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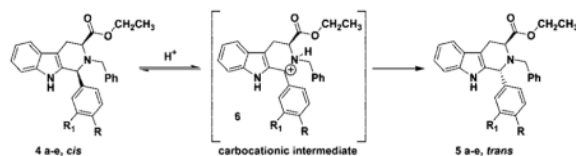
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Study of the Cis to Trans Isomerization of 1-Phenyl-2,3-disubstituted Tetrahydro- β -carboline at C(1). Evidence for the Carbocation-Mediated Mechanism

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Abstract



The present study was undertaken to shed light on the mechanism of the epimerization of *cis*-1,2,3-trisubstituted tetrahydro- β -carboline into the *trans* isomers via a potential carbocationic intermediate at C(1). In order to study the pathway involved in C(1)–N(2) bond cleavage, the electronic character of the carbon atom at C-1 was altered by substitution of electron-rich and electron-poor phenyl rings at this position. This provided direct evidence of the effects of charge at the proposed site of the carbocationic intermediate. In this regard, a diverse set of 1-(phenyl substituted)-2-benzyl-3-ethoxycarbonyl-1,2,3,4-tetrahydro- β -carboline has been synthesized via the Pictet–Spengler reaction by condensation of L-tryptophan derivatives with electron-poor and electron-rich aromatic aldehydes. The epimers involved in the isomerization mechanism were investigated by dynamic 1H and ^{13}C NMR spectroscopic and X-ray crystallographic analyses. The kinetic studies, which involved conversion of *cis* diastereomers into their *trans* counterparts, were carried out in dilute TFA/ CH_2Cl_2 . The 1-(4-methoxyphenyl) *cis* diastereomer epimerized at a much faster rate into the corresponding *trans* diastereomer than the related 1-(4-nitrophenyl) *cis* diastereomer epimerized. These observations provide support for the carbocationic intermediate in the C(1)–N(2) scission process. The understanding of this epimerization process is of importance when Pictet–Spengler reactions are carried out under acidic conditions during the synthesis of indole alkaloids.

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Supporting Information Available: 1H and ^{13}C NMR spectra of compounds **2a–e**, **3a–e**, **4a–e** and **5a–e**; COSY, HSQC, and HMBC 2D spectra for compounds **4a–e** and **5a–e**; X-ray crystallographic data and ORTEP plots for **2e**, **3e**, **4a**, and **5a** · HCl. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 tetrahydroisoquinolines¹ 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 mechanisms which operate in alcoholism.^{4,5} The enantiospecific Pictet–Spengler reaction, in particular, has stimulated widespread interest in both organic and medicinal chemistry^{6–18} and has resulted in the total synthesis of a number of natural products including (–)-alstophylline,^{19,20} (–)-macralstonine,^{21,22} ajmaline²³ and (–)-raumacline.^{21,24} Ungemach et al.⁶ reported on the diastereospecific Pictet–Spengler reaction after condensation of N_b -benzyltryptophan methyl ester with aldehydes which resulted in the 100% stereoselective formation of *trans*-1,3-disubstituted diastereomers. 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.^{25,26} These studies conclusively indicated that the steric bulk of the incoming carbonyl compound, the substituents at the N_b -nitrogen (N2) position and the size of ester function play major roles in the diastereoselective formation of the *trans* isomer. 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. In efforts aimed at the investigation of the mechanism of the isomerization at C(1), a set of readily accessible electron-donating and electron-withdrawing aromatic aldehydes have been reacted with tryptophan ethyl ester to provide 1-phenyl substituted tetrahydro- β -carbolines (Scheme 1).

It is well documented that N_a -methyl, N_b -benzyl tryptophan alkyl esters undergo the Pictet–Spengler reaction in nonacidic aprotic media with aldehydes of varied steric bulk to furnish the *trans* and *cis* diastereomers in an approximate ratio of 4:1, with the *trans* isomer predominating.²⁵ Furthermore, the diastereomeric ratio changes to approximately 3:2 for N_a -H, N_b -H tryptophan alkyl esters in both nonacidic and acidic media. Aldehydes as small as acetaldehyde provide the *cis* diastereomer in excess.²⁵ These diastereomers are usually separated via silica gel chromatography; however, the separation remained difficult in many cases due to their close retention times. This is especially important in large scale reactions. On the other hand, the thermodynamically more stable *trans* isomer, an important chiral intermediate in the total synthesis of macroline/sarpagine/ajmaline indole alkaloids,^{27–31} could be exclusively obtained by epimerization of the *cis* stereoisomer or a mixture of the *cis* and *trans* isomers of the N_b -benzylated moieties under acidic conditions.^{3,32–35} On the basis of the elegant work of Joule et al. on reserpine,³⁶ three potential intermediates, depicted in Figure 1, were considered for this epimerization process at C(1).

Among the three potential intermediates (**6**, **7**, **8**) depicted in Figure 1, the *cis* to *trans* epimerization process, which proceeds by protonation of the N_b -nitrogen atom with concomitant cleavage of the C(1)–N(2) bond followed by reclosure to the *trans* isomer, cation **6** is the most consistent with recent evidence.^{25,34,35,37} Importantly, intermediate **7** has been excluded on the basis of epimerizations carried out in CF₃COOD.²⁵ The carbocation **6**, so generated, after rotation of the C-1/C-9a carbon–carbon bond, could recyclize to provide the more thermodynamically stable *trans* diastereomer.^{34,35} Recent results during the synthesis of alkoxy substituted indole alkaloids indicated that such an intermediate might be involved especially in the case of indoles substituted at C(4) or C(6) with methoxyl groups.^{31,38–41} This epimerization afforded 100% stereoselective formation of the *trans* diastereomer, specifically at C-1, under standard acidic conditions of TFA/CH₂Cl₂.²⁵ Similar findings have been observed by Han et al.³⁷ during a conformational study of *cis* and *trans* N_a -methyl and N_a -H substituted N_b -benzyl diesters. Evidence from simple kinetic studies is in agreement with the

presence of the carbocationic intermediate **6** in these isomerizations. Furthermore, analysis of the conformations of the isomers by NMR spectroscopy provided a structural basis for the generation of carbocationic intermediate, **6**, in the cis to trans isomerization (at C-1).³⁷ It was felt that preparation of 1-phenyl substituted tetrahydro- β -carbolines from substituted benzaldehydes and tryptophan ethyl ester would provide a means to study the C(1)–N(2) scission process by varying the electronic character at C(1), the direct site of the proposed carbocation (see **6**). Examination of the results described herein via kinetic data is in agreement with the generation of the carbocationic intermediate **6** as a key intermediate in this cis to trans epimerization process. This is, presumably, important with regard to Pictet–Spengler reactions carried out under acidic conditions in both the tetrahydro- β -carboline and tetrahydroisoquinoline series.

Results and Discussion

It is well accepted that the Pictet–Spengler condensation of N_a -H, N_b -H tryptophan alkyl esters provides a mixture of cis and trans isomers.^{25,26} It is clear that the presence of a benzyl group on the N_b -nitrogen atom affects the diastereochemical outcome of the Pictet–Spengler reaction to provide the corresponding trans diastereomer, often stereospecifically under acidic conditions. In this regard, systematic variation of substituents which contain electron donating or electron withdrawing groups at C-1 should effect the stabilization of a carbocationic intermediate, consequently, affecting the rate of the epimerization process. In this vein, three experiments were devised which employed a Pictet–Spengler cyclization, followed by N_b -benzylation and then kinetic experiments on the cis to trans epimerization. The synthetic process employed to access the cis and trans isomers is depicted in Schemes 1, 2, and 3. The pure cis and trans isomers represented by **2** and **3**, respectively, were prepared analogous to the method employed by Zhang^{20,21,24,42} for related N_a -methyl tetrahydro- β -carbolines. First, the Pictet–Spengler cyclization of L-tryptophan ethyl ester (**1**) with substituted aryl aldehydes provided the optically active N_a -H, N_b -H-1,2,3,4-tetrahydro- β -carbolines. However, in many cases the Pictet–Spengler reaction was carried out in benzene/TFA to prevent epimerization at C-3 when electron-rich aldehydes were employed.^{25,26}

A number of aldehydes including 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-chlorobenzaldehyde, 4-tolualdehyde and 4-methoxybenzaldehyde were reacted with the free base of tryptophan ethyl ester. This afforded a series of 1-aryl substituted-3-ethoxycarbonyl-tetrahydro- β -carbolines. As expected, the process tolerated a diverse set of aromatic aldehydes. The Pictet–Spengler cyclization resulted in a mixture of cis and trans isomers which were then separated by careful flash column chromatography. Excellent yields of tetrahydro- β -carbolines were obtained upon stirring for 30 h with 4-nitro- and 3-nitrobenzaldehydes in nonacidic, aprotic media, providing a cis: trans ratio of 2:3. On the other hand, nonacidic aprotic media was less effective when electron-rich aldehydes were employed (Table 1). Very poor yields of tetrahydro- β -carbolines were observed and oftentimes epimerization occurred at the tryptophan chiral center.^{25,43} These reactions did not go to completion in 30 h and yields were less than 40% (Table 1). The yields could be improved on prolonged heating; however, the optical purity of the products was low (**2e**, $[\alpha]_D^{28}$ –6.0) under these conditions. In order to effect cyclization, it was necessary to add TFA to the reaction medium to increase the rate of the Pictet–Spengler cyclization and to prevent epimerization of the chiral center in the intermediate imine.²⁵ Each of these individual Pictet–Spengler reactions were repeated in the presence of 1–2 equiv of TFA which produced the tetrahydro- β -carbolines in 4–7 h in high optical purity. Indeed, the reactions cleanly provided the cis and trans diastereomers (**2c–2e**, cis; **3c–3e**, trans) in reasonable yields. The cis (**2c–2e**) and trans (**3c–3e**) diastereomers prepared under acidic conditions were isolated, and the ratio of cis to trans diastereomer remained approximately 2:3, respectively. An overall increase in optical purity (**2e**, $[\alpha]_D^{28}$ –14.5) was observed under acidic

conditions. The successful formation of the desired tetrahydro- β -carbolines was established by ^1H NMR, ^{13}C NMR, and mass spectrometry. The stereochemical configuration of *cis*-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro- β -carboline (**2e**) and *trans*-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro- β -carboline (**3e**) was confirmed as *cis* and *trans* by single crystal X-ray crystallography, respectively (Figures S1 and S2, Supporting Information).

The N_b -alkylation of the N_b -H tetrahydro- β -carbolines (*cis*-**2**; *trans*-**3**) was achieved by stirring either the *cis* or *trans* diastereomer (individually) in the presence of Hunig's base (*N,N*-diisopropylethylamine, DIPEA) and benzyl bromide in dry acetonitrile. These mixtures were heated at reflux for 8–24 h under an inert atmosphere (Schemes 3 and 4). Purification by rapid flash column chromatography gave the N_a -H, N_b -benzyl-1,2,3-trisubstituted tetrahydro- β -carbolines (*cis*-**4**; *trans*-**5**). Epimerization was not observed in the alkylation. The benzylation step was also successful if a *cis* and *trans* mixture was employed as the starting material; however, separation of the diastereomers remained tedious due to the close R_f values (i.e., for **4a** and **5a**, TLC, silica gel, *cis* 0.50; *trans* 0.45, EtOAc/hexane). Therefore, the *cis* and *trans* isomers (**2** and **3**) were separated and individually alkylated with benzyl bromide. Attempts to achieve N_b -benzylation using bases other than Hunig's base, such as triethylamine, pyridine, and Na_2CO_3 , as well as in different solvents (DMSO, CH_2Cl_2 , or dioxane) afforded only a trace of the desired tetrahydro- β -carbolines. Among the various solvents employed, CH_3CN was the most effective. Assignment of the proton and carbon resonances of the *cis* (**4**) and *trans* (**5**) isomers was carried out on the basis of 1D and 2D NMR (COSY, HSQC, HMBC) experiments. The data are presented in Tables S1 and S2, respectively, and the spectra are provided in the Supporting Information. Inspection of the proton and carbon spectra of the individual diastereomers clearly demonstrated a marked difference between the *cis* and *trans* isomers, in particular, the proton resonances between δ 3.30 and 3.50 were quite distinct. Examination of the ^1H NMR spectrum of the *cis* isomer (see **4a**) indicated the presence of two distinct signals for the two nonequivalent, diastereotopic methylene protons of $\text{H}_{4\text{ax}}$ (δ 3.18, ddd, $J = 15.6, 5.1, 1.0$ Hz) and $\text{H}_{4\text{eq}}$ (δ 3.44, ddd, $J = 15.6, 6.3, 1.3$ Hz). Both protons appear as a significant doublet of doublets with a common geminal coupling constant of 15.6 Hz and an additional vicinal coupling constant of 6.3 Hz ($^3J \text{ H}_3\text{--H}_{4\text{ax}}$) and 5.1 Hz ($^3J \text{ H}_3\text{--H}_{4\text{eq}}$), respectively. The structures of the N_b -benzyl *cis* and *trans* diastereomers (**4a** and **5a**) were confirmed by X-ray analysis (Figures S3 and S4, Supporting Information).

The effect of the 4-substituted phenyl substituent at C(1) on the rate of the *cis* to *trans* isomerization in the N_b -benzyl series was studied, analogous to the method of Han.³⁷ The pure N_a -H, N_b -benzyl *cis* diastereomers, **4a–e** were dissolved in dilute TFA in CH_2Cl_2 and allowed to stir at room temperature (Table 2). At 30 min intervals, an aliquot of the reaction mixture was removed and quenched with cold, dilute, mild base (Na_2CO_3). The concentrated sample was then taken up in CDCl_3 . The progress of the reaction was monitored by ^1H NMR spectroscopy and the ratio of *cis*:*trans* diastereomers was determined by integration of the proton spectrum of the crude material. Analysis of the proton NMR spectra showed the collapse of individual doublets ($\text{H}_{4\text{a}}$ and $\text{H}_{4\text{b}}$) in the *cis* compound with emergence of a doublet centered between the individual doublets for the *trans* isomer. The initial progress of the reaction, as indicated by TLC, illustrated the epimerization of the entire series had been completed in less than 4 h (Table 2). Analysis of the data in Table 2 indicated the 4-methoxy substituted *cis* isomer **4e** epimerized at a more rapid rate than the corresponding 4-nitro *cis* analog (**4a**). More importantly, analysis of the optical rotations indicated that the optical activity had been retained.

The *cis* isomer, **4a**, $[\alpha]_{\text{D}}^{28} -57.2$ (*c* 1.50, CHCl_3), epimerized to the *trans* diastereomer, **5a**, with 100% conversion and a rotation of $[\alpha]_{\text{D}}^{28} -73.6$ (*c* 1.50, CHCl_3). When the above rotation of the *trans* isomer from the epimerization process was compared to the *trans* isomer **5a** originally

obtained from the N_b -benzylation of **3a** \rightarrow **5a** (Scheme 3), they were found to be identical. Analysis of this data further supported the proposed mechanism of C(1)–N(2) scission via the carbocationic intermediate **6**. In addition, the optical rotation data eliminated the possibility of epimerization at C(3). Had epimerization occurred at C(3), the enantiomer of **5a** would have been formed and the rotation would have been equal but opposite in sign, namely $[\alpha]_D^{28} +73.6$. In addition, comparison of the NMR and mass spectral data for the two trans isomers **5a** confirmed they were identical. With the intent of determining the final equilibrium ratio of this epimerization, the trans diastereomer (**5a**) was heated in excess acid (at length). At no time was any of the cis isomer (**4a**) observed nor the corresponding N_b -benzyl tryptophan ethyl ester, **9**, which would have arisen from a retro Pictet–Spengler/hydrolysis process (Scheme 4).³⁵ In all of the epimerization experiments, **9** was not detected by TLC or NMR spectroscopy, arguing against a retro Pictet–Spengler mechanism.³⁵ To investigate this trend further, the 3-nitro-, 4-chloro- and 4-methylphenyl substituted *cis*-tetrahydro- β -carboline (**4b**, **4c**, **4d**) were employed in the kinetic study. Similar trends were observed in the above series (Table 2), and the conversions yielded optically active trans diastereomers.

The rate of epimerization was related to the amount of electron density on the 1-phenyl substituent. Examination of the data clearly indicated the 4-nitro- (**4a**), 3-nitro- (**4b**), and 4-chlorophenyl (**4c**) *cis*- N_b -benzyl substituted isomers epimerized at a slower rate than the corresponding 4-methyl- (**4d**) and 4-methoxyphenyl (**4e**) substituted analogs. Donation of electrons from the methoxyl group, presumably, stabilized the carbocationic intermediate at C(1) in **6** (see Figure 1), thereby stabilizing intermediate **10** via an oxonium ion contributor **11**, as well as iminium ion form **12** (see Figure 2). Previous results with 6-methoxy indoles, pioneered by Zhang and Cox et al., observed stabilization of the carbocationic pathway (**6**, Figure 1) by electron donation of the methoxyl substituent on ring A.^{20,26,33,37} In the case of the 4-methylphenyl substituted tetrahydro- β -carboline **5d**, the rate of isomerization of *cis* **4d** to trans **5d** also increased when compared to that of **4a** \rightarrow **5a**. The 4-nitro group effectively retarded the acid induced epimerization of the *cis* isomer into the trans diastereomer as the nitro and chloro groups withdrew electron density from the phenyl group and destabilized the carbocationic intermediate (see Figure 3) which would result from C(1)–N(2) cleavage. This trend, the rate enhancement in the case of **4d** and **4e** as compared to the rate decrease with **4a** and **4b**, is in agreement with the mechanism of C(1)–N(2) scission via a carbocationic intermediate **6** (Scheme 5). A similar trend might be expected for the retro-Pictet–Spengler process as electron donation would stabilize iminium ion **8**. However, if protonation at the indole-2 position was the rate determining step, an electron withdrawing group (i.e., NO_2) would presumably increase the rate of protonation at the indole-2 position and the 4-methoxyphenyl substituent would decrease the rate (Scheme 4). Therefore, the rate of epimerization would have increased. This is the exact opposite of what was observed here. Further experimentation is in progress to address this issue.

Conclusion

The Pictet–Spengler reaction of L-tryptophan ethyl ester with aromatic aldehydes provided a mixture of the *cis* (**2**) and *trans* (**3**) diastereomers in approximately a 2:3 ratio, as expected.^{6, 25,26} Chromatographic separation and N_b -benzylation of the pure *cis* and *trans* isomers, respectively, gave the required *cis*- N_b -benzyl tetrahydro- β -carboline (see **4**) and *trans*- N_b -benzyl diastereomers (see **5**) for the study of the C(1)–N(2) scission process. This study focused on the stabilization of the carbocationic intermediate (see **6**) in a more direct fashion than previously possible.^{35,37} It is clear that the 4-methoxyphenyl C(1) substituted *cis* isomer **4e** isomerized at a more rapid rate than the corresponding isomerization of the 4-nitrophenyl analog *cis*-**4a** to *trans*-**5a** (see Table 2) under acidic conditions. The rate of isomerization of the *cis*-4-nitrophenyl isomer and the 4-methoxyphenyl *cis* diastereomer were in agreement

with the ability to stabilize the incipient carbocation at C(1). During the epimerization experiments, **9** was not observed, which would be formed by a retro Pictet–Spengler/hydrolysis process of iminium intermediate **8**.³⁵ These results lend more direct support for the involvement of a carbocationic intermediate at C(1) in the C(1)–N(2) scission process, however, similar results might be observed for the retro Pictet–Spengler mechanism, depending on the rate determining step. Therefore, intermediate **8** cannot be entirely excluded. If protonation at C-2 in the retro Pictet–Spengler mechanism is the rate determining step, the 4-nitrophenyl substituent at C-1 would increase the rate of epimerization whereas the 4-methoxyphenyl substituent would decrease the rate. This is opposite to what was observed and argues against the retro Pictet–Spengler mechanism. Further work is in progress to better distinguish between these two reaction mechanisms. These results have implications with regard to the use of asymmetric Pictet–Spengler reactions in acidic media in the synthesis of natural products.^{12–14,19–22,24}

Experimental Section

General Procedure for the Preparation of Both Cis and Trans Diastereomers (**2a**, **2b**, **3a**, **3b**) via the Pictet–Spengler Reaction of Aromatic Aldehydes under Nonacidic Conditions

L-Tryptophan ethyl ester (**1**, 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. The corresponding aldehyde (0.070 mol, 1.2 equiv) was added to the reaction mixture and was then heated to reflux for 18–24 h under argon, until all of the tryptophan ethyl ester, **1**, was consumed as indicated by TLC (silica gel, hexanes:EtOAc, 3:1). The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure. Examination of the TLC (silica gel, hexanes:EtOAc, 3:1) of the crude mixture indicated only two major spots 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 pure cis and trans diastereomers, **2a–b** and **3a–b**, respectively.

General Procedure for the Preparation of Both Cis and Trans Diastereomers (**2c**, **2d**, **2e**, **3c**, **3d**, **3e**) via the Pictet–Spengler Reaction of Aromatic Aldehydes under Acidic Conditions

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 process. To the reaction mixture was added trifluoroacetic acid (0.116 mol, 2.0 equiv), and this was followed by addition of the aldehyde in dry benzene (0.070 mol, 1.2 equiv). The mixture was heated to reflux for 4–8 h under argon, until all of the tryptophan ethyl ester, **1**, 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 cold, saturated NaHCO₃ (3 × 300 mL) to remove TFA. The organic layer was separated and dried (Na₂SO₄). 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, **2c–e** and **3c–e**, respectively.

General Procedure for the Alkylation of the *N*₆-H Tetrahydro- β -carbolines (**4a–e**, **5a–e**)

To a solution of tetrahydro- β -carboline **2** or **3** (5.8 mmol, 1 equiv) in dry acetonitrile (10 mL) were added Hunig's base (*N,N*-diisopropylethylamine, DIPEA) (8.7 mmol, 1.5 equiv) and benzyl bromide (7.0 mmol, 1.2 equiv). This mixture was heated to reflux for 8–24 h under argon. 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 (K₂CO₃) and concentrated in vacuo to yield a brown

oil. Analysis of the crude material 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 isomer **4** or **5**, respectively, as an oil which was then triturated to form a pale yellow or white solid.

General Procedure for the Kinetic Epimerization Experiments (4a–e → 5a–e)

To a solution of pure diastereomer **4** (0.015 mol) in dry CH₂Cl₂ (5 mL) was added dilute TFA (a solution of 0.2 mL of TFA dissolved in 10 mL of CH₂Cl₂ was prepared; from this dilution only 0.2 mL was employed). The mixture was allowed to stir at rt and at 30 min intervals (as indicated in Table 1); 1 mL of reaction solution was removed and diluted with CH₂Cl₂ (25 mL) after which it was then quenched with cold aq 0.1 N NH₄OH (2 × 50 mL). The organic layer was separated and dried (K₂CO₃). The solvent was removed under reduced pressure, and the residue was taken up in CDCl₃ to determine the ratio of the two diastereoisomers by integration of the ¹H NMR spectrum (see Table 2).

L-Tryptophan Ethyl Ester (1)

To a saturated solution of 100% ethyl alcohol (6 L) and HCl (anhydrous) was added L-tryptophan (500 g, 2.45 mol). The reaction vessel was brought to reflux overnight and then cooled to 5 °C after all the starting material was consumed as indicated by TLC (NH₄OH, hexanes:EtOAc, 2:1, silica gel). A white precipitate formed which was filtered in vacuo and dried. Multiple crystallizations were performed on the filtrate, leaving the HCl salt of **1** (690 g, 2.44 mol, 99%). This material was extracted with cold, saturated NaHCO₃ and CH₂Cl₂ (3 × 300 mL), when required, for the Pictet–Spengler reactions. ¹H NMR (500 MHz, CDCl₃): δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 4.21–4.14 (m, 2H), 3.83 (dd, *J* = 7.6 Hz, 5.0 Hz, 1H), 3.30 (dd, *J* = 14.3 Hz, 4.9 Hz, 1H), 3.07 (dd, *J* = 14.0 Hz, 7.6 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 175.6, 137.0, 128.5, 123.4, 122.4, 119.8, 119.2, 111.7, 111.5, 61.1, 55.2, 31.4, 15.0.

cis-1-(4-Nitrophenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic Acid Ethyl Ester (2a)

The general procedure was followed. L-Tryptophan ethyl ester (13.5 g, 0.058 mol) and 4-nitrobenzaldehyde (11.8 g, 0.078 mol) were used to obtain the product. Mp: 164 °C. [α]_D²⁸: –74.5 (c 6.40, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.47 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.26–7.19 (m, 2H), 5.42 (s, 1H), 4.39–4.30 (m, 2H), 4.02 (dd, *J* = 10.9 Hz, 4.1 Hz, 1H), 3.32 (ddd, *J* = 14.9 Hz, 4.0 Hz, 1.9 Hz, 1H), 3.11–3.06 (m, 1H), 2.30 (br s, 1H), 1.42 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 172.7, 148.5, 148.3, 136.8, 133.5, 130.2, 129.7, 127.4, 123.0, 120.6, 119.1, 111.3, 109.9, 61.9, 58.6, 57.2, 25.9, 14.9. MS (EI) *m/e* (rel intensity): 365 (M⁺, 93), 292 (100), 264 (65), 243 (40), 217 (85), 169 (41), 144 (50). HRMS calcd for C₂₀H₁₉N₃O₄ (M + H)⁺ 365.1376; found, 365.1305. The product was used directly in a following step.

trans-1-(4-Nitrophenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic Acid Ethyl Ester (3a)

The general procedure was followed. L-Tryptophan ethyl ester (13.5 g, 0.058 mol) and 4-nitrobenzaldehyde (11.8 g, 0.078 mol) were used to obtain the product. Mp: 119 °C. [α]_D²⁸: –86.4 (c 6.40, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.18 (s, 1H), 7.14–7.07 (m, 2H), 5.67 (s, 1H), 4.48–4.40 (m, 2H), 4.20 (t, *J* = 5.4 Hz, 1H), 3.64 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 3.52 (dd, *J* = 6.8 Hz, 2.9 Hz, 1H), 2.28 (br s, 1H), 1.84 (t, *J* = 6.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 174.0, 149.8, 148.2, 136.7, 132.2, 129.8, 127.3, 124.4, 123.0, 120.3, 118.9, 111.4, 109.5, 61.7, 54.7, 53.1, 25.1, 14.6. MS (EI) *m/e* (rel intensity): 365 (M⁺, 100), 292 (57), 243 (33), 217 (73), 169 (32),

144 (33). HRMS calcd for $C_{20}H_{19}N_3O_4$ ($M + H$)⁺ 365.1376; found, 365.1394. The product was used directly in a following step.

***cis*-2-Benzyl-1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (4a)**

The general procedure was followed. **2a** (2.0 g, 5.5 mmol), DIPEA (1.1 g, 8.2 mmol), and benzyl bromide (1.1 g, 6.4 mmol) were used to obtain the product. Mp: 166–170 °C. $[\alpha]_D^{28}$: –57.2 (*c* 1.50, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.0, 2H), 7.42 (s, 1H), 7.38–7.34 (m, 4H), 7.32–7.27 (m, 2H), 7.24–7.18 (m, 2H), 5.10 (s, 1H), 4.08 (d, *J* = 14.5 Hz, 1H), 4.01 (d, *J* = 14.5 Hz, 1H), 3.98–3.93 (m, 2H), 3.80–3.76 (m, 1H), 3.42 (dd, *J* = 6.4, 1.4 Hz, 1H), 3.19 (dd, *J* = 8.4, 3.8 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 148.7, 147.9, 138.0, 137.0, 131.8, 130.4, 129.7, 128.8, 127.9, 127.1, 123.9, 122.8, 120.3, 119.0, 111.4, 108.4, 61.2, 61.14, 61.09, 58.5, 23.9, 14.4. MS (EI) *m/e* (rel intensity): 455 (M^+ , 26), 382 (100), 265 (15), 217 (35). Anal. Calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 70.91; H, 5.75; N, 9.25.

***trans*-2-Benzyl-1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (5a)**

The general procedure was followed. **3a** (2.1 g, 5.8 mmol), DIPEA (1.1 g, 8.5 mmol), and benzyl bromide (1.2 g, 7.0 mmol) were used to obtain the product. Mp: 81 °C. $[\alpha]_D^{28}$: –73.6 (*c* 1.50, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 7.36 (d, *J* = 6.6 Hz, 2H), 7.33 (d, *J* = 3.9 Hz, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.21–7.16 (m, 2H), 5.62 (s, 1H), 4.22–4.19 (m, 1H), 4.14–4.11 (m, 1H), 4.05 (d, *J* = 13.8 Hz, 1H), 3.98 (t, *J* = 4.8 Hz, 1H), 3.80 (d, *J* = 13.8 Hz, 1H), 3.30–3.28 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 150.5, 148.3, 139.1, 137.1, 133.5, 130.1, 129.0, 127.9, 127.3, 124.5, 122.7, 120.2, 118.9, 111.4, 107.9, 60.9, 56.6, 55.2, 24.7, 14.7. MS (EI) *m/e* (rel intensity): 455 (M^+ , 25), 382 (57), 364 (100), 217 (42). HRMS calcd for $C_{27}H_{25}N_3O_4$ ($M + H$)⁺ 455.1845; found, 455.1784.

***cis*-1-(3-Nitrophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (2b)**

The general procedure was followed. L-Tryptophan ethyl ester (17.1 g, 0.074 mol) and 3-nitrobenzaldehyde (12.9 g, 0.085 mol) were used to obtain the product. Mp: 185 °C. $[\alpha]_D^{28}$: +77.06 (*c* 2.00, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.64–7.60 (m, 2H), 7.41 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.25–7.19 (m, 2H), 5.46 (s, 1H), 4.39–4.33 (m, 2H), 4.03 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.32 (dd, *J* = 15.2, 4.0 Hz, 1H), 3.12–3.07 (m, 1H), 2.68 (br s, 1H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 149.0, 143.8, 136.8, 135.3, 133.5, 130.4, 127.4, 124.1, 124.0, 122.9, 120.4, 118.9, 111.4, 110.2, 61.8, 58.6, 57.2, 25.9, 14.7. MS (EI) *m/e* (rel intensity): 365 (M^+ , 89), 292 (100), 264 (66), 243 (46), 217 (80), 169 (49), 144 (44). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.59; H, 5.04; N, 11.27.

***trans*-1-(3-Nitrophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (3b)**

The general procedure was followed. L-Tryptophan ethyl ester (17.1 g, 0.074 mol) and 3-nitrobenzaldehyde (12.9 g, 0.085 mol) were used to obtain the product. Mp: 173 °C. $[\alpha]_D^{28}$: –71.27 (*c* 2.00, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.64–7.60 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.33–7.27 (m, 2H), 7.27–7.19 (m, 2H), 5.61 (s, 1H), 4.27–4.20 (m, 2H), 3.99 (t, *J* = 5.8 Hz, 1H), 3.35 (dd, *J* = 15.4, 5.6 Hz, 1H), 3.22 (dd, *J* = 17.0, 6.4 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 149.1, 145.0, 136.8, 134.9, 132.2, 130.1, 127.4, 123.8, 123.6, 122.9, 120.3, 118.9, 111.4, 109.5, 61.6, 54.7, 53.2 25.0, 14.6. MS (EI) *m/e* (rel intensity): 365 (M^+ , 100),

336 (30), 292 (78), 243 (39), 217 (70), 169 (41), 144 (31). HRMS calcd for $C_{20}H_{19}N_3O_4$ ($M + H$)⁺ 365.1376; found, 365.1422. The product was used directly in a following step.

***cis*-2-Benzyl-1-(3-nitrophenyl)-2,3,4,9-tetrahydro-1*H*- β -carbo-line-3-carboxylic Acid Ethyl Ester (4b)**

The general procedure was followed. **2b** (2.0 g, 5.5 mmol), DIPEA (1.1 g, 8.2 mmol), and benzyl bromide (1.1 g, 6.4 mmol) were used to obtain the product. Mp: 167–168 °C. $[\alpha]_D^{28}$: –48.2 (*c* 6.80, $CHCl_3$). ¹H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.45 (s, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.35–7.32 (m, 2H), 7.29–7.26 (m, 2H), 7.25–7.20 (m, 2H), 5.11 (s, 1H), 4.06 (d, *J* = 14.7 Hz, 1H), 4.03 (d, *J* = 14.3 Hz, 1H), 3.99–3.93 (m, 2H), 3.82–3.78 (m, 1H), 3.45 (dd, *J* = 14.8, 6.6 Hz, 1H), 3.19 (dd, *J* = 15.2, 3.6 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, $CDCl_3$): δ 173.3, 148.6, 143.5, 138.1, 137.0, 135.7, 131.9, 129.8, 129.7, 128.8, 127.8, 127.1, 124.6, 123.3, 122.8, 120.3, 119.0, 111.4, 108.5, 61.5, 61.4, 61.3, 58.8, 24.0, 14.4. MS (EI) *m/e* (rel intensity): 455 (M^+ , 11), 382 (100), 352 (8), 264 (8), 217 (20). Anal. Calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 71.31; H, 5.62; N, 9.02.

***trans*-2-Benzyl-1-(3-nitrophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (5b)**

The general procedure was followed. **3b** (0.5 g, 1.4 mmol), DIPEA (0.27 g, 2.1 mmol), and benzyl bromide (0.28 g, 1.6 mmol) were used to obtain the product. Mp: 158–160 °C. $[\alpha]_D^{28}$: –54.0 (*c* 6.80, $CHCl_3$). ¹H NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.39–7.27 (m, 5H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.23–7.18 (m, 2H), 5.64 (s, 1H), 4.23–4.18 (m, 1H), 4.15–4.12 (m, 1H), 4.05 (d, *J* = 13.8 Hz, 1H), 4.00 (t, *J* = 4.7 Hz, 1H), 3.83 (d, *J* = 13.8 Hz, 1H), 3.31 (d, *J* = 4.8 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, $CDCl_3$): δ 172.8, 149.1, 145.4, 139.2, 137.1, 135.2, 133.7, 130.2, 129.0, 127.8, 127.3, 124.1, 123.6, 122.6, 120.1, 118.9, 111.4, 107.7, 60.9, 56.8, 55.2, 24.8, 14.7. MS (EI) *m/e* (rel intensity): 455 (M^+ , 26), 382 (63), 364 (100), 217 (51). Anal. Calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 71.16; H, 5.52; N, 8.83.

***cis*-1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (2c)**

The general procedure was followed. L-Tryptophan ethyl ester (13.5 g, 0.058 mol), 4-chlorobenzaldehyde (9.4 g, 0.067 mol), and TFA (13.2 g, 0.12 mol) were used to obtain the product. Mp: 140–142 °C. ¹H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.41 (s, 3H), 7.32 (s, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.23–7.17 (m, 2H), 5.29 (s, 1H), 4.38–4.31 (m, 2H), 4.00 (dd, *J* = 7.1, 4.1 Hz, 1H), 3.28 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.08–3.03 (m, 1H), 2.42 (br s, 1H), 1.41 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, $CDCl_3$): δ 173.1, 139.8, 136.7, 134.9, 134.6, 130.4, 129.6, 127.5, 122.6, 120.2, 118.8, 111.4, 109.7, 61.7, 58.5, 57.3, 26.1, 14.7. MS (EI) *m/e* (rel intensity): 354 (M^+ , 50), 281 (84), 253 (67), 218 (100), 169 (42), 144, (63). Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.89. Found: C, 67.75; H, 5.35; N, 7.75. HRMS calcd for $C_{20}H_{19}ClN_2O_2$ ($M + H$)⁺ 355.1213; found, 355.1217. The product was used directly in a following step.

***trans*-1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (3c)**

The general procedure was followed. L-Tryptophan ethyl ester (13.5 g, 0.058 mol), 4-chlorobenzaldehyde (9.4 g, 0.067 mol), and TFA (13.2 g, 0.12 mol) were used to obtain the product. Mp: 152 °C. ¹H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.30–7.20 (m, 5H), 5.43 (s, 1H), 4.26–4.22 (m, 2H), 3.96 (t,

$J = 6.6$ Hz, 1H), 3.25 (dd, $J = 5.4, 1.0$ Hz, 1H), 3.20–3.18 (m, 1H), 2.42 (br s, 1H), 1.33 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 174.0, 141.7, 136.7, 134.4, 133.2, 130.2, 129.3, 127.4, 122.6, 120.1, 118.8, 111.4, 109.1, 61.6, 54.7, 52.9, 25.1, 14.6. MS (EI) m/e (rel intensity): 354 (M^+ , 74), 281 (84), 253 (27), 217 (100), 169 (44), 144 (64). HRMS calcd for $\text{C}_{20}\text{H}_{19}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 355.1213; found, 355.1221. The product was used directly in a following step.

***cis*-2-Benzyl-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (4c)**

The general procedure was followed. **2c** (1.5 g, 4.2 mmol), DIPEA (0.81 g, 6.2 mmol), and benzyl bromide (0.86 g, 5.0 mmol) were used to obtain the product. Mp: 156 °C. $[\alpha]_{\text{D}}^{28}$: +66.92 (c 1.04, CHCl_3). ^1H NMR (500 MHz, CDCl_3): δ 7.60 (d, $J = 8.2$ Hz, 1H), 7.38–7.28 (m, 10H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.22–7.16 (m, 2H), 4.98 (s, 1H), 4.10 (d, $J = 14.8$ Hz, 1H), 3.97 (d, $J = 14.8$ Hz, 1H), 3.92–3.88 (m, 2H), 3.82–3.78 (m, 1H), 3.42 (dd, $J = 16.4, 3.0$ Hz, 1H), 3.13 (dd, $J = 16.0, 5.2$ Hz, 1H), 1.18 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 173.6, 139.3, 138.4, 136.8, 134.2, 133.1, 131.1, 129.6, 129.0, 128.6, 127.6, 127.2, 122.5, 120.1, 118.9, 111.2, 108.0, 61.30, 61.28, 61.1, 57.6, 24.3, 14.3. MS (EI) m/e (rel intensity): 444 (M^+ , 38), 371 (100), 337 (23), 254 (40), 218 (53). Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{ClN}_2\text{O}_2$: C, 72.88; H, 5.66; N, 6.30. Found: C, 73.01; H, 5.80; N, 6.26. HRMS calcd for $\text{C}_{27}\text{H}_{25}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 455.1683; found, 445.1665.

***trans*-2-Benzyl-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (5c)**

The general procedure was followed. **3c** (0.63 g, 1.8 mmol), DIPEA (0.34 g, 2.7 mmol), and benzyl bromide (0.36 g, 2.1 mmol) were used to obtain the product. Mp: 172 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.59 (d, $J = 7.4$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.43 (s, 1H), 7.39–7.29 (m, 7H), 7.27 (d, $J = 7.4$ Hz, 1H), 7.21–7.15 (m, 2H), 5.51 (s, 1H), 4.22–4.17 (m, 1H), 4.14–4.11 (m, 1H), 4.00–3.98 (m, 2H), 3.87 (d, $J = 13.8$ Hz, 1H), 3.28–3.26 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 173.4, 141.3, 139.7, 137.0, 134.8, 134.2, 130.7, 129.4, 129.0, 128.9, 127.7, 127.5, 122.3, 119.9, 118.7, 111.3, 107.2, 60.8, 56.5, 54.8, 24.8, 14.7. MS (EI) m/e (rel intensity): 444 (M^+ , 63), 371, (85), 353 (100), 279 (34), 254 (49), 217 (91). HRMS calcd for $\text{C}_{27}\text{H}_{25}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 444.1605; found, 444.1509.

***cis*-1-(4-Methylphenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (2d)**

The general procedure was followed. L-Tryptophan ethyl ester (18.0 g, 0.077 mol), 4-methylbenzaldehyde (10.7 g, 0.089 mol), and TFA (17.6 g, 0.15 mol) were used to obtain the product. Mp: 230–235 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.60 (d, $J = 8.2$ Hz, 1H), 7.47 (s, 1H), 7.34–7.32 (m, 2H), 7.27–7.24 (m, 3H), 7.21–7.16 (m, 2H), 5.27 (s, 1H), 4.36–4.30 (m, 2H), 4.01 (dd, $J = 11.0, 4.2$ Hz, 1H), 3.28 (dd, $J = 15.0, 4.2$ Hz, 1H), 3.09–3.03 (m, 1H), 2.45 (s, 3H), 2.30 (br s, 1H), 1.40 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 173.2, 138.8, 138.2, 136.6, 135.4, 130.0, 129.0, 127.7, 122.3, 120.0, 118.7, 111.3, 109.3, 61.6, 58.7, 57.5, 26.2, 21.6, 14.7. MS (EI) m/e (rel intensity): 334 (M^+ , 100), 305 (26), 261 (93), 233 (74), 218 (88), 169 (36), 144 (41). Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.31; H, 6.52; N, 8.02. HRMS calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 335.1760; found, 335.1756. The product was used directly in a following step.

***trans*-1-(4-Methylphenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (3d)**

The general procedure was followed. L-Tryptophan ethyl ester (18.0 g, 0.077 mol), 4-methylbenzaldehyde (10.7 g, 0.089 mol), and TFA (17.6 g, 0.15 mol) were used to obtain the product.

Mp: 174 °C. $[\alpha]_D^{28}$: -48.19 (*c* 2.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.62–7.59 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23–7.17 (m, 6H), 5.45 (s, 1H), 4.27–4.20 (m, 2H), 4.01 (t, *J* = 6.7 Hz, 1H), 3.32 (dd, *J* = 15.4, 4.8 Hz, 1H), 3.18 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.58 (br s, 1H), 2.40 (s, 3H), 1.33 (t, *J* = 6.6 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 174.1, 139.6, 138.3, 136.6, 133.9, 129.8, 128.7, 127.6, 122.3, 119.9, 118.7, 111.3, 108.9, 61.4, 55.2, 53.0, 25.1, 21.5, 14.6. MS (EI) *m/e* (rel intensity): 334 (*M*⁺, 100), 305 (48), 261 (85), 246 (28), 232 (42), 218 (85), 169 (38), 144 (36). Anal. Calcd for C₂₁H₂₂N₂O₂: C, 75.42; H, 6.63; N, 8.83. Found: C, 75.21; H, 6.61; N, 8.17.

***cis*-2-Benzyl-1-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic Acid Ethyl Ester (4d)**

The general procedure was followed. **2d** (1.1 g, 3.3 mmol), DIPEA (0.6 g, 4.6 mmol), and benzyl bromide (0.66 g, 3.9 mmol) were used to obtain the product. Mp: 149–150 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.58 (d, *J* = 7.4 Hz, 1H), 7.38–7.25 (m, 8H), 7.23 (d, *J* = 6.6 Hz, 1H), 7.20–7.14 (m, 4H), 4.97 (s, 1H), 4.13 (d, *J* = 14.9 Hz, 1H), 3.96 (d, *J* = 14.9 Hz, 1H), 3.89–3.81 (m, 3H), 3.42 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.11 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.40 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 173.7, 138.6, 138.2, 137.6, 136.8, 134.2, 129.7, 129.6, 128.4, 127.43, 127.36, 122.1, 119.9, 118.7, 111.2, 107.5, 62.1, 61.7, 61.0, 57.0, 24.9, 21.6, 14.3. MS (EI) *m/e* (rel intensity): 424 (*M*⁺, 26), 351 (100), 259 (21), 234 (47), 218 (57). HRMS calcd for C₂₈H₂₈N₂O₂ (*M* + *H*)⁺ 424.2151; found, 424.2149.

***trans*-2-Benzyl-1-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic Acid Ethyl Ester (5d)**

The general procedure was followed. **3d** (4.0 g, 0.012 mol), DIPEA (2.3 g, 0.018 mol), and benzyl bromide (2.4 g, 0.014 mol) were used to obtain the product. Mp: 174 °C. $[\alpha]_D^{28}$: -48.19 (*c* 2.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.57 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 1H), 7.37–7.34 (m, 4H), 7.31–7.29 (m, 1H), 7.25–7.20 (m, 3H), 7.19–7.13 (m, 2H), 5.50 (s, 1H), 4.21–4.18 (m, 1H), 4.14–4.10 (m, 1H), 3.99 (t, *J* = 4.8 Hz, 1H), 3.97 (d, *J* = 13.8 Hz, 1H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.27 (d, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 173.6, 140.1, 139.6, 138.2, 136.9, 135.7, 129.9, 129.3, 129.0, 128.8, 127.6, 127.5, 121.9, 119.7, 118.6, 111.2, 106.8, 61.1, 60.6, 56.5, 54.7, 24.9, 21.6, 14.7. MS (EI) *m/e* (rel intensity): 424 (*M*⁺, 78), 351 (93), 333 (100), 259 (41), 234 (36), 218 (67). Anal. Calcd for C₂₈H₂₈N₂O₂: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.08; H, 6.83; N, 6.47.

***cis*-1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic Acid Ethyl Ester (2e)**

The general procedure was followed. L-Tryptophan ethyl ester (18.5 g, 0.053 mol), 4-methoxybenzaldehyde (8.3 g, 0.061 mol), and TFA (12.0 g, 0.11 mol) were used to obtain the product. Mp: 134–138 °C. $[\alpha]_D^{28}$: -14.5 (*c* 2.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.60 (d, *J* = 8.2 Hz, 1H), 7.52 (s, 1H), 7.36 (d, *J* = 8.6, 2H), 7.26 (d, *J* = 6.8, 1H), 7.22–7.16 (m, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.25 (s, 1H), 4.36–4.31 (m, 2H), 4.00 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.87 (s, 3H), 3.28 (dd, *J* = 15.0, 4.2 Hz, 1H), 3.08–3.03 (m, 1H), 2.46 (br s, 1H), 1.40 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 173.3, 160.3, 136.6, 135.6, 133.3, 130.2, 127.7, 122.3, 120.0, 118.7, 114.7, 111.3, 109.4, 61.6, 58.5, 57.5, 55.8, 26.2, 14.7. MS (EI) *m/e* (rel intensity): 350 (*M*⁺, 100), 321 (29), 277 (80), 249 (71), 218 (62), 204 (37), 169 (39), 144 (39). Anal. Calcd for C₂₁H₂₂N₂O₃: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.77; H, 6.37; N, 7.75.

***trans*-1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (3e)**

The general procedure was followed. L-Tryptophan ethyl ester (18.5 g, 0.053 mol), 4-methoxybenzaldehyde (8.3 g, 0.061 mol), and TFA (12.0 g, 0.11 mol) were used to obtain the product. Mp: 190–192 °C. $[\alpha]_D^{28}$: –44.0 (*c* 2.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.62 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.23–7.17 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 1H), 4.28–4.20 (m, 2H), 4.00 (t, *J* = 6.1 Hz, 1H), 3.86 (s, 3H), 3.32 (dd, *J* = 15.4, 5.4 Hz, 1H), 3.17 (dd, *J* = 16.2, 7.0 Hz, 1H), 2.51 (br s, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 174.2, 159.9, 136.6, 134.7, 134.1, 130.0, 127.6, 122.3, 119.9, 118.7, 114.5, 111.3, 108.9, 61.4, 55.8, 54.8, 53.0, 25.1, 14.6. MS (EI) *m/e* (rel intensity): 350 (M⁺, 100), 321 (55), 277 (71), 262 (33), 248 (50), 218 (55), 204 (43), 169 (44), 144 (36), 134 (26). Anal. Calcd for C₂₁H₂₂N₂O₃: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.66; H, 6.46; N, 7.90.

***cis*-2-Benzyl-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (4e)**

The general procedure was followed. **2e** (1.5 g, 4.3 mmol), DIPEA (0.83 g, 6.2 mmol), and benzyl bromide (0.87 g, 5.1 mmol) were used to obtain the product. Mp: 131–133 °C. $[\alpha]_D^{28}$: –48.2 (*c* 2.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.58 (d, *J* = 7.4 Hz, 1H), 7.37–7.30 (m, 7H), 7.28–7.24 (m, 2H), 7.20–7.14 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.96 (s, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.95 (d, *J* = 14.9 Hz, 1H), 3.90–3.82 (m, 3H), 3.85 (s, 3H), 3.41 (dd, *J* = 14.4, 7.4 Hz, 1H), 3.10 (dd, *J* = 16.0, 5.0 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 173.7, 159.8, 138.8, 136.8, 134.3, 132.6, 130.9, 129.6, 128.4, 127.39, 127.36, 122.2, 119.9, 118.8, 114.3, 111.2, 107.6, 61.8, 61.7, 61.0, 57.0, 55.8, 24.8, 14.3. MS (EI) *m/e* (rel intensity): 440 (M⁺, 37), 376 (100), 274 (22), 250 (42), 218 (37). Anal. Calcd for C₂₈H₂₈N₂O₃: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.43; H, 6.46; N, 6.34.

***trans*-2-Benzyl-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*- β -carboline-3-carboxylic Acid Ethyl Ester (5e)**

The general procedure was followed. **3e** (1.5 g, 4.3 mmol), DIPEA (0.83 g, 6.2 mmol), and benzyl bromide (0.87 g, 5.1 mmol) were used to obtain the product. Mp: 150–151 °C. $[\alpha]_D^{28}$: –52.0 (*c* 2.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 11.4 Hz, 2H), 7.40 (s, 1H), 7.35 (d, *J* = 4.4 Hz, 4H), 7.31–7.28 (m, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.18–7.12 (m, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.48 (s, 1H), 4.21–4.16 (m, 1H), 4.13–4.10 (m, 1H), 3.97 (t, *J* = 4.9 Hz, 1H), 3.93 (d, *J* = 2.6 Hz, 2H), 3.85 (s, 3H), 3.25 (d, *J* = 5.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 173.6, 159.9, 140.1, 136.9, 135.7, 134.6, 130.5, 129.0, 128.7, 127.6, 127.5, 121.9, 119.7, 118.6, 114.5, 111.2, 106.8, 60.64, 60.62, 56.5, 55.7, 54.6, 24.9, 14.7. MS (EI) *m/e* (rel intensity): 440 (M⁺, 73), 367 (88), 349 (100), 275 (23), 250 (39), 218 (37). HRMS calcd for C₂₈H₂₈N₂O₃ (M + H)⁺ 440.2100; found, 440.2091.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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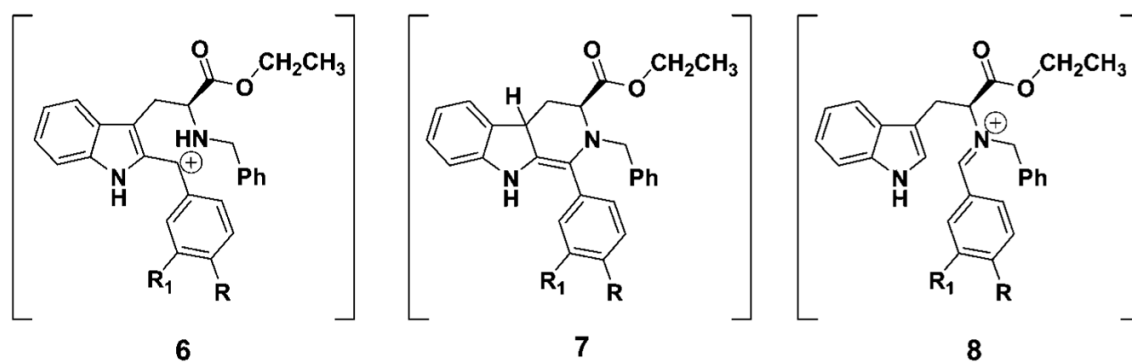


Figure 1.
Proposed intermediates in the cis to trans epimerization.

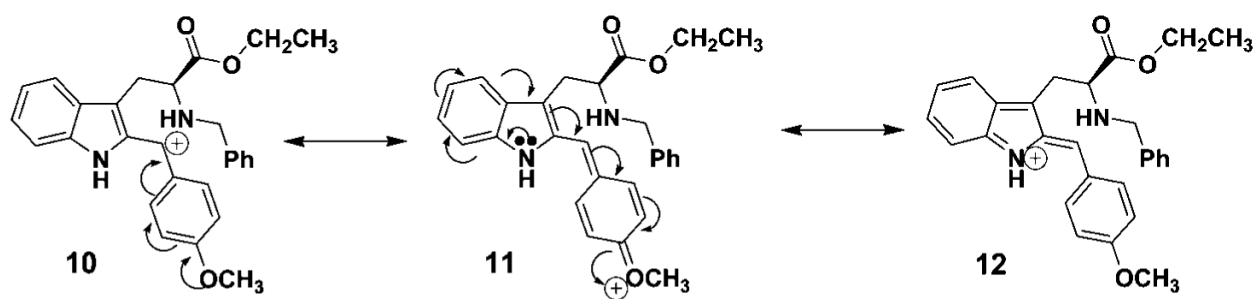


Figure 2.
Stabilization of the carbocation intermediate via electron donating effects.

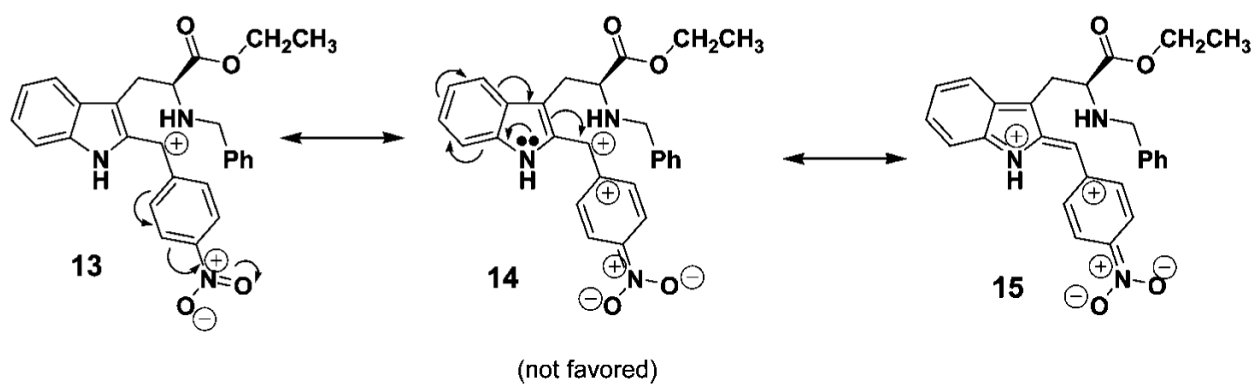
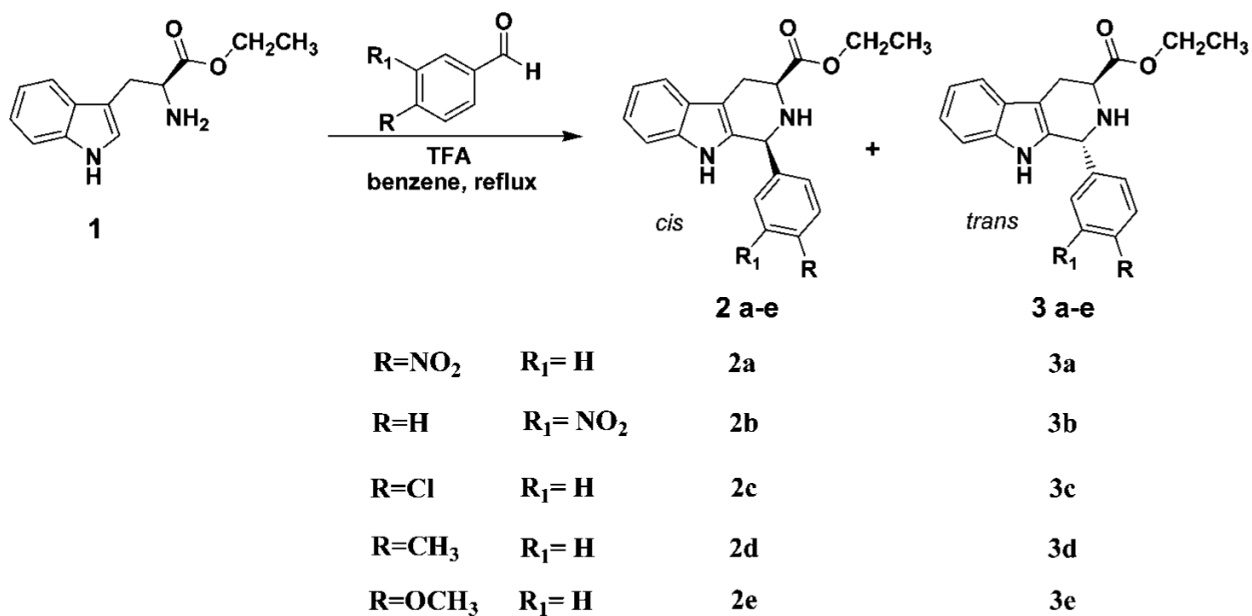
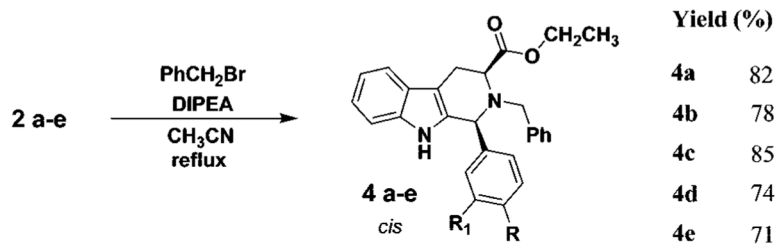
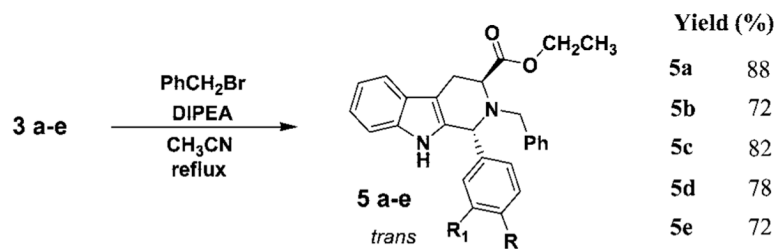


Figure 3.
Effect of the *p*-nitro group on the stability of the carbocationic intermediate.

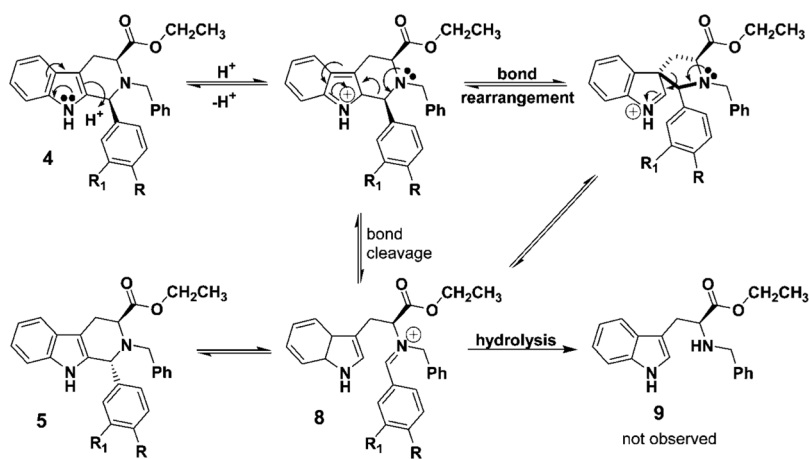


Scheme 1.
 Synthesis of *Cis* and *Trans* N_α -H, N_β -H Tetrahydro- β -carbolines via the Pictet-Spengler Reaction

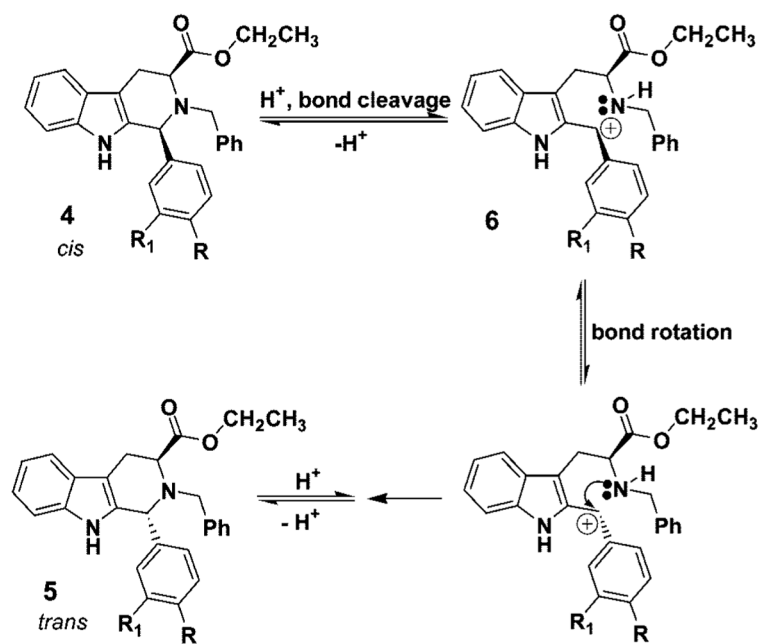
**Scheme 2.** N_b -Benzylation of the Cis Diastereomers



Scheme 3.
 N_b -Benzylation of the Trans Diastereomers



Scheme 4.
Retro Pictet–Spengler Process

**Scheme 5.**

Proposed Mechanism for Epimerization of the Cis Diastereomers into the Trans Isomers via Carbocationic Intermediate 6

Table 1
Ratio of Cis and Trans Diastereomers of 1,3-Disubstituted Tetrahydro- β -carboline

diastereomer	R	R ₁	nonacidic media cis:trans ratio	acidic media cis:trans ratio	yield [%] ^a cis + trans
2a, 3a	NO ₂	H	48:52	NA	88 ^b
2b, 3b	H	NO ₂	43:57	NA	84 ^b
2c, 3c	Cl	H	30:70	45:55	76 ^c
2d, 3d	CH ₃	H	38:62	40:60	78 ^c
2e, 3e	OCH ₃	H	33:67	45:55	82 ^c

^a Isolated yield.

^b Determined under aprotic conditions.

^c Determined under acidic conditions.

Table 2
Acid-Mediated Epimerization of Cis Diastereomers (4) into Trans ODiastereomers (5)

entry	R	R ₁	epimerization process	approximate ratio of cis:trans isomers ^d				
				initial	0.5 h	1 h	1.5 h	3 h
<div><div><div><div><div>4 a – e</div><div>cis</div></div><div><div>TFA</div><div>→</div><div>CH₂Cl₂</div><div>rt</div></div><div><div>5 a – e</div><div>trans</div></div></div></div></div>								
4a (cis)	NO ₂	H	4a → 5a	100:0	78:22	35:55	14:86	6:94
4b (cis)	H	NO ₂	4b → 5b	100:0	70:30	40:60	25:75	0:100
4c (cis)	Cl	H	4c → 5c	100:0	58:52	19:81	0:100	
4d (cis)	CH ₃	H	4d → 5d ^b	100:0	2:98	0:100		
4e (cis)	OCH ₃	H	4e → 5e ^b	100:0	0:100			
5a (trans)	NO ₂	H	5a → 4a ^c	0:100				0:100
5e (trans)	OCH ₃	H	5e → 4e ^c	0:100				0:100

^aThe cis to trans ratio was determined by analysis of the proton NMR spectrum of the crude reaction mixture.

^bThe epimerization of **4d** and **4e** containing electron-donating substituents on the aromatic ring was completed in 30 min.

^cThe trans to cis conversion was not observed in the last two reactions.