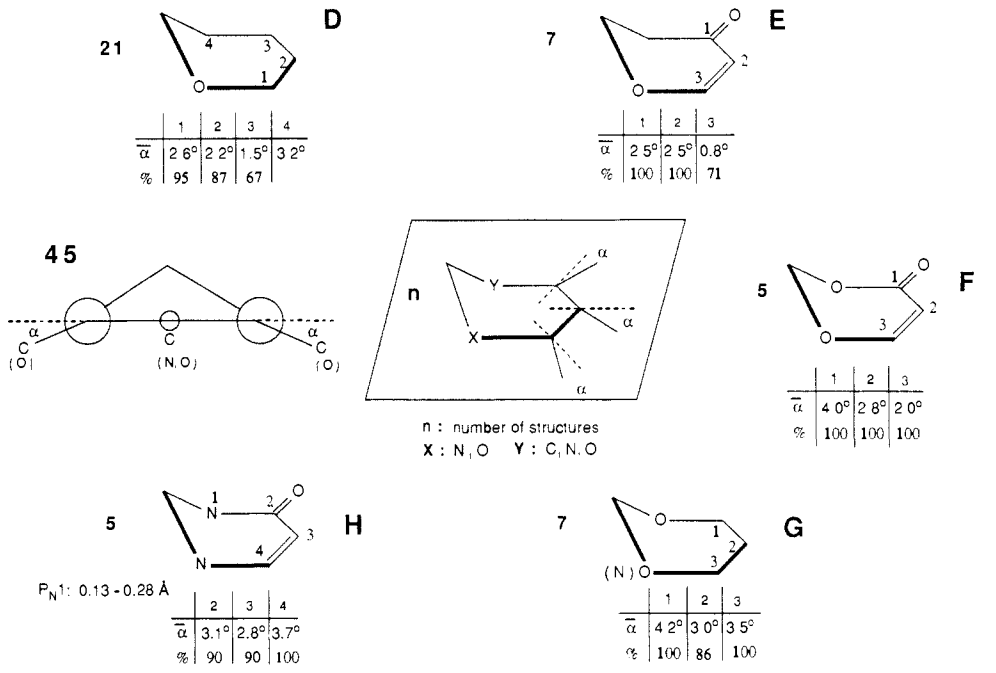
(39) The coordinates, net charges, and overlap populations of the calculated structure are available as supplementary material.

(40) Thermodynamically controlled formation of simple dioxanones from aldehydes and hydroxybutanoic acid leads to the cis products with selectivities of ca. 90%,[19] much smaller than those observed in the reaction described here!

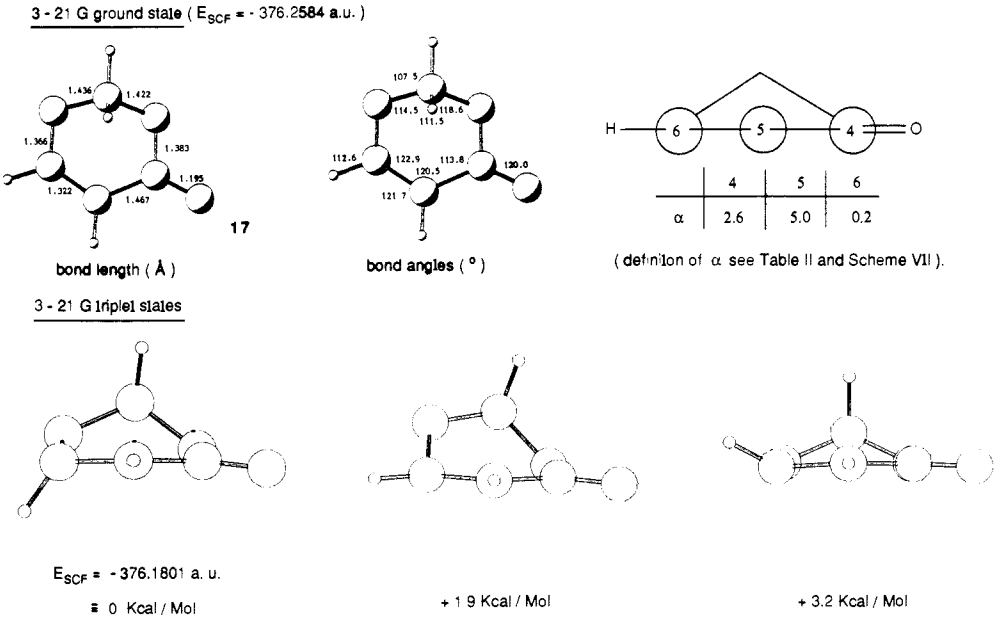
(41) Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, *26*, 6015.

(42) On the other hand, the base-catalyzed, low-yield addition of thiophenol (→ **6**) is probably thermodynamically controlled.

Scheme VII



Scheme VIII



by stereogenic centers that are separated from the reacting double bond through a heteroatom as in enamines, enol ethers (K),[44] their allylic analogues (L),[45,46] or structures with even further remote inducing centers. In the case of enamines and allylic amines[47-51] the nitrogen atom is pyramidal; it may be a stereogenic center in the structural unit $R^1R^2R^3N$; and can thus transmit steric effects. In the contrary, the oxygen atom in R^1OR^2 is not a stereogenic center. Still, it can exert powerful directional (ster-

(43) See for instance the discussions about additions to adamantanones: (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. (c) Laube, Th.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876.

(44) Only a few selected examples can be referred to here: Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. Charlton, J. L. *Tetrahedron Lett.* **1985**, *26*, 3413. Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498. Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. Frauenrath, H.; Phillipps, Th. *Angew. Chem.* **1986**, *98*, 261; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 274.

(45) See for instance the following recent papers and references cited therein: Maruoka, K.; Yamamoto, H. *Angew. Chem.* **1985**, *97*, 670; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668. Mash, E. A.; Nelson, K. A.; Heidt, Ph. C. *Tetrahedron Lett.* **1987**, *28*, 1865. Enders, D. In *Asymmetric Synthesis*; Academic: Orlando, FL, 1984; Vol. 3, pp 275–341. Lutomisci, K. A.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 2542.

(46) Seebach, D.; Imwinkelried, R.; Weber, Th. In *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4.

(47) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, Ch. *Helv. Chim. Acta* **1978**, *61*, 3108.

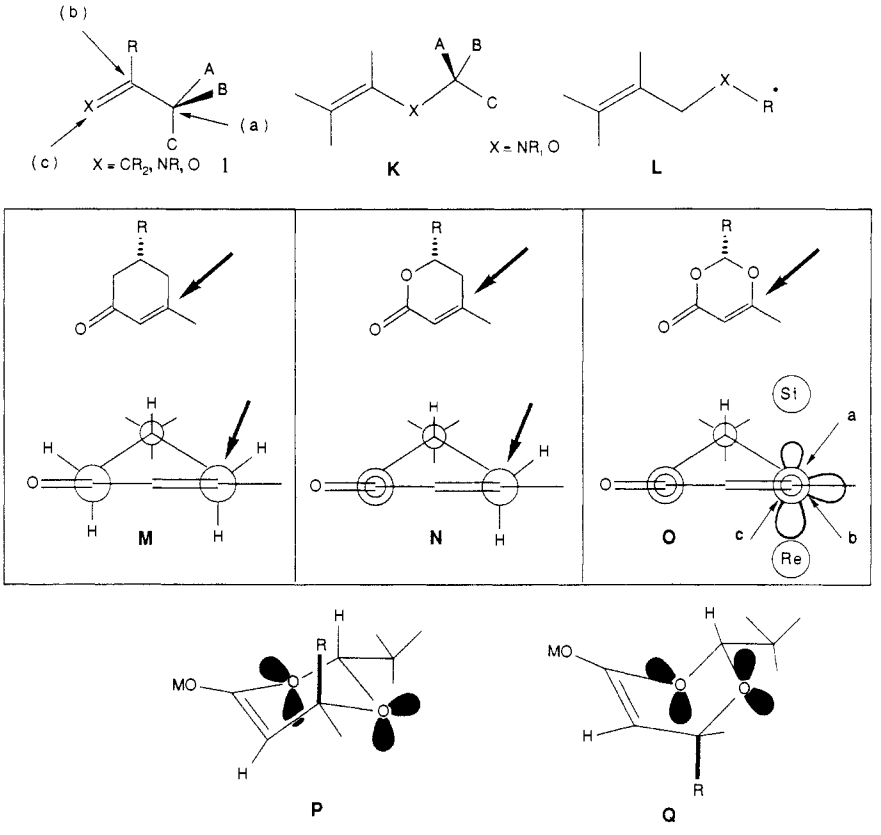
(48) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637.

(49) Li–enolates of carboxylic acid amides: Bauer, W.; Laube, Th.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. Laube, Th.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373.

(50) (a) Müller, K.; Brown, L. D. *Helv. Chim. Acta* **1978**, *61*, 1407. (b) Meyer, R. *Helv. Chim. Acta* **1978**, *61*, 1418.

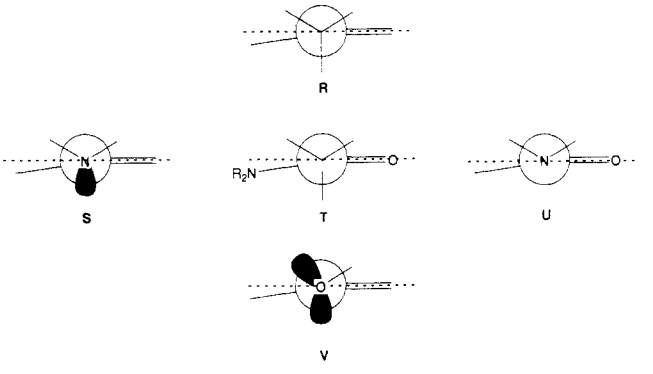
(51) Amides and peptides with pyramidal nitrogen: Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 251. Carlsen, N. R.; Radom, L.; Rodwell, W. R.; Riggs, N. V. *J. Am. Chem. Soc.* **1979**, *101*, 2233. Cieplak, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 271. Weber, Th.; Aeschimann, R.; Maetzke, Th.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365.

Scheme IX



eoelectronic[25,26,52]) effects if its two lone pairs of electrons are different, see for instance the "ether-type" oxygen in dioxanone **11** (Scheme V). If we apply the most reliable ("first order") effects[53] for discussing stereoselective additions to trigonal centers, i.e. maximum staggering[54] or minimization of torsional strain[55] in the transition state,[56] to the dioxinones, the observed selectivity a in O is formally analogous to that reported for cyclohexenones[57] M and lactones[58] N, see Scheme IX.[59] By attack of a nucleophile from the *Si* face of dioxinone **1**, a chair conformer P of an enolate is formed.[60] Only the *Si* approach of R would be subject to kinetic stereoelectronic control [n → $(\sigma^*)^\ddagger$] starting from the nonplanar dioxinone conformation O with a Bürgi–Dunitz trajectory[61a] (see a and b), and keeping the substituent on the acetal center in a pseudoequatorial position. A boat conformer Q would result from a trajectory c. In addition to stereoelectronic assistance by an electron pair on the adjacent oxygen in both approaches (O → P and O → Q), there is formally an E_2-anti relationship in the

Scheme X



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(55) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 701. Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205. For reviews, see: Thomas, A. F. *Deuterium Labeling in Organic Chemistry*; Meredith: New York, 1971. Toromanoff, E. *Tetrahedron* **1980**, *36*, 2809. Bucourt, R. *Top. Stereochem.* **1974**, *8*, 158.

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(59) Considering the fact that the difference between staggered and eclipsed conformations becomes smaller as substituents on one center of the single bond are replaced by electron pairs, the especially high selectivity for axial or *Si* attack on the dioxinones—lacking substitution in the α-position of the reacting trigonal center—still appears surprizing. The following rotational barriers (in kilocalories/mole) have been reported: CH_3CH_3 (2.9), CH_3–NH_2 (2.0), CH_3–OH (1.1); HO–OH (7.0, spp, eclipsed and 1.1 app, eclipsed, respectively). Millen, D. J. In *Progress in Stereochemistry*; de la Mare, P., Klyne, W., Eds.; Butterworths: London, 1966; Vol. 3, pp 128–168.

(60) It is evident from crystal structures of ester enolates that the R group on oxygen is not coplanar with the π-system, i.e. the oxygen is no more sp^2 hybridized: Seebach, D.; Amstutz, R.; Laube, Th.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

(61) For the Bürgi–Dunitz structure–reactivity correlation see the following references: (a) Bürgi, H.-B. *Angew. Chem.* **1975**, *87*, 461; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460. Bürgi, H.-B., Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153. Dunitz, J. D. *X-ray Analysis and the Structure of Organic Molecules*; Cornell University: Ithaca, NY, 1979. (b) For exponential perturbation correlation between ground state molecular structure and activation energy see: Kirby, A. J.; Jones, P. G. *J. Am. Chem. Soc.* **1984**, *106*, 6207. Bürgi, H.-B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 2924. Bürgi, H.-B.; Dubler-Steudle, K. C., submitted for publication in *J. Am. Chem. Soc.* (c) The general applicability of linear perturbation to simulate changes in ground-state geometries is discussed in: Bürgi, H.-B.; Dunitz, J. D. *Acta Crystallogr., Sect. B: Struct. Sci.*, in press.

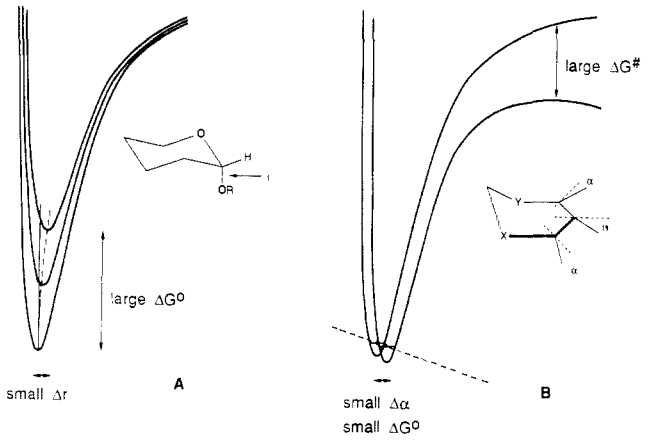

Figure 1. Perturbation of Morse functions that lead to small distortions in the ground state can result in large energy differences in the transition state. (A) Exponentially increasing perturbation,[61b] (B) linear perturbation[61c] of a Morse function (in order to make the small change in the ground state visible; the curve resulting from subtraction of a linearly increasing increment has been moved somewhat to the right).

chair and an E_2-syn relationship[62] in the boat between the developing bond and an electron pair on the vinylogous oxygen.

There are several, partially conflicting models by which the most favorable, the reactive conformation for attack with maximum staggering on trigonal centers has been proposed to be deducible.[62-70] None of them is directly applicable[71-73] to the additions to dioxinones of both cuprates and H_2. In a polar model,[70] nucleophiles attack preferentially from the face of the double bond system that is less electron-rich. This would be the case with the dioxinones if we assume that the ring oxygens are hybridized between sp^2 and sp^3 (*Re* lobe larger than *Si* lobe in O) and/or that the nonbonding sp^2 lone pair of electrons is displaced toward the *Re* face by the out-of-plane disposition of the acetal carbon.[64,74]

To which extent can the pyramidalization of the trigonal carbon atoms in the sofa-conformers D–H (Scheme VII) be used as a guide to discuss reactivity and selectivity? Trigonal carbons ("sp^2 centers") have been recognized to be pyramidal[74-78] rather than planar (a) when put into an unsymmetrical environment,[74-76] (b) when part of distorted, strained systems,[74-76] (c) when strongly polarized,[77] and (d) in electronically excited states.[78] Pyramidalization was discovered experimentally,[47,51,79] it follows from molecular modeling calculations,[50b,80,81] and it results from theory applying various levels of computation.[81-86] The ground states of polycyclic hydrocarbons have so far been the main objects in studies of this basic phenomenon. An international symposium and the volume containing the proceedings,[74] entire book chapters,[75] and extensive review articles[76] have been devoted to it (see R in Scheme X). Systems involving nonbonding electron pairs that have been investigated are enamines and amides[47-51] (see S–U), We have now discovered pyramidalization in monocyclic enol ether and α,β-unsaturated carbonyl systems (see V) by X-ray crystal structure analysis and we retrieved dozens of similar examples from the Cambridge crystallographic data base[87] (Scheme VII). The experimental findings are confirmed by ab initio calculations of the parent heterocycle, in addition providing a measure for the energies involved in the pyramidalization, which are very small indeed, This is in agreement with the notion[76,81] that ground-state pyramidalization is not causing stereoselectivity (a transition-state effect) but that both phenomena have the same origin.[88]

There is another way of describing this type of correlation between ground state geometry distortions and activation energy differences. If a force is acting to lengthen a bond or change an angle, a very small geometric distortion in the new ground state may correspond to an appreciable change in activation energy. For bond lengths, this has been described[61b] by using a modified Morse function, see Figure 1A. For the case at hand this is demonstrated in Figure 1B.

Thus, if a small degree of pyramidalization of a trigonal center next to a tetrahedral center (R in Scheme X) is caused by the tendency to minimize torsional strain, approach of a reagent from the same direction into which pyramidalization has occurred will minimize torsion even more. In contrast, approach from the opposite site would increase torsional strain. The energy difference

(62) Vogel, E.; Carvatti, G.; Frack, P.; Aristoff, P.; Moody, Ch.; Becher, A. M.; Felix, D.; Eschenmoser, A. *Chem. Lett.* **1987**, 219. Winter, C. E. *J. Chem. Ed.* **1987**, *64*, 587.

(63) Least-motion principle: Tee, O. S. *J. Am. Chem. Soc.* **1969**, *91*, 7144.

(64) (a) Nonequivalent orbital extension: Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (b) Huisgen's factor "X": Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. C. *J. Am. Chem. Soc.* **1980**, *102*, 3951. (c) Orbital distortion: Burgess, E. M.; Liotta, Ch. C. *J. Org. Chem.* **1981**, *46*, 1703.

(65) $\pi \rightarrow \sigma^*$ donation in the neighboring bond in nucleophilic and $\sigma \rightarrow \pi^*$ donation in electrophilic additions: Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. Klein, S. *Tetrahedron* **1974**, *30*, 3349. Anh, N. T.; Eisenstein, O. *Top. Curr. Chem.* **1980**, *88*, 145.

(66) For collections of examples, see for instance: Bernhard, W.; Fleming, I.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1984**, 28. Chow, H. F.; Fleming, I. *Tetrahedron Lett.* **1985**, *26*, 397. Fleming, I.; Lewis, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 149. McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601. Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464. Franck, R. W.; John, T. V.; Olegniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106. Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. *Tetrahedron Lett.* **1987**, *27*, 3187.

(67) Hyperconjugation: (a) Reference 43b,c. (b) Spanget, J.; Gleiter, R. *Tetrahedron Lett.* **1982**, *23*, 2435.

(68) $\sigma \rightarrow (\sigma^*)^*$ Donation: ref 43a and Johnson, C. R.; Tait, B. O.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875.

(69) There is still a controversy about whether a C–H or a C–C bond is the better antiperiplanar donor: Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580.

(70) Nucleophile attack from the face of smaller, electrophilic attack from the face of larger negative charge density: Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7396. Kahn, S. D.; Hehre, W. J. *Ibid.* **1986**, *108*, 7399. Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *Ibid.* **1987**, *109*, 650. Kahn, S. D.; Hehre, J. *Ibid.* **1987**, *109*, 663 and 666.

(71) The Cieplak model[43a,68] predicts that in "electron-deficient transition states" the best donor bond (lowest lying σ-orbital) should be antiperiplanar to the developing σ-bond [$\sigma \rightarrow (\sigma^*)^*$ donation], irrespective of the nature of the reaction (polar/nonpolar, electrophilic, nucleophilic, radical, pericyclic).[72] Formally, a nonbonding electron pair takes the role of the donor in the present case. For a discussion of stereoselective protonations of enols and enolates, see also: Zimmermann, H. E. *Acc. Chem. Res.* **1987**, *20*, 263.

(72) See also the very similar rotational barriers of an α-carbon next to an electrophilic, radical, or nucleophilic transition state of addition to a trigonal center as calculated by Houk et al., ref 53a.

(73) Corey suggests[41] that an app acceptor σ-bond is most favorable for cuprate additions, see also footnote 65.

(74) *Stereochemistry and Reactivity of Systems Containing π-Electrons*; Proceedings of a Symposium held in 1982, in honor of Prof. P. Bartlett; Watson, W. H., Ed.; Verlag Chemie: Deerfield and Weinheim, 1983.

(75) Greenberg, A.; Liebmann, J. F. In *Strained Organic Molecules*; Academic: New York, 1978.

(76) (a) Houk, K. N. Chapter 1 (pp 1–40) in ref 74. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G. *J. Mol. Struct.* **1983**, *103*, 197. (c) Houk, K. N.; Rondan, N. G.; Brown, F. K. *Isr. J. Chem.* **1983**, *23*, 3.

(77) Sudden polarization and pyramidalization: Salem, L. *Acc. Chem. Res.* **1979**, *12*, 87. Brooks, B. R.; Schaefer, H. F. *J. Am. Chem. Soc.* **1979**, *101*, 307. Volland, W. V.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 533.

(78) (a) *Einführung in die Photochemie*; Becker, H. G. O., Ed.; G. Thieme Verlag: Stuttgart, 1983. (b) Wiesner, K. *Tetrahedron* **1975**, *31*, 1655.

(79) Burnell, E. E.; Diehl, P. *Can. J. Chem.* **1972**, *50*, 3566. For a recent example (X-ray structure): Butler, R. N.; Gillan, A. M.; McArdle, P.; Cunningham, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1016.

(80) Burkert, U. *Angew. Chem.* **1981**, *93*, 602; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 572.

(81) Houk, K. N.; Rondan, N. G.; Brown, F. K.; Jorgensen, W. C.; Madura, J. D.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 5980.

(82) Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 6941.

(83) Wagner, H. U.; Szeimies, G.; Chandrasekhar, J.; Schleyer, P. v. R.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1978**, *100*, 1210.

(84) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan-Nelson, G.; Domelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482.

(85) Wipff, G.; Morokuma, K. *Chem. Phys. Lett.* **1980**, *74*, 400.

(86) Wipff, G.; Morokuma, K. *Tetrahedron Lett.* **1980**, *21*, 4446.

(87) A similar search for bicyclic alkenes has been performed by Watson, W. H., mentioned in footnote 13 of ref 81.

(88) Which in turn is common with the origin of the higher stability of staggered vs eclipsed ethane.[76,81]

between the two transition states will be larger than the one between the oppositely pyramidalized ground states.

We cannot resist the temptation of making the following extending statement; *the steric course of attack on a trigonal center can be predicted from the direction of its pyramidalization* (reaction occurs preferentially from the direction into which the center is pyramidalized).[89] The degree and direction of pyramidalization can be determined experimentally if the species involved are stable and will in many cases be available from crystallographic data files. Thanks to vastly improved computational facilities, structures of increasing complexity are now subject to rigorous calculations, and the case reported here might help to raise confidence among synthetic chemists for using this tool even for predicting reactivity of species not amenable to experimental structure determination.

For excited-state reactions[77,78,81] the computational approach is essentially the only one producing structural data of the species involved, see for instance the photocycloadditions to α,β-unsaturated carbonyl compounds (DNA bases,[90] cycloalkenones).[78b,91-94] Photocycloaddition and Michael addition/hydrogenation occur from diastereotopic faces of the dioxinone system (Scheme VI).[23,24] This is compatible with the direction of pyramidalization of two of the three triplets that we found by computation (Scheme VIII). In triplets, pyramidalization is so strong that it now may be the origin of the observed stereoselectivities.

We are aware of the possible pitfalls en route from crystal and gas-phase structures (ground state) to reactive conformations in solution (transition states), i.e. of the Curtin–Hammett principle.[95,96] Nowadays, the necessary care in doing this is provided by molecular modeling of transition states.[53]

Experimental Section

General Methods. Merck Kieselgel 60 (silica, mesh size 0.040–0.064) was used for flash chromatography. Specific rotations were determined with $CHCl_3$ as solvent at 25 °C. All NMR spectra were recorded with TMS as internal standard in $CDCl_3$ as solvent. Signals marked with an asterisk (*) disappear on addition of D_2O. Buffer solution of pH 7 was prepared by dissolving potassium dihydrogen phosphate (85 g) and sodium hydroxide (14.5 g) in water (950 mL).

(2*R*)-2-*tert*-Butyl-6-dimethyl-1,3-dioxan-4-one (5a). Cuprous(I) iodide (2.17 g, 11.4 mmol) was suspended in ether (14 mL), and methyllithium (14 mL, 22.7 mmol, 1.6 M in ether) was added over 20 min at 0 °C. The yellow solution was cooled to −75 °C, dioxinone **1** (643 mg, 3.78 mmol) in ether (7 mL) was added, and the reaction mixture was warmed to −20 °C over a period of 2 h. The yellow suspension was quenched with ammonia/saturated ammonium chloride (35 mL, 1:1) and stirred at 0 °C open to the atmosphere until it became blue. The solution was extracted with ether (3 × 200 mL), dried, and evaporated to give **5a** (654 mg, 93%) as a solid, which was pure according the ^1H NMR data: mp 46.0–46.6 °C (hexane); $[\alpha]_D$ +9.7° (*c* 1.10); IR (KBr) 2980 (m), 2940 (m), 2880 (w), 1755 (s), 1745 (s), 1490 (m), 1365 (m), 1315 (m), 1260 (s), 1135 (m), 1095 (m), 985 (s), 970 cm^{-1} (s); ^1H NMR δ 0.97 (s, *tert*-butyl), 1.31 (s, CH_3), 1.34 (s, CH_3), 2.52 (d, J = 16.2 Hz, A part of the AB system, $CH_AC{=}O$), 2.62 (d, J = 16.2 Hz, B part of the AB system), $CH_BC{=}O$), 4.96 (s, OCHO); ^{13}C NMR δ 23.96, 26.55, 29.69, 34.57, 42.24, 72.84, 103.00, 169.84; MS, *m/z* 187 (M^+ + 1, 8), 186 (M^+, 0.2), 185 (M^+ − 1, 1.1), 129 (55), 101 (16), 87 (32), 85 (35), 84 (17), 83 (100), 71 (16), 69 (8), 59 (81), 58 (50), 57 (87), 56 (89), 55 (23), 43 (40), 41 (45), 39 (10), 29 (16), 27 (7). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.33; H, 10.10.

(2*R*,6*S*)-2-*tert*-Butyl-6-methyl-6-(trideuteriomethyl)-1,3-dioxan-4-one (5b). Via the procedure described for **5a**, cuprous(I) iodide (1.55 g, 8.1 mmol) in ether (10 mL), (trideuteriomethyl)lithium (15 mL, 16.25 mmol, 1.08 M in ether), and dioxinone **1** (460 mg, 2.7 mmol) in ether (5 mL) gave the dioxanone **5b** (477 mg, 93%, ds >98%) as a solid, which was pure according to the ^1H NMR data: mp 46–47 °C (hexane); $[\alpha]_D$ +10.2° (*c* 1.22); IR (KBr) 2980 (s), 2940 (m), 2880 (m), 2230 (w), 1750 (s), 1490 (m), 1440 (m), 1410 (m), 1380 (m), 1365 (s), 1320 (s), 1290 (s), 1260 (s), 1230 (s), 1190 (m), 1120 (s), 1090 (m), 1050 (m), 1030 (m), 970 (s), 950 (s), 870 (m), 790 (w), 770 (m), 730 cm^{-1} (m); ^1H NMR δ 0.97 (s, *tert*-butyl), 1.30 (s, CH_3), 2.52 (d, J = 16.2 Hz, A part of the AB system, $CH_AC{=}O$), 2.61 (d, J = 16.2, B part of the AB system, $CH_BC{=}O$), 4.96 (s, OCHO); ^{13}C NMR δ 23.95, 25.43, 25.68, 25.93, 29.60, 34.54, 42.15, 72.67, 102.99, 169.82; MS, *m/z* 190 (M^+ + 1, 0.1), 188 (M^+ − 1, 0.2), 132 (20), 88 (6), 87 (11), 86 (100), 85 (10), 71 (5), 62 (33), 60 (7), 59 (53), 58 (10), 57 (43), 46 (8), 44 (6), 43 (20), 42 (7), 41 (24), 39 (8), 31 (6), 29 (17), 27 (8). Anal. Calcd for $C_{10}H_{15}D_3O_3$: C, 63.46; H, 9.59. Found: C, 63.05; H, 10.08.

(2*R*,6*S*)-2-*tert*-Butyl-6-ethyl-6-methyl-1,3-dioxan-4-one (5c). Ethylmagnesium bromide (17.6 mL, 35.25 mmol, 2 M in THF) was added dropwise to cuprous(I) chloride (349 mg, 3.53 mmol) at 0 °C over 10 min. The dark reaction mixture was diluted with ether (48 mL) and then cooled to −75 °C. Dioxinone **1** (3 g, 17.6 mmol) in ether (36 mL) was added over 70 min at −75 °C. After being stirred for 2 h at this temperature, the solution was quenched with pH 7 buffer (6 mL) and then allowed to warm up to 20 °C. Ammonia and saturated ammonium chloride (24 mL, 1:1) were added, and the mixture was stirred in contact with air until it became blue. The solution was extracted with ether (4 × 60 mL), dried, and evaporated to give **5c** (2.51 g, 71%) as an oil, which was pure according to ^1H NMR data (>98% ds). The residue was further purified by flash chromatography (hexane/ether, 3:1) to give the dioxanone **5c** (1.9 g, 54%): mp 32–33 °C; $[\alpha]_D$ +9.9° (*c* 1.05); IR ($CHCl_3$) 3010 (w), 2980 (s), 2940 (m), 2880 (m), 1750 (s), 1480 (w), 1460 (w), 1400 (m), 1360 (m), 1300 (s), 1260 (m), 1100 (m), 980 cm^{-1} (s); ^1H NMR δ 0.94 (t, J = 7.4 Hz, CH_3), 0.97 (s, *tert*-butyl), 1.23 (s, CH_3), 1.5–1.8 (m, CH_2), 2.48 (d, J = 15.9, A part of the AB system, $CH_AC{=}O$), 2.65 (d, J = 15.9, B part of the AB system, $CH_BC{=}O$), 4.92 (s, OCHO); ^{13}C NMR δ 7.61, 23.99, 26.42, 32.53, 34.60, 41.05, 75.13, 103.00, 170.24; MS, *m/z* 201 (M^+ + 1, 0.2), 199 (M^+ − 1, 0.3), 171 (7), 143 (26), 115 (13), 98 (7), 97 (100), 87 (13), 85 (35), 73 (38), 71 (12), 70 (68), 69 (36), 57 (37), 55 (32), 43 (40), 42 (11), 39 (8), 29 (16), 27 (7). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.15; H, 10.40.

(2*R*,6*S*)-2-*tert*-Butyl-6-methyl-6-propyl-1,3-dioxan-4-one (5d). (a) **Stoichiometric Cuprate.** Cuprous(I) iodide (666.5 mg, 3.5 mmol) was suspended in ether (20 mL) and propyllithium (7 mL, 7 mmol, 1 M in hexane) was added at 0 °C. The dark suspension was cooled to −75 °C, dioxinone **1** (0.5 g, 2.94 mmol) in ether (20 mL) was added, and the mixture was stirred at −75 °C over 2 h. The suspension was quenched with ammonia/saturated ammonium chloride (30 mL, 1:1), extracted, dried, and evaporated to give **5d** (500 mg, 79%, >98% ds) as an oil, which was pure according to the ^1H NMR analysis. A sample was further purified by flash chromatography (eluant hexane/ether, 3:1): $[\alpha]_D$ +12.7° (*c* 1.36); IR ($CHCl_3$) 2980 (m), 2960 (s), 2940 (m), 2910 (m), 2870 (m), 1750 (s), 1485 (m), 1405 (m), 1370 (m), 1310 (m), 1260 (s), 980 cm^{-1} (s); ^1H NMR δ 0.93–0.98 (m, 3 H), 0.97 (s, 9 H, *tert*-butyl), 1.24 (s, 3 H, CH_3), 1.33–1.44 (m, 2 H, CH_2), 1.45–1.66 (m, 2 H, CH_2), 2.47 (d, J = 15.9 Hz, 1 H, A part of the AB system, $CH_AC{=}O$), 2.65 (d, J = 15.9 Hz, 1 H, B part of the AB system, $CH_BC{=}O$), 4.93 (s, 1 H, OCHO); ^{13}C NMR δ 14.40, 16.61, 23.96, 26.93, 34.56, 41.31, 42.27, 74.94, 102.97, 170.21; MS, *m/z* 213 (M^+ − 1, 0.5), 171 (17), 157 (35), 129 (19), 111 (100), 87 (27), 85 (31), 84 (49), 83 (32), 69 (27), 57 (25), 56 (44). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.19; H, 10.52.

(b) Catalytic CuCl. Propylmagnesium bromide (7.2 mL, 14.1 mmol, 2 M in ether) was added to cuprous(I) chloride (139 mg, 1.42 mmol) at −20 °C over 10 min. When the mixture became purple, it was diluted with ether (24 mL) and cooled to −75 °C. Dioxinone **1** (1.2 g, 7.05 mmol) in ether (12 mL) was added dropwise over 45 min at −75 °C. The reaction mixture was warmed to −50 °C over a period of 5 h and then quenched with ammonia/saturated ammonium chloride (14 mL, 1:1). The solution was stirred at 20 °C in contact with air until it became blue, extracted with ether (3 × 100 mL), dried, and evaporated to give **5d** (1.38 g, 91%, ds >98%) as a solid, which was pure according to ^1H NMR data. For the analytical data, refer to the procedure employing stoichiometric organocopper reagent.

(2*R*,6*S*)-2-*tert*-Butyl-6-butyl-6-methyl-1,3-dioxan-4-one (5e). Cuprous(I) iodide (1.33 g, 7 mmol) was suspended in ether (50 mL), and butyllithium (9.3 mL, 14 mmol, 1.5 molar in hexane) was added at 0 °C. The dark solution was cooled to −75 °C, and dioxinone **1** (1 g, 5.9 mmol) in ether (10 mL) was added. The reaction mixture was stirred at −75 °C over 2 h, quenched with ammonia/ammonium chloride (50 mL, 1:1), stirred in contact with air, extracted with ether (3 × 50 mL), dried, and

(89) Pyramidalization of a trigonal center with three different substituents renders it stereogenic.

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evaporated to give **5e** (0.945 g, 70.5%, >98% ds) as an oil, which was pure according to the ^{1}H NMR data: $[\alpha]_D$ +6.7° (*c* 2.05); IR ($CHCl_3$) 2960 (s), 2940 (m), 2880 (m), 1750 (s), 1480 (m), 1410 (s), 1380 (m), 1370 cm^{-1} (m); ^{1}H NMR δ 0.92 (m, 3 H, CH_3), 0.97 (s, 9 H, *tert*-butyl), 1.24 (s, 3 H, CH_3), 1.30–1.40 (m, 4 H, CH_2CH_2), 1.50–1.70 (m, 2 H, CH_2), 2.48 (d, J = 15.9 Hz, AB system, 1 H, CH_AC=O), 2.67 (d, J = 15.9 Hz, AB system, 1 H, CH_BC=O), 4.92 (s, 1 H, OCHO); ^{13}C NMR δ 14.03, 22.94, 23.99, 25.39, 26.94, 34.56, 39.60, 41.35, 74.85, 102.83, 169.96; MS, *m/z* 227 (M^+ – 1, 0.5), 171 (56), 143 (22), 125 (100), 98 (35), 97 (41), 85 (64), 83 (39), 57 (84), 56 (91), 43 (82), 41 (85). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.09; H, 10.77.

(2*R*,6*S*)-2-*tert*-Butyl-6-methyl-6-octyl-1,3-dioxan-4-one (5f). (a) Stoichiometric Cuprate. Cuprous(I) iodide (666.4 mg, 3.5 mmol) was suspended in ether (30 mL), and octyllithium (7.4 mL, 7 mmol, 0.95 M) was added at 0 °C. The solution was cooled to −75 °C and dioxinone **1** (250 mg, 1.5 mmol) in 3 mL of ether was added over 15 min. The reaction mixture was stirred at this temperature over 2 h, quenched with ammonia/saturated ammonium chloride (25 mL, 1:1), and stirred at 0 °C in contact with air until it became blue. The solution was extracted with ether (3 × 35 mL), dried, and evaporated to give **5f** (245 mg, 57%, >98% ds), which was pure according to the ^{1}H NMR analysis. A sample was further purified by flash chromatography (eluant hexane/ether, 4:1): $[\alpha]_D$ +3.59° (*c* 0.93); IR ($CHCl_3$) 2980 (m), 2960 (s), 2940 (s), 2870 (m), 2860 (m), 1750 (s), 1480 (m), 1460 (m), 1410 (m), 1370 (m), 1310 (m), 980 cm^{-1} (s); ^{1}H NMR δ 0.88 (m, 3 H), 0.97 (s, 9 H, *tert*-butyl), 1.24–1.28 (m, 14 H), 1.54–1.63 (m, 3 H), 2.48 (d, J = 15.9 Hz, 1 H, A part of the AB system, CH_AC=O), 2.65 (d, J = 16.0 Hz, 1 H, B part of the AB system, CH_BC=O), 4.92 (s, 1 H, OCHO); ^{13}C NMR δ 14.08, 22.63, 23.18, 23.98, 26.94, 29.17, 29.43, 29.84, 31.79, 34.57, 39.92, 41.37, 74.92, 103.02, 170.44; MS, *m/z* 283 (M^+ – 1), 227 (29), 199 (35), 181 (100), 171 (63), 154 (28), 153 (11), 139 (11), 97 (14), 85 (44), 83 (14), 69 (14), 57 (27), 56 (23). Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.60; H, 11.44.

(b) Catalytic CuCl. Octylmagnesium bromide (9 mL, 25.2 mmol, 2.8 M in ether) was added to cuprous(I) chloride (100 mg, 1 mmol) at −20 °C over 10 min. The dark purple solution was diluted with ether (24 mL) and cooled to −75 °C. Dioxinone **1** (1.2 g, 7.05 mmol) in ether (12 mL) was added dropwise over 45 min at −75 °C. The reaction mixture was warmed to −50 °C, stirred at this temperature for 3.5 h, and then quenched with ammonia/saturated ammonium chloride (14 mL, 1:1). The solution was stirred at 0 °C in contact with air until it became blue, extracted with ether (3 × 100 mL), dried, and evaporated to give **5f** (1.42 g, 71%, >98% ds) as an oil, which was pure according to the ^{1}H NMR analysis. For the analytical data, refer to the procedure employing stoichiometric organocopper reagent.

(2*R*,6*R*)-2-*tert*-Butyl-6-methyl-6-phenyl-1,3-dioxan-4-one (5g). Cuprous(I) iodide (3.36 g, 17.62 mmol) was suspended in ether (40 mL), and phenyllithium (17.62 mL, 35.24 mmol, 2 M in ether/benzene) was added over 90 min at 0 °C. The solution was stirred at this temperature for 15 min and cooled to −50 °C, and a solution of the dioxinone **1** (1 g, 5.88 mmol) in ether (10 mL) was added at −50 °C over 30 min. The reaction mixture was warmed to −20 °C and stirred at this temperature for 15 h, quenched with ammonia/saturated ammonium chloride (50 mL, 1:1), and stirred in contact with air at 0 °C until it became blue. The solution was extracted with ether (3 × 200 mL), dried, and evaporated. The residue was purified by flash chromatography (eluant hexane/ether, 3:1) to give **5g** (1.07 g, 73%, >98% ds) as a solid: mp 51.2–51.6 °C; $[\alpha]_D$ −98.7° (*c* 1.00); IR (KBr) 3090 (w), 3030 (w), 2980 (m), 2960 (m), 2930 (m), 2870 (w), 1740 (s), 1600 (w), 1580 (w), 1480 (w), 1450 (m), 1430 (m), 1410 (m), 1360 (m), 1340 (m), 1310 (s), 1280 (m), 1260 (m), 1240 (s), 1210 (m), 1100 (m), 1080 (m), 1030 (m), 980 (s), 860 (m), 770 (m), 700 (m); ^{1}H NMR (90 MHz) δ 1.05 (s, *tert*-butyl), 1.55 (s, CH_3), 2.90 (d, J = 16.0 Hz, A part of the AB system, CH_AC=O), 3.15 (d, J = 16.0 Hz, B part of the AB system, CH_BC=O), 4.75 (s, OCHO), 7.32 (m, 5 H aromat); ^{13}C NMR δ 24.12, 32.25, 34.99, 41.24, 77.04, 103.87, 124.72, 127.93, 128.87, 144.25, 169.11; MS, *m/z* 248 (M^+, 1), 191 (31), 163 (13), 147 (5), 146 (7), 145 (45), 122 (5), 121 (48), 119 (11), 118 (100), 117 (33), 115 (8), 105 (27), 103 (15), 91 (13), 78 (11), 77 (18), 71 (7), 57 (60), 51 (8), 43 (25), 41 (23), 39 (10), 29 (14), 27 (7). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.53; H, 8.32.

(2*R*,6*S*)-6-Allyl-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one (5h). Cuprous(I) iodide (3.7 g, 19.44 mmol) was suspended in ether (24 mL), and allyllithium (26 mL, 36.4 mmol, 1.4 M in ether) was added at −20 °C over 40 min. The black suspension was cooled to −75 °C, the dioxinone **1** (1.1 g, 6.48 mmol) in ether (12 mL) was added over 45 min at −75 °C, and the mixture was warmed to −50 °C over 4 h. The reaction mixture was quenched with ammonia/saturated ammonium chloride (50 mL, 1:1) and stirred at 0 °C in contact with air until it became blue, extracted with ether (3 × 150 mL), dried, and evaporated. The residue was purified by flash chromatography (hexane/ether, 3:1) to give a mixture of **5h** (0.727 g, 62.5%, >98% ds) and phenol (0.437 g). Two further flash chromatographic purifications (dichloromethane/hexane, 4:1) gave pure **5h** (0.43 g, 31%) as an oil: $[\alpha]_D$ +18.1° (*c* 1.39); IR ($CHCl_3$) 3080 (w), 3020 (w), 3010 (w), 2980 (m), 2960 (m), 2910 (m), 2870 (w), 1750 (s), 1640 (w), 1480 (m), 1405 (m), 1365 (m), 1310 (s), 1250 (s), 1110 (m), 1100 (m), 980 (s), 925 (m); ^{1}H NMR δ 0.97 (s, *tert*-butyl), 1.26 (s, CH_3), 2.37 (d, 2 H, J = 7.3 Hz, CCH_2C=), 2.43 (d, J = 15.9 Hz, A part of the AB system, CH_AC=O), 2.74 (d, J = 15.9 Hz, B part of the AB system, CH_BC=O), 4.95 (s, OCHO), 5.20 (m, 2 H, CH_2=), 5.72–5.88 (m, 1 H, C=CHC); ^{13}C NMR δ 23.90, 27.57, 34.55, 40.15, 44.62, 74.45, 103.08, 119.58, 131.87, 169.78; MS, *m/z* 213 (M^+ + 1, 0.1), 211 (M^+ – 1, 0.1), 171 (18), 109 (46), 87 (29), 86 (5), 85 (89), 82 (22), 81 (20), 71 (6), 69 (8), 67 (36), 57 (25), 55 (6), 43 (100), 41 (34), 39 (16), 29 (14), 27 (8). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.87; H, 10.05.

(2*R*,6*R*)-2-*tert*-Butyl-6-ethyl-6-methyl-1,3-dioxan-4-one (5i). Cuprous(I) iodide (4.65 g, 24.4 mmol) was suspended in ether (60 mL), and methyllithium (30.5 mL, 48.8 mmol, 1.6 molar) was added over 20 min at 0 °C. The brown solution was cooled to −75 °C, and dioxinone **2** (1.5 g, 8.14 mmol) in ether (15 mL) was added dropwise at −75 °C. The yellow suspension was warmed to −20 °C over 1 h, stirred at this temperature for 1 h, and quenched with ammonia/saturated ammonium chloride (50 mL, 1:1). The mixture was stirred at 0 °C in contact with air until it became blue, extracted with ether (3 × 150 mL), dried, and evaporated to give **5i** (1.47 g, 90%, >98% ds) as a yellow oil, which was pure according to the ^{1}H NMR data. The oil was further chromatographed on silica gel with hexane/ether, 3:1, as eluant to give **5i** (1.11 g, 68%) as a colorless oil: $[\alpha]_D$ +12.5° (*c* 2.07); IR ($CHCl_3$) 3010 (w), 2980 (s), 2930 (m), 2880 (m), 1750 (s), 1480 (m), 1460 (m), 1400 (m), 1380 (m), 1370 (m), 1300 (m), 1250 (s), 1130 (m), 1100 (m), 1040 (m), 1030 (m), 980 cm^{-1} (s); ^{1}H NMR δ 0.92 (t, J = 7.5 Hz, CH_3), 0.97 (s, *tert*-butyl), 1.29 (s, CH_3), 1.58 (m, 2 H, CCH_2C), 2.51 (d, J = 16.4 Hz, A part of the AB system, CH_AC=O), 2.58 (d, J = 16.4 Hz, B part of the AB system, CH_BC=O), 4.95 (s, OCHO); ^{13}C NMR δ 7.55, 23.99, 24.80, 34.70, 35.45, 40.43, 74.94, 102.62, 170.29; MS, *m/z* 171 (4), 143 (25), 115 (13), 99 (4), 98 (7), 97 (100), 87 (10), 85 (21), 73 (40), 71 (15), 70 (92), 69 (37), 57 (44), 55 (42), 45 (4), 43 (41), 42 (14), 41 (38), 39 (15), 29 (28), 27 (15). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.72; H, 10.20.

(2*R*,6*S*)-2-*tert*-Butyl-6-butyl-6-[[(dimethyl-*tert*-butylsilyl)oxy]methyl]-1,3-dioxan-4-one (5k). Cuprous(I) iodide (254 mg, 1.33 mmol) was suspended in ether (2 mL), and butyllithium (1.7 mL, 2.66 mmol, 1.55 M in hexane) was added at 0 °C. The black suspension was cooled to −75 °C, the dioxinone **3** (133 mg, 0.44 mmol) in ether (1 mL) was added at −75 °C, and the mixture was stirred over 3 h at this temperature. The solution was quenched with ammonia/saturated ammonium chloride (1:1) and stirred at 0 °C in contact with air until it became blue, extracted with ether, dried, and evaporated. The residue was purified by flash chromatography (eluant dichloromethane/ether) to give **5k** (110 mg, 70%, >98% ds) as an oil: $[\alpha]_D$ +15.8° (*c* 0.72); IR ($CHCl_3$) 2960 (s), 2940 (s), 2860 (m), 1755 (s), 1480 (m), 1460 (m), 1400 (m), 1370 (m), 1100 (s); ^{1}H NMR δ 0.05 (s, 6 H, $(CH_3)_2Si$), 0.88 (s, 9 H, *tert*-butyl), 0.89–0.93 (m, 3 H, CH_3), 0.97 (s, 9 H, *tert*-butyl), 1.18–1.38 (m, 4 H), 1.51–1.62 (m, 2 H), 2.45 (d, J = 16.2 Hz, 1 H, A part of the AB system, CH_AC=O), 2.71 (d, J = 16.2 Hz, 1 H, B part of the AB system, CH_BC=O), 3.41 (d, J = 10.1 Hz, 1 H, A part of the AB system, CH_AO), 3.46 (d, J = 10.2, 1 H, B part of the AB system, CH_BO), 4.90 (s, 1 H, OCHO); MS, *m/z* 302 (1), 301 (6), 255 (7), 215 (46), 173 (48), 171 (100), 127 (15), 115 (12), 85 (36), 75 (63), 73 (49), 57 (32), 41 (20), 29 (12). Anal. Calcd for $C_{19}H_{38}O_4Si$: C, 63.64; H, 10.68. Found: C, 63.59; H, 10.55.

(2*R*,6*S*)-2-*tert*-Butyl-6-methyl-6-(phenylthio)-1,3-dioxan-4-one (6). Dioxinones **1** (22.9 mg, 0.135 mmol) and thiophenol (0.1 mL, 0.6 mmol) were stirred in THF (0.5 mL) with 1 drop of triethylamine over 16 h at 25 °C. The reaction mixture was chromatographed on Merck silica gel plate (60 F_{254}) with hexane/ether (3:1) to give the dioxanone 6 (9.8 mg, 26%): ^{1}H NMR δ 1.04 (s, 9 H, *tert*-butyl), 1.55 (s, 3 H, CH_3), 2.86 (A part of the AB system, J = 16.8 Hz, CH_AC=O), 2.93 (B part of the AB system, J = 16.8 Hz, CH_BC=O), 5.34 (s, 1 H, OCHO), 7.30–7.58 (m, 5 H, arom); NOE measurements irradiation, 1.55 → positive NOE 1.04 and 2.93; irradiation, 5.34 → positive NOE 2.86.

(±)-2-Methyl-6-butyl-6-methyldioxan-4-one (7). Cuprous(I) iodide (450 mg, 2.37 mmol) was suspended in ether (15 mL), and butyllithium (3.3 mL, 4.8 mmol, 1.5 M in hexane) was added over 5 min at 0 °C. The dark solution was cooled to −75 °C, and the dioxinone 4 (300 mg, 2.34 mmol) in ether (3 mL) was added at −75 °C over 10 min. The reaction mixture was stirred at −75 °C over 2 h, quenched with ammonia/saturated ammonium chloride (15 mL, 1:1) in contact with air, extracted with ether (3 × 30 mL), dried, and evaporated to give **7** (338 mg, 78%, >98% ds) as an oil: ^{1}H NMR δ 0.92 (m, 3 H, CH_3), 1.26 (s, 3 H, CH_3),

1.22-1.38 (m, 2 H, CH_2), 1.47 (d, J = 5.1 Hz, CH_3), 1.55-1.63 (m, 4 H, CH_2CH_2), 2.48 (d, J = 16.0 Hz, AB system, 1 H, CH_AC=O), 2.66 (d, J = 16.0 Hz, AB system, 1 H, CH_BC=O), 5.52 (q, J = 5.0 Hz, 1 H, OCHO); ^{13}C NMR δ 13.71, 20.52, 22.84, 25.45, 27.18, 29.83, 41.13, 70.64, 95.10, 172.53.

(3*S*)-3-Methyl-3-hydroxypentanoic Acid (8a) (General Procedure A). Dioxanone **5c** (423 mg, 2.1 mmol) was dissolved in THF (4 mL) and hydrochloric acid (6 mL, 1 N) and stirred at 20 °C over 45 min. The reaction mixture was extracted with ether (3 × 40 mL), dried, and evaporated. The residue was purified by flash chromatography (eluant hexane/ether, 1:2) to give the acid **8a** (166.4 mg, 60%) as an oil: $[\alpha]_D$ -0.94° (c 2.26); IR ($CHCl_3$) 3700-2400 (br), 3660 (w), 3500 (m), 2980 (s), 2940 (m), 2880 (m), 2630 (w), 1700 (s), 1460 (m), 1405 (m), 1380 (m), 1210 (s), 1140 (m), 940 (m), 880 cm^{-1} (m); ^{1}H NMR δ 0.94 (t, J = 7.5 Hz, CH_3), 1.28 (s, CH_3), 1.60 (q, J = 7.5 Hz, CH_2), 2.51 (d, J = 15.7 Hz, A part of the AB system, CH_AC=O), 2.60 (d, J = 15.7 Hz, B part of the AB system, CH_BC=O), 6.2-7.2* (br, OH, COOH); ^{13}C NMR δ 8.30, 25.98, 34.51, 44.20, 71.86, 177.38; MS, m/z 117 (5), 103 (25), 99 (7), 85 (42), 73 (33), 72 (6), 61 (6), 60 (5), 57 (25), 55 (13), 45 (8), 43 (100), 42 (8), 41 (7), 39 (6), 29 (12), 27 (8). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.08; H, 9.39.

(3*R*)-3-Methyl-3-hydroxypentanoic Acid (*ent*-8a). Via general procedure A, 407.7 mg (2.03 mmol) of dioxanone **5l** gave the acid ***ent*-8a** (268.3 mg, 86%) as an oil, $[\alpha]_D$ +107° (c 2.25).

(3*R*)-3-Phenyl-3-hydroxybutanoic Acid (8b). Via general procedure A, 200 mg (1.18 mmol) of dioxanone **5g** gave after 48 h of reaction time the acid **8b** (136.6 mg, 65%) as a solid: mp 83.4-83.7 °C (lit.[14] mp 83-84 °C), $[\alpha]_D$ -10.22° (c 1.34, EtOH) (lit.[14] $[\alpha]_D$ +9.07° (c 3.76, EtOH), for the S isomer (92% ee)).

(*S*)-Mevalolactone. Dioxanone **5h** (125 mg, 0.59 mmol) was dissolved in methanol (10 mL) and treated with ozone at -78 °C until the colour of the reaction mixture became blue. Sodium borohydride (22.3 mg, 0.59 mmol) was added, and the suspension was stirred over 2 h at 0 °C. After evaporation of the solvent, the residue was dissolved in sodium hydroxide[1] (1 mL, 1 N) and stirred at 0 °C for 13 h. The solution was acidified (HCl, 5 N), extracted with chloroform (3 × 20 mL), dried, and evaporated. The residue was purified by flash chromatography (eluant ethyl acetate) to give (*S*)-mevalolactone (19.7 mg, 25%) as a colorless oil, $[\alpha]_D$ +21.2° (c 1.69, EtOH) (lit.[15] $[\alpha]_D$ +21.7° (c 0.75, 95% EtOH)).

(2*R*)-2-*tert*-Butyl-5-deuterio-6-methyl-2*H*,4*H*-1,3-dioxin-4-one (5-Deuterio-1). (2*R*)-5-Bromo-2-*tert*-butyl-6-methyl-2*H*,4*H*-1,3-dioxinone[6] (700 mg, 2.8 mmol) was dissolved in benzene (15 mL); 10% Pd/C (375 mg) and Et_3N (0.4 mL, 2.8 mmol) were added, and the mixture was stirred under D_2 for 2 h. The suspension was filtered, and the residue was purified by flash chromatography (eluant hexane/ether, 3:1) to give the deuteriated dioxinone 5-deuterio-**1** (385 mg, 80%) as a solid. According to the ^{1}H NMR and the MS analyses, the isotopic purity was ≥95%. For the analytical data of the 5-H compound, see ref 6.

(2*R*,5*S*,6*R*)-2-*tert*-Butyl-5-deuterio-6-methyl-1,3-dioxan-4-one (10). 5-Deuterio-**1** (182 mg, 1.06 mmol) was dissolved in ethyl acetate (14 mL). 10% Pd/C (60 mg) was added, and the mixture was stirred for 22 h under a hydrogen atmosphere (26 atm). The suspension was filtered and evaporated, and the residue was purified by flash chromatography (eluant hexane/ether, 3:1) to give **10** (173 mg, 94%) as a solid. According to the ^{1}H NMR and the MS analyses, the isotopic purity was ≥95%. For the analytical data of the 5-H compound see ref 19.

X-ray Analysis. All intensity measurements were carried out with an ENRAF NONIUS CAD4 diffractometer with a graphite monochromator (Mo Kα radiation, A = 0.7107 Å). The structures were solved by[97] SHELX 86 and refined with the use of the X-RAY 72 system.[98]

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Supplementary Material Available: Tables containing crystallographic data, atomic coordinates and displacement parameters, and bond lengths and angles of **11** and **12**, calculated coordinates, net charges, and overlap populations (9 pages). Ordering information is given on any current masthead page.

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Facilitation of Electrochemical Oxidation of Dialkyl Sulfides Appended with Neighboring Carboxylate and Alcohol Groups†

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Abstract: The electrochemical oxidation of variously 2-substituted 6-(methylthio)bicyclo[2.2.1]heptanes in acetonitrile was studied by using cyclic voltammetry. Three compounds, endo acid salt **1h**, endo primary alcohol **1c**, and endo tertiary alcohol **1g**, were found to oxidize much more easily in the presence of trace amounts of bromide ion. Controlled potential electrolysis of endo acid salt **1h** in the presence of 2,6-di-*tert*-butylpyridine and a small amount of water gave endo acid sulfoxide **5a**. Such oxidation in the presence of ^{18}O-labeled water led to the incorporation of the label into the oxygen atoms of both the sulfoxide and carboxylate moieties of endo acid sulfoxide **5a**. This result suggested the intermediacy of acyloxysulfonium salt **6**. This salt was prepared by bromine oxidation of endo acid salt **1h** at low temperatures, characterized spectroscopically, and hydrolyzed to endo acid sulfoxide **5a**. Controlled potential electrolysis of endo primary alcohol **1c** and endo tertiary alcohol **1g** in the presence of 2,6-di-*tert*-butylpyridine produced the corresponding alkoxysulfonium salts **7a** and **7b**, respectively. These data are interpreted in terms of bromide catalysis of the thioether oxidation with neighboring carboxylate or alcohol participation.

Electrochemical evidence, which supported the hypothesis that certain groups proximate to a sulfur atom of a thioether but not bonded to it facilitate the oxidation at sulfur by neighboring group participation, was communicated.[1] That is, the peak potential for oxidation of dialkyl sulfides appended with neighboring carboxylate or alcohol moieties was over 500 mV more cathodic than that for control compounds. The overall 2e$^-$ oxidation was suggested to occur with concomitant bond formation between an

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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