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A diastereoselective construction of pyrazinoisoquinoline skeletons via tandem cyclization of phenylalanine derivatives: a facile synthesis of optically active pyrazinoisoquinolines

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ABSTRACT

A facile and stereocontrolled construction of optically active pyrazinoisoquinoline skeletons based on tandem cyclization of enantiopure phenylalanine derivatives was examined. The reaction provided optically active 6,11b-*trans* pyrazinoisoquinoline ring systems in excellent diastereoselectivity, and this method was applicable to the cyclization of phenylalanine derivatives with diverse substituents.

1. Introduction

A series of pyrazinoisoquinoline derivatives is of considerable interest recently because of their various biological activities, such as antischistosomal, antifungal, and antiprotozoal actions.[1] The skeleton is a simple tricyclic ring system possessing a stereogenic center at C-11b, which are closely related to biological differences.[1a] Whereas synthetic routes for racemic pyrazinoisoquinolines have intensively been studied, only several methods for the construction of the optically active ring systems have been reported, in which the Pictet–Spengler cyclization employing chiral auxiliaries[2] or amino acids[3] as chiral inductors, radical cyclization from peptide acetals,[4] and asymmetric transfer hydrogenation of dihydroisoquinoline using a chiral catalyst[5] were utilized as a key step.

However, these approaches by the Pictet–Spengler cyclization, one of the most widely used method in this field, have difficulty in synthesizing optically active pyrazinoisoquinolines with diversity. A chiral auxiliary mediated Pictet–Spengler reaction of phenylethylamines generally requires alkoxy or hydroxy groups on the aromatic ring (Fig. 1a) and thus has limitations in synthesizing tetrahydroisoquinolines without electron-donating substituents (Fig. 1b) as described by Koomen et al.[6] In fact, almost all the reported methods using asymmetric or stereocontrolled Pictet–Spengler cyclization[2b,3] were limited to synthesizing pyrazinoisoquinolines bearing alkoxyl groups.[7] In addition, most of the approaches required multistep processes for the construction of the tricyclic ring systems due to stepwise cyclization.

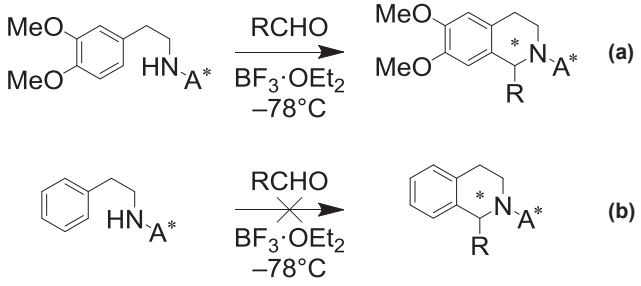

Fig. 1. Reported asymmetric Pictet–Spengler cyclization.

N-Acyliminium ions are versatile intermediates particularly for the synthesis of natural alkaloids.[8] It has been reported that intramolecular reactions of cyclic *N*-acyliminium ions with π-nucleophiles led to a preference for the formation of 1,3-*trans* products due to steric control by the substituents already present in the ring[9] or along the chain connecting the π-nucleophile and nitrogen atom.[10] We envisage that (i) the tricyclic ring system would be constructed in one step from amido-acetal **1** that generates a cyclic

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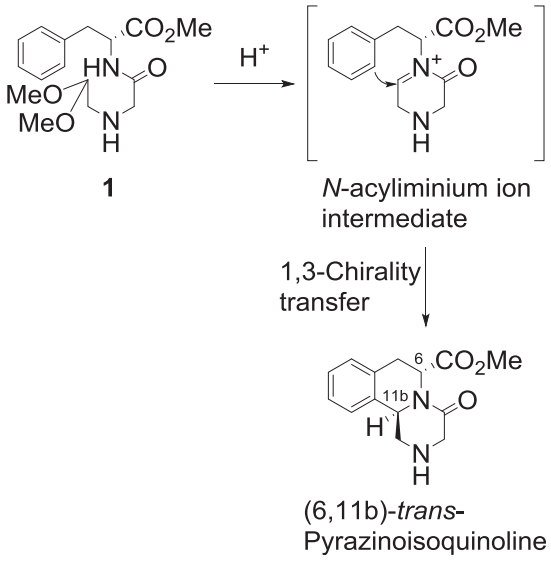
N-acyliminium ion intermediate *in situ* by the Pictet–Spengler cyclization and (ii) incorporation of enantiopure amino acid as a chiral inductor into **1** would introduce a new chiral center during the ring-closing step through 1,3-chirality transfer preferentially to afford a 6,11b-*trans* pyrazinoisoquinoline skeleton (Scheme 1). Our goal is an effective synthesis of optically active pyrazinoisoquinoline derivatives with diverse sets of electron-donating and electron-withdrawing substituents on the aromatic ring. In this paper, we report a stereocontrolled construction of 6*R*,11b*R*-*trans* pyrazinoisoquinoline skeletons based on our new approach from substituted D-phenylalanines.



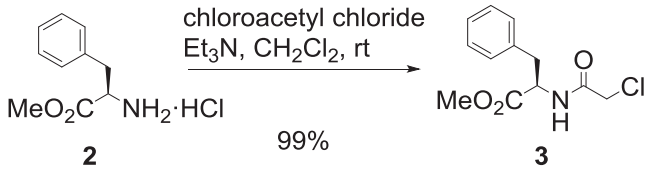
Scheme 1. The Pictet–Spengler reaction of a cyclic *N*-acyliminium ion intermediate.

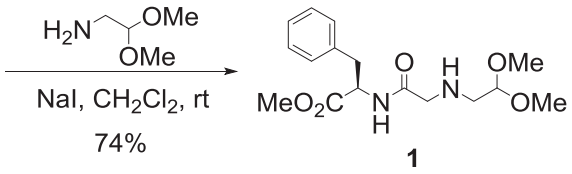
2. Results and discussion

To examine suitable conditions for the stereocontrolled Pictet–Spengler-type cyclization, amido-acetal **1** as an *N*-acyliminium ion precursor was prepared from D-phenylalanine methyl ester hydrochloride (**2**) (Scheme 2). Treatment of chloroacetyl chloride with **2**, followed by amination of **3** using aminoacetaldehyde dimethyl acetal afforded **1** in a good yield. Then, Brønsted or Lewis acid was employed as a catalyst to generate the cyclic *N*-acyliminium ion intermediate and to promote subsequent cyclization. The results are listed in Table 1. All acids except CF_3SO_3H and TFA provided the desired product, **4a**, as a single isomer at room temperature.[11] Concentrated H_2SO_4 afforded **4a** smoothly in a moderate yield (entry 1).[12] CH_3SO_3H gave the highest level of the yield and diastereoselectivity (entry 2). Under the lower acidic conditions, none of the cyclized products was obtained probably due to decomposition of the *N*-acyliminium ion intermediate (entry 4), whereas increased acidity lowered the diastereoselectivity (entry 3). Although the elevation of reaction temperature accelerated cyclization using CH_3SO_3H, the diastereoselectivity slightly decreased (entry 7). Moreover, elongated reaction time under heat conditions resulted in a lowering of the yield of **4a** and an increase in degradation products (entry 8). Compared to Brønsted acids, Lewis acids gave **4a** in lower yields (entries 5 and 6).

The relative conformation of **4a** and **4b** was implied by NOESY experiments. The 2D NOESY of minor isomer **4b** (*cis*) showed a decisive correlation neither between the C-11b proton at 4.62 ppm and C-6 proton at 4.98 ppm nor between the C-11b proton and methyl ester protons at 3.53 ppm. In contrast, that of **4a** (*trans*) did not show a decisive correlation between the C-11b proton at 4.99 ppm and C-6 proton at 5.73 ppm, whereas a selective excitation of the C-11b proton resulted in an observation of NOE crosspeaks at the methyl ester protons (3.66 ppm) in the 1D NOESY experiment, suggesting that the relative conformation of **4a** is 6,11b-*trans*. In addition, **4a** was converted into (*R*)-(−)-praziquantel in two steps to confirm its stereochemistry unequivocally (Scheme 3). Thus, hydrolysis of **4a** with hydrochloric acid, followed by *N*-acylation with cyclohexanecarbonyl chloride provided **5** in 67% yield. Compound **5** was subjected to the Barton decarboxylation[13] to give **6** in 52% yield and high enantiomeric excess (≥99.5%), which was confirmed by chiral HPLC in comparison with the racemic sample, and its physical and spectroscopic data were identical with the reported data for (*R*)-(−)-praziquantel.[1a,5,14] On the basis of these results, the stereochemistry of **4a** was confirmed as 6*R*,11b*R*-*trans*.

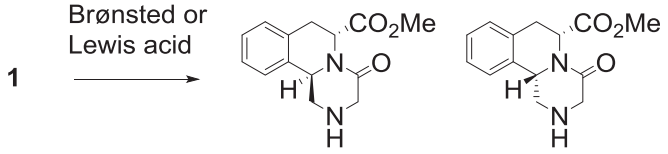
The high stereoselectivity observed in this cyclization is elucidated by the difference of transition states determining a favorable attack of the aromatic ring onto the face of the *N*-acyliminium ion intermediate (Scheme 4). Thus, the cyclization pathway would





Scheme 2. Synthesis of amido-acetal **1**.

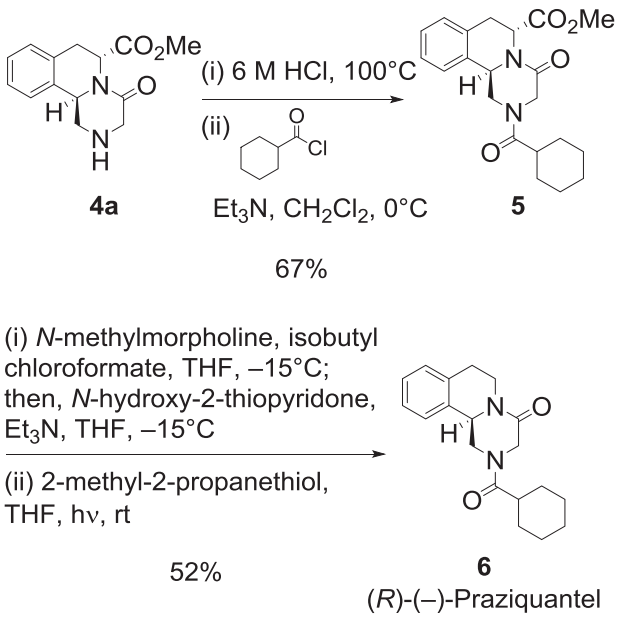
Table 1
The Pictet–Spengler cyclization of **1**[a]



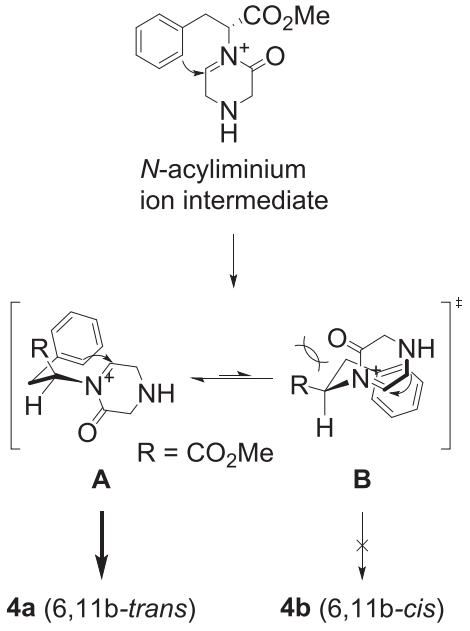
4a (6,11b-*trans*) **4b** (6,11b-*cis*)

Entry	Acid	Solvent	Temperature	Yield of **4a** (%)[b]	Diastereomeric excess (%)[c]
1	H_2SO_4 (concd)[d]	—	rt	58	96.1
2	CH_3SO_3H	—	rt	80	99.0
3	CF_3SO_3H	—	rt	47[h]	74.7
4	TFA	—	rt	—[i]	—
5	$TiCl_4$[e]	CH_2Cl_2	rt	5	98.2
6	$BF_3{\cdot}OEt_2$[e]	CH_2Cl_2	rt	26	98.9
7	CH_3SO_3H[f]	—	70 °C	80	97.4
8	CH_3SO_3H[g]	—	70 °C	63	97.3

[a] Unless otherwise noted, the reaction was carried out with **1** (0.3 mmol) and acid (3 mmol) for 48 h.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC analysis of the crude product mixture.
[d] H_2SO_4 (1.8 mmol), 14 h.
[e] $TiCl_4$ (1.5 mmol) or $BF_3{\cdot}OEt_2$ (1.5 mmol) in CH_2Cl_2 (2 mL).
[f] 0.5 h.
[g] 13 h.
[h] Compound **4b** was isolated in 8% yield.
[i] The cyclized products were not detected.



Scheme 3. Conversion of **4a** into (*R*)-(−)-praziquantel.



Scheme 4. Stereochemical outcome of *N*-acyliminium cyclization.

proceed via a chair-like transition state (**A** or **B**), and conformation **B** would be disfavored because of A$^{(1,3)}$ strain between the pseudo-equatorial carbomethoxy and piperazinone carbonyl groups in the transition state.[15]

Substituted *N*-acyliminium ion precursors **11a**–**e** were then subjected to the optimized Pictet–Spengler conditions to clarify scope and limitations. Compounds **11a**–**e** were prepared by the same procedure as described in Scheme 2 from **9a**–**e**, which were derivatized from commercially available D-phenylalanines **7a**–**c** and **8a**,**b** (Scheme 5). CH_3SO_3H was applied as a catalyst for the Pictet–Spengler cyclization of *para*-substituted **11a**–**c** (Table 2, condition A). The cyclization reaction of **11a** bearing the methyl group proceeded smoothly to give **12a** in a high yield (entry 1), whereas that of **11b** bearing the electron-donating group (*p*-methoxy) afforded **12b** in a low yield (entry 2) and that of **11c** bearing the electron-withdrawing group (*p*-Cl), which was much less nucleophilic in the ring-closing step did not provide the cyclized product (entry 4). Unlike the reaction of **1**, elevated reaction temperature in the CH_3SO_3H-catalyzed cyclization of **11c** resulted in a decomposition of **11c** and/or the *N*-acyliminium ion intermediate, and the cyclized product was not obtained (entry 5). In contrast, it was found that H_2SO_4 was sufficient for clean conversion in the case of electron-deficient substrates **11c**–**e** (Table 2, entry 6–8, condition B), and the desired products **12c**–**e** were obtained as a single isomer in moderate yields (43–61%). However, treatment of **11b** in the presence of H_2SO_4 afforded a complex mixture instead of the cyclized product **12b**, probably because this cyclization conditions toward **11b** led to a polymerization of **11b** and/or the *N*-acyliminium ion intermediate. Although mildly acidic conditions were employed for the cyclization of **11b**, the desired product **12b** was not obtained. Thus, treatment of **11b** with CH_3SO_3H in dichloromethane (entry 3) gave unreacted amido-acetal and **12b**, which was inseparable from a complex product mixture. Treatment of **11b** with TFA also afforded a complex product mixture and unreacted amido-acetal, and none of the cyclized products was detected in the crude product by ^{1}H NMR and LC/MS. We suppose that the low reactivity of **11b** would result from a mesomeric effect of the methoxy group on the *meta* position. The cyclization using CH_3SO_3H and H_2SO_4 provided the desired *trans* products in excellent diastereoselectivity.[16]

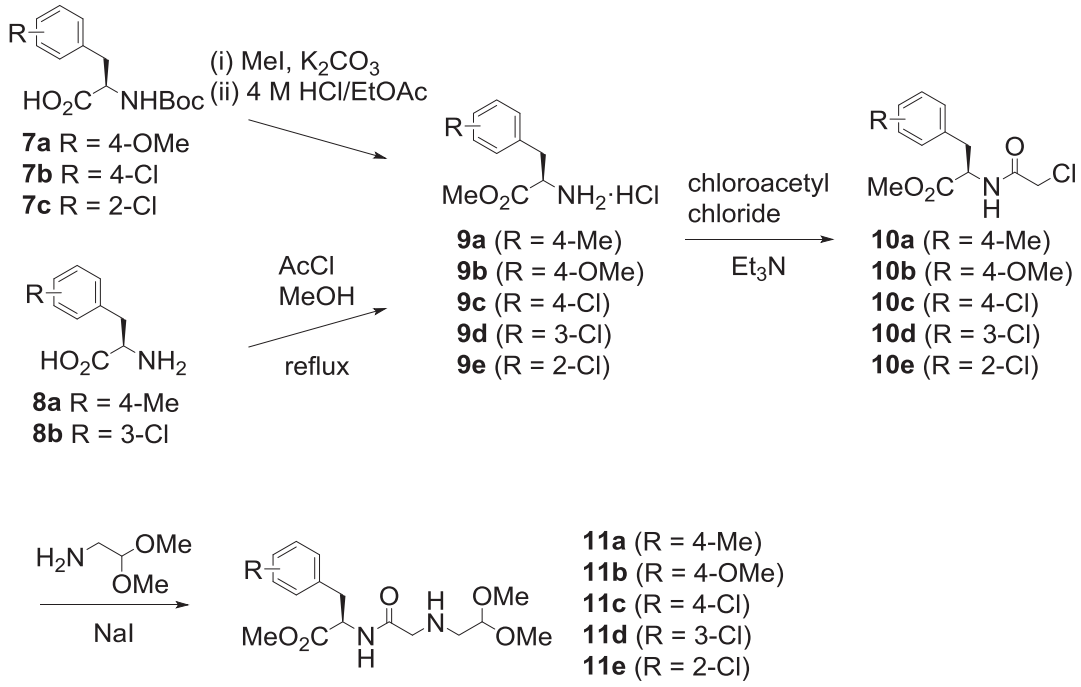
3. Conclusions

In conclusion, a facile and stereocontrolled construction of optically active pyrazinoisoquinoline skeletons via tandem cyclization of phenylalanine derivatives was achieved. The Brønsted acid-catalyzed Pictet–Spengler reaction of cyclic *N*-acyliminium ion intermediates readily generated from D-phenylalanines directly provided 6*R*,11b*R*-*trans* pyrazinoisoquinolines in excellent diastereoselectivity through 1,3-chirality transfer. Furthermore, electron-deficient phenylalanine derivatives successfully cyclized using H_2SO_4 as an acid catalyst to afford the desired products in satisfactory yields and excellent diastereoselectivity. Therefore, this method is applicable to the synthesis of optically active pyrazinoisoquinolines with diverse functional groups and would provide easy access to a wide range of pharmacologically interesting pyrazinoisoquinolines.

4. Experimental

4.1. General

Melting point (mp) was determined on a Büchi B-535 melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 or AVANCE 600 spectrometer, and chemical shifts were expressed in δ (ppm) values with tetramethylsilane as an internal standard. IR spectra were obtained with a PerkinElmer Spectrum One FT-IR spectrometer. Analytical HPLC was conducted on a Capcellpak C_{18} column (5 μm, 4.6×250 mm) eluted with 0.05% (v/v) TFA in water (solvent A) and 0.05% (v/v) TFA in acetonitrile (solvent B), according to the following elution gradient: 5–100% B over 40 min at a flow rate of 1.0 mL/min. LC/MS spectra were recorded on a Waters LC/MS system using a Acquity UPLC BEH C_{18} column (2×50 mm) coupled with micromass ZQ as a MS detector, and the elution gradient of 5–98% B over 1 min was used. HRMS spectra were recorded on a LTQ Orbitrap Velos Pro mass spectrometer equipped with an ESI Lockspray source for accurate mass values. Specific optical rotations were recorded on a Jasco P-2000 polarimeter.



Scheme 5. Synthesis of amido-acetals **11a**–**e**.

Table 2
Scope and limitations of the Pictet–Spengler cyclization

12a–e (6*R*,11b*R*-*trans*)

Entry	Amido-acetal **11**	Conditions[a]	Product (yield)[b]	$[\alpha]_D^{25}$[c]
1	**11a** (R=4-Me)	A	**12a**: R=10-Me (80%)	−149.8
2	**11b** (R=4-OMe)	A[d]	**12b**: R=10-OMe (18%)	−188.3
3	**11b** (R=4-OMe)	A[e]	—[g]	—
4	**11c** (R=4-Cl)	A	—[h]	—
5	**11c** (R=4-Cl)	A[f]	—[h]	—
6	**11c** (R=4-Cl)	B	**12c**: R=10-Cl (61%)	−153.3
7	**11d** (R=3-Cl)	B	**12d**: R=9-Cl (61%)	−164.5
8	**11e** (R=2-Cl)	B	**12e**: R=8-Cl (43%)	−147.8

[a] Unless otherwise noted, the reaction was carried out under the following conditions. Condition A: amido-acetal **11** (0.3 mmol) and CH_3SO_3H (3 mmol) at room temperature for 48 h. Condition B: amido-acetal **11** (0.3 mmol) and concentrated H_2SO_4 (1.8 mmol) at room temperature for 14 h.
[b] Isolated yield after column chromatography.
[c] *c* 0.5, $CHCl_3$.
[d] 8 h.
[e] CH_3SO_3H (1.5 mmol) in CH_2Cl_2 (0.2 mL).
[f] 70 °C, 1 h.
[g] Complex mixture.
[h] The cyclized product was not detected.

4.2. Synthesis of D-phenylalanine methyl ester hydrochlorides 9a–e

*4.2.1. Synthesis of **9a**,**d**.* Acetyl chloride (1.0 mL, 14.1 mmol) was added dropwise to MeOH (15 mL) at 0 °C. After stirring for 15 min at 0 °C, D-4-methylphenylalanine (**8a**) (1.0 g, 5.6 mmol) was added, and the reaction mixture was heated to reflux for 38 h. After cooling, the solvent was evaporated under reduced pressure to give **9a** as a colorless solid, which was used in the next step without further purification.

*4.2.1.1. (R)-4-Methylphenylalanine methyl ester hydrochloride (**9a**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.28 (s, 3H), 3.05 (dd, *J*=13.9, 6.1 Hz, 1H), 3.13 (dd, *J*=13.9, 6.7 Hz, 1H), 3.67 (s, 3H), 4.23 (t, *J*=6.4 Hz, 1H), 7.10–7.16 (m, 4H), 8.58 (br s, 3H); LC/MS (ESI) *m*/*z*: 194.3 $[M+H]^+$.

*4.2.1.2. (R)-3-Chlorophenylalanine methyl ester hydrochloride (**9d**).* Yield 94%, amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.10 (d, *J*=6.2 Hz, 2H), 3.71 (s, 3H), 4.38 (t, *J*=6.0 Hz, 1H), 7.19–7.20 (m, 1H), 7.35–7.40 (m, 3H), 8.38 (br s, 3H); LC/MS (ESI) *m*/*z*: 214.3 $[M+H]^+$.

*4.2.2. Synthesis of **9b**,**c**,**e**.* To a solution of (*R*)-*N*-(*tert*-butoxycarbonyl)-4-methoxyphenylalanine (**7a**) (1.0 g, 3.4 mmol) in DMF (10 mL) was added K_2CO_3 (0.51 g, 3.7 mmol) and iodomethane (0.22 mL, 3.6 mmol). After stirring at room temperature for 3 h, H_2O was added, and the whole was extracted with diethyl ether. The extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to give crude *N*-Boc-phenylalanine methyl ester. To a solution of the obtained compound in EtOAc (5 mL) was added 4 M HCl/EtOAc solution (15 mL). After stirring for 3 h at room temperature, the solution was evaporated under reduced pressure. The resulting precipitate was collected by filtration and washed with diethyl ether to give **9b** as a colorless solid (0.72 g, 92% yield).

*4.2.2.1. (R)-4-Methoxyphenylalanine methyl ester hydrochloride (**9b**).* Yield 92%, colorless solid. Mp 181–182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.03 (dd, *J*=13.8, 6.7 Hz, 1H), 3.10 (dd, *J*=13.9, 5.9 Hz, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 4.22 (t, *J*=6.6 Hz, 1H), 6.89 (d, *J*=8.7 Hz, 2H), 7.15 (d, *J*=8.7 Hz, 2H), 8.56 (br s, 3H); LC/MS (ESI) *m*/*z*: 210.3 $[M+H]^+$.

*4.2.2.2. (R)-4-Chlorophenylalanine methyl ester hydrochloride (**9c**).* Yield 95%, colorless solid. Mp 202–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.15 (ddd, *J*=22.9, 14.2, 6.7 Hz, 2H), 3.69 (s, 3H), 4.29 (t,

J=6.7 Hz, 1H), 7.28 (d, J=8.7 Hz, 2H), 7.39–7.42 (m, 2H), 8.64 (br s, 3H); LC/MS (ESI) m/z: 214.2 $[M+H]^+$.

*4.2.2.3. (R)-2-Chlorophenylalanine methyl ester hydrochloride (**9e**).* Yield 98%, colorless solid. Mp 155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.26 (ddd, J=24.1, 13.9, 7.7 Hz, 2H), 3.61 (s, 3H), 4.17 (dd, J=8.7, 6.6 Hz, 1H), 7.32–7.36 (m, 2H), 7.38–7.42 (m, 1H), 7.45–7.50 (m, 1H), 8.73 (br s, 3H); LC/MS (ESI) m/z: 214.2 $[M+H]^+$.

4.3. Synthesis of (*R*)-*N*-(2-chloroacetyl)phenylalanine methyl esters 3 and 10a–e

To a solution of D-phenylalanine methyl ester hydrochloride (**2**) (10.0 g, 46.4 mmol) and Et_3N (14 mL, 102 mmol) in CH_2Cl_2 (100 mL) was added chloroacetyl chloride (4.4 mL, 55.6 mmol) at 0 °C. After stirring at room temperature for 1 h, H_2O was added, and the whole was extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–50% hexane/EtOAc) to give **3** as colorless oil (11.8 g, 99% yield).

*4.3.1. (R)-N-(2-Chloroacetyl)phenylalanine methyl ester (**3**).* Colorless oil. $[\alpha]_D^{25}$ −54.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (ddd, J=20.1, 13.9, 6.2 Hz, 2H), 3.74 (s, 3H), 4.03 (dd, J=17.0, 15.4 Hz, 2H), 4.87 (dt, J=8.2, 6.2 Hz, 1H), 6.95 (br s, 1H), 7.11–7.13 (m, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.79, 42.37, 52.49, 53.38, 127.35, 128.70, 129.20, 135.30, 165.55, 171.23; IR (ATR) ν 3326, 3031, 2944, 1728, 1645, 1536, 1496, 1446, 1368, 1350, 1225, 1205, 1154, 1117 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}ClNO_3$ ($[M+H]^+$): 256.0735, found: 256.0732.

*4.3.2. (R)-N-(2-Chloroacetyl)-4-methylphenylalanine methyl ester (**10a**).* Yield 73% from **8a**, colorless oil. $[\alpha]_D^{25}$ −57.0 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.11 (ddd, J=18.0, 13.9, 5.6 Hz, 2H), 3.74 (s, 3H), 4.03 (dd, J=15.9, 15.4 Hz, 2H), 4.84 (dt, J=7.8, 5.6 Hz, 1H), 6.94 (br s, 1H), 6.99 (d, J=7.7 Hz, 2H), 7.11 (d, J=7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.09, 37.36, 42.42, 52.48, 53.44, 129.08, 129.43, 132.13, 136.99, 165.56, 171.33; IR (ATR) ν 3342, 3023, 2942, 1730, 1655, 1533, 1445, 1368, 1353, 1261, 1229, 1150, 1119 cm^{-1}; HPLC (220 nm) 99.6% (t_R=23.4 min); LC/MS (ESI) m/z: 270.3 $[M+H]^+$.

*4.3.3. (R)-N-(2-Chloroacetyl)-4-methoxyphenylalanine methyl ester (**10b**).* Yield 94%, colorless oil. $[\alpha]_D^{25}$ −56.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.10 (ddd, J=16.5, 13.9, 5.7 Hz, 2H), 3.74 (s, 3H), 3.79 (s, 3H), 4.03 (dd, J=16.2, 15.2 Hz, 2H), 4.83 (dt, J=8.2, 5.7 Hz, 1H), 6.83–6.86 (m, 2H), 6.95 (br s, 1H), 7.03 (d, J=8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.96, 42.42, 52.48, 53.52, 55.23, 114.14, 127.22, 130.25, 158.88, 165.55, 171.34; IR (ATR) ν 3300, 3006, 2954, 2838, 1741, 1662, 1612, 1511, 1439, 1364, 1245, 1215, 1177, 1118, 1031 cm^{-1}; HPLC (220 nm) 98.6% (t_R=21.0 min); LC/MS (ESI) m/z: 286.3 $[M+H]^+$.

*4.3.4. (R)-N-(2-Chloroacetyl)-4-chlorophenylalanine methyl ester (**10c**).* Yield 99%, colorless oil. $[\alpha]_D^{25}$ −53.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.10 (dd, J=13.9, 5.6 Hz, 1H), 3.16 (dd, J=13.9, 5.6 Hz, 1H), 3.75 (s, 3H), 4.03 (dd, J=16.4, 15.4 Hz, 2H), 4.86 (dt, J=7.9, 5.6 Hz, 1H), 6.96 (br s, 1H), 7.03–7.06 (m, 2H), 7.26–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.23, 42.38, 52.62, 53.29, 128.88, 130.57, 133.34, 133.89, 165.61, 171.04; IR (ATR) ν 3296, 3048, 2943, 1740, 1729, 1661, 1537, 1491, 1445, 1366, 1265, 1203, 1120, 1087 cm^{-1}; HPLC (220 nm) 98.0% (t_R=23.9 min); LC/MS (ESI) m/z: 290.3 $[M+H]^+$.

*4.3.5. (R)-N-(2-Chloroacetyl)-3-chlorophenylalanine methyl ester (**10d**).* Yield 92%, colorless oil. $[\alpha]_D^{25}$ −47.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.10 (dd, J=13.9, 6.2 Hz, 1H), 3.16 (dd, J=13.9, 5.7 Hz, 1H), 3.76 (s, 3H), 4.04 (s, 2H), 4.86 (dt, J=7.7, 5.9 Hz, 1H), 6.99–7.02 (m, 2H), 7.12 (s, 1H), 7.24–7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.50, 42.38, 52.64, 53.27, 127.39, 127.60, 129.45, 129.94, 134.51, 137.43, 165.66, 170.98; IR (ATR) ν 3299, 3063, 2954, 1740, 1661, 1527, 1477, 1435, 1361, 1214, 1179, 1080 cm^{-1}; HPLC (220 nm) 92.9% (t_R=23.8 min); LC/MS (ESI) m/z: 290.3 $[M+H]^+$.

*4.3.6. (R)-N-(2-Chloroacetyl)-2-chlorophenylalanine methyl ester (**10e**).* Yield 95%, colorless oil. $[\alpha]_D^{25}$ −21.6 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.21 (dd, J=13.9, 7.7 Hz, 1H), 3.37 (dd, J=13.9, 6.1 Hz, 1H), 3.75 (s, 3H), 3.99 (dd, J=22.4, 15.2 Hz, 2H), 4.90 (dt, J=8.0, 5.6 Hz, 1H), 7.05 (br s, 1H), 7.18–7.23 (m, 3H), 7.36–7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.37, 42.33, 52.68, 52.74, 127.04, 128.84, 129.78, 131.30, 133.66, 134.50, 165.73, 171.30; IR (ATR) ν 3300, 3063, 2954, 1741, 1661, 1527, 1476, 1436, 1363, 1265, 1214, 1178, 1053 cm^{-1}; HPLC (220 nm) 94.3% (t_R=23.0 min); LC/MS (ESI) m/z: 290.3 $[M+H]^+$.

4.4. Synthesis of amido-acetals 1 and 11a–e

To a solution of **3** (5.0 g, 19.6 mmol) in CH_2Cl_2 (50 mL) was added NaI (2.9 g, 19.6 mmol) and aminoacetaldehyde dimethyl acetal (4.3 mL, 40.1 mmol). After stirring at room temperature for 24 h, additional aminoacetaldehyde dimethyl acetal (2.1 mL, 19.6 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The whole was washed with H_2O, and the aqueous layer was extracted with CH_2Cl_2. The extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–5% $CHCl_3$/MeOH) to give **1** as colorless oil (4.7 g, 74% yield).

*4.4.1. (R)-N-[N-(2,2-Dimethoxyethyl)glycinyl]phenylalanine methyl ester (**1**).* Colorless oil. $[\alpha]_D^{25}$ −43.2 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.60 (dd, J=12.3, 5.7 Hz, 1H), 2.66 (dd, J=12.3, 5.1 Hz, 1H), 3.10 (dd, J=13.8, 6.7 Hz, 1H), 3.18 (dd, J=13.8, 6.1 Hz, 1H), 3.26 (dd, J=22.2, 17.2 Hz, 2H), 3.34 (s, 3H), 3.35 (s, 3H), 3.73 (s, 3H), 4.31 (t, J=5.4 Hz, 1H), 4.88 (dt, J=8.2, 6.2 Hz, 1H), 7.13 (d, J=6.7 Hz, 2H), 7.23–7.32 (m, 3H), 7.64 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.91, 50.92, 52.12, 52.27, 52.60, 54.02, 54.04, 103.45, 127.08, 128.55, 129.18, 136.01, 171.39, 172.00; IR (ATR) ν 3335, 2951, 2833, 1741, 1668, 1512, 1455, 1439, 1361, 1197, 1126, 1056 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{25}N_2O_5$ ($[M+H]^+$): 325.1758, found: 325.1754.

*4.4.2. (R)-N-[N-(2,2-Dimethoxyethyl)glycinyl]-4-methylphenylalanine methyl ester (**11a**).* Yield 79%, colorless oil. $[\alpha]_D^{25}$ −43.2 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.60 (dd, J=12.3, 5.7 Hz, 1H), 2.66 (dd, J=12.3, 5.1 Hz, 1H), 3.06 (dd, J=13.8, 6.7 Hz, 1H), 3.13 (dd, J=13.8, 6.2 Hz, 1H), 3.26 (dd, J=21.5, 16.9 Hz, 2H), 3.34 (s, 3H), 3.35 (s, 3H), 3.73 (s, 3H), 4.31 (t, J=5.4 Hz, 1H), 4.85 (dt, J=8.2, 6.2 Hz, 1H), 7.01 (d, J=7.7 Hz, 2H), 7.09 (d, J=7.7 Hz, 2H), 7.61 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.06, 37.50, 50.94, 52.17, 52.26, 52.68, 54.02, 103.48, 129.07, 129.29, 132.86, 136.66, 171.38, 172.09; IR (ATR) ν 3334, 2950, 2833, 1742, 1668, 1513, 1441, 1362, 1197, 1126, 1056 cm^{-1}; HPLC (220 nm) 99.1% (t_R=18.6 min); LC/MS (ESI) m/z: 339.5 $[M+H]^+$.

*4.4.3. (R)-N-[N-(2,2-Dimethoxyethyl)glycinyl]-4-methoxyphenylalanine methyl ester (**11b**).* Yield 75%, colorless oil. $[\alpha]_D^{25}$ −37.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.61 (dd, J=12.3, 5.7 Hz, 1H), 2.67 (dd, J=12.3, 5.1 Hz, 1H), 3.04 (dd, J=14.2, 6.2 Hz, 1H), 3.11 (dd, J=14.2, 5.9 Hz, 1H), 3.27 (dd, J=20.6, 17.0 Hz, 2H), 3.35 (s, 3H), 3.36 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 4.32 (t, J=5.4 Hz, 1H), 4.84 (dt, J=8.2, 6.0 Hz, 1H), 6.81–6.84 (m, 2H),

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7.02–7.06 (m, 2H), 7.61 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.11, 50.99, 52.19, 52.25, 52.78, 54.01, 54.05, 55.21, 103.50, 114.01, 127.98, 130.21, 158.71, 171.36, 172.11; IR (ATR) ν 3335, 2951, 2835, 1742, 1669, 1612, 1511, 1442, 1362, 1246, 1178, 1126, 1057, 1032 cm^{-1}; HPLC (220 nm) 96.7% (t_R=16.9 min); LC/MS (ESI) m/z: 355.5 $[M+H]^+$.

*4.4.4. (R)-N-[N-(2,2-Dimethoxyethyl)glycinyl]-4-chlorophenylalanine methyl ester (**11c**).* Yield 74%, colorless oil. $[\alpha]_D^{25}$ −37.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.61 (dd, J=12.4, 5.4 Hz, 1H), 2.68 (dd, J=12.4, 5.2 Hz, 1H), 3.07 (dd, J=13.9, 6.2 Hz, 1H), 3.16 (dd, J=14.1, 5.9 Hz, 1H), 3.27 (dd, J=20.0, 17.0 Hz, 2H), 3.35 (s, 3H), 3.36 (s, 3H), 3.73 (s, 3H), 4.32 (t, J=5.2 Hz, 1H), 4.87 (dt, J=8.2, 6.2 Hz, 1H), 7.06–7.08 (m, 2H), 7.24–7.28 (m, 2H), 7.66 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.34, 51.04, 52.18, 52.38, 52.50, 54.09, 54.15, 103.50, 128.73, 130.57, 133.03, 134.60, 171.41, 171.79; IR (ATR) ν 3331, 2951, 2833, 1742, 1668, 1511, 1492, 1438, 1361, 1197, 1126, 1091, 1057, 1015 cm^{-1}; HPLC (220 nm) 98.2% (t_R=19.2 min); LC/MS (ESI) m/z: 359.4 $[M+H]^+$.

*4.4.5. (R)-N-[N-(2,2-Dimethoxyethyl)glycinyl]-3-chlorophenylalanine methyl ester (**11d**).* Yield 66%, colorless oil. $[\alpha]_D^{25}$ −39.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.63 (dd, J=12.4, 5.6 Hz, 1H), 2.69 (dd, J=12.4, 5.1 Hz, 1H), 3.07 (dd, J=13.9, 6.7 Hz, 1H), 3.16 (dd, J=13.9, 5.7 Hz, 1H), 3.28 (dd, J=20.6, 17.0 Hz, 2H), 3.35 (s, 3H), 3.37 (s, 3H), 3.74 (s, 3H), 4.35 (t, J=5.4 Hz, 1H), 4.87 (dt, J=8.5, 6.2 Hz, 1H), 7.01–7.04 (m, 1H), 7.13 (s, 1H), 7.20–7.23 (m, 2H), 7.70 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.61, 51.07, 52.18, 52.39, 52.51, 54.08, 54.16, 103.50, 127.32, 127.37, 129.45, 129.83, 134.31, 138.19, 171.49, 171.70; IR (ATR) ν 3331, 2951, 2833, 1742, 1669, 1510, 1477, 1434, 1360, 1201, 1126, 1056 cm^{-1}; HPLC (220 nm) 93.7% (t_R=19.1 min); LC/MS (ESI) m/z: 359.4 $[M+H]^+$.

*4.4.6. (R)-N-[N-(2,2-Dimethoxyethyl)glycinyl]-2-chlorophenylalanine methyl ester (**11e**).* Yield 66%, colorless oil. $[\alpha]_D^{25}$ −17.9 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.63 (dd, J=12.3, 5.6 Hz, 1H), 2.68 (dd, J=12.3, 5.1 Hz, 1H), 3.19 (dd, J=14.2, 8.4 Hz, 1H), 3.24 (dd, J=25.6, 17.5 Hz, 2H), 3.32–3.37 (m, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 3.73 (s, 3H), 4.38 (t, J=5.4 Hz, 1H), 4.92 (td, J=8.4, 6.1 Hz, 1H), 7.18–7.22 (m, 3H), 7.34–7.37 (m, 1H), 7.72 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.41, 50.99, 51.87, 52.14, 52.44, 54.04, 54.10, 103.50, 126.92, 128.55, 129.65, 131.20, 134.27, 134.49, 171.54, 172.01; IR (ATR) ν 3301, 2948, 2838, 1738, 1650, 1519, 1475, 1439, 1230, 1181, 1126, 1048 cm^{-1}; HPLC (220 nm) 99.1% (t_R=18.5 min); LC/MS (ESI) m/z: 359.2 $[M+H]^+$.

4.5. Synthesis of pyrazinoisoquinoline derivatives 4a,b and 12a–e

To amido acetal **1** or **11a–e** (0.3 mmol) was added CH_3SO_3H (3.0 mmol) or concentrated H_2SO_4 (1.8 mmol), and the reaction mixture was stirred at room temperature for the time indicated on Table 1 or Table 2. The resulting reaction mixture was neutralized with 1 M NaOH, and the whole was extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–9% $CHCl_3$/MeOH) to give **4a** or **11a–e** as an oily product.

*4.5.1. (6R,11bR)-4-Oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid methyl ester (**4a**).* Yield 80%, colorless oil. $[\alpha]_D^{25}$ −130.2 (c 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.95 (dd, J=13.3, 10.2 Hz, 1H), 3.16 (dd, J=16.1, 6.2 Hz, 1H), 3.26 (dd, J=16.1, 3.6 Hz, 1H), 3.60 (d, J=17.7 Hz, 1H), 3.66 (s, 3H), 3.71 (ddd, J=13.3, 4.2, 1.3 Hz, 1H), 3.76 (dd, J=17.8, 1.3 Hz, 1H), 4.99 (dd, J=10.2, 4.0 Hz, 1H), 5.73 (dd, J=6.2, 3.6 Hz, 1H), 7.12–7.14 (m, 1H), 7.17–7.25 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 29.93, 49.15, 49.16, 49.20, 51.93, 54.55, 124.22, 126.52, 126.79, 128.63, 131.38, 132.45, 167.46, 170.46; IR (ATR) ν 3315, 2953, 1736, 1636, 1455, 1434, 1406, 1316, 1200, 1177, 1120, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_3$ $([M+H]^+)$: 261.1234, found: 261.1228.

*4.5.2. (6R,11bR)-10-Methyl-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid methyl ester (**12a**).* Yield 80%, colorless oil. $[\alpha]_D^{25}$ −149.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 2.93 (dd, J=13.3, 10.2 Hz, 1H), 3.11 (dd, J=16.1, 6.1 Hz, 1H), 3.21 (dd, J=16.1, 3.6 Hz, 1H), 3.60 (d, J=17.9 Hz, 1H), 3.65 (s, 3H), 3.68 (dd, J=13.8, 4.1 Hz, 1H), 3.76 (d, J=17.9 Hz, 1H), 4.95 (dd, J=10.2, 4.1 Hz, 1H), 5.73 (dd, J=6.1, 3.6 Hz, 1H), 6.93 (s, 1H), 7.03 (d, J=8.2 Hz, 1H), 7.07 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.21, 30.13, 49.70, 49.75, 49.84, 52.43, 55.16, 125.33, 128.19, 128.80, 129.03, 132.76, 136.67, 168.02, 171.07; IR (ATR) ν 3316, 2953, 1737, 1639, 1433, 1404, 1315, 1199, 1177, 1151, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_3$ $([M+H]^+)$: 275.1390, found: 275.1385.

*4.5.3. (6R,11bR)-10-Methoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid methyl ester (**12b**).* Yield 18%, colorless oil. $[\alpha]_D^{25}$ −188.3 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.94 (dd, J=13.4, 10.3 Hz, 1H), 3.08 (dd, J=15.7, 6.2 Hz, 1H), 3.19 (dd, J=15.7, 3.6 Hz, 1H), 3.60 (d, J=18.0 Hz, 1H), 3.65 (s, 3H), 3.66 (dd, J=13.4, 4.1 Hz, 1H), 3.75 (dd, J=18.0, 1.1 Hz, 1H), 3.79 (s, 3H), 4.95 (dd, J=10.3, 4.1 Hz, 1H), 5.73 (dd, J=6.2, 3.6 Hz, 1H), 6.64 (d, J=2.1 Hz, 1H), 6.78 (dd, J=8.7, 2.6 Hz, 1H), 7.10 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.74, 49.68, 49.83, 49.84, 52.44, 55.22, 55.30, 110.49, 112.92, 123.91, 130.13, 134.02, 158.54, 167.97, 171.06; IR (ATR) ν 3316, 2953, 2838, 1736, 1638, 1505, 1432, 1405, 1314, 1263, 1199, 1175, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_4$ $([M+H]^+)$: 291.1339, found: 291.1336.

*4.5.4. (6R,11bR)-10-Chloro-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid methyl ester (**12c**).* Yield 61%, colorless oil. $[\alpha]_D^{25}$ −153.3 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.93 (dd, J=13.4, 10.3 Hz, 1H), 3.10 (dd, J=16.4, 6.2 Hz, 1H), 3.23 (dd, J=16.4, 3.1 Hz, 1H), 3.60 (d, J=17.4 Hz, 1H), 3.66 (s, 3H), 3.67 (ddd, J=13.4, 4.1, 1.0 Hz, 1H), 3.76 (dd, J=18.0, 1.0 Hz, 1H), 4.95 (dd, J=10.3, 4.1 Hz, 1H), 5.77 (dd, J=6.2, 3.1 Hz, 1H), 7.11 (s, 1H), 7.13 (d, J=5.1 Hz, 1H), 7.20 (dd, J=8.2, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.99, 49.36, 49.63, 49.68, 52.58, 54.87, 125.08, 127.60, 130.42, 130.60, 132.82, 134.69, 167.87, 170.71; IR (ATR) ν 3314, 2953, 1736, 1639, 1487, 1430, 1401, 1313, 1201, 1178, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}ClN_2O_3$ $([M+H]^+)$: 295.0844, found: 295.0841.

*4.5.5. (6R,11bR)-9-Chloro-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid methyl ester (**12d**).* Yield 61%, colorless oil. $[\alpha]_D^{25}$ −164.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.90 (dd, J=13.3, 10.2 Hz, 1H), 3.12 (dd, J=16.4, 6.1 Hz, 1H), 3.24 (dd, J=16.4, 3.1 Hz, 1H), 3.60 (d, J=17.9 Hz, 1H), 3.67 (s, 3H), 3.67 (dd, J=13.3, 4.1 Hz, 1H), 3.76 (d, J=17.9 Hz, 1H), 4.96 (dd, J=10.2, 4.1 Hz, 1H), 5.79 (dd, J=6.1, 3.1 Hz, 1H), 7.06 (d, J=8.7 Hz, 1H), 7.19 (s, 1H), 7.22 (dd, J=8.2, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.29, 49.17, 49.63, 49.82, 52.60, 54.87, 126.37, 127.36, 129.10, 131.41, 133.10, 133.87, 167.86, 170.64; IR (ATR) ν 3315, 2953, 1737, 1640, 1434, 1403, 1314, 1296, 1199, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}ClN_2O_3$ $([M+H]^+)$: 295.0844, found: 295.0841.

*4.5.6. (6R,11bR)-8-Chloro-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid methyl ester (**12e**).* Yield 43%, colorless oil. $[\alpha]_D^{25}$ −147.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.89 (dd, J=13.1, 10.0 Hz, 1H), 3.05 (dd, J=17.2, 6.6 Hz, 1H), 3.52 (dd, J=17.2, 2.6 Hz, 1H), 3.59 (d, J=17.9 Hz, 1H), 3.67 (s, 3H), 3.68 (m, 1H), 3.76 (dd, J=17.9, 1.0 Hz, 1H), 5.01 (dd, J=10.0, 4.1 Hz, 1H), 5.87 (dd, J=6.6, 2.6 Hz, 1H), 7.05 (d, J=7.7 Hz, 1H), 7.20 (t,

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J=7.7 Hz, 1H), 7.31 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.89, 48.77, 49.56, 50.01, 52.63, 54.80, 123.37, 127.77, 128.06, 130.19, 134.68, 135.17, 167.81, 170.67; IR (ATR) ν 3314, 2953, 1737, 1640, 1447, 1405, 1314, 1230, 1201, 1177, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}ClN_2O_3$ ([M+H]$^+$): 295.0844, found: 295.0841.

*4.5.7. (6R,11bS)-4-Oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a] isoquinoline-6-carboxylic acid methyl ester (**4b**).* The title compound was obtained as the minor isomer by CF_3SO_3H-catalyzed cyclization (Table 1, entry 3). Yield 8%, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.17 (dd, J=15.2, 6.1 Hz, 1H), 3.25 (dd, J=15.2, 2.5 Hz, 1H), 3.31 (dd, J=12.4, 10.3 Hz, 1H), 3.53 (s, 3H), 3.65 (d, J=17.4 Hz, 1H), 3.72 (d, J=17.4 Hz, 1H), 3.91 (dd, J=12.4, 3.8 Hz, 1H), 4.62 (dd, J=10.3, 4.0 Hz, 1H), 4.98 (dd, J=6.1, 2.5 Hz, 1H), 7.13–7.19 (m, 2H), 7.25–7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 31.15, 46.72, 50.02, 52.20, 54.03, 54.47, 122.81, 127.42, 127.56, 127.97, 133.65, 135.05, 168.19, 170.94; LC/MS (ESI) m/z: 261.3 [M+H]$^+$.

4.6. Synthesis of (*R*)-(−)-praziquantel 6

*4.6.1. (6R,11bR)-2-Cyclohexanecarbonyl-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline-6-carboxylic acid (**5**).* A solution of **4a** (0.50 g, 1.9 mmol) in 6 M HCl (5 mL) was heated to reflux for 39 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was triturated with EtOAc/EtOH (10: 1), and the solid was collected by filtration to give crude (6*R*,11b*R*)-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrazino[2,1-*a*]isoquinoline-6-carboxylic acid hydrochloride (0.50 g). To a suspension of the obtained carboxylic acid (0.30 g) in CH_2Cl_2 (6 mL) was added Et_3N (0.3 mL, 2.2 mmol) and cyclohexanecarbonyl chloride (0.16 g, 1.1 mmol) at 0 °C. After stirring at 0 °C for 1 h, 1 M HCl was added, and the whole was extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–45% $CHCl_3$/MeOH) to give **5** as an amorphous solid (0.28 g, 67% yield). $[\alpha]_D^{25}$ −42.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26–1.88 (m, 10H), 2.43–2.48 (m, 1H), 3.11–3.26 (m, 3H), 4.05–5.04 (m, 4H), 5.49–5.56 (m, 1H), 7.20 (m, 4H); IR (ATR) ν 3285, 2926, 2853, 1617, 1410, 1300, 1217, 748 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_4$ ([M+H]$^+$): 357.1809, found: 357.1803.

*4.6.2. (R)-2-Cyclohexanecarbonyl-1,2,3,6,7,11b-hexahydro-pyrazino [2,1-a]isoquinolin-4-one, (R)-(−)-praziquantel (**6**).* To a solution of **5** (0.15 g, 0.42 mmol) in THF (2 mL) was added *N*-methylmorpholine (51 μL, 0.46 mmol) and isobutyl chloroformate (63 mg, 0.46 mmol) at −15 °C. After stirring at the same temperature for 30 min, a solution of *N*-hydroxy-2-thiopyridone (64 mg, 0.51 mmol) and Et_3N (70 μL, 0.51 mmol) in THF (0.5 mL) was added. The mixture was stirred at −15 °C for 1 h under nitrogen atmosphere, sheltered from the light (aluminum foil). The precipitate of *N*-methylmorpholine hydrochloride was filtered and washed with THF. The yellow filtrate was irradiated in the presence of 2-methyl-2-propanethiol (0.47 mL, 4.2 mmol) with a lamp (200 W) at room temperature in a water bath until the color has disappeared. Then, H_2O was added, and the whole was extracted with EtOAc. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–90% hexane/EtOAc) to give **6** as a colorless solid (68 mg, 52% yield), which was recrystallized from heptane/EtOAc (1: 1). Mp 106–107 °C, lit.[5] mp 113–115 °C, lit.[14] mp 107–108 °C; $[\alpha]_D^{25}$ −153.6 (*c* 1.0, $CHCl_3$), lit.[5] $[\alpha]_D^{23}$ −135.0 (*c* 1, $CHCl_3$), lit.[1a] $[\alpha]_D^{20}$ −149.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26–1.31 (m, 3H), 1.50–1.82 (m, 7H), 2.44–2.56 (m, 1H), 2.77–3.03 (m, 3.8H), 3.25 (m, 0.2H), 3.87 (d, J=17.5 Hz, 0.2H), 4.08 (d, J=17.5 Hz, 0.8H), 4.36 (m, 0.2H), 4.47 (d, J=17.5 Hz, 0.8H), 4.79–4.88 (m, 2.2H), 5.16 (m, 0.8H), 7.17–7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 28.7, 29.0, 29.2, 39.1, 40.8, 45.2, 49.0, 55.0, 125.5, 127.0, 127.5, 129.3, 132.8, 134.8, 164.4, 174.8; IR (ATR) ν 2924, 2854, 1642, 1440, 757 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{25}N_2O_2$ ([M+H]$^+$): 313.1911, found: 313.1906.

References and notes

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16. Any *cis*-isomers of **12a–e** were not detected in the crude reaction mixture by 400 MHz ^{1}H NMR and LC/MS, and the distereoselectivity could not be calculated.