Control of the Stereochemistry of Kinetic Protonation: Intramolecular Proton Delivery[1,2]

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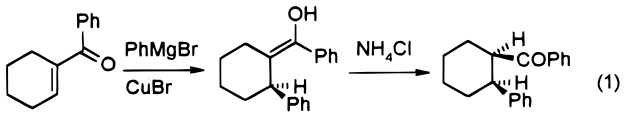
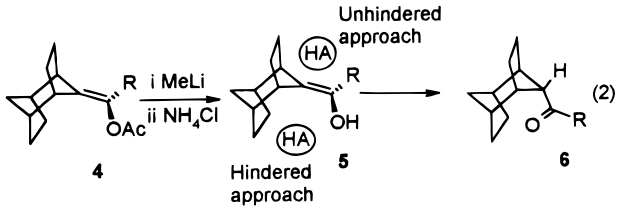
Four decades ago, we noted that for delocalized carbanions and enols the protonation transition state is close to sp^2 hybridized and that, as a consequence, under kinetic control protonation takes place from the less hindered approach, most often with formation of the less stable of two possible stereoisomers. The initial report was followed by an extensive series of examples. Nevertheless, a major question remained, namely whether it was possible to deliver the proton to the more hindered face of such a species using intramolecular proton transfer. To this end, silyl ether precursors to the enols of 3-benzoyl-*endo*-6-phenyl-*exo*-6-pyridylbicyclo[3.1.0]hexane and its *endo*-6-pyridyl-*exo*-6-phenyl stereoisomer were synthesized. The corresponding enols were generated with fluoride anion. The *endo*-phenyl enol stereoisomers, on kinetic protonation, led stereoselectively to the *endo*-3-benzoyl product resulting from the less hindered protonation. In stark contrast, the *endo*-6-pyridyl enol isomer led stereoselectively to the *exo*-3-benzoyl ketone by intramolecular proton delivery. However, the kinetic orders of the stereochemistries differ; the intramolecular process requires additional proton donor molecules. The log of the ratio of the two stereochemistries is linear with the log of the proton donor concentration with the slope giving the difference in kinetic orders. An aromatic cyclic 14 electron Hückel transition state is proposed. Additionally, the roles of acyl, nitro and cyano delocalizing groups were analyzed with ab initio computations.

Introduction

A very large number of organic reactions proceed by way of transient delocalized carbanions and enolic intermediates. Knowing the stereochemistry of protonation of these species then is tantamount to knowing the stereochemistry of the organic reactions. It was in 1955 that one of us suggested that the α-carbon in the transition state for ketonization of enols is close to sp^2 hybridized with the consequence that protonation occurs from the less hindered side of the enolate π-bond.[3] Most often, the less hindered approach of a proton donor leads to the less stable of two diastereomers. One example is depicted in eq 1.



Here the enolate of **2**, generated from the cuprate addition to benzoylcyclohexene **1**, was protonated with ammonium cation to give the less stable of two stereoisomers (i.e., **3**).[3] That the concept applies to other delocalized carbanions was also demonstrated.[4] A more recent example is outlined in eq 2.



In this case, the enolate of **5** is generated by reaction of methyllithium with enol acetate **4**. The less hindered approach of the proton donor, ammonium cation, leads to the less stable of two stereoisomers.[5] Spanning the four decades we have reported a rather large number of examples of the phenomenon.[3−16] This has included both enolates and other delocalized carbanions and a variety of reactions. Additionally, the literature has provided

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(1) (a) This is paper 252 of the general series. (b) For a preliminary report of the present study, see: Zimmerman, H. E.; Ignatchenko, A. *J. Am. Chem. Soc.* **1998**, *120*, 12992−12993.

(2) Paper 249, see Zimmerman, H. E. *J. Phys. Chem. A* **1998**, *102*, 5616−5621. For paper 250, see: Zimmerman, H. E.; Sebek, P.; Zhu, Z. *J. Am. Chem. Soc.* **1998**, *98*, 8549−8550.

(3) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557.

(4) Zimmerman, H. E.; Nevins, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559−6561.

(5) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *48*, 1637−1646.

(6) Zimmerman, H. E. *J. Amer. Chem. Soc.* **1956**, *78*, 1168−1173.

(7) (a) For sulfone-stabilized carbanions the protonation transition state has been shown to be closer to sp^3 hybridized. Zimmerman, H. E.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1960**, *82*, 2505−2511. (b) Zimmerman, H. E.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1958**, *80*, 3060−3064.

(8) Zimmerman, H. E.; Giallombardo, H. J. *J. Am. Chem. Soc.* **1956**, *78*, 6259−6263.

(9) Zimmerman, H. E. *J. Am. Chem. Soc.* **1957**, *79*, 6554−6558.

(10) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1958**, *80*, 2893−2896.

(11) Zimmerman, H. E.; Chang, W.-H. *J. Am. Chem. Soc.* **1959**, *81*, 3634−3643.

(12) Zimmerman, H. E.; Mais, A. *J. Am. Chem. Soc.* **1959**, *81*, 3644−3651.

(13) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1959**, *81*, 4305−4308.

(14) Zimmerman, H. E. Base-Catalyzed Rearrangements. In Molecular Rearrangements; DeMayo, P., Ed. Interscience: New York, 1963; Chapter 6, pp 345−406.

(15) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091−6096.

(16) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268.

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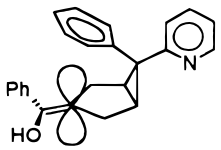
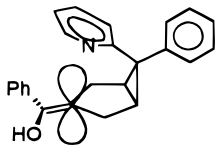
support for the concept,[17] and we have reviewed the literature as well.[16]

Thus, the phenomenon has been of consequence to synthetic organic chemistry while being of interest mechanistically as an example of kinetic control. With this background it was of interest to determine if the converse stereochemistry might be obtained by intramolecular delivery of the proton. For this study, the two enols **7-Exo** and **7-Endo**



7-exo



7-endo

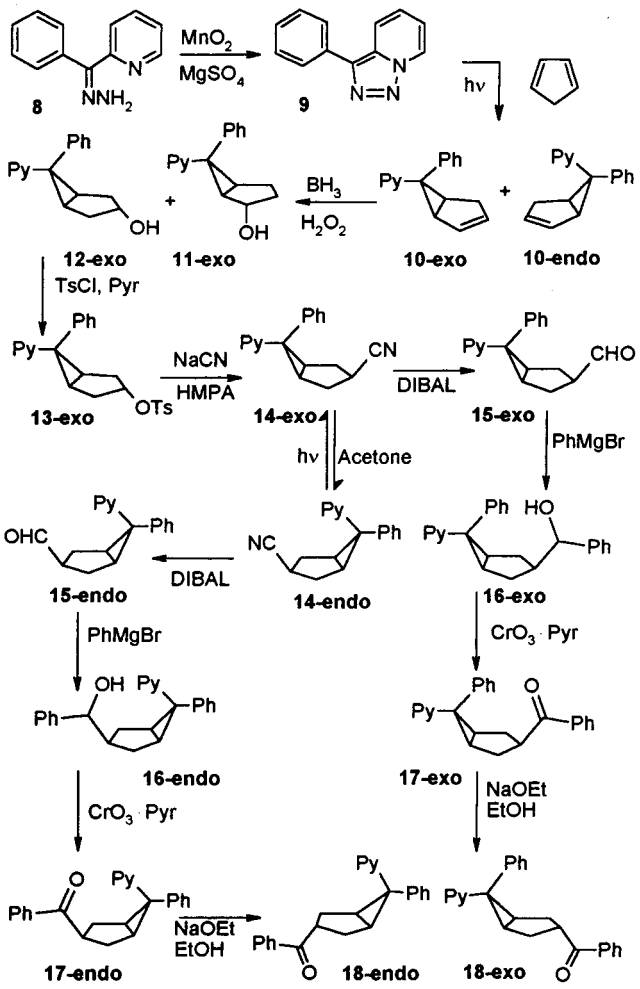
were selected with the idea that the endo pyridyl group in **7-Endo** might selectively deliver a proton to the hindered face of the enolic π-bond.

Results

The synthesis of the corresponding ketones and of precursors to the enols is illustrated in Scheme 1. In these synthetic efforts we encountered a number of intriguing results.

The initial step involved the addition of phenyl-2-pyridylcarbene[18] to cyclopentadiene with the objective of formation of the endo and exo stereoisomers of 6-(2-pyridyl)-6-phenylbicyclo[3.1.0]hex-2-ene. The carbene was generated photochemically from triazole **9**. It was observed that the *exo*-2-pyridyl-*endo*-phenyl stereoisomer (**10-Exo**) was formed stereoselectively with the *exo*-pyridyl to *endo*-pyridyl isomers being formed in a ratio of 4:1. The source of this selectivity is discussed below in the Interpretative Section. However, because the *endo*-pyridyl stereoisomers were formed in lesser quantities and yet were required for intramolecular proton-transfer experiments, a means of converting an *endo*-phenyl series compound to its *endo*-pyridyl counterpart was desired. This was found in the acetone sensitized equilibration of the endo and exo stereoisomers of 3-cyano-6-(2-pyridyl)-6-phenylbicyclo[3.1.0]hexane (i.e., **14-Endo** and **14-Exo**). Interestingly, again there was a preference for the *exo*-pyridyl stereoisomer, here in a 10:1 ratio. This point is also discussed below in the Interpretative Section.

Scheme 1. Synthesis of Ketones and Enol Precursors



The synthesis was designed to avoid several pitfalls. For example, the *endo*-3-cyano reactants, **14-Exo** and **14-Endo**, were converted to the corresponding benzoyl ketones **17-Exo** and **17-Endo** by first converting these to the corresponding aldehydes **15-Exo** and **15-Endo**, conversion to the alcohols **16-Exo** and **16-Endo** and, thence, to the desired ketones **17-Exo** and **17-Endo**. While this seems to be an indirect route, the direct conversion of the nitriles to the desired ketones proceeded with extensive epimerization of the cyano and keto groups. When this epimerization was desired, it was accomplished with sodium ethoxide to afford the *exo*-ketones **18-Endo** and **18-Exo**.

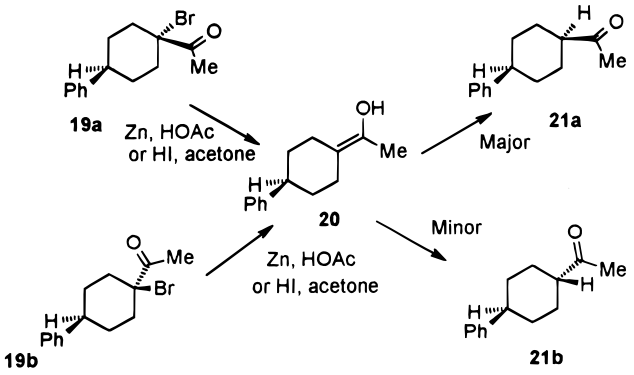
Although the mode of synthesis, the spectral data, and the equilibration of the *endo*-benzoyl (**17-Endo** and **17-Exo**) to *exo*-benzoyl (**18-Endo** and **18-Exo**) ketones, respectively, provided evidence for the validity of the stereochemical assignments; nevertheless, X-ray structures were obtained for a strategically selected series of compounds, namely **10-Exo**, **12-Exo**,**14-Endo**, **14-Exo**,**17-Endo**, **18-Exo**, and **22-Exo**.

One mode of enol generation used in our past research was the treatment of α-bromoketones with dilute hydriodic acid in acetone.[3,5,6,8,10,11] That this proceeds via the enol to give the corresponding debrominated ketone was noted to be clear from consideration of microscopic reversibility. The reaction of a ketone with a halogen is well known to proceed via an enolic intermediate to afford

(17) (a) Adam, W.; Nava-Salgado, V. O. *J. Org. Chem.* **1995**, *60*, 578−584. (b) Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713−1719. (c) Hirai, H.; Sawada, K.; Aratani, M.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 1739−1742. (d) Kametani, T.; Tsubuki, M.; Higurashi, K.; Honda, T. *J. Org. Chem.* **1986**, *51*, 2932−2939. (e) Williams, T. W.; Crumbie, R.; Mosher, H. S. *J. Org. Chem.* **1985**, *50*, 91−97. (f) Fleming, I.; Lewis, J. *J. Chem. Soc., Chem. Commun.* **1985**, 149−151. (g) Grieco, P. A.; Majetich, G. F.; Ohfune, Y. *J. Am. Chem. Soc.* **1981**, *104*, 4226−4233. (h) Gillissen, H. M. J.; Buck, H. M. *J. Org. Chem.* **1982**, *47*, 5214−5132. (i) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1764−1765. (j) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739−8856. (k) Knölker, H.-J.; Ecker, A.; Struwe, P.; Steinmeyer, A.; Müller, G.; Neef, G. *Tetrahedron* **1997**, *53*, 91−108. (l) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett* **1993**, 461−462. (m) Tamura, R.; Watanabe, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895−4899. (n) Rehders, F.; Hoppe, D. *Synthesis* **1992**, 859−861.

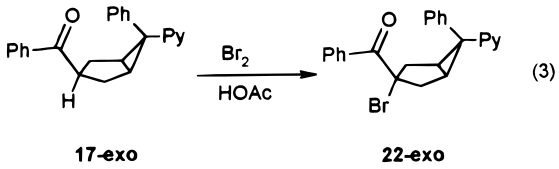
(18) (a) Cf. the extensive work of Wentrup on pyridyl-substituted carbenes with evidence for a tautomeric relationship between 2-pyridylcarbenes and the isomeric triazopyridines: Wentrup, C. *Helv. Chim. Acta* **1978**, *61*, 1755−1763. (b) Mayor, C.; Wentrup, C. *J. Am. Chem. Soc.* **1975**, *97*, 7467−7480.

Scheme 2. Hydriodic Acid Debromination as a Mode of Enol Generation



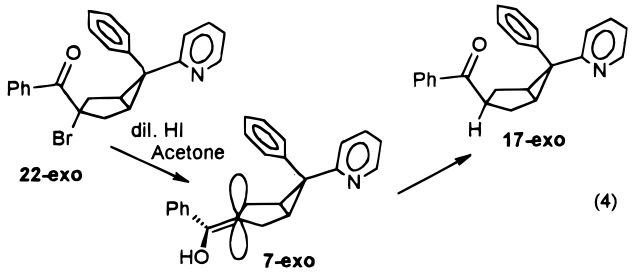
a haloketone and hydrogen halide. The present reaction with HI and bromoketone, in leading to dehalogenated product plus iodine, is mechanistically the microscopic reverse, except that here the use of iodine has reversed the thermodynamics in favor of ketone and halogen. One example[9] is shown in Scheme 2. Here it has been shown that the same product distribution resulted from enol generation from either of the two stereoisomeric β-bromoketones **19a** and **19b** and that the enol **20** protonated stereoselectively to afford the less stable, cis isomer **21a** with **21b** being minor.

In the present study, bromination of *exo*-pyridyl ketone **17-Exo** proceeded smoothly to afford the corresponding bromoketone **22-Exo**. Note eq 3.



(3)

Treatment with dilute hydriodic acid in acetone, mildly acidic enough so that the debrominated ketones were unequilibrated, led cleanly to 3-*endo*-benzoyl-6-*endo*-phenyl-6-*exo*-pyridylbicyclo[3.1.0]hexane (**17-Exo**), the product of protonation from the less hindered side of the exocyclic enolic π-bond. Note eq 4.



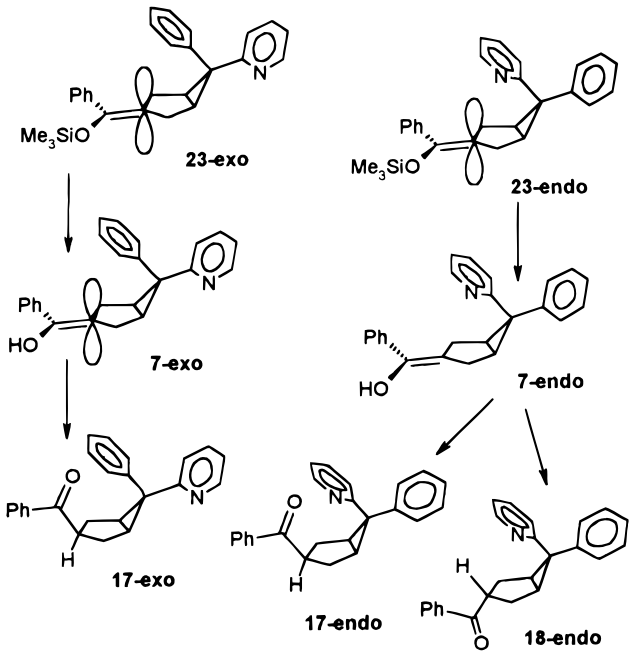
(4)

In contrast, attempted bromination of the *endo*-pyridyl ketone **17-Endo** did not afford the desired α-bromoketone in appreciable yield, and the chemistry of this isomer was not pursued.

More practical enol precursors were found to be the silyl enol ethers **23-Exo** and **23-Endo** of enols **7-Exo** and **7-Endo**. The enols were generated smoothly on treatment[19] with tetrabutylammonium fluoride. In the case

(19) (a) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181−187. (b) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257−3258.

Scheme 3. Enol Generation from the Silyl Enol Ethers With Fluoride

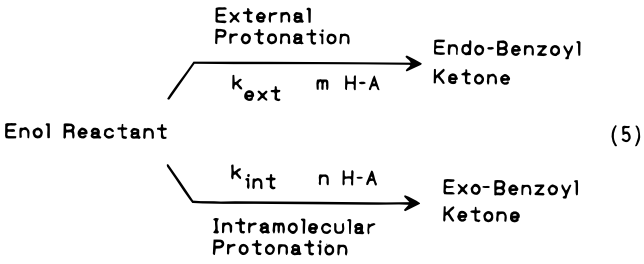


of the *endo*-phenyl stereoisomer (**23-Exo**), only one protonation product was formed, namely **17-Exo**. Runs were made with tetrabutylammonium fluoride in THF with ammonium chloride as the proton donor in one case and acetic acid in the other. We note that protonation in both cases results from the less hindered approach to the α-carbon of the enol. Details are given in Table 1 of the Supporting Information. Also note Scheme 3.

However, kinetic protonation in the *endo*-pyridyl system led to results that were dependent on choice and concentration of proton donor. Thus, treatment of the *endo*-pyridylsilyl enol ether **23-Endo** with tetrabutylammonium fluoride and ammonium chloride in THF led to the same preference for intermolecular protonation observed with the *exo*-pyridyl stereoisomer **23-Exo**. In contrast, under conditions used with the *exo*-pyridyl stereoisomer (8.6%, 1.44 M acetic acid in THF), protonation of the α-carbon of the *endo*-pyridyl isomer **23-Endo** occurred preferentially from the more hindered approach to afford benzoyl ketone **18-Endo**; the ratio of intramolecular to intermolecular protonation (i.e., **18-Endo/17-endo**) was 97.0:3.0 as determined by quantitative HPLC analysis. Isolation and NMR analysis confirmed the identities of the protonation products. Formic acid in THF led, again, to a similar stereoisomer ratio favoring intramolecular protonation and formation of **18-Endo**. However, with decreasing concentrations of acetic acid, the preference for endo protonation slowly diminished until with 1.86% (0.31 M) acetic acid in THF a ratio of 4:1 endo/exo protonation resulted, and with 0.5% (0.08 M) acetic acid a ratio of 1:2.4 resulted with exo protonation now being preferred. A similar trend was encountered in solvents DMSO and isopropanol as well as with formic acid in THF.

An important point is that control runs established that the rate of equilibration of the *endo*-benzoyl (**17**) to *exo*-benzoyl (**18**) stereoisomers was very slow and not observed appreciably under conditions of enol ketonization. Thus, the stereochemical results reported above are, indeed, kinetic.

If we consider the partition between the two stereochemical ketonization processes shown in eq 5, we can see that the ratio of rates of formation of the two ketones of the *endo*-pyridyl series, *exo*-benzoyl ketone **18** and *endo*-benzoyl ketone **17**, should be independent of (e.g.) acetic acid concentration if both of the processes are same order in the acid. For formation of the *exo*-benzoyl ketone (i.e., **18**), the intramolecular protonation



product, to be enhanced by increasing acid concentration, this reaction must be of higher kinetic order in the acid.

"Differential plots" were employed to check this conclusion. Equations 6a,b give the rates of formation of the two stereoisomeric ketonization products as v_{ext} for the external protonation (order m) and v_{int} for the higher order (n) intramolecular ketonization; k_{ext} and k_{int} are the corresponding rate constants. In eq 7, P_{int} and P_{ext} represent the amounts of the two stereoisomers at any given time, and P_{int}/P_{ext} gives the product ratio during the ketonization reaction. Integration to complete reaction affords, in logarithmic form, eq 8b. This reveals that a plot of the log of the ratio of stereoisomers obtained in several runs against the log of the proton donor (H−A) concentration should afford a slope $n - m$, which is the difference in H−A reaction orders for the two stereoisomeric protonation processes, intramolecular and intermolecular. A slope of zero would signify the same dependence on proton donor concentration for internal and external protonations, while a positive slope signifies a greater order for intramolecular protonation as has been suggested above. The differential plots are given in Figure 1. The similarity of the acetic and formic acid runs in THF is of interest, and Figure 1e plots these together.

$$v_{ext} = dP_{ext}/dt = k_{ext}[H-A]^m[Enol] \quad (6a)$$

$$v_{int} = dP_{int}/dt = k_{int}[H-A]^n[Enol] \quad (6b)$$

$$dP_{int}/dP_{ext} = (k_{int}/k_{ext})[H-A]^{n-m} \quad (7)$$

$$P_{int}/P_{ext} = (k_{int}/k_{ext})[H-A]^{n-m} \quad (8a)$$

$$\log(P_{int}/P_{ext}) = (n - m)\log[H-A] + \log(k_{int}/k_{ext}) \quad (8b)$$

The average slope for THF runs (Figure 1a−d) is 1.17, while in DMSO (Figure 1d) the slope is 2.1. If either stereochemistry were a mixture of two kinetic orders, there would not be the observed linearity. Also, the intercepts of the plots of Figure 1 give, in principle, the ratio of rate constants (k_{int}/k_{ext}). Excluding DMSO, these intercepts were in the range of 0.93−1.17 corresponding to a rate ratio of 10. The slope in three of the solvents gives a difference ($n - m$) of unity. If external protonation is a simple process and first order in proton donor, then the external protonation in the three solvents is second order.

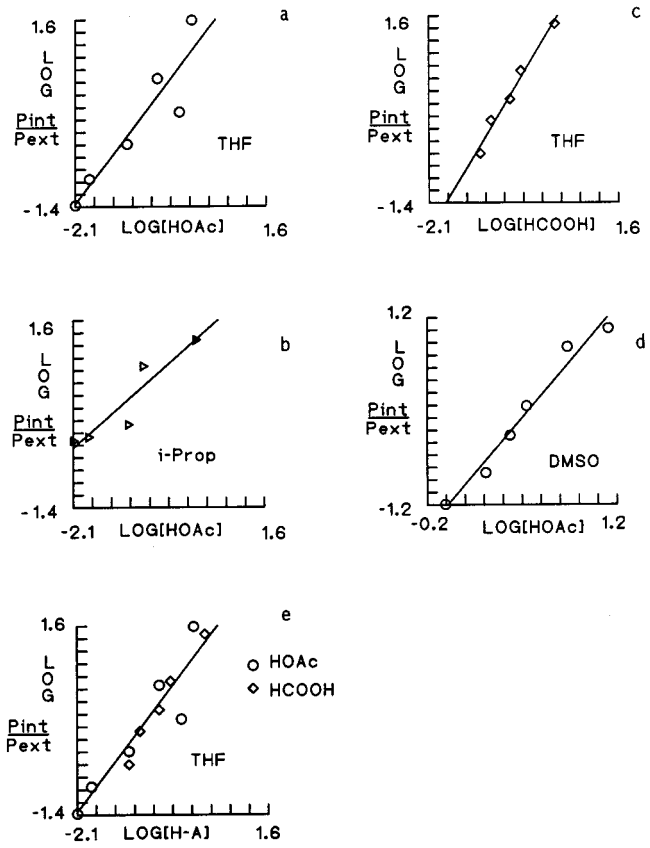


Figure 1. Differential plots: (a) acetic acid−THF; (b) acetic acid−isopropyl alcohol; (c) formic acid−THF; (d) acetic acid−DMSO; (e) acetic and formic acids in THF. Note: The intercepts are calculated for an abscissa of zero.

The experimental details of the kinetics are given in the Supporting Information (note Table 1). Also note the Experimental Section for further details on the stereochemistry and kinetic runs including control experiments.

Computational Results

Finally, it seemed worthwhile to ascertain the extent and nature of electron delocalization in enolates, nitronates, and cyano-stabilized carbanions. For this, we used Gaussian94 and Gaussian98[20a] along with Weinhold NBO Analysis[20b] applied to nine systems—three enolates (**24**, **27**, and **30**), three nitronates (**25**, **28**, and **31**), and three cyano-stabilized carbanions (**26**, **29**, and **32**); see Figure 2. The salient features of these computations are given in Table 1, which includes the α-carbon electron density, the electron density on the heteroatoms in each case, the deformation angle at the α-carbon, and the molecular energy.[21] The deformation angle is defined in

(20) (a) Gaussian 94, Revision D, and Gaussian 98, Revision A.6: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, C.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challocombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998. (b) Reed, A.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.

Table 1. Some Salient Feature of the Geometry-Optimized Delocalized Systems

molecule	α-carbon density	heterodensity	deformation angle (deg)	B3LYP energy[a,b]
enolate **24**	1.4442	1.6327	179.4755	−153.2072
nitronate **25**	1.4557	1.6501[c]	180.0000	−244.4060
cyano anion **26**	1.6893	1.3635	141.9151	−132.1225
dimethyl enolate **27**	1.3431	1.6323	179.0648	−231.8476
dimethyl nitronate **28**	1.2430	1.7158[c]	179.9315	−323.0464
dimethyl nitrile **29**	1.4917	1.4105	178.9583	−210.7549
cyclohexyl enolate **30**	1.3430	1.6334	177.2824	−348.5882
cyclohexyl nitronate **31**	1.3527	1.6470[c]	179.9287	−439.7861
cyclohexyl nitrile **32**	1.5312	1.3708	164.6802	−327.4971

[a] 6-31G* basis. [b] Hartrees. [c] For each oxygen.

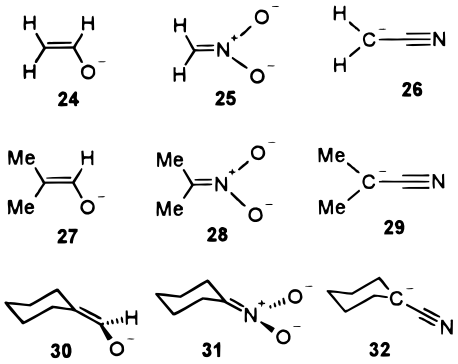


Figure 2. Six-electron delocalized systems.

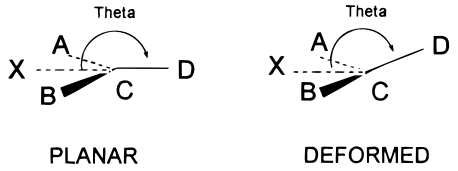


Figure 3. Deformation angle θ. D is the delocalizing group. X is a "ghost atom" (see text).

Figure 3, where atom D is a delocalizing group (acyl, nitro, or cyano), A and B are substituents (H, Me, or methylene), and X is a "ghost atom", placed in the A−B−C plane midway between A and B. This permits simple evaluation of the deformation angle θ.

Also, it seemed important to determine the energetic consequences of deforming the delocalizing group in the unsubstituted molecules **24**, **25**, and **26**. For a 40° deformation from planarity, the enolate energy rose 2.57 kcal/mol, the nitro energy rose 1.50 kcal/mol, while the cyano-substituted anion rose only 0.6 kcal/mol when forced into planarity.

Discussion

There are several points to be discussed, namely (a) the stereochemistry of kinetic protonation of the *endo*-phenyl enol, (b) the stereochemistry of protonation of the *endo*-pyridyl enol, (c) the preferential formation of the *exo*-pyridyl bicyclic in the cyclopentadiene−carbene cycloaddition, (d) the triplet steady-state equilibration of the *endo*- and *exo*-pyridyl bicyclics favoring the *exo*-pyridyl stereoisomer, and (e) the computational results.

First, ketonization of the *endo*-phenyl enol **7-Exo** to give the less stable *endo*-benzoyl stereoisomeric ketone **17-Exo** showed complete stereoselectivity within HPLC experimental error; this corresponds to a selectivity of over 1000:1. Inspection of molecular models shows the endo lobe of the α-carbon p-orbital to be severely blocked by the C-6 *endo*-phenyl group. The stereoselectivity seems to be of the same order as that observed for the tricyclic system **5** we studied earlier.[5] Control by steric accessibility to the α-carbon is a phenomenon we originally reported in 1955. The theory depends on the protonation transition state being an early one with the α-carbon still being close to sp^2 hybridized. Not only ketone enolates and enols are subject to this control but other delocalized species such aci-nitro anions.[4,15] The principle has been discussed, and many examples have been given in a long series of our articles[3−16] including a reasonably comprehensive review.[16] Still, the literature contains examples where the mechanistic basis for preferential formation of less stable protonation products has not been recognized.

Nevertheless, there is a second factor to be considered, a stereoelectronic one. In very early work, Corey[22] has noted that for cases where the C−H bond of the protonated product may or may not overlap with the product carbonyl π-system, there is an energetic preference for that stereochemistry in which the developing α C−H bond remains in conjugation with the carbonyl group. Typical examples are found in endocyclic six-membered ring enols where there is a preference for axial protonation.[22,23] More recently, an interesting case has been reported by Stork.[24]

Overlap is not a factor in the case of exocyclic enols, since with either approach there is usually continued overlap between the α-carbon p-orbital and the carbonyl group as the molecule proceeds to ketone product. Nevertheless, the relative energetic importance of the two controlling factors is one we are presently studying.

We turn now to the second, and perhaps more novel, result of interest, namely the stereochemistry of protonation of the *endo*-pyridyl enol. With a weakly acidic proton donor such as ammonium, the normal external proton attack from the less hindered side of the π-system is observed. With the ca. 10 pK_a of ammonium and the ca. 5 pK_a of pyridinium (aqueous values), proton transfer from ammonium to the pyridyl nitrogen is quite energeti-

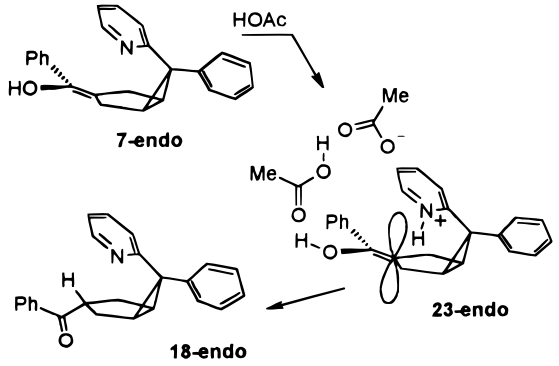
(21) (a) Extensive and very pretty computations have been carried out by Wiberg on carbanions with and without delocalizing groups.[21b] At the time of computation we were unaware of these. However, it is of interest to compare the results, where comparable systems are considered. These are qualitatively similar despite different computational methods and basis orbitals. (b) Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327−6334.

(22) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269−6278.

(23) For example, see: Shea, K. J.; Wada, E. *J. Am. Chem. Soc.* **1982**, *104*, 5715−5729.

(24) Stork, G. E.; Manabe, K.; Longbin, L. *J. Am. Chem. Soc.* **1998**, *120*, 1337−1338.

Scheme 4. Mechanism for Protonation of the *endo*-Pyridyl Enol



cally unfavorable and uninvolved. Thus, the preferred stereochemistry is the same as that in the *endo*-phenyl case.

However, with acetic acid present (pK_a 4.7), one anticipates the presence of the protonated *endo*-pyridyl moiety. Molecular modeling shows that the *endo*-pyridyl proton may approach within 1.6 Å of the α-carbon and thus transfer the proton intramolecularly.

We must take into account the observation of pyridine−acetic acid clusters[25] as well as the finding that equilibration of such clusters is a rapid process as noted from NMR.[26] But, ketonization of enols is slow by comparison.[27] Hence, we can conclude from the linearity of the kinetic plots either that any clustering is constant as the proton donor concentration is varied or, more simply, that acid molecules bound in clusters to the pyridyl groups are released prior to transition state formation.

One initially puzzling point was the mechanistic source of the difference in the internal and external protonation processes. We see from the kinetics that the *endo*-pyridyl enol **7-Endo** utilizes one more (e.g.) acetic acid molecule than the *exo*-pyridyl enol **7-Exo**. While the role of the acetic acid is subject to some conjecture, we do know that enolates protonate more rapidly than their enol conjugate acids[28] just as nitronates protonate more rapidly than their aci-nitro conjugate acids.[4,15]

A reasonable possibility is depicted in Scheme 4 where the role of the second acetic acid molecule is to hydrogen bond to the acetate of the ion pair with migration of the negative charge from acetate to this second acetic acid and thus provide a species able to convert the enol to enolate. In contrast, the *exo*-pyridyl isomer has geometry not permitting such a mechanism, and with ammonium cation as the proton source, neither isomer can partake of this process.

A final point of interest is that the cyclic transition state is an aromatic one with 14 delocalized electrons and no enforced orbital phase inversions.[29]

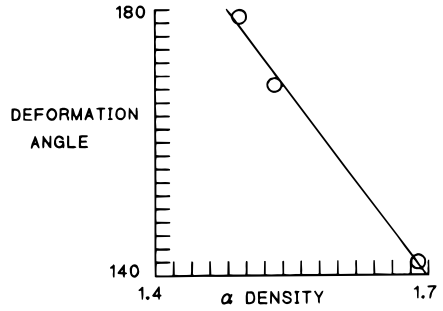


Figure 4. Geometry vs delocalization for the cyano-stabilized anions.

Relevance of the Computational Aspects

The different geometries of the cyano-substituted anions from those of the enolates and nitronates were intriguing in view of the similarity of the stereochemistry of kinetic protonation in all three cases (vide infra). Further, the planarity of the dimethyl cyano methide **29** contrasts with the partial pyramidalization of the simplest cyano member **26** and the cyanocyclohexyl anion **32**.

Three effects are involved in delocalized carbanions. Delocalization favors planarity as does relief of steric interactions incurred on pyramidalization. But with weak delocalization, maximizing s-weighting of the electron pair trends towards sp^3 hybridization with resulting loss of planarity. All three systems—enolate, nitronate, and cyano anion—reveal shallow minima and small energy changes on deformation. In the case of the enolates and nitronates, planarization dominates. The balance of effects is closer in the cyano anion situation with only 0.6 kcal/mol separating the deformed and planar conformations. Figure 4 shows the weak dependence of delocalization on the deformation angle for the parent cyano anion case. Slight pyramidalization dominates for two of the three cyano anions. However, steric repulsive forces in the dimethyl cyanomethide anion lead to the observed planarization. Van der Waals forces along with the electronic preference lead to the cyclohexyl cyanomethide anion being slightly deformed from planarity. Nevertheless, the approach to planarity accounts for kinetic protonation occurring from the less hindered side of the π anionic system as experimentally observed.[31] Hence, for all systems—enolate, nitronate, and cyano—kinetic protonation is similar.

Additional Aspects

One interesting aspect of the present study is not related to the stereochemistry of protonation but, instead, derives from two steps of the synthesis as noted in the Results.

Thus, in the initial reaction of phenyl pyridyl carbene there was a preference for formation of the *exo*-pyridyl (**10-Exo**) relative to the *endo*-pyridyl (**10-Endo**) stereo-

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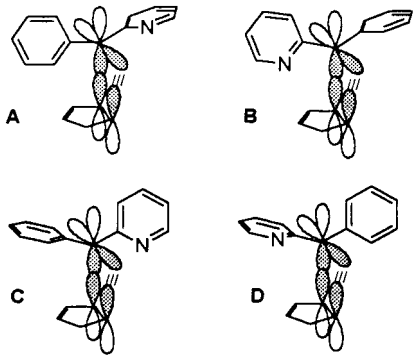
(30) (a) Takano, S. *Chem. Lett.* **1982**, 733−736. (b) Takano, S.; Kudo, J.; Takahashi, M.; Ogasawara, K. *Tetrahedron Lett.* **1986**, 2405−2408. (c) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogaswara, K. *Chem. Lett.* **1982**, 733−736. (d) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, 5567−5569. (e) Takano, S.; Yamada, S.; Numata, H.; Hatakeyama, S.; Ogasawara, K. *Heterocycles* **1983**, *20*, 2159−2162. (f) Takano, S.; Tanaka, M.; Seo, M.; Hirama, M.; Ogasawara, K. *J. Org. Chem.* **1985**, *50*, 931−936.
(31) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205−1215. Note also ref 30.

Scheme 5. Four Species in the Addition of Phenyl Pyridyl Carbene to Cyclopentadiene



isomer. Similarly, in the acetone-sensitized equilibration of the cyano-bicyclics **14-Exo** and **14-Endo** the steady-state ratio favored the former (i.e., **14-Exo**). While this was a synthetic impediment it proved to be theoretically interesting. Thus, Scheme 5 depicts the addition of the pyridyl phenyl carbene to the cyclopentadiene ring with four of the most reasonable alternative stereochemical geometries. These pictures show one σ bond forming more rapidly than the other as would result from a triplet addition. This must be followed, or accompanied, by intersystem crossing to give S_o to permit the final three-membered ring to form. Each aromatic ring is either close to perpendicular to the five ring or twisted 90° from this. Species **A** and **B** exhibit severe steric interactions between the perpendicular *endo*-aryl group and the five-membered ring and seem unlikely to be utilized. In comparing species **C** and **D**, we note that the electron-rich nonbonded benzylic orbital in **D** is orthogonal to the *endo*-pyridyl ring while in **C** it overlaps with the *exo*-pyridyl π-system. Since delocalization by a pyridyl ring is more effective than ordinary benzylic resonance, we conclude that species **C** is preferred, which is in accord with the preferential formation of the *exo*-pyridyl stereoisomer. Also, having the odd electron delocalized into the pyridyl ring should enhance the spin-orbit coupling required for three-membered ring closure.

In the case of the photochemical triplet equilibration of the cyano-bicyclics **14-Exo** and **14-Endo** we are dealing with a steady state. Either (i) sensitized triplet energy transfer to the *endo*-pyridyl isomer is more efficient than to the *exo*-pyridyl counterpart, (ii) the triplet of the **14-Endo** stereoisomer undergoes three-ring opening more readily than the **14-Exo** counterpart, (iii) the open triplet diradical intersystem crosses to S_o and closes more rapidly with the pyridyl in the exo conformation, or (iv) some of all of the preceding are factors.

Conclusion

The stereochemistry of kinetic protonation of enols, enolates, and other delocalized species has been an area of special interest and value. The number of reactions proceeding by way of these transient species is quite large, and hence, an understanding of the stereochemistry of this mechanistic step permits one to understand the stereochemistry of the overall reactions. Curiously, in 1956, our initial suggestion of this phenomenon of the near-planar delocalized species preferentially giving rise to the less stable of two stereoisomers by the less hindered protonation was not immediately accepted, and yet in view of the utility in obtaining desired stereochemistry it is not surprising that the concept has been rediscovered[30−32] several times and that many recent publications cite only the rediscoveries. However, now the concept is accepted but its source sometimes goes unrecognized.

Experimental Section

General Procedures. All reactions were performed under an atmosphere of dry nitrogen. Column chromatography was performed on silica gel (Matheson, Coleman and Bell, grade 62, 60-200 mesh) mixed with Sylvania 2282 phosphor and slurry packed into quartz columns to allow monitoring with a hand-held UV lamp. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent and are reported in ppm downfield from tetramethylsilane. Solvents were dried following standard methods.

General Procedure for X-ray Crystallography Analysis. X-ray diffraction data were collected on a Siemens P4/CCD diffractometer for single crystals of each compound. Lorentz and polarization corrections were applied, and each structure was solved under the appropriate space group symmetry by direct methods using Shelx86 or SHELXTL.[33] Hydrogen atom positions were calculated and refined with a rigid model. Full-matrix least-square refinement on F^2 was carried out employing anisotropic displacement parameters for all non-hydrogen atoms and isotropic displacement parameters for all hydrogen atoms. The coordinates for all compounds studied by X-ray crystallography were deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

2-Benzoylpyridine. A modified procedure of Glover and Jones was used.[34] From 2-cyanopyridine (20.8 g, 0.20 mol) there was obtained 28.9 g (79%) of product. An analytical sample distilled under vacuum (bp 145−146 °C at 3 mmHg) (lit.[34] bp 107 °C/0.1 mmHg).

2-Benzoylpyridine Hydrazone. This was prepared by a modification of the method of Boyer, Borgers, and Wolford.[35] From 18.3 g (0.1 mol) of 2-benzoylpyridine there was obtained 15.26 g (78%) of colorless needles of the hydrazone, mp 96−104 °C. An analytical sample was distilled: bp 160−170 °C/0.35 mmHg; mp 108−110 °C from EtOAc (lit.[35] mp 106−108 °C).

4-Phenyl[1,2,3]triazolo[1,5-*a*]pyridine. Starting with 7.63 g (38.7 mmol) of 2-benzoylpyridine hydrazone, 5.66 g (75%) of pure product was obtained as colorless prisms: mp 111−112 °C (lit.[35] mp 113−115 °C).

Irradiation of 4-Phenyl[1,2,3ltriazolo[1,5-*a*]pyridine. In a typical run, 2.00 g (9.95 mmol) of the triazole in 350 mL of cyclopentadiene was photolyzed in an immersion well apparatus with a 0.25 N copper sulfate filter using a 400 W lamp for 16 h. The solution was concentrated in vacuo, removing excess cyclopentadiene and dicyclopentadiene. The dark oily residue was chromatographed on a 4.5 × 50 cm silica gel column with hexane−ethyl acetate gradient elution to yield

(32) (a) Relatively recently, the phenomenon has been reported anew[32b] with the same comment that countless syntheses proceed via formal carbanions as enolates which in the final step are protonated to give less stable isomers. The mechanistic analysis followed that in our publications. But it was stated that there had been hardly any systematic study of the stereochemistry of protonation. No reference was made to the earlier studies except for listing of our review. (b) Hünig, S. In *Houben-Weyl, Methods of Organic Chemistry, Protonation of Carbanions and Polar Double Bonds*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme Verlag: Stuttgart, 1996; Vol. E21D 7, pp 3851−3911.

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four main fractions: (1) 6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo-[3.1.0]hex-2-ene **10-Exo** as colorless prisms: 0.67 g (28%); mp 96−97 °C (from hexane−ether); TLC R_f 0.85 (hexane−ethyl acetate 10:1); ^{1}H NMR δ 2.08 (dq, J = 18.0, 2.4 Hz, 1H), 2.61 (sym m, 1H), 2.65−2.82 (br m, 2H), 5.14 (sym m, 1H), 5.77 (sym m, 1H), 6.52 (dt, J = 8.1, 0.9 Hz, 1H), 6.87 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.09−7.28 (br m, 6 H), 8.41 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR δ 33.5, 34.7, 40.5, 42.7, 119.9, 122.1, 126.4, 128.0, 131.3, 132.0, 133.3, 136.5, 148.7, 164.4. Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.71; H, 6.59; N, 5.96. This structure was also confirmed by X-ray analysis.

(2) 6-*endo*-(Pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hex-2-ene (**10-Endo**) as a yellow oil: 0.17 g (7%); TLC R_f 0.50 (hexane−ethyl acetate 10:1); ^{1}H NMR δ 2.38 (m, 2H), 2.65 (m, 2H), 5.12 (sym m, 1H), 5.82 (dt, J = 7.6, 2.1 Hz, 1H), 6.98−7.19 (m, 7H), 7.49 (dt, J = 7.7, 1.9 Hz, 1H), 8.48 (ddd, J = 4.9, 0.8 Hz, 1H); HRMS m/z (M^+) calcd for $C_{17}H_{15}N$ 233.1204, obsd 233.1180.

(3) 1,2-Di(pyridyl-2)-1,2-diphenylethane as colorless crystals: 0.40 g (24%); mp 242−244 °C (lit.[36] mp 242−244 °C); TLC R_f 0.30 (hexane−ethyl acetate 10:1). The NMR spectrum is in agreement with the literature data.[36]

(4) The fourth fraction was 0.37 g (19%) of the starting 4-phenyl[1.2.3]triazolo[1,5-*a*]pyridine: TLC R_f 0.20 (hexane−ethyl acetate 10:1).

Hydroboration of 6-*exo*-(Pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hex-2-ene (10-Exo). To a solution of 4.66 g (20 mmol) of 6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hex-2-ene in 40 mL of dry tetrahydrofuran at 0 °C was added 10 mL of diborane (1 M in THF, 10 mmol). The mixture was stirred at 0 °C for 1 h and then for 6 h under reflux. After the mixture was cooled to −10 °C, 800 mg (20 mmol) of sodium hydroxide solution in 10 mL of water, and then 6.0 mL of 30% hydrogen peroxide (60 mmol) was added slowly with stirring. After being stirred for 2 h at rt, the mixture was poured into 100 mL of saturated ammonium chloride solution and methylene chloride extracted (5 × 30 mL), and the combined organic layers were washed with saturated sodium sulfate solution, dried over sodium sulfate, and concentrated. The residue was chromatographed on a 4.5 × 50 silica gel column with hexane−ethyl acetate gradient elution to give two isomeric alcohols: (1) 3-*exo*-hydroxy-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]-hexane (**12-Exo**) as large colorless needles: 2.91 g (58%); mp 124−125 °C (from ethyl acetate); TLC R_f 0.20 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 1.86 (br s, 1H), 1.93 (sym m, 2H), 2.25 (dd, J = 13.8, 7.5 Hz, 2H), 2.38 (dd, J = 3.7, 1.5 Hz, 2H), 2.86 (quintet, J = 7.2 Hz, 1H), 6.58 (dt, J = 8.1 Hz, 1.1), 6.95 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.25−7.45 (m, 6H), 8.44 (ddd, J = 4.8, 1.8 0.9 Hz, 1H); ^{13}C NMR DEPT-135 δ 33.9 (CH), 36.7 (CH_2), 38.0 (−C−), 72.1 (COH), 119.9 (CH), 121.7 (CH), 127.0 (CH), 129.0 (CH), 131.4 (CH), 135.5 (CH), 137.6 (−C−, Ph), 148.6 (CH, Pyr), 164.2 (−C−, Pyr); HRMS m/z (M^+) Calcd for $C_{17}H_{17}NO$ 251.1310, obsd 251.1301. Anal. Calcd for $C_{17}H_{17}$-NO: C, 81.23; H, 6.82; N, 5.58. Found: C, 81.22; H, 6.86; N, 5.48. The structure was confirmed by X-ray. (2) 2-*exo*-hydroxy-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (**11-Exo**) as colorless microcrystals: 1.86 g (37%); mp 116−119 °C; TLC R_f 0.15 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 0.36−0.49 (m, 1H), 1.40 (dd, J = 14.7, 9.9 Hz, 1H), 1.80 (dd, J = 13.6, 8.8 Hz, 1H), 2.12−2.31 (m, 1H), 2.46−2.55 (m, 2H), 4.30 (d, J = 5.1 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 6.96−7.00 (m, 1H), 7.27−7.41 (m, 6H), 8.47−8.48 (m, 1H); ^{13}C NMR: 24.8, 33.6, 35.2, 38.2, 42.8, 74.7, 120.1, 121.9, 127.0, 128.9, 130.7, 135.6, 137.6, 148.7, 163.9; HRMS m/z (M^+) calcd for $C_{17}H_{17}NO$ 251.1310, obsd 251.1301.

3-*exo*-(*p*-Toluenesulfonoxy)-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (13-Exo). 3-*exo*-Hydroxy-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (4.43 g, 17.6 mmol) was dissolved in 25 mL of dry pyridine, and 5.05 g (26.5 mmol) of tosyl chloride was added while the pyridine solution was stirred in an ice bath. After being stirred for 4 h, the solution was placed in a refrigerator for 16 h. The pyridine solution was slowly poured into a stirring solution prepared from 12 mL of 12 M HCl and 40 g of crushed ice. The resulted mixture was filtered, and the solid was dried and crystallized from ethyl acetate to yield 6.16 g of colorless plates (86%): mp 167−169 °C; TLC R_f 0.60 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.14 (m, 4H), 2.39 (t, J = 1.2 Hz, 2H), 2.45 (s, 3H), 3.16 (quintet, J = 7.6 Hz, 1H), 6.55 (dt, J = 8.1, 1.1 Hz, 1H), 6.96 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H), 7.01−7.71 (m, 10H), 8.44 (ddd, J = 4.7, 2.0, 0.9 Hz, 1H). Anal. Calcd for $C_{24}H_{23}NO_3S$: C, 71.08; H, 5.72; N, 3.45. Found: C, 71.40; H, 5.93; N, 3.40.

3-*endo*-Cyano-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo-[3.1.0]hexane (14-Exo). To a stirred suspension of sodium cyanide (1.10 g, 22.5 mmol) in 20 mL of HMPA was added 3.04 g (7.5 mmol) of 3-*exo*-(p-toluenesulfonoxy)-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane. The reaction mixture was stirred at 70 °C for 4 days and poured into 25 mL of water. The solid was filtered, air dried, and chromatographed on silica gel using hexane−ethyl acetate gradient elution to give 0.31 g (16%) of 6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hex-2-ene, 0.36 g (19%) of 3-*exo*-hydroxy-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane, and 1.1 g (56%) of 3-*endo*-cyano-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane: mp 237−238 °C; TLC R_f 0.45 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.05−2.14 (br m, 2H), 2.54−2.64 (br m, 4H), 3.11 (m, 1H), 6.58 (dt, J = 8.1, 1.1 Hz, 1H), 6.99 (ddd, J = 7.5, 4.8, 0.9 Hz, 1H), 7.01−7.56 (br m, 6H), 8.47 (dq, J = 4.8, 1.1 Hz); ^{13}C NMR DEPT-135 δ 30.2 (1C, CH), 31.8 (2C, CH), 37.4 (2C, CH_2), 41.4 (1C, −C−), 120.3 (1C, Py CH), 120.9 (1C, CN), 121.6, 128.2, 129.6, 132.8, 134.4 (1C, Ph −C−), 135.7, 148.7 (1C, Py CH), 163.5 (1C, Py −C−); IR (CCl_4, cm^{-1}) 2252.5. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.02; H, 6.18; N, 10.55. This structure was confirmed by X-ray analysis.

6-*exo*-Pyridyl-6-*endo*-phenylbicyclo[3.1.0]hexan-3-*endo*-carboxaldehyde (15-Exo). 3-*endo*-Cyano-6-*exo*-(2-pyridyl)-6-*endo*-phenylbicyclo[3.1.0]hexane (0.05 g, 0.19 mmol) in toluene (10 mL) was stirred under nitrogen at −78 °C, and DIBAL (0.30 mL of 1 M solution in hexane, 0.3 mmol, 1.58 equiv) was slowly added via a syringe. The mixture was stirred for 1 h at −78 °C and for 1 h more at −30 °C and poured into an ammonium chloride and ice mixture. Acetic acid (10%, 5.0 mL) was added. After being stirred for 30 min, the organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The extracts were washed with saturated $NaHCO_3$ and saturated NaCl and then dried (Na_2SO_4). Concentration afforded 50 mg of product aldehyde as a colorless solid: mp 179−182 °C; TLC R_f 0.55 (hexane/ethyl acetate 1:1); ^{1}H NMR δ 2.31−2.49 (m, 6H), 2.70-2.80 (m, 1H), 6.54 (dt, J = 8.1, 1.0 Hz, 1H), 6.97 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.25−7.47 (m, 6H), 8.20 (s, 1H), 8.47 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR 28.3, 36.8, 38.8, 52.3, 119.9, 121.2, 127.9, 129.1, 132.4, 135.1, 135.5, 148.6, 164.0, 202.5; IR (cm^{-1}) 1717.2. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.11; H, 6.50; N, 5.32. Found: C, 81.76; H, 6.58; N, 5.21.

3-*endo*-(Phenylhydroxymethyl)-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (16-Exo). To the Grignard reagent prepared from 10 mg (0.42 mmol) of magnesium turnings and 45 mg (0.3 mmol) of phenyl bromide in 1.0 mL of ether was added 53 mg (0.20 mmol) of 6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane-3-*endo*-carboxaldehyde in 0.50 mL of dry benzene with stirring at rt. Stirring was continued at the same temperature for 2 h. The reaction mixture was poured into 5.0 mL of cold saturated ammonium chloride solution followed by ether extraction (3 × 5 mL), washing with saturated sodium sulfate, drying (Na_2SO_4), and concentrating in vacuo. The residue was recrystallized from ether−hexane to give 37 mg (54%) of pure product as colorless microcrystals: mp 136−137 °C; TLC R_f 0.50 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 1.25 (ddd, J = 14.5, 8.1, 1.8 Hz, 1H), 1.62 (bs, 1H), 1.73−1.89 (m, 2H), 2.34−2.53 (m, 3H), 2.71−2.88 (m, 1H), 2.93 (d, J = 9.3 Hz, 1H), 6.59 (dt, J = 8.1, 1.1 Hz, 1H), 6.94 (ddd, J = 7.4, 4.8, 1.1 Hz, 1H), 6.98−7.01 (m, 2H), 7.16−7.36 (m, 6H), 7.40-7.46 (m, 1H), 7.52−7.57 (m, 2H), 8.45 (ddd, J = 4.8, 1.8, 0.7 Hz, 1H); ^{13}C NMR δ 30.1, 30.9, 37.7, 38.5 (2C), 42.5, 52.7, 119.9, 121.4, 126.5, 127.3, 127.5, 128.2, 129.0, 133.8, 135.5, 136.4, 144.1, 148.8, 164.5; IR (cm^{-1}) 3241.4: HRMS m/z (M^+) calcd (M^+) = 341.1780, obsd 341.1782. Anal. Calcd for $C_{24}H_{23}N_2O$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.09; H, 6.81; N, 4.20.

3-*endo*-Benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo-[3.1.0]hexane (17-Exo). A solution of 34 mg (0.10 mmol) 3-*endo*-(phenylhydroxymethyl)-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane in 1.0 mL of methylene chloride (1.0 mL) was added to Collins reagent prepared from 0.12 g of chromium trioxide and 2.0 mL of pyridine. The mixture was stirred at rt for 30 min and then poured into 2.0 mL of saturated sodium chloride solution and extracted with methylene chloride. Concentration afforded 34 mg of a colorless solid that was recrystallized from ethyl acetate−hexane: mp 158−159 °C; TLC R_f 0.65 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.24−2.32 (m, 2H), 2.46−2.57 (m, 4H), 3.94 (ddd, J = 19.1, 10.5, 6.6 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.95 (ddd, J = 7.4, 4.8, 0.9 Hz, 1H), 7.18−7.21 (m, 2H), 7.23−7.53 (m, 9H), 8.46−8.48 (m, 1H); ^{13}C NMR δ 30.0, 37.5, 41.9, 52.7, 119.9, 121.5, 127.2, 128.0, 128.2, 129.1, 132.0, 133.1, 135.2, 135.5, 137.2, 148.7, 164.4, 199.4; IR (cm^{-1}) 1682.0. HRMS *m*/*z* calcd (M^+) = 339.1623, obsd 339.1623. Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.37; H, 5.96; N, 4.23.

3-*exo*-Benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo-[3.1.0]hexane (18-Exo). Treatment of 3-*endo*-benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (34 mg, 0.10 mmol) with ethanolic sodium ethoxide, prepared from 230 mg of sodium, for 20 h at rt gave 34 mg of product: mp 124−125 °C; TLC R_f 0.80 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.07−2.24 (m, 3H), 2.38 (sym m, 2H), 2.51 (dd, J = 3.5, 1.3 Hz, 2H), 6.68 (dt, J = 8.1, 1.1 Hz, 1H), 6.98 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.31−7.41 (m, 2H), 7.43−7.57 (m, 9H), 8.49 (ddd, J = 4.8, 2.0, 0.9 Hz, 1H); IR (cm^{-1}) 1687.4; HRMS *m*/*z* (M^+) calcd for $C_{24}H_{21}NO$ 339.1623, obsd 339.1610. This structure was confirmed by X-ray analysis.

Bromination of 3-*endo*-Benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (17-Exo). Bromine (0.52 mL, 10 mmol) was diluted with acetic acid to 100 mL, and 2.2 mL (0.22 mmol) of this was added to a stirred solution of 3-*endo*-benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]-hexane (68 mg, 0.20 mmol) in 0.25 mL of acetic acid (2.0 mL) at rt. Hydrobromic acid (25 μL of 48%, 0.22 mmol) was added via a microsyringe. Immediate decolorization was observed. After 5 min, the reaction mixture was poured onto cracked ice and extracted with methylene chloride (3 × 10 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum, and the solid residue was recrystallized from methylene chloride−hexane to yield 52 mg (62%) of 3-*exo*-bromo-3-*endo*-benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo-[3.1.0]hexane **22-Exo** as colorless microcrystals: mp 167−168 °C; TLC R_f 0.75 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.57 (d, J = 16.5 Hz, 2H), 2.84 (t, J = 2.9 Hz, 2H), 2.97−3.05 (m, 2H), 6.53 (dt, J = 8.1, 1.1 Hz, 1H); 7.00 (ddd, J = 7.7, 4.8, 1.1 Hz, 1H); 7.13−7.16 (m, 2H), 7.25−7.39 (m, 6H), 7.45−7.51 (m, 1H), 7.85−7.89 (m, 2H), 8.53 (ddd, J = 4.8, 1.8, 0.7 Hz, 1H); IR (cm^{-1}) 1670.9. Anal. Calcd for $C_{24}H_{20}BrNO$: C, 68.91; H, 4.82; N, 3.35. Found: C, 68.77; H, 4.66; N, 3.69. This structure was confirmed by X-ray analysis.

Debromination of 3-*exo*-bromo-3-*endo*-benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane with HI in Acetone. Hydriodic acid (1.82 mL of 47%, 10 mmol) was diluted by acetone to 10 mL. The resulting solution (0.22 mL, 0.22 mmol) was added to the solution of the bromoketone (42 mg, 0.1 mmol) in acetone (2.0 mL) with stirring at rt. There was an immediate color of iodine. After 5 min, water (5 mL) was added. The mixture was extracted with methylene chloride (3 × 5 mL). The organic layer was washed with saturated sodium hydrogen sulfite, dried over sodium sulfate, and concentrated under vacuum. The crude residue (40 mg) was dissolved in deuteriochloroform and analyzed by NMR spectroscopy, which showed only the *endo*-benzoyl isomer.

3-[Trimethylsilyloxy(phenyl)methylidene]-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (23-Exo). To a solution of 68 mg (0.2 mmol) of 3-*endo*-benzoyl-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane in 1.0 mL of dry THF at −65 °C was added 0.4 mL of LDA (1 M in THF, 0.4 mmol). The mixture was stirred at −65 °C for 20 min, and 0.050 mL (0.40 mmol) of trimethylchlorosilane was added. After being stirred for 20 min at ambient temperature, the mixture was poured into 10 mL of saturated ammonium chloride solution, prepared from distilled water, and ether extracted (3 × 10 mL). Combined organic layers were washed with distilled water (10 mL) and dried over sodium sulfate. After concentration, the residue was recrystallized from hexane to yield 61 mg (74%) of colorless microcrystals: mp 105−106 °C; TLC R_f 0.95 (hexane−ethyl acetate 1:1); ^{1}H NMR δ −0.15 (s, 9H), 2.37−2.47 (m, 3H), 2.61−2.67 (m, 1H), 2.77−2.86 (m, 2H), 6.54 (d, J = 8.1 Hz, 1H), 6.82−6.86 (m, 2H), 6.92−6.96 (m, 1H), 7.09−7.33 (m, 9H), 8.46−8.48 (m, 1H); ^{13}C NMR δ 0.5, 31.2, 31.6, 34.3, 35.3, 37.6, 117.1, 119.7, 121.6, 121.7, 126.5, 126.6, 127.1, 128.0, 128.4, 131.1, 135.4, 136.2, 139.2, 148.6, 165.0; the IR spectrum showed no carbonyl group signals; HRMS *m*/*z* (M^+) calcd for $C_{27}H_{29}NOSi$ 411.2018, obsd 411.2010.

Conversion of 3-*endo*-Cyano-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane into 3-*endo*-Cyano-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane by Irradiation in Acetone. A solution of 3-*endo*-cyano-6-*exo*-(pyridyl-2)-6-*endo*-phenylbicyclo[3.1.0]hexane (3.0 g) in 3.0 L of acetone was purged with vanadous ion purified nitrogen in a water-jacketed photolysis flask for 15 min and then irradiated with a 400 W mercury lamp for 2 h. The acetone was concentrated in vacuo and the residue analyzed by NMR. Crystallization from acetone recovered 2.30 g of the starting material. The mother liquor was subjected to column chromatography using a 2.5 × 35 cm silica gel column and a methylene chloride−ethyl acetate−hexane (4:1:4) solution as an eluent. Two fractions were collected: (1) 0.40 g of the starting material and (2) 0.30 g of 3-*endo*-cyano-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane (**14-Endo**) as a colorless solid: mp 182−183 °C; TLC R_f 0.35 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.25−2.27 (m, 2H), 2.29−2.36 (m, 2H), 2.48−2.59 (m, 2H), 3.05−3.16 (m, 1H), 7.08−7.25 (m, 6H), 7.32 (ddd, 7.7, 1.1, 0.7 Hz, 1H), 7.70 (dt, J = 7.7, 1.8 Hz, 1H), 8.71 (ddd, J = 4.8, 1.8, 0.7 Hz, 1H); ^{13}C NMR δ 29.4, 31.5, 34.9, 41.5, 121.1, 122.4, 126.1, 126.7, 127.2, 128.2, 137.0, 145.1, 150.4, 156.6; IR (cm^{-1}) 2231.2; HRMS *m*/*z* (M^+) calcd 260.1313, obsd 260.1324. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.02; H, 6.18; N, 10.55. This structure was confirmed by X-ray analysis.

6-*endo*-(Pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane-3-*endo*-carboxaldehyde (15-Endo). 3-*endo*-Cyano-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane (0.52 g, 1.98 mmol) in toluene (100 mL) was stirred under nitrogen at −30 °C, and DIBAL (3.6 mL of 1.0 M solution in toluene, 3.6 mmol, 1.8 equiv) was slowly added via syringe. The mixture was stirred for 30 min at −30 °C and poured into an ammonium chloride and ice mixture. Five mL of aqueous acetic acid (10%) was added and the mixture stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 × 20 mL), the combined organic extracts were washed with saturated sodium bicarbonate and saturated NaCl and dried over sodium sulfate, concentrated in vacuo, and the residue was crystallized from ethyl acetate to yield 0.40 g (76%) of colorless plates: mp 119−121 °C; TLC R_f 0.25 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.17−2.22 (m, 2H), 2.34−2.45 (m, 2H), 2.56 (dd, J = 14.3, 3.8 Hz, 2H), 2.81 (tt, J = 12.1, 3.7 Hz, 1H), 7.07−7.22 (m, 6H), 7.28 (dt, J = 7.7, 1.1 Hz, 1H), 7.63 (dt, J = 7.4, 1.8 Hz, 1H), 8.37 (s, 1H), 8.61 (ddd, J = 4.8, 1.8, 1.1 Hz, 1H); ^{13}C NMR δ 27.6, 34.3, 39.7, 52.9, 122.3, 125.9, 126.8, 127.1, 128.2, 136.8, 145.6, 149.7, 157.4, 202.4 IR (cm^{-1}) 1717.3; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{17}NO$ 263.1310, obsd 263.1313.

The mother liquor was subjected to silica gel chromatography eluting with ethyl acetate−hexane (2:3) to yield 80 mg (15%) of 6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane-3-*exo*-carboxaldehyde as colorless plates: mp 110-112 °C, TLC R_f 0.40 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 1.06−1.16 (m, 1H), 2.13−2.20 (m, 6H), 7.08−7.26 (m, 6H), 7.33 (dt, J = 7.7, 1.1 Hz, 1H), 7.65 (dt, J = 7.7, 1.8 Hz, 1H), 8.63 (ddd, J = 4.8, 1.8, 0.7 Hz, 1 H), 9.39 (d, J = 2.2 Hz, 1H); ^{13}C NMR δ 28.0, 33.2, 39.0, 49.5, 121.6, 124.9, 126.0, 127.3, 128.2, 136.8, 145.1, 150.1, 158.8, 201.7; HRMS *m*/*z* (M^+) calcd 263.1310, obsd 263.1300. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.11; H, 6.50; N, 5.32. Found: C, 81.57; H, 6.45; N, 5.40.

3-*endo*-(Phenylhydroxymethyl)-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane (16-Endo). To an ether solution of phenylmagnesium bromide (1 M, 1.5 mL) was added the solution of 6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]-hexane-3-*endo*-carboxaldehyde (263 mg, 1 mmol) in 5.0 mL of dry benzene with stirring at rt. Stirring was continued at the same temperature for 2 h. The reaction mixture was poured into 5 mL of cold saturated ammonium chloride solution followed by ether extraction (3 × 5 mL). The combined ether solution was washed with saturated sodium sulfate, dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized from ether−hexane to give 276 mg (81%) of product as colorless microcrystals: mp 144−145 °C; TLC R_f 0.20 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 1.44 (ddd, J = 14.3, 9.2, 2.2 Hz, 1H), 1.73−1.90 (m, 2H), 2.02 (s, 1H), 2.10 (dt, J = 7.4, 2.2 Hz, 1H), 2.22 (dt, J = 7.4, 1.8 Hz, 1H), 2.32−2.42 (m, 1H), 2.78 (sextuplet, J = 9.2 Hz, 1H), 3.04 (d, J = 9.2 Hz, 1H), 7.01 (dd, J = 7.7, 1.8 Hz, 1H), 7.04−7.25 (m, 9H), 7.29 (d, J = 7.7 Hz, 1H), 7.69 (dt, J = 7.7 Hz, 1.8, 1H), 8.69 (ddd, J = 5.9, 1.8, 0.7 Hz, 1H); ^{13}C NMR δ 29.5, 30.4 (1C), 35.1 (1C), 35.4 (1C), 43.6 (1C), 53.9 (1C), 77.5 (1C), 121.5 (1C), 125.7 (1C), 126.3 (2C), 127.3 (2C), 127.4 (1C), 127.9 (1C), 128.1 (4C), 136.5 (1C), 143.9 (1C), 146.1 (1C), 149.8 (1C), 158.8 (1C); IR (cm^{-1}) 3232.8; HRMS m/z (M^+) calcd for $C_{24}H_{23}NO$ 341.1780, obsd 341.1807.

3-*endo*-Benzoyl-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo-[3.1.0]hexane (17-Endo). A solution of 340 mg of (1 mmol) 3-*endo*-(phenylhydroxymethyl)-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane in methylene chloride (10 mL) was added to Collins reagent prepared from 1.0 g of chromium trioxide and 5.0 mL of pyridine. The mixture was stirred at rt for 30 min. It was poured into 2 mL of saturated sodium chloride solution in water and extracted with methylene chloride. Concentration in vacuo gave 340 mg of a colorless solid that was crystallized from ethyl acetate−hexane: mp 170-171 °C; TLC R_f 0.55 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 2.24 (t, J = 2.2 Hz, 2H), 2.47−2.51 (m, 4H), 3.90-4.02 (m, 1H), 7.06−7.21 (m, 6H), 7.27 (dt, J = 7.7, 1.1 Hz, 1H), 7.31−7.37 (m, 2H), 7.41−7.46 (m, 1H), 7.52−7.55 (m, 2H), 7.63 (dt, J = 7.7, 1.8 Hz, 1H), 8.51 (ddd, J = 4.8, 1.8, 1.1 Hz, 1H); ^{13}C NMR 29.7, 34.9, 42.3, 52.3, 121.5, 125.7, 127.2, 127.3, 128.0, 128.1, 128.2, 132.1, 136.6, 136.8, 146.1, 149.9, 157.6, 199.3; IR (cm^{-1}) 1686.7; HRMS m/z (M^+) calcd for $C_{24}H_{21}NO$ 339.1623, obsd 339.1616. This structure was confirmed by X-ray analysis.

Treatment of 21 mg of this material with ethanolic sodium ethoxide, prepared from 1.0 mL of ethanol and 23 mg (1.0 mmol) of sodium, for 20 h at rt gave 17 mg of 3-*exo*-benzoyl-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane (**18-Endo**): mp 149−150 °C; TLC R_f 0.70 (hexane−ethyl acetate 1:1); ^{1}H NMR δ 1.94−2.03 (m, 1H), 2.25 (t, J = 1.5 Hz, 2H), 2.29−2.44 (m, 4H), 7.09−7.27 (m, 6H), 7.31−7.37 (m, 2H), 7.42−7.50 (m, 2H), 7.52−7.57 (m, 2H), 7.74 (dt, J = 7.4, 1.8 Hz, 1H), 8.75 (ddd, J = 4.8, 1.8, 1.1 Hz, 1H); ^{13}C NMR δ 31.1, 33.0, 38.5, 44.2, 121.6, 125.1, 125.9, 127.4, 128.1, 128.2, 128.3, 132.8, 136.5, 136.8, 145.2, 150.0, 159.7, 200.4; IR (cm^{-1}) 1680.4; HRMS m/z (M^+) calcd for $C_{24}H_{21}NO$ 339.1623, obsd 339.1625.

3-[Trimethylsilyloxy(phenyl)methylidene]-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane (23-Endo). To a solution of 68 mg (0.2 mmol) of 3-*endo*-benzoyl-6-*endo*-(pyridyl-2)-6-*exo*-phenylbicyclo[3.1.0]hexane in 1.0 mL of dry THF at −65 °C was added 0.40 mL of LDA (1 M in THF, 0.4 mmol). The mixture was stirred at −65 °C for 20 min, and 0.050 mL (0.4 mmol) of trimethylchlorosilane was added. After being stirred for 20 min at ambient temperature, the mixture was poured into 10 mL of saturated ammonium chloride solution, prepared from distilled water, and ether extracted (3 × l0 mL). The combined organic layers were washed with distilled water (10 mL) and dried over sodium sulfate. After solvent concentration, the residue was crystallized from hexane to yield 53 mg (64%) of colorless microcrystals: mp 78−79 °C; TLC R_f 0.80 (hexane−ethyl acetate 1:1); ^{1}H NMR δ −0.12 (s, 9H); 2.12 (dd, J = 3.0, 2.2 Hz, 2H); 2.54−2.60 (m, 1H) overlapped with 2.63 (dd, J = 16.5, 1.5 Hz, 1H); 2.79 (dd, J = 6.2, 2.6 Hz, 1H); 3.03 (dd, J = 16.5, 1.5 Hz; 1H); 6.84−6.88 (m, 2H); 7.00 (ddd, J = 7.4, 4.8, 1.1 Hz, 1H); 7.05−7.21 (m, 9H); 7.44 (dt, J = 7.7, 1.8 Hz, 1H); 8.40 (ddd, J = 4.8, 1.8, 1.1 Hz, 1H) IR showed no carbonyl group signals; HRMS m/z (M^+) calcd for $C_{27}H_{29}NOSi$ 411.2018, obsd 411.1993.

Enol Generation from the Silyl Enol Ethers. In a typical run, to 1.0 mg of the trimethylsilyloxy enol derivative of the *endo*-pyridyl ketone in 5.0 μL of acetic acid and 500 μL of THF there was added 5.0 μL of 1.0 M tetrabutylammonium fluoride in THF. The reaction mixture was stirred at rt for 5 min. Then water−ether quenching and extraction afforded a mixture of the *endo*- and *exo*-benzoyl products. The mixture was analyzed as described above by HPLC to give the *endo*- and *exo*-benzoyl isomers in a 2.5:97.5 ratio.

In a parallel run starting with the *endo*-phenyl silyl enol ether and with the same conditions, a 98.4:1.6 ratio of *endo*-benzoyl to *exo*-benzoyl products was obtained. In these acetic acid runs, the concentration of acetic acid was varied as listed in Table 1. Runs with DMSO replacing the THF and formic acid replacing the acetic acid were done similarly. Additionally, aqueous ammonium chloride runs were similarly performed using THF as a cosolvent. The HPLC fractions from 20 runs were combined and subjected to NMR analysis. Also, in larger scale runs, NMR analysis was also employed.

(A) The residual material from 20 of the kinetic runs used for HPLC analysis was combined and the resulting mixture separated by column chromatography on silica gel, using hexane−ethyl acetate 10:1 as an eluent. Two compounds thus obtained were identified by ^{1}H NMR analysis as the *exo*-benzoyl and *endo*-benzoyl isomers and revealed only peaks deriving from the *endo*- and *exo*-benzoyl epimers.

(B) To a solution of 17 mg of the *endo*-pyridyl enol ether (0.05 mmol) in 8.50 mL of THF and 0.170 mL of acetic acid was added tetrabutylammonium fluoride (1 M in THF, 0.085 mL) at rt. After 10 min, the standard workup and ether extraction was done as described above. ^{1}H NMR analysis showed peaks at δ 3.90-4.02 characteristic for the proton at position 3-exo of the *endo*-benzoyl isomer and δ 1.94−2.03 characteristic for the proton at position 3-endo of the *exo*-benzoyl isomer that were used to give a 1:4.84 ratio (i.e., 17%:83%) of *endo*-benzoyl to *exo*-benzoyl isomers. Less accurately, the integration of the δ 8.75 vs 8.51 α-pyridyl proton peaks gave the *endo*-benzoyl−*exo*-benzoyl ratio as 1:5.76 (i.e., 14%:86%). Thus, the NMR analysis was comparable to the ratio found by the HPLC method.

Analysis of Kinetic Protonation Runs. The ratio of the endo to the exo product was determined by HPLC using a Zorbax silica gel column, 6 nm, 0.46 cm × 25 cm with a flow rate 1.0 mL/min of hexane−ethyl acetate (4:1) eluent. UV monitoring was at 254 nm and in some runs at 270 nm. Automatic integration was followed by correction for the differing absorbtivities at these wavelengths. The correction at 254 nm was 1.20:1 for the *endo*-benzoyl−*exo*-benzoyl ratio in the case of the 3-benzoyl-6-*endo*-pyridyl-6-*exo*-phenylbicyclo-[3.1.0]hexanes. A larger correction was observed at 270 nm, and thus, data at 250 nm was used.

Stability of 3-*endo*-Benzoyl-6-*endo*-pyridyl-6-*exo*-phenylbicyclo[3.1.0]hexane under Protonation Conditions. (a) The *endo*-pyridyl-*endo*-benzoylbicyclic ketone (4.0 mg, 0.0118 mmol) was dissolved in 2.0 mL of THF and 0.20 mL of AcOH. The resulting solution was sealed under nitrogen atmosphere and left at rt for kinetic measurements. Small portions of this solution (0.2 mL) were taken with 2.0 mL of ether and 2.0 mL of water at the end of 2, 20, 30, and 60 h. The water layer was extracted with ether (2 × 2 mL). The combined ether solution was washed with water, dried over sodium sulfate, and concentrated under vacuo. The residue was analyzed by HPLC, as described earlier. The results are summarized in Table 2a.

(b) 3-*endo*-Benzoyl-6-*endo*-pyridyl-6-*exo*-phenylbicyclo[3.1.0]-hexane (4.0 mg, 0.0118 mmol) was dissolved in 2.0 mL of AcOH, and 0.080 mL of tetrabutylammonium fluoride solution (1 M in THF) was added. The resulting solution was sealed under nitrogen atmosphere and left at rt for kinetic measurements. Small portions of this solution (0.20 mL) were taken with 2.0 mL of ether and 2.0 mL of water at the end of 5 min, 30 min, 6 h, 16 h, and 27 h. The water layer was ether extracted (3 × 2 mL). The combined extracts were washed with water (3 × 2 mL), dried over sodium sulfate, and concentrated

Table 2. Equilibration Runs[a]

(a) without added fluoride		(b) with added fluoride	
time, h	exo−endo ratio	time	exo−endo ratio
2	1.1:98.9	5 min	4.1:95.9
20	2.1:97.9	30 min	8.4:91.6
30	2.4:97.6	6 h	15.2:84.8
60	3.1:96.9	16 h	31.2:68.8
		27 h	46.3:53.7

[a] The concentration of bicyclic was 5.4×10^{-3} M.

in vacuo. The residue was analyzed by HPLC, as described earlier. The results with added fluoride are summarized in Table 2b. The concentrations employed were 3.8×10^{-2} M Bu_4NF, 16.8 M AcOH, and 5.4×10^{-3} M of reactant bicyclic ketone.

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Supporting Information Available: Detailed experimental procedures for 2-benzoylpyridine, 2-benzoylpyridine hydrazone (**8**), and 4-phenyl[1.2.3]triazolo[1,5-*a*]pyridine (**9**) are given. Also, Table 1 gives kinetic data with product ratios in various solvents as a function of proton donor concentration. This material is available free of charge via the Internet at http://pubs.acs.org.

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