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The α-Effect in the Stereochemistry of Kinetic Ketonization of Enols[1,2]

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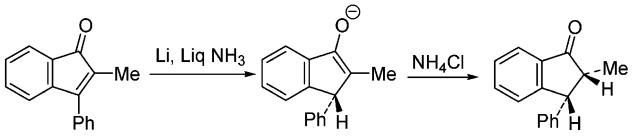
Kinetic control of the stereoselectivity of protonation of enolates and other strongly delocalized anionic species is involved in a large number of organic reactions. Protonation occurring from the less hindered side of the, e.g., enolic system affords the less stable of two diastereomers. However, one apparent discrepancy has been in the synthesis of prostaglandins. The present research deals with the source of this behavior. A curious effect of the substituent at the enolic α carbon was uncovered. In certain instances an α substituent is forced to twist into a conformation blocking the proton donor from its side, thus reversing the stereochemistry of protonation. In the course of this research, a number of five-ring enols of varying structure were investigated. Finally, the ketonization reaction course has been studied theoretically.

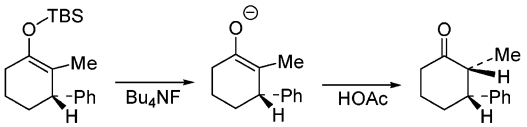
Introduction

In a long series of publications,[3] dating back to 1955, we have described the stereochemical course of kinetic protonation of enols of widely varying structures. Since a rather large variety of reactions proceed via enolic intermediates, an understanding of the basic mechanism provides a basis for dealing with this broad array of organic reactions. In these studies, we have noted that the ketonization process is highly exothermic, proceeds via a transition state in which the α carbon is close to sp^2 hybridized, and undergoes protonation at this α carbon from the less hindered side of the enolic system. The consequence is that the less stable of two diastereomeric ketone products is favored.[3a]

Two typical and interesting reactions are shown in eqs 1 and 2. These are representative of the large set of



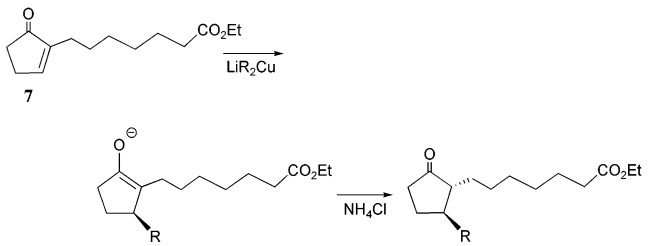
1 2 3 (1)



4 5 6 (2)

examples studied over the years[3] following our initial discovery of the phenomenon.[3a] That in eq 1 derives from one of our earlier studies[3b] while that in eq 2 comes from the present study and is discussed below. It needs to be noted that after the initial discovery, and continuing to the present time, there has been a large number of parallel examples contributed in the literature.[4,5]

With the immense set of examples affording less stable diastereomers, the chemistry involved in prostaglandin synthesis was puzzling. Throughout the prostaglandin literature, ketonization stereochemistry is the reverse of that superficially anticipated. For example, the conjugate addition of cuprates to cyclopentenones, as depicted in eq 3, involves ketonization of enolates as **8** and invariably leads to the more stable trans stereoisomers.[6]



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R = $(CH2)_nCH_3$ n = 1,2,4,7

8 9 (3)

Hence, the present study had as its goal, studying and understanding the stereochemistry of ketonization of endo-cyclic five-membered ring enols. We selected examples having short- and long-chain α substituents and long-chain and phenyl β substitution.

Results

Syntheses. The syntheses utilized the standard cuprate addition to 2-substituted cyclopentenones **13** followed by trapping with *tert*-butyldimethylsilyl chloride to afford the desired silyl enol ethers **14**. These are ideal

(1) Part 273 of our general series.
(2) Part 272: Zimmerman, H. E.; Novak, T. *J. Org. Chem.* **2003**, *68*, 5056−5066.

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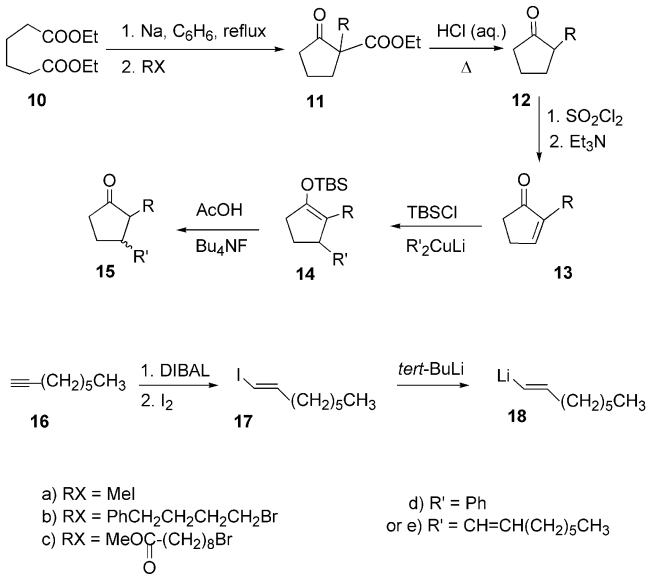
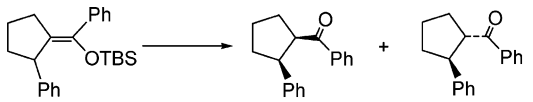
SCHEME 1. Preparation of Silyl Enol Ethers



enol precursors to be reacted with tetrabutylammonium fluoride. For preparative purposes, standard workup with ammonium chloride, following the cuprate addition, afforded varying ratios of the corresponding cis and trans ketones required as authentic ketonization products (Scheme 1).

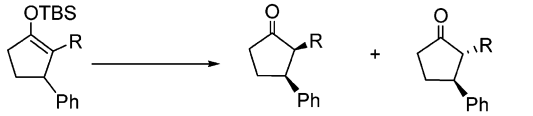
Ketonization Stereochemistry. With some of our recent studies in mind,[7] we selected ketonization conditions employing tetrabutylammonium fluoride−acetic acid desilylation to convert the silyl enol ethers to their enolic counterparts. That the stereochemical reaction course in the examples studied was determined by kinetics without product equilibration and was established by the constancy of the ketone stereoisomer ratio which was independent of (a) the extent of conversion, (b) the reaction time, and (c) the acid concentration (within the limits employed).

The first example studied was that already presented in eq 2. In accord with the large variety of known examples affording the cis and less stable diastereomer, this reaction led to a 91% predominance of the cis ketonization product. However, since the aim was to understand the prostaglandin system, the remaining examples studied are five-membered ring enolic systems. These are outlined in eqs 4−6. It is seen that for protonation of the endo-cyclic enols, the stereoselectivity varies. Three cases (eqs 5i−iii) exhibit the usual kinetic preference for formation of the cis-diastereomer, while two examples (eqs 6ii,iii) show a kinetic preference for the trans stereoisomer. One five-ring example (eq 6i) exhibits little selectivity, and the one exo-cyclic example (see eq 4) leads to the cis stereoisomer predominantly.



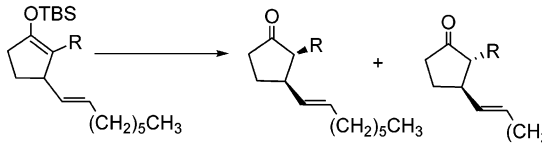
(4)

19	20 cis	20 trans
	89 %	11 %



(5i,ii,iii)

21	22 cis	22 trans
i) R = Me	75 %	25 %
ii) R = $(CH_2)_4Ph$	60 %	40 %
iii) R = $(CH_2)_8CO_2Me$	60 %	40 %



(6i,ii,iii)

23	24 cis	24 trans
i) R = Me	54%	46 %
ii) R = $(CH_2)_4Ph$	30%	70%
iii) R = $(CH_2)_8CO_2Me$	30%	70 %

Thus, we have examples which follow the traditional cis-diastereomer formation and also examples of the "prostaglandin-type" trans isomer formation. The source of the difference remains to be determined.

Computational Efforts

In one previous ketonization study we employed molecular mechanics to assess the difference in alternative

(3) (a) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557. (b) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168−1173. (c) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *48*, 1637−1646. (d) Zimmerman, H. E.; Giallombardo, H. J. *J. Am. Chem. Soc.* **1956**, *78*, 6259−6263. (e) Zimmerman, H. E. *J. Am. Chem. Soc.* **1957**, *79*, 6554−6558. (f) Zimmerman, H. E.; Nevins, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559−6561. (g) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1958**, *80*, 2893−2896. (h) Zimmerman, H. E.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1958**, *80*, 3060−3064. (i) Zimmerman, H. E.; Chang, W.-H. *J. Am. Chem. Soc.* **1959**, *81*, 3634−3643. (j) Zimmerman, H. E.; Mais, A. *J. Am. Chem. Soc.* **1959**, *81*, 3644−3651. (k) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1959**, *81*, 4305−4308. (l) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091−6096.

(4) (a) The number of literature examples is large; one review is given in ref 4b. (b) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268.

(5) (a) Krause, N.; Ebert, S.; Haubich, A. *Liebigs Ann. Recl.* **1997**, 2409−2418. (b) Davies, H. M. L.; Hodges, L. M.; Gregg, T. M. *J. Org. Chem.* **2001**, *66*, 7898−7902. (c) Takano, S.; Kudo, J.; Takahashi, N.; Ogasawara, K. *Tetrahedron Lett.* **1986**, 2405−2408. (d) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogaswara, K. *Chem. Lett.* **1982**, 733−737. (e) Hunig, S. in Houben-Weyl, Methods of Organic Synthesis **1996**, Vol. E21D 7, 3851−3911. (f) Interestingly, these references seem unaware the source of the protonation discovery, and the phenomenon has been reported as a new discovery in ref 5c−e.

(6) (a) Schaub, R. E.; Weiss, M. J. *Tetrahedron Lett.* **1973**, 129−130. (b) Griego, P. A.; Reap, J. J. *J. Org. Chem.* **1973**, *38* (19), 3413−3415. (c) Bernady, K. F.; Poletto, J. F.; Weiss, M. J. *Tetrahedron Lett.* **1975**, 765−768. (d) Poletto, J. F.; Bernady, K. F.; Kupfar, D.; Partridge, R.; Weiss, M. J. *J. Med. Chem.* **1975**, *18* (4), 359−362. (e) Smith, A. B., III; Wexler, B.; Slade, J. S. *Tetrahedron Lett.* **1980**, *21*, 3237−3240. (f) Tolstikov, G. A.; Miftakhov, M. S. *J. Org. Chem. USSR.* **1984**, *19* (10), 1793−1798. (g) Kruger, G.; Harde, C.; Bohlmann, F. *Tetrahedron Lett.* **1985**, *26* (49), 6027−6030. (h) Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III *J. Am. Chem. Soc.* **1986**, *108* (10), 2662−2674. (i) Cho, B. P.; Chadha, V. K.; Le Breton, G. C.; Venton, D. L. *J. Org. Chem.* **1986**, *51*, 4279−4284. (j) Holland, H. L.; Ratemi, E. S.; Contreras, L. *Can. J. Chem.* **1994**, *72*, 1−5.

(7) (a) Zimmerman, H. E.; Ignatchenko, A. *J. Am. Chem. Soc.* **1998**, *120*, 12992−12993. (b) Zimmerman, H. E.; Ignatchenko, A. *J. Org. Chem.* **1999**, *64*, 6635−6645. (c) Zimmerman, H. E.; Wang, P. *Org. Lett.* **2002**, *4*, 2593−2595. (d) Zimmerman, H. E.; Wang, P. *J. Org. Chem.* **2002**, *69*, 9216−9226.

approaches of the proton donor to the p-orbital of the α carbon.[3c] Thus, with two types of behavior, "traditional" and "prostaglandin-like", computations on these promised to reveal the source of the differing behavior.

Molecular mechanics computations were carried out on cyclopentenyl enolates with (a) long α chains but phenyl as the β substituent (case A), (b) a short (e.g., methyl) α substituent but a long β chain (case B), and (c) long α chains as well as long β chains (case C). For simplicity and semiquantitative purposes, a simple bromine atom (van der Waals radii 1.95 Å) was employed to simulate an attacking proton donor. A perpendicular approach to the enolic α carbon and an Amber force field were used.[8] In cases B and C, the β chain contains a double bond in order to simulate the prostaglandin structure. The energetics of syn and anti attack are given below for the three cases in Figure 1A−C.We note that at very short distances between the donor and the enolate moiety, the plots become unrealistic with unreasonably large energies, since no provision in the computations takes into account enolate relaxation from sp^2 toward sp^3.

The conformations employed for the enolic species are global minima. A variety of higher energy of local minima with conformational differences in the long chains were encountered but not utilized. We note that in cases A and C the α and β groups remain on opposite faces of the molecule. Indeed, some conformations were encountered as local minima with the α and β chains oriented closer to the same face of the five-membered ring. However, these proved to be of higher energy (ca. 1.2 kcal/mol). Note that we define the "anti face" as that anti to the β chain and the "syn face" as that syn to the β chain.

Before proceeding to the Discussion, it is sufficient to comment that the lower energy approach is variable depending on which system is involved.

Discussion

One of the most interesting aspects of the results, both experimental and computational, is the marked variation of overall reaction stereoselectivity resulting from what seems to be relatively minor changes in structure.

Consistent Trends as a Function of Structure. First we consider the example of the six-membered ring enolate **5** in eq 2 which led to a preference for formation of the cis stereoisomer. It is seen from Figure 2, which approximates the molecular mechanics optimization, that the top lobe of the α p-orbital is less hindered by the phenyl group at carbon 3. Protonation then leads to the *cis*-2-methyl-3-phenylcyclohexanone. One notes that the protonation is effectively an "equatorial process" in terms of product conformation. However, in an early transition state the equatorial character presumably has not appreciably developed.[9]

Turning now to the five-membered ring enolic systems, we need to interpret the considerable variation in reaction stereochemistry which superficially seems random. However, on closer inspection, it is seen that there really are three categories as depicted in Figure 1A−C.

As noted, these correspond to **(**A**)** having a β phenyl group, **(**B**)** having a methyl group α and a long chain β, and **(**C**)** having a long chain at both the α and β carbons. The long chain β groups incorporate a double bond in analogy to the prostaglandin structures while for the α long chain, carbomethoxyloctyl and phenylbutyl were used.

Within these three categories, the stereochemical outcome is seen to be constant and consistent. Thus, in the case (i.e., A) of the β-phenyl enolic systems, it is not surprising that the predominant product is the cis stereoisomer. This is seen in Figure 1A where the less hindered approach to the α carbon is anti to the β-phenyl group. Refer also to eq 5 and the ratios listed. This stereochemistry arises from protonation anti to the β substituent.

In case B with an α-methyl group, inspection of Figure 1B reveals little preference for either approach to the α carbon. In this case, syn and anti protonation are energetically similar. The effect of the long β chain is small as a consequence of its orientation away from the α carbon p-orbital, and little selectivity results experimentally and computationally.

In case C with long α and β chains, there is the curious preference for formation of the trans product stereochemistry resulting from protonation syn to the β substituent. This result, along with the stereochemistry of cases A and B, requires discussion below.

Also remaining is the example of the exo-cyclic cyclopentane enolic system of **19** where protonation anti to the ring phenyl group results from the less hindered attack and is unremarkable.

Mechanistic Rationale of the α Effect. Of the three endo-cyclic five ring types, it is case C which still requires discussion. Here we find from geometry optimization that the long α chains twist to a side of the five-membered ring opposite to the long-chain β substituents. The net effect is that the face of the five-ring which is less hindered is syn to the β substituent. The twisted α chain's hindrance overrides the steric effect of the β group. We term this the "α effect", and this is responsible for the unusual prostaglandin chemistry. While twisting occurs in case A as well, the bulk of the phenyl group dominates.

A General Point Regarding Stereoselectivity and Energetic Differences. There is a general point which needs comment. Thus, throughout in the stereochemistry of kinetic protonation, the energy differences controlling stereoselectivity seem small, a few kilocalories or less. One might be tempted to dismiss the importance of such differences. However, it has been noted in one of our earlier papers that when stereoselectivity shows a consistent trend in one direction such small energy differences should not be ignored. To the synthetic organic chemist a 90% yield is quite different than a 10 percent yield, yet a 10:1 stereoselectivity corresponds to only 1.4 kcal/mol.

(8) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M., Jr.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179−5197.

(9) (a) The role of greater overlap of the carbonyl p-system with the developing α σ C−H bond has been noted by Corey.[9b] (b) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269−6278. (c) This is a factor which, although real, seems to be energetically small.[4b]

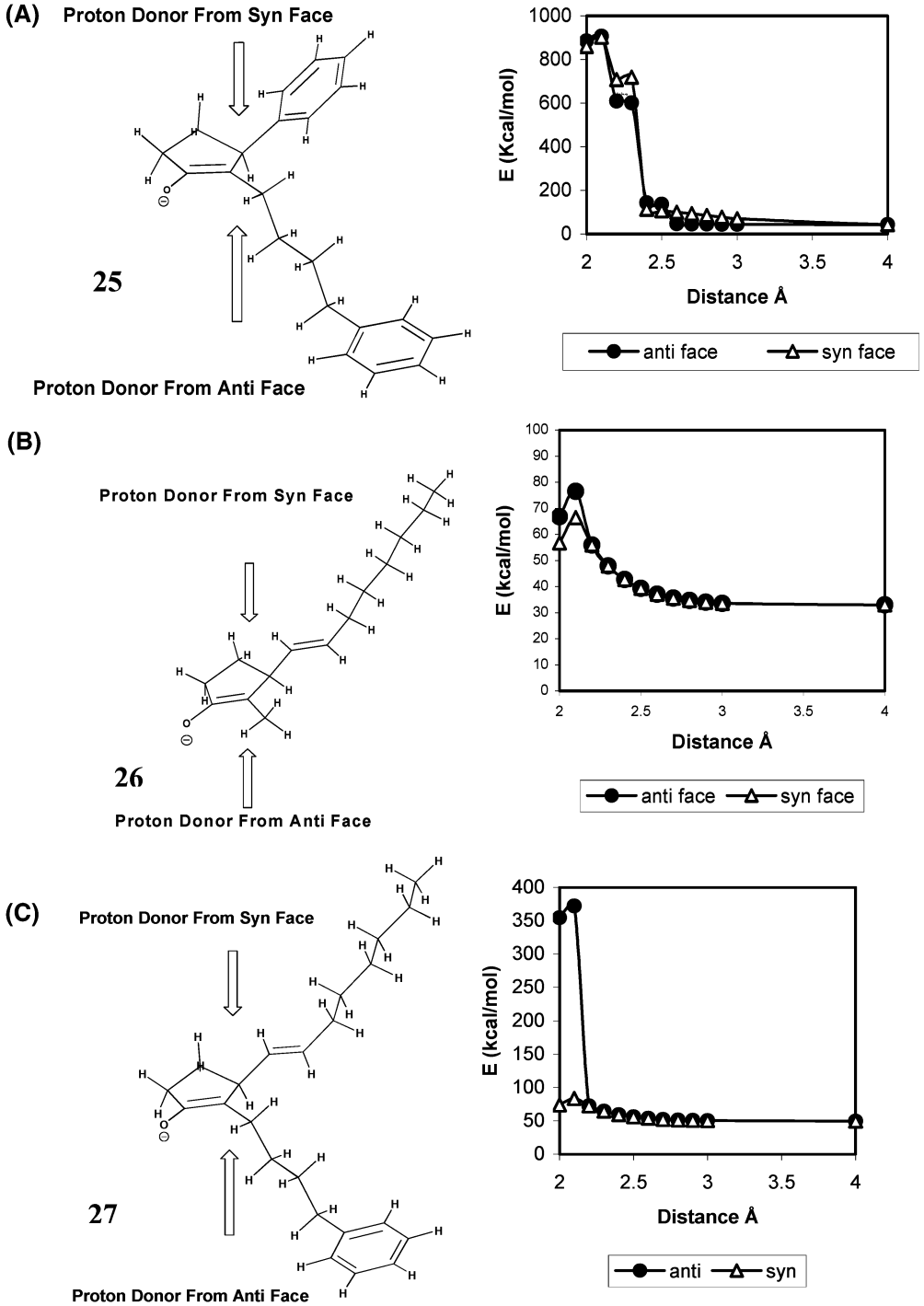


FIGURE 1. (A) Lower energy attack is from the anti face. (B) Small energy differences. (C) Lower energy attack from the syn face.

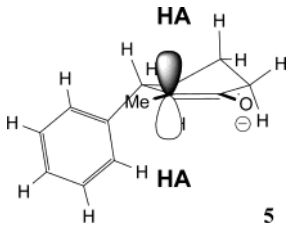


FIGURE 2. Approach of the proton donor preferred trans to the phenyl.

Conclusion: Consideration of the Results of the Present Study in the Context of the Literature Background

Our original efforts on the stereochemistry of kinetic protonation in 1955 derived from the obvious importance of ketonization stereochemistry to a very large number of organic reactions proceeding via enolic intermediates, and our interest in the area has continued over the years[3] and includes a 1987 review[4b] of the situation as of that time. Also, we've noted that it is not surprising that our phenomenon has been rediscovered more than once.[5c−e]

While the original postulate of less hindered protonation to give the less stable diastereomer largely still holds true, we note that there are exceptions. One exception results from intramolecular proton transfer to the more hindered face of the enolate system.[7] The prostaglandin chemistry provides an example where the more stable of two alternative diastereomers is preferred, but the less hindered approach, again, is involved.

Experimental Section

***tert*-Butyldimethylsilyl Enol Ether of Phenyl(2-phenylcyclopentyl)methanone (19).** To a solution of diisopropylamine (0.20 mL, 1.2 mmol) in 4.0 mL of THF was added 0.60 mL of 2.0 M BuLi under nitrogen at −72 °C. The reaction mixture was stirred for 30 min and HMPA (0.42 mL, 2.4 mmol) was added, followed by in 2.0 mL of THF solution of phenyl-(2-phenylcyclopentyl)methanone (120 mg, 0.48 mmol) and TBSCl (186 mg, 1.2 mmol). The reaction temperature was allowed to gradually reach room-temperature overnight and was quenched with 3.0 mL of water. The aqueous layer was ether extracted (3 × 3.0 mL), the combined extracts dried over $MgSO_4$ and concentrated in vacuo. The crude product was subjected to column chromatography eluted with hexane to give 100.0 mg (62.5%) of the silyl enol ether (**19**) as a colorless oil: R_f (hexane) 0.15; IR ($CDCl_3$) 3023, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.45−7.15 (m, 10H), 4.15 (m, 1H), 2.55−2.30 (m, 2H), 2.20−2.05 (m, 1H), 1.75−1.55 (m, 3H), 0.64 (s, 9H), −0.28 (s, 3H), −0.51 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 146.6, 143.2, 139.8, 128.6, 128.0, 127.9, 127.7, 127.3, 125.2, 46.8, 37.1, 31.5, 25.6, 24.6, −3.9, −4.3; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{24}H_{32}OSi$ 364.2222, obsd 364.2235.

General Procedure for Preparation of *tert*-Butyldimethylsilyl Enol Ethers of α,β-Disubstituted Cyclopentanones. The α,β-disubstituted cyclopentanones were prepared by trapping the enolates generated from 1,4-addition of the corresponding cuprate reagents to the α-substituted cyclopentenones. In a typical run, to a suspension of $CuBr{\cdot}Me_2S$ (0.62 g, 3.0 mmol) in 7.5 mL of THF was added 4.8 mL of 1.2 M PhLi (6.0 mmol) under nitrogen in an ice−water bath with stirring for 15 min before 1.5 mL of a THF solution of 2-methylcyclopentenone (0.14 g, 1.5 mmol) was added dropwise. The mixture stirred for an additional 30 min. Then HMPA (0.52 mL, 3.0 mmol) was introduced, followed by TBSCl (0.47 g, 3.0 mmol) in 1.5 mL of THF and Et_3N (0.41 mL, 3.0 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched with saturated $NaHCO_3$. THF was removed in vacuo, the aqueous layer was ether extracted (3 × 10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was subjected to column chromatography (ether/hexane = 1/10) to yield 0.34 g (80%) of silyl enol ether **21i** as a colorless oil: R_f (ether/hexane = 1/10) 0.82; IR ($CDCl_3$) 1686, 1462, 1257, 889, 837 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.36−7.14 (m, 5H), 3.60 (broad, 1H), 2.55−2.29 (m, 3H), 1.79−1.66 (m, 1H), 1.40 (s, 3H), 1.00 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$, δ) 148.6, 146.8, 128.2, 127.5, 125.9, 115.8, 51.8, 33.0, 30.8, 25.7, 18.1, 10.6, −3.9, −4.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{18}H_{28}OSi$ 288.1909, obsd 288.1899.

***tert*-Butyldimethylsilyl enol ether of 2-methyl-3-phenylcyclohexanone (4):** IR ($CDCl_3$) 1678 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.32−7.24 (m, 2H), 7.21−7.14 (m, 3H), 3.33 (m, 1H), 2.14 (m, 2H), 1.96−1.85 (m, 1H), 1.72−1.50 (m, 3H), 1.44 (s, 3H), 0.98 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 146.0, 145.9, 128.4, 128.1, 125.8, 113.0, 46.6, 32.8, 30.7, 25.9, 20.1, 18.3, 15.4, −3.6, −3.8; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{19}H_{30}OSi$ 302.2066, obsd 302.2070.

***tert*-Butyldimethylsilyl enol ether of 3-phenyl-2-(4-phenylbutyl)cyclopentanone (21ii):** IR ($CDCl_3$) 1677 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.30−7.05 (m, 10H), 3.70−3.60 (m, 1H), 2.56−2.15 (m, 6H), 1.75−1.15 (m, 6H), 0.96 (s, 9H), 0.17 (s, 3H), 0.16 (s, 1H); ^{13}C NMR ($CDCl_3$, δ) 148.7, 146.9, 142.9, 128.4, 128.3, 128.1, 127.6, 125.9, 125.5, 119.8, 49.4, 35.6, 33.0, 31.3, 30.9, 29.7, 26.8, 25.7, 24.5, 18.1, 3.9; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{27}H_{38}OSi$ 406.22692, obsd 406.2705.

***tert*-Butyldimethylsilyl enol ether of 9-(2-oxo-5-phenylcyclopentyl)nonanoic acid methyl ester (21iii):** IR ($CDCl_3$) 2928, 2855, 1741, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.31−7.24 (m, 2H), 7.20−7.13 (m, 3H), 3.73−3.67 (m, 1H), 3.66 (s, 3H), 2.51−2.10 (m, 6H), 1.80−1.40 (m, 4H), 1.30−1.10 (m, 10H), 0.97 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 174.3, 148.4, 146.9, 128.2, 127.6, 125.8, 120.1, 51.4, 49.4, 34.1, 33.0, 30.9, 29.5, 29.2, 29.1, 27.1, 25.7, 24.9, 24.7, 18.1, −3.9, −4.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{27}H_{44}O_3Si$ 444.3060, obsd 444.3063.

***tert*-Butyldimethylsilyl enol ether of 2-methyl-3-oct-1-enylcyclopentanone (23i):** IR ($CDCl_3$) 1688 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 5.36 (*ABX*$_2$, J = 15.0, 7.0 Hz, 1H), 5.21 (A*B*X, J = 15.0, 8.5 Hz, 1H), 2.90 (m, 1H), 2.35−2.20 (m, 2H), 2.15−1.90 (m, 3H), 1.60=1.50 (m, 1H), 1.45 (s, 3H), 1.40−1.25 (m, 8H), 0.95 (s, 9H), 0.80 (m, 3H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, δ) 147.3, 134.5, 129.8, 115.4, 48.9, 32.7, 32.4, 31.8, 29.7, 28.8, 28.0, 25.7, 22.7, 18.1,14.1, 10.4, −4.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{20}H_{38}OSi$ 322.2692, obsd 322.2686.

***tert*-Butyldimethylsilyl enol ether of 3-oct-1-enyl-2-(4-phenylbutyl)cyclopentanone (23ii):** IR ($CDCl_3$) 1678 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.15−7.35 (m, 5H), 5.33 (ABX$_2$, J = 15.0, 7.0 Hz, 1H), 5.19 (ABMX$_2$, J = 15.0, 9.0, 1.0 Hz, 1H), 3.0 (m, 1H), 2.60 (td, J = 7.0, 3.0 Hz, 2H), 2.3−1.9 (m, 6H), 1.85−1.75 (m, 1H), 1.55−1.25 (m, 13H), 0.93 (s, 9H), 0.90 (m, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 147.4, 134.6, 129.7, 128.4, 128.3, 125.5, 46.8, 35.8, 32.7, 32.4, 31.8, 31.5, 29.6, 28.8, 28.1, 27.0, 25.7, 24.5, 22.7, 18.1, 14.1, −4.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{29}H_{48}OSi$ 440.3474, obsd 440.3484.

***tert*-Butyldimethylsilyl enol ether of 9-(2-oct-1-enyl-5-oxocyclopentyl)nonanoic acid methyl ester (23iii):** R_f (dichloromethane) 0.6; ^1H NMR ($CDCl_3$, δ) 5.36 (ABX$_2$, J = 15.0, 7.0 Hz, 1H), 5.20 (ABMX$_2$, J = 15.0, 9.0, 1.0 Hz, 1H), 3.67 (s, 3H), 3.05 (m, 1H), 2.35−2.20 (m, 3H), 2.15−2.06 (m, 1H), 2.05−1.95 (m, 2H), 1.80−1.70 (m, 1H), 1.65−1.60 (m, 2H), 1.55−1.45 (m, 1H), 1.40−1.20 (m, 20H), 0.94 (s, 9H), 0.89 (m, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 174.7, 147.6, 135.1, 130.0, 120.1, 60.5, 51.8, 47.2, 34.5, 33.1, 32.8, 32.2, 30.1, 30.0, 29.8, 29.7, 29.6, 29.2, 28.6, 27.8, 26.1, 25.0, 23.1, 18.7, 14.5, −3.6.

General Procedure for Kinetic Protonation Study. In a typical run, to a 7.7 mL THF solution of silyl enol ether of 3-oct-1-enyl-2-(4-phenylbutyl)cyclopentanone **(23ii)** (140.0 mg, 0.31 mmol) was added 0.62 mL of glacial acetic acid solution (2.0 M in THF, 1.23 mmol) followed by 0.62 mL of 1.0 M Bu_4-NF (1.0 M in THF, 0.62 mmol). The reaction mixture was stirred at room temperature, and small aliquots (1.0 mL) of solution were treated with ether and water at the end of 1 and 4 h. The aqueous layer was ether extracted, and the combined extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a mixture of the cis and trans ketones. The aliquots and residue were analyzed by ^1H NMR. There was no epimerization observed.

In the case of ketone **24ii-cis**, 14 mg of **24** (trans/cis = 65/35) dissolved in 1.1 mL of THF was stirred with 0.17 mmol of AcOH and 0.086 mmol of Bu_4NF for 3.5 h. No epimerization was observed.

The stereochemistry of all compounds has been established by NMR experiments and by cis to trans isomerization under basic or acidic conditions. The cis/trans ratio of stereoisomers was determined in all cases by integration of the characteristic signals in each isomer pairs. The pure diastereomers were obtained from column chromatography, thin-layer chromatography, or HPLC.

***trans*-2-Methyl-3-phenylcyclohexanone (6-trans).** A mixture of 2-methyl-3-phenylcyclohexanone (trans/cis = 9/91) was stirred with NaOMe in MeOH for 2 days giving the trans isomer: IR ($CDCl_3$) 1708 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.37−7.29 (m, 2H), 7.27−7.17 (m, 3H), 2.70−2.40 (m, 4H), 2.20−2.10 (m, 1H), 2.02−1.90 (m, 2H), 1.85−1.69 (m, 1H), 0.81 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, δ) 212.4, 143.9, 128.6, 127.2, 126.6, 53.2, 50.5, 41.8, 34.5, 26.5, 12.3; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{13}H_{16}O$ 188.1201, obsd 188.1198. This compound has been reported.[10]

***cis*-2-Methyl-3-phenylcyclohexanone (6-cis):** IR ($CDCl_3$) 1706 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.32−7.26 (m, 2H), 7.24−7.17 (m, 1H), 7.14−7.09 (m, 2H), 3.34 (m, 1H), 2.74 (m, 1H), 2.62−2.50 (m, 1H), 2.41−2.30 (m, 1H), 2.10−1.95 (m, 3H), 1.82−1.70 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, δ) 214.6, 141.8, 128.3, 127.9, 126.3, 49.6, 47.7, 38.9, 27.4, 23.7, 12.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{13}H_{16}O$ 188.1201, obsd 188.1196.

***cis*-Phenyl(2-phenylcyclopentyl)methanone (20-cis):** R_f (dichloromethane/hexane = 2/3) 0.35; IR ($CDCl_3$) 1677 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.62 (m, 2H), 7.38 (m, 1H), 7.26 (m, 2H), 7.07−6.93 (m, 5H), 4.15 (dt, J = 8.8, 7.5 Hz, 1H), 3.60 (q, J = 8.5 Hz, 1H), 2.40−1.70 (m, 6H); ^{13}C NMR ($CDCl_3$, δ) 202.3, 141.8, 138.0, 132.0, 128.1, 127.9, 127.7, 125.9, 51.4, 49.9, 32.9, 28.7, 24.6; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{18}H_{18}O$ 250.1358, obsd 250.1346.

***trans*-Phenyl(2-phenylcyclopentyl)methanone (20-trans):** R_f (dichloromethane/hexane = 2/3) 0.41; IR ($CDCl_3$) 1678 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.82 (m, 2H), 7.49 (m, 1H), 7.37 (m, 2H), 7.25 (m, 5H), 3.82 (m, 1H), 3.65 (m, 1H), 2.35−1.80 (m, 6H); ^{13}C NMR ($CDCl_3$, δ) 202.2, 144.7, 132.8, 128.4, 127.3, 126.1, 54.7, 48.3, 35.3, 32.0, 25.8; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{18}H_{18}O$ 250.1358, obsd 250.1368.

Conversion of *cis*-Phenyl(2-phenylcyclopentyl)methanone (20-cis) to *trans*-Phenyl(2-phenylcyclopentyl)-methanone (20-trans). Phenyl(2-phenylcyclopentyl)methanone (**20-cis**) (110 mg) was added to a sodium ethoxide solution prepared from 10.0 mL of ethanol and 20 mg of Na. The clear solution was kept at room temperature for 24 h. The reaction mixture then was treated with 20 mL of water and filtered. The precipitate was washed with water and dried to give 105 mg (95%) of phenyl(2-phenylcyclopentyl)methanone (**20-trans**).

***trans*-2-Methyl-3-phenyl-cyclopentanone (22i-trans):** IR ($CDCl_3$) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.45−7.20 (m, 5H), 2.82 (td, J = 11.2, 5.0 Hz, 1H), 2.63−2.49 (m, 1H), 2.38−2.17 (m, 3H), 2.04−1.88 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, δ) 219.5, 142.2, 129.4, 127.0, 51.2, 50.8, 37.6, 29.4, 12.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{12}H_{14}O$ 174.1045, obsd 174.1039. This compound has been reported.[11]

***cis*-2-Methyl-3-phenylcyclopentanone (22i-cis):** ^1H NMR ($CDCl_3$, δ) 7.36−7.20 (m, 3H), 7.16−7.09 (d, J = 8.0 Hz, 2H), 3.59 (q, J = 7.0 Hz, 1H), 2.67−2.15 (m, 5H), 0.79 (d, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, δ) 221.0, 140.8, 128.5, 127.9, 126.5, 47.8, 45.8, 36.8, 25.6, 10.8. This compound has been reported.[11,12]

Conversion of *cis*-2-Methyl-3-phenylcyclopentanone (22i-cis) to *trans*-2-Methyl-3-phenylcyclopentanone (22i-trans). A mixture of **22i** (45.0 mg, cis/trans = 1:1) was treated with KOH (41.0 mg) in 7.0 mL of MeOH and stirred overnight. After conventional workup, only **6-trans** was left on the basis of ^1H NMR analysis.

***trans*-3-Phenyl-2-(4-phenylbutyl)cyclopentanone (22ii-trans):** IR ($CDCl_3$) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.40−7.00 (m, 10H), 2.96 (td, J = 12.0, 6.0 Hz, 1H), 2.60−2.15 (m, 6H), 2.00−1.80 (m, 1H), 1.70−1.10 (m, 6H); ^{13}C NMR ($CDCl_3$, δ) 219.5, 142.9, 142.5, 128.7, 128.3, 128.2, 127.1, 126.8, 125.5, 55.7, 48.6, 38.3, 35.5, 31.5, 30.2, 27.7, 26.3; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{21}H_{24}O$ 292.1827, obsd 292.1826.

***cis*-3-Phenyl-2-(4-phenylbutyl)cyclopentanone (22ii-cis):** IR ($CDCl_3$) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.37−7.03 (m, 10H), 3.56 (q, 7.0 Hz, 1H), 2.50−2.10 (m, 7H), 1.70−1.00 (m, 6H); ^{13}C NMR ($CDCl_3$, δ) 220.1, 142.5, 141.1, 128.5, 128.3, 128.2, 127.8, 126.5, 125.5, 53.7, 45.2, 36.1, 35.5, 31.2, 26.9, 26.7, 25.0; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{21}H_{24}O$ 292.1827, obsd 292.1817. **7-cis** was converted to **7-trans** under basic conditions.

***trans*-9-(2-Oxo-5-phenylcyclopentyl)nonanoic Acid Methyl Ester (22iii-trans).** A mixture of **22iii** (cis/trans = 60/40) was stirred with NaOMe in MeOH overnight at room temperature. Only **22iii-trans** remained on the basis of ^1H NMR analysis of the crude product. Conventional workup gave the pure **22iii-trans**: IR ($CDCl_3$) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.38−7.31 (m, 2H), 7.29−7.23 (m, 3H), 3.66 (s, 3H), 2.99 (td, J = 12.0, 6.0 Hz, 1H), 2.56−2.45 (m, 1H), 2.40−2.25 (m, 4H), 1.98−1.85 (m, 1H), 1.70−1.50 (m, 3H), 1.35−1.05 (m, 12H); ^{13}C NMR ($CDCl_3$, δ) 219.7, 174.3, 143.0, 128.7, 127.1, 126.8, 55.8, 51.4, 48.6, 38.3, 34.1, 30.2, 29.6, 29.1, 27.9, 26.5, 24.9; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{21}H_{30}O_3$ 330.2195, obsd 330.2189.

***trans*-2-Methyl-3-oct-1-enylcyclopentanone (24i-trans):** IR ($CDCl_3$) 1742 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 5.51 (ABX_2, J = 15.0, 7.0 Hz, 1H), 5.38 ($ABMX_2$, J = 15.0, 7.5, 1.0 Hz, 1H), 2.40−1.75 (m, 7H), 1.70−1.50 (m, 1H), 1.40−1.25 (m, 8H), 1.03 (d, J = 6.9 Hz, 3H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, δ) 220.4, 131.9, 131.8, 50.2, 48.4, 37.2, 32.5, 31.7, 29.4, 28.7, 28.0, 22.6, 14.1, 11.9; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{14}H_{24}O$ 208.1827, obsd 208.1822.

***cis*-2-Methyl-3-oct-1-enylcyclopentanone (24i-cis):** IR ($CDCl_3$) 1742 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 5.48 (ABX_2M, J = 15.0, 7.0, 0.5 Hz, 1H), 5.28 ($ABMX_2$, J = 15.0, 9.0, 1.2 Hz, 1H), 2.90 (m, 1H), 2.40−1.75 (m, 7H), 1.40−1.25 (m, 8H), 0.96 (d, J = 6.9 Hz, 3H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, δ) 221.1, 132.5, 128.4, 48.0, 43.7, 35.8, 32.6, 31.7, 29.4, 28.7, 27.9, 26.7, 22.6, 14.1, 10.4; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{14}H_{24}O$ 208.1827, obsd 208.1829.

***trans*-3-Oct-1-enyl-2-(4-phenyl-butyl)cyclopentanone (24ii-trans):** IR ($CDCl_3$) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.30−7.12 (m, 5H), 5.49 (ABX_2, J = 15.5, 6.5 Hz, 1H), 5.34 ($ABMX_2$, J = 15.5, 8.0, 1.0 Hz, 1H), 2.65−2.55 (t, J = 7.5 Hz, 2H), 2.40−1.25 (m, 22H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$, δ) 220.2, 142.7, 132.4, 131.6, 128.3, 128.2, 125.6, 54.7, 46.1, 37.7, 35.7, 32.5, 31.7, 29.4, 28.8, 28.2, 27.6, 26.5, 22.6, 14.1; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{23}H_{34}O$ 326.2610, obsd 326.2594.

***cis*-3-Oct-1-enyl-2-(4-phenylbutyl)cyclopentanone (24ii-cis):** IR ($CDCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.30−7.10 (m, 5H), 5.46 (ABX_2, J = 15.0, 6.5 Hz, 1H), 5.21 ($ABMX_2$, J = 15.0, 9.5, 1.2 Hz, 1H), 3.00−2.85 (m, 1H), 2.65−2.55 (t, J = 7.5 Hz, 2H), 2.45−1.25 (m, 21H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$, δ) 218.8, 142.7, 132.6, 128.4, 128.2, 128.0, 125.6, 53.8, 42.6, 35.7, 35.5, 32.6, 31.7, 31.4, 29.4, 28.8, 27.0, 25.2, 22.6, 14.1; HRMS-EI m/z $[M]^{\bullet+}$ calcd for $C_{23}H_{34}O$ 326.2610, obsd 326.2615.

***trans*-9-(2-Oct-1-enyl-5-oxocyclopentyl)nonanoic Acid Methyl Ester (24iii-trans).** A mixture of **24iii** (trans/cis = 70/30) was refluxed with *p*-TsOH in MeOH overnight; only the trans isomer was left: ^1H NMR ($CDCl_3$, δ) 5.50 (ABX_2M, J = 15.0, 7.0, 0.5 Hz, 1H), 5.35 ($ABMX_2$, J = 15.0, 9.0, 1.2 Hz, 1H), 3.67 (s, 3H), 2.45−2.25 (m, 4H), 2.15−1.95 (m, 3H), 1.80 (m, 1H), 1.65−1.20 (m, 21H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, δ) 221.1, 175.0, 133.1, 132.2, 55.5, 52.1, 46.7, 38.5, 34.8, 33.2, 32.4, 30.5, 30.1, 29.9, 29.8, 29.5, 28.9, 28.4, 27.5, 25.7, 23.3, 14.8. The stereochemistry was also assigned with GCOSY, DQ-COSY, and NOE experiments.

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Supporting Information Available: General experimental procedures, spectroscopic data, and details of the molecular mechanics and ab initio computations. This material is available free of charge via the Internet at http://pubs.acs.org.

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