Tetrahedron: *Asymmetry* 24 (2013) 50–55

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Two optimized synthetic pathways toward a chiral precursor of Mivacurium chloride and other skeletal muscle relaxants

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ARTICLE INFO

Article history:
Received 26 October 2012
Accepted 16 November 2012

ABSTRACT

A chiral precursor of Mivacurium chloride, (*R*)-5′-methoxylaudanosine, was prepared using two different methods. The chiral resolution of racemic 5′-methoxylaudanosine, typically used in industry, was carried out in parallel with a procedure consisting of asymmetric transfer hydrogenation (ATH) and reductive methylation. A novel one-pot synthetic step was developed for the synthesis of racemic 5′-methoxylaudanosine. In both routes, the enantioselectivity was high but further purification was necessary to reach the level of a pharmaceutical standard. The individual synthetic steps reported herein can also be used for the synthesis of analogous bistetrahydroisoquinoline-based skeletal muscle relaxants.

1. Introduction

The use of skeletal muscle relaxants is inevitable in surgery under anesthesia.[1–3] For example, when performing endotracheal intubation, neuromuscular blocking drugs are administered under general anesthesia in order to facilitate the intubation and avoid discomfort to the patient. In this regard, Mivacurium chloride is a commonly used non-depolarizing neuromuscular blocking agent with a rapid onset. Its short duration of action, stemming from its rapid metabolism by cholinesterase, makes it a suitable relaxant for short surgical procedures.

The bistetrahydroisoquinoline-based Mivacurium chloride (Fig. 1) contains four stereogenic centers and a C=C double bond, giving a total of 20 possible isomers. However, the active pharmaceutical ingredient (API) is a mixture of only three isomers with defined configurations *E*, (1*R*), and (1′*R*), varying only at nitrogen atoms the 2- and 2′-positions. The synthesis thus involves a chiral intermediate, (*R*)-*N*-methyl-(6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline), also known as (*R*)-5′-methoxylaudanosine, and in this way the configurations (1*R*) and (1′*R*) are introduced in the title molecule.

In the original synthesis of Mivacurium chloride,[4] racemic 5′-methoxylaudanosine is treated with (−)-2,3-dibenzoyl-L-tartaric acid (L-dibenzoyltartaric acid) and the diastereomeric salt is crystallized to obtain the (*R*)-enantiomer (route A in Scheme 1). While the chiral resolution represents an additional step that requires a stoichiometric amount of the chiral reagent, allowing only 50% theoretical yield of the enantiomer, no transition metals are employed, which is beneficial from both economical and ecological viewpoints.

An alternative way of preparing the enantiomerically pure chiral precursor is via asymmetric synthesis; in this method, the desired enantiomer of the chiral product is formed directly with high atom economy. The most convenient enantioselective route is the asymmetric transfer hydrogenation (ATH)[5] of an analogous imine compound, and subsequent reductive methylation (route B in Scheme 1). Samano et al. described the synthesis of structurally similar Gantacurium chloride[6] and other neuromuscular blockers,[7] which contain a 1-phenyl-1,2,3,4-tetrahydroisoquinoline (1-Ph-THIQ) moiety prepared via ATH of a corresponding 1-phenyl-3,4-dihydroisoquinoline (1-Ph-DHIQ). In that case, [RuCl((1*R*,2*R*)-*N*-naphthalenesulfonyl-1,2-diphenylethylenediamine)(η^6-benzene)], or [RuCl((*R*,*R*)-NpsDPEN)(η^6-benzene)], was used as the catalyst. More common complexes, such as commercially available [RuCl((*S*,*S*)-TsDPEN)(η^6-*p*-cymene)] (TsDPEN = *N*-tosyl-1,2-diphenylethylene-1,2-diamine), which easily reduces 1-Me-DHIQs and 1-Bn-DHIQs, fail in the case of 1-Ph-DHIQs.[8] Therefore, the ATH of the corresponding 1-phenyldihydroisoquinolines (1-Ph-DHIQs) is typically carried out with different catalysts other than those used for the ATH of 1-Me-DHIQs or 1-Bn-DHIQs. The conditions reported for the preparation of Gantacurium chloride could not be transferred to the synthesis of Mivacurium chloride where no experimental details are known for the ATH step.[9]

Herein we report a comparison of two synthetic pathways toward the synthesis of (*R*)-5′-methoxylaudanosine: the commonly

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http://dx.doi.org/10.1016/j.tetasy.2012.11.012

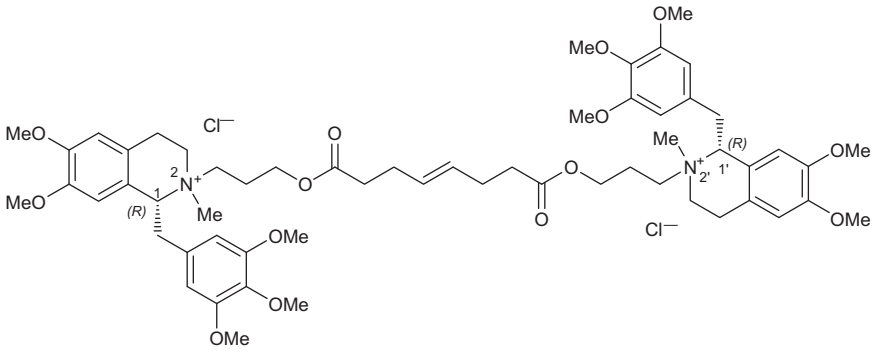
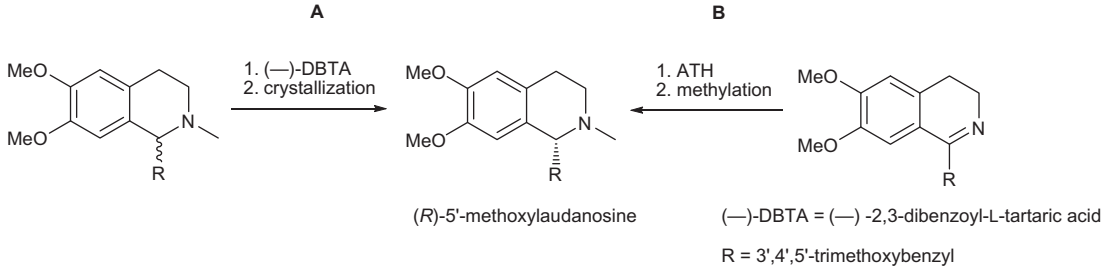


Figure 1. Structure of Mivacurium chloride.



Scheme 1. Two synthetic routes toward (*R*)-5′-methoxylaudanosine. Route A: chiral resolution of 5′-methoxylaudanosine with L-dibenzoyltartaric acid; Route B: asymmetric transfer hydrogenation (ATH) of an imine with subsequent methylation.

used chiral resolution of a racemate (route A) and the asymmetric transfer hydrogenation with subsequent reductive methylation (route B). The precursor can be used not only for the synthesis of Mivacurium chloride, but also for other neuromuscular blockers containing this structural fragment.[10,11]

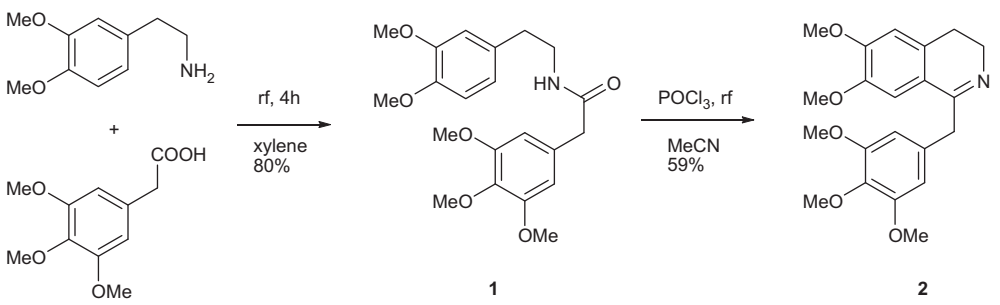
2. Results and discussion

Both synthetic pathways described below start from imine **2**, which was prepared by Bischler–Napieralski cyclodehydration[12] of amide **1** (Scheme 2). According to the reported procedures,[13,14] amide **1** is typically synthesized at temperatures around 180 °C with moderate yield. We developed an alternative method in which the mixture was heated in xylene at reflux for 4 h. Water was then removed azeotropically in a Dean-Stark apparatus, which shifted the equilibrium favourably and thus full conversion to product was achieved. After recrystallization from ethanol, **1** was obtained in 80% yield.

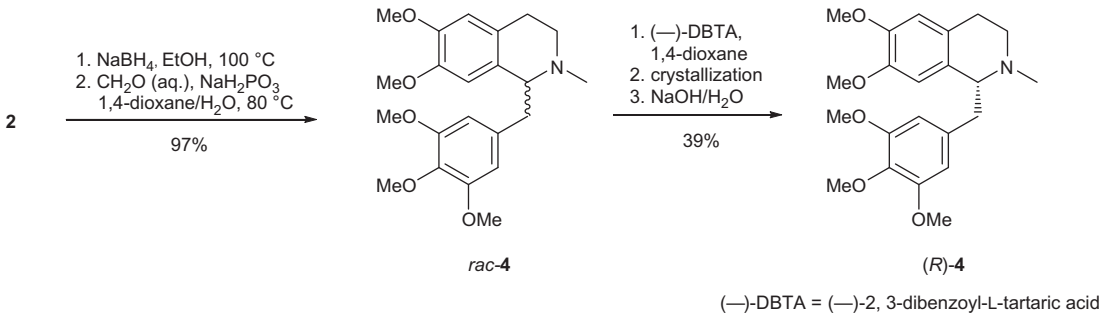
Compound **2** was used as a precursor for all of the syntheses described below and therefore the yields of **1** and **2** were not included in the final calculations of overall yields, which served for the comparison of synthetic pathways A and B (vide infra).

The first part of our work is dedicated to the development of a synthetic procedure for the production of the chiral precursor (*R*)-5′-methoxylaudanosine (*R*)-**4** from racemic mixture *rac*-**4**. For the preparation of *rac*-**4** from imine **2**, we developed a novel one-pot procedure consisting of a non-stereospecific reduction and reductive methylation of the nitrogen atom (Scheme 3). The reduction was carried out by using $NaBH_4$ (1.25 equiv) in a mixture of 1,4-dioxane and ethanol at reflux. For the methylation step we employed a system consisting of formaldehyde and sodium phosphonate pentahydrate in water. It was found that temperatures between 60 and 80 °C were optimal. Higher temperatures led to intensive evaporation of formaldehyde, which polymerized on the cooling surface of the reflux condenser. On the other hand, the use of lower temperatures was connected with the necessity of longer reaction times. Eventually, a temperature of 80 °C was employed, giving a faster reaction rate yet still a low rate of evaporation of the formaldehyde.

The resolution was carried out by crystallization of *rac*-**4** with L-dibenzoyltartaric acid, which formed the diastereomeric salt **5**. Several solvents were examined for the crystallization. While THF and cyclohexane appeared to be inappropriate (no crystals were obtained), the addition of toluene greatly helped the crystal



Scheme 2. Synthesis of amide **1** and subsequent Bischler–Napieralski cyclodehydration to imine **2**.



Scheme 3. One-pot synthesis of *rac*-**4** and its resolution to give (*R*)-**4** (route A).

growth although the enantioselectivity was rather low, meaning that both isomers crystallized easily. Finally, it was found that a combination of 1,4-dioxane with toluene, or even 1,4-dioxane itself, represented a suitable system. Therefore, amine *rac*-**4** was dissolved in 1,4-dioxane with L-dibenzoyltartaric acid at 80 °C to form salt **5**. At temperatures above 80 °C, degradation of **5** took place, leading to a yellow-colored sample which we presumed to be the product of a base-catalyzed elimination of benzoic acid from L-dibenzoyltartarate. The mixture was stirred vigorously in order to rapidly dissolve the salt. After dissolving the solids completely, the mixture was left to cool down slowly to room temperature until crystals of **5** appeared. The crystals were separated, dissolved in aqueous solution of NaOH and the free base (*R*)-**4** was extracted in dichloromethane.

The low yield of the resolution step is a typical drawback that can sometimes be solved by racemization of the opposite enantiomer and resolution of the racemate obtained. In an effort to achieve this, the following reagents were tested for the racemization of (*S*)-**4**: $[RuCl_2(p\text{-cymene})]_2$, 10% Pd/$BaSO_4$, 5% Pd/C, NaOH, NaH, and sodium naphthalene. However, palladium catalysts caused hydrogenolysis of the benzyl moiety while the other reagents did not provoke any racemization; thus, the low yield issue could not be resolved. Another option was the conversion of (*S*)-**4** to imine **2** which would require demethylation followed by dehydrogenation. Nevertheless, this expensive and complex idea would most probably not help the goal of increasing the process economics by making use of by-product (*S*)-**4**.

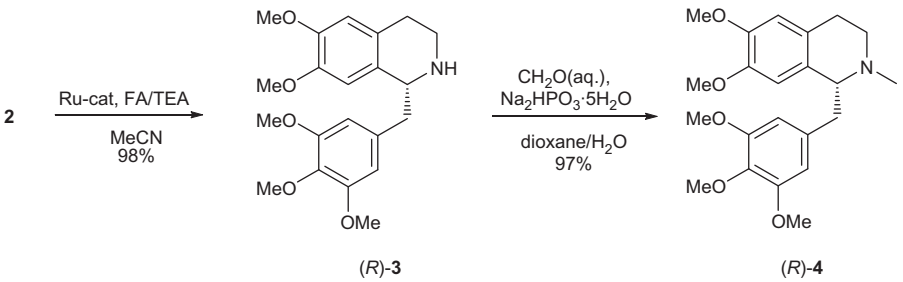
Route B involved the enantioselective synthesis of chiral intermediate (*R*)-**3** followed by reductive methylation (Scheme 4). Intermediate (*R*)-**3** was prepared by ATH of **2** using [RuCl((*S*,*S*)-TsDPEN)(η^6-*p*-cymene)] as a catalyst and HCOOH/triethylamine mixture as the hydrogen donor. Conveniently, the catalyst is commercially available since it is the most frequently used modification of Noyori's complexes of this type.[15] Optimization of the reaction conditions of the ATH was necessary since the performance of this catalytic system can be affected by changing various parameters such as concentration, catalyst loading, selection of base, temperature, and so on.[16] The screening kinetic experiments were first followed in situ by NMR spectroscopy.[17] Inspired by the results of Zhang et al., who found that different bases in the HCOOH/amine hydrogen donor system led to different enantioselectivities in the ATH of a ketone,[18] we examined the influence of the base on the ATH of an imine (Table 1). Although no substantial differences in enantioselectivity were found, significant variations in terms of reaction rate were observed. While secondary amines and pyridine did not accelerate the hydrogenation, diisopropyl(ethyl)amine (DIPEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) outperformed triethylamine, which is typically used. Despite the notable improvement in the case of DIPEA, we decided to use triethylamine since it is much less expensive than DIPEA, whose benefit for this reaction was deemed not worthwhile for its cost.

On a preparative scale, the ATH of **2** was carried out under similar conditions as for the screening experiments conducted in an NMR tube. Further optimization could be achieved by lowering the catalyst loading from 2% to 0.5%, thus decreasing the cost. The resulting decrease of the reaction rate could be compensated for by increasing the concentration of the reaction mixture by a factor of 8. Concomitantly, the consumption of solvents was greatly reduced. Under such mild conditions, the reaction reached full conversion in 6 h to afford amine (*R*)-**3** in 98% yield and 95% ee.

The final step of route B was the N-methylation of (*R*)-**3** to give (*R*)-**4** in 97% yield under similar reaction conditions as those employed in route A (vide supra).

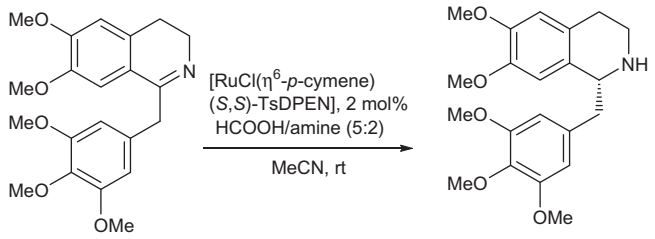
Synthetic pathways A and B were then compared. Using route A, enantiomerically enriched product (*R*)-**4** was obtained from imine **2** in 36% yield and with 98% ee. However, compound (*S*)-**4** could not be used further and thus the yield could not be increased. Although the enantioselectivity was very high, the pharmaceutical industry typically requires >99.5% ee, which was only possible by repeated crystallization.

Route B afforded the target compound in 95% yield with 95% ee, that is, little material was lost during the synthesis. Final removal of the residual Ru catalyst from the product (e.g. by commercially



Scheme 4. Synthesis of (*R*)-**4** by ATH of **2** followed by a reductive methylation (route B). Ru-cat is [RuCl(η^6-*p*-cymene)(*S*,*S*)-TsDPEN] (TsDPEN = *N*-tosyl-1,2-diphenylethylene-1,2-diamine).

Table 1
Screening of the influence of the base used in the HCOOH/amine hydrogen donor mixture in the ATH of **2**



2

Base		ee[a] (%)	k[b] (10^{-3} mmol mg_{cat}^{-1} min^{-1})
Tertiary	Triethylamine	95.0	3.96
	DIPEA[c]	95.7	6.72
	DABCO[d]	94.5	2.78
	Quinuclidine	94.6	2.50
	DBU[e]	94.9	4.44
Secondary	Piperidine	91.6	1.71
	Morpholine	95.6	1.20
	Pyrrolidine	94.6	0.35
Aromatic	Pyridine	n.d.[f]	0

[a] Enantiomeric excess determined by NMR after chiral solvation with (*R*)-(−)-(2,2,2-trifluoro-1-(9-anthryl)ethanol).
[b] k = zero-order rate constant determined from the initial linear region of the conversion-time plot measured by NMR.
[c] *N*-Diisopropylethylamine.
[d] 1,4-Diazabicyclo[2.2.2]octane.
[e] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[f] Since no reaction occurred, the ee could not be determined.

available metal scavengers such as Smopex®) and increasing the enantiomeric purity by recrystallization (vide supra) would slightly lower the overall yield and increase the cost.

3. Conclusion

Herein, two synthetic routes were optimized for (*R*)-5′-methoxylaudanosine as a chiral precursor of a short-acting non-depolarizing skeletal muscle relaxant Mivacurium chloride and its structural analogues. In the chiral resolution of racemic 5′-methoxylaudanosine, which was prepared according to a novel one-pot synthetic procedure, the enantiomerically enriched product was obtained in 36% yield. On the contrary, asymmetric transfer hydrogenation afforded the compound in 95% yield. In both cases, although the enantioselectivity was very high, further increases using a second crystallization was necessary since the pharmaceutical product should be synthesized with >99.5% ee. Crystallization of the product from the ATH procedure led to only a small amount of the material being lost compared to the high amounts of waste in the chiral resolution. For this reason, the asymmetric route seems to be more economical although both methods are feasible.

4. Experimental

4.1. Instrumentation

NMR spectra were acquired on Varian ^{UNITY}*Inova*-400 and Bruker Avance III 400 MHz spectrometers. ^{1}H and ^{13}C NMR spectra of substrates were measured in $CDCl_3$, whose residual signals (δ_H 7.265 ppm, δ_C 77.00 ppm) were used as internal standards for the chemical shift scale. Standard software was used, as supplied by the manufacturers (Varian Inc., Palo Alto, USA, and Topspin 2.1, Bruker Biospin GmbH, Rheinstetten Germany). Chemical shifts are given in δ scale [ppm] and coupling constants in Hz. Digital resolution enabled us to report chemical shifts of protons to 2 and coupling constants to 1 and carbon chemical shifts to 2 decimal places. Gas chromatography was conducted on a Varian CP-3800 with a flame ionization detector (FID) equipped with a non-polar 60 m column (Varian VF-1) with the inner diameter of 0.25 mm and a polydimethylsiloxane stationary phase (0.25 μm). Nitrogen (99.99%) was used as a carrier gas. Optical rotations were measured on a Perkin Elmer 241 polarimeter at the indicated concentration with units of g/100 mL. High resolution mass spectrometry measurements were carried out on a LTQ Orbitrap Velos (Thermo Fisher Scientific, USA) spectrometer. Heated electrospray ionization in positive ($HESI^+$) or negative ($HESI^-$) mode was used as an ion source. Full-scan mass spectra (range of m/z = 100–2000 Da with at a resolution of 30,000) were acquired using a continual infusion of the samples solutions (concentration: 1 μg/ml, flow: 2 μL/min). The conditions on the mass spectrometer were optimized to the following values: spray voltage 3000 V ($HESI^+$)/−2500 V ($HESI^-$), vaporizer temperature 40 °C, sheath gas pressure (nitrogen) 5 psi, aux gas pressure (nitrogen) 2 ArbU and capillary temperature 270 °C. The data were acquired and processed using the Thermo Xcalibur software, version 2.1.0 (Thermo Fisher Scientific, USA).

4.2. Chemicals

Phosphorus oxychloride, tetraphosphorus decaoxide, pyrrolidine, *N*-diisopropylethylamine, 1,4-diazabicyclo[2.2.2]octane, triethylamine, piperidine, morpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, quinuclidine, formic acid, (−)-2,3-dibenzoyl-L-tartaric acid, (*R*)-(−)-(2,2,2-trifluoro-1-(9-anthryl)ethanol), and (*S*,*S*)-[RuCl(η^6-*p*-cymene)(*N*-Ts-diphenylethylenediamine)] were purchased from Sigma–Aldrich (Steinheim, Germany). *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4,5-trimethoxyphenylacetamide was synthesized by CMS Chemicals (Slovakia) by using the procedure described below. Ethanol, methanol, diethyl ether, xylene, acetonitrile, toluene, and chloroform were obtained from Penta (Czech Republic). $CDCl_3$ and CD_3CN were obtained from Armar Chemicals (Switzerland). Methyl *tert*-butyl ether was used from the resources of the Department of Organic Technology, ICT Prague.

4.3. Syntheses

4.3.1. Synthesis of *N*-(3,4-dimethoxyphenethyl)-3,4,5-trimethoxyphenylacetamide 1

A 500 mL round-bottomed flask equipped with a Dean-Stark apparatus was charged with xylene (300 mL), 2-(3,4-dimethoxyphenyl)ethylamine (75.3 g, 0.416 mol, 1.1 equiv), and 3,4,5-trimethoxyphenylacetic acid **1** (85.5 g, 0.378 mol) and the mixture was heated at reflux by the azeotropic removal of water for 4 h. After cooling to 60 °C, the mixture was diluted with hexane (300 mL) and cooled to 5 °C. The solid was filtered off, washed with hexane (300 mL), and dried to afford 150 g (100%) of white solid which was purified by crystallization from 96% ethanol (750 mL). The solid was filtered off, washed with chilled ethanol (100 mL), and dried. Yield of **1**: 117.5 g, 80%. ^{1}H NMR (400.00 MHz, $CDCl_3$, 293.2 K): δ 2.68 (2H, t, J = 6.9 Hz, H-4), 3.43 (2H, dt, J = 5.2, 6.9 Hz, H-3), 3.44 (2H, s, *i*-CH_2), 3.78 (6H, s, *m*-OCH_3), 3.81 (3H, s, 7-OCH_3), 3.82 (3H, s, *p*-OCH_3), 3.84 (3H, s, 8-OCH_3), 5.52 (1H, t, J = 5.2 Hz, H-2), 6.36 (2H, s, H-*ortho*), 6.48 (1H, dd, J = 2.0, 8.1 Hz, H-10), 6.63 (1H, d, J = 2.0 Hz, H-6), 6.70 (1H, d, J = 8.1 Hz, H-9). ^{13}C NMR (100.58, $CDCl_3$, 293.2 K): δ 34.80 (C-4), 40.61 (C-3), 44.05 (C-11), 55.71 (7-OCH_3, 8-OCH_3), 55.96 (*m*-OCH_3), 60.73 (*p*-OCH_3), 106.15 (C-*ortho*), 110.96 (C-9), 111.46 (C-6), 120.45 (C-10), 130.28 (C-*ipso*), 130.85 (C-5), 136.96 (C-*para*), 147.52 (C-8), 148.91 (C-7), 153.42 (C-*meta*), 170.71 (C-1). HRMS ($HESI^+$) m/z calculated for $[M+H]^+$: 390.1911; found: 390.19087. Further characterization can be found in the literature.[14,19]

4.3.2. Synthesis of 6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-3,4-dihydroisoquinoline 2

At first, *N*-[2-(3,4-dimethoxyphenyl)ethyl]-3,4,5-trimethoxyphenylacetamide **1** (39.1 g, 100 mmol) was dissolved in dry acetonitrile (250 mL) under an argon atmosphere. Phosphorus oxychloride (47 mL, 500 mmol) was then added gradually over 30 min. The mixture was stirred at 100 °C for 4 h. The volatiles were removed on a rotary evaporator and a yellow solid was obtained, which was hydrolyzed with water (100 mL). The solution was alkalized with a concentrated solution of sodium hydroxide (120 g) in water. After reaching pH = 12, a concentrated solution of sodium sulfite (1.3 g, 10 mmol) was added to minimize the oxidation of the product. The slurry was cooled down to 35 °C and extracted with chloroform (4 × 60 mL). The combined organic extracts were washed with water (2 × 30 mL), dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator (10 torr, bath temperature 50 °C). The crude product (35 g) was obtained as a yellow solid, which was recrystallized from methanol (150 mL). Yield of **2**: 22.0 g, 59.0%. ^{1}H NMR (400.00 MHz, $CDCl_3$, 293.2 K): δ 2.64 (2H, m, H-4), 3.72 (2H, m, H-3), 3.75 (3H, s, 7-OCH_3), 3.78 (3H, s, 4′-OCH_3), 3.79 (6H, s, 3′,5′-OCH_3), 3.87 (3H, s, 6-OCH_3), 3.95 (2H, s, 1-CH_2), 6.53 (2H, s, H-2′,6′), 6.66 (1H, s, H-5), 6.98 (1H, s, H-8). ^{13}C NMR (100.58 MHz, $CDCl_3$, 293.2 K): δ 25.74 (C-4), 43.76 (1-CH_2), 47.22 (C-3), 55.84 (6-OCH_3), 55.90 (7-OCH_3), 55.96 (3′,5′-OCH_3), 60.75 (4′-OCH_3), 105.41 (C-2′,6′), 109.39 (C-8), 110.15 (C-5), 121.56 (C-8a), 131.74 (C-4a), 133.78 (C-1′), 136.42 (C-4′), 147.11 (C-7), 150.59 (C-6), 153.20 (C-3′,5′), 165.20 (C-1). HRMS (HESI$^+$) *m*/*z* calculated for [M+H]$^+$: 372.1805; found: 372.18017. Further characterization can be found in the literature.[19]

4.3.3. Synthesis of racemic *N*-Me-6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline *rac*-4

Imine **2** (765 mg, 2.00 mmol) was dissolved in a mixture of ethanol (1 mL) and 1,4-dioxane (5 mL). Next, $NaBH_4$ (55 mg, 1.5 mmol) was added and the reaction mixture was heated at 100 °C. After 3 h, the reaction was close to full conversion. Then $NaBH_4$ (40 mg, 1.1 mmol) dissolved in ethanol (1.5 mL) was added and the solution was stirred for 30 min. An aqueous solution of formaldehyde (2 mL, 30% w/w) and sodium phosphonate pentahydrate (1.1 g, 5.1 mmol) dissolved in water (5 mL) were added and the mixture was stirred for 75 min at 80 °C. The reaction mixture was diluted with water (100 mL) and brine (20 mL), after which sodium hydroxide (300 mg, 7.5 mmol) was then added. The mixture was extracted with MTBE (3 × 50 mL), and the organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness on a rotary evaporator. Yield of *rac*-**4**: 774 mg, 97.0%. ^{1}H NMR (399.89 MHz, $CDCl_3$, 303.2 K): 2.52 (3H, s, 2-CH_3), 2.58 (1H, ddd, *J* = 15.8, 4.7, 4.0 Hz H-4u), 2.71 (1H, dd, *J* = 13.5, 8.2, H-1-CH_2-u), 2.75 (1H, m, H-3u), 2.83 (1H, ddd, *J* = 16.0, 15.8, 5.8 Hz H-4d), 3.13 (1H, dd, *J* = 13.5, 4.5, H-1-CH_2-d), 3.15 (1H, m, H-3d), 3.54 (3H, s, 7-OCH_3), 3.69 (1H, dd, *J* = 8.2, 4.5, H-1), 3.74 (6H, s, 3′,5′-OCH_3), 3.77 (3H, s, 4′-OCH_3), 3.80 (3H, s, 6-OCH_3), 6.00 (1H, s, H-8), 6.28 (2H, s, H-2′,6′), 6.54 (1H, s, H-5). ^{13}C NMR (100.58 MHz, $CDCl_3$, 303.2 K): 25.23 (C-4), 41.40 (1-CH_2), 42.40 (2-CH_3), 46.61 (C-3), 55.40 (7-OCH_3), 55.67 (6-OCH_3), 55.95 (3′,5′-OCH_3), 60.65 (4′-OCH_3), 64.5 (C-1), 106.76 (C-2′,6′), 111.14 (C-8), 111.21 (C-5),125.71 (C-4a), 128.83 (C-8a), 135.44 (C-1′), 136.23 (C-4′), 146.21 (C-7), 147.28 (C-6), 152.76 (C-3′,5′). HRMS (HESI$^+$) *m*/*z* calculated for [M+H]$^+$: 388.2118; found: 388.21210. Further characterization can be found in the literature.[20]

4.3.4. Synthesis of (*R*)-6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*)-3

At first, [RuCl(η^6-*p*-cymene)(*S*,*S*)-TsDPEN] (31.8 mg, 0.05 mmol) was dissolved in acetonitrile (5 mL), after which an HCOOH/TEA complex 5:2 (16.7 mL, 40.0 mmol) was added and the mixture was stirred at room temperature for 5 min. Imine **2** (3.71 g, 10 mmol) dissolved in acetonitrile (15 mL) was then added and the mixture was stirred for 6 h. The reaction mixture was evaporated to dryness to give a viscous substance, which was subsequently dissolved in water (100 mL) and acidified with concentrated hydrochloric acid (15 mL). The acidic aqueous phase was extracted with dichloromethane (6 × 20 mL) to remove the catalyst. The solution was rendered strongly alkaline by the addition of a concentrated aqueous solution of NaOH and the amine was extracted with diethyl ether (5 × 30 mL), washed with brine (30 mL), dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to give the target product. Yield of (*R*)-**3**: 3.67 g, 98.4%. ^{1}H NMR (399.89 MHz, $CDCl_3$, 303.2 K): 2.62 (1H, ddd, *J* = 15.9, 5.8, 4.9 Hz, H-4u), 2.72 (1H, ddd, *J* = 15.9, 7.1, 5.3 Hz, H-4d), 2.78 (1H, dd, *J* = 13.5, 9.1 Hz, H-1-CH_2-u), 2.86 (1H, ddd, *J* = 11.9, 7.1, 4.9 Hz, H-3u), 3.11 (1H, dd, *J* = 13.5, 4.5 Hz, H-1-CH_2-d), 3.16 (1H, d, *J* = 11.9, 5.8, 5.3 Hz, H-3d), 3.77 (3H, s, 7-OCH_3), 3.78 (9H, s, 3′,4′,5′-OCH_3), 3.79 (3H, s, 6-OCH_3), 4.09 (1H, dd, *J* = 9.1, 4.5 Hz, H-1), 6.41 (2H, s, H-2′,6′), 6.54 (1H, s, H-5), 6.59 (1H, s, H-8). ^{13}C NMR (100.58 MHz, $CDCl_3$, 303.2 K): 29.22 (C-4), 40.76 (C-3), 42.81 (1-CH_2), 55.52 (6-OCH_3), 55.67 (7-OCH_3), 55.77 (3′,5′-OCH_3), 60.50 (4′-OCH_3), 105.85 (C-2′,6′), 109.05 (C-8), 111.56 (C-5), 127.17 (C-4a), 130.00 (C-8a), 134.41 (C-1′), 136.19 (C-4′), 146.67 (C-7), 147.15 (C-6), 152.92 (C-3′,5′). HRMS (HESI$^+$) *m*/*z* calculated for [M+H]$^+$: 374.1962; found: 374.19579. Further characterization can be found in the literature.[21]

4.3.5. Synthesis of (*R*)-*N*-Me-6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*)-4 from (*R*)-3

Amine (*R*)-**3** (740 mg, 2.00 mmol) was dissolved in 1,4-dioxane (10 mL). The aqueous solution of formaldehyde (10 mL, 30% w/w) and sodium phosphonate pentahydrate (2.2 g, 10 mmol) dissolved in water (10 mL) was then added and the mixture was stirred at 60 °C for 40 min and then at 80 °C for 3 h. The reaction mixture was diluted with an aqueous solution of sodium hydroxide (150 mL, 10% w/w) and extracted with MTBE (3 × 150 mL). The combined organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness on a rotary evaporator. Yield of (*R*)-**4**: 744 mg, 97.0%. $[\alpha]_D^{20} = -46.0$ (*c* 1.26, $CHCl_3$). Further characterization can be found in the literature.[20]

4.3.6. Synthesis of (*R*)-*N*-Me-6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium (−)-2,3-dibenzoyl-L-tartarate 5 from *rac*-4

Amine *rac*-**4** (531 mg, 1.37 mmol) and (−)-2,3-dibenzoyl-L-tartaric acid (491 mg, 1.37 mmol) were dissolved in 1,4-dioxane (4 mL) and stirred at 80 °C. The mixture was left to cool down slowly after being inoculated with a standard of the product. The crystals formed were filtered on sintered glass, rinsed with a 1:1 mixture of 1,4-dioxane and hexane (10 mL), washed with hexane (5 mL), and dried in an air stream for 5 min. Finally, the crystals were dried in vacuo for 2 h (10 torr, bath temperature 50 °C). Yield of **5**: 400 mg, 39.1%. ^{1}H NMR (399.89 MHz, $CDCl_3$, 303.2 K): 2.50 (1H, m, H-1-CH_2-u), 2.72 (3H, s, 2-CH_3), 2.81 (1H, dd, *J* = 5.8, 17.7 Hz, H-4u), 2.94 (1H, m, H-4d), 3.27 (1H, m, H-3u), 3.37 (3H, s, 7-OCH_3), 3.52 (1H, m, H-3, H-1-CH_2-d), 3.63 (3H, s, 3′,5′-OCH_3), 3.77 (3H, s, 4′-OCH_3), 3.81 (3H, s, 6-OCH_3), 5.60 (1H, s, H-8), 5.97 (2H, s, CH_{tart}), 6.11 (2H, s, H-2′,6′), 6.54 (1H, s, H-5), 7.30 (4H, m, H-*meta*$_{tart}$), 7.43 (2H, m, H-*para*$_{tart}$), 8.03 (4H, m, H-*ortho*$_{tart}$). ^{13}C NMR (100.58 MHz, $CDCl_3$, 303.2 K): 21.18 (C-4), 38.95 (2-CH_3), 41.60 (1-CH_2), 43.82 (C-3), 55.34 (7-OCH_3), 55.85 (6-OCH_3), 56.03 (3′,5′-OCH_3), 60.66 (4′-OCH_3), 64.51 (C-1), 73.31 (CH_{tart}), 107.02 (C-2′,6′), 110.94 (C-5), 111.51 (C-8),120.54 (C-4a), 121.48 (C-8a), 128.12 (C-*meta*$_{tart}$), 129.60 (C-*ipso*$_{tart}$), 129.95 (C-*ortho*$_{tart}$), 131.35 (C-1′), 132.89 (C-*para*$_{tart}$), 136.71 (C-4′), 147.02 (C-7), 148.89 (C-6), 152.97 (C-3′,5′), 165.53 (COO^-_{tart}), 170.62 ($COOH_{tart}$). HRMS

(HESI$^+$) m/z calculated for $[M+H]^+$: 388.2118; found: 388.21220. HRMS (HESI$^-$) m/z calculated for $[M-H]^-$: 357.0602; found: 357.06025.[†]

4.3.7. Synthesis of (*R*)-*N*-Me-6,7-dimethoxy-1-(3′,4′,5′-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*)-4 from 5

Enantiomerically enriched salt **5** (400 mg, 0.54 mmol) was dissolved in water (5.5 mL) and a solution of NaOH (3 mL, 7% w/w) was added. The mixture was extracted with dichloromethane (4 × 10 mL), the extract obtained was dried over anhydrous magnesium sulfate, and evaporated to dryness on a rotary evaporator. Yield of (*R*)-**4**: 197 mg, 94.8%.

4.4. Asymmetric transfer hydrogenation screening experiments

4.4.1. Kinetic experiments

Kinetic experiments and determination of ee were carried out by following a previously reported protocol.[17]

The base (30.1 μL, 0.22 mmol) and formic acid (20.4 μL, 0.54 mmol) were pre-mixed in CD_3CN (580 μL) in an NMR tube and the ^1H NMR spectrum was measured in order to allow proper shimming. The catalyst dissolved in CD_3CN (64 μL, 8.5 mM) was added into the tube and the reaction was started by adding the substrate (10 mg, 27 μmol) dissolved in CD_3CN (100 μL). The rubber stopper was pierced to prevent pressure generation caused by gases formed during the reaction. ^1H NMR spectra were acquired in regular 2–5 min intervals.

4.4.2. Determination of the enantioselectivity

A saturated solution of sodium carbonate (1 mL) was used to quench the reaction and the samples were extracted with diethyl ether (3 × 1 mL) from the alkalized solution. The ether phase was washed with water (3 × 1 mL). The organic phase was dried over anhydrous sodium sulfate, diethyl ether was removed in a stream of argon and the sample was dissolved in $CDCl_3$.

The ee value was determined according to a previously described procedure.[17] (*R*)-(−)-(2,2,2-Trifluoro-1-(9-anthryl)ethanol) (Pirkle's alcohol) was added so that the alcohol:amine ratio was at least 3:1. Since the precise amount of THIQ in the sample was not known, the ratio was controlled by spectra integration. The single enantiomer of Pirkle's alcohol formed diastereomeric solvates with the enantiomers of the THIQ. The signals of the H-2′,6′ protons of the benzyl moiety were used for the integration.

Acknowledgments

This work was financially supported by the Grant Agency of the Czech Republic (Grants GACR 104/09/1497 and P106/12/1276), and by a Grant for the long-term conceptual development of the Institute of Microbiology (RVO: 61388971).

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[†] The salt was characterized by observing **4** in the HESI$^+$ mode and L-dibenzoyltartaric acid in the HESI$^-$ mode. HRMS (HESI$^-$) of L-dibenzoyltartaric acid: m/z calculated for $[M-H]^-$: 357.0602; found: 357.06022.