Diasteroselective Cyclizations with Enantiopure Malonaldehyde Monocycloacetals

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The synthesis of a series of enantiopure malonaldehyde monocycloacetals is described. Treatment of **8b** with L-tryptophan methyl ester, 5-methoxytryptamine, and tryptamine, respectively, in the Pictet−Spengler condensation gave the corresponding enantiomerically pure key precursors **1**−**3** and **17**−**21** in only two steps. Using a chiral amino-diol successfully realized the kinetic resolution of racemic carbolines **23** and **24**.

Introduction

Enantiomerically pure indoloquinolizines **5**, **6** and their 9-methoxy derivatives are interesting target compounds because of their use as building blocks for the synthesis of various indole and oxindole alkaloids with potential biological activities.[1] The development of efficient synthetic methods for this type of chiral intermediates is actively pursued worldwide. Unfortunately, the apparently facile route to the enantiomers of these compounds via decarboxylation of the corresponding 6-carboxylate derivatives was unsuccessful. Thus, the preparation of enantiomerically pure indoloquinolizine derivatives has mainly been carried out by stepwise introduction of functional groups into the indole ring. Moreover, careful choice of parameters such as reaction sequence and reaction condition is necessary to achieve the formation of pure enantiomers in this class compounds. The optically pure ketones **5** and **6** were previously synthesized in seven steps from L-tryptophan methyl ester starting with a Pictet−Spengler condensation (Scheme 1).[2]

Consequently, our objective was to find a simple and straightforward access to enantiomerically pure compounds **3** and **4**, the key intermediates in the preparation of the enantiomers **5** and **6**. We thus decided to utilize the optically pure malonaldehyde monocycloacetals as an advanced intermediate for the enantioselective synthesis, since these compounds have been the subject of continuing synthetic interest in our laboratory over the years. In this area, we did also develop a new type of chiral reagent derived from easily available natural amino acids. Applying these tools, we herein report the synthesis of the enantiomerically pure precursors **3**, **4** and their 6-methoxy derivatives **21**, **22** in only two steps utilizing optically pure malonaldehyde monocycloacetals as the chiral director.

Results and Discussion

We previously described a general method for the synthesis of malonaldehyde monoacetals via transacetalization or selective hydrolysis of 1,1,3,3-tetramethoxypropane and its analogues.[3] More recently, the scope of the transacetalization of 1,1,3,3-tetramethoxypropane was expanded to chiral amino-diol and 1,3-dioxacyclic diastereomers, thus affording a versatile approach to the optically pure malonaldehyde monocycloacetals[4]

For our initial studies we selected the mixed bisacetals **7** as starting material and the readily available diasteromeric aldehyde **8** as the key intermediate (Scheme 2). At 50 °C using oxalic acid and silica gel as the catalyst the mixed bisacetals **7a**−**d** were converted into the expected aldehydes **8a**−**d** in 80−85% yield. The relative stereochemistry of all optically pure compounds could be established on the basis of their spectroscopic parameters, especially those of ^{1}HNMR, including NOESY experiments.

The cis-2,5-disubstituted configurations of **8a**, **8c**, **8d** as well as the cis-2,5,6-trisubstituted configuration of **8b** were assigned by NOESY experiments and further confirmed by thermal isomerizations. An NOE was observed between the NH at 5-position and the CH_2 at 2-position in each of **8a**, **8c**, **8d**, and NOEs between the NH at 5-position, the CH_3 at 4-position, and the CH_2 at 2-position in **8b** were also observed. The optical purities of **8b**−**d** were confirmed by measurements with the chiral shift reagent tris[3-(heptauoropropylhydroxymethylene)-(+)-campthorato]europium(III). Since no line splitting was observed, one can deduce that the products are enantiomercially pure within the limits of detection by ^{1}H NMR. None of the compounds investigated showed any signs of configurational instability during the conditions applied.

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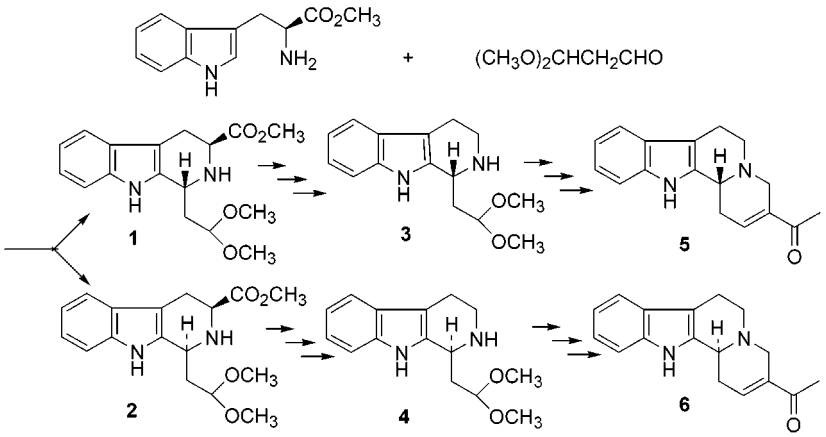
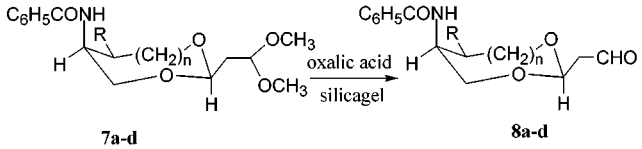
Scheme 1. Preparation of Enantiomerically Pure Indoloquinolizines



Scheme 2. Preparation of Optically Pure Malonaldehyde Monocycloacetals



	a	b	c	d
R	H	CH_3	H	H
n	0	0	1	2

To explore the configuration dependent reactivity of the optically pure precursors and further identify the configuration of the intermediates, **8b** was then treated with *N*-[2-hydroxy-1- (hydroxymethyl)ethyl]benzamide (**9**), (1*S*,2*R*)-*N*-[2-hydroxy-1-(hydroxymethyl)propyl]benzamide (**10**), and (1*S*)-*N*-[3-hydroxy-1-(hydroxymethyl)-propyl]benzamide (**11**), respectively. From all of these reactions the corresponding malonaldehyde biscycloacetals **12**, **13**, and **14** were satisfactorily obtained in 80−89% yield (Scheme 3).

The study was then extended to the configurational stability of the malonaldehyde biscycloacetals **12** and **13**. Stirring in chloroform at 45 °C for 2 h, **12** and **13** were quantitatively converted into **15** and **16**, respectively. These transformations prove that **15** and **16** are thermodynamically more stable than **12** and **13**, which means that the acetalizations mentioned above are kinetically controlled. The NOESY experiments of **12**, **13**, **15**, and **16** gave NOEs between the CH_3 at 4-position and the CH_2 at 2-position, and also between the CH_3 at 4-position and the NH at 5-position in the (4-methyl-1,3-dioxan-5-yl)-benzamide moiety only, suggesting the (2*S*,4*R*,5*R*)/(2,5-trans) configuration for **12** and **15** and the (2*S*,4*R*,5*R*)/(2*S*,4*S*,5*S*) configuration for **13** and **16**. The NOESY experiment of **14** gave NOEs between the CH_3 at 4-position and the CH_2 at 2-position, between the CH_3 at 4-position and the NH at 5-position in (4-methyl-1,3-dioxan-5-yl)benzamide moiety, and between the CH_2 at 2-position and the NH at 5-position in the (1,3-dioxan-5-yl)benzamide moiety, indicating its (2*S*,4*R*,5*R*)/(2*S*,5*R*) configuration.

As these results indicated optically active malonaldehyde monocycloacetals to be convenient chiral synthons, we were encouraged to investigate their application for an enantioseletive synthesis of the important precursors **3**, **4**, **21**, and **22**. On treatment of **8b** with L-tryptophan methyl ester in a Pictet−Spengler condensation, the two diastereomers **17** and **18** were obtained in 50% and 30% yield, respectively. This has to be compared to the Pictet−Spengler condensation of L-tryptophan methyl ester and 1,1,3,3-tetramethoxypropane, which gave a very similar mixture of (cis)-1,3-disubstituted carboline (**1**) and (trans)-1,3-disubstituted carboline (**2**) in 66% and 33% yield, respectively. Next, the correlation between the chirality of aldehyde **8b** and the absolute configuration of cyclization products was investigated with 5-methoxytryptamine replacing L-tryptophan methyl ester in the Pictet−Spengler condensation. To our great satisfaction, under the similar experimental conditions the Pictet−Spengler condensation gave the (1*R*)-1-substituted carboline **19** stereospecifically. In the presence of methanol **19** was subsequently converted into the expectant compound **21** in 89% yield. With tryptamine replacing L-tryptophan methyl ester in the Pictet−Spengler condensation the cyclization product without purification was treated with methanol directly to provide the enantiomerically pure **3** in high yield (Scheme 4). In this case **8b** was exclusively favorable to the formation of C_1 R-configuration, which demonstrates the versatility of the new chiral director.

As a possible explanation for the configurational outcome, one may assume auxiliary dependent face-selectivity for the nucleophilic attack to the enamine-doublebond in the generally accepted transition state (A) of Pictet−Spengler cyclizations. The configuration generated this way would then uneventfully be carried through to the final product (D) (see Figure 1).

Having noticed this remarkable directing effect of the acetals formed from diol **10**, we were encouraged to check its options in transacetalization experiments. To our delight the racemic 6-methoxycarboline **23** underwent a

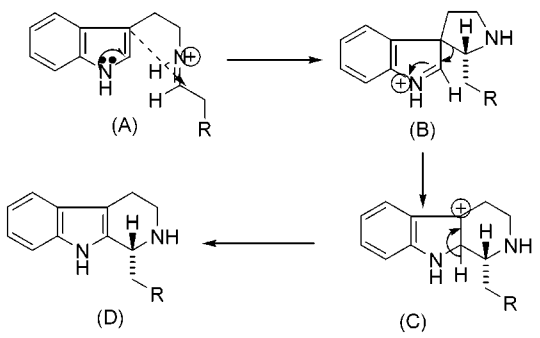
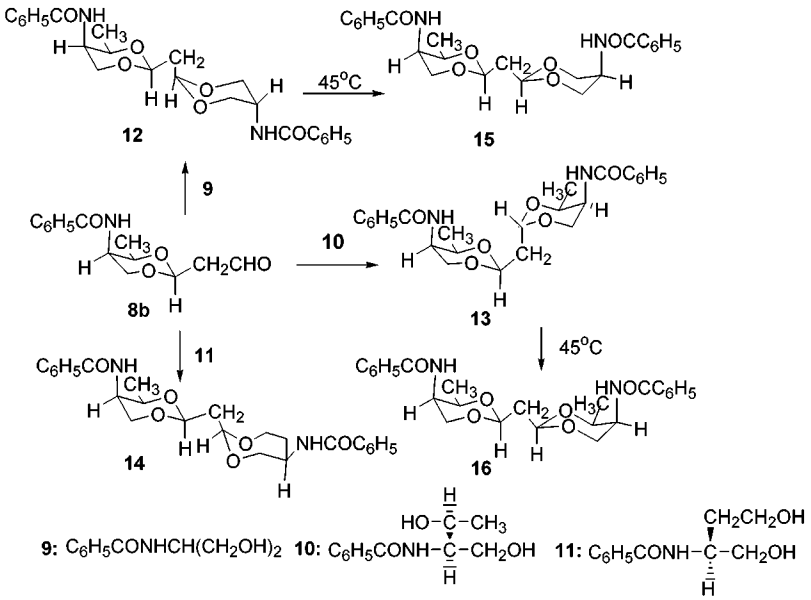
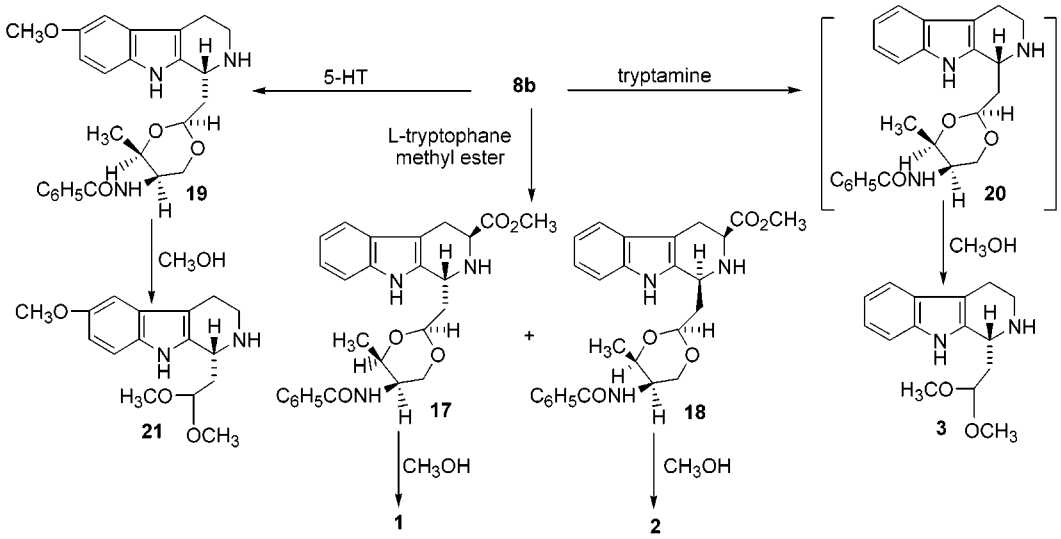


Figure 1. The possible mechanism of the enantiospecific Pictet−Spengler condensation.

Scheme 3. The Stereospecific Acetalization of 8b



Scheme 4. The Enantiospecific Pictet−Spengler Condensation of 8b

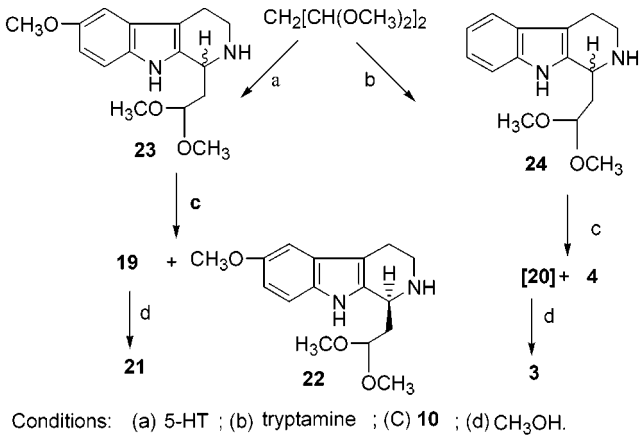


highly enantioselective acetalization with only the corresponding *R*-configuration giving rise to the diastereomer **19**. The unreacted enantiomer **22** was isolated directly. In the presence of methanol **19** was converted into the enantiomer **21**.

With the racemic carboline **24** replacing **23** the highly enantioselective acetalisation with also only the corresponding *R*-configuration giving rise to the diastereomer **20** which was not purified and treated with methanol directly converting into the enantiomer **4**. The unreacted enantiomer **3** was isolated directly again (see Scheme 5).

The clear-cut kinetic resolution together with the experiments described above disclose a high degree of chiral recognition for diol **10** and its derivatives.

Scheme 5. The Knetic Resolution of Racemic Carbolines Based on the Stereospecific Transacetalization



Conditions: (a) 5-HT ; (b) tryptamine ; (C) **10** ; (d) CH_3OH.

Conclusion

In summary, we have developed a short and efficient synthesis of enantiomerically pure alkaloid building blocks from easily accessible enantiopure malonaldehyde monocycloacetals. Our synthesis compares favorably in terms of the use of the simple reagents and transformations with the previously reported syntheses. Studies on applying the approach for other reactions and substrates are in progress in our laboratory.

Experimental Section

General. Melting points are uncorrected. Unless otherwise stated, all reactions were run under a nitrogen atmosphere (1 bar). ^{1}H NMR spectra were recorded at 300 or 500 MHz in deuteriochloroform with tetramethylsilane as internal standard. Chromatography was performed with Qingdao silical gel H. Optical rotations were determined at 20 °C.

General Procedure for Preparing Malonaldehyde Monocycloacetals (8a−d). The suspension of 0.16 mmol of the mixed bisacetals **7a**−**d**, 10.0 mg of oxalic acid, 10.0 mg of silica gel, and 10.0 mL of chloroform was stirred at 50 °C for 48−60 h until TLC analysis ($CHCl_3/CH_3OH$, 40:1) indicated complete disappearance of the starting materials **7a**−**d**. The reaction mixture was cooled, neutralized with sodium carbonate, and filtered. The filtrate was evaporated to remove chloroform. The residue was purified by chromatography ($CHCl_3/CH_3OH$, 60:1) to yield the malonaldehyde monocycloacetals **8a**−**d**. The compound **8a** had the following properties. The properties for compounds **8b**−**d** are provided in the Supporting Information.

***cis*-*N*-(2-Formylmethyl-1,3-dioxane-5-yl)benzamide (8a).** Compound **8a** was obtained as a colorless syrup in 85% yield. IR (film) 3305, 1760, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76 (d, J = 2.4 Hz, 2H), 4.31 (d, J = 4.8 Hz, 2H), 4.34 (d, J = 4.5 Hz, 2H), 4.46 (m, J = 2.7 Hz, 1H), 4.96 (t, J = 4.5 Hz, 1H), 5.87 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 6.9 Hz, 2H), 7.52 (t, J = 6.0 Hz, 1H), 7.73 (d, J = 6.9 Hz, 2H), 9.79 (t, J = 1.8 Hz, 1H); FAB-MS m/z 250 [M + H]. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07; N, 5.62. Found: C, 62.69; H, 6.14; N, 5.68.

General Procedure for Preparing Malonaldehyde Biscycloacetals (12−14). The suspensoion of **8b** (263.0 mg, 0.10 mmol), 300 mg of anhydrous magnesium chloride, *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide (**9**, 195.0 mg, 0.10 mmol), or (1*S*,2*R*)-*N*-[2-hydroxy-1-(hydroxymethyl)propyl]benzamide (**10**, 209.0 mg, 0.10 mmol), or (1*S*)-*N*-[3-hydroxy-1-(hydroxymethyl)propyl]benzamide (**11**, 209.0 mg, 0.10 mmol), and 10 mL of chloroform was stirred at room temperature for 8−10 h until TLC analysis ($CHCl_3/CH_3OH$, 40:1) indicated complete disappearance of the starting materials. After filtration and evaporation, the residue was purified by chromatography ($CHCl_3/CH_3OH$, 50:1) to provide the corresponding malonaldehyde biscycloacetals **12**, **13**, and **14**, respectively. The compound **12** had the following properties. The properties for compounds **13** and **14** are provided in the Supporting Information.

***N*,*N*′-Methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl][*trans*-1,3-dioxan-2,5-diyl]bisbenzamide (12).** Compound **12** was obtained as a colorless powder in 86% yield. IR (KBr) 3547, 3450, 1635, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.6 Hz, 3H), 2.06 (t, J = 5.7 Hz, 2H), 3.99 (d, J = 9.9 Hz, 2H), 4.31 (d, J = 5.7 Hz, 1H), 4.34 (d, J = 4.8 Hz, 1H,), 4.68 (t, J = 5.7 Hz, 1H), 4.84 (t, J = 5.4 Hz, 1H), 5.71 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 9.9 Hz, 1H), 7.46 (t, J = 7.2 Hz, 4H), 7.50 (t, J = 7.2 Hz, 2H), 7.73 (d, J = 7.4 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H); FAB-MS m/z 441 [M + H]$^+$. Mp 183−186 °C. $[\alpha]_D$ +30.0 (c 0.02, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.56; H, 6.38; N, 6.15.

Configuration Conversion of 12 and 13. A solution of the kinetically controlled product, **12** (220.0 mg, 0.50 mmol) or **13** (227.0 mg, 0.50 mmol), concentrated hydrochloric acid (0.02 mL), and chloroform (8.00 mL) was stirred at 45 °C for 10 h until TLC ($CHCl_3/CH_3OH$, 30:1) indicated complete disappearance of **12** or **13**. After neutralization, filtration, and evaporation the residue was purified, and the thermodynamically stable product **15** or **16** was obtained. The properties for compounds **15** and **16** are provided in the Supporting Information.

Methyl (1*R*,3*S*,2′*S*,4′*R*,5′*R*)- and (1*S*,3*S*,2′*S*,4′*R*,5′*R*)- 1-(5′-benzoylamino-4′-methyl-1′,3′-dioxane-2′-yl)methyl-1,2,3,4-tetrahydrocarboline-3-carboxylate (17 and 18). To a solution of 450.0 mg (2.06 mmol) of L-tryptophan methyl ester in 10.0 mL of chloroform were added 543.0 mg (2.06 mmol) of monocycloacetal **8b** and 50.0 mg of anhydrous sodium sulfate. The suspension was stirred at 60 °C for 60 h. The resultant was filtered, and the filtrate was evaporated to give a syrup which was separated by chromatography ($CHCl_3/CH_3OH$, 25:1) to afford 477.0 mg (50%) of **17** as a colorless crystal and 286.0 mg (30%) of **18** as a colorless crystal. The compound **17** had the following properties. The properties for compound **18** are provided in the Supporting Information.

Methyl (1*R*,3*S*,2′*S*,4′*R*,5′*R*)- 1-(5′-benzoylamino-4′-methyl-1′,3′-dioxane-2′-yl)-methyl-1,2,3,4-tetrahydrocarboline-3-carboxylate (17): mp 96−97 °C. IR (KBr) 3465, 3457, 3396, 1705, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.6 Hz, 3H), 2.13 (dd, J = 7.2 Hz, J = 4.2 Hz, 2H), 2.41 (s, 1H, NH), 3.00 (dd, J = 7.2 Hz, J = 5.4 Hz, 1H), 3.10 (dd, J = 7.2 Hz, J = 5.4 Hz, 1H), 3.17 (s, 3H), 3.95 (t, J = 6.0 Hz, 1H), 4.04 (d, J = 10.4 Hz, 2H), 4.08 (m, 1H), 4.15 (q, J = 6.3 Hz, 1H), 4.50 (t, J = 4.2 Hz, 1H), 4.98 (t, J = 3.6 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H), 7.11 (p, J = 9.0 Hz, 2H), 7.26 (d, J = 6.9 Hz, 1H), 7.46 (p, J = 6.6 Hz, 4H), 7.85 (d, J = 7.2 Hz, 2H), 8.36 (s, 1H); FAB-MS m/z 464 [M + H]$^+$. $[\alpha]_D$ −39.4° (c 0.018, $CHCl_3/CH_3OH$, 1:1). Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.36; H, 6.31; N, 9.07. Found: C, 67.42; H, 6.36; N, 9.14.

(1*R*,2′*S*,4′*R*,5′*R*)-1-(5′-Benzoylamino-4′-methyl-1′,3′-dioxan-2′-yl)methyl-6-methoxy-1,2,3,4-tetrahydrocarboline-3-carboline (19). To a solution of 391.4 mg (2.06 mmol) of 5-methoxytryptamine in 10.0 mL of chloroform were added 543.0 mg (2.06 mmol) of monocycloacetal **8b** and 50.0 mg of anhydrous sodium sulfate. The suspension was stirred at 60 °C for 80 h. The resultant was filtered, and the filtrate was evaporated to give a syrup which was separated by chromatography ($CHCl_3/CH_3OH$, 25:1) to afford 754.0 mg (86%) of **19**, as colorless crystals: mp 120−121 °C. IR (KBr) 3465, 3500, 3460, 1640, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.0 Hz, 3H), 2.22 (dd, J = 6.6 Hz, J = 3.5 Hz, 2H), 2.74 (s, 1H), 2.75 (t, J = 4.2 Hz, 1H), 3.14 (t, J = 5.8 Hz, 1H), 3.33 (t, J = 4.2 Hz, 1H), 3.35 (t, J = 5.8 Hz, 1H), 3.82 (s, 3H), 4.01 (d, J = 10.8 Hz, 1H), 4.02 (m, J = 6.0 Hz, 1H), 4.09 (d, J = 6.6 Hz, 1H), 4.14 (m, 1H), 4.49 (t, J = 5.7 Hz, 1H), 4.93 (t, J = 5.7 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 4.5 Hz, 1H), 6.99 (d, J = 9.1 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.81 (d, J = 7.5 Hz, 2H), 8.62 (s, 1H); FAB-MS m/z 436 [M + H]$^+$. $[\alpha]_D$ −24° (c 0.02, $CHCl_3/CH_3OH$, 1:1). Anal. Calcd for $C_{25}H_{29}N_3O_4$: C, 68.93; H, 6.72; N, 9.65. Found: C, 69.01: H, 6.80; N, 9.70.

Racemic 1-(2′,2′-Dimethoxyethyl)-6-methoxy-1,2,3,4-tetrahydrocarboline 23. At room temperature the stirred solution of 190.0 mg (1.00 mmol) of 5-methoxytryptamine and 164.0 mg (1.00 mmol) of 1,1,3,3-tetramethoxypropane in 10.0 mL of chloroform/methanol (1:1) was mixed with 40.0 mg of hydrochloric acid. The suspension was stirred at room temperature for 72 h, and then TLC analysis indicated complete disappearance of the materials. The resultant was neutralized with 100.0 mg of sodium carbonate and filtered, and the filtrate was evaporated to give a syrup which was purified by chromatography ($CHCl_3/CH_3OH$, 20:1) to afford 249.0 mg (86%) of **23**. The properties for compound **23** are provided in the Supporting Information.

The Kinetic Resolution of Racemic 1-(2′,2′-Dimethoxyethyl)-6-methoxy-1,2,3,4-tetrahydrocarboline 23. To a stirred solution of 190.0 mg (1.00 mmol) of racemic **23** and 104.5 mg (0.5 mmol) of (2*S*,3*R*)-2-benzoylamino-1,3-butanediol (**10**) in 15.0 mL of chloroform was added 10.0 mg of PPTS. The suspension was stirred at room temperature for 3 d, and then TLC analysis indicated complete disppearance of (2*S*,3*R*)-2-benzoylamino-1,3-butanediol. The reaction mixture was washed with aqueous sodium chloride (10%, 10 mL × 3). The chloroform phase was separated and dried with Na_2SO_4. After evaporation, the residue was purified by chromatography ($CHCl_3/CH_3OH$, 20:1) to afford 209.0 mg (48%) of **19** and 89.3 mg (47%) of **22**. The compound **22** was obtained as a colorless powder: mp 215−217 °C. IR (KBr) 3300, 3245 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 1H), 1.99 (t, J = 4.6 Hz, 1H), 2.41 (t, J = 7.2 Hz, 1 H), 2.78 (m, 2 H), 3.04 (m, J = 11.7 Hz, 1H), 3.34 (m, J = 11.0 Hz, 1H), 3.41 (s, 3H), 3.42 (s, 3H), 3.865 (s, 3H), 4.651 (dd, J = 3.6 Hz, J = 2.4 Hz, 1H), 4.18 (dd, J = 7.2 Hz, J = 3.6 Hz, 1H), 6.90 (dd, J = 8.5 Hz, J = 3.4 Hz, 1H), 6.93 (d, J = 3.1 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 8.71 (s, 1H); FAB-MS m/z

291 $[M + H]^+$. $[\alpha]_D$ −15.6° (*c* 0.92, CH_3OH). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.17; H, 7.64; N, 9.65. Found: C, 66.12; H, 7.61; N, 9.58.

(1*R*,2′*S*,4′*R*,5′*R*)-1-(5′-Benzoylamino-4′-methyl-1′,3′-dioxane-2′-yl)methyl-1,2,3,4-tetrahydrocarboline-3-carboline (20). To a solution of 320.0 mg (2.00 mmol) of tryptamine in 10.0 mL of chloroform were added 527.2 mg (2.00 mmol) of monocycloacetal **8b** and 50.0 mg of anhydrous sodium sulfate. The suspension was stirred at 60 °C for 120 h. The resultant was filtered, and the filtrate was evaporated to give a syrup which was separated by chromatography ($CHCl_3/CH_3OH$, 20:1) to afford 681.0 mg (84%) of crude **20**, which was directly used in next reaction without further purification.

(1*R*)-1-(2′,2′-Dimethoxyethyl)-6-methoxy-1,2,3,4-tetrahydrocarboline (21). To a stirred solution of 209.0 mg (0.48 mmol) of **19** in 10.0 mL of methanol was added 5.0 mg of 6 N hydrochloric acid. The reaction mixture was stirred at room temperature until TLC analysis ($CHCl_3/CH_3OH$, 20:1) indicated complete disappearance of **19**. The reaction mixture was neutralized with sodium carbonate and filtered. The filtrate was evaporated to remove methanol. The residue was purified by chromatography ($CHCl_3/CH_3OH$, 20:1) to yield 124.0 mg (89%) of **21**. The properties for compound **21** are provided in the Supporting Information.

Racemic 1-(2,2-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline (24). The stirring solution of 31.2 mg (0.2 mmol) of tryptamine in 5 mL of chloroform and 3 mL of methanol was acidified with 80 mg of concentrated hydrochloric acid to pH 2 at room temperature. To the solution 32.8 mg (0.2 mmol) of 1,1,3,3-tetramethoxypropane was added. The reaction mixture was stirred at room temperature for 45 h by which time TLC analysis ($CHCl_3$:CH_3OH, 16:1) indicated complete disappearance of tryptamine and neutralized with sodium carbonate. After filtration and evaporation the residue was purified by chromatograph $CHCl_3/CH_3OH$ (30:1) furnished 39.0 mg (75%) of **24**, as colorless powder. The properties for compound **24** are provided in the Supporting Information.

The Kinetic Resolution of Racemic 1-(2′,2′-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline 24. To a stirred solution of 260.3 mg (1.00 mmol) of racemic **24** and 104.5 mg (0.5 mmol) of (2*S*,3*R*)-2-benzoylamino-1,3-butanediol (**10**) in 15.0 mL of chloroform was added 10.0 mg of PPTS. The suspension was stirred at room temperature for 3 d, and then TLC ($CHCl_3/CH_3OH$, 20:1) analysis indicated complete disppearance of (2*S*,3*R*)-2-benzoylamino-1,3-butanediol (**10**). The reaction mixture was washed with aqueous sodium chloride (10%, 10 mL × 3). The chloroform phase was separated and dried with Na_2SO_4. After evaporation the residue was purified by chromatography ($CHCl_3/CH_3OH$, 20:1) to afford 186.4 mg (46%) of **20** and 122.3 mg (47%) of **4**. The properties for compound **4** are provided in the Supporting Information.

(1*R*)-1-(2,2-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline (3). To a stirred solution of 186.4 mg of **20** in 10.0 mL of methanol was added 5.0 mg of 6 N hydrochloric acid. The reaction mixture was stirred at room temperature until TLC analysis ($CHCl_3/CH_3OH$, 20:1) indicated complete disappearance of **20**. The reaction mixture was neutralized with sodium carbonate and filtered. The filtrate was evaporated to remove methanol. The residue was purified by chromatography ($CHCl_3/CH_3OH$, 20:1) to yield the 106.6 mg of (89%) **3**. The properties for compound **3** are provided in the Supporting Information.

Methyl (1*R*,3*S*)- and (1*S*,3*S*)-1-(2′,2′-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate (1 and 2). To a stirred solution of 50.0 mg (0.11 mmol) of **17** or **18** in 10.0 mL of methanol was added 5.0 mg of 6 N hydrochloric acid. The reaction mixture was stirred at room temperature for 12 h until TLC analysis ($CHCl_3/CH_3OH$, 20:1) indicated complete disappearance of the starting materials. The reaction mixture was neutralized with sodium carbonate and filtered. The filtrate was evaporated to remove methanol. The residue was purified by chromatography ($CHCl_3/CH_3OH$, 30:1) to yield the 31.3 mg (89%) of **1** or 30.0 mg (85%) of **2**, respectively. The properties for compound **1** and **2** are provided in the Supporting Information.

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Supporting Information Available: The characterization data for compounds **1**−**24**. This material is available free of charge via the Internet at http/pubs.acs.org.

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