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Inter- and Intramolecular Stereoselective Protonation of Enols[1,2]

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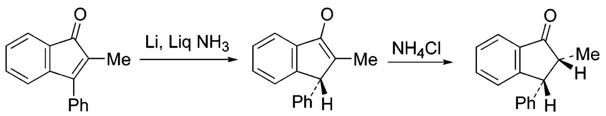
Kinetic control of the stereoselectivity of protonation of enolates and other delocalized species commonly affords the less stable diastereomer as a consequence of the considerable exothermicity and resulting sp^2 transition-state hybridization of the α-carbon. Protonation then is from the less hindered face of the enolate. The present study is aimed at reversing this phenomenon by intramolecular delivery of the proton. The approach employed required the synthesis of two enolate precursors, one with a 2-pyridyl group strategically close to the α-carbon and the other with a phenyl group in the same location. The synthesis required 15 steps and involved new methodology. Intramolecular proton transfer, reversing the usual stereoselectivity, was successful. The selectivity proved to depend on several factors including the exo versus endo configuration of the diastereomer reacting, the proton donor employed, and the concentration of the proton donor. A kinetic analysis permitted the determination of the relative reaction orders of the protonation on the two faces of the enolate.

1. Introduction

Background. A very large number of organic reactions involve the protonation of enol and enolate intermediates. Conjugate additions to enones, decarboxylation of *β*-ketoacids, malonic acids, dehalogenation of α-haloketones, deprotonation−protonation of ketones and esters, Birch−Barton−Stork lithium−ammonia reduction of enones, and nucleophilic addition to ketenes are some examples. Protonation of nitronates proceeds similarly. Many of these examples have been summarized, and a long series of our publications have provided evidence for the generality of the phenomenon.[3]

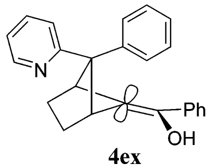
This kinetic control results from the proton transfer being highly exothermic with an early transition state. Thus, the hybridization of the α-carbon remains close to sp^2 hybridized, and the approach of the proton donor occurs preferentially to the less hindered face of the delocalized species (enol, enolate, nitronate, etc.). Equation 1 provides one example.[3d]



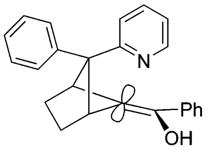
1 2 3 (1)

In view of this intriguing phenomenon, it was of considerable interest to ascertain whether the stereoselectivity might be reversed. One approach involves intramolecular proton transfer by a moiety located on the hindered face of the enolate. We have provided one example of this in a previous study,[4] and it remained to be determined if intramolecular proton transfer really is a general phenomenon.

This was the intent of the present investigation. The enols of interest are the exo and endo pyridyl diastereomers **4ex** and **5en** below. We note here that "endo" at C-6 refers to the aryl being cisoid to the functional group, and "syn" at the α-carbon (i.e., C-5) refers to the proximity to the aryl group.



4ex



5en

2. Results

Synthetic Approach. The silyl enol ethers of these enols promised to be ideal enol precursors. Of particular interest were the *tert*-butyldimethylsilyl enol ethers of the benzoyl ketones **26en** and **26ex**. Note the discussion of this point below. Scheme 1 outlines the synthesis of these precursors. A number of the steps of the synthetic sequence are especially noteworthy. The basic five-membered ring formation leading to cyclopentene **8** began with *cis*-1,4-dichloro-2-butene. This led, as shown, to **8**, accompanied by cyclopropane **9** in a 1:3 ratio. However, thermal conversion from **9** to **8** brought the yield to 50%.

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[1] This is paper 267 of our general series.

[2] For paper 266 and a preliminary communication of the present study, see Zimmerman, H. E.; Wang, P. *Org. Lett.* **2002**, *4*, 2593−2595.

[3] (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268 and references therein. (b) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557. (c) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *48*, 1637−1646. (d) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168−1173.

[4] Zimmerman, H. E.; Ignatchenko A. *J. Org. Chem.* **1999**, *64*, 6635−6645.

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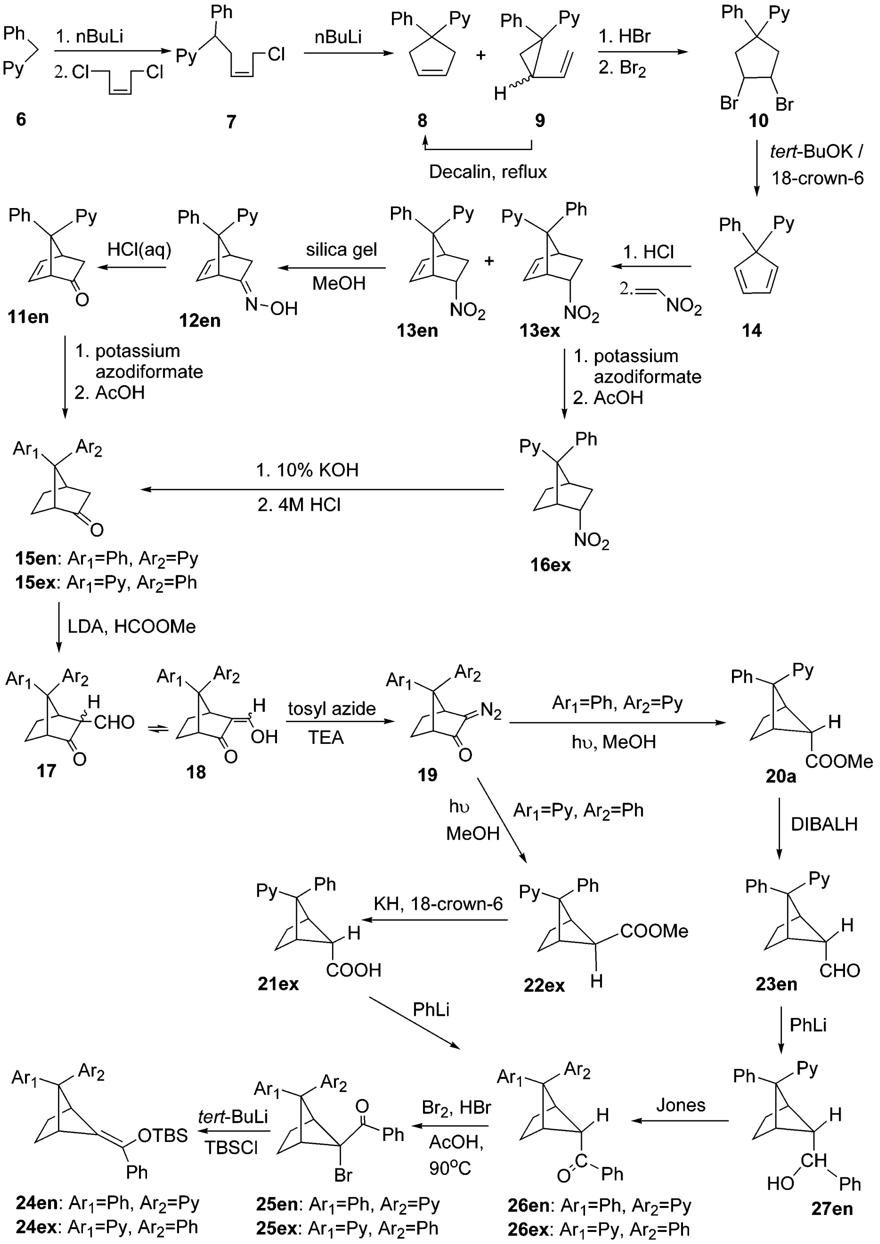
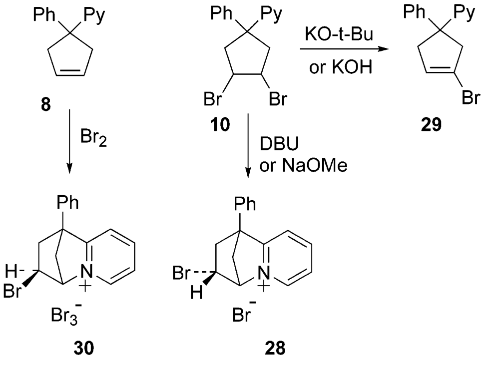
SCHEME 1. Synthesis of required compounds



A particularly difficult step was the conversion of dibromide **10** to the cyclopentadiene **14**. With a variety of bases, two undesired products were obtained. Both DBU in DMF and sodium methoxide in THF afforded an intramolecular S_N2 product **28** as shown in Scheme 2. Potassium *tert*-butoxide in THF and potassium hydroxide in ethanol afforded the vinyl bromide **29**; again, see Scheme 2. However, the desired elimination product **14** resulted nicely with potassium *tert*-butoxide in 18-crown-6 ether; this led to a selective elimination in 86% yield to afford phenylpyridyl cyclopentadiene **14**. The transformation proved to be quite temperature-dependent, giving the vinyl bromide as a minor product at room temperature but the desired diene **14** exclusively at lower temperatures.

SCHEME 2. Side reactions of interest



The Diels–Alder reaction of nitroethylene with cyclopentadiene **14** nicely afforded both the endo and exo stereoisomers of norbornene **13** in a 3:2 ratio. And the exo product **13ex** was reduced to the corresponding norbornane **16ex**. Only the exo isomer proved to be of value in the subsequent sequence employing a Nef reaction and leading to the norbornyl ketone **15ex**, as depicted in Scheme 1. Although the reduction–Nef approach—gave low yields in the endo series, the reversed sequence proved practical, this involving the initial conversion to the norbornenone **11en** followed by reduction to the keto norborane **15en**. One limitation was that under standard Nef conditions nitronorbornene **13en** had been found in previous work[5] to give a rearrangement and not to afford the desired ketone **11en**. But conditions using a silica gel conversion to oxime **12en** circumvented the problem.

A particularly interesting step was the Wolff rearrangement of the diazoketones **19ex** and **19en**. Strikingly, the reaction in methanol proceeded with stereochemistry depending on which diastereomer was used. Thus, **19en** afforded product **20a** primarily with an anti carbomethoxyl group whereas **19ex** led mainly to product **22ex** with a syn carbomethoxyl group. This result was independent of whether pure methanol was used or, instead, 5 or 10% methanol in benzene was employed. The differing stereoselectivity is dramatic; this finding is considered below in the context of the reaction mechanisms.

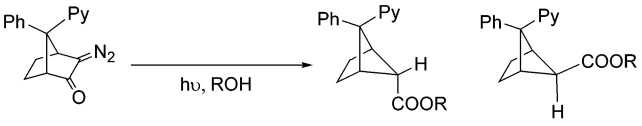
We required the endo and exo pyridyl benzoyl ketone diastereomers, **26ex** and **26en**. The exo-pyridyl isomer **26ex** was obtained relatively easily from acid **21ex**, as shown in Scheme 1. However, the phenyllithium reaction led to poor yields when applied to the endo acid **21en**. But, the route via aldehyde **23en** proved useful.

A real challenge was presented by the need for the silyl enol ethers of the benzoyl ketones, **26en** and **26ex**. One unsuccessful approach was deprotonation and silation. LDA, LTMP, and potassium hydride with crown ether all proved incapable of removing the α-proton of the exo-pyridyl ketone **26ex**. In contrast, both ketones, **26en** and **26ex**, reacted nicely with bromine and 2 equiv of HBr in acetic acid to afford the α-bromo ketones **25en** and **25ex**. The configurations at the α-carbon were assigned on a mechanistic basis. The success of this route results from the bromination having a rate-limiting step of carbonyl protonation and the loss of the α-proton from the resulting cationic species, a process less subject to steric inhibition. No large base must approach the proton to be removed. Each of the two α-bromoketones was readily converted to the *tert*-butylsilyl enol ethers **24en** and **24ex** on reaction with *tert*-butyllithium and *tert*-butyldimethylsilyl chloride.

Some Further Synthetic Aspects Including a Discussion of Side Reactions. Above, we have indicated that the conversion of dibromide **10** to the desired cyclopentadiene led to an intramolecular S_N2 reaction to afford a pyridinium product **28** as well as to the undesired vinyl bromide **29** depending on reaction conditions. This chemistry is outlined in Scheme 2. Scheme 2 also includes the reaction of cyclopentene **8**, which led to another pyridinium product **30**, whose structure was established from X-ray analysis.

Another item is the Wolff rearrangement that has been mentioned as a source of the endo and exo diastereomeric methyl esters **20a** (anti) and **22ex** (syn). The reaction, however, deserved further exploration in view of the intramolecular protonation observed in the case of the endo-pyridyl diastereomer. For reasons to be considered in the Interpretative Discussion section, we also studied the reaction of the endo pyridyl diastereomer **19en** in *tert*-butyl alcohol and in aqueous dioxane. Interestingly, in contrast to the methanol runs that led to a stereoselectivity of 89:11 in favor of the more stable epimeric (anti) ester **20a**, runs using *tert*-butyl alcohol led to a ratio of 4:6 in favor of the less stable syn isomer **31c**. In water, the stereoselectivity here was 92:8 in favor of the more stable anti epimer **20b**. The results of the Wolff rearrangement are outlined in Scheme 3.

SCHEME 3. Wolff rearrangement results



19en **20** **31**

a. R = Me, **20a** : **31a** = 89 : 11
b. R = H, **20b** : **31b** = 92 : 8
c. R = tert-Bu, **20c** : **31c** = 40 : 60

Choice of Modes of Enol Generation. What was required for this study were methods of generating the enols whose ketonization stereochemistry was to be studied. It has been noted above that the silyl enol ethers were considered and synthesized. Thus, one of the most promising methods involves the reaction of silyl enol ethers with fluoride anion. This is a reaction studied primarily by Noyori,[6] who nicely demonstrated that silyl enol ethers on reaction with the fluoride anion afford isolable enolates. Additionally, enolates generated in this fashion have proven useful in reacting with electrophiles. Thus, **24en** and **24ex** seemed ideal precursors.

Several important results were derived from our fluoride—acetic acid enolate generation reactions. The first point is that without fluoride it was observed that the silyl enol ethers, **24en** and **24ex**, were unreactive. The second observation was that as the acetic acid concentration was increased the reactions slowed. This is attributed to acetic acid protonating the fluoride anion and diminishing the free fluoride concentration. The important point is that free fluoride anion is required for the desilylation. Finally, tetrabutylammonium chloride proved an unreactive substitute for the fluoride.

The second approach employed has already been indicated in the synthesis described above. Thus, the diazoketones **19en** and **19ex** seemed likely to be useful precursors. Here, it is well known that the reaction affords ketenes that then, with alcohols or water, afford enols that lead onward to ester or acid final products.

Differences with Different Donors and Overall Syn—Anti Stereoselectivities. A remarkable result we encountered was the finding for the endo enol **5en** that the overall protonation stereochemistry changed as different proton donors were utilized. See Scheme 4. This was more dramatic than the stereochemistry with exo enol **4ex**, where there were only quantitative differences with different donors but where invariably the preferred stereochemistry was derived from the less hindered protonation.

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(5) Zimmerman, H. E.; Wang, P. *Helv. Chim. Acta* **2001**, *84*, 1342—1346.

(6) (a) Nayori has characterized a sulfonium enolate of 1-phenyl-2-propanone obtained by reaction of a silyl enol ether with fluoride. Additionally, in a less pure form, he has similarly generated a tetrabutylammonium enolate. (b) Nayori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598—1608. (c) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181—187.

SCHEME 4. Major reaction stereochemistry

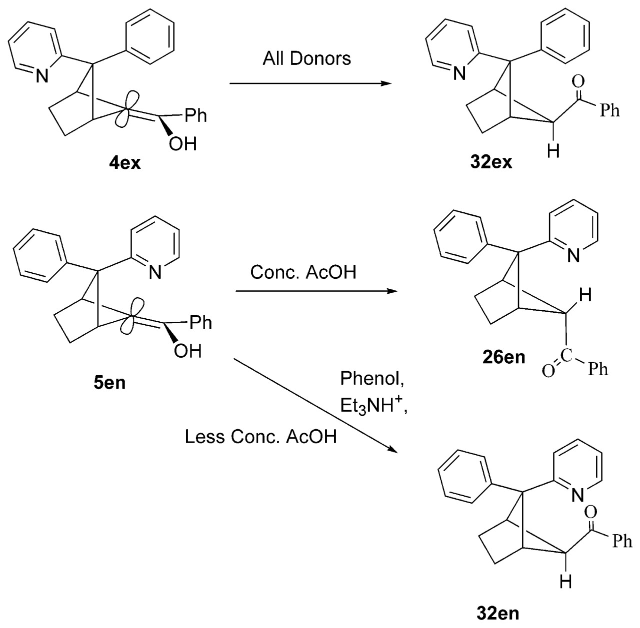

TABLE 1. Stereoselectivity[a] with Four Different Proton Donors with Selected Donor Concentrations

diastereomer	proton donor			
	HOAc	phenol	Et_3NHCl	HCl
endo phenyl	7.3:1	19:1	9:1	1:0
endo pyridyl	1:24[b]	5.7:1	3:1	1:5.3[c]

[a] Ratio of products **32ex** to **26ex** for the enol **4ex** and **32en** to **26en** for the enol **5en**. [b] Ratio given for 1.4 M HOAc. [c] Ratio given for 0.022 M HCl.

Thus, endo enol **5en**, at the higher acetic acid concentrations, afforded a preference for the more hindered approach (i.e., anti product configuration). Conversely, independent of the donor concentration, phenol and also triethylammonium chloride proceeded via the less hindered protonation (i.e., syn product).

As with the acetic acid runs, protonation by hydrochloric acid afforded both stereochemistries, depending on acid concentration. However, the effect of acid concentration was reversed. At low HCl concentration, the lower-energy product (i.e., anti) resulted in excess, whereas at higher HCl concentrations, the higher-energy product (i.e., syn) predominated. These major reaction preferences are outlined in Table 1.

Quantitative Observations of the Acetic Acid Protonation. In our previous studies[4] of intra- versus intermolecular protonation, we have noted that the ratio P_{int}/P_{ext} of the two reaction modes may be obtained as in eq 2.

$$\log(P_{int}/P_{ext}) = (n - m) \log[HA] + \log(k_{int}/k_{ext}) \quad (2)$$

P_{int} is the extent of product formation via a reaction that is nth order in proton donor. This is assumed to correspond to intramolecular protonation (i.e., product **26en**). P_{ext} is the extent of product formation via an m-order reaction and is assumed to correspond to intermolecular protonation (i.e., product **32en**). Linearity provides confirmation of the assumptions. Thus, n is then the reaction order of the proton donor in the intramolecular protonation process, and m is the order in the intermolecular counterpart. The intercept provides the log of the ratio of the rate constants for the two modes.

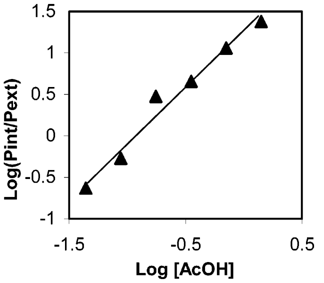

FIGURE 1. Stereoselectivity versus acetic acid concentration.

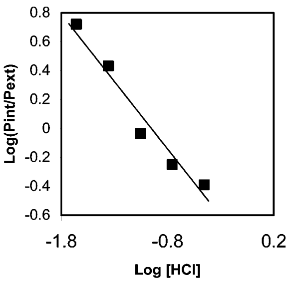

FIGURE 2. Stereoselectivity versus HCl concentration for **24en**.

Figure 1 depicts the plot of the data for acetic acid runs in acetonitrile. The detailed data are given in Supporting Information. The slope of the plot gives us the value of $(n - m)$, or the difference in the proton-donor reaction orders. Remarkably, in the case of acetic acid, the slope was very close to unity. This indicates that one extra molecule of proton donor is used in the intramolecular ketonization process compared with the intermolecular reaction. This is to be interpreted in the Discussion section below. We note that this dependence on acetic acid concentration is a kinetic phenomenon and does not result from equilibration. Control runs showed that the thermodynamically less stable epimer **32en** was not epimerized to the more stable **26en** under the conditions used. Additionally, the linearity (see Figure 1) and fit to eq 2 provide support for kinetic control.

Protonation by Further Donors. In contrast to the acetic acid protonation stereochemistry, fluoride ketonization utilizing phenol led primarily to diastereomer **32en**, the result of external, less hindered protonation. Whereas discussion of the differing stereochemistry is delayed (vide infra), we do note that phenol is insufficiently acidic to protonate the pyridyl nitrogen. Analogously, use of triethylammonium chloride led to the same diastereomer **32en**. Reasoning similar to that for the phenol protonation can account for the result. However, in the Discussion section, we interpret the stereochemistry with varying proton donors as a function of their sizes as well as their pK_a's. The detailed data for phenol and triethylammonium, along with that for hydrochloric acid (vide infra), are provided in Supporting Information.

A superficially remarkable result was obtained using hydrochloric acid as the proton donor, as seen in the plot in Figure 2 for the endo-pyridyl enol ether **24en**. Here, the $\log(P_{int}/P_{ext})$ plot is seen to have a negative slope, the

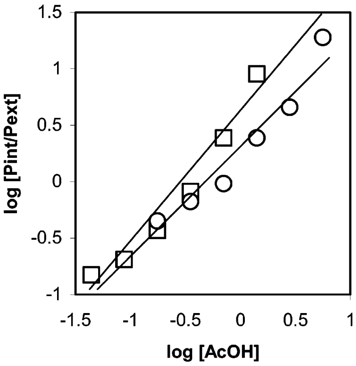

FIGURE 3. Solvent effects on the diastereoselectivity of acetic acid protonation. THF (□)and DMSO (○).

converse of the acetic acid case (cf. Figure 1). Also, in the HCl runs, the stereoselectivities and the qualitative rates were independent of added fluoride anion. Thus, the *tert*-butyldimethylsilyl enol ether is capable of directly protonating at the α-carbon. Again, as in the acetic acid runs above, the process is kinetically controlled. This is seen (a) from control runs showing the less stable diastereomer **32en** to be stable to epimerization under the reaction conditions, (b) from the linearity in Figure 2 and the fit to the kinetics predicated on nonequilibrating conditions, and (c) from the preferential formation of the less stable ketone **32en** with the higher acid concentrations and preferential formation of the more stable isomer **26en** when lower acid concentrations were employed. This last result is the reverse of that expected if one were dealing with acid-catalyzed equilibration.

In the case of the exo-pyridyl enol ether **24ex**, ketonization proved to be independent of acid concentration and led exclusively to the less stable ketone **32ex**, the isomer expected as a result of less hindered protonation. Thus, there is a dramatic difference in the behavior of the endo and exo pyridyl enol ethers.

Solvent Effects. Interestingly, the eq 2 plots for the three solvents used—acetonitrile, THF, and DMSO—had remarkably similar slopes, close to unity. The experimental scatter is minor and less than the variation in the measured slopes. Figure 3 summarizes the experimental data for the other two solvents, and the detailed data are in Supporting Information.

3. Interpretative Discussion

General. The first observation to be made is that the phenomenon of intramolecular proton transfer is a reality, as it has now been demonstrated in two systems—the present one and the bicyclo[3.1.0]hexane system we studied earlier.[4] At the outset, before beginning the rather arduous synthesis, there was no promise of anything but steric effects being controlling.[7] Indeed, with phenol and triethylammonium chloride only the well-established[3] and ubiquitous less hindered protonation stereochemistry resulted. Fortunately, acetic acid in acetonitrile was used in our initial experiments and this did lead to evidence for protonation from the more hindered face of the enol.

Interpretation—More Hindered Protonation versus the Acetic Acid Concentration Dependence. With 1.4 M acetic acid, the ratio of protonation from the more hindered enol face to protonation from the less hindered side of the enol **5en** was 24:1. Runs in THF and DMSO showed lower stereoselectivity (9:1 in THF and 19:1 in DMSO). The more hindered protonation in the case of the endo enol **5en** results from a preference for intramolecular delivery of the proton from the 2-pyridyl nitrogen to the α-carbon of the enol. The endo phenyl enol **4ex** proceeds with the usual[3] less hindered approach of the proton donor and serves as a comparison model.

As described in the Results section, it was quickly ascertained that the stereoselectivity for **5en** was a function of the proton donor concentration and followed eq 2. This contrasts with the protonation of the endo phenyl enol **4ex**, whose stereochemistry proved to be independent of proton donor concentration. Equation 2 had been derived with the assumption that the reaction orders for intramolecular and intermolecular protonation may differ and are n and m, respectively, and that the slope of the plot is $n - m$. Indeed, for enol **4ex**, the stereoselectivity is independent of acid concentration, $n - m$ is zero, and a slope of zero results.

In the case of the endo 2-pyridyl enol **5en** with acetic acid, there is a positive slope of unity, which means that the formation of **26en** involves one more acid protonating molecule than **32en**. This provides further evidence for the endo 2-pyridyl diastereomer reacting by a mechanism that is different from that for the endo phenyl isomer.

Hence, there are several noteworthy points. First, the endo 2-pyridyl protonation gives different stereochemistry than the endo phenyl isomer. Second, the reaction kinetics differs for the two processes. Additionally, there is the mechanistic matter that the 2-pyridyl nitrogen is ideally positioned to deliver a proton intramolecularly to the more hindered side of the enol π system. Here we have the essentials of our picture of the endo-pyridyl mechanism.

An important point is that one cannot assume that protonation by acetic acid involves one proton in either the endo phenyl case or the less hindered protonation in the endo-pyridyl reaction. Thus, it is known[8] that acetic acid not only forms a dimer, but there is also evidence for a trimer at low temperature. Additionally, there is evidence that the trimer is capable of protonating pyridine whereas the monomer tends to only hydrogen bond; the dimer protonates partially. For simplicity, it is convenient to assume that external protonation is by one acetic acid molecule (i.e., $m = 1$) and that the intramolecular transfer thus involves two donor acetic acid molecule since $n - m$ is unity. Nevertheless, all we really know is that one more acetic acid molecule is used for intramolecular delivery compared with the number used for external attack. Hence, it is possible that the acetic acid trimer, being acidic enough to protonate the pyridine nitrogen, is the preferred species for intramolecular

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[7] (a) Success was had despite not following the sage advice of Professor R. B. Woodward, who noted that it is wise to plan research with maximum flexibility as the end rather than a single positive or negative result at the end with no alternatives. (b) Private communication to H.E.Z.

[8] (a) Smirnov, S. N.; Golubev, N. S.; Denisov, G. S.; Bendict, H.; Schah-Mohammdei, P.; Limbach, H.-H. *J. Am. Chem. Soc.* **1996**, *118*, 4094−4101. (b) Golubev, N. S.; Smirnov, S. N.; Gindin, V. A.; Denisov, G. S.; Benedict, H.; Limbach, H.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12055−12056.

proton transfer whereas protonation of the enolic α-carbon does not require this enhanced acidity and the dimer suffices.

Discussion—Phenol and Ammonium Results. The observation of the common less hindered protonation by phenol and the ammonium ion for both the endo phenyl and the endo pyridyl diastereomers is not only striking in view of its contrast with the acetic acid protonation but also important in providing confirmation of the acetic acid mechanism. Thus, phenol and triethylammonium proton donors differ from acetic acid in being weaker acids by 5 orders of magnitude if one uses the acidity in water. Whereas the estimates for the solvents used are approximate, it is clear that these acids are incapable of completely protonating a pyridyl nitrogen although hydrogen bonding is possible. There is an additional factor, namely, the greater steric bulk of these two proton donors, that adds to diminished hydrogen bonding to the somewhat inaccessible pyridine nitrogen in a conformation for intramolecular transfer by phenol and triethylammonium. Hence, we can understand a preference for the unhindered protonation, perhaps modified slightly by some intramolecular transfer involving a hydrogen-bonded species.

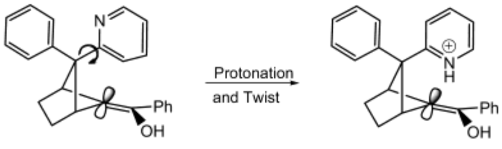
Discussion—Hydrochloric Acid Reversal. Several of the results with hydrochloric acid protonation are unique and of special interest. The first is the unusual plot in Figure 2, with the slope being the inverse of the usual one as in Figure 1. HCl differs from the other proton donors used in being a much stronger acid. Thus, 1 equiv is certain to be tied up irreversibly in protonating the pyridyl group. Still, this proton is available for intramolecular protonation. Once protonated, the pyridyl ring no longer has the ability or is required to utilize additional protons, and intramolecular attack becomes independent of the HCl concentration beyond that first proton. At this point, intramolecular protonation is zeroth order in HCl. However, the external protonation process does utilize protons in the medium and will be first order in HCl. This means that the external attack is enhanced with increasing HCl concentration whereas the intramolecular process is not. This is the reverse of what occurs with acetic acid. To paraphrase, eq 2 predicts a negative slope. Added to this reversal of proton donor dependence is the observation that in the more concentrated range of runs, pyridinium exhibits behavior similar to that of an endo phenyl group in providing steric hindrance to protonation. Thus, the pyridyl group has two possible roles—it may act as a site of intramolecular transfer to the more hindered face of the enolic system at low HCl concentrations, or fully protonated, it may act as a bulky moiety preventing protonation from this face at these higher HCl concentrations.

A second item of special interest is the observation that fluoride is not required for ketonization with hydrochloric acid. Protonation of the *tert*-butyldimethylsilyl enol ether exhibits behavior parallel to that of the enol itself. Ketonization of both enols and enolates, being highly exothermic and thus having early transition states, utilizes relatively planar transition states. In the present case, the release of a silyl cation seems quite parallel to the release of a proton in the simple enol examples. Silyl cations are, indeed, known to be reasonably stable species.[9] The basic stereochemical conclusions would not differ in the event that the chloride anion assisted the loss of the silyl moiety.

A final aspect of the hydrochloric ketonizations concerns the endo-phenyl diastereomer, where the stereoselectivity is independent of acid concentration and proceeds exclusively by a less hindered attack of the proton donor to afford the less stable benzoyl diastereomer **32ex**.

Interpretation—Stereochemistry of the Wolff Rearrangement. One item that seemed to be unexpected was the stereochemistry of the photochemical Wolff rearrangement of diazoketone **19en** in methanol. Despite methanol being considerably less acidic than phenol or the triethylammonium cation, the preferred kinetic stereochemistry afforded the anti epimer of diastereomer **20a**, as shown in Scheme 3. The result was clearly kinetic since runs at different times were invariant. However, that *tert*-butyl alcohol runs led to an inverted ratio with the less stable diastereomeric ester being preferred suggests that the small size of methanol is a factor that permits hydrogen bonding to the pyridine nitrogen and thus intramolecular transfer.

Interpretation—Geometry of Proton Delivery by Pyridyl. A final matter is the geometry of proton delivery by the endo-pyridyl moiety. It seems probable that protonation initially occurs in a pyridyl conformation in which the nitrogen is most accessible. Protonation then is followed by a twist and intramolecular delivery as depicted in eq 3.



5en **33** (3)

4. Conclusions

In considering the overall significance of the present study, we need to comment on the importance of proton transfer in organic chemistry, both synthetic and mechanistic. Thus, an understanding of the phenomenon is critical to an understanding of the myriad reactions[10] involving enolic intermediates. The present study and one previous case[4] we have presented represent a dramatic departure from the ubiquitous phenomenon of less hindered protonation to give the less stable of alternative diastereomeric carbonyl compounds. In our earlier review,[3] we listed just 25 examples of kinetic protonation via the less hindered route.[11] However, a rather interesting conjecture now seems possible. For those examples where (a) less than total stereoselectivity was observed and where (b) the molecule had non-hydrocarbon groups, one may inquire whether some of the more hindered protonation derives from contributions from an intramolecular effect of the type described in the present study. Another item is suggested by the present study, namely,

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[9] Lambert, J. B.; Zhang, S.; Ciro, S. M. *Organometallics* **1994**, *13*, 2430−2443, report of a series of stable silyl cations as tetraaryl borate salts.

[10] (a) Also, an understanding of proton transfer in carbonyl compounds is relevant to certain biochemical phenomena (note ref 10b). (b) Harris, T. K.; Cole, R. N.; Comer, F. I.; Mildvan, A. S. *Biochemistry* **1998**, *37*, 16828−16838.

what other intramolecular proton transfer moieties may successfully operate. This is a matter that we are currently pursuing.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 250, 300, or 500 MHz. ^{13}C NMR spectra were recorded at 75 or 125 MHz. ^{1}H and ^{13}C chemical shifts were measured relative to internal Me_4Si and $CDCl_3$, respectively. Mass spectra were obtained in EI and ESI modes. X-ray diffraction data were collected with the use of an area detector. Each structure was solved under the appropriate space-group symmetry by a direct method using SHELXTL. Column chromatography (CC) was performed on silica gel (35−75 μm or 60−200 mesh) mixed with 1% (v/v) of a fluorescent indicator (phosphor green, UV254), and the slurry was packed into quartz columns to allow monitoring with a hand-held UV lamp. Column chromatography was also performed on alumina absorption (80−200 mesh). Preparative thick-layer chromatography was carried out with silica gel coated on glass (10−40 μm, mixed with a fluorescent indicator (1%, v/v) and gypsum binder (10%), 50 g of silica gel, 105 mL of water, 20 cm × 20 cm plate). Melting points (uncorrected) were determined in open capillaries with a heating block. Exploratory photolysis was carried out with a 450-W medium-pressure mercury lamp. Solvents were dried following standard methods. Workup as usual (solvent) consisted of extraction with the indicated solvent and drying the organic layer over Na_2SO_4.

4-Phenyl-4-(pyridin-2-yl)cyclopentene (8). Benzyl-2-pyridine (38.0 g, 0.22 mol) dissolved in 1.2 L of freshly distilled THF was stirred under nitrogen at −78 °C, and *n*-BuLi (70 mL, 3.5 M) was added through a long-needle syringe. The resulting dark-red mixture was stirred for 3 h at −78 °C and then added to 800 mL of a THF solution of 1,4-dichloro-2-butene (37.0 g, 0.30 mol) with mechanical stirring under nitrogen at −78 °C through a cannula over 30 min. After 2.5 h of stirring at −78 °C, the reaction mixture was treated with another equiv of *n*-BuLi (70 mL, 3.5 M) and stirred for 6 h more and allowed to warm slowly to room temperature. Workup as usual (ether) gave a dark oil. The oil was refluxed in 1.5 L of decalin for 36 h. Decalin was then removed by vacuum distillation. The residue was subjected to chromatography on a 10 cm × 50 cm silica gel column and was eluted with hexanes−ether (3:1). The collected fraction was decolorized with charcoal−silica gel (1:1) and concentrated to yield a light-yellow solid, which was recrystallized from its hexane solution to yield 24 g (50%) of 4-phenyl-4-(2′-pyridyl)cyclopentene (**8**) as colorless crystals: mp 53 °C; R_f 0.5 (hexanes−ether 3:1); IR 3055, 2924, 2850, 1587, 1567, 1492, 1468, 1427 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.54 (m, 1H), 7.53 (m, 1H), 7.25 (m, 4H), 7.16 (m, 2H), 7.08 (m, 1H), 5.81 (s, 2H), 3.43 (d, J = 14.0 Hz, 2H), 3.04 (d, J = 14.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ) 167.3, 149.1, 148.1, 135.9, 129.2, 128.0, 126.8, 125.6, 122.4, 120.7, 57.6, 45.1; HRMS-EI m/z (M^+) calcd for $C_{16}H_{15}N$: 221.1204, obsd: 221.1197.

5-Phenyl-5-(pyridin-2-yl)cyclopent-1,3-diene (14). To 4-phenyl-4-pyridylcyclopentene (4.4 g, 20 mmol) dissolved in 100 mL of ether at room temperature was added 2.3 mL of HBr (47−49%). A white precipitate formed upon the addition of HBr. The suspension was stirred for 10 min, 1.1 mL of bromine (21 mmol) was then added, and the reaction was stirred at room temperature for 45 min. Ether was removed in vacuo, and the residue was dissolved in 70 mL of CH_2Cl_2. The solution was washed with $NaHCO_3$ solution, with $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated to yield a brown oil. The brown oil and 18-crown-6 (15.8 g, 60 mmol) dissolved in 300 mL of THF were stirred under N_2 at −78 °C, and *t*-BuOK (6.85 g, 60 mmol) was added. The reaction mixture darkened slowly and was stirred overnight with a gradual rise of temperature to ambient. The solvent was removed in vacuo, and the residue was redissolved in CH_2Cl_2. The solution was washed with brine, dried over $MgSO_4$, and concentrated to yield a brown oil. The oil was subjected to chromatography on a 5 cm × 40 cm silica gel column and eluted with CH_2Cl_2 to yield 3.7 g (86%) of 5-phenyl-5-pyridyl-cyclopent-1,3-diene (**14**) as a pale-yellow oil: IR 3058, 1583, 1489, 1464, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.54 (m, 1H), 7.54 (td, J = 7.8, 1.8 Hz, 1H), 7.31 (dt, J = 8.7, 0.9 Hz, 1H), 7.23−7.15 (m, 5H), 7.10−7.05 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 6.96 (m, 2H), 6.45 (m, 2H); ^{13}C NMR ($CDCl_3$, δ) 161.64, 149.13, 143.49, 141.16, 136.22, 130.15, 128.25, 127.05, 126.56, 122.00, 121.59, 70.87; HRMS-EI m/z (M^+) calcd for $C_{16}H_{13}N$: 219.1048, obsd: 219.1039.

5-Nitro-7-phenyl-7-(pyridin-2-yl)bicyclo[2.2.1]hept-2-ene (13). Nitroethylene was prepared by using published procedures.[12] 2-Nitroethanol[13] (28.0 g, 0.31 mol) and phthalic anhydride (68.8 g, 0.46 mol) were heated at 150 °C under 80 mm of Hg until the phthalic anhydride melted. The temperature was then raised to 180 °C, and 20.2 g (89%) of nitroethylene was collected as a light-green liquid that was stable for months in the freezer or as a chloroform solution at ambient temperature.

To 5-phenyl-5-(2′-pyridyl)cyclopentadiene (**14**) (4.0 g, 18.3 mmol) dissolved in 100 mL of ether was added 20 mL of HCl (1.0 M in ether) at room temperature. A white precipitate formed upon the addition of HCl. Ether was removed in vacuo, and the residue was washed with ether (2 × 20 mL). The residue that dissolved in 1.0 mL of dichloromethane was stirred under nitrogen at room temperature, and nitroethylene (2.7 g, 37.4 mmol) was added through a syringe. The reaction flask was then sealed and stirred for 72 h. The thick brown oil that formed was diluted with dichloromethane. The organic layer was washed with $NaHCO_3$ solution, dried, and concentrated in vacuo to yield a dark oil that was chromatographed on a 5 cm × 40 cm silica gel column and eluted with dichloromethane. The first fraction was 2.4 g (45%) of 5-nitro-7-*exo*-phenyl-7-*endo*-(pyridin-2-yl) bicyclo[2.2.1]hept-2-ene (**13en**): R_f 0.27 (CH_2Cl_2); mp 125 °C; IR 3063, 3003, 1385, 1359 (strong), 1373 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.52 (d, J = 5.0 Hz, 1H), 7.55 (td, J = 8.0, 2.0 Hz, 1H), 7.30−7.00 (m, 7H), 6.40 (dd, J = 5.7, 3.3 Hz, 1H), 5.95 (dd, J = 5.7, 2.7 Hz, 1H), 5.12 (dt, J = 8.5, 3.5 Hz, 1H), 4.61 (m, 1H), 3.90 (m, 1H), 2.20 (ddd, J = 14.0, 8.5, 3.5 Hz, 1H), 2.05(dd, J = 14.0, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, δ) 162.1, 149.4, 142.3, 138.5, 136.9, 130.3, 128.2, 127.6, 126.1, 121.6, 121.3, 84.3, 53.1, 48.2, 29.9; HRMS-EI m/z (M^+) calcd for $C_{18}H_{15}N_2O_2$: 292.1212, obsd: 292.1217. The second fraction was exo-pyridyl adduct **13ex** (2.0 g, 38%): R_f 0.20 (CH_2Cl_2); mp 109.5−110.5 °C; IR 3061,3004,1587, 1540 (strong), 1373 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.39 (d, J = 5.0 Hz, 1H), 7.50 (m, 3H), 7.30 (t, J = 7.2 Hz, 2H), 7.15 (m, 1H), 6.38 (dd, J = 6.0, 3.5 Hz, 1H), 5.93 (dd, J = 6.0, 3.0 Hz, 1H), 5.00 (dt, J = 8.5, 3.5 Hz, 1H), 4.65 (s, 1H), 4.05 (s, 1H), 2.35 (ddd, J = 13.5, 8.5,3.5 Hz, 1H), 2.04 (dd, J = 13.5, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, δ) 162.8, 148.7, 141.5,

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(11) (a) This seems to be increasingly of interest. Perhaps it is not remarkable that our 1955 concept has been rediscovered twice (refs 11b−h) and that the rediscoveries are often cited and the original work overlooked (e.g., note ref 11i). (b) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205−1215. (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) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, 5567−5569. (f) Takano, S.; Yamada, S.; Numata, H; Hatakeyama, S.; Ogasawara, K. *Heterocycles* **1983**, *20*, 2159−2162. (g) Takano, S.; Tananka, M.; Seo, M.; Hirama, M.; Ogasawara, K. *J. Org. Chem.* **1985**, *50*, 931−936. (h) Note also Hünig, S.; Houben-Weyl, Protonation of Carbanions and Polar Double Bonds. In *Methods of Organic Chemistry;* Helmchen, G., Ed.; Stuttgart, 1996; Vol. E21D 7, pp 3851−3911, where the origin of the concept is not given while being the main subject of the review. (i) Krause, N.; Ebert, S.; Haubrich, A. *Liebigs Ann/Recl* **1997**, 2409−2418.

(12) Ranganathan, D.; Rao, C. B.; Ranganenthan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185−1189.

(13) Noland, W. E. *Org. Synth.* **1961**, *41*, 67−72.

138.9, 136.0, 130.5, 129.0, 127.0, 126.4, 121.2, 120.8, 84.2, 52.9, 48.0, 29.8; HRMS-EI *m/z* (M$^+$) calcd for $C_{18}H_{16}N_2O_2$: 292.1212, obsd: 292.1208. The stereochemistry was assigned by an NOE experiment.

7-*exo*-Phenyl-7-*endo*-(pyridin-2-yl)bicyclo[2.2.1]hept-5-en-2-one (11en). Method A. 5-Nitro-7-*exo*-phenyl-7-*endo*-(pyridin-2-yl)bicyclo[2.2.1]hept-2-ene (**13en**) (1.0 g, 3.4 mmol) mixed with 50.0 g of activated silica gel[14] (8.5 mol NaOMe/kg silica gel) was heated at 150 °C for 2.5 h, and the solid mixture turned brown. The mixture was cooled to room temperature and washed with dichloromethane. The dichloromethane solution was concentrated in vacuo, and the residue was subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with dichloromethane−diethyl ether (9:1) to yield 0.42 g (47%) of 7-*exo*-phenyl-7-*endo*-(pyridin-2-yl)bicyclo[2.2.1]hept-5-en-2-one (**11en**).

Method B. 5-Nitro-7-*exo*-phenyl-7-*endo*-(pyridin-2-yl)bicyclo-[2.2.1]hept-2-ene (**13en**) (96 mg, 0.33 mmol) dissolved in 50 mL of MeOH was poured onto a 2 cm × 30 cm silica gel column. The column stood for 3 weeks, and then the material on the column was washed out with MeOH and concentrated in vacuo to yield the corresponding oxime **12en**: IR 3230.2 cm^{-1}; ^{1}H NMR (CDCl$_3$, δ) 10.05 (s, 1H), 8.45 (d, 1H), 7.45−6.80 (m, 8H), 6.35 (m, 1H), 6.00 (m, 1H), 4.30 (s, 1H), 4.10 (s, 1H), 2.35−2.10 (m, 2H); ^{13}C NMR (CDCl$_3$, δ) 163.2, 161.7, 149.1, 142.1, 138.7, 136.5, 130.9, 127.8, 125.8, 122.1, 121.1, 75.8, 65.6, 53.7, 47.3, 30.0, 15.0; HRMS-ESI *m/z* (MH$^+$) calcd for $C_{18}H_{17}N_2O$: 277.1341, obsd: 277.1329.

Oxime **12en** dissolved in 10 mL of HCl (0.8 M) was heated at 90 °C for 1.5 h. The aqueous solution was then cooled to room temperature and neutralized with NaHCO$_3$ powder. Workup as usual (dichloromethane) gave a brown oil that was chromatographed on a 2 cm × 30 cm silica gel column. Elution with dichloromethane−diethyl ether (9:1) gave 75 mg (88%) of **11en**: R_f 0.43; mp 163−164 °C; IR 1741 cm^{-1}; ^{1}H NMR (CDCl$_3$, δ) 8.53 (m, 1H), 7.52 (td, J = 7.8, 1.8 Hz, 1H), 7.35−7.00 (m, 7H), 6.60 (dd, J = 5.4, 2.7 Hz, 1H), 5.98 (t, J = 2.7 Hz, 1H), 4.08 (s, 1H), 4.04 (m, 1H), 1.95 (d, J = 16.5 Hz, 1H), 1.87 (dd, J = 16.5, 3.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, δ) 213.1, 162.0, 149.4, 142.8, 141.6, 136.7, 128.4, 128.2, 128.0, 126.4, 122.2, 121.7, 63.1, 47.0, 36.2; HRMS-EI *m/z* (M$^+$) calcd for $C_{18}H_{15}NO$: 261.1154, obsd: 261.1148.

7-*exo*-Phenyl-7-*endo*-(pyridin-2-yl)bicyclo[2.2.1]hept-2-one (15en). Method A. To 5-nitro-7-*exo*-phenyl-7-*endo*-(pyridin-2-yl)bicyclo[2.2.1]hept-2-ene (**13en**) (1.13 g, 3.87 mmol) and potassium azodiformate (2.0 g, 10.0 mmol) stirred in 40 mL of MeOH in an ice bath was added 5.0 mL of a MeOH solution of acetic acid (1.4 mL, 24.0 mmol) over 2 h with a syringe pump. The reaction mixture was stirred for 90 min more and then poured into 50 mL of water and neutralized with NaHCO$_3$. Workup as usual (dichloromethane) gave 1.16 g of 5-nitro-7-*exo*-phenyl-7-*endo*-(pyridin-2-yl)bicyclo[2.2.1]-heptane **16en**: mp 115 °C; IR 1542 cm^{-1}; ^{1}H NMR (CDCl$_3$, δ) 8.51 (ddd, J = 5.0, 1.5, 1.0 Hz, 1H), 7.54 (td, J = 7.5, 2.0 Hz, 1H), 7.47−7.41 (m, 2H), 7.35 (dt, J = 8.0, 1.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 2H), 7.14 (tt, J = 8.0, 1.0 Hz, 1H), 7.03 (ddd, J = 7.5, 5.0, 1.5 Hz, 1H), 4.94 (dtd, J = 8.5,4.0,2.0 Hz, 1H), 3.97 (t, J = 4.0 Hz, 1H), 3.31 (t, J = 4.0 Hz, 1H), 2.32 (dd, J = 9.0, 4.0 Hz, 1H), 2.01 (qt, J = 11.0, 4.0 Hz, 1H), 1.83 (m, 1H), 1.71−1.50 (m, 2H), 1.41−1.30 (m, 1H); ^{13}C NMR (CDCl$_3$, δ) 162.4, 149.4, 142.7, 128.6, 127.0, 126.4, 122.0, 121.3, 86.4, 68.1, 48.1, 41.9, 31.9, 27.1, 21.3; HRMS-EI *m/z* (M$^+$) calcd for $C_{18}H_{15}N_2O_2$: 294.1368, obsd: 294.1358.

16en (1.16 g) was stirred with 70 mL of 10% KOH(aq) for 48 h. The solution turned blue upon the addition of 98 mL of HCl (4.0 M). The solution was heated in an oil bath (100−105 °C) for 50 h, and the color changed slowly from blue to green and finally to golden green. The solution was cooled, neutralized with NaHCO$_3$ to a pH of ca. 7−8, and extracted with dichloromethane. The combined organic layers were dried and concentrated. The residue was subjected to chromatography on a 4 cm × 30 cm silica gel column and eluted with hexane−dichloromethane−diethyl ether (2:2:1) to give 0.53 g (53%) of **15en**.

Method B. To 7-*exo*-phenyl-7-*endo*-(pyridin-2-yl)bicyclo-[2.2.1]hept-5-en-2-one (**11en**) (1.49 g, 5.69 mmol) in 50 mL of MeOH cooled in an ice−water bath was added potassium azodiformate (3.30 g, 17.07 mmol). Ten milliliters of a MeOH solution of acetic acid (2.3 mL, 40.0 mmol) was added over 5 h. The reaction mixture was stirred for an additional 2 h, more potassium azodiformate (2.0 g) was then added, and 5.0 mL of a MeOH solution of acetic acid (1.5 mL) was added over 4.5 h. The reaction mixture was poured into 60 mL of water and worked up as usual (dichloromethane). The residue was subjected to chromatography on a 4 cm × 30 cm silica gel column, and 0.70 g of **15en** was obtained along with 0.30 g of recovered unreacted starting material (**11en**). The column was washed with MeOH−diethyl ether (1:1) to give ca. 0.50 g of a complex mixture that was heated in 50 mL of 0.8 M HCl at 80 °C for 3 h, and **15en** was obtained as a single product. The combined **15en** fractions weighed 1.17 g (78%). R_f 0.32 (dichloromethane−diethyl ether 9:1); mp 157−159 °C; IR 1744 cm^{-1}; ^{1}H NMR (CDCl$_3$, δ) 8.45 (d, J = 5.0 Hz, 1 H), 7.48−7.12 (m, 7H), 6.94 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 3.64 (d, J = 4.0 Hz, 1H), 3.58 (m, 1H), 2.12−1.80 (m, 4H), 1.62−1.46 (m, 2H); ^{13}C NMR (CDCl$_3$, δ) 215.9, 162.2, 149.0, 141.3, 136.33, 128.5, 126.9, 126.4, 122.4, 121.2, 65.2, 56.2, 44.2, 41.9, 26.4, 22.3; HRMS-EI *m/z* (M$^+$) calcd for $C_{18}H_{17}NO$: 263.1310, obsd: 263.1311.

7-*endo*-Phenyl-7-*exo*-(pyridin-2-yl)bicyclo[2.2.1]hept-2-one (15ex). 5-Nitro-7-*endo*-phenyl-7-*exo*-(pyridin-2-yl)bicyclo-[2.2.1]hept-2-ene (**13ex**) (2.0 g, 6.8 mmol) and 4.0 g of (20.6 mmol) potassium azodiformate were stirred in 70 mL of MeOH in an ice bath. Five milliliters of a of MeOH solution of acetic acid (2.74 mL, 48 mmol) was added with a syringe pump over 3.0 h and then stirred for an additional 3 h. The reaction mixture was added to 60 mL of diluted NaHCO$_3$, and workup as usual (dichloromethane) gave 1.98 g (98.5%) of 5-nitro-7-*endo*-phenyl-7-*exo*-(pyridin-2-yl)bicyclo[2.2.1]heptane (**16ex**): mp 144 °C; IR 1542 cm^{-1}; ^{1}H NMR (CDCl$_3$, δ) 8.50 (d, J = 5.0 Hz, 1H), 7.60−7.50 (m, 3H), 7.35 (m, 3H), 7.15 (m, 1H), 7.00 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 4.80 (m, 1H), 3.95 (s, 1H), 3.35 (s, 1H), 2.35−2.10 (m, 2H), 1.80−1.30 (m, 4H); ^{13}C NMR (CDCl$_3$, δ) 162.3, 149.2, 141.6, 136.5, 128.9, 127.2, 126.7, 121.4, 121.0, 86.3, 67.8, 48.1, 41.6, 31.5, 27.2, 21.3; HRMS-EI *m/z* (M$^+$) calcd for $C_{18}H_{15}N_2O_2$: 294.1368, obsd: 294.1378.

16ex (1.98 g) was treated with 100 mL of 10% KOH(aq), stirred for 36 h, and then treated with 140 mL of 4.0 M HCl. The solution became blue immediately and was stirred for 1 h at room temperature and then at 90 °C for 2.5 h. The reaction mixture was cooled, neutralized with NaHCO$_3$ to pH of ca. 7−8, and worked up as usual (dichloromethane). The residue was subjected to chromatography on a 4 cm × 30 cm silica gel column and eluted with hexane−dichloromethane−ether (2:2:1) to yield **15ex**, which was crystallized from ether−hexane solution to give 1.40 g (78%) of **15ex** as colorless crystals: R_f 0.33 (hexane−dichloromethane−diethyl ether 2:2:1); mp 196 °C; IR 1732 cm^{-1}; ^{1}H NMR (CDCl$_3$, δ) 8.54 (d, J = 5.0 Hz, 1H), 7.55 (td, J = 8.0, 1.8 Hz, 1H), 7.49−7.01 (m, 7H), 3.64 (m, 2H), 2.20−1.50 (m, 6H); ^{13}C NMR (CDCl$_3$, δ) 216.2, 162.0, 149.4, 141.9, 136.5, 128.7, 127.7, 126.7, 121.63, 121.2, 65.0, 56.4, 44.2, 42.0, 26.5, 22.6; HRMS-EI *m/z* (M$^+$) calcd for $C_{18}H_{17}NO$: 263.1310, obsd: 263.1310.

3-Diazo-7-*endo*-phenyl-7-*exo*-pyridin-2-yl-bicyclo[2.2.1]-heptan-2-one (19ex). To a solution of diisopropylamine (0.84 mL, 5.5 mmol) in 2.5 mL of freshly distilled THF under nitrogen at −78 °C was added 3.6 mL of *n*-BuLi (1.45 M, 5.2 mmol). The reaction was stirred for 45 min at −78 °C. **15ex** (1.24 g, 4.7 mmol) dissolved in 15 mL of THF was cooled to −78 °C under nitrogen, and LDA was added. The reaction mixture was allowed to warm to room temperature slowly, and 5.0 mL of solvent was removed in a nitrogen stream. HCOOMe

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[14] Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1977**, *99*, 11−12.

(2.0 mL, 12.0 mmol) was then added, and the reaction mixture was stirred for 48 h. A yellow cake formed, and the reaction mixture was concentrated in vacuo. Dichloromethane was added to the residue, and the solution was extracted with 10% KOH. The organic layer was dried and concentrated to yield 0.64 g of starting material **15ex**. The combined aqueous layers were then neutralized with 4.0 M HCl to a pH of ca. 6, and workup as usual (dichloromethane) gave a mixture of isomers of formyl ketones (0.67 g) as a brown solid. The brown solid was dissolved in 15 mL of dichloromethane to give a dark purple solution that was cooled in an ice bath. Tosyl azide (0.47 g, 2.4 mmol) was added, followed by triethylamine (0.48 g, 4.8 mmol). The reaction mixture was stirred overnight in darkness, the solvent was then removed, and the residue was subjected to chromatography on a 2 cm × 30 cm neutral alumina column and eluted with dichloromethane−hexane (2:1) to give 0.44 g of **19ex** (67% based on consumed **15ex**) as bright-yellow crystals: R_f (silica gel TLC) 0.30 (dichloromethane−ether 9:1); IR 2076, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.55(d, $J = 4.5$ Hz, 1H), 7.57 (td, $J = 8.0$, 2.0 Hz, 1H), 7.50−7.45 (m, 2H), 7.28−7.10 (m, 4H), 7.07 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H), 4.46 (t, $J = 2.5$ Hz, 1H), 3.68 (dd, $J = 4.0$, 2.0 Hz, 1H), 2.10−1.54 (m, 4H); ^{13}C NMR ($CDCl_3$, δ) 198.9, 160.9, 149.4, 141.6, 136.7, 127.4, 126.8, 126.5, 121.5, 121.3, 66.7, 55.9, 46.9, 27.6, 23.0; HRMS-EI m/z ([M − N_2]$^+$) calcd for $C_{18}H_{15}NO$: 261.1154, obsd: 261.1151.

3-Diazo-7-*exo*-phenyl-7-*endo*-pyridin-2-yl-bicyclo[2.2.1]-heptan-2-one (19en). To a solution of diisopropylamine (0.82 mL, 5.3 mmol) in 1.8 mL of freshly distilled THF under nitrogen at −78 °C was added 3.9 mL of *n*-BuLi (1.33 M, 5.2 mmol). The mixture was stirred at −78 °C for 1 h. 7-*exo*-Phenyl-7-*endo*-(pyridin-2-yl) bicyclo[2.2.1]hept-2-one (**15en**) (1.17 g, 4.43 mmol), dissolved in 8.0 mL of THF was cooled to −78 °C under nitrogen, and LDA was added. The reaction was stirred overnight and allowed to warm slowly to room temperature. HCOOMe (1.4 mL, 8.4 mmol) was then added, and a yellow suspension formed. The reaction mixture was stirred for 48 h and concentrated in vacuo. Diethyl ether was added, and mixture was extracted with 5% KOH. The organic layer was dried over $MgSO_4$ and concentrated to yield 0.60 g of starting material **15en**. The recovered starting material was subjected to the above procedure again. The combined aqueous layer was then neutralized with 4.0 M HCl to a pH of ca. 6, and workup as usual (dichloromethane) gave a mixture of isomers of formyl ketones (1.01 g) as a brown solid. The solid was dissolved in 20 mL of dichloromethane to give a dark-purple solution. To the solution cooled in an ice bath was added tosyl azide (0.686 g, 3.5 mmol), followed by triethylamine (0.703 g, 7.0 mmol). The reaction mixture was kept dark and stirred and then concentrated in vacuo. The residue was subjected to chromatography on a 2 cm × 30 cm neutral alumina column and eluted with dichloromethane−hexane (2:1) to yield 0.65 g (65%) of **19en** as a bright-yellow solid: R_f (silica gel TLC) 0.33 (dichloromethane−ether 9:1); IR 2076, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.48 (d, $J = 5.0$ Hz, 1H), 7.50 (td, $J = 8.0$, 2.0 Hz, 1H), 7.44−7.15 (m, 6H), 6.99 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H), 4.52 (m, 1H), 3.69 (m, 1H), 2.06−1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, δ) 198.8, 161.9, 149.4, 140.4, 136.6, 128.8, 126.9, 126.5, 122.0, 121.5, 67.3, 55.81, 46.6, 27.2, 23.1; HRMS-EI m/z ([M − N_2]$^+$) calcd for $C_{18}H_{15}NO$: 261.1154, obsd: 261.1135.

Methyl 6-*endo*-Phenyl-6-*exo*-pyridin-2-yl-bicyclo[2.1.1]-hexane-5-carboxylate (22ex). 3-Diazo-7-*endo*-phenyl-7-*exo*-pyridin-2-yl-bicyclo[2.2.1]heptan-2-one (**19ex**) (98 mg, 0.31 mmol) dissolved in 200 mL of MeOH was irradiated for 40 min in a Hanovia box with a $CuSO_4$ filter solution. The reaction mixture was concentrated in vacuo to give a light-brown residue that was subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with hexane−dichloromethane−diethyl ether (2:2:1) to yield **22ex** (71%): R_f 0.15 (hexane−dichloromethane−diethyl ether 2:2:1); mp 152−153 °C; IR 1723 cm^{-1}; ^{1} H NMR (CDCl, δ_3) 8.46 (m, 1H), 7.61 (m, 2H), 7.49 (td, $J = 7.5$, 2.0 Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 2H), 7.09 (t, $J = 7.5$ Hz, 2H), 6.94 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H), 3.78 (s, 2 H), 3.06 (s, 3H), 2.31 (s, 1H), 1.81−1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, δ) 172.8, 164.2, 149.2, 141.4, 136.1, 129.5, 127.6, 126.5, 121.2, 120.4, 64.4, 52.5, 50.8, 48.0, 25.4; HRMS-EI (M$^+$) (m/z) for $C_{19}H_{19}NO_2$ calcd 293.1416; obsd 293.1415.

Methyl 6-*exo*-Phenyl-6-*endo*-pyridin-2-yl-bicyclo[2.1.1]-hexane-5-carboxylate (20en). 3-Diazo-7-*exo*-phenyl-7-*endo*-pyridin-2-yl-bicyclo[2.2.1]heptan-2-one (**19en**) (84 mg, 0.29 mmol) dissolved in 200 mL of MeOH was irradiated for 40 min in a Hanovia box with a $CuSO_4$ filter solution. The reaction mixture was concentrated in vacuo to give a light-brown solid that was subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with diethyl ether to afford 66 mg (78%) of **20en**: R_f 0.73 (hexane−dichloromethane−diethyl ether 2:2:1); mp 103−104 °C; IR 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.51 (m, 1H), 7.53 (td, $J = 7.5$, 2.0 Hz, 1H), 7.44 (dt, $J = 7.5$, 1.0 Hz, 1H), 7.28−7.19 (m, 4H), 7.10 (m, 1H), 7.01 (ddd, $J = 7.5$, 5, 1.5 Hz, 1H), 3.68 (d, $J = 2.5$ Hz, 2H), 3.61 (s, 3H), 2.63 (m, 1H), 1.78 (m, 2H), 1.62 (m, 2H); ^{13}C NMR (δ) 172.4, 163.3, 149.3, 141.8, 136.3, 128.2, 127.2, 125.9, 122.4, 121.0, 61.5, 51.2, 48.1, 46.3, 26.4; HRMS-EI (M$^+$) (m/z) for $C_{19}H_{19}NO_2$ calcd 293.1416; obsd 293.1418.

6-Phenyl-6-pyridin-2-yl-bicyclo[2.1.1]hexane-5-carbaldehyde (23en). Methyl 6-*exo*-phenyl-6-*endo*-pyridin-2-yl-bicyclo[2.1.1]hexane-5-carboxylate (**20en**) (199 mg, 0.68 mmol) dissolved in 5.0 mL of dry toluene at −78 °C under nitrogen was slowly added to 1.0 mL of DIBAL-H (1.0 M in hexanes). The reaction mixture was stirred for 2 h and quenched with 4 mL of aqueous MeOH. Workup as usual (dichloromethane) gave an oil. The oil was subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with diethyl ether to yield 129 mg (80%) of **23en** as a clear oil: R_f 0.63 (diethyl ether); IR 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 9.62 (d, $J = 1.0$ Hz, 1H), 8.50 (ddd, $J = 5.0$, 2.0, 1.0 Hz, 1H), 7.53 (td, $J = 8.0$, 2.0 Hz, 1H), 7.43 (dt, $J = 8.0$, 1.0 Hz, 1H), 7.29−7.18 (m, 4H), 7.15−7.08 (m, 1H), 7.04−6.99 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H), 3.78 (d, $J = 2.5$ Hz, 1H), 2.47 (m, 1H), 1.80−1.65 (m, 4H); ^{13}C NMR (δ) 202.7, 163.0, 149.2, 141.1, 136.3, 128.3, 127.0, 126.0, 122.4, 121.1, 62.0, 52.3, 47.6, 21.8; HRMS-ESI [MH + CH_3OH]$^+$ (m/z) for $C_{19}H_{22}NO_2$ calcd 296.1650; obsd 296.1638.

6-Phenyl-6-pyridin-2-yl-bicyclo[2.1.1]hexane-5-carboxylic Acid (21ex). To a suspension of excess KH in THF under nitrogen was added a THF solution of methyl 6-*endo*-phenyl-6-*exo*-pyridin-2-yl-bicyclo[2.1.1]-hexane-5-carboxylate (22ex) (35 mg, 0.12 mmol) and 18-crown-6 (63 mg, 0.239 mmol). The reaction mixture was stirred overnight at room temperature and was quenched with MeOH, neutralized with AcOH, and concentrated in vacuo. The residue was treated with water and dichloromethane. Workup as usual gave the crude product. A second run was carried out with 80 mg (0.273 mmol) of 22ex under the same conditions. The combined crude products were subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with diethyl ether to yield 101 mg (92%) of 21ex: mp 237−238 °C; IR 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 9.90 (s, 1H broad), 8.70 (dd, $J = 5.0$, 1.0 Hz, 1H), 7.59 (m, 3H), 7.27 (t, $J = 7.5$ Hz, 2H), 7.15 (m, 2H), 7.07 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H), 3.70 (d, $J = 3.0$ Hz, 2H), 2.91(s, 1H), 1.95 (d, $J = 8.0$ Hz, 2H), 1.59 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (δ) 176.2, 161.8, 148.2, 141.8, 137.4, 128.6, 128.1, 126.6, 122.5, 121.2, 60.3, 48.1, 46.2, 22.4; HRMS-ESI [M − H]$^+$ (m/z) for $C_{18}H_{16}NO_2$ calcd 278.1181; obsd 278.1189.

Phenyl-(6-*endo*-phenyl-6-*exo*-pyridin-2-yl-bicyclo[2.1.1]-hex-5-yl)-methanone (26ex). To a solution of 6-phenyl-6-pyridin-2-yl-bicyclo[2.1.1]hexane-5-carboxylic acid (**21ex**) (122 mg, 0.44 mmol) in 7.0 mL of dry diethyl ether under nitrogen at room temperature was added 0.92 mL of PhLi (1.0 M, 0.92 mmol). After 10 min, the reaction was quenched with aqueous AcOH and extracted with chloroform. The concentrated residue was subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with dichloromethane−diethyl ether (9:1) to yield 60 mg (40%) of **26ex**, which was recrystallized from dichloromethane: mp 240 °C; IR 1667 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 8.50 (d, J = 4.5 Hz, 1H), 7.85 (m, 2H), 7.71 (m, 2H), 7.55−7.09 (m, 8H), 6.98 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 3.81 (d, J = 2.5 Hz, 2H), 3.32 (s, 1H), 1.77−1.70 (dd, J = 12.0, 5.0 Hz, 2H), 1.62−1.54 (dd, J = 12.0, 5.0 Hz, 2H); ^{13}C NMR (δ) 200.5, 162.4, 149.3, 142.6, 136.2, 136.1, 132.9, 128.7, 128.5, 128.0, 127.9, 126.5, 121.9, 120.6, 61.2, 50.7, 49.5, 22.1; HRMS-ESI $[MNa]^+$ (m/z) for $C_{24}H_{21}NONa$ calcd 362.1521; obsd 362.1533. The structure was confirmed by X-ray analysis.

Phenyl-(6-*exo*-phenyl-6-*endo*-pyridin-2-yl-bicyclo[2.1.1]hex-5-yl)-methanone (26en). Method A. 3-Diazo-7-*exo*-phenyl-7-*endo*-pyridin-2-yl-bicyclo[2.2.1]heptan-2-one (**19en**) (234 mg, 0.81 mmol) was irradiated in 250 mL of dioxane−water (1:1) for 135 min. The reaction mixture was concentrated in vacuo and then diluted with dichloromethane. The organic solution was extracted with 5% KOH (5 × 10 mL), and the combined aqueous layers were neutralized with HCl and then acidified with AcOH. Workup as usual (chloroform) gave 173 mg (76%) of **21en**: IR 1708.2 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 10.05 (s, broad, 1H), 8.58 (d, J = 5.0 Hz, 1H), 7.55 (m, 2H), 7.30−7.20 (m, 4H), 7.15−7.00 (m, 2H), 3.72 (d, J = 2.5 Hz, 2H), 2.66 (s, 1H), 1.89 (d, J = 8.0 Hz, 2H), 1.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR (δ) 176.2, 162.8, 148.6, 141.3, 137.2, 128.3, 127.2, 126.0, 122.8, 121.4, 61.2, 48.0, 46.4, 22.3; HRMS-ESI $[M - H]^+$ (m/z) for $C_{18}H_{16}NO_2$ calcd 278.1181; obsd 278.1174.

21en (123 mg, 0.44 mmol) dissolved in 6.0 mL of dry diethyl ether under nitrogen at room temperature was treated with 4.0 mL of PhLi (0.89 M, 3.52 mmol) in ether. After 5 min, the reaction mixture was poured into 10 mL of 4.0 M HCl, and the pH was adjusted to ca. 10 with KOH. The two layers were separated, and the aqueous layer was acidified with AcOH and extracted with chloroform to give 50 mg of unreacted starting material **21en**. The organic layer was dried and concentrated. The residue was subjected to column chromatography on a 2 cm × 30 cm silica gel column to yield 38 mg of **26en** (43% based on the consumed starting material).

Method B. 6-Phenyl-6-pyridin-2-yl-bicyclo[2.1.1]hexane-5-carbaldehyde (**23en**) (74 mg, 0.28 mmol) dissolved in 1.5 mL of dry diethyl ether under nitrogen at room temperature and 0.37 mL of PhLi (0.89 M, 0.33 mmol) were combined. The reaction mixture was stirred for 10 min and then poured into an NH_4Cl solution. Workup as usual (dichloromethane) gave the alcohol **27en**. The crude product of **27en** dissolved in 3.0 mL of acetone was treated with Jones reagent (2.94 M, 0.28 mmol) for 15 min. Acetone was removed in vacuo, and the residue was treated with 5% KOH and dichloromethane and worked up as usual. The residue was subjected to chromatography on a 2 cm × 30 cm silica gel column and eluted with dichloromethane−ether (9:1) to yield **26en**, which was recrystallized from dichloromethane to give 80 mg (84%) of **26en** as colorless needle crystals: R_f 0.57 (dichloromethane−diethyl ether 9:1); IR 1667.4 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 8.59 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 7.93−7.87 (m, 2H), 7.63−7.36 (m, 5H), 7.27−7.22 (m, 4H), 7.15−7.04 (m, 2H), 3.89 (d, J = 2.5 Hz, 2H), 3.13 (s, 1H), 1.76−1.55 (m, 4H); ^{13}C NMR (δ) 200.2, 163.7, 149.3, 141.7, 136.5, 136.2, 132.9, 128.5, 128.3, 128.0, 127.3, 125.9, 122.6, 121.2, 61.9, 51.1, 49.5, 22.1; HRMS-ESI $[MNa]^+$ (m/z) for $C_{24}H_{21}NONa$ calcd 362.1521; obsd 362.1538. This structure was confirmed by X-ray analysis.

5-**Bromo-6-*endo*-phenyl-6-*exo*-pyridin-2-yl-bicyclo[2.1.1]hex-5-yl)-phenyl-methanone (25ex).** Phenyl-(6-*endo*-phenyl-6-*exo*-pyridin-2-yl-bicyclo[2.1.1]hex-5-yl)-methanone (**26ex**) (58 mg, 0.17 mmol) with 43 μL of HBr (0.34 mmol, 48%) dissolved in 1.0 mL of AcOH was heated in an oil bath (∼100 °C), and 2.0 mL of Br_2 (0.20 mmol, 0.1 M solution in AcOH) was added. The reaction mixture was stirred in the oil bath for 30 h and then cooled and neutralized with KOH solution. Workup as usual (dichloromethane) gave the residue that was chromatographed on a silica gel column and eluted with dichloromethane−diethyl ether (9:1) to yield 57 mg (80%) of **25ex**: mp 182−183 °C (decomposed to a dark-brown oil); IR 1666 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 8.42 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 7.54−7.38 (m, 5H), 7.28−7.21 (m, 2H), 7.17 (td, J = 7.0, 1.0 Hz, 1H), 7.08 (dt, J = 7.5, 1.0 Hz, 1H), 6.98−6.81 (m, 3H), 6.48 (td, J = 7.0, 1.0 Hz, 1H), 4.26 (dt, J = 6.0, 1.0 Hz, 1H), 4.20 (dt, J = 6.0, 1.0 Hz, 1H), 2.35 (m, 1H), 2.27 (m, 1H), 1.98 (m, 1H), 1.86 (m, 1H); ^{13}C NMR (δ) 191.4, 164.1, 149.1, 139.0, 136.4, 134.7, 132.2, 130.8, 129.3, 128.9, 128.3, 127.6, 127.4, 126.8, 121.5, 120.8, 73.9, 60.8, 54.2, 54.0, 25.95, 24.7; HRMS-ESI $[MH]^+$ (m/z) for $C_{24}H_{21}BrNO$ calcd 418.0806; obsd 418.0798.

***tert*-Butyldimethylsilyloxy Enol Ether of 26-exo (24ex).** (5-Bromo-6-*endo*-phenyl-6-*exo*-pyridin-2-yl-bicyclo-[2.1.1]hex-5-yl)-phenyl-methanone (**25ex**) (78 mg, 0.19 mmol) dissolved in 4.0 mL of THF under nitrogen was cooled at −78 °C. HMPA (0.24 mL, 1.20 mmol) was added, followed by 0.53 mL of *t*-BuLi (1.16 M, 0.61 mmol) and 1.0 mL of a THF solution of TBS chloride (189 mg, 1.20 mmol). The reaction was stirred overnight and allowed to warm slowly to room temperature. The solvent was removed in vacuo, and the residue was subjected to chromatography on a 2 cm × 30 cm silica gel column. Elution with hexane−dichloromethane−diethyl ether (2:2:1) gave 82 mg (97%) of **24ex** as a colorless oil: R_f 0.33 (hexane−dichloromethane−diethyl ether (2:2:1); IR, no carbonyl absorption; ^1H NMR ($CDCl_3$, δ) 8.54 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 7.53 (td, J = 7.5, 2.0 Hz, 1H), 7.46−7.40 (m, 2H), 7.24−6.98 (m, 10H), 3.91 (d, J = 6.0 Hz, 1H), 3.74 (d, J = 6.0 Hz, 1H), 1.91−1.64 (m, 4H), 0.90 (s, 9H), −0.13 (s, 3H), −0.25 (s, 3H); ^{13}C NMR (δ) 162.8, 149.3, 143.3, 138.6, 136.1, 128.3, 127.7, 127.6, 127.2, 126.7, 126.5, 125.8, 122.3, 120.7, 118.9, 62.0, 51.9, 50.8, 25.8, 25.0, 24.9, 18.2, −4.4, −4.5, −26.3; HRMS-ESI $[MNa]^+$ (m/z) for $C_{30}H_{35}NOSiNa$ calcd 476.2386; obsd 476.2363.

***tert*-Butyldimethylsilyloxy Enol Ether of 26-endo (24en).** To phenyl-(6-*endo*-phenyl-6-*exo*-pyridin-2-yl-bicyclo-[2.1.1]hex-5-yl)-methanone (**26en**) (230 mg, 0.68 mmol) suspended in 3.0 mL of AcOH was added 0.25 mL of HBr (48%, 2.0 mmol), followed by 20 mL of Br_2 (0.1 M in AcOH, 2.0 mmol). After the reaction mixture was heated at 95 °C for 28 h, AcOH was removed by vacuum distillation. The residue was treated with 5% KOH and dichloromethane. Workup as usual (dichloromethane) gave **25en**, which was used directly for the next step without further purification. Spectral data for **25en**: IR 1675.1 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.77 (d, J = 5.0 Hz, 1H), 7.61 (m, 2H), 7.45 (td, J = 7.0, 1.0 Hz, 1H), 7.35−7.15 (m, 8H), 7.12−7.04 (m, 1H), 6.77 (ddd, J = 7.0, 5.0, 1.0 Hz, 1H), 4.43 (d, J = 6.0 Hz, 1H), 4.23 (d, J = 6.0 Hz, 1H), 2.36−2.15 (m, 2H), 2.00−1.90 (m, 2H); ^{13}C NMR (δ) 191.2, 160.7, 148.3, 144.1, 135.8, 134.4, 132.4, 129.1, 128.4, 128.1, 127.8, 126.8, 126.7, 126.0, 125.3, 121.2, 74.2, 61.4, 54.4, 54.1, 25.8, 25.0; HRMS-ESI $[MH]^+$ (m/z) for $C_{24}H_{21}BrNO$ calcd 418.0806; obsd 418.0819.

25en dissolved in 15 mL of freshly distilled THF under nitrogen was cooled at −78 °C, and 0.85 mL of HMPA (4.4 mmol) was added, followed by 1.9 mL of *t*-BuLi (1.16 M, 2.2 mmol). Three milliliters of a THF solution of TBS chloride (0.685 g, 4.4 mmol) was then added. The reaction was stirred overnight and allowed to warm slowly to room temperature. The solvent was removed in vacuo, and the residue was subjected to chromatography on a 2 cm × 30 cm silica gel column. Elution with hexane−dichloromethane−ether (2:2:1) yielded 300 mg (98%) of **24en** as a colorless oil that is very stable at ambient temperature: IR, no carbonyl absorption; ^1H NMR ($CDCl_3$, δ) 8.42 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 7.44 (td, J = 7.5, 2.0 Hz, 1H), 7.34 (dt, J = 8.0, 1.5 Hz, 1H), 7.29−7.08 (m, 11H), 6.93 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 3.92 (q, J = 6.0 Hz, 2H), 1.86−1.66 (m, 4H), 0.89 (s, 9H), −0.17 (s, 3H), −0.28 (s, 3H); ^{13}C NMR (δ) 164.2, 148.7, 141.9, 138.6, 135.7, 128.2, 127.7, 127.6, 127.5, 126.7, 126.7, 125.9, 122.2, 120.6, 62.8, 51.3, 50.5, 25.8, 24.8, 24.6, 18.2, −4.5; HRMS-ESI $[MNa]^+$ (m/z) for $C_{30}H_{35}NOSiNa$ calcd 476.2386; obsd 476.2382.

Requirement for Fluoride for Desilylation. It was observed that with all of the reactants present except for tetrabutylammonium fluoride no reaction occurred. Additionally, in the acetic acid, phenol, and triethylammonium chloride reactions, as the proton donor concentration was increased, the desilylation reaction slowed.

Kinetic Protonation Study. In a typical run with acetic acid as the proton donor, to the CH_3CN solution of *tert*-butyldimethylsilyloxy enol ether **24en** (0.022 M, 0.44 mL) was added 2.2 μL of acetic acid, followed by 19.4 μL of 1.0 M tetrabutylammonium floride in THF. The reaction mixture was stirred at room temperature for 4 h. Then, water−dichloromethane quenching and extraction afforded a mixture of the anti and syn benzoyl products (**26en** and **32en**, respectively) and the starting material **24en**. The mixture was analyzed by ^{1}H NMR to give the anti and syn benzoyl isomers ratio **26en/32en**.

In a typical run with HCl as the proton donor, to the CH_3CN solution of *tert*-butyldimethylsilyloxy enol ether **24en** (0.022 M, 0.44 mL) was added 4.8 μL of 4.0 M HCl. The reaction mixture was stirred at room temperature for 3 min. Then, water−dichloromethane quenching and extraction afforded a mixture of the anti and syn benzoyl products. The mixture was analyzed by ^{1}H NMR to give the anti and syn benzoyl isomers ratio **26en**/**32en**. The ratio of **26en**/**32en** did not change with longer reaction times (e.g., 15 min under the same reaction conditions).

The material from the kinetic runs was combined and subjected to silica gel chromatography using dichloromethane−hexane−ether (2:2:1) to afford **26en** and **32en** from the endo diastereomeric runs and **26ex** and **32ex** from the exo runs.

Spectral data for **32ex**: IR 1675.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.45 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H), 7.54−7.46 (td, J = 7.5, 2.0 Hz, 1H), 7.45−7.41 (dt, J = 7.5, 1.5 Hz, 1H), 7.40−7.25 (m, 6H), 7.10−7.05 (d, J = 8.0 Hz, 1H), 7.03−6.91 (m, 4H), 4.01 (s, 2H), 2.83 (s, 1H), 2.02−1.75 (m, 4H); ^{13}C NMR (δ) 198.9, 164.3, 149.2, 141.6, 137.5, 136.2, 132.0, 129.4, 127.9, 127.8, 127.5, 126.5, 121.2, 120.4, 119.5, 63.9, 58.7, 49.4, 25.8; HRMS-ESI [MNa]$^+$ (m/z) for $C_{24}H_{21}NONa$ calcd 362.1521; obsd 362.1515.

Spectral data for **32en**: IR 1679.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 8.02 (ddd, J = 4.5, 2.0, 1.0 Hz, 1H), 7.52−7.05 (m, 12H), 6.90 (ddd, J = 7.0, 4.5, 1.0 Hz, 1H), 4.05 (s, 2H), 2.94 (s, 1H), 2.01−1.79 (m, 4H); ^{13}C NMR (δ) 198.7, 163.2, 148.1, 144.3, 137.1, 135.7, 132.2, 128.5, 128.3, 128.1, 127.6, 126.7, 125.7, 124.7, 121.2, 64.4, 58.8, 49.5, 25.9; HRMS-ESI [MNa]$^+$ (m/z) for $C_{24}H_{21}NONa$ calcd 362.1521; obsd 362.1530.

Stability of 6-*exo*-Phenyl-6-*endo*-pyridin-2-yl-bicyclo-[2.1.1]hexane-5-benzoketone (32en). In a typical run, to 6-*exo*-phenyl-6-*endo*-pyridin-2-yl-bicyclo[2.1.1]hexane-5-benzoketone (**32en**) (15 mg, 0.044 mmol) dissolved in 2.0 mL of CH_3CN was added acetic acid (162.2 μL, 2.816 mmol), followed by 88.0 μL of tetrabutylammonium floride in THF (0.088 mmol, 1.0 M). The reaction mixture was stirred at room temperature, and small portions of this solution (0.3.0 mL) were taken with 2.0 mL of dichloromethane and 2.0 mL of water at the end of 1, 2, 4, and 50 h. The aqueous layer was extracted with dichloromethane (3 × 2 mL), and the combined extracts were washed with water (3 × 2 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was analyzed by ^{1}H NMR. There was no epimerization observed.

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Supporting Information Available: Kinetic data and X-ray data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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