linear relation (correlation coefficient of 0.94).

Thus, it is for the first time demonstrated[12] that the remote electronegative substitution of a stereogenic center can have the same significant effect on the sense of π-facial diastereoselection both in nucleophilic and electrophilic reactions.[13,14] This result constitutes a challenging test for the theories of stereoelectronic control in π-facial diastereoselection. Several propositions that explicitly deal with the nature of such a control in cyclohexane-related systems have been advanced over the last 20 years, most notably those of Felkin,[15] Klein,[16] Ashby,[17] Nguyen,[18] and Cieplak.[2] It is interesting to notice that except for the last one, these models fail to predict or explain the effects of remote [C(-3) or C(-4)] electronegative substitution of the cyclohexane ring on stereochemistry of cyclohexanone and methylenecyclohexane reactions.

Klein postulated that nucleophiles and electrophiles would display opposite preferences in a given system of 1,2-diastereoselection in apparent disagreement with the accumulated experimental data.[19] Felkin et al. and Nguyen et al. did not attribute any role in stereoselection to the interactions involving the ring CC bonds. In fact, Felkin et al.[15b] proposed that the preferred "axial" epoxidation of unhindered exocyclic olefins by peracids results from "equatorial" torsional strain, due to repulsion of the exocyclic methylene and the equatorial C(2)-H and C(6)-H bonds; obviously, no eclipsing interactions involving the incipient bond can occur in the transition state for such a reaction. The model of Nguyen et al.[18b] can be generalized to include ring CC interactions, but it predicts, then, an increase in the proportion of equatorial nucleophilic attack with an increase in the electronegativity of a remote 3-equatorial substituent in opposition to the experimental results. In contrast, the findings reported here appear to be consistent with the Cieplak postulate that the stereochemistry of reactions of cyclohexanones, methylenecyclohexanes, thianes, etc. could be controlled by the same orbital interactions regardless of the reaction mechanism.[2] The explanation of stereoselection in reactions of the cyclohexane related system based on the Cieplak proportion[2] is as follows. During axial attack of a reagent, the vacant orbital σ^*_t that develops along with the formation of the incipient bond interacts with the filled orbitals of the C(2)-H and C(6)-H bonds. During equatorial attack, the σ^*_t orbital interacts with the filled orbitals of the ring bonds C(2)-C(3) and C(5)-C(6). The effect of steric hindrance favors, obviously, the equatorial attack. The effect of hyperconjugative σ assistance, however, favors the axial attack, because the CH bonds are better donors than the CC bonds,[20] and consequently the σ_{CH}, σ^*_t stabilization energy is greater than the σ_{CC}, σ^*_t stabilization energy. If the energy level of the σ^*_t orbital is sufficiently low, that is, if the electron affinity of the transition state is sufficiently high, the difference in σ_{CH} and σ_{CC} hyperconjugative assistance will offset the steric hindrance. It should be stressed that this must be true for any reaction—polar addition (*nucleophilic or electrophilic*!), radical addition or recombination, cycloaddition, etc.—provided the transition state is electron deficient.

This model predicts that the electron-withdrawing substitution at the C-(3), which decreases donor power of the ring bonds, will decrease σ_{CC} assistance of the equatorial transition state and, thereby, increase the percentage of the axial approach. The findings reported here appear consistent with the Cieplak model but are in opposition to those predicted by application of the Felkin,[15] Klein,[16] Ashley,[17] and Nguyen[18] models.

Acknowledgment is made to the donors of the Petroleum Research Fund administrated by the American Chemical Society and to the National Science Foundation (CHE86-07956) for support of the work at Wayne State University.

(12) Srivastava and le Noble have recently reached the same conclusions; see the preceding communication.

(13) For the reports on the examination of such effects in reactions of nucleophilic additions to ketones, see: ref 1 and Danishefsky et al. (Danishefsky, S. J.; Langer, M. *J. Org. Chem.* **1985**, *50*, 3672.).

(14) Several earlier studied that pioneered this approach were flawed for various reasons: (a) Agami, C.; Kazakos, A.; Levisalles, J. *Tetrahedron Lett.* **1975**, *16*, 2035. (The C-3 substituents are axial.) (b) Moreau, G. *Bull. Soc. Chim. Fr.* **1972**, 2814. (The use of 2-*t*-Bu group to lock cyclohexanone conformation has been questioned, see: references in Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 765, 777.) (c) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459. (Wrong assignment of the diasteromer structures, see ref 1.)

(15) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2203.

(16) (a) Klein, J. *Tetrahedron Lett.* **1973**, *14*, 4307. (b) Klein, J. *Tetrahedron* **1974**, *30*, 3349.

(17) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. (Predictions of Klein's and Ashby's models are identical.)

(18) Nguyen, T. A.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Huet, J.; Maroni-Barnaud, Y.; Nguyen, T. A.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, *17*, 159.

(19) Agami, Kazakos, and Levisalles (ref 14a) were first to suggest that the effect of ring substitution on the stereochemistry of hydride reduction of cyclohexanones refutes the Klein model.

(20) This assumption is consistent with a wealth of data on the properties of the axial and equatorial bonds and on conformational equilibria of cyclohexane derivatives, see ref 2. See, also: Brown, H. C.; Periasamy, M.; Perumal, P. T. *J. Org. Chem.* **1984**, *49*, 2754 (for a recent appraisal of the Baker-Nathan order problem). Edlund, U. *Org. Magn. Reson.* **1978**, *11*, 516 (for a demonstration of the Baker-Nathan order in the ground state).

Crystal Structure of the Complex 5-Phenyladamantan-2-one-Pentachloroantimony. Hyperconjugative Effects in an Activated Ketone

Thomas Laube* and Hans Ulrich Stilz

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule Zürich ETH-Zentrum, Universitätstrasse 16 CH-8092 Zürich, Switzerland

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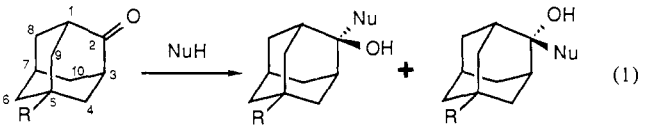
The addition of a nucleophile to a carbonyl group is one of the most important C-C bond-forming processes. Many efforts have been made to explain and predict the diastereoselectivity of nucleophilic attack.[1] The importance of steric factors is generally accepted, but the nature of electronic interaction between the carbonyl group and adjacent groups is controversial.[2-4] LeNoble et al.[5] have recently shown that nucleophilic addition to adamantan-2-ones with substituents at C5 of **1** must be controlled



(1)

1 cis - **2** trans - **2**

by electronic factors (steric factors being practically equal for both faces of the carbonyl group). Electron-withdrawing substituents favor syn approach (product *trans*-**2**) and electron-donating groups lead to anti approach (product *cis*-**2**). Hyperconjugative interactions in **1** are described by resonance formulas of type **1′** and **1*** in the "first sphere" and of type **1″** and **1**** in the "second sphere". If the C5-R bond is a better donor than the C7-H bond, then the primed resonance formulas are more important than the starred ones. If C7-H is a better donor than C5-R, then the starred resonance formulas have higher weights. Finally, σ participation[5] can be described by resonance formulas of type **1**† (cf. the Wagner-Meerwein rearrangement[6]). The contribution

(1) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Chêrest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

(2) Houk, K. N.; Wu, Y.-D. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Verlagsgesellschaft: Weinheim, 1987; p 247.

(3) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(4) Klein, J. *Tetrahedron* **1974**, *30*, 3349.

(5) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

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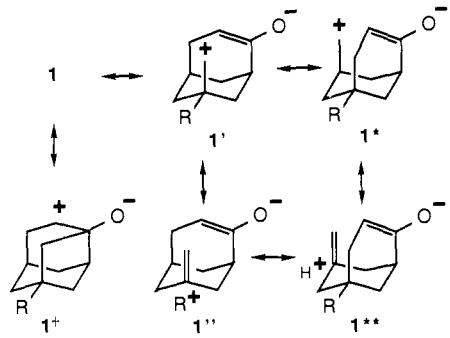
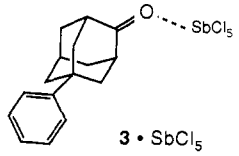


(2)

of these types of resonance formulas in the description of ground-state adamantanones is certainly quite small—otherwise it would have previously been detected in the crystal structures of ketones. However, for nucleophilic attack to take place, the carbonyl group is normally activated by metal complexation[7] or protonation, and the thus enhanced carbocation character of the carbonyl C atom should result, for the case of **1**, in higher weights for the primed, starred, and crossed resonance formulas.[8] To test this hypothesis, we have performed the X-ray structure analysis of the complex[9] 5-phenyladamantan-2-one–pentachloroantimony (**3**·$SbCl_5$)[10] (see Figure 1). Due to disorder it is not possible to



3 • $SbCl_5$

obtain crystal structure analyses of simply substituted adamantanones;[13] therefore, we compare the geometry of the symmetrized cage[11] of **3**·$SbCl_5$ with the calculated structure of adamantanone[12] (see Figure 2, top). As predicted by the resonance formulas **1'** and **1***, the carbonyl bond is lengthened, the bonds to the α carbons (C1–C2 and C2–C3) are shortened, and all C_α–C_β bonds are lengthened again. From the course of nucleophilic additions to **3** one expects[3,5] that the C7–H bond is the better donor than the C5–C11 bond and that, therefore, the starred resonance formulas are more important. Indeed the electron-releasing properties of the C7–H bond are reflected by a shortening of the C7–C8 and C7–C10 bonds and a flattening of C7,[14] whereas donor properties

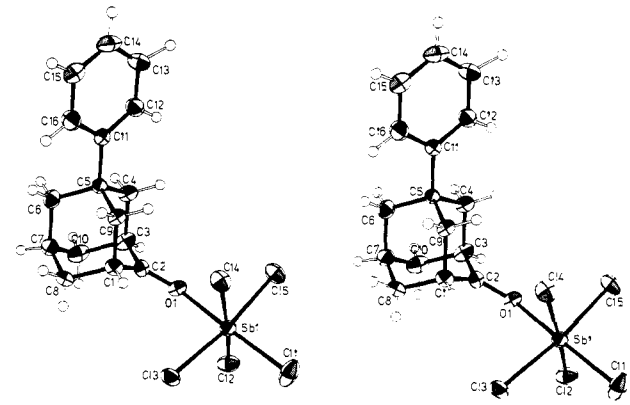
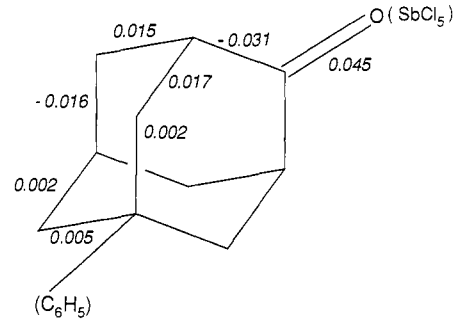


Figure 1. ORTEP stereoview of **3**·$SbCl_5$. Displacement ellipsoids are drawn at the 50% probability level; hydrogen atoms are represented by spheres with a radius of 0.1 Å.



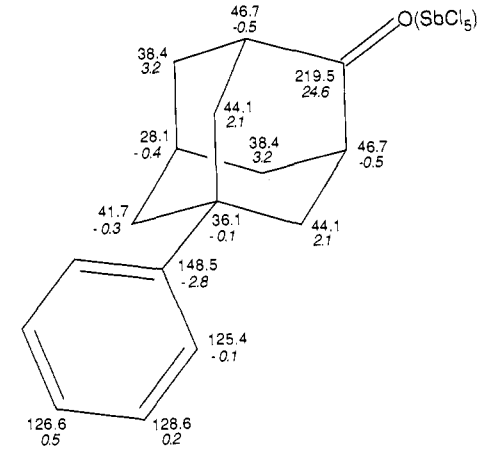


Figure 2. Top: Bond length *differences* between the symmetrized adamantanone cage[11] of **3**·$SbCl_5$ and the calculated structure (MM2) of adamantanone.[12] (Mean standard deviations of **3**·$SbCl_5$, σ_{C-C} = 0.008; of the symmetrized cage, σ_{C-C} = 0.006 Å.) Bottom: ^{13}C NMR chemical shifts[16] of **3** (upper values) and ^{13}C NMR chemical shift *differences*[16] between **3**·$SbCl_5$ (the enantiomers are rapidly exchanging, therefore averaged signals for C1/C3, etc.) and **3** (lower values).

of the C5–C11 bond cannot be detected.[15] To support this interpretation we have measured low-temperature ^{13}C NMR spectra[16] of **3** and **3**·$SbCl_5$. Upon complexation with $SbCl_5$ the

(6) Lenoir, D.; Mison, P.; Hyson, E.; v. Ragué Schleyer, P.; Saunders, M.; Vogel, P.; Telkowski, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 2157.

(7) Amstutz, R.; Dunitz, J. D.; Laube, T.; Schweizer, W. B.; Seebach, D. *Chem. Ber.* **1986**, *119*, 434.

(8) These effects can be clearly detected in the X-ray structures of alicyclic carbocations: Laube, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 349. Laube, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 560.

(9) The crystals of **3** are disordered, see ref 5. For the NMR analysis of the coordination geometry of adamantanone–shift reagent complexes, see: Raber, D. J.; Peters, J. A.; Nieuwenhuizen, M. S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 853.

(10) Synthesis of **3**: Geluk, H. W. *Synthesis* **1972**, *7*, 374. X-ray structure analysis of **3**·$SbCl_5$: Enraf Nonius CAD4 diffractometer, Mo Kα radiation, graphite monochromator, measurement at −90 °C, space group $P2_1/c$, a = 12.886 (4) Å, b = 10.800 (3) Å, c = 14.247 (2) Å, β = 73.98 (2)°, V = 1905.6 Å^3, ρ_{calcd} = 1.831 g·cm^{-3}, 5046 reflections up to θ = 27°, 2705 with $I > 3\sigma_I$. Position of Sb atom determined with the Patterson option of SHELX84, all other non-hydrogen atoms by difference Fourier synthesis with SHELX76. Refinement (Sb, Cl, C, O anisotropic, H isotropic) with unit weights, finally in the XRAY system with $w = 1/\sigma_I^2$, yielded R = 0.028, R_w = 0.042.

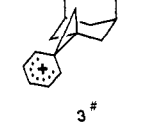
(11) Calculated by least-squares adjustment of the cage of **3**·$SbCl_5$ to its mirror image (O1, C1–C11, adjacent hydrogens with relative weights 0.1 included) and subsequent averaging of corresponding positions.

(12) Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1981**, *37*, 1081.

(13) Most of these compounds are plastically crystalline; for adamantanone, see: Amoureux, J. P.; Bee, M. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *B36*, 2636. Two recent X-ray structures of other carbonyl–Lewis acid complexes: Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112. See, also: literature cited therein.

(14) Distances Δ from the plane through their three carbon neighbors in the cage: Δ(C5) = 0.545, Δ(C7) = 0.510 Å. (The carbonyl group is distorted due to steric interactions of the $SbCl_5$ moiety with C1, C8, C9—therefore, Δ(C2) = −0.029 Å and the direction of the distortion are meaningless here.)

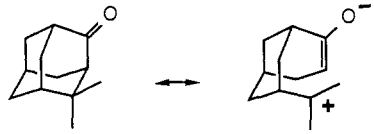
(15) The situation may be complicated by a small influence of a phenylium ion resonance formula **3**#. The phenyl ring is slightly bent toward C9; C11 is more shielded in the complex ($\Delta(\delta\,^{13}C)$ = −2.8 ppm; the spiro C atom in phenylium ions has $\delta\,^{13}C$ = 68.8 ppm: Olah, G. A.; Porter, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 6877.).



3#

carbonyl C2 and all β carbon atoms (C4, C8, C9, C10) become significantly deshielded (see Figure 2, bottom).

For comparison we have also measured the ^{13}C NMR spectra of 4,4-dimethyladamantan-2-one (**4**)[17] and its complex **4**·$SbCl_5$. The predominance of resonance formula **4'** (tertiary cationic center at C4!) is expressed by the strong downfield shift of C4 by ca. 6 ppm upon complexation.



(3)

4 **4'**

It seems reasonable to conclude that hyperconjugation can lead to different π electron distributions on the two faces of a carbonyl group.

Acknowledgment. We thank Prof. Dr. Dieter Seebach for generous financial support, Prof. Dr. Jack D. Dunitz for providing us with X-ray measuring time, and Brigitte Brandenberger and Felix Bangerter for technical assistance (^{13}C NMR spectra).

Supplementary Material Available: Lists of fractional coordinates, thermal parameters, bond lengths, bond angles, and torsion angles of **3**·$SbCl_5$, data of the symmetrized structure, and ^{13}C NMR data (15 pages). Ordering information is given on any current masthead page.

(16) All ^{13}C NMR spectra (75 MHz) were measured in CD_2Cl_2 between −80 and −95 °C. The complexes were synthesized in 2-g scales, in some cases recrystallized, and then redissolved in CD_2Cl_2.

(17) Blaney, F.; Faulkner, D.; McKervey, M. A.; Step, G. *J. Chem. Soc. C* **1972**, 2697.

A Sulfur-Mediated Total Synthesis of *d,l*-Methynolide

E. Vedejs,* R. A. Buchanan, P. Conrad, G. P. Meier, M. J. Mullins, and Y. Watanabe

S. M. McElvain Laboratory of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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We report a total synthesis of *d,l*-methynolide (**1**) based on organosulfur ring expansion methodology.[1] Remote stereocontrol over a chain of 10 carbons is demonstrated in medium-sized ring intermediates by using a combination of local conformer preferences and stereoelectronic effects to define relative stereochemistry.

The starting point for the current study was the eight-membered sulfide **2**, prepared by highly stereospecific ring expansion as described earlier.[2,3] Reduction at the C-4,C-5 double bond (methynolide numbering) of **3** (prepared from **2** + *i*-Bu_2AlH) was necessary at this stage. The route had been designed with the expectation that local conformer preferences of allylic substituents for the pseudoequatorial geometry[4] would ensure that diimide reduction of **3** would occur via transition state **4**, similar to the favored local geometry of **3** with diimide approaching the less hindered olefin face. Unusual conditions proved necessary.[5] No reduction occurred below ca. 120 °C, but syringe pump addition of excess $TsNHNH_2$ to **3** in diglyme–ethylene glycol–Et_3N at 180 °C gave 64% conversion and, eventually, 84% of isolated **5** after several recycles. No diastereomers could be detected. Swern oxidation, Wittig olefination, and protection steps (Scheme I) then gave the alkenes **6** (62% overall) to set the stage for introduction of the remaining carbons.

The alkene sulfide **6** was S-alkylated with triflate **7**[6] and treated with 2,6-lutidine to induce ylide ring expansion. Surprisingly, a *kinetic* 16:1 ratio of isomers identified as **10** and **11** was obtained (76%) even though **6** was a 1:1 diastereomer mixture due to equilibration at the Wittig stage. Control experiments proved that each purified diastereomer **6a** or **6b** gave a different major sulfonium salt but the same major 2,3-sigmatropic shift product **10**. These results are most readily explained if local geometry preferences of the eight-membered ring favor S-alkylation from below, regardless of α-vinyl stereochemistry. Ring expansion via the transoid vinyl rotamers of ylides **8** or **9** then accounts for the formation of **10**. This is important because the C-10 stereochemistry α to sulfur has been controlled relative to the remote asymmetric centers at C-2,C-6 and can now be used to control the C-11 center.

Reduction of **10** with $LiEt_3BH$ (−78 °C) gave **12** (94%), **13** (4%), and 1–1.5% of a third isomer. Since **13** was formed as the major product from **11** (generated in situ via enolization of **10**), reduction selectivity of **10** according to the Felkin–Anh[7] mode was >60:1, presumably due to the presence of an α-sulfur substituent. Felkin–Anh selectivity was established specifically for the conversion of **11** to **13** by an X-ray structure determination of the crystalline product, and the stereochemistry for **12** (noncrystalline) was assigned by analogy. The X-ray study proved that all of the other stereocenters had been introduced correctly.

After alcohol protection and sulfur oxidation, **14** was subjected to an oxidative activation sequence which had been developed earlier for conversion of cyclic sulfides into lactones.[8,9] Quenching the sulfoxide anion of **14** with chlorodiphenylphosphine, followed by iodine catalyzed S to P oxygen transfer, gave **15** (60% overall). Horner–Bestmann oxygenation of phosphine oxide **15** then produced the desired thiolactone **16** together with recovered **15** (70% efficiency after recycle; 50% conversion). After silyl ether cleavage ($HF/H_2O/CH_3CN$), thiolactone **17** was subjected to camphorsulfonic acid catalysis in benzene (70 °C) to effect S to O acyl transfer (63%). This step converts the cyclic sulfur intermediate into the macrolide without resorting to high dilution conditions.[9]

Final removal of sulfur could be achieved by exploiting the photochemistry of phenacyl sulfides as previously reported.[10] Sunlamp irradiation of phenacyl sulfide **19** (obtained from **18** and phenacyl triflate[6]) in the presence of the *tert*-butyldimethylsilyl nitronate ester of nitroethane[11] as thio ketone trap, followed by fluoride-induced cleavage of the resulting cycloadducts,[10] generated **20** (74%) without affecting the α,β-unsaturation or the adjacent asymmetric center.

Next, it was necessary to introduce the correct oxidation pattern at C-7,C-10. Epoxidation of **20** with MCPBA gave a single epoxide diastereomer **21** (80%). The stereochemistry assignment is based on control by the local conformer effect of allylic C-6 methyl.[4] Upon treatment with DBU, keto epoxide **21** gave enone **22** in 70% yield (Scheme II). The last (C-10 methyl) carbon of methynolide could now be attached by organometallic addition, but CH_3Li in THF attacked the least hindered face of the ketone carbonyl[12] and formed largely the unnatural C-10 alcohol (3:1

(1) Vedejs, E. *Acc. Chem. Res.* **1984**, *106*, 358. Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878.

(2) Vedejs, E.; Mullins, M. J. *J. Org. Chem.* **1979**, *44*, 2947.

(3) Modifications in the original scheme were studied by Dr. J. Schaffhausen and will be described in the full paper.

(4) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058. Vedejs, E.; Dent, W. H., III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 0000.

(5) Buchi, G.; Wuest, H. *J. Org. Chem.* **1979**, *44*, 546.

(6) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

(7) For similar selectivity in acyclic α-alkylthio ketones, see: Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775, 4779. Higher Felkin–Anh selectivity is typical of cyclic sulfide analogues: Vedejs, E.; Joseph, N., unpublished results.

(8) Vedejs, E.; Meier, G. P.; Powell, D. W.; Mastalerz, H. *J. Org. Chem.* **1981**, *46*, 5253.

(9) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046. Vedejs, E.; Buchanan, R. A. *J. Org. Chem.* **1984**, *49*, 1840.

(10) Vedejs, E.; Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573.

(11) Calvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697.

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