# *Communications*

## Syn–Anti Isomerism in the 1,3-Dipolar Cycloaddition to Cis-3,4-Disubstituted Cyclobutenes. 3. Charge-Transfer, Electrostatic, and Steric Effects

*Summary:* A highly selective syn attack was observed in the reaction of several 1,3-dipoles with cyclobutene **1**. On the other hand, the reactions of cyclobutenes **2** and **3** with the same 1,3-dipoles gave rise to dominant or specific anti addition. The role of charge-transfer interactions and steric and electrostatic factors in determining face selectivity is clarified.

*Sir:* The face selectivity observed in the cycloaddition of cis-3,4-disubstituted cyclobutenes with diazomethane has been found to be related to the nonplanarity (see $\alpha^0$ values in Table 2) of the olefinic moiety of the dipolarophile and to the consequent energetic asymmetry of out of plane distortions.[1,2]

With the aim of detecting other factors that could be important in determining face selectivity we investigated experimentally the cycloadditions of *cis*-3,4-diacetoxycyclobutene (**1**), 2,4-dioxabicyclo[3.2.0]hept-6-en-3-one (**2**), and bicyclo[3.2.0]hept-6-ene (**3**), with diazoethane, 2-diazopropane, 3,4-dihydroisoquinoline *N*-oxide, *N*-*tert*-butylnitrone, benzonitrile phenylimide, benzonitrile oxide, and phenylglyoxylonitrile oxide (Table I;[3] Scheme I). The collection of 1,3-dipoles spans a wide range of steric, electrostatic, and charge-transfer attributes.[4] In the theoretical investigation another remarkable cyclobutene, bicyclo[2.1.0]pent-2-ene (**4**), has been added. Compound **4** has been reported to afford only anti adducts in the reaction with 1,3-dipoles.[5]

**Table I. Experimental Syn:Anti Ratios for the Reactions of Different 1,3-Dipoles with 1–3**

| 1,3-dipole $a{\equiv}b^+{-}c^-$ | syn:anti | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| diazomethane | 100:0[a] | 36:64[b] | 0:100[b] |
| diazoethane | 100:0 | 25:75 | 0:100 |
| 2-diazopropane | 70:30 | 9:91 | 0:100 |
| 3,4-dihydroisoquinoline *N*-oxide | 82:18[c] | 5:95[d] | 0:100 |
| *N*-*tert*-butylnitrone | 77:23 | 2:98 | 0:100 |
| benzonitrile phenylimide | 77:23 | ≤5:95 | 0:100 |
| benzonitrile oxide | 90:10 | 17:83 | 0:100 |
| phenylglyoxylonitrile oxide | 95:5 | 34:66[b] | 0:100[b] |

[a] Reference 1. [b] Reference 11. [c] Gandolfi, R.; Ratti, M.; Toma, L.; De Micheli, C. *Heterocycles* **1979**, *12*, 897. [d] De Micheli, C.; Gamba, A.; Gandolfi, R.; Scevola, R. *J. Chem. Soc., Chem. Commun.* **1976**, 246.

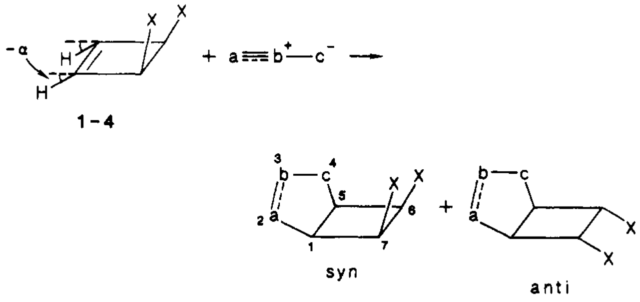
**Table II. $\alpha$ Values [Olefinic Hydrogens Out-of-Plane Bending (deg)] for Ground-State ($\alpha^0$) and for Isoenergetic Distorted ($\alpha_{\text{anti bent}}$ and $\alpha_{\text{syn bent}}$) Molecules and Charge-Transfer Interaction Energy Differences [$\Delta E_{CT} = E_{CT,\text{syn-attack}} - E_{CT,\text{anti-attack}}$] (kcal/mol) for Reactions of Selected 1,3-Dipoles with Bent Cyclobutenes 1–4**

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| $\alpha^0$ | −2.6[a] | 0.5[b] | 0.9[b] | 7.1[b] |
| $\alpha_{\text{anti bent}}$ | −21.7 | −18.0 | −18.0 | −13.2 |
| $\alpha_{\text{syn bent}}$ | 16.9 | 20.0 | 20.0 | 25.8 |

| | $\Delta E_{CT}$ (kcal/mol)[c] | | | |
|---|---|---|---|---|
| $a{\equiv}b^+{-}c^-$ | 1 | 2 | 3 | 4 |
| $CH_2N_2$ | −0.83 | 0.29 | 0.31 | 2.14 |
| $Me_2CN_2$ | −0.82 | 0.29 | 0.30 | 2.13 |
| $CH_2N(t\text{-Bu})O$ | −0.67 | 0.24 | 0.26 | 1.77 |
| PhCNO | −0.53 | 0.18 | 0.22 | 1.41 |
| PhCOCNO | −0.56 | 0.19 | 0.22 | 1.47 |

[a] STO-3G optimization (see ref 7). [b] 4-31G optimization (see ref 7). [c] INDO calculations (see ref 9).

**Scheme I**



**1**, X = OAc; **2**, X⌒X = OCOO; **3**, X⌒X = $CH_2CH_2CH_2$; **4**, X⌒X = $CH_2$

Noteworthy is the fact that the type II 1,3-dipoles, in particular the "electron poor" phenylglyoxylonitrile oxide, exhibit a behavior very similar to that of type I "electron rich" diazomethane and diazoethane.[6] It is quite evident that, whatever the 1,3-dipole, the four dipolarophiles tend

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(1) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Poppi, A. L.; Rastelli, A. *Tetrahedron Lett.* **1985**, *26*, 4653.

(2) The preference of partially formed bonds to be staggered, with respect to bonds in 3- and 4-position of cyclobutenes, in the TS (Houk's "staggered model": Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162) does not seem to give an acceptable answer to this problem (Caramella, P.; Marinone Albini, F.; Vitali, D.; Rondan, N. G.; Wu, Y.-D. Schwartz, T. R.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 1875).

(3) Cycloaddition reactions were carried out in ether at room temperature. Total yields range from 60% to 90%; the adducts proved stable under reaction and workup conditions. The ratio between syn (lower ($R_f$) and anti (higher $R_f$) isomers was evaluated by column chromatography. Only adducts formed via exo transition states were detected in the reactions of 3,4-dihydroisoquinoline *N*-oxide with **1** and **2**, while in the case of **3** very small amounts (≈1%) of an anti-endo adduct could also be isolated. Syn attack by diazoethane on **1** and **2** gave rise to only one of the two possible epimers [that one with $H_4$ (for numbering see Scheme I) oriented endo with respect to the cyclobutane ring] whereas both epimers (ratio ≈ 2:1) were produced in the anti attack by the same 1,3-dipole on **2** and **3**. The structures of the adducts were assigned on the basis of analytical and spectroscopic data. As for $^1H$ NMR data, $J_{1,7}$ and $J_{5,6}$ are ≥5.0 Hz, indicative of a cis relationship, in the syn adducts and ≤3.0 Hz in the anti adducts; in the syn adducts from the reactions of **1** with nitrile oxides one of the acetoxy group (both the acetoxy groups in the syn adduct of benzonitrile phenylimide with **1**) experiences an upfield shift (≈0.4 ppm); in the syn adducts from the reactions of diazoalkanes and nitrones with **1** and **2**, the sterically hindered $H_{4,\text{endo}}$ (or methyl) is definitively less shifted to higher field than the $H_{4,\text{endo}}$ in the related anti adducts, on passing from $CDCl_3$ to $C_6D_6$. Moreover, the adducts from **1** and **2** were chemically correlated.

(4) $\epsilon_{HOMO,CH_2N_2} - \epsilon_{LUMO,1} = 13.4$ eV and $\epsilon_{LUMO,CH_2N_2} - \epsilon_{HOMO,1} = 16.1$ eV, whereas $\epsilon_{HOMO,PhCOCNO} - \epsilon_{LUMO,1} = 14.9$ eV and $\epsilon_{LUMO,PhCOCNO} - \epsilon_{HOMO,1} = 13.1$ eV, (INDO calculations).

(5) Adam, W.; Beinhauer, A.; De Lucchi, O.; Rosenthal, R. J. *Tetrahedron Lett.* **1983**, *24*, 5727.

(6) The recent Hehre's reactivity model (Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663, and references cited therein) does not satisfactorily explain our experimental data, at least if diazomethane is considered more nucleophilic than phenylglyoxylonitrile oxide.

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to impose their own stereochemical demand: syn attack for **1**, anti attack for **3** (and **4**), and mixture for **2**. However, it is equally clear that 1,3-dipoles other than diazomethane tend to increase the percentage of anti adduct, with the exception of diazoethane and, to a lesser extent, of phenylglyoxylonitrile oxide.

Does the charge-transfer interaction energy ($E_{CT}$) between occupied and unoccupied molecular orbitals of the different dipole–dipolarophile pairs play a role in determining the absolute and relative face selectivity found?

It is obvious that the approach of the 1,3-dipoles on the syn (anti) face of anti (syn) ground-state bent cyclobutenes ought to be assisted, already at the very beginning of the interaction of the reacting partners, by a larger CT interaction, as compared to the anti (syn) attack. In fact, the overlap integrals between the interacting orbitals favor the attack on the side where the lobe of the hybrid atomic orbitals is bigger than the other. An adequate way to illustrate this effect and to quantitatively evaluate the differences in CT energies for the two diastereofacial attacks is to consider for each dipolarophile a pair of syn and anti isoenergetic bent molecules. In fact, when a deformation of olefinic hydrogens (toward the TS geometries) corresponding to 4.0 ± 0.1 kcal/mol over the stable optimized geometries[7] was imposed, a larger anti (see $\alpha_{\mathrm{anti\ bent}}$ in Table II) than syn ($\alpha_{\mathrm{syn\ bent}}$) deformation was observed in **1**, whereas the opposite happened in **2**–**4**.[8]

Differences between charge-transfer energies ($\Delta E_{CT}$), calculated according to Salem's equation, for syn and anti attack on isoenergetic anti and syn bent forms, respectively, of each dipolarophile are reported in Table II.[9] A dominance of syn attack (negative values) and of anti attack (positive values) is predicted for **1** and **4**, respectively, whereas **2** and **3** are candidates for mixtures with a slight preference for the anti adducts. Theoretical results are more related (signs and values) to the differences of the corresponding overlap (interaction) integrals, than to the specific 1,3-dipole involved.[9] This notwithstanding a dominance of $\mathrm{HOMO}_{1,3\text{-dipole}}$–$\mathrm{LUMO}_{\mathrm{dipolarophile}}$ interaction in the case of $CH_2N_2$ and $\mathrm{LUMO}_{1,3\text{-dipole}}$–$\mathrm{HOMO}_{\mathrm{dipolarophile}}$ in the case of PhCOCNO.[4] Thus when the interaction integrals were held fixed, $\Delta E_{CT}$ became negligible (ranging from ≤0.01 for the reactions of **1** to ≤0.08 for the reactions of **2**–**4**).[10]

Thus, we may conclude that the trend found in $\Delta E_{CT}$ is strictly related to the out-of-plane asymmetry: a large $E_{CT}$ for the anti attack corresponds to an easier syn bending of olefinic hydrogens and vice versa. In other words $E_{CT}$ cooperates with energy asymmetry of out-of-plane distortions in the attempt to dictate face selectivity in compound **1**–**4**. However, the 100% face selectivity observed for the reactions of **3** is at variance with theoretical predictions and it is clear that $E_{CT}$ and energy asymmetry do not explain the specificity of 1,3-dipoles in modulating syn:anti ratios for a given cis-3,4-disubstituted cyclobutene.

As for compound **3**, we have recently shown that this compound prefers a boat conformation in which a severe steric hindrance is present on the syn face.[11] Steric effects also show up clearly in the decrease of syn attack on passing from diazomethane and diazoethane to sterically more demanding 2-diazopropane. Moreover the electrostatic potential-energy maps for diazomethane and *N-tert*-butylnitrone give strong evidence of how nitrones could be very sensitive to electrostatic repulsions and tend to avoid areas of high electron density such as that of nuclei carrying lone pairs.

Experimental and theoretical investigations on a larger series of cyclobutenes (with different acyclic and cyclic allylic substituents as well as electron-withdrawing and electron-donating substituents on the double bond) are under way in our laboratory in order to definitively assess the relative roles of the various factors in directing π-face selectivity as well as the underlying causes of π-pyramidalization.

**Acknowledgment.** We thank the Ministero della Pubblica Istruzione and CNR for financial support.

**Registry No.** **1**, 71348-58-8; *syn*-**1**–diazomethane adduct, 101219-81-2; **1**-diazoethane adduct, 113749-59-0; *syn*-**1**–2-diazopropane adduct, 113749-60-3; *anti*-**1**–2-diazopropane adduct, 113829-20-2; **1**–3,4-dihydroisoquinoline *N*-oxide adduct, 113829-19-9; *syn*-**1**–*N*-*tert*-butylnitrone adduct, 113749-61-4; *anti*-**1**–*N*-*tert*-butylnitrone adduct, 113829-21-3; *syn*-**1**–benzonitrile phenylimide adduct, 113749-62-5; *anti*-**1**–benzonitrile phenylimide adduct, 113829-22-4; *syn*-**1**–benzonitrile oxide adduct, 91622-90-1; *anti*-**1**–benzonitrile oxide adduct, 113829-23-5; *syn*-**1**–phenylglyoxylonitrile oxide adduct, 113749-63-6; *anti*-**1**–phenylglyoxylonitrile oxide adduct, 113829-24-6; **2**, 33186-71-9; *syn*-**2**–diazomethane adduct, 101312-87-2; *anti*-**2**–diazomethane adduct, 101219-80-1; **2**-diazoethane adduct, 113749-64-7; *sny*-**2**–2-diazopropane adduct, 113749-65-8; *anti*-**2**–2-diazopropane adduct, 113829-26-8; **2**–3,4-dihydroisoquinoline *N*-oxide adduct, 113829-25-7; *syn*-**2**–*N*-*tert*-butylnitrone adduct, 113749-66-9; *anti*-**2**–*N*-*tert*-butylnitrone adduct, 113829-99-5; *syn*-**2**–benzonitrile phenylimide adduct, 113749-67-0; *anti*-**2**–benzonitrile phenylimide adduct, 113829-27-9; *syn*-**2**–benzonitrile oxide adduct, 113749-68-1; *anti*-**2**–benzonitrile oxide adduct, 113829-28-0; *syn*-**2**–phenylglyoxylonitrile oxide adduct, 113749-69-2; *anti*-**2**–phenylglyoxylonitrile oxide adduct, 113829-29-1; **3**, 4927-03-1; *anti*-**3**–diazomethane adduct, 101219-79-8; **3**–diazoethane adduct, 113749-70-5; *anti*-**3**–diazopropane adduct, 113749-71-6; **3**–3,4-dihydroisoquinoline oxide adduct, 113749-72-7; *anti*-**3**–*N*-*tert*-butylnitrone adduct, 113749-73-8; *anti*-**3**–benzonitrile phenylimide adduct, 113749-74-9; *anti*-**3**–benzonitrile oxide adduct, 113749-75-0; *anti*-**3**–phenylglyoxylonitrile oxide adduct, 113749-76-1; **4**, 5164-35-2; diazomethane, 334-88-3; diazoethane, 1117-96-0; 2-diazopropane, 2684-60-8; 3,4-dihydroisoquinoline *N*-oxide, 24423-87-8; *N*-*tert*-butylnitrone, 41012-82-2; benzonitrile phenylimide, 15409-32-3; benzonitrile oxide, 873-67-6; phenylglyoxylonitrile oxide, 31879-18-2.

**Supplementary Material Available:** s character of the π-type hybrid atomic orbitals of the isoenergetic anti and syn bent forms of **1**–**4**, overlap integrals between the 1,3-dipole π-orbitals and the π-type hybrid atomic orbitals of the isoenergetic anti and syn bent forms of dipolarophiles **1**–**4**, $\Delta E_{CT}$ calculated with fixed interaction integrals, and electrostatic potential-energy maps for diazomethane and *N*-*tert*-butylnitrone (2 pages). Ordering in-

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(7) 4-31G optimization for compounds **2**–**4** with the following constraints: $C_s$ symmetry and C=C, C(sp$^3$)–H, and C(sp$^2$)–H bond lengths fixed to the standard values 1.342, 1.094, and 1.083 Å, respectively. STO-3G optimization for compound **1** with the following constraint: $C_s$ symmetry, cyclobutene ring geometry assumed from the *cis*-3,4-dichlorocyclobutene experimental geometry, and OAc geometry fixed to standard values. For previous STO-3G calculations on **4**, see: Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436.

(8) This is simply a way to translate the different deformation energies, required to give rise to equal (e.g., 20°) syn and anti distortions of the olefinic hydrogens,[1] into differences between the dihedral angles of the two opposite distortions brought about by the same amount of energy.

(9) MO calculations have been done in the INDO approximation with the use of hybrid atomic orbitals (HAO) basis calculated according to the maximum localization criterion (Pozzoli, S. A.; Rastelli, A.; Tedeschi, M. *J. Chem. Soc., Faraday Trans. 2* **1973**, 256). This basis represents an appropriate choice for comparing distorted molecules where HAO's instead of pure $p_Z$ AO's are involved in the π-system. The interaction integrals are taken as proportional to the overlap integrals $S_{CX}$ which are higher for hybrids having more s character, that is, for more distorted molecules.

(10) In fact MO energies and coefficients of syn and anti bent molecules are similar.

(11) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Rastelli, A. *J. Chem. Soc., Perkin Trans 2*, in press.

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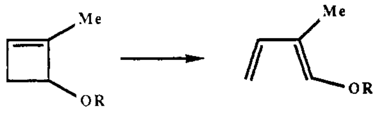
## Electronic Control of the Stereoselectivities of Electrocyclic Reactions of Cyclobutenes against Incredible Steric Odds

*Summary:* Experimental studies of the electrocyclic reactions of 2- and 3-*tert*-butyl-3-(trimethylsiloxy)cyclobutene and of 3-methoxy-3-*tert*-butylcyclobutene confirm ab initio computational predictions.

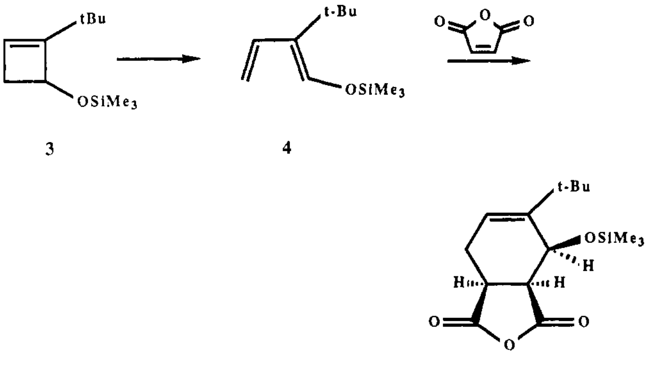
*Sir:* Several years ago, two of us reported that the electrocyclic opening of 3-hydroxy, -deuteroxy, and -trimethylsiloxy derivatives of 2-methylcyclobutene (**1a–c**) gave only products **2** arising from outward rotation of the oxygen substituents even though these products appear to be less stable than those arising from inward rotation.[2] Subsequent experiments by Kirmse[3] and Dolbier[4] and calculations by Rondan and Houk[5] showed that donor substituents at C3 display a large preference for outward rotation in these electrocyclizations.



1 2

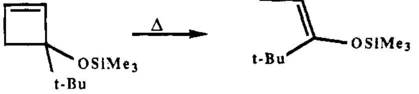
We now wish to report new experimental results which indicate that the preference of an oxygen substituent at C3 for outward rotation significantly exceeds that of a *tert*-butyl group. Calculations on the transition structures for electrocyclic reactions of various model systems and for 3-hydroxy-3-*tert*-butylcyclobutene provide an explanation of these results and confirm that substituent effects are approximately additive.

When 2-*tert*-butyl-3-(trimethylsiloxy)cyclobutene (**3**) is heated in deuteriochloroform at 95–100 °C for 1.5 h, a single silyl dienol ether, **4**, is obtained. When the reaction is carried out in the presence of maleic anhydride (1.1 molar equiv), a single Diels–Alder adduct, **5**, is formed. The cis configuration of the siloxy substituent and the anhydride grouping is established by the size of the vicinal coupling constant (2.8 Hz) of the respective methine protons. Their cis relationship is confirmed by NOE measurements.



3 4 5

More telling is the thermal behavior of 3-*tert*-butyl-3-(trimethylsiloxy)cyclobutene (**6**) and 3-*tert*-butyl-3-methoxycyclobutene (**12**). Heating **6** in deuterochloroform for 4 h cleanly affords a single product, which must have the more hindered *E* geometry, **7**. Attempts to capture **7** with maleic anhydride are unavailing; polymerization predominates. Clearly, the cisoid conformation required for the Diels–Alder cycloaddition is inaccessible. Further support for the configuration of **7** is found by treating 2,2-dimethylhex-4-en-3-one (**8**) with LDA at -78 °C, followed by addition of trimethylsilyl chloride. Only one silyl ether, **9**, which is different from **7**, is found, indicating that the less encumbered *Z* dienolate **10** is formed rather than the *E* isomer **11**.[6] The structures of both **7** and **9** are unambiguously confirmed by their characteristic $^{13}$C NMR spectra.[7] In **9**, the contiguous trimethylsiloxy group shields the $\gamma$ carbon atom, (106.23 ppm) whereas in **7**, it does not (109.62 ppm). The effect is mutual and the silylmethyl $^{13}$C shifts appear at 1.04 and 1.91 ppm, respectively.[8] The geometries of **7** and **9** were confirmed by NOE measurements.



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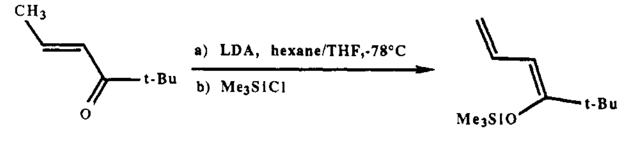

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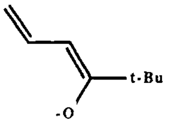

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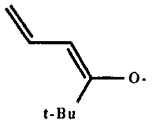

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(1) (a) UCLA. (b) Geneve. (c) IBM.

(2) Jefford, C. W.; Boschung, A. F.; Rimbault, C. G. *Tetrahedron Lett.* **1974**, *38*, 3387.

(3) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 1871.

(4) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871. Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. L.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1987**, *109*, 219.

(5) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708.

(6) For related examples of the exclusive formation of *Z*-enolates, see: Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. Fellman, P.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 1349.

(7) $^{13}$C NMR (CDCl$_3$, 50 MHz): compound **7**, 161.05, 132.73, 111.87, 109.62, 37.83, 29.72, 1.91 ppm; compound **9**, 161.17, 132.48, 112.24, 106.23, 36.51, 28.39, 1.04 ppm.

(8) Kalinowski, H. O.; Berger, S.; Braun, S. *$^{13}$C-NMR-Spektroskopie*; G. Thieme Verlag: Stuttgart, 1984; pp 263–264.

0022-3263/88/1953-2125$01.50/0