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Enantioselective Synthesis of Some Tetracyclic Isoquinoline Alkaloids by Asymmetric Transfer Hydrogenation Catalysed by a Chiral Ruthenium Complex

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Summary. Asymmetric transfer hydrogenation catalysed by chiral ruthenium complexes was the method for enantioselective synthesis of (*R*)-(+)-coralydine, (*S*)-(−)-homoprotoberberine, and (*S*)-(+)-homoaporphine in fair to excellent enantiomeric purity.

Keywords. Bioorganic chemistry; Diastereomers; Ligands; Natural products; Reductions.

Introduction

Alkaloids constitute a structurally diverse class of nitrogen heterocycles that can be found in many plants and even mammalian organisms and often disclose a profound physiological activity. Plant extracts containing alkaloids have been employed all over the history for their toxicity or valuable medicinal properties. From a vast amount of over 12000 alkaloids found to-date, many of them still serve as important pharmaceuticals, including indispensable chemotherapeutics as vincristine and vinblastine, stimulants like caffeine, together with analgetics, like codeine or morphine [1, 2].

Isoquinolines form the largest group of alkaloids. Particularly, 1-benzyl and 1-ethylphenyl-1,2,3,4-tetrahydroisoquinolines seem to occupy a central position in this group being biosynthetically correlated with almost all known structural variations (Figs. 1 and 2).

Some natural alkaloids possess the (1*R*) configuration, while the opposite stereochemistry could also be found in several others. Because of the fact that a multitude of natural alkaloids and also several of their synthetic analogues exhibit important physiological activity, many academic and pharmaceutical research

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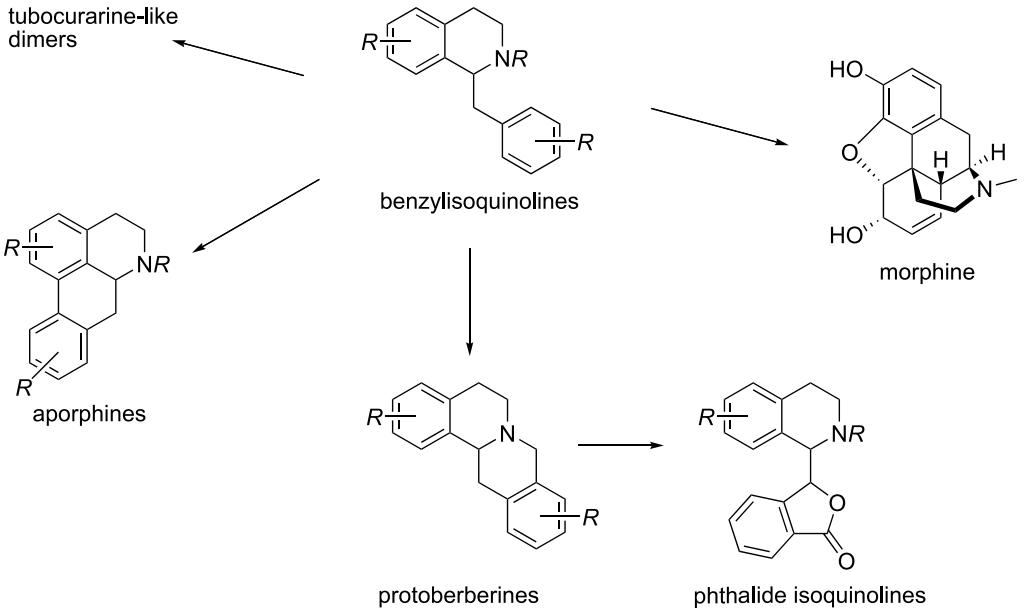


Fig. 1. Selected biosynthetic relations in benzylisoquinolines

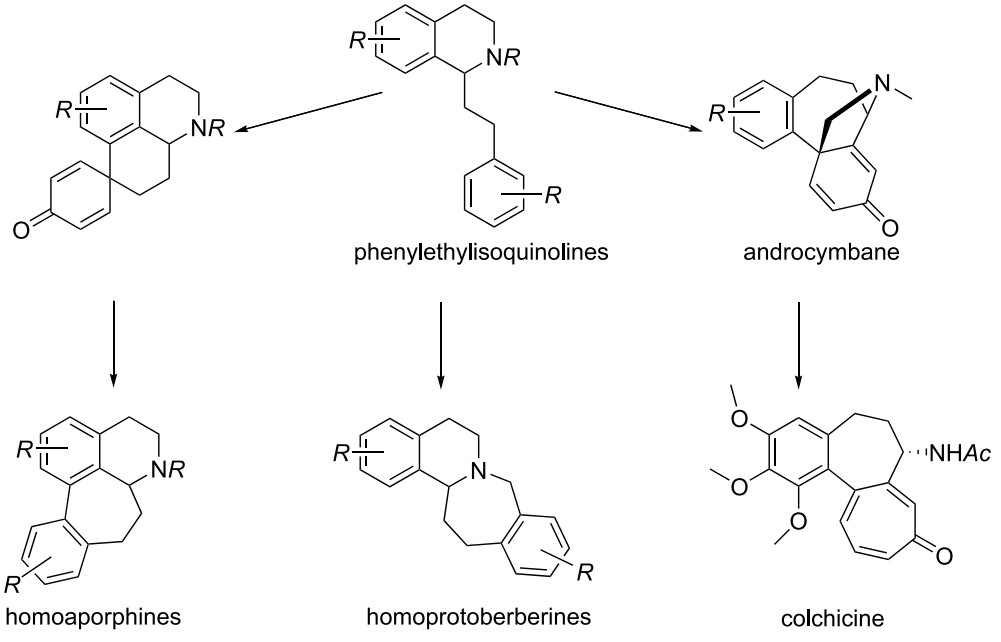


Fig. 2. Selected biosynthetic relations in homobenzylisoquinolines

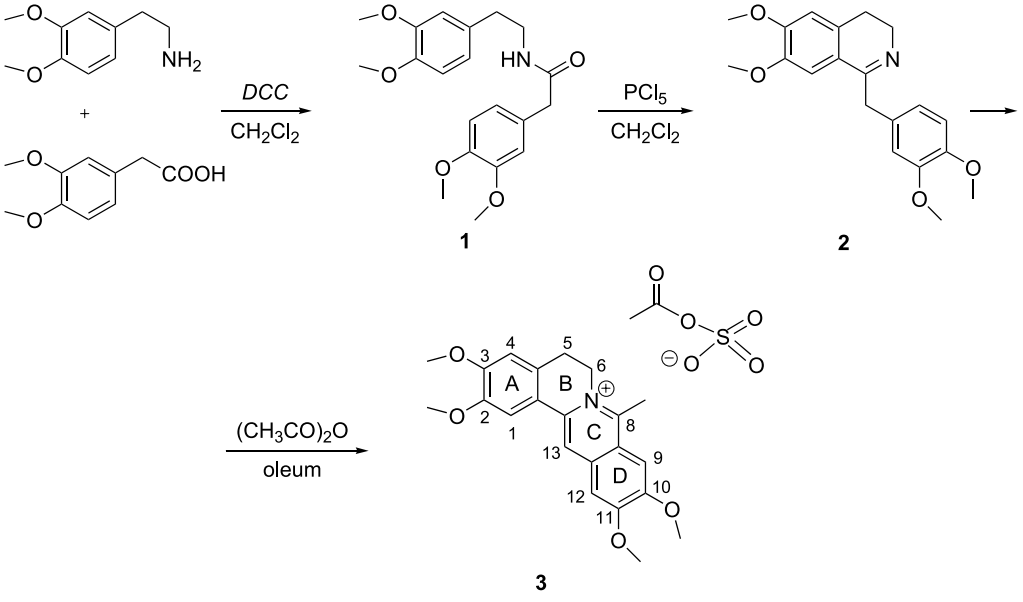
groups are involved in the synthesis of these compounds. Due to a severe biodiscrimination of enantiomers within organisms and, as a consequence, the diverse action of stereoisomers of bioactive compounds, there is a growing interest in development of stereoselective methods of synthetic procedures. Recently, exploration of catalytic or biomimetic approaches seem to be the most attractive.

Results and Discussion

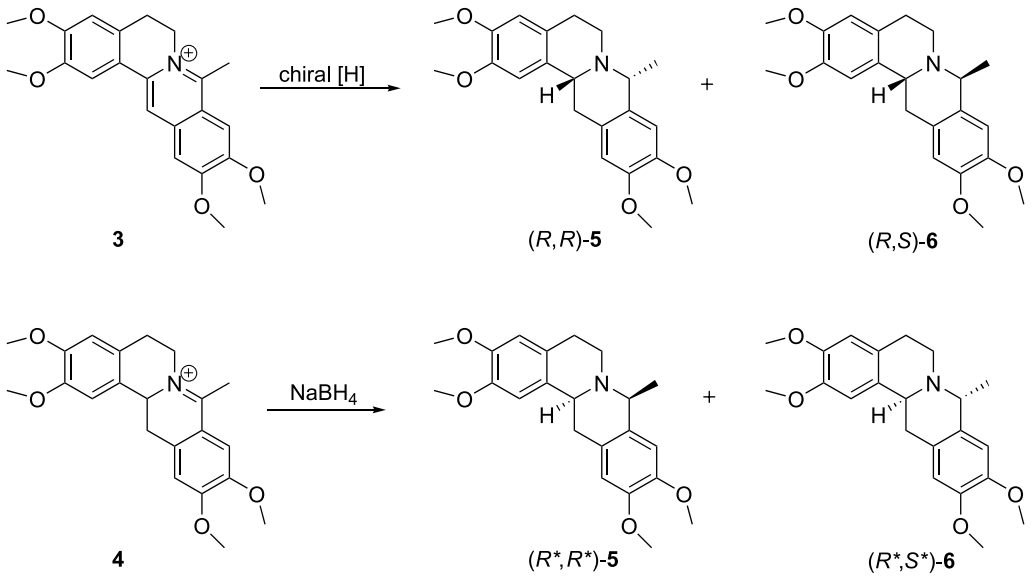
Most tetrahydroisoquinoline alkaloids have a stereogenic center at their C-1 position, and different stereoselective synthesis paths have been focused on the chirality control at this position. There are some general procedures for the construction of isoquinoline skeleton. Among them, the *Pictet-Spengler* [3, 4] and the *Bischler-Napieralski* cyclization followed by enantioselective reduction are the most widely used. In particular, the chirality induction on the imine moiety formed during the *Bischler-Napieralski* reaction appears the most promising in considered use of catalytic reduction (hydrogenation) methods. In this publication we wish to concentrate on two classes of isoquinoline derivatives, namely protoberberines and homoprotoberberines.

Protoberberines display a wide range of substitution patterns at A and D rings, which is sometimes additionally complicated by the presence of three stereogenic centers at C-8, C-13, and C-13a. Since the diverse biological activity is dependent on the stereochemistry at these carbon atoms, several efforts directed toward the asymmetric synthesis have been undertaken. The goals of our project was two-fold. First, we wanted to explore the diastereoselectivity in establishing the relative configuration between C-13a and C-8 carbon atoms in the prochiral protoberberine salt, 2,3,10,11-tetramethoxy-8-methyl-5,6-dihydroisoquino[3,2-*a*]isoquinolinium acetosulfate (**3**). We choose **3** as it is a readily available [5] precursor for protoberberines. After a slight modification we found the procedure suitable even for large scale operations. The starting salt **3** was thus obtained by a modified procedure given by *Makhey* [5], according to Scheme 1.

It is already well established that 2,3,10,11-tetramethoxy-8-methyl-5,6,13,13a-tetrahydroisoquino[3,2-*a*]isoquinolinium chloride (**4**) (an analogue of **3**) underwent reduction with sodium borohydride in *THF*, providing diastereomeric



Scheme 1



Scheme 2

tetrahydroprotoberberines: (8*R**,13a*R**)-2,3,10,11-tetramethoxy-8-methyl-5,8,13,13a-tetrahydro-6*H*-isoquino[3,2-*a*]isoquinoline ((±)-**5**, coralydine) and (8*R**,13a*S**)-2,3,10,11-tetramethoxy-8-methyl-5,8,13,13a-tetrahydro-6*H*-isoquino[3,2-*a*] isoquinoline ((±)-**6**, *O*-methylcorytenchirine) in a proportion of approx. 4:1 [6] (Scheme 2). This protocol appeared therefore quite attractive in view of a newly proposed chiral modification of the borohydride reagent with chiral, non-racemic carboxylic acids [7]. We thus subjected **3** to a series of reductions employing the reagents described in [7] and also using several additional acids (Fig. 3).

The results that we obtained were disappointing. We observed the tendency of a diastereoselective formation of **5** along with relatively low enantioselectivity. Preliminary results are summarized in Table 1.

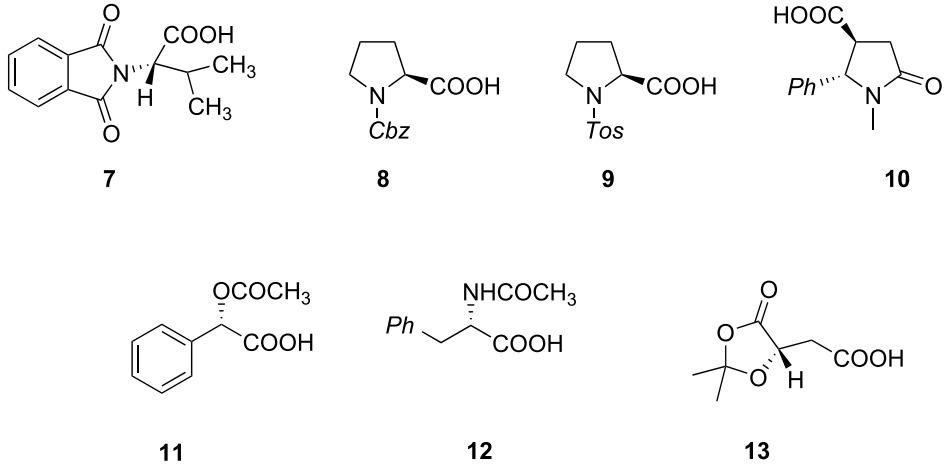


Fig. 3. Carboxylic acids used for borohydride modification

Table 1. Stereoselective reductions of salt **3** with chiral borohydrides

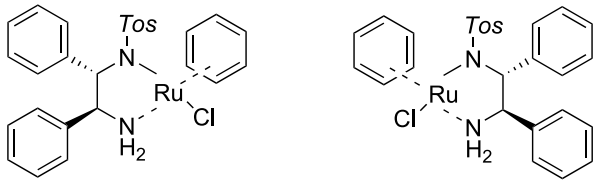
Chiral acid	Total yield of **5** and **6**	Ratio **5**:**6**	Enantiomeric purity of **5**	Configuration of **5**
	%		% *ee*	
7	37.8	4.1:1	2.3	(*S*,*S*)
8	93.9	8.8:1	17.4	(*R*,*R*)
9	92.9	1.9:1	2.3	(*S*,*S*)
10	92.0	4.8:1	7.4	(*S*,*S*)
11	65.0	3.1:1	5.5	(*S*,*S*)
12	94.8	4.9:1	2.1	(*S*,*S*)
13	86.6	6.7:1	5.9	(*S*,*S*)

The highest enantioselectivity was obtained in the case of borohydride modified with (2*S*)-1-[2-(benzyloxy)-2-oxoethyl]pyrrolidine-2-carboxylic acid (**8**) (17.4% *ee* of coralydine (*R*,*R*)-**5**).

Much better results were obtained employing the conditions for asymmetric transfer hydrogenation proposed by *Noyori* [8]. This method we found superior over the former procedure in both chemical yield and stereoselectivity. We observed that asymmetric reduction of **3** was best effected with a 5:2 formic acid-triethylamine mixture in acetonitrile containing the chiral Ru complex (*S*,*S*)-**14** (Fig. 4) [8]. It is noteworthy that this protocol is an attractive alternative for catalytic high pressure homogenous hydrogenation over chiral phosphine-rhodium complexes due to its operational simplicity and the absence of hazardous conditions.

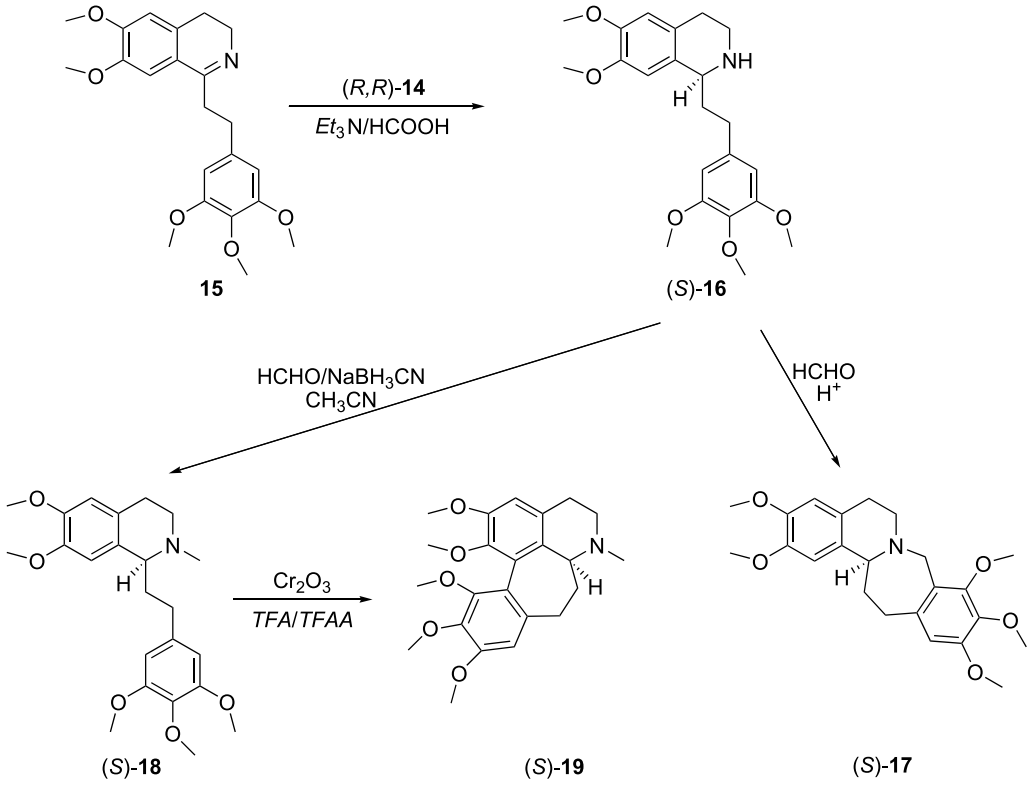
Even at room temperature the reaction proceeded smoothly giving almost complete consumption of **3** and highly diastereoselective formation of coralydine (*R*,*R*)-**5**. The chirality transfer was fair (63% *ee*) but variations of the temperature and solvents did not give satisfactory results. We found this reaction virtually temperature independent in point of view of selectivity but simultaneously it was highly suppressed in chemical yield. Fortunately, it proved relatively easy to purify the resulted alkaloid to a high degree of optical purity by crystallization of its hydrochloride [9].

Much better results were obtained in the asymmetric synthesis of another class of isoquinoline alkaloids – homoprotoberberine and homoaporphine. The prochiral 6,7-dimethoxy-1-[2-(3,4,5-trimethoxyphenyl)ethyl]-3,4-dihydroisoquinoline (**15**) seemed to be a good candidate for the attempted reduction. This compound is readily



(*S*,*S*)-**14** (*R*,*R*)-**14**

Fig. 4. *Noyori*'s chiral catalysts for the asymmetric transfer hydrogenation



Scheme 3

accessible in almost 87% chemical yield from 3,4-dimethoxyphenylethylamine and 3,4,5-trimethoxydihydrocinnamic acid according to a slightly modified known procedure [10, 11]. In order to illustrate the possible preparation of another enantiomeric series, we also used (*R*,*R*)-**14** (Fig. 4) for the reduction of imine **15**. The reaction was completed in 12 h to afford after standard work-up (1*S*)-6,7-dimethoxy-1-[2-(3,4,5-trimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (**16**) as an almost exclusive (*S*)-enantiomer (as indicated by ^{1}H NMR of its *Mosher*'s acid derivative) in quantitative yield. Compound **16** was further transformed into enantiomerically pure (14a*S*)-2,3,10,11,12-pentamethoxy-5,6,8,13,14,14a-hexahydroisoquino[2,1-*b*][2] benzazepine (**17**) (Scheme 3) [12].

Yet another type of the tetracyclic isoquinoline alkaloids was proved accessible by the application of a procedure of non-phenolic oxidative coupling recently proposed in this laboratory [13]. Thus, amine (*S*)-**16** after its transformation into (1*S*)-6,7-dimethoxy-2-methyl-1-[2-(3,4,5-trimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (**18**) was subjected to the oxidation procedure catalyzed by chromium(III) oxide to afford (6a*S*)-1,2,10,11,12-pentamethoxy-6-methyl-4,5,6,6a,7,8-hexahydrobenzo[6,7]cyclohepta[1,2,3-ij]isoquinoline (**19**) in 28% chemical yield and in >99% optical purity.

In conclusion, it seems that asymmetric synthesis of different classes of isoquinoline alkaloids can be performed in good stereoselective manner by the use of enantioselective transfer hydrogenation of imines or iminium salts.

Experimental

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 200 and 500 MHz for ^{1}H NMR and at 50 and 125 MHz for ^{13}C NMR. Tetramethylsilane (*TMS*) or solvents were used as internal standards. Chemical shifts were reported in ppm. Mass spectra were collected on AMD 604 apparatus. Optical rotation was measured on a Perkin-Elmer 247 MC polarimeter. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized using UV light or iodine vapour. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 mesh, Merck) using mixtures $CHCl_3$:CH_3OH as solvents. Melting points were determined on a *Boetius* hot-plate microscope and are uncorrected. All solvents used in the reactions were anhydrous.

2-(3,4-Dimethoxyphenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (**1**)
A sample of 4.9 g 3,4-dimethoxyphenylacetic acid (25 mmol) was added under Ar to a solution of 4.5 g 3,4-dimethoxyphenethylamine (25 mmol) in 50 cm^3 CH_2Cl_2 with stirring. The reaction mixture was cooled in an ice bath to 0°C, and 5.8 g *N,N′*-dicyclohexylcarbodiimide (*DCC*, 28 mmol) was added followed by stirring for 15 min. Then, the ice bath was removed and the stirring was continued at room temperature for 24 h. After that time, a mixture of 50 cm^3 dioxane:H_2O (3:2) was added and the contents of the flask were stirred for 1 h. The solvents were then evaporated and the white mass thus obtained was diluted with 50 cm^3 CH_2Cl_2 and filtered from the dicyclohexylurea. The organic filtrate was washed successively with saturated NaCl solution, 5% HCl, and saturated solution of $NaHCO_3$. The organic extract was then dried ($MgSO_4$) and evaporated. The crude product was crystallized from methanol to give 4.55 g (93%) of the pure amide **1** as white solid, mp 125–127°C (Ref. [5] 125°C). All spectral data were identical with those of Ref. [5].

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**2**)
Phosphorus pentachloride (0.9 g, 4.2 mmol) was added during 30 min in three portions to a chilled (0°C) solution of 1 g **1** (2.8 mmol) in 15 cm^3 of dry CH_2Cl_2 under Ar and the mixture was stirred for 30 min. Then, the ice bath was removed and the mixture was stirred at room temperature for 24 h. The reaction mixture was then poured onto a saturated solution of $NaHCO_3$ and the contents of the flask were stirred for 1 h. The aqueous layer was extracted twice with 10 cm^3 CH_2Cl_2 and the combined organic extracts were washed with saturated solution of $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated to give **2**. Since **2** was prone to air oxidation, all operations should be conducted under Ar. The dihydroisoquinoline **2** was used without further purification for the preparation of **3**.

2,3,10,11-Tetramethoxy-8-methyl-5,6-dihydroisoquino[3,2-a]isoquinolinium acetosulfate (**3**)
The following preparation is the modification of literature procedure [5]. Fuming (20%) H_2SO_4 (1.2 cm^3) was added to 4.9 cm^3 of freshly distilled acetic anhydride (exothermic) whereby the mixture became wine-red in colour. This mixture was heated at gentle reflux for 10 min. Then, a solution of 1 g **2** (2.9 mmol) in 2 cm^3 of freshly distilled acetic anhydride was added under Ar and the resulting mixture was heated at reflux for 60 min and then cooled to room temperature. Methanol (6 cm^3) was added dropwise and the mixture was stirred for 30 min. The solid product which deposited after cooling in an ice bath for 30 min, was filtered off and washed successively with distilled H_2O (2×), methanol (2×), and ether (2×). The crude product was recrystallized from methanol to give 1.18 g (80%) **3** as a yellow solid, mp 279–280°C (Ref. [5] 277–279°C). All spectral data were identical with those reported in Ref. [5].

(8R,13aR)-2,3,10,11-Tetramethoxy-8-methyl-5,8,13,13a-tetrahydro-6H-isoquino[3,2-a]isoquinoline (**5**) *and (8S,13aR)-2,3,10,11-Tetramethoxy-8-methyl-5,8,13,13a-tetrahydro-6H-isoquino[3,2-a]isoquinoline* (**6**)
Representative procedure for the reduction of salt **3** with chiral borohydride reagent modified with chiral, non-racemic carboxylic acids: 1 g (*S*)-*N*-benzyloxycarbonylproline (4.01 mmol) in 10 cm^3 CH_2Cl_2 was added to a suspension of 51 mg $NaBH_4$ (1.34 mmol) in 20 cm^3 CH_2Cl_2 in an ice bath.

The mixture was stirred at room temp for 3 h. Then 168.8 mg dihydroprotoberberine salt **3** (0.33 mmol) in 10 cm^3 of dry CH_2Cl_2 was added. The whole mixture was stirred for 12 h and the solvent was evaporated followed by the addition of a solution of 25 cm^3 25% NaOH to the solid residue. The mixture was stirred for 30 min and subsequently was extracted with ether (3×20 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed. The residue was separated by flash column chromatography (silica gel, $CHCl_3$:CH_3OH = 99:1) to give 48 mg (93.9%) **5** and **6**.

(8R,13aR)-2,3,10,11-Tetramethoxy-8-methyl-5,8,13,13a-tetrahydro-6H-isoquino[3,2-a]isoquinoline (**5**)

The catalyst (*S*,*S*)-**14** was prepared by stirring of 6 mg dichloro(η^6-benzene)ruthenium(II) and 7.3 mg of (1*S*,2*S*)-1,2-diphenyl-*N*-(4-tolylsulfonyl)ethylenediamine in 5 cm^3 of acetonitrile for 10 min as described in Ref. [13]. Formic acid/triethylamine mixture (1.01 cm^3:1.49 cm^3) and (*S*,*S*)-**14** were added to a solution of 0.5 g **3** in 10 cm^3 of acetonitrile. After stirring at room temp for 12 h, the mixture was made basic by addition of aqueous Na_2CO_3 solution and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give 310 mg (85%) **5** as an oil; $[\alpha]_D^{20} = +143.1^\circ\ cm^2\ g^{-1}$ ($c = 0.98$, $CHCl_3$) (Ref. [15] $[\alpha]_D^{20} = +227^\circ\ cm^2\ g^{-1}$ ($c = 1$, $CHCl_3$)), 63% *ee*. All spectral data were identical with those reported in Ref. [15].

Coralydine **5** was transformed into its HCl salt, which crystallized from acetone-diethyl ether to give 20 mg **5**·HCl; mp 247–250°C; $[\alpha]_D^{20} = +130.0^\circ\ cm^2\ g^{-1}$ ($c = 1.05$, $CHCl_3$) (Ref. [9] mp 246–250°C, $[\alpha]_D^{20} = -130.4^\circ\ cm^2\ g^{-1}$ ($c = 1.27$, $CHCl_3$)).

6,7-Dimethoxy-1-[2-(3,4,5-trimethoxyphenyl)ethyl]-3,4-dihydroisoquinoline (**15**)

A mixture of 1.44 g 3,4,5-trimethoxydihydrocinnamic acid (6 mmol) and 1 g 3,4-dimethoxyphenethylamine (5.5 mmol) in 100 cm^3 of anhydrous xylene that contained 10 mg of *p*-toluenesulphonic acid was refluxed under Ar with a *Dean-Stark* water trap. The solvent was evaporated and the oily residue was quenched with 50 cm^3 of ethanol to yield, after drying, the appropriate amide which was taken to the next step without further purification. Thus, amide (1 g, 2.5 mmol) was dissolved in 50 cm^3 CH_2Cl_2 containing a suspended PCl_5 (770 mg, 3.7 mmol) and the mixture was stirred under Ar overnight at room temp. The contents of the flask were then carefully poured onto a suspension of 2.5 g $NaHCO_3$ in 150 cm^3 H_2O. Extraction with CH_2Cl_2, drying, and evaporation afforded imine **15** as viscous syrup (831 mg, 87%) [10].

(1S)-6,7-Dimethoxy-1-[2-(3,4,5-trimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (**16**)

The catalyst (*R*,*R*)-**14** was prepared as described for **5**. Formic acid/triethylamine mixture (1.01 cm^3:1.49 cm^3) and (*R*,*R*)-**14** were added to a solution of 510 mg of imine **15** in 10 cm^3 of acetonitrile. After stirring at room temperature for 12 h, the mixture was made basic by addition of aqueous Na_2CO_3 solution and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by flash chromatography to give 470 mg (91.7%) of compound **16** as an oil; $[\alpha]_D^{20} = -13.9^\circ\ cm^2\ g^{-1}$ ($c = 1.45$, $CHCl_3$) (Ref. [16] $[\alpha]_D^{20} = -14.1^\circ\ cm^2\ g^{-1}$ ($c = 0.34$, $CHCl_3$)), 98.6% *ee*. All spectral data were identical with those reported in Ref. [16]. A small sample of **16** was subjected to the determination of stereomer composition by ^{1}H NMR of its *Mosher*'s acid derivative according to the procedure of Ref. [14]. It confirmed the optical purity value being >99% *ee*.

(14aS)-2,3,10,11,12-Pentamethoxy-5,6,8,13,14,14a-hexahydroisoquino[2,1-b][2]benzazepine (**17**)

A 100 mg sample (*S*)-**16** (0.26 mmol) was mixed with 1 drop conc. HCl in 3 cm^3 H_2O and then 1 cm^3 37% aq. HCHO was added to the mixture. After refluxing for 2 h under Ar, the mixture was made basic with 25% NaOH aq. solution and was extracted 4 times with benzene. The extract was washed with saturated NaCl solution, dried, and evaporated to afford 98 mg (95%) **17** as an oil;

$[\alpha]_D^{20} = -113.1^\circ\,cm^2\,g^{-1}$ ($c = 1$, *Me*OH), (Ref. [11] $[\alpha]_D^{20} = -112.5^\circ\,cm^2\,g^{-1}$ ($c = 1$, *Me*OH)), >99% *ee*. All spectral data were identical with those reported in Ref. [16].

(1S)-6,7-Dimethoxy-2-methyl-1-[2-(3,4,5-trimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (**18**)

To the solution of 100 mg (*S*)-**16** (0.26 mmol) in CH_3CN samples of 97 mm^3 37% aq. HCHO (1.28 mmol) and 26 mg $NaBH_3CN$ (0.42 mmol) were added. The mixture was stirred for 3 h at room temp. After that time 20 cm^3 NaOH (10%) was added and the mixture was extracted with CH_2Cl_2 (3×15 cm^3). The organic layer was washed with 10% HCl and the acidic aqueous layer was again basified with 20% NaOH and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated to give 88.1 mg (85%) of crude **18**. The residue was purified with flash chromatography to give 83 mg (80%) (*S*)-**18** as an oil; $[\alpha]_D^{20} = -6^\circ\,cm^2\,g^{-1}$ ($c = 1$, *Me*OH), (Ref. [16] $[\alpha]_D^{20} = +6.1^\circ\,cm^2\,g^{-1}$ ($c = 0.92$, *Me*OH)), >99% *ee*. All spectral data were identical with those reported in Ref. [16].

(6aS)-1,2,10,11,12-Pentamethoxy-6-methyl-4,5,6,6a,7,8-hexahydrobenzo[6,7]cyclohepta[1,2,3-ij]isoquinoline (**19**)

Chromium(III) oxide was freshly prepared by pyrrolytic decomposition of $(NH_4)_2Cr_2O_7$ and was used without further purification. Thus 180 mg of chromium(III) oxide (1.16 mmol) were suspended in 10 cm^3 CH_2Cl_2 containing 2.5 cm^3 *TFA* along with 0.32 cm^3 *TFAA*. The mixture was refluxed for 20 min and cooled to 0°C. A sample of 50 mg (*S*)-**18** (0.125 mmol) in 2 cm^3 CH_2Cl_2 was then added dropwise with stirring followed by the addition of 0.11 cm^3 $BF_3 \cdot Et_2O$ (0.44 mmol). The mixture was stirred at room temperature under Ar. After 48 h the mixture was evaporated and treated with a sat. $NaHCO_3$ solution. CH_2Cl_2 (10 cm^3) was added and the solids were removed by filtration. The aq. layer was extracted with CH_2Cl_2 (2×5 cm^3), and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography to give 14 mg (28%) (*S*)-**19** as an oil; $[\alpha]_D^{20} = +74^\circ\,cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$), (Ref. [12] $[\alpha]_D^{20} = +68.1^\circ\,cm^2\,g^{-1}$ ($c = 0.84$, $CHCl_3$)), >99% *ee*. All spectral data were identical with those reported in Ref. [12].

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