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Mechanistic Studies on the *Cis* to *Trans* Epimerization of Trisubstituted 1,2,3,4-Tetrahydro-β-carbolines

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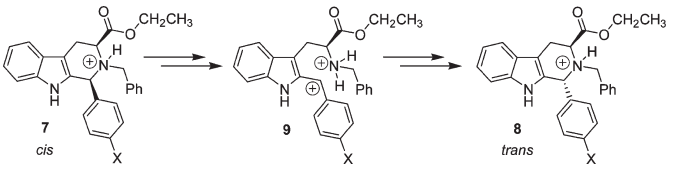

It is well-known that N_b-benzyltryptophan alkyl esters undergo the Pictet−Spengler reaction with aldehydes to furnish both *cis*- and *trans*-1,2,3,4-tetrahydro-β-carbolines, with the *trans* isomer predominating. Epimerization at C-1 took place under acidic conditions to produce, exclusively, the thermodynamically more stable *trans* diastereomer via internal asymmetric induction. Recent kinetic experiments provided insight into the *cis* to *trans* epimerization mechanism involved in the Pictet−Spengler reaction of 1,2,3-trisubsituted tetrahydro-β-carbolines. Since the epimerization reaction had been shown to be sensitive to electronic effects at C-1, the rate data for a series of 1-phenyl-substituted 1,2,3,4-tetrahydro-β-carbolines was investigated via a Hammett study. Analysis of the data supported the presence of a positively charged intermediate with a ρ value of −1.4, although the existence of an iminium ion intermediate or a carbocationic intermediate could not be determined from this data alone. Analysis of the rate of epimerization demonstrated first-order kinetics with respect to TFA following the initial protonation of the substrate. This observation was consistent with the formation of a doubly protonated intermediate as the rate-determining step in the carbocation-mediated *cis* to *trans* epimerization process. In addition, the observed first-order rate dependence was inconsistent with the retro-Pictet−Spengler mechanism since protonation at the indole-2 position was not rate determining as demonstrated by kinetic isotope effects. Based on this kinetic data, the retro-Pictet−Spengler pathway was ruled out for the *cis* to *trans* epimerization of 1,2,3-trisubstituted 1,2,3,4-tetrahydro-β-carbolines, while the olefinic mechanism had been ruled out by experiments carried out in TFA-*d*.

Introduction

The Pictet−Spengler reaction,[1] which involves the cyclization of electron-rich aryl or heteroaryl groups onto imine or iminium ion electrophiles, has long been a standard method for the construction of both tetrahydroisoquinolines[1] and tetrahydro-β-carbolines.[2] These privileged scaffolds appear in a diverse array of biologically active compounds; both of these ring systems are popular choices for combinatorial libraries targeted at drug discovery.[3] Recent advances in medicinal chemistry include potential implications for β-carbolines in the treatment of alcoholism.[4,5] The enantiospecific Pictet−Spengler reaction, in particular, has stimulated widespread interest in both organic and medicinal chemistry[6−19]

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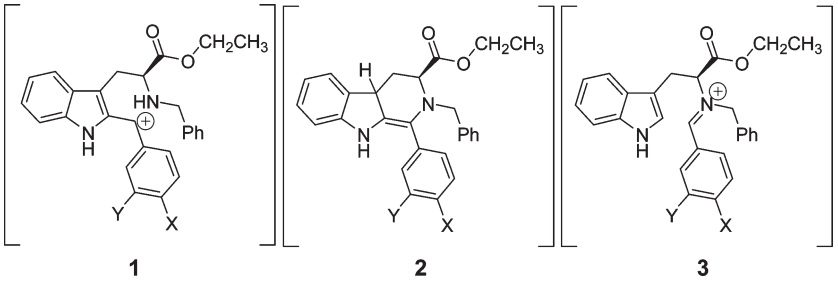

FIGURE 1. Proposed intermediates in the *cis* to *trans* epimerization.

and has resulted in the total synthesis of a number of natural products including vincamajinine, alstonisine, macralstonidine, (−)-alstophylline, (−)-macralstonine, ajmaline, and (−)-raumacline.[20] Alternatively, several groups have extended the scope to examine the ratio of *cis*/*trans* isomers of the Pictet−Spengler reaction employing tryptophan derivatives with aldehydes and this has been reviewed.[21,22] The development of chiral auxiliaries by Reddy[8] and Nakagawa[23,24] provided the basis for asymmetric Pictet−Spengler reactions. In addition, Nakagawa[10] had also explored Brønsted acid assisted Lewis acids in stoichiometric amounts to induce stereoselectivity in the Pictet−Spengler reaction. Recently, important examples of external asymmetric induction via organocatalysis have been applied to the Pictet−Spengler cyclization. Jacobsen et al.[12,16,17] have developed chiral thiourea catalysts for the asymmetric Pictet−Spengler reaction of tryptamines. Alternatively, List[13] and van Maarseveen[14,15,18] have investigated chiral phosphoric acid catalysts with much success.

Although progress has been made in regard to synthesis, interestingly, the mechanism of the *cis* to *trans* isomerization in the presence of Brønsted acids has not been fully defined. Three potential mechanistic pathways have been proposed and their intermediates are depicted in Figure 1. The olefinic pathway had been previously ruled out with aliphatic substituents at the C-1 position[22] and was therefore not considered in the kinetic analysis. A structural basis for the development of the proposed carbocationic intermediate had been described by Han.[25] The conformation of the C-ring was found to be important during the epimerization process; ultimately, the *p*-orbital of the developing carbocation was thought to overlap well with the indole π-electrons. In efforts aimed to investigate the mechanism of the isomerization at C-1, a set of readily accessible electron-donating and electron-withdrawing substituted aromatic aldehydes have been reacted with L-tryptophan ethyl ester, followed by N_b-benzylation, to provide optically active *cis* and *trans* 1,2,3-trisubsituted tetrahydro-β-carbolines.[26] In a general sense, electron-rich substituents on aromatic rings at the C-1 position enhanced the rate of the *cis* to *trans* epimerization.[26] This result was in agreement with the proposed carbocationic mechanism of epimerization, although the retro-Pictet−Spengler process could not be completely ruled out at that time.[26] In this work, the kinetics of the *cis* to *trans* epimerization of 1,2,3-trisubsituted tetrahydro-β-carbolines was studied to elucidate the mechanism of this epimerization.

Results and Discussion

Since the general trend of rates of epimerization was in place, a detailed kinetic study was designed. A Hammett linear free energy relationship is a common method in the application of kinetic data to mechanistic problems.[27,28] In order to use this method, the parent 1-phenyltetrahydro-β-carboline (**7d**) was employed as one of the molecules to be studied. This parent substrate was obtained from benzaldehyde and L-tryptophan ethyl ester when stirred under the conditions of the Pictet−Spengler cyclization previously described.[26] In addition, substrates which carried a series of substituents with a range of electron densities at the C-1 position were easily obtained by a Pictet−Spengler cyclization, followed by separation of the *cis* and *trans* diastereomers and subsequent N_b-benzylation, as previously described (Scheme 1 and Table 1).[26] Several of the analogues were very sensitive to acid-induced epimerization; therefore, large quantities of base were used during the alkylation reaction.

Since the synthesis of a series of electronically altered molecules had been completed (see Supporting Information for details), the Hammett analysis was undertaken. Instead of removing aliquots of the reaction mixture during the epimerization process with TFA as previously executed,[26]

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SCHEME 1. Synthesis of Trisubstituted 1,2,3,4-Tetrahydro-β-carbolines

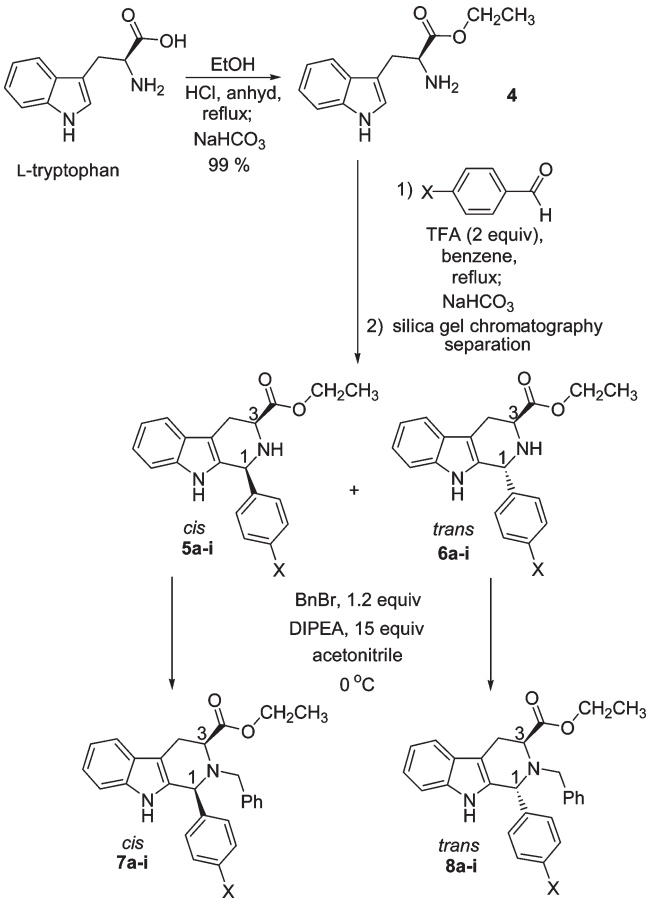


TABLE 1. Products from the Pictet–Spengler Reaction and N_b-Benzylation

	Pictet–Spengler products			alkylation products			
X	*cis*	*trans*	yield,[a,b] (%)	*cis*	yield,[a,c] (%)	*trans*	yield,[a,c] (%)
Et	**5a**	**6a**	90	**7a**	69	**8a**	68
^{i}Pr	**5b**	**6b**	91	**7b**	55	**8b**	59
^{t}Bu	**5c**	**6c**	87	**7c**	61	**8c**	60
H	**5d**	**6d**	95	**7d**	64	**8d**	68
F	**5e**	**6e**	91	**7e**	75	**8e**	72
Cl	**5f**	**6f**	76	**7f**[d]	85	**8f**[d]	82
Br	**5g**	**6g**	88	**7g**	64	**8g**	68
NO_2	**5h**	**6h**	88	**7h**[d]	82	**8h**[d]	88
OMe	**5i**	**6i**	82	**7i**	71	**8i**	72

[a]Yields are not optimized. [b]*cis* + *trans*. [c]*Cis* and *trans* compounds were alkylated individually. [d]1.5 equiv of DIPEA at reflux.

more detailed observations were obtained by observing the *cis*/*trans* ratio in situ. In the present case, ^{1}H NMR spectroscopy had proven useful as a means to observe both of these species. In the following experiments, the *cis* to *trans* ratio was determined by integration of ^{1}H NMR spectra while the epimerization of the *cis* isomer into its *trans* counterpart was followed by ^{1}H NMR spectroscopy. Beside the less laborious nature of observations of the reaction in the spectrometer, the real strength of this method was the ability to obtain more data over the course of the reaction progress for the rate studies.

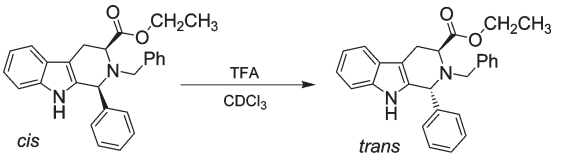
Experiments designed to determine useful reaction conditions to study the epimerization process in situ were not trivial. Sampling rate of the detection method (^{1}H NMR), detection interference of either reagents or intermediates, as well as detection of both the *cis* and *trans* epimers proved to be of importance in the experimental design. First, the reaction conditions were set up in order to observe the reaction on a reasonable time scale with the ability to monitor the *cis* to *trans* conversion. Also, reactants or intermediates must not interfere with the detection of either isomer. In order to obtain useful data, the acid (and its concentration), the *cis* isomer concentration, and the temperature were parameters that were altered.

Initially, the effect of the acid strength on rate was studied. Several acids were employed in the epimerization reaction at different concentrations. Acetic acid proved to be insufficient since epimerization of **7d** (12.5 mM) was very slow under the concentrations used (8.7 M). In addition, the significant signal of the acetic acid hydrogen atoms in the ^{1}H NMR spectrum significantly reduced the signals of the tetrahydro-β-carbolines in the spectrum, which indicated acetic acid may not be the optimal catalyst to study the *cis* to *trans* epimerization by this method. In an attempt to increase the rate of epimerization, formic acid was employed in a higher concentration (13.3 M) than that employed for acetic acid. In this case, the ratio of *cis*/*trans* isomers was unable to be determined since the formic acid signal was too strong to permit observation of the signals from the tetrahydro-β-carbolines of interest. To reduce the formic acid signal, the concentration was reduced to 6.6 M. The clarity of the spectrum remained poor, and the *cis*/*trans* ratio could not be determined; therefore, the use of formic acid was abandoned. Since this issue complicated data analysis, an acid which does not contain unnecessary hydrogen atoms associated with the molecule would be beneficial. The use of deuterated acids would be useful in this case; however, the inherent cost of these acids was not the optimal solution. Trifluoroacetic acid (TFA) was chosen on the basis of this criteria as well as its increased acidity.

Initial attempts with TFA suggested that this acid would be useful with regard to the clarity of the spectrum; however, the protons at C-4 were broadened in the ^{1}H NMR spectrum. The integration of these signals could not be used as previously described[26] to determine the epimeric ratio; however, the triplet from the ethyl ester function of the *cis* isomer **7d** (δ 1.26 ppm) was noticeably shifted upfield as compared to the *trans* isomer **8d** (δ1.16 ppm) (see Figures S1 and S2, Supporting Information). This chemical shift difference permitted the concentration of both isomers to be monitored over the course of the epimerization process.

Due to the increased acidity of TFA as compared to either acetic or formic acid, TFA concentrations of 1.7 M of TFA promoted the rate of the epimerization of the parent **7d** ([**7d**] = 12.5 mM) in less than 1 min. Since the standard ^{1}H spectrum required approximately 1 min (16 scans), molar concentrations would not permit observation of the rate of the process. In this regard, the concentration of TFA was reduced significantly by means of dilution in $CDCl_3$ to 2.7 mM while the concentration of **7d** was kept constant. After 1 h, the proton spectrum was taken of the reaction mixture. Approximately 20% of the *trans* isomer was present, based on the integration of the NMR spectrum. These

TABLE 2. Effect of TFA Concentration on the Rate of Epimerization



[TFA] (mM)	k_{obs}[a] (s^{-1})	std dev	std error
13.5	0.0016	0.0001	< 0.0001
18.0	0.0025	0.0001	0.0001
22.5	0.0031	0.0003	0.0002
27.0	0.0049	0.0004	0.0003
67.5	0.0122	0.0007	0.0005

[a]Average of two runs; [**7d**] = 5.0 mM for all experiments; T = 303.0 K.

conditions could be used to monitor the reaction; however, in an effort to minimize reaction times and collect more data in a timely fashion, the TFA concentration was increased. It was found that TFA concentrations up to 67 mM could be used to obtain measurable rate constants when the concentration of the substrate (**7d**) was equal to 5.0 mM (Table 2).

Since it was known that electron-donating substituents on the phenyl ring at C-1 increased the rate of the epimerization, the 4-methoxy-substituted substrate **7i** was subjected to the epimerization process under the same conditions as **7d**; [**7i**] = 12.5 mM, [TFA] = 13.5 mM. Since the rates are compared to one another in a free-energy relationship, all reaction conditions were kept exactly the same. Upon addition of TFA to the *cis* isomer of **7i**, unfortunately, the *cis* to *trans* epimerization took place in less than 3 min. Analysis of the first proton spectrum in the kinetic experiment showed that all the *cis* isomer had been converted completely into the *trans* diastereomer. On the other hand, when catalytic amounts of TFA were employed in order to measure the rate of this reaction **7i**→**8i**, this provided excellent results (see Figure S3, Supporting Information); however, the same reaction conditions were not ideal for phenyl rings with electron-withdrawing substituents at the C-1 position due to the extremely long reaction times. For example, data could not be collected in a reasonable time frame for the *p*-nitrophenyl analogue **7h** since epimerization was only 70% complete after 15 h (Figure S4, Supporting Information). Since the methoxy group was strongly electron donating ($\sigma^+ = -0.78$), it was believed rate data obtained by ^{1}H NMR spectroscopy for this substrate (**7i**) would not be possible under the same reaction conditions required for the remaining compounds in the series and it was therefore excluded from the kinetic analysis.

Since the *p*-methoxyphenyl analogue **7i** reacted too rapidly to obtain accurate rate data, the upper limit of reactivity (electron donating) in order to observe the rate of epimerization by NMR was determined. The σ^+ value of an ethyl function located in the *para* position of a phenyl group was −0.30, which was less able to stabilize a positively charged intermediate when compared to that of a methoxy substituent located in the same position (−0.78); therefore the *p*-ethyl substituted analogue (**7a**) should not react as fast as the *p*-methoxy-substituted analog (**7i**). When the *p*-ethylphenyl substrate **7a** was subjected to the standard epimerization conditions, fortunately the rate could be followed by ^{1}H NMR spectroscopy. Because of this observation, a series of 1-(*para*-substituted)-phenyltetrahydro-β-carbolines could now be employed in the epimerization experiments. Since rate data was obtained for *p*-ethyl analogue **7a**, any substituents with a σ^+ value greater than −0.30 could be used in the Hammett analysis.[29]

In this regard, the series of molecules illustrated in Scheme 1 and Table 1 (**7a**−**h**) was employed to determine if a linear free energy relationship existed for the epimerization reaction, which, in turn, would provide insight into the mechanism of the epimerization. Each kinetic experiment was set up with the following conditions: [*cis*] = 12.5 mM, [TFA] = 13.5 mM, T = 303 K. Data for compounds **7a**−**g** were obtained over a reasonable time frame; i.e., complete epimerization occurred in 15−30 min for this series of substrates. Because the rates could be observed for this series of molecules, the data was manipulated further; each spectrum of a kinetic experiment was integrated manually to obtain the concentration of the *cis* isomer and was then plotted for each compound over time. Essentially, a first-order decay of the *cis* isomer was observed for each compound; however, the initial region of each plot appeared to be more linear in nature than an actual exponential decay (see Figure S5, Supporting Information). It was thought this could be due to an insufficient amount of TFA present during the initial stages of the reaction. If this were the case, a lower concentration of TFA would increase this effect; the linear portion of the plot would extend further throughout the process. To test this hypothesis, the acid concentration was reduced to catalytic amounts (see Figure S6, Supporting Information). Indeed, as the amount of acid catalyst was reduced, the reaction plot became more linear over the epimerization process. This observation can be understood because the catalytic amount of TFA had cycled via equilibrium, presumably, through the epimerization process to the point wherein equimolar concentrations were present between the *cis* isomer and TFA. Just past the equimolar point, TFA would become an excess reagent, which would then make the reaction essentially pseudo-first-order, which resulted in a first-order exponential decay.

Since it was now known that a slight excess of TFA (13.5 mM) was insufficient to produce a pseudo-first-order decay from time = 0, the concentration of TFA was increased to 27.0 mM. Typically, 10 equiv of reagent were required to satisfy pseudo-first-order conditions; however, since this epimerization reaction was catalytic, an excess of TFA completely protonated the *cis* isomer. A study of the amount of TFA required to completely protonate the *cis* isomer indicated that 1.5 equiv was the minimum amount of TFA that would produce a first-order decay as the *cis* isomer was converted into the *trans* diastereomer over time (see Figure S7, Supporting Information).

Once the final reaction conditions were set, the series of *para*-substituted substrates (**7a**−**h**) were subjected to the epimerization process and followed by ^{1}H NMR spectroscopy. The plots fit a first-order model very well (Figure S8, Supporting Information), which permitted extraction of the pseudo-first-order rate constants (see Table 3). Since all of the kinetic experiments were carried out under the same reaction conditions, a Hammett plot could be constructed. Here, the observed rate constants were compared directly to that of the unsubstituted parent compound, **7d**. As

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TABLE 3. Observed Rate Constants of the *Cis* to *Trans* Isomerization

compd	substituent	k_{obs}[a] (s^{-1})	std dev	std error
7a	Et	0.0073	0.0006	0.0003
7b	^{i}Pr	0.0062	0.0003	0.0002
7c	^{t}Bu	0.0062	0.0004	0.0002
7d	H	0.0018	< 0.0001	< 0.0001
7e	F	0.0026	< 0.0001	< 0.0001
7f	Cl	0.0017	< 0.0001	< 0.0001
7g	Br	0.0015	0.0001	< 0.0001
7h	NO_2	0.0001	< 0.0001	< 0.0001

[a]Average of three experiments.

mentioned previously, electron-donating substituents (either by resonance or by induction) increased the rate of epimerization and, therefore, are expected to produce a negative slope in the Hammett plot. In fact, this was exactly what was observed (see Figure 2). Since the data was scattered around the linear regression line, it was clear the data did not fit the Hammett linear free energy relationship well when the standard σ_{para} values were employed. When σ^{+}_{para} values were used, however, the data correlated much better (Figure 3). The key substrate (**7e**) which was used to confirm that σ^{+}_{para} values should be used in this mechanistic study had been prepared (see the Supporting Information). The σ_{para} value for a fluorine atom in the *para* position of a benzene ring was 0.06 while the σ^{+}_{para} value was −0.07. If the parent **7d** epimerized at C-1 slower than the *p*-fluoro analogue **7e**, σ^{+}_{para} values should be employed in the Hammett plots. Indeed, this was the exact observation. Hence, analysis of this observation indicated that a positively charged intermediate was in direct resonance with the substituent at the *para* (4′) position under study, and the Hammett ρ value was found to be −1.4. The negative slope was in agreement with the expected value since positive charge builds up throughout the course of the reaction process. However, the observed ρ value of −1.4 was considerably less than typical ρ values for benzylic cations. The decreased sensitivity to changes in the substitution pattern could be attributed to electron delocalization from the neighboring indole ring, which also stabilized the proposed carbocationic intermediate.

The Hammett plot produced here could not be used to unequivocally distinguish between the carbocationic mechanism or the retro-Pictet−Spengler pathway for the epimerization process. Both the carbocationic intermediate as well as the iminium ion intermediate are in direct resonance with a substituent at the *para* position of the phenyl ring at C-1. However, by careful examination of both proposed mechanisms, differences could be noticed when the concentration of TFA was altered.

Observation of the data shown in Figure 4 clearly indicated the rate of epimerization of **7d** increased as the concentration of TFA increased and indicated first-order kinetics after protonation of the starting material. Since this reaction was carried out with excess quantities of acid

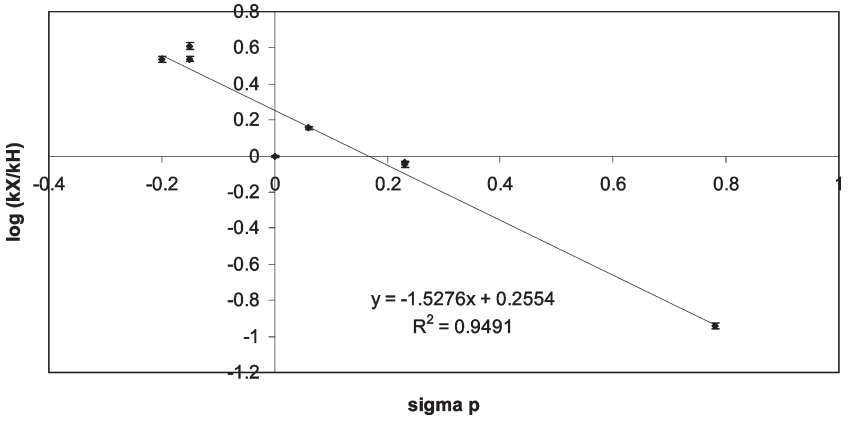


FIGURE 2. Hammett plot with σ_{para} values.

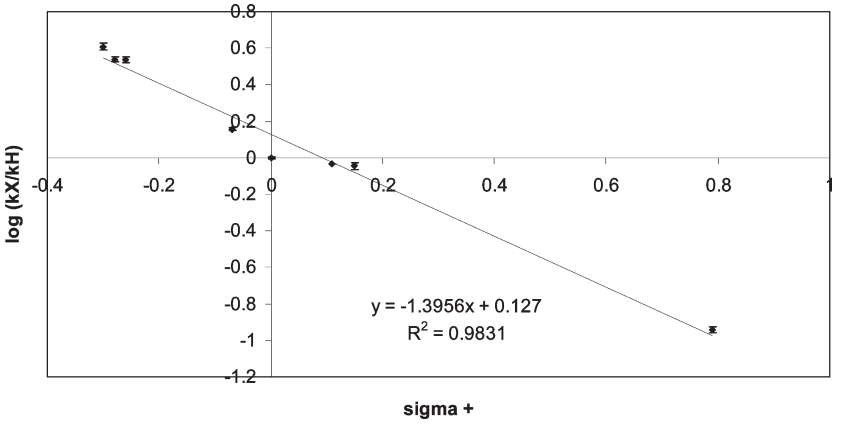


FIGURE 3. Hammett plot with σ^{+}_{para} values.

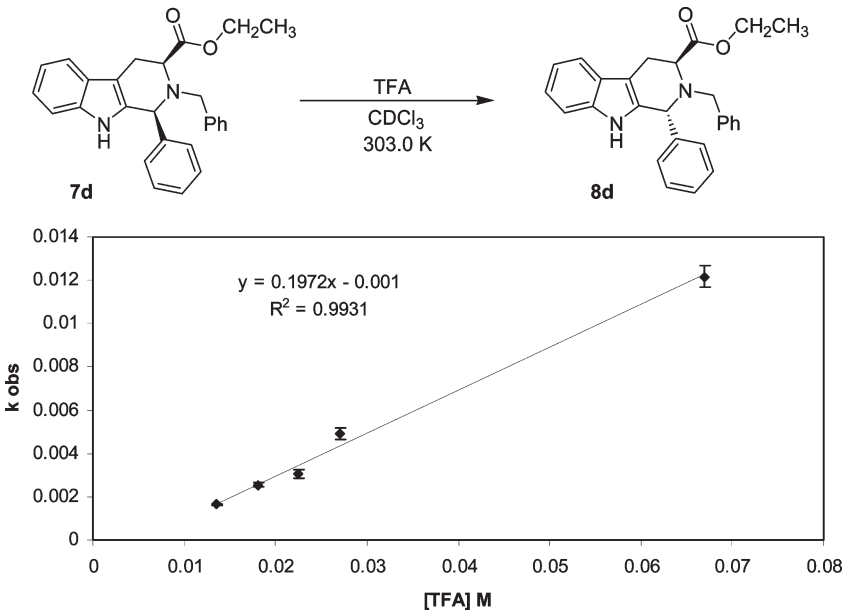


FIGURE 4. Effect of the TFA concentration on the rate.

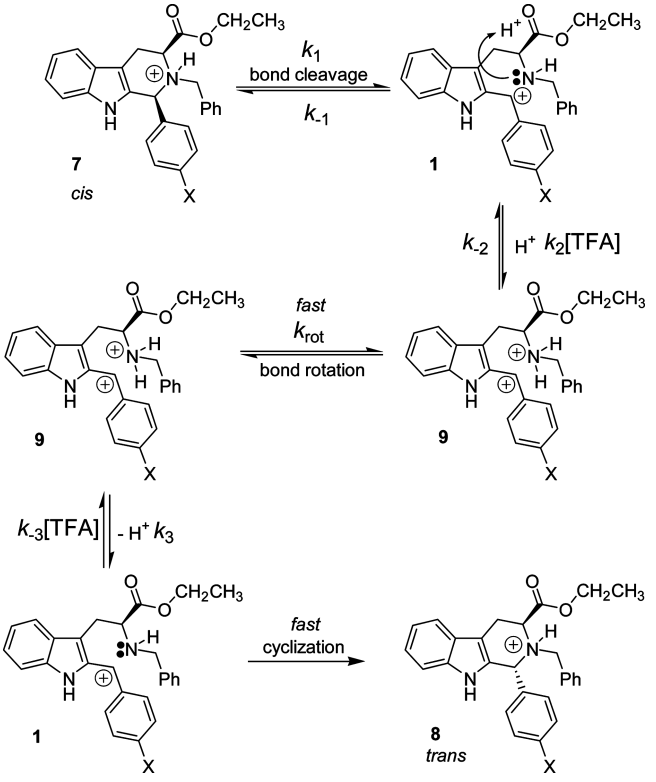
catalyst, the rate should not change to a significant degree as the catalyst (TFA) concentration was altered if one catalyst molecule was involved in the epimerization process. However, this was not the case, which suggested that the acid catalyst was more involved in the epimerization mechanism than a single protonation. In this case, it was believed that TFA was involved in a double protonation. In the proposed carbocationic mechanism, the initial protonation took place at the N_b-nitrogen atom. As this mechanistic route progressed and the carbocationic intermediate was formed, a second protonation took place on the N_b-nitrogen atom (see Scheme 2). First-order kinetics was observed with respect to the concentration of TFA as would be expected when $k_{-1} \gg k_2$[TFA].

In the carbocationic mechanism, a doubly protonated intermediate such as **9** would form following C−N bond cleavage (Scheme 2). The rate at which **9** would form would increase as the concentration of TFA was increased. In order for cyclization to take place, **9** would have to be deprotonated, which would be slowed in the presence of a higher concentration of TFA; however, the rate of the reaction would not be affected to a large extent as the concentration of such an intermediate would remain small over time due to its instability. Therefore, this step was not considered as the rate determining step. In this case, a rate enhancement would be observed for each mechanistic step when the TFA concentration was increased. This was exactly what was observed (Figure 4). In fact, after initial protonation of the starting material (as detected by ^{1}H NMR spectroscopy), first-order kinetics with respect to the concentration of TFA was observed, therefore the rate was dependent upon k_2 and the concentration of TFA.

As reported by Shudo et al.,[30] doubly charged intermediates have been proposed in the tetrahydroisoquinoline series. In these cases, strong acids, such as TFA and trifluoromethanesulfonic acid (TfOH), were used to catalyze the Pictet−Spengler reaction.

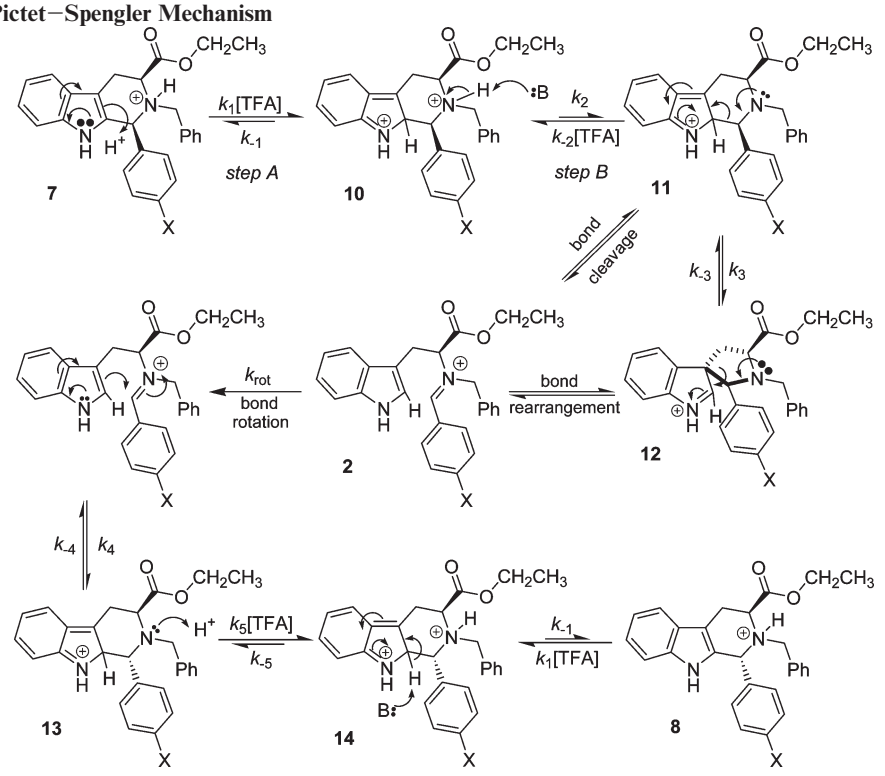
(30) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611.

SCHEME 2. Carbocation-Mediated Mechanism Including a Second Protonation

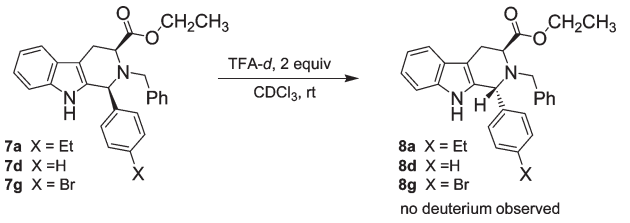


The acid dependence of these reactions suggested that a dicationic electrophile (diprotonated imine) was the reactive intermediate.[30] The same concept could be applied to the *cis* to *trans* epimerization mechanism under study here, as shown in Scheme 2. The second protonation would take place after the carbocation had formed. During the time of the second protonation, the C-3/C-4 bond would have time to rotate to the more stable *trans* configuration, followed by N_b-deprotonation

SCHEME 3. Retro-Pictet−Spengler Mechanism



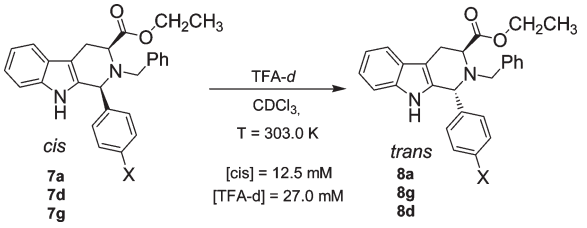
SCHEME 4. *Cis* to *Trans* Epimerization Process in TFA-*d* on 1-Substituted Phenyltetrahydro-β-carbolines 7a, 7d, and 7g



and recyclization to form the *trans* product. This type of mechanism would be consistent with the rate data shown in Figure 4 since the reaction rate was first order in the concentration of TFA even after initial protonation of the starting material.

On the other hand, if the retro-Pictet−Spengler pathway was involved, the initial protonation step (step A, Scheme 3) to form **10** would increase in rate as the concentration of TFA increases. However, the rate of the subsequent deprotonation to form **11** (step B, Scheme 3) would decrease in rate as the concentration of TFA was increased. When a high concentration of TFA was present, the concentration of **10** would increase over the course of the reaction. In all of these steps, the N_b-nitrogen would remain protonated since its pK_a was much greater than the carbon at the indole-2 position. In fact, the retro-Pictet−Spengler mechanism cannot proceed with this N_b-nitrogen atom protonated. Although the protonated (**10**) and unprotonated (**11**) forms are in equilibrium, the likelihood of the free amine being present becomes increasingly smaller as the concentration of TFA increases. Therefore, deprotonation (step B, Scheme 3) was presumably the rate-determining step. This was contrary to the data depicted in Figure 4 and was inconsistent with first-order kinetics with respect to the concentration of TFA.

TABLE 4. KIE Experiments on 1-Substituted Phenyltetrahydro-β-carbolines



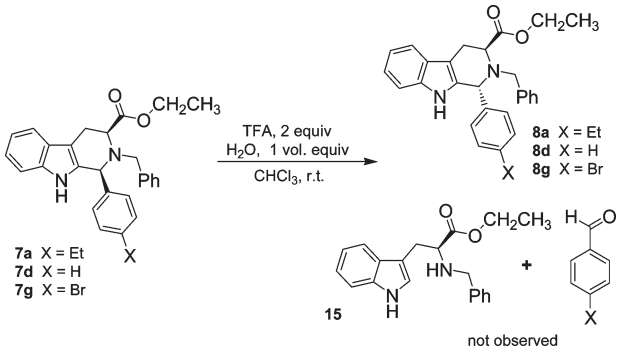
compd	substituent X	k_{obs} avg (s^{-1})	$k-d_{obs}$ avg (s^{-1})	KIE
7a	Et	0.0073	0.0060	**1.21**
7d	H	0.0018	0.0015	**1.20**
7g	Br	0.0016	0.0013	**1.30**

To determine if protonation at the indole-2 position was or was not the rate-determining step in the retro-Pictet−Spengler process, kinetic isotope experiments were designed and executed. Since primary KIEs are observable when an acid is involved in the rate-determining step, such experiments, in support of the other kinetic experiments, would provide useful mechanistic information about the epimerization process. If, in fact, this protonation was the rate-determining step, strong primary kinetic isotope effects (KIE) would be observed. The rate would be noticeably decreased when the epimerization was run in TFA-*d*. Since protonation/deprotonation of the nitrogen atom is fast (due to basicity), the isotope effect would not be observed for these mechanistic steps. In fact, similar experiments have

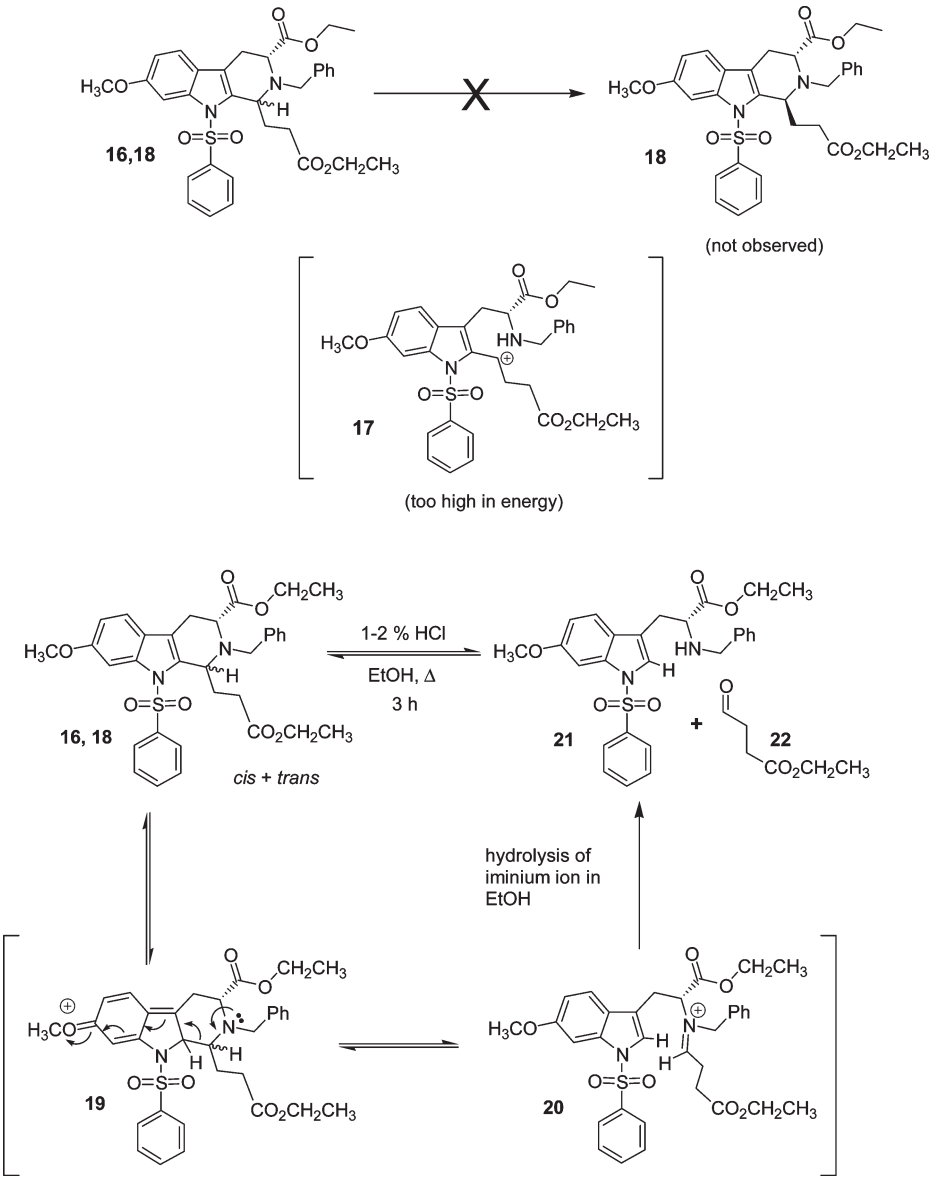
(31) Maresh, J. J.; Giddings, L.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stockigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710.

been carried out by O'Connor et al. in regard to the biosynthesis of indole alkaloids.[31] A deuterium atom was synthetically installed at the indole-2 position of tryptamine, followed by a Pictet−Spengler reaction with propanal under acidic conditions. KIEs between 2.0 and 2.6 were observed by O'Connor et al., which suggested that deprotonation at the indole-2 position was the rate-determining step in the Pictet−Spengler reaction.[31] Similar results were expected in these experiments if, in fact, protonation (or deprotonation) at the indole-2 position was the rate-determining step in the retro-Pictet−Spengler process. Each experiment was set up to keep the same reaction conditions as the reactions run earlier in TFA: that is to say, the concentration of starting *cis* isomer, concentration of TFA-*d*, and reaction temperature (303 K) in the NMR spectrometer (Scheme 4) were maintained as before. A small primary kinetic isotope effect (1.2−1.3) was observed (Table 4). The KIEs observed here were much smaller than those observed by O'Connor et al.[31] This data was inconsistent with the retro-Pictet−Spengler mechanism for the *cis* to *trans* epimerization process since a strong KIE was not observed. Therefore, it was concluded

SCHEME 5. ***Cis* to *Trans* Epimerization in the Presence of Water**



SCHEME 6. **Proposed Mechanism of the Retro-Pictet−Spengler Process Observed by Hamaker**[34]



that protonation at the indole-2 position was not the rate-determining step in the *cis* to *trans* epimerization of 1-(4′-substituted)-phenyltetrahydro-β-carbolines.

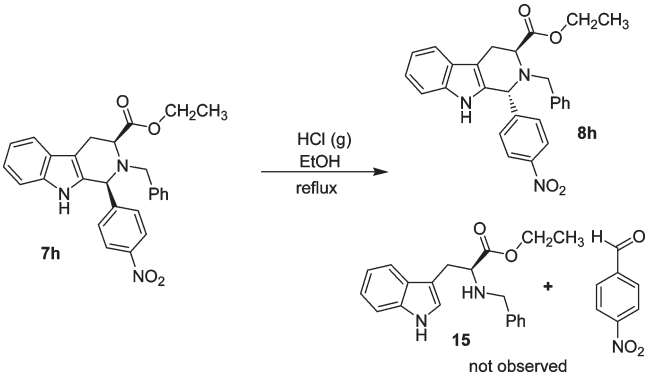
In addition to a study of the rates of epimerization for 1-(4′-substituted)-phenyltetrahydro-β-carbolines, chemical experiments were also conducted in order to determine the mechanism of the *cis* to *trans* epimerization. Czerwinski[32] had shown that deuterium was not incorporated into the *trans* product in the presence of deuterated TFA which confirmed that the olefinic mechanism had not occurred in the *cis* to *trans* isomerization. This same experiment was carried out in the 1-(4′-substituted)-phenyltetrahydro-β-carboline series (**7a**, **7d**, **7g**) to determine if different substituent patterns altered the outcome of that process. The *cis* substrate (**7a**, **7d**, **7g**) was dissolved in $CDCl_3$, and TFA-*d* was added (Scheme 4). The *cis* to *trans* epimerization process was allowed to take place, and the ^{1}H NMR spectrum was taken following aqueous workup. Full integration of the C-1 proton was observed in the spectrum. This was identical to the result observed by Czerwinski[32] which unequivocally indicated that the olefinic mechanism did not occur in the 1-(4′-substituted)-phenyltetrahydro-β-carboline series which was in agreement with the earlier work of Joule et al.[33] Therefore, this mechanism did not occur with 1-alkyl or 1-aryl substituents.

If the *cis* to *trans* epimerization proceeded through the retro-Pictet−Spengler mechanism, N_b-benzyltryptophan ethyl ester **15** would be an expected product if the reaction was carried out in the presence of water. Here, the iminium ion intermediate would be hydrolyzed to the tryptophan ethyl ester derivative **15** and the corresponding aldehyde. In this vein, the parent **7d** (12.5 mM) was dissolved in $CDCl_3$. Prior to the addition of TFA, 1.0 volume equiv of water (13.9 M) was added to the reaction medium. The TFA (27.0 mM) was then added, and the epimerization reaction was allowed to take place (Scheme 5). The reaction was monitored by TLC, and the ^{1}H NMR spectrum was acquired when the *cis* to *trans* epimerization was complete. At no time was N_b-benzyltrytophan ethyl ester **15** or the corresponding aryl aldehyde observed by TLC or by ^{1}H NMR spectroscopy. Hydrolysis of the ethyl ester was also not observed. With a large excess of water present in the reaction medium, N_b-benzyltryptophan ethyl ester would be expected if the iminium ion was formed in a retro-Pictet−Spengler process since this would be favored entropically. Since the epimerization was complete for the parent **7d**, the same reaction was carried out for both the *p*-ethylphenyl, **7a**, and *p*-bromophenyl, **7g**, substrates. The same result was realized in both of these cases, which suggested that the mechanism of epimerization did not change as the electronic nature at the C-1 position was varied. This data was consistent with the carbocationic mechanism since hydrolysis of a proposed iminium ion which would arise in the retro-Pictet−Spengler process was not observed.

In a separate earlier experiment, Hamaker[34] had shown that a retro-Pictet−Spengler mechanism was forced to occur if a strong electron-withdrawing group was installed on the indole N_a-nitrogen atom. This result was observed when a N_a-sulfonamide derivative **16** was reacted in ethanolic HCl. The N_b-benzyl tryptophan derivative **21** was the exclusive product of this process in the N_a-sulfonamido case of Hamaker;[34] the *trans* isomer **18** was not observed (see Scheme 6). It was believed this result was observed because the electron withdrawal of the sulfonamide retarded stabilization of the carbocationic intermediate **17** which prevented cleavage of the C−N bond. However, continued heating in ethanolic HCl resulted in the production of the tryptophan alkyl ester **21**, presumably via a retro-Pictet−Spengler reaction through iminium ion intermediate **20**. Since the retro-Pictet−Spengler mechanism had been postulated to take place in the N_a-sulfonamide case, the *cis* to *trans* epimerization of the N_a-H case, **7h**, was carried out under similar reaction conditions (Table 4). In this case, hydrolysis of the tetrahydro-β-carboline ring system to give N_b-benzyltryptophan ethyl ester **15** or the corresponding aryl aldehyde (or acetal) did not occur (see Table 5). After 3 h at reflux in concentrated ethanolic HCl, a mixture of *cis* and *trans* isomers was detected by TLC. This was confirmed by ^{1}H NMR spectroscopy following aqueous workup. The products of this reaction were then resubjected to the same reaction conditions overnight. The following day, decomposition was observed by TLC, but no N_b-benzyltryptophan ethyl ester **15** or *p*-nitrobenzaldehyde was observed by TLC or by NMR spectroscopy at any time during these reactions.

To minimize the possibility of decomposition, a 1:2 dilution of concentrated ethanolic HCl with EtOH was used as the solvent/reagent system. After 2 days at reflux, a mixture of *cis* and *trans* isomers was again observed by TLC in the 1-(4′-nitro)-phenyltetrahydro-β-carboline case, **7h**. Additional ethanolic HCl was added to the reaction mixture in order to increase the rate of epimerization. The appearance of more of the *trans* 1-(4′-nitro)-phenyltetrahydro-β-carboline diastereomer **8h** was observed after 4 h. The reaction was continued for an additional 2 days at which point a mixture of *cis* and *trans* isomers remained, accompanied by

TABLE 5. ***Cis* to *Trans* Epimerization of 1-(4′-Nitro)tetrahydro-β-carboline 7h under the Conditions of Hamaker[34]**

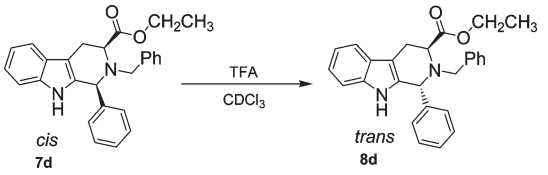


ethanolic HCl	time	**7h** (%)	**8h** (%)	**15** (%)
saturated solution	3 h	90	10	$<1^a$
	10 h[c]	ND	ND	ND
1:2 dilution with EtOH	2 d	60	40	$<1^b$
	4 d	25	75	$<1^b$

[a]Analyzed by ^{1}H NMR. [b]By TLC. [c]Decomposition occurred.

(32) Czerwinski, K. M. Ph.D. Thesis, University of Wisconsin−Milwaukee, **1995**.
(33) Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053.
(34) Hamaker, L. K. Ph.D. Thesis, University of Wisconsin−Milwaukee, **1995**.

TABLE 6. Temperature Effect on Rate[a]



temp (K)	k_{obs}[b] (s^{-1})
313.0	0.0132
308.0	0.0059
303.0	0.0018
300.0	0.0012
298.0	0.0007

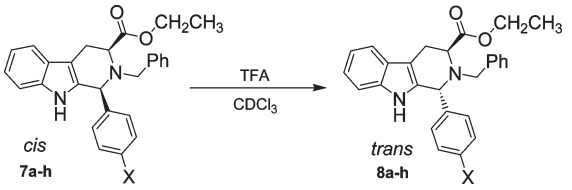
[a][*cis*] = 12.5 mM; [TFA] = 27.0 mM. [b]Average of three experiments.

slight decomposition as observed by TLC. The reaction was stopped at this point since it was clear that hydrolysis of an iminium ion intermediate from a retro-Pictet–Spengler mechanism did not occur vs an authentic sample of **15**.

Electron withdrawal at the C-1 position via the *p*-nitro group did not promote a retro-Pictet–Spengler process as was the case with the N_a-sulfonamide species of Hamaker.[34] In the cases with an indole, or an electron-rich indole, electron density flowed away from the indole ring during the formation of the proposed carbocationic intermediate. This was contrary to a retro-Pictet–Spengler-type mechanism wherein electrons flow into the indole ring when the iminium ion was formed.[34] Therefore, it was reasonable to believe that the retro-Pictet–Spengler mechanism did not occur in the *cis* to *trans* epimerization process of 1,2,3,4-tetrahydro-β-carbolines when indole, or an electron-rich indole, was employed.

Enthalpies and entropies of activation were determined from kinetic data. Such data was acquired for the parent **7d** at temperatures ranging from 298 to 313 K (Table 6).

TABLE 7. Energies of Activation[a]



compd	substituent X	$\sigma\rho$	E_a (kJ/mol)
7a	Et	0.4187	152.3[a]
7b	^{i}Pr	0.3908	152.3[a]
7c	^{t}Bu	0.3629	152.3[a]
7d	H	0.0000	**152.7**
7e	F	0.0977	152.6[a]
7f	Cl	−0.1535	152.9[a]
7g	Br	−0.2093	152.9[a]
7h	NO_2	−1.1025	153.8[a]

[*cis*] = 12.5 mM; [TFA] = 27.0 mM. [a]Data were calculated based on the Hammett plot and assumed negligible change in $\Delta S^{\ddagger}$.

The rate data collected as shown in Table 6 was then plotted according to the Arrhenius equation (Figure 5) to obtain energy of activation (E_a) data for the parent substrate, **7d**, and was determined to be 153.7 kJ/mol. Since the Arrhenius equation correlated rate data directly to the energy of activation, the differences in rates, namely the ρ value from Figure 3, was employed to determine the E_a for the series of compounds under study. The activation energies ranged from 152.3 to 153.8 kJ/mol for the series of 1-(4′-substituted)-phenyl-1,2,3,4-tetrahydro-β-carbolines (see Table 7).

In order to obtain more specific thermodynamic data, the rate data from Table 6 for 1-phenyltetrahydro-β-carboline **7d** was employed to construct an Eyring plot (Figure 6). The enthalpy of activation ($\Delta H^{\ddagger}$) and the entropy of activation ($\Delta S^{\ddagger}$) were extracted from the linear plot and were

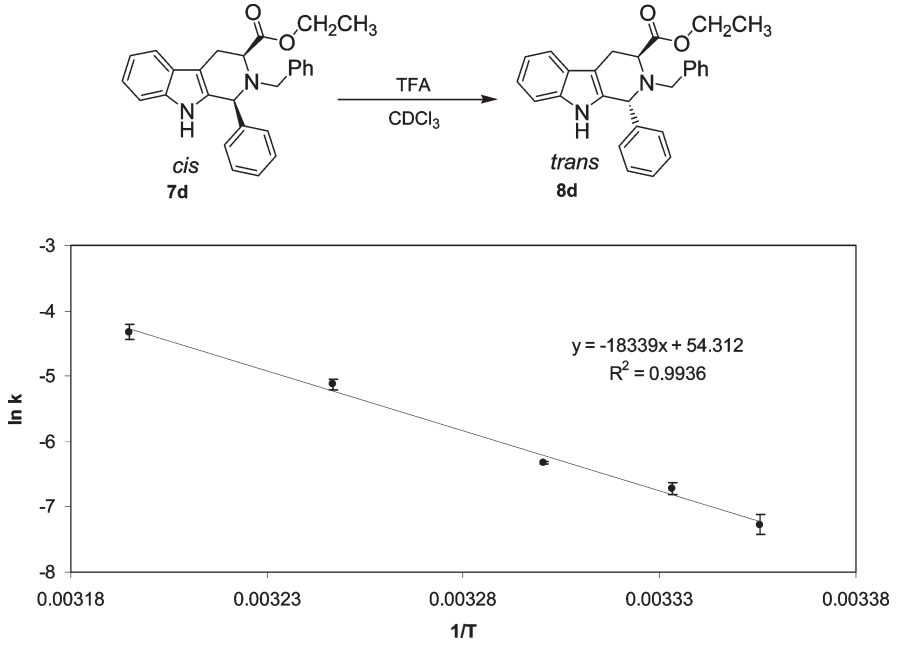


FIGURE 5. Arrhenius plot.

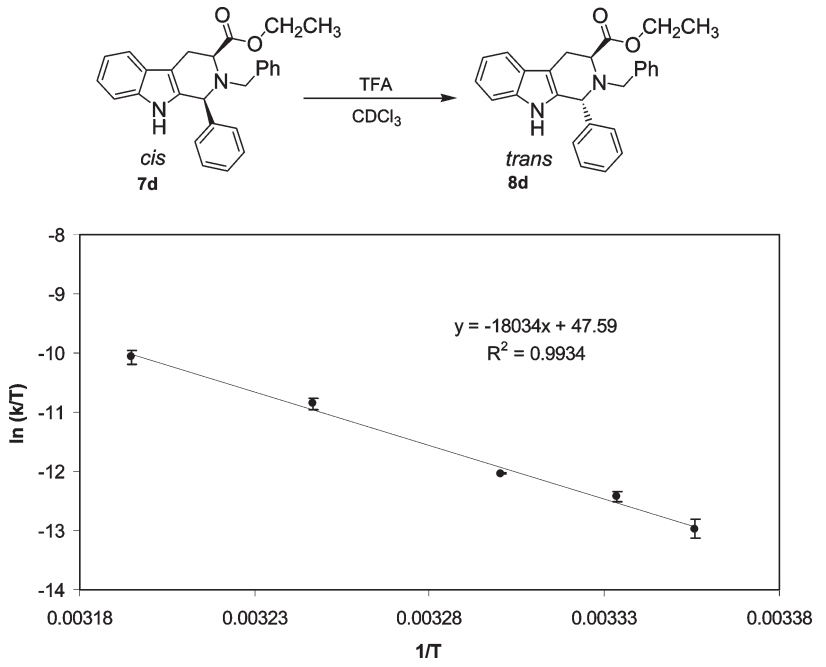
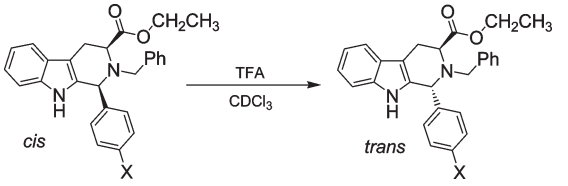


FIGURE 6. Eyring plot.

TABLE 8. Thermodynamic Data[a]



compd X	substituent X	σ^+	$\sigma\rho$	$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta H^{\ddagger}$[a] (kJ/mol)	$\Delta S^{\ddagger}$ [a] (J/K mol)
7a	Et	−0.30	0.4187	87.5	146.7[d]	200[d]
7b	^{i}Pr	−0.28	0.3908	87.7	147.0[d]	200[d]
7c	^{t}Bu	−0.26	0.3629	87.8	147.2[d]	200[d]
7d	H	0.00	0.0000	**89.9**[c]	**150.2**[b]	**199**[b]
7e	F	−0.07	0.0977	89.4	149.4[d]	200[d]
7f	Cl	0.11	−0.1535	90.8	150.4[d]	200[d]
7g	Br	0.15	−0.2093	91.2	150.4[d]	200[d]
7h	NO_2	0.79	−1.1025	96.3	156.9[d]	200[d]

[*cis*] = 12.5 mM; [TFA] = 27.0 mM ; at 303.0 K. [a]If $\Delta S^{\ddagger}$ remains reasonably constant. [b]Determined graphically from the Eyring plot. [c]Calculated from $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. [d]Data were calculated based on the Hammett plot and assumed negligible change in $\Delta S^{\ddagger}$.

determined to be 150.2 kJ/mol and 199 J/K·mol, respectively and the data is depicted in Table 8. Since both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined, the Gibb's free energy of activation ($\Delta G^{\ddagger}$) was calculated to be 89.9 kJ/mol. It was important to realize that the Hammett free energy relationship correlated rate data to the free energy of the reaction. Since the Hammett plot was constructed and $\Delta G^{\ddagger}$ had been determined for 1-phenyltetrahydro-β-carboline **7d**, $\Delta G^{\ddagger}$ for the remaining compounds studied in the Hammett analysis were determined, and the data is presented in Table 8. The difference in $\Delta G^{\ddagger}$ across the series of compounds was found to be 8.8 kJ/mol. Presumably, $\Delta S^{\ddagger}$ remained relatively constant throughout the series of compounds studied in the Hammett analysis. Due to the relatively small effect of $\Delta S^{\ddagger}$ on $\Delta G^{\ddagger}$, small changes in entropy would not affect $\Delta G^{\ddagger}$ to a significant degree. If this were true, $\Delta H^{\ddagger}$ was calculated for the remaining compounds and the data is shown in Table 8.

Conclusions

Three potential mechanistic pathways have been considered for the *cis* to *trans* epimerization of 1,2,3-trisubstituted 1,2,3,4-tetrahydro-β-carbolines. One of these, the olefinic pathway, had been ruled out by Czerwinski[32] and in the present study by deuterium-labeling experiments. Results from epimerizations carried out in TFA-*d* indicated that no deuterium was incorporated at the C-1 position, which would be necessary if the olefinic pathway was to take place. The remaining two mechanisms of epimerization, namely the

carbocationic pathway and the retro-Pictet−Spengler pathway, were compared on a kinetic basis.

A series of 1-(4′-substituted)-phenyltetrahydro-β-carbolines were synthesized by the Pictet−Spengler cyclization in order to study the *cis* to *trans* epimerization mechanism. In order to study this trend in more detail, the epimerization reaction was followed by ^{1}H NMR spectroscopy. The observed pseudo-first-order rate constants were determined graphically, which permitted a quantitative comparison of the rates of epimerization of each of the 1-(4′-substituted)-phenyltetrahydro-β-carbolines studied (**7a**−**h**). The observed rate constants were employed to construct a Hammett plot, which correlated to a line very well when σ^+ values were utilized. A ρ value of −1.4 was observed for the series of compounds studied and the negative slope was consistent with a positively charged intermediate. The magnitude of the ρ value was found to be considerably smaller than those expected for a benzylic cation, however this effect was attributed to electron delocalization from the neighboring indole ring, thus stabilizing the proposed carbocationic intermediate.

It was believed that a second protonation took place at the N_b-nitrogen atom after formation of the carbocationic intermediate, which resulted in a dicationic intermediate. The observed first-order kinetics with respect to TFA (after initial protonation of the substrate) was consistent with the formation of the dicationic intermediate in the carbocationic mechanism as this was determined to be the rate-determining step. On the other hand, pseudo-first-order kinetics was not expected in the retro-Pictet−Spengler process since the formation of the iminium ion intermediate required the N_b-nitrogen atom to be unprotonated.

Kinetic isotope experiments were devised and carried out where small primary kinetic isotope effects of 1.2−1.3 were observed for three separate tetrahydro-β-carbolines. The determined KIEs were considerably smaller than those reported by O'Connor[31] for deprotonation at the indole-2 position in the Pictet−Spengler mechanism. This implied that protonation at the indole-2 position was not involved in the rate-determining step of the *cis* to *trans* epimerization process. Therefore, the retro-Pictet−Spengler mechanism was ruled out since the rate of epimerization was dependent upon the concentration of TFA (first-order kinetics after protonation of the substrate) and protonation at the indole-2 position was not involved in the rate-determining step.

In separate, chemical experiments, N_b-benzyltryptophan ethyl ester was not observed when 1-(4′-substituted)-phenyltetrahydro-β-carbolines were epimerized with TFA in the presence of water or under the ethanolic HCl conditions of Hamaker.[34] Presumably, the iminium ion intermediate did not form in either case, and thus, the retro-Pictet−Spengler process did not occur since neither of these two products was observed by TLC or ^{1}H NMR spectroscopy.

In conclusion, a Hammett study alone was insufficient to distinguish between a carbocation-mediated pathway and a retro-Pictet−Spengler pathway in the 1-(4′-substituted)-phenyl-1,2,3,4-tetrahydro-β-carboline series. However, analysis of both rate data and chemical experiments proved to be inconsistent with the retro-Pictet−Spengler mechanism, and it was thus ruled out. On the other hand, the data were found to be consistent with a carbocationic mechanism for the C-1/N-2 bond scission process in the isomerization of *cis* N_b-benzyltetrahydro-β-carbolines into their more stable *trans* diastereomers. This process has important implications in regard to the total synthesis of indole alkaloids by internal asymmetric induction.

Experimental Section

General Procedure for the Preparation of Both *Cis* and *Trans* Diastereomers via the Pictet−Spengler Reaction of Aromatic Aldehydes under Acidic Conditions.[26] L-Tryptophan ethyl ester (13.5 g, 0.058 mol) was added to a 500-mL three-neck round-bottom flask containing dry benzene (300 mL). The flask was attached to a Dean−Stark trap topped by a reflux condenser for azeotropic removal of water during the course of the reaction. Trifluoroacetic acid (0.12 mol, 2.0 equiv) was added, and this was followed by addition of the aldehyde in dry benzene (0.070 mol, 1.2 equiv). The mixture was allowed to heat to reflux for 4−8 h under argon until all of the tryptophan ethyl ester was consumed as indicated by TLC (silica gel, hexanes/EtOAc, 3:1). The reaction mixture was then cooled to rt, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (300 mL) and washed with a solution of cold, saturated $NaHCO_3$ (3 × 300 mL) to remove TFA. The organic layer was separated and dried (Na_2SO_4). Analysis by TLC (silica gel, hexanes/EtOAc, 3:1) of the crude oil indicated the presence of two major components along with some unreacted aldehyde. The residue was chromatographed on silica gel (gradient elution, EtOAc/hexane = 1:10, 2:10, 3:10, 4:10) to provide the pure *cis* and *trans* diastereoisomers, respectively.

***cis*-1-Phenyl-1,2,3,4-tetrahydro-9*H*-β-carboline-3-carboxylic Acid Ethyl Ester (5d).** The general procedure was followed, and the *cis*/*trans* diastereomers were separated by column chromatography on silica gel. L-Tryptophan ethyl ester·HCl (20.1 g, 0.075 mol), benzaldehyde (8.3 mL, 0.081 mol), and TFA (13.2 mL, 0.18 mol) were used to obtain the *cis* isomer (95% overall yield, *cis* + *trans*). **5d**: mp 161−163 °C; $[\alpha]^{27}_D$ −8.89 (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.47−7.41 (m, 5H), 7.27−7.24 (m, 1H), 7.23−7.17 (m, 2H), 5.31 (s, 1H), 4.38−4.29 (m, 2H), 4.02 (dd, J = 11.2, 4.2 Hz, 1H), 3.30 (ddd, J = 15.1, 4.2, 1.8 Hz, 1H), 3.11−3.06 (m, 1H), 2.68 (br s, 1H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 141.1, 136.6, 135.1, 129.4, 129.13, 129.10, 127.6, 122.4, 120.1, 118.7, 111.4, 109.4, 61.7, 59.2, 57.4, 26.1, 14.7; MS (EI) *m*/*e* (rel intensity) 320 (M^+, 69), 247 (65), 218 (100), 169 (42), 144 (36), 77 (45). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.21; H, 6.40; N, 8.66. This material was employed in a later step.

***cis*-1-(4-Isopropylphenyl)-1,2,3,4-tetrahydro-9*H*-β-carboline-3-carboxylic Acid Ethyl Ester (5b).** The general procedure was followed, and the *cis*/*trans* diastereomers were separated by column chromatography on silica gel. L-Tryptophan ethyl ester·HCl (20.1 g, 0.074 mol), 4-isopropylbenzaldehyde (13.6 mL, 0.090 mol), and TFA (13.2 mL, 0.18 mol) were used to obtain the *cis* isomer (91% overall yield, *cis* + *trans*). **5b**: mp 195−197 °C; $[\alpha]^{27}_D$ −15.56 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.61 (m, 1H), 7.58 (s. 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.25−7.23 (m, 1H), 7.22−7.17 (m, 2H), 5.26 (s, 1H), 4.37−4.30 (m, 2H), 4.00 (dd, J = 11.2, 4.2 Hz, 1H), 3.29 (dd, J = 14.2, 4.2 Hz, 1H), 3.10−3.05 (m, 1H), 3.00 (p, J = 6.9 Hz, 1H), 2.60 (br s, 1H), 1.40, (t, J = 7.2 Hz, 3H), 1.34 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 149.8, 138.5, 136.6, 135.4, 129.1, 128.9, 127.6, 127.5, 127.3, 122.3, 120.0, 118.7, 111.4, 109.3, 61.6, 58.8, 57.5, 34.4, 26.2, 24.5, 24.4, 14.7; MS (EI) *m*/*e* (rel intensity) 362 (M^+, 94), 289 (87), 261 (54), 218 (100), 169 (32), 144 (33). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.35; H, 7.35; N, 7.61. This material was employed in a later step.

General Procedure for the Alkylation of the N_b-H Tetrahydro-*β*-carbolines.[26] Hunig's base (*N*,*N*-diisopropylethylamine, DIPEA; 87.0 mmol, 15 equiv) and benzyl bromide (7.0 mmol, 1.2 equiv) were added to a solution of tetrahydro-*β*-carboline (**5a**−**e**,**g**,**i**, **8a**−**e**,**g**; 5.8 mmol, 1 equiv) in dry acetonitrile (10 mL). This mixture was cooled to 0 °C and allowed to come to rt overnight. The solvent was removed under reduced pressure, and the residue was dissolved in cold EtOAc (10 mL) to remove the salt of the Hunig's base which had precipitated. The solution was filtered, and the filtrate was dried (Na_2SO_4) and concentrated in vacuo to yield a brown oil. Analysis of the crude material by TLC indicated the presence of a major component along with some unreacted benzyl bromide and starting material. The residue was purified on a silica gel column via flash chromatography (hexane/EtOAc 7:1) to yield the pure N_b-benzyltetrahydro-*β*-carboline isomer, respectively, as an oil which was then triturated with hexanes to form a pale yellow solid or white solid.

***cis*-2-Benzyl-1-(4-ethylphenyl)-1,2,3,4-tetrahydro-9*H*-*β*-carboline-3-carboxylic Acid Ethyl Ester (7a).** The modified general procedure was followed. The *cis* N_b-H analogue **5a** (0.50 g, 1.1 mmol), DIPEA (3.3 mL, 18.9 mmol), and benzyl bromide (0.2 mL, 1.5 mmol) were used to obtain the *cis* N_b-benzyl isomer (69%). **7a**: $[\alpha]^{27}_D$ −86.49 (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 1H), 7.39−7.24 (m, 9H), 7.20 (d, J = 8.1, 2H), 7.18−7.16 (m, 2H), 4.99 (s, 1H), 4.13 (d, J = 14.8 Hz, 1H), 3.98 (d, J = 14.8 Hz, 1H), 3.87 (dd, J = 7.9, 3.8 Hz, 1H), 3.86−3.75 (m, 2H), 3.43 (dd, J = 15.6, 6.3 Hz, 1H), 3.11 (dd, J = 15.2, 4.9 Hz, 1H), 2.69 (dd, J = 15.2, 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 144.5, 138.8, 137.8, 136.8, 134.1, 129.8, 128.5, 128.4, 127.44, 127.37, 122.2, 119.9, 118.8, 111.2, 107.6, 62.0, 61.5, 61.1, 57.2, 29.0, 24.6, 16.0, 14.4; MS (EI) *m*/*e* (rel intensity) 438 (M^+, 31), 365 (100), 248 (30), 218 (54). Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.51; H, 6.92; N, 6.35.

***cis*-2-Benzyl-1-(4-*tert*-butylphenyl)-1,2,3,4-tetrahydro-9*H*-*β*-carboline-3-carboxylic Acid Ethyl Ester (7c).** The modified general procedure was followed. The *cis* N_b-H analogue **5c** (0.52 g, 1.4 mmol), DIPEA (3.6 mL, 20.6 mmol), and benzyl bromide (0.3 mL, 2.1 mmol) were used to obtain the *cis* N_b-benzyl isomer (61%). **7c**: mp 155−156 °C; $[\alpha]^{27}_D$ +48.57 (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8 Hz, 1H), 7.41−7.32 (m, 7H), 7.29−7.25 (m, 4H), 7.20−7.15 (m, 2H), 5.02 (s, 1H), 4.12 (d, J = 14.7 Hz, 1H), 4.01 (d, J = 14.7 Hz, 1H), 3.88 (dd, J = 6.5, 5.2 Hz, 1H), 3.86−3.81 (m, 1H), 3.72−3.67 (m, 1H), 3.44 (dd, J = 15.6, 6.6 Hz, 1H), 3.11 (dd, J = 14.9, 4.4 Hz, 1H), 1.36 (s, 9H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 151.2, 139.0, 137.3, 136.7, 133.9, 129.6, 129.5, 128.5, 127.4, 125.7, 122.1, 119.9, 118.8, 111.2, 107.8, 61.7, 61.1, 61.0, 57.5, 35.0, 31.8, 24.2, 14.4; MS (EI) *m*/*e* (rel intensity): 466 (M^+, 25), 393 (90), 275 (26), 218 (100). Anal. Calcd for $C_{31}H_{34}N_2O_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.85; H, 7.53; N, 5.93.

Procedure for the ^{1}H NMR Kinetics Experiments. The 1,2,3-trisubstituted 1,2,3,4-tetrahydro-*β*-carboline (**7a**−**h**; 1.25×10^{-5} mol, 12.5 mM final concentration) was dissolved into $CDCl_3$ (800 μL) and then transferred to an NMR tube. The proton spectrum was taken, and then the tube was ejected. The TFA (200 μL of a 135 mM solution in $CDCl_3$, 27.0 mM final concetration) was quickly added to the tube and the tube injected into the spectrometer with an internal temperature of 303.0 K. The sample was locked and shimmed before starting the kinetic experiment. A series of 50 spectra were taken over the course of 48 min for all compounds except for the 4-nitro compound (**7h**), where 50 spectra were taken over an 11 h period. The resulting 2D data set was then phased manually and then divided into 50 equal slices, each representing one ^{1}H spectrum. Each spectrum was integrated with the *trans* isomer calibrated to one proton. The ratio of *cis* to *trans* isomers was then determined, which allowed for the calculation of the *cis* isomer concentration. The concentration data was then plotted against time. A first-order exponential decay was realized, and the pseudo-first-order rate constant was determined graphically.

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Supporting Information Available: Supplemental figures, complete experimental procedures, synthetic procedures, and compound characterization data as well as ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.