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Efficient and Practical Syntheses of Enantiomerically Pure (*S*)-(−)-Norcryptostyline I, (*S*)-(−)-Norcryptostyline II, (*R*)-(+)-Salsolidine and (*S*)-(−)-Norlaudanosine *via* a Resolution-Racemization Method†

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Four racemic tetrahydroisoquinolines (*RS*)-(±)-**1**−**4** were prepared from homoveratrylamine via amidation, Bischler-Napieralski reaction and the subsequent reduction. The enantiomerically pure tetrahydroisoquinolines (*S*)-(−)-norcryptostyline I [(*S*)-(−)-**1**], (*S*)-(−)-norcryptostyline II [(*S*)-(−)-**2**], (*R*)-(+)-salsolidine [(*R*)-(+)-**3**] and (*S*)-(−)-norlaudanosine [(*S*)-(−)-**4**] were then obtained in 45%, 40%, 41% and 38% yields, respectively, via resolution of the racemic compounds (*RS*)-(±)-**1**−**4** with half equivalent of chiral acids. In addition, the enantiomerically enriched compounds (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4** from the mother liquors were efficiently racemized via a one-pot redox method in almost quantitative yields.

Keywords tetrahydroisoquinolines, norcryptostyline, salsolidine, norlaudanosine, resolution, racemization

Introduction

Although stereoselective synthesis of chiral compounds has made a great progress in past decades,[1] resolution remains one of the most important methods for preparing chiral compounds especially in large scale or industrial syntheses,[2] because it has some advantages such as simplicity, easy operation, free of expensive chiral reagents or ligands, no harsh reaction conditions, and so on. Normally, the maximum yield of resolution is limited to 50%, but if the unwanted enantiomer could be efficiently racemized for re-resolution, and the cycle of resolution-racemization[3] could be repeated many times, thus the yield of the wanted enantiomer could be theoretically increased to 100%. Furthermore, from a sustainable chemistry point of view, the unwanted enantiomer should be better converted to the desired enantiomer via the racemization-resolution process to minimize the waste as far as possible.

1,2,3,4-Tetrahydroisoquinolines (THIQs), especially 1-substituted THIQs, are a very important kind of heterocyclic compounds because of their various biological activities.[4] (*S*)-(−)-Norcryptostyline I [(*S*)-(−)-**1**], (*S*)-(−)-norcryptostyline II [(*S*)-(−)-**2**], (*R*)-(+)-salsolidine [(*R*)-(+)-**3**] and (*S*)-(−)-norlaudanosine [(*S*)-(−)-**4**] are the four useful 1-substituted THIQs (see Figure 1), which can be readily converted to the corresponding alkaloids (*S*)-(+)-cryptostyline I,[5] (*S*)-(+)-cryptostyline II,[5,6] (*R*)-(+)-carnegine[7] and (*S*)-(+)-laudanosine.[8] (*S*)-(−)-Norlaudanosine [(*S*)-(−)-**4**] can also be easily transformed to the alkaloid (*S*)-(−)-xylopinine.[8,9] Both (*R*)-(+)-salsolidine [(*R*)-(+)-**3**] and its enantiomer (*S*)-(−)-salsolidine [(*S*)-(−)-**3**] are naturally occuring compounds, they can be isolated from various plant sources.[10] Many synthetic methods for enantioselective syntheses of 1-substituted THIQs and their derivatives have been explored,[10a,11] but the resolution method of 1-substituted THIQs is less stud-

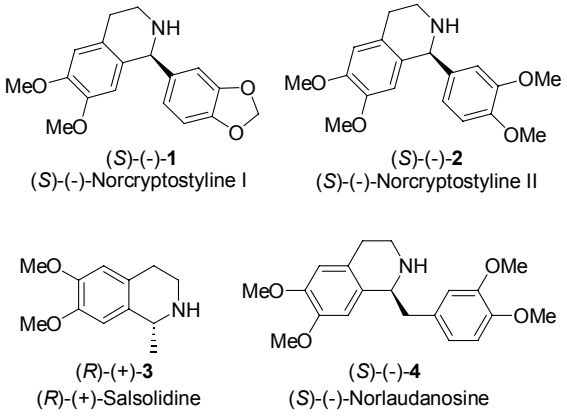

Figure 1 Structures of the four targeted 1-substituted THIQs.

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† Dedicated to Professor Chengye Yuan and Professor Li-Xin Dai on the occasion of their 90th birthdays.

ied.[12] Herein, we want to report efficient and practical syntheses of the four useful enantiomerically pure 1-substituted THIQs **1**—**4** via a resolution-racemization method.

Results and Discussion

(±)-Norcryptostyline I [(*RS*)-(±)-**1**] and (±)-norcryptostyline II [(*RS*)-(±)-**2**] can be directly prepared by Pictet-Spengler reaction in moderate yields according to Coskun's report,[13] but this method is obviously not practical because of use of the corrosive trifluoroacetic acid (CF_3COOH) as the solvent. Herein, it was found that the synthetic method as shown in Scheme 1 could be used for the scalable and practical preparations of the racemic THIQs (*RS*)-(±)-**1**—**4**.

As shown in Scheme 1, homoveratrylamine was first treated with 1.2 equiv. of carboxylic chlorides RCOCl [R＝3,4-(OCH_2O)-Ph, 3,4-$(MeO)_2$-Ph and 3,4-$(MeO)_2$-$PhCH_2$] or acetic anhydride (R＝CH_3) in the presence of 2.0 equiv. of sodium hydroxide in a biphasic mixed solvent of dichloromethane and water (CH_2Cl_2/H_2O＝2∶1), the corresponding amides **5a**—**5d** were obtained in almost quantitative yields. The amides **5a**—**5d** were then exposed to 2.0 equiv. of phosphoryl trichloride at reflux in ethyl acetate to furnish 3,4-dihydroisoquinolines **6a**—**6d** *via* Bischler-Napieralski reaction.[14] Subsequently, the above compounds **6a**—**6d** could be used as such for the next step, and were reduced by 2.0 equiv. of KBH_4 in methanol to afford the racemic THIQs **1**—**4** in 96%, 97%, 95% and 81% yields, respectively. The yield of THIQ (*RS*)-(±)-**4** is relatively low, because the intermediate 3,4-dihydroisoquinoline **6d** could be smoothly oxidized by O_2 (air) under basic or even neutral conditions. As can be seen from Scheme 2, when a solution of 3,4-dihydroisoquinoline **6d** in ethyl acetate was stirred at room temperature under air for 10 h, 3,4-dihydropapaveraldine[15] **7** could be obtained in 90% yield via the benzylic oxidation.

With the racemic THIQs (*RS*)-(±)-**1**—**4** in hands, we then attempted the chiral resolutions of them to prepare enantiomerically pure THIQs (*S*)-(−)-**1**, (*S*)-(−)-**2**, (*R*)-(＋)-**3** and (*S*)-(−)-**4**. A literature search showed that the resolution of racemic THIQs (*RS*)-(±)-**1** and **2** with *L*-(−)-diacetone-2-keto-gulonic acid as the resolving agent,[5] the resolution of racemic THIQ (*RS*)-(±)-**3** with *L*-(＋)-tartaric acid as the resolving agent,[16] and the reslution of racemic THIQ (*RS*)-(±)-**4** with (＋)-*α*-bromocamphorsulphonic acid as the resolving agent[17] have been reported. However, all of these reported resolutions suffered from low yields and the use of excessive chiral resolving agents. Herein, we want to report novel efficient resolutions of racemic THIQs (*RS*)-(±)-**1**—**4** with 0.5 equiv. of inexpensive chiral acids as the resolving agents. As can be seen from the Table 1, *N*-tosyl-*L*-phenylalanine was used as the resolving agent for the resolution of racemic THIQ (*RS*)-(±)-**1**; *L*-mandelic acid was used as the resolving agent for the resolution of racemic THIQ (*RS*)-(±)-**3**; *N*-acetyl-*L*-phenylalanine was used as the resolving agent for the resolutions of racemic THIQs (*RS*)-(±)-**2** and (*RS*)-(±)-**4**. Enantiomerically pure THIQs (*S*)-(−)-**1**, (*S*)-(−)-**2**, (*R*)-(＋)-**3** and (*S*)-(−)-**4** were obtained in 45%, 40%, 41% and 38% yields, respectively.

High pressure liquid chromatography (HPLC) method using a chiral column is often a good choice for determining the enantiomeric purity of chiral compounds, but NMR method using a chiral solvating agent (CSA)[18] might be another more time-efficient and inexpensive choice. The enantiomeric purities of the above four chiral THIQs (*S*)-(−)-**1**, (*S*)-(−)-**2**, (*R*)-(＋)-**3** and (*S*)-(−)-**4** are greater than 99% (*ee*＞98%), which can be determined by the NMR method with CSAs in $CDCl_3$. As can be seen from Figure 2, in the ^1H NMR

Scheme 1 Preparations of racemic THIQs (*RS*)-(±)-**1**—**4**

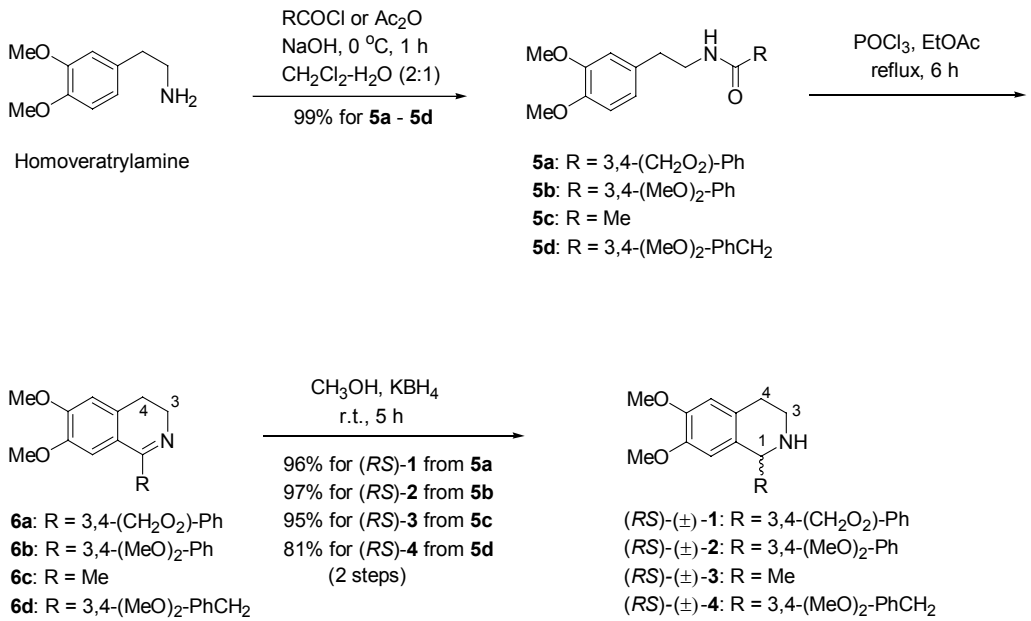

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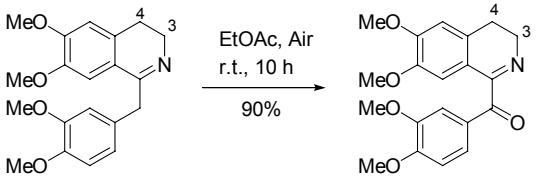
Table 1 Resolution of racemic THIQs (*RS*)-(±)-**1**—**4** by using 0.5 equiv. of chiral acids as the resolving agents

THIQs	Chiral acid (0.5 equiv.)	Solvent	$[\alpha]_D^{20}$ (*R*/*S*)	*ee*[a]/%	Yield/%
1	*N*-Ts-*L*-Phenylalanine	I[b]: EtOH II[c]: EtOAc/EtOH (1∶1)	−23.7[d] (*S*)	＞98	45
2	*N*-Ac-*L*-Phenylalanine	I[b]: EtOH II[c]: EtOAc/EtOH (3∶1)	−35.0[e] (*S*)	＞98	40
3	*L*-Mandelic acid	I[b]: EtOAc/*i*-PrOH (5∶1) II[c]: EtOAc/*i*-PrOH (7∶1)	+59.7[f] (*R*)	＞98	41
4	*N*-Ac-*L*-Phenylalanine	I[b]: EtOAc/EtOH (5∶1) II[c]: EtOAc	−27.9[g] (*S*)	＞98	38

[a] Determined by ^{1}H NMR ($CDCl_3$, 500 MHz) with chiral acids as the CSAs (see Figure 2). [b] Resolution: the mixture was stirred at reflux for 3 h in the designated solvent. [c] Purification: the suspension of the salt was stirred at reflux for 6 h in the designated solvent. [d] Optical rotation of (*S*)-(−)-**1**: $[\alpha]_D^{20}$ =−23.7 (*c* 1.10, $CHCl_3$) {lit.[5] $[\alpha]_D^{20}$ =−23.0 ($CHCl_3$)}. [e] Optical rotation of (*S*)-(−)-**2**: $[\alpha]_D^{20}$ =−35.0 (*c* 1.00, $CHCl_3$) {lit.[5] $[\alpha]_D^{20}$ =−34.0 ($CHCl_3$)}. [f] Optical rotation of (*R*)-(+)-**3**: $[\alpha]_D^{20}$ =+59.7 (*c* 1.10, EtOH) {lit.[16a] $[\alpha]_D^{20}$ =+59.5 (*c* 4.39, EtOH)}. [g] Optical rotation of (*S*)-(−)-**4**: $[\alpha]_D^{20}$ =−27.9 (*c* 1.20, $CHCl_3$) {lit.[9] $[\alpha]_D^{20}$ =−27.6 (*c* 2.50, $CHCl_3$)}.

Scheme 2 Conversion of compound **6d** to compound **7**



6d 3,4-Dihydropapaveraldine **7**

spectra of each of the racemic THIQs (*RS*)-(±)-**1**—**4**, the absorbing peak of H-1 (proton at the C-1 position) split into two groups in the presence of various CSAs as indicated in Figure 2. In comparison, in the ^{1}H NMR spectra of each of the above described chiral THIQs (*S*)-(−)-**1**, (*S*)-(−)-**2**, (*R*)-(+)-**3** and (*S*)-(−)-**4**, only one absorbing peak of H-1 appeared in the presence of the same CSA, meaning that only one enantiomer existed in each of the chiral THIQs to be measured.

Chiral compounds usually can be racemized by thermal methods, base-catalyzed methods, acid-catalyzed methods, enzyme-catalyzed methods, redox methods, and so on.[19] In this article, we have tried the racemization of the enantiomerically enriched THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4** from the mother liquors by both base-catalyzed and redox methods.

We first examined a base-catalyzed method for the racemization of THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3**

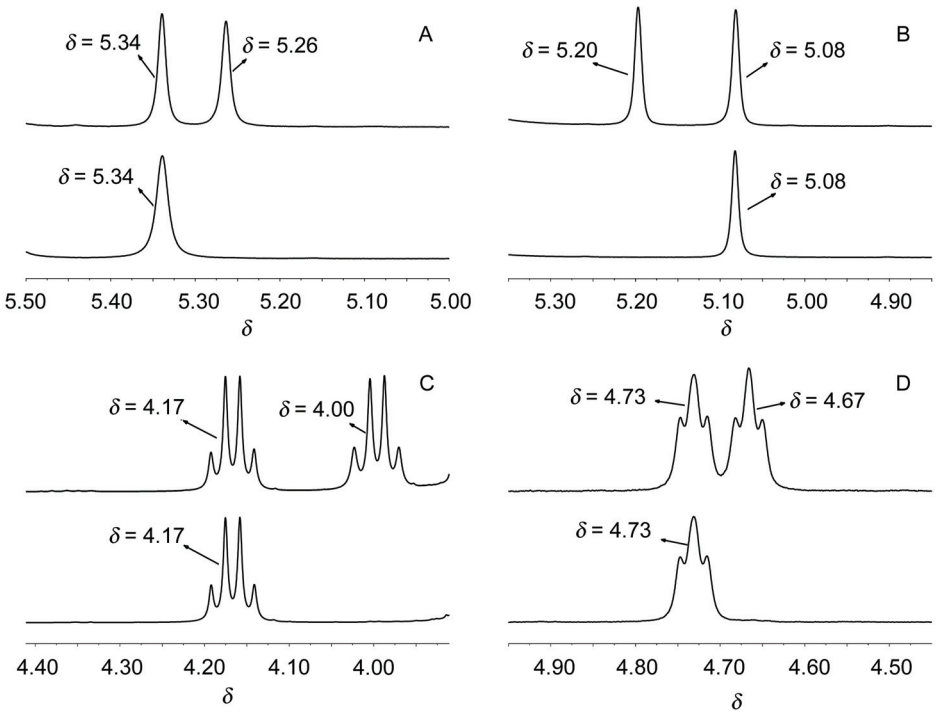


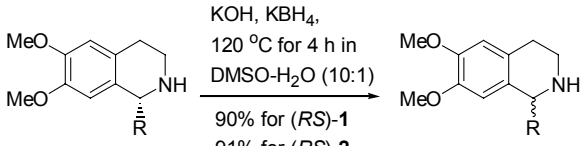
Figure 2 Determination of purities of chiral THIQs **1**—**4** by NMR method using chiral acids as the chiral solvating agents (CSAs). CSA: (A) 1 equiv. of dibenzoyl-*D*-tartaric acid; (B) 1 equiv. of *N*-(*p*-tosyl)-*L*-phenylalanine; (C) 1 equiv. of *L*-mandelic acid; (D) 3 equiv. of *N*-(*p*-tosyl)-*L*-leucine.

and (*R*)-(+)-**4**. As shown in Scheme 3, 1-aryl-THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2** smoothly underwent racemization at 120 ℃ in aqueous dimethyl sulfoxide (DMSO/H_2O=10∶1) in the presence of 3.0 equiv. of KOH and 2.0 equiv. of KBH_4 under an atmosphere of nitrogen (or argon) to afford racemic THIQs (*RS*)-(±)-**1** and (*RS*)-(±)-**2** in 90% and 91% yields, respectively. Exclusive removal of oxygen was necessary, otherwise THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2** could be oxidized by oxygen. The above base-catalyzed racemization of 1-aryl-THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2** might follow the same mechanism as proposed in a previous report.[3a] Regrettably, the above base-catalyzed racemization was not applicable for 1-alkyl-THIQs (*S*)-(−)-**3** and (*R*)-(+)-**4** probably because of the low acidity of the H-1 protons of 1-alkyl-THIQs (*S*)-(−)-**3** and (*R*)-(+)-**4**.

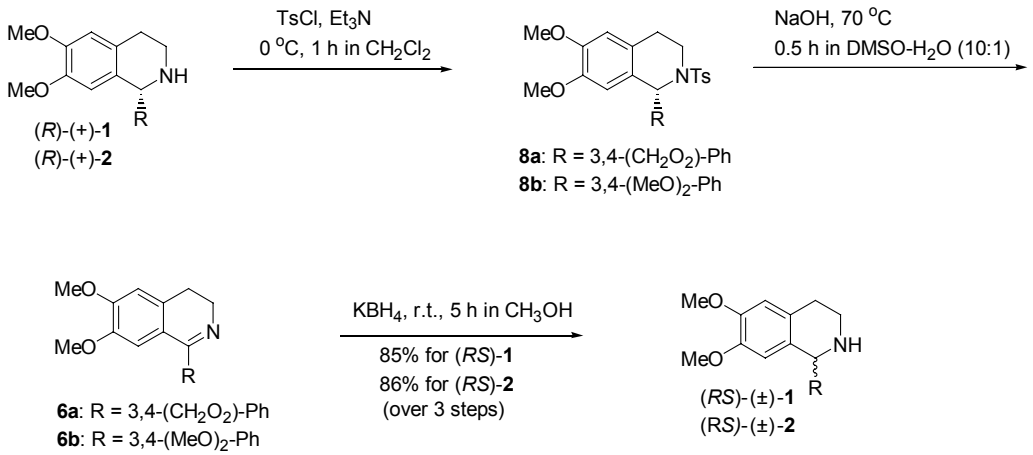
We next examined two redox methods (Schemes 4 and 5) for the racemization of THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4**. As shown in Scheme 4, the first redox method can only be applied to the racemization of 1-aryl-THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2**. It contained the following three steps: THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2** were treated with 1.1 equiv. of *p*-toluenesulfonyl chloride and 2.0 equiv. of triethylamine in dichloromethane to afford *N*-Ts-THIQs **8a** and **8b** in nearly quantitative yields. *N*-Ts-THIQs **8a** and **8b** were then treated with 3.0 equiv. of NaOH at 70 ℃ in aqueous DMSO (DMSO/H_2O=10∶1) to give dihydroisoquinolines **6a** and **6b** by *β*-elimination.[20] Subsequently, compounds **6a** and **6b** were reduced by 2.0 equiv. of KBH_4 in methanol to furnish the racemic THIQs (*RS*)-(±)-**1** and (*RS*)-(±)-**2** in 85% and 86% overall yields, respectively.

As shown in Scheme 5, the second redox method can be applicable for the racemization of both 1-aryl-THIQs and 1-alkyl-THIQs. It contained the following

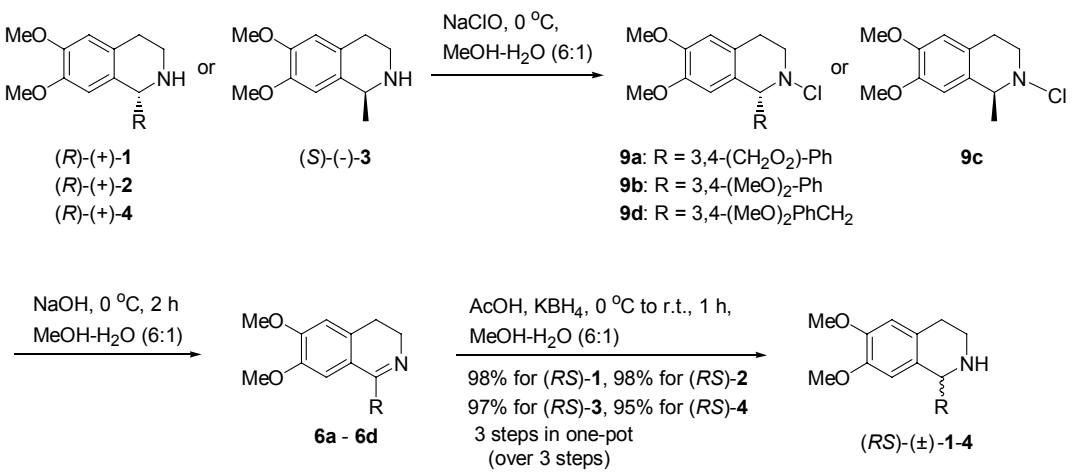
Scheme 3 Base-catalyzed racemization of 1-aryl THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2**



Scheme 4 Redox racemization of THIQs (*R*)-(+)-**1** and (*R*)-(+)-**2** via *N*-Ts-THIQs intermediates



Scheme 5 One-pot redox racemization of THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4** via *N*-Cl-THIQs intermediates



three steps: THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4** were treated with 1.5 equiv. of NaClO and 2.0 equiv. of NaOH at 0 ℃ in aqueous methanol (MeOH/H_2O=6∶1) to give *N*-Cl-THIQs **9a**−**9d**,[21] which immediately underwent *β*-elimination to afford the corresponding dihydroisoquinolines **6a**−**6d**. Subsequently, compounds **6a**−**6d** were reduced by 2.0 equiv. of KBH_4 in the presence of 5.0 equiv. of AcOH in the same solvent to afford the racemic THIQs (*RS*)-(±)-**1**−**4** in 98%, 98%, 97% and 95% overall yields, respectively. Notably, the above redox racemizations of THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4** were accomplished in a one-pot procedure without isolation of intermediates *N*-Cl-THIQs **9a**−**9d** and compounds **6a**−**6d**.

Conclusions

In conclusion, a resolution-racemization process of 1-substituted THIQs (*RS*)-(±)-**1**−**4** has been investigated. Accordingly, enantiomerically pure (*S*)-(−)-norcryptostyline I [(*S*)-(−)-**1**], (*S*)-(−)-norcryptostyline II [(*S*)-(−)-**2**], (*R*)-(+)-salsolidine [(*R*)-(+)-**3**] and (*S*)-(−)-norlaudanosine [(*S*)-(−)-**4**] were efficiently synthesized. Several methods for the racemization of the enantiomerically enriched THIQs (*R*)-(+)-**1**, (*R*)-(+)-**2**, (*S*)-(−)-**3** and (*R*)-(+)-**4** from the mother liquors have been studied, and it was found that the mild one-pot redox racemization via *N*-Cl-THIQs intermediates was the most efficient and convenient method. In addition, NMR method using appropriate CSAs for determining the enantiomerical purities of chiral THIQs (*S*)-(−)-**1**, (*S*)-(−)-**2**, (*R*)-(+)-**3** and (*S*)-(−)-**4** was discussed.

Experimental

General methods

^{1}H NMR and ^{13}C NMR spectra were acquired on Bruker AM-500 or AM-400, chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Melting points were determined on a Mel-TEMP II apparatus. Optical rotations of chiral compounds were measured on WZZ-1S automatic polarimeter at room temperature. Column chromatography was performed on silica gel (Qingdao Ocean Chemical Corp.). All chemicals were analytically pure, and were used as such from commercial suppliers.

General procedure for preparation of amides 5a−5d

A mixture of the carboxylic acid RCOOH (120.0 mmol), chloroform (20 mL) and thionyl chloride (28.55 g, 240.0 mmol) was stirred at reflux for 2 h, chloroform and the excessive thionyl chloride were then removed by vacuum distillation. The residue was dissolved in dichloromethane (40 mL), and the resulting solution was sealed with a drying tube ($CaCl_2$), and should be immediately used.

Homoveratrylamine (18.12 g, 99.98 mmol) was dissolved in dichloromethane (160 mL), and a solution of sodium hydroxide (8.000 g, 200.0 mmol) in water (100 mL) was added. While the biphasic solution was vigorously stirred and cooled to 0 ℃ by an ice-bath, a solution of the above prepared carboxylic chloride RCOCl (120.0 mmol) or acetic anhydride (7.206 g, 120.0 mmol) in dichloromethane (40 mL) was slowly added over 30 min. After the addition was finished, the biphasic mixture was further stirred at 0 ℃ for 1 h. Two phases were then separated, and the aqueous phase was extracted twice with dichloromethane (50 mL×2). Extracts were combined, and dried over anhydrous magnesium sulfate. Solvent was then removed by vacuum distillation. The solid residue was triturated in aqueous ethanol (EtOH/H_2O=1∶1), pure amides **5a**−**5d** as off-white crystals were obtained in almost quantitative yields by suction through a Buchner funnel.

Characterization data of amides **5a**−**5d** are as follows:

***N*-(3,4-Dimethoxyphenethyl)-3,4-methylenedioxybenzamide (5a)** Off-white crystals. m.p. 113−114 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.85 (t, *J*=7.0 Hz, 2 H, $(MeO)_2PhCH_2$), 3.64 (td, J_1=7.0 Hz, J_2=5.3 Hz, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.99 (s, 2H, OCH_2O), 6.39 (t, *J*=5.3 Hz, 1H, NH), 6.70−6.85 (m, 4H, Ar-H), 7.18−7.25 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 35.23, 41.38, 55.79, 55.89, 101.66, 107.52, 107.93, 111.32, 111.90, 120.65, 121.41, 128.80, 131.47, 147.62, 147.90, 148.97, 150.22, 166.79; IR (KBr) *v*: 3304, 2968, 2938, 2842, 1765 (weak), 1641, 1608, 1548, 1517, 1488, 1315, 1262, 1241, 1143, 1027, 936, 808, 700 cm^{-1}. HRMS calcd for $C_{18}H_{19}NO_5$ [M^+]: 329.1263, found 329.1262.

***N*-(3,4-Dimethoxyphenethyl)-3,4-dimethoxybenzamide (5b)** Off-white crystals. m.p. 152−153 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.87 (t, *J*=7.0 Hz, 2H, $(MeO)_2PhCH_2$), 3.66 (td, J_1=7.0 Hz, J_2=5.3 Hz, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.48 (t, *J*=5.3 Hz, 1H, NH), 6.73−6.77 (m, 2H, Ar-H), 6.81 (d, *J*=8.5 Hz, 2H, Ar-H), 7.22 (dd, J_1=8.5 Hz, J_2=1.9 Hz, 1H, Ar-H), 7.41 (d, *J*=1.9 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 35.27, 41.37, 55.78, 55.87, 55.91, 55.95, 110.20, 110.45, 111.28, 111.94, 119.25, 120.65, 127.18, 131.51, 147.61, 148.87, 148.96, 151.60, 167.06; IR (KBr) *v*: 3293, 2966, 2928, 2839, 1732 (weak), 1630, 1546, 1516, 1457, 1320, 1258, 1233, 1137, 1021, 823, 713 cm^{-1}. HRMS calcd for $C_{19}H_{23}NO_5$ [M^+]: 345.1576; found 345.1578.

***N*-(3,4-Dimethoxyphenethyl)acetamide (5c)** Off-white solid crystals. m.p. 96−97 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 1.95 (s, 3H, CH_3 in Ac), 2.77 (t, *J*=7.0 Hz, 2H, $(MeO)_2PhCH_2$), 3.46−3.54 (m, 2H, CH_2N), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.60

(brs, 1H, NH), 6.72 (s, 1H, Ar-H), 6.73 (d, J=7.9 Hz, 1H, Ar-H), 6.82 (d, J=7.9 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.11, 35.14, 40.86, 55.74, 55.81, 111.26, 111.81, 120.56, 131.47, 147.48, 148.84, 170.28; IR (KBr) v: 3253, 3086, 2993, 2929, 2841, 1730 (weak), 1633, 1568, 1520, 1473, 1263, 1236, 1157, 1140, 1020, 815, 766, 611 cm^{-1}; MS (EI) *m/z* (%): 223 [M^+] (8), 164 (100), 151 (38), 149 (17), 137 (2), 121 (2), 107 (4), 91 (1). HRMS calcd for $C_{12}H_{17}NO_3$ [M^+]: 223.1208, found 223.1209.

***N*-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (5d)** Off-white crystals. m.p. 123－124 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.68 (t, J=6.9 Hz, 2H, $(MeO)_2PhCH_2CH_2N$), 3.44 (td, J_1=6.9 Hz, J_2=5.7 Hz, 2H, CH_2N), 3.47 (s, 2H, CH_2CON), 3.83 (s, 6H, two OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.53 (t, J=5.7 Hz, 1H, NH), 6.53 (dd, J_1=8.1 Hz, J_2=1.8 Hz, 1H, Ar-H), 6.62 (d, J=1.8 Hz, 1H, Ar-H), 6.65－6.75 (m, 3H, Ar-H), 6.80 (d, J=8.0 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.97, 40.69, 43.41, 55.79, 55.81, 55.83, 55.87, 111.06, 111.36, 111.63, 112.32, 120.55, 121.56, 127.20, 131.03, 147.57, 148.22, 148.95, 149.18, 171.23; IR (KBr) v: 3325, 3062, 3005, 2914, 2838, 1731 (weak), 1642, 1544, 1517, 1470, 1232, 1143, 1026, 856, 765 cm^{-1}; MS (EI) *m/z* (%): 359 [M^+] (9), 195 (4), 164 (100), 151 (29), 107 (4). HRMS calcd for $C_{20}H_{25}NO_5$ [M^+]: 359.1733, found 359.1732.

General procedure for the preparation of 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines (6a－6d)

An amide **5** (60.00 mmol) was dissolved in EtOAc (200 mL), and $POCl_3$ (18.40 g, 120.0 mmol) was dropwise added over 5 min. The mixture was then heated and stirred at reflux under an atmosphere of nitrogen (or argon) for 6 h. After the Bischler-Napieralski reaction was finished as monitored by TLC (EtOAc/hexane＝2∶1), the solvent was removed by vacuum distillation. The residue was then partitioned between CH_2Cl_2 (200 mL) and an aqueous solution of K_2CO_3 (15% *w*/*w*, 200 mL). Two phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (100 mL×2). Organic extracts were combined, and dried over anhydrous $MgSO_4$. Solvent was removed by vacuum distillation to give 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines **(6a－6d)** as pale yellow crystals. Compounds **6a－6c** were pure enough, and could be used as such for the next step. Compound **6d** was purified by flash chromatography (eluent: CH_2Cl_2/MeOH＝25∶1).

Characterization data of amides **6a－6d** are as follows:

1-(3,4-Methylenedioxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (6a) Pale yellow crystals. m.p. 109－110 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.71 (t, J=7.3 Hz, 2H, both H-4), 3.768 (s, 3H, OCH_3), 3.770 (t, J=7.3 Hz, 2H, both H-3), 3.95 (s, 3H, OCH_3), 6.02 (s, 2H, OCH_2O), 6.78 (s, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 6.86 (d, J=8.0 Hz, 1H, Ar-H), 7.11 (dd, J_1=8.0 Hz, J_2=1.4 Hz, 1H, Ar-H), 7.14 (d, J=1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.03, 47.49, 56.01, 56.17, 101.26, 107.83, 109.25, 110.21, 111.50, 121.45, 123.08, 132.75, 133.28, 147.00, 147.60, 148.59, 150.84, 165.96; IR (KBr) v: 2935, 2834, 1734 (weak), 1603, 1560, 1512, 1488, 1443, 1355, 1279, 1238, 1112, 1037, 933, 800 cm^{-1}. HRMS calcd for $C_{18}H_{17}NO_4$ [M^+]: 311.1158, found 311.1157.

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (6b) Pale yellow crystals. mp. 169－170 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.72 (t, J=7.2 Hz, 2H, both H-4), 3.76 (s, 3H, OCH_3), 3.79 (t, J=7.2 Hz, 2H, both H-3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.80 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.92 (d, J=8.3 Hz, 1H, Ar-H), 7.17 (dd, J_1=8.3 Hz, J_2=1.6 Hz, 1H, Ar-H), 7.25 (d, J=1.6 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.06, 47.53, 55.91, 55.92, 56.00, 56.11, 110.19, 110.26, 111.53, 111.66, 121.52, 121.82, 131.77, 132.79, 146.92, 148.69, 150.00, 150.74, 166.07; IR (KBr) v: 2938, 2888, 2837, 1738 (weak), 1602, 1563, 1514, 1462, 1355, 1279, 1256, 1210, 1160, 1113, 1017, 865, 801 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{21}NO_4$ [M^+]: 327.1471, found 327.1473.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (6c) Pale yellow crystals. m.p. 108－109 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.37 (s, 3H, CH_3), 2.64 (t, J=7.5 Hz, 2H, both H-4), 3.63 (t, J=7.5 Hz, 2H, both H-3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.69 (s, 1H, Ar-H), 6.99 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.39, 25.65, 46.95, 55.85, 56.09, 108.83, 110.11, 122.36, 130.98, 147.30, 150.67, 163.49; IR (KBr) v: 2945, 2925, 2839, 1627, 1604, 1574, 1516, 1288, 1277, 1215, 1159, 1063, 874, 810 cm^{-1}; MS (EI) *m/z* (%): 205 [M^+] (100), 204 (53), 190 (48), 188 (8), 174 (11), 160 (7), 147 (6), 131 (3), 118 (4), 103 (3), 91 (4), 77 (4). HRMS calcd for $C_{12}H_{15}NO_2$ [M^+]: 205.1103, found 205.1102.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (6d) Pale yellow crystals. m.p. 99－100 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.65 (t, J=7.6 Hz, 2H, both H-4), 3.73 (t, J=7.6 Hz, 2H, both H-3), 3.76 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.99 (s, 2H, $(MeO)_2PhCH_2$), 6.66 (s, 1H, Ar-H), 6.78 (d, J=8.7 Hz, 1H, Ar-H), 6.82－6.90 (m, 2H, Ar-H), 7.00 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.79, 43.04, 47.16, 55.78, 55.81, 55.88, 55.97, 109.55, 110.20, 111.21, 111.56, 120.64, 121.56, 130.59, 131.79, 147.16, 147.59, 148.97, 150.62, 165.59; IR (KBr) v: 2934, 2834, 1606, 1573, 1516, 1465, 1447, 1356, 1447, 1234, 1147, 1022, 856, 811, 764 cm^{-1}; MS (EI) *m/z* (%): 341 [M^+] (57), 340 (100), 326 (40), 310 (36), 294 (12), 279 (6), 266 (4), 252 (3), 155 (7), 151 (8), 107 (2). HRMS calcd for $C_{20}H_{23}NO_4$ [M^+]: 341.1627, found 341.1628.

General procedure for preparation of racemic 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (*RS*)-(±)-1−4

1-Substituted 3,4-dihydro-6,7-dimethoxylisoquinolines **6** (50.00 mmol) was dissolved in methanol (150 mL), KBH_4 (5.400 g, 100.1 mmol) was added in small portions over 20 min. After the addition was finished, the mixture was further stirred at room temperature for 5 h. Methanol was removed by vacuum distillation, the residue was then partitioned between dichloromethane (200 mL) and water (100 mL). Two phases were separated, and the aqueous phase was extracted twice with dichloromethane (50 mL×2). Extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of dichloromethane under vacuum gave crude solid products. Crude compounds (*RS*)-(±)-**1**−**3** were triturated in a mixed solvent of ethyl acetate and hexane (1∶2), and the suspension was filtered by suction to afford pure (*RS*)-(±)-**1**−**3** in 96%, 97% and 95% yields, respectively. Crude compound (*RS*)-(±)-**4** was purified by flash chromatography (eluent: CH_2Cl_2/MeOH=20∶1) to afford pure compound (*RS*)-(±)-**4** in 81% yield.

Characterization data of racemic THIQs (*RS*)-(±)-**1**−**4** are as follows:

1-(3,4-Methylenedioxyphenyl)−6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*RS*)-(±)-1 White crystals. m.p. 135−136 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.04 (brs, 1H, NH), 2.68−2.76 (m, 1H, H-4), 2.86−2.95 (m, 1H, another H-4), 2.98−3.06 (m, 1H, H-3), 3.16−3.25 (m, 1H, another H-3), 3.67 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.98 (s, 1H, H-1), 5.94 (s, 2H, OCH_2O), 6.27 (s, 1H, Ar-H), 6.62 (s, 1H, Ar-H), 6.69−6.79 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 29.89, 42.49, 56.41, 56.47, 61.80, 101.54, 108.41, 109.72, 111.50, 111.99, 122.77, 128.22, 130.55, 139.64, 147.36, 147.64, 148.21, 148.28; IR (KBr) *v*: 3425, 3253, 2910, 1610, 1519, 1488, 1445, 1251, 1216, 1124, 1043, 943, 835, 762 cm^{-1}; MS (EI) *m/z* (%): 313 [M^+] (58), 312 (77), 298 (14), 282 (6), 268 (3), 254 (7), 239 (2), 192 (100), 181 (8), 176 (8), 148 (6), 81 (3). HRMS calcd for $C_{18}H_{19}NO_4$ [M^+]: 313.1314, found 313.1312.

1-(3,4−Dimethoxyphenyl)−6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*RS*)-(±)-2 White crystals. m.p. 104−105 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.20 (brs, 1H, NH), 2.68−2.78 (m, 1H, H-4), 2.90−3.00 (m, 1H, another H-4), 3.02−3.10 (m, 1H, H-3), 3.19−3.28 (m, 1H, another H-3), 3.65 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.876 (s, 3H, OCH_3), 3.878 (s, 3H, OCH_3), 5.00 (s, 1H, H-1), 6.27 (s, 1H, Ar-H), 6.63 (s, 1H, Ar-H), 6.75−6.86 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 29.73, 42.72, 56.31, 56.355, 56.358, 56.361, 61.93, 111.19, 111.41, 111.90, 112.31, 121.73, 128.06, 130.60, 137.84, 147.48, 148.08, 148.80, 149.47; MS (EI) *m/z* (%): 329 [M^+] (68), 328 (91), 314 (19), 298 (9), 286 (3), 269 (13), 254 (3), 238 (4), 192 (100), 176 (7), 164 (3). HRMS (ESI) calcd for $C_{19}H_{23}NO_4$ [M^+]: 329.1627; found: 329.1628.

6,7-Dimethoxy-1-methyl−1,2,3,4-tetrahydroisoquinoline (*RS*)-(±)-3 White crystals. m.p. 48−49 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.44 (d, *J*=6.6 Hz, 3H, CH_3), 1.80 (brs, 1H, NH), 2.61−2.68 (m, 1H, H-4), 2.75−2.84 (m, 1H, another H-4), 2.96−3.05 (m, 1H, H-3), 3.22−3.28 (m, 1H, another H-3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.05 (q, *J*=6.6 Hz, 1H, H-1), 6.57 (s, 1H, Ar-H), 6.63 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.15, 29.81, 42.09, 51.56, 56.24, 56.39, 109.51, 112.21, 127.14, 132.72, 147.66, 147.74; IR (KBr) *v*: 3408, 2966, 2935, 2837, 1612, 1520, 1464, 1404, 1257, 1227, 1136, 1115, 997, 860 cm^{-1}; MS (EI) *m/z* (%): 207 [M^+] (6), 192 (100), 176 (10), 163 (2), 148 (5), 131 (2), 91 (2), 77 (2). HRMS calcd for $C_{12}H_{17}NO_2$ [M^+]: 207.1259, found 207.1258.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*RS*)-(±)-4 White crystals. m.p. 79−80 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.85 (brs, 1H, NH), 2.64−2.81 (m, 2H, both H-4), 2.81−2.95 (m, 2H, CH_2 beside C-1), 3.12−3.25 (m, 2H, both H-3), 3.84 (s, 3H, OCH_3), 3.86 (s, 6H, two OCH_3), 3.88 (s, 3H, OCH_3), 4.13 (dd, J_1=9.1 Hz, J_2=4.1 Hz, 1H, H-1), 6.60 (s, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 6.76 (s, 1H, Ar-H), 6.78−6.86 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 29.46, 40.90, 42.19, 55.81, 55.84, 55.89, 55.96, 56.83, 109.29, 111.24, 111.76, 112.33, 121.41, 127.37, 130.32, 131.37, 146.95, 147.39, 147.62, 148.89; IR (KBr) *v*: 3598, 3332, 2995, 2934, 2833, 1608, 1514, 1464, 1262, 1233, 1113, 1029, 858, 803, 768 cm^{-1}; MS (EI) *m/z* (%): 343 [M^+] (1), 340 (4), 206 (1), 192 (100), 176 (7), 151 (3), 148 (3), 131 (1), 118 (1), 107 (1). HRMS calcd for $C_{20}H_{25}NO_4$ [M^+]: 343.1784, found 343.1788.

Formation of 3,4-dihydropapaveraldine (7) Compound **6d** (1.000 g, 2.929 mmol) was dissolved in ethyl acetate (15 mL). The solution was stirred at room temperature under air for 10 h. Ethyl acetate was removed by vacuum distillation, and the residue was purified by flash chromatography (eluent: EtOAc/hexane=1∶5) to afford 3,4-dihydropapaveraldine **7** (936.5 mg, 2.635 mmol) in 90% yield. m.p. 188−190 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.82 (t, *J*=8.0 Hz, 2H, both H-4), 3.79 (s, 3H, OCH_3), 3.93 (t, *J*=8.0 Hz, 2H, both H-3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.76 (s, 1H, Ar-H), 6.88 (d, *J*=8.4 Hz, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 7.60 (dd, J_1=8.4 Hz, J_2=1.9 Hz, 1H, Ar-H), 7.67 (d, *J*=1.9 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.44, 47.27, 56.01, 56.02, 56.12, 56.14, 109.68, 110.05, 110.53, 111.29, 119.53, 126.57, 128.63, 131.07, 147.67, 149.18, 151.69, 154.18, 164.63, 192.77; IR (KBr) *v*: 2969, 2833, 1728, 1660, 1583, 1515, 1460, 1361, 1278, 1269, 1134, 1024, 866, 631 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{21}NO_5$ [M^+]: 355.1420, found 355.1421.

Typical procedure for the resolution of racemic 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (*RS*)-(±)-1−4

Racemic compound (*RS*)-(±)-**1** (4.010 g, 12.80

mmol) was dissolved in absolute ethanol (80 mL), and the resulting solution was transferred into a three-necked round bottom flask, which was equipped with a mechanical stirrer and a condenser. The powdered *N*-tosyl-*L*-phenylalanine (2.045 g, 6.403 mmol) was added in portions. After the addition was finished, the mixture was vigorously stirred at reflux for 3 h. After the mixture was cooled down to room temperature, the white solid was collected on Buchner funnel by suction. The solid was totally transferred into the above three-necked round bottom flask, a mixed solvent of ethyl acetate (50 mL) and ethanol (50 mL) was added. The suspension was then vigorously stirred at reflux for 6 h. After the suspension was cooled down to room temperature, it was filtered by suction. White solid was then partitioned between dichloromethane (100 mL) and an aqueous solution of ammonia (60 mL, 10% *w*/*w*). Two phases were separated, and the aqueous phase was twice extracted with dichloromethane (50 mL×2). The extracts were combined, and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum afforded pure (*S*)-(−)-norcryptostyline I (*S*)-(−)-**1** (1.805 g, 5.760 mmol) as white crystals in 45% yield, $[\alpha]_D^{20}$ = –23.7 (*c* 1.10, $CHCl_3$) {lit.[5] $[\alpha]_D^{20}$ =–23.0 ($CHCl_3$)}.

The mother liquors of the above suctions were combined in a flask, and were then concentrated under vacuum to give a viscous oil. An aqueous solution of ammonia (65 mL, 10% *w*/*w*) and dichloromethane (120 mL) were then added into the flask. After the mixture was vigorously stirred for 15 min, two phases were separated with a separatory funnel, and the aqueous phase was twice extracted with dichloromethane (60 mL×2). The extracts were combined, and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum afforded (*R*)-(+)-norcryptostyline I (*R*)-(+)-**1** (2.208 g, 7.046 mmol) as off-white crystals in 55% yield and with 82% *ee*, $[\alpha]_D^{20}$ =+19.4 (*c* 1.25, $CHCl_3$).

The results for the resolution of the other racemic THIQs (*RS*)-(±)-**2**−**4** are as follows:

(*S*)-(−)-Norcryptostyline II (*S*)-(−)-**2** was obtained in 40% yield, $[\alpha]_D^{20}$ =–35.0 (*c* 1.00, $CHCl_3$) {lit.[5] $[\alpha]_D^{20}$ = –34.0 ($CHCl_3$)}. (*R*)-(+)-Norcryptostyline II (*R*)-(+)-**2** was recovered from the mother liquor in 60% yield and with 67% *ee*, $[\alpha]_D^{20}$ =+23.4 (*c* 1.05, $CHCl_3$).

(*R*)-(+)-Salsolidine (*R*)-(+)-**3** was obtained in 41% yield, $[\alpha]_D^{20}$ =+59.7 (*c* 1.10, EtOH) {lit.[16a] $[\alpha]_D^{20}$ = +59.5 (*c* 4.39, EtOH)}. (*S*)-(−)-Salsolidine (*S*)-(−)-**3** was recovered from the mother liquor in 59% yield and with 69% *ee*, $[\alpha]_D^{20}$ =–41.3 (*c* 1.10, EtOH).

(*S*)-(−)-Norlaudanosine (*S*)-(−)-**4** was obtained in 38% yield, $[\alpha]_D^{20}$ = –27.9 (*c* 1.20, $CHCl_3$) {lit.[9] $[\alpha]_D^{20}$ =–27.6 (*c* 2.50, $CHCl_3$)}. (*R*)-(+)-Norlaudanosine (*R*)-(+)-**4** was recovered from the mother liquor in 62% yield and with 61% *ee*, $[\alpha]_D^{20}$ =–27.9 (*c* 1.20, $CHCl_3$).

Base-catalyzed racemization of the enantiomerically enriched 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (*R*)-(+)-1 and (*R*)-(+)-2

The enantiomerically enriched 1-aryl-THIQ (*R*)-(+)-**1** or (*R*)-(+)-**2** (5.000 mmol) was dissolved in DMSO (20 mL). An aqueous solution of KOH (842.0 mg, 15.01 mmol) in H_2O (2 mL) was added, and KBH_4 (540.0 mg, 10.01 mmol) was also added. The mixture was then heated to 120 ℃, and stirred at this temperature for 4 h under an atmosphere of nitrogen. The mixture was cooled down to room temperature, and water (50 mL) was slowly added. When the mixture was stirred for about 15 min, off-white crystals precipitated. The suspension was filtered by suction, racemic compound (*RS*)-(±)-**1** (1.410 g, 4.500 mmol) or (*RS*)-(±)-**2** (1.500 g, 4.554 mmol) was then obtained in 90% or 91% yield after drying overnight.

Redox racemization of the enantiomerically enriched 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (*R*)-(+)-1 and (*R*)-(+)-2 *via* *N*-tosyl-THIQs intermediates

The enantiomerically enriched 1-aryl-THIQ (*R*)-(+)-**1** or (*R*)-(+)-**2** (5.000 mmol) was dissolved in dichloromethane (40 mL). After the solution was cooled down to 0 ℃ by an ice-bath, Et_3N (1.015 g, 10.03 mmol) and TsCl (1.050 g, 5.508 mmol) were added in turn. The resulting solution was then stirred at 0 ℃ for 1 h, and an aqueous solution of K_2CO_3 (20 mL, 10% *w*/*w*) was added. After the mixture was vigorously stirred for 10 min, two phases were separated, and the aqueous phase was extracted twice with dichloromethane (20 mL×2). Organic extracts were combined and dried over anhydrous $MgSO_4$. After dichloromethane was removed by evaporation, *N*-Ts-THIQs **8a** or **8b** was obtained, and was then used as such for the next step.

N-Ts-THIQs **8a** or **8b** was dissolved in DMSO (15 mL), and an aqueous solution of NaOH (600.0 mg, 15.00 mmol) in water (1.5 mL) was added. The mixture was warmed to 70 ℃, and stirred at this temperature for 2.5 h under an atmosphere of nitrogen (or argon). After the reaction mixture was cooled down to room temperature, dichloromethane (80 mL) and water (60 mL) were added. Two phases were separated, and the aqueous phase was extracted twice with dichloromethane (50 mL×2). Extracts were combined, and dried over anhydrous $MgSO_4$. Removal of the solvent gave compound **6a** or **6b**, which was immediately dissolved in methanol (30 mL). KBH_4 (540.0 mg, 10.01 mmol) was added in portions, and the mixture was stirred at room temperature for 5 h. Methanol was then removed by vacuum distillation, and the residue was partitioned between dichloromethane (50 mL) and water (40 mL). Two phases were separated, and the aqueous phase was extracted twice with dichloromethane (25 mL×2). Extracts were combined, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave an oily residue, which

was purified by flash chromatography (eluent: CH_2Cl_2/MeOH＝20∶1) to afford racemic compound (*RS*)-(±)-**1** (1.332 g, 4.251 mmol) or (*RS*)-(±)-**2** (1.417 g, 4.302 mmol) in 85% or 86% yield.

Typical procedure for one-pot redox racemization of the enantiomerically enriched 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (*R*)-(＋)-1, (*R*)-(＋)-2, (*S*)-(−)-3 and (*R*)-(＋)-4 via *N*-chloro-THIQs intermediates

The enantiomerically enriched 1-aryl-THIQs (*R*)-(＋)-**1** (5.000 mmol) was dissolved in methanol (30 mL), and the solution was cooled down to 0 ℃ by an ice-bath. A freshly prepared aqueous solution (5 mL) of sodium hypochloride (1.5 mol/L) and sodium hydroxide (2.0 mol/L) was dropwise added over 10 min, and the mixture was further stirred at 0 ℃ for 2 h. TLC showed that *N*-chloro-THIQs **9a** was first formed during the reaction, but then absolutely changed into compound **6a**. Acetic acid (1.500 g, 24.99 mmol) was added, KBH_4 (540.0 g, 10.01 mml) was then added in small portions over 15 min. After the addition was finished, the mixture was further stirred at 0 ℃ for 1 h. Methanol was removed by vacuum distillation, the residue was partitioned between dichloromethane (50 mL) and water (40 mL). Two phases were separated, and the aqueous phase was extracted twice with dichloromethane (25 mL×2). Extracts were combined, and dried over anhydrous $MgSO_4$. Evaporation of dichloromethane gave racemic compound (*RS*)-(±)-**1** (1.535 g, 4.899 mmol) as white crystals in 98% yield.

Supporting Information

Copies of spectra of ^1H and ^{13}C NMR of compounds **1**—**4**, **5a**—**5d**, **6a**—**6d** and **7**.

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