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Enantioselective synthesis of (+)-trypargine and (+)-crispine E

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Abstract

Asymmetric transfer hydrogenation was used as a key step in the synthesis of two guanidine-derived alkaloids (+)-trypargine and (+)-crispine E. The enantiomeric compositions of key intermediates were established on the basis of ¹H NMR spectra with chiral solvating agents. The absolute stereochemistry was proven by X-ray crystallography.

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1. Introduction

Synthetic organic chemistry has been aimed at the stereoselective construction of complex derivatives for the last few decades since it has been proven that enantiomers of a given molecule differ usually in their bioactivity. Nitrogen containing compounds are widely distributed in nature and also many synthetic amines are valuable pharmaceuticals and therefore methods directed toward their stereoselective preparation have been the subject of a number of investigations. Among a variety of developed methods, the catalytic stereoselective addition to imines is of particular interest.¹ The asymmetric transfer hydrogenation (ATH) procedure has also gained a prominent position due to its experimental simplicity and usually high efficiency of the chiral induction. Since 2-propanol or formic acid (usually in the presence of triethylamine) is used as a hydrogen source, manipulation with hydrogen can be avoided. The ATH procedure was initially applied for ketone reduction and a number of successful examples of enantioselective preparations of secondary alcohols can be found in the literature.² In the 1990s, Novori et al. reported³ that Ru(II) complexes of monosulfonylated 1,2-diamines, such as (1R,2R)-N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) and its enantiomer could be applied for the reduction of prochiral imines. The detailed mechanistic studies on this process by Noyori and Hashiguchi⁴ and other groups⁵ led to development of the 'metal-ligand bifunctional catalysis' model.⁶

We have already demonstrated the utility of TsDPEN ligand in the enantioselective synthesis of various sensitive 1-fatty acid-derived 1,2,3,4-tetrahydroisoquinolines and 1,2,3,4-tetrahydro- β -carbolines,⁷ some tri- and tetracyclic alkaloids⁸ and also heterocyclic pharmaceuticals.⁹

2. Results and discussion

In this paper we present an effective, enantioselective synthesis of two simple guanidine-derived alkaloids: (+)-trypargine 1 and (+)-crispine E 3 (Fig. 1). In the case of the latter alkaloid, it is the first synthesis of this compound.

Trypargine (-)-1 is a unique tetrahydro- β -carboline mammalian alkaloid of high toxicity, first isolated from the African

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Figure 1. Structures of guanidine-derived alkaloids 1-3.

rhacophorid frog *Kassina Senegalensis* by Akizawa et al.¹⁰ Recently, (-)-**1** was also found in a previously undescribed ground ascidian *Eudistoma* sp.¹¹ Interestingly, a very similar compound, 6-hydroxy-trypargine **2**, was identified as a potent neurotoxin in the venom of the Brazilian web spider *Parawixia bistriata*.¹² Already in the mid 1980s, (-)-trypargine **1** was the subject of a stereoselective synthesis by Japanese authors.¹³ Their synthesis started with D-tryptophan and proceeded in 11 steps with 12.5% overall yield and required the use of diazomethane.

Being encouraged by our previous positive results in the application of ATH in the enantioselective alkaloids synthesis, we decided to explore the use of this method in the preparation of optically active trypargine and related derivatives.

To reach this goal, γ -aminobutyric acid **4** was first converted (according to the known procedure¹⁴) to its *N*-phthaloyl derivative **5**, which in turn was converted to the corresponding acid chloride **6**. This chloride reacted with tryptamine (CH₂Cl₂, 0 °C, 1.5 equiv of Et₃N) to afford amide **7** in 82% yield. The amide was then treated with phosphorous oxychloride in refluxing acetonitrile (the Bischler–Napieralski reaction¹⁵) to give imine **8** (85% yield, Scheme 1).

Subsequent asymmetric transfer hydrogenation on imine **8** was performed under classical Noyori conditions.^{3,9} Initially, a combination of *N*-tosyl-(1*R*,2*R*)-diphenylethylenediamine and [RuCl₂(η^6 -benzene)]₂ forms the catalyst (*S*,*S*)-**9**, which was then used in *S*/*C*=160 ratio in a solution of formic acid and triethylamine (5:3 v/v mixture, Scheme 1) (Fig. 2).



Figure 2. The structure of ATH complex.

The isolated, optically active amine **10**, which was formed in 89% yield, showed a single peak during the HPLC analysis on ChiraDex[®], ChiraSep[®] or DNBPG¹⁶ column. However, we found that the racemic amine **10** obtained by the hydrogenation of imine **8** also showed a single peak. It means that the HPLC analysis on these columns cannot be applied for the enantiomeric excess determination of the amine **10**. Therefore, we decided to apply an alternative procedure for the ee determination, which was based on the generation of dynamic associates formed between the investigated base **10** and (+)-(*R*)-*tert*-butyl-phenylphosphinothioic acid **15** or its seleno-congener **16**,¹⁷ (Fig. 3) and their observation by ¹H NMR spectroscopy.

The signal of the indole NH proton in the racemic **10** appeared, upon addition of 2 equiv of **15** into the NMR tube, as two well-separated signals at δ 8.87 and 8.96 ppm. In the spectrum of the crude (+)-**10**, obtained after the ATH procedure, only one signal was observed. This allowed to assume that the isolated sample was enantiomerically pure (within the limit of NMR measurements—ee>98%).

Comparable results were obtained when phosphinoselenic acid 16 was used as a chiral solvating agent. Although the



Figure 3. Chiral solvating agents.



Scheme 1.

chemical yield of the amine **10** was reasonably high, a small amount of unreacted imine **8** constituted a persistent impurity, which could not be easily removed even after a repeated crystallization. In this respect, the use of (S,S)-**13** as a catalyst was found to be more effective since it allowed a complete reduction of the imine **8** after 3 h (93% ee and 94% isolated yield of **10**). A single crystallization gave the enantiopure material.

The X-ray analysis of a single crystal of (+)-10 proved the (*R*)-absolute configuration at a stereogenic carbon atom in this compound (Fig. 4).¹⁸



Figure 4. The molecule of (+)-10. The non-hydrogen atoms are shown as 30% probability ellipsoids.

With the enantiopure amine (+)-10 in hand, we completed the synthesis of trypargine 1 in three simple steps. Thus, the removal of the phthaloyl group in (+)-10 was accomplished with hydrazine in EtOH at rt. The formed diamine proved to be unstable and therefore it was not isolated and purified but was directly subjected to derivatization with N,N'-bis(Boc)-S-methylisothiourea in DMF at room temperature¹⁹ to give the protected trypargine 11 in 53% yield (calculated based on 10). The final, enantiomeric form of the natural alkaloid, (+)-1, was obtained, as its hydrochloride salt, in quantitative yield after the removal of *Boc* groups with TFA in dichloromethane at room temperature and subsequent exchange of the anion by repeated evaporation with methanolic HCl. All analytical data of the isolated compound were in full agreement with the published ones.²⁰ The second alkaloid, crispine E (3), is a constituent of a basic fraction obtained from *Carduus crispus* Linn. (welted thistle), the plant intensively studied for its promising pharmacological activity.²¹ However, so far this compound has not been a subject of synthetic evaluation. Due to the obvious similarity to trypargine 1, the reaction sequence leading to crispine E also started with the acid **6**, from which imine **19** was prepared in 85% yield (Scheme 2).

In contrast to the previous results, the enantioselective reduction with ruthenium complex **9** gave amine **20** in approx. 60% ee, albeit in quantitative yield. Apparently, the presence of the indole NH is important to the creation of a well-defined transition state in which the substrate molecule is incorporated into the coordination sphere of the ruthenium atom. The enantiomeric excess of this compound was initially estimated on the basis of ¹H NMR measurements of diastereomeric associates derived from phosphinothioic acid **15** but the indicative signals at δ 6.48 and 6.49 ppm were not base-line separated. In a search for a more efficient diastereodiscriminating agent, we found that compound **17**²² allowed much better visualization of the enantiomeric, and it turned out that the enantiomeric excess of the analyzed sample was equal to 65%.

To improve the enantioselectivity of the reduction step, we used a series of catalysts **9**, **12**–**14**, for the ATH reaction. Considering results of the published mechanistic studies,⁵¹ we also checked the relationship between the degree of the chiral induction and other reaction parameters such as concentration, the order of addition of the substrates, formic acid and triethylamine. The results, summarized in Table 1, indicate that the bulkiness of the η -component in the molecule of the complex constitutes a major factor that may influence the efficiency of the reduction. Indeed, when ruthenium complex (*S*,*S*)-**12** was used, the reaction gave the product **20** in 89% ee and with good yield (90%), and the reaction was completed after 2 h.

After a single recrystallization from ethyl acetate, the enantiopure amine **20** was obtained. Its absolute configuration was determined by a single-crystal X-ray diffraction study of its *N*-*p*bromobenzoyl derivative (Fig. 5).²³ Subsequent transformations,



3178

Scheme 2.

Table 1 Optimization of the ATH procedure on imine **19**

Catalyst	HCOOH/Et ₃ N	Temp	Time	Yield (%)	$[\alpha]_D$	ee
(<i>S</i> , <i>S</i>)- 9	5:2	rt	3 h	88	+18.8	65
	5:2	0 °C	8 h	71	+18.9	65
(S,S)-12	5:2	rt	2 h	90	+25.7	89
(S,S)-13	5:2	rt	20 min	97	+19.7	68
	10:2	rt	24 h	86	+1.6	6
	5:2 ^a	rt	45 min	90	+20.1	70
	5:2 ^b	rt	10 min	98	+17.6	60
	5:2	0 °C	30 min	87	+20.4	71
	5:2	−35 °C	8 h	_	+19.4	67
(S,S)-14	5:2	rt	1 h	96	+14.4	50

^a Et₃N was introduced gradually from 0 to 2 equiv.

^b HCOOH was introduced gradually from 0 to 5 equiv.

similar to those applied to the synthesis of (+)-trypargine 1, led to the final enantiopure (+)-crispine E 3 in 38% overall yield (based on amine 20).



Figure 5. Conformation of the molecule and the numbering scheme. All nonhydrogen atoms are shown as 30% probability ellipsoids.

3. Experimental

3.1. General

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ¹H NMR and at 125 MHz for ¹³C NMR or at 200 MHz for ¹H NMR and at 50 MHz for ¹³C NMR. The spectra were measured in CDCl₃ or CD₃OD and are given as δ values (in ppm) relative to TMS. Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer and were obtained as solids in KBr. Mass spectra were collected on Quatro LC Micromass and LCT Micromass TOF HiRes apparatus. Optical rotations were measured on a Perkin-Elmer 247MC polarimeter. TLC analyses were performed on silica gel plates (Merck Kieselgel GF254) and visualized using UV light or iodine vapor. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230-400 mesh, Merck) using mixtures of chloroform/methanol as eluent. Melting points were determined on a Boetius hot-plate microscope and were uncorrected. All solvents used in the reactions were anhydrous. The single-crystal X-ray measurements were carried out on either Oxford Diffraction Xcalibur R κ -axis diffractometer with CCD Ruby detector (crystals of **10** and *N-p*-bromobenzoyl derivative of **20**). In all cases, Cu K α characteristic radiation was applied. After the initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine the structures. SHELXS97²⁴ and SHELXL-97²⁵ programs were used for these tasks. The absolute structures were estimated by applying Flack parameter²⁶ values calculated using Friedel pair reflections for each structure.

3.2. 4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-N-[2-(1H-indol-3-yl)ethyl]butanamide (7)

A mixture of γ -phthalimidobutyric acid (6.3 g, 27 mmol) 5 and thionyl chloride (11 mL) was heated for 1 h at 70 °C. The excess of thionyl chloride was removed under reduced pressure and the residue was dissolved in CHCl₃ (100 mL). To a stirred solution of tryptamine (4.3 g, 27 mmol) and triethylamine (7 mL) in CHCl₃ (200 mL), the γ -phthalimidobutyryl chloride 6 solution was added over a period of 20 min. The mixture was stirred at room temperature for 2 h, treated with aqueous Na_2CO_3 solution, and extracted with chloroform (2×50 mL). The organic phase was washed with brine $(2 \times 50 \text{ mL})$, dried over MgSO₄, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel using chloroform/methanol 20:1 to give 8.3 g of the product 7 (82%) as yellow solid, mp 70–72 °C. ¹H NMR (500 MHz, CDCl₃): $\delta = 1.98$ (quintet, J=6.8 Hz, 2H), 2.14 (t, J=7.3 Hz, 2H), 2.96 (t, J=6.8 Hz, 2H), 3.57 (q, J=6.8 Hz, 2H), 3.66 (t, J=6.8 Hz, 2H), 5.96 (t, J=5 Hz, 1H), 7.04-7.08 (m, 2H), 7.15 (t, J=7.8 Hz, 1H), 7.33 (d, J=7.8 Hz, 1H), 7.57 (d, J=7.8 Hz, 1H), 7.70–7.81 (m, 4H), 8.38 (br s, 1H). ¹³C NMR $(125 \text{ MHz}, \text{ CDCl}_3): \delta = 25.0, 25.4, 34.0, 37.4, 39.9, 111.4,$ 113.0, 118.8, 119.5, 122.2, 122.3, 123.4, 127.5, 132.1, 134.2, 136.6, 168.7, 172.0. HRMS (ESI) calcd for C₂₂H₂₁N₃O₃Na $([M+Na]^+)$ m/z 398.1481, found 398.1485.

3.3. 2-[3-(4,9-Dihydro-3H-β-carbolin-1-yl)propyl]-1Hisoindole-1,3(2H)-dione (**8**)

To a stirred solution of 7 (3 g, 8 mmol) in CH₃CN (30 mL), POCl₃ (4 mL) was added and the reaction mixture was refluxed for 2 h. The excess of POCl₃ and the solvent were removed in vacuo and the residue was dissolved in CH₂Cl₂ (60 mL). The solution was washed with 25% aqueous NH₃ and brine, and finally evaporated (after drying over MgSO₄). The residue was crystallized from MeOH to give 2.55 g (85%) of compound 8 as yellow solid, mp 92–94 °C. ¹H NMR (500 MHz, CD₃OD): δ =2.04 (t, J=7 Hz, 2H), 2.70 (t, J=8.5 Hz, 2H), 3.67 (t, J=8.5 Hz, 2H), 3.74 (t, J=7 Hz, 2H), 7.02 (t, J=7.5, 1H), 7.19 (t, J=7.5, 1H), 7.35 (d, J=7.5, 1H), 7.45 (d, J=7.5, 1H), 7.67–7.72 (m, 4H). ¹³C NMR (125 MHz, CD₃OD): δ =20.0, 27.0, 27.1, 38.5, 49.9, 113.3, 117.9, 120.8, 120.9, 123.9, 125.5, 126.4, 129.4, 133.3, 135.2, 138.9, 163.6, 169.8. HRMS (ESI) calcd for $C_{22}H_{20}N_{3}O_{2}$ ([M+H]⁺) *m/z* 358.1555, found 358.1550.

3.4. 2-[3-(2,3,4,9-Tetrahydro-1H-β-carbolin-1-yl)propyl]1Hisoindole-1,3(2H)-dione (**10**)

The catalyst (R,R)-9 was pre-formed from $[RuCl_2(C_6H_6)]_2$ $(3 \text{ mg}, 6 \mu \text{mol})$ and (1R, 2R)-1,2-diphenyl-N-(p-toluoylsulfonyl)ethylenediamine (4.4 mg, 12 µmol) in 4 mL of CH₃CN. To a solution of the imine 8 (464 mg, 1.3 mmol) in CH₃CN (5 mL), a 5:2 formic acid/triethylamine mixture (1.5 mL) was introduced, followed by the addition of the pre-formed catalyst. The mixture was then stirred at room temperature for 48 h and after evaporation of the solvents, the residue was basified with 25% aqueous NH3 and extracted with chloroform. The organic phase was dried over MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using chloroform/methanol 30:1 to afford 428 mg (92% yield) of compound (+)-(R)-10 as yellow solid, mp 69– 71 °C, $[\alpha]_{D}^{23}$ +40.6 (c 1, CHCl₃) (>98% ee). ¹H NMR (500 MHz, CDCl₃): δ =2.26-2.76 (m, 2H), 3.00-3.05 (m, 1H), 3.25-3.32 (m, 1H), 3.40-3.51 (m, 4H), 3.76-3.79 (m, 2H), 4.09–4.16 (m, 1H), 7.07 (t, J=7.5 Hz, 1H), 7.13 (t, J=7.5 Hz, 1H), 7.33 (d, J=7.5 Hz, 1H), 7.46 (d, J=7.5 Hz, 1H), 7.69–7.71 (m, 2H), 7.82–7.85 (m, 2H), 8.53 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ =22.9, 25.3, 31.9, 37.7, 42.0, 51.7, 109.0, 111.1, 118.1, 119.3, 121.6, 123.5, 127.5, 132.1, 134.3, 135.9, 136.0, 168.9. HRMS (ESI) calcd for $C_{22}H_{22}N_{3}O_{2}([M+H]^{+}) m/z$ 360.1712, found 360.1713.

3.5. N,N''-Bis(Boc)N'-[3-(2,3,4,9-tetrahydro-1H- β -carbolin-1-yl)propyl]guanidine (**11**)

To a solution of (1R)-(+)-10 (1.3 g, 3.6 mmol) in 35 mL of ethanol, 0.3 mL (8.19 mmol) of anhydrous hydrazine in ethanol (1.5 mL) was added. The mixture was refluxed for 1.5 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in DMF (20 mL) then N,N'-bis(Boc)-S-methylisothiourea (1.57 g, 5.4 mmol) and DMAP (8.8 mg, 0.072 mmol) were added. The mixture was stirred at room temperature for 3 h and after evaporation of the solvents, the residue was purified by column chromatography on silica gel using chloroform/methanol 25:1 to afford 897 mg (53% yield) of compound (+)-(R)-11 as yellow solid, mp 112–114 °C, $[\alpha]_{D}^{23}$ –76.3 (c 1.04, CHCl₃). ¹H NMR $(500 \text{ MHz}, \text{ CDCl}_3)$: $\delta = 1.50 \text{ (s, 9H)}, 1.51 \text{ (s, 9H)}, 1.70 - 1.90$ (m, 4H), 2.69-2.80 (m, 2H), 3.03-3.08 (m, 1H), 3.29-3.34 (m, 1H), 3.41-3.49 (m, 2H), 4.13-4.16 (m, 1H), 7.08 (t, J=7.5 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 7.36 (d, J=7.5 Hz, 1H), 7.48 (d, J=7.5 Hz, 1H), 8.45 (t, J=5.1 Hz, 1H), 8.67 (s, 1H), 11.54 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ =23.0, 25.5, 28.3, 28.6, 31.6, 40.7, 42.4, 52.1, 79.7, 83.5, 109.2, 111.3, 118.1, 119.4, 121.5, 127.6, 136.0, 136.1, 153.6, 156.8, 163.8. HRMS (ESI) calcd for C₂₅H₃₈N₅O₄ ([M+H]⁺) m/z 472.2924, found 472.2918.

3.6. (R)-(+)-Trypargine (1)

To a solution of **11** (150 mg, 0.32 mmol) in 10 mL of CH_2Cl_2 a volume of 1.5 mL of TFA was added. The mixture

was then stirred at room temperature for 1 h, and concentrated under reduced pressure. The residue was then treated with MeOH/HCl and evaporated to give product **1** as yellow solid, mp 210–212 °C, $[\alpha]_D^{23}$ +34.3 (*c* 1, MeOH) {lit.^{13a} mp 204– 207 °C, $[\alpha]_D^{15}$ +37.2 (*c* 0.54, MeOH)}, {natural trypargine hydrochloride:¹⁰ mp 210–213 °C, $[\alpha]_D^{27}$ -34.2 (*c* 1.02, MeOH)}. ¹H NMR (500 MHz, CD₃OD): δ =1.82–1.93 (m, 2H), 2.04– 2.12 (m, 1H), 2.30–2.39 (m, 1H), 2.79–3.05 (m, 1H), 3.07–3.15 (m, 1H), 3.27–3.36 (m, 2H), 3.37–3.46 (m, 1H), 3.67–3.75 (m, 1H), 4.69–4.76 (m, 1H), 7.05 (t, *J*=7.5 Hz, 1H), 7.15 (t, *J*=7.5 Hz, 1H), 7.39 (d, *J*=8 Hz, 1H), 7.46 (d, *J*=8 Hz, 1H). ¹³C NMR (125 MHz, CD₃OD): δ =19.4, 25.8, 30.5, 42.0, 43.0, 54.5, 107.4, 112.4, 119.1, 120.6, 123.5, 127.4, 129.7, 138.3, 158.6. IR (KBr, cm⁻¹): 3388, 3174, 2941, 1664, 1650, 1453, 746. HRMS (ESI) calcd for C₁₅H₂₂N₅ ([M+H]⁺) *m/z* 272.1875, found 272.1872.

3.7. N-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(1,3-dioxo-1,3dihydro-2H-isoindol-2-yl)butanamide (18)

A mixture of γ -phthalimidobutyric acid (6.3 g, 27 mmol) **5** and thionyl chloride (11 mL) was heated for 1 h at 70 °C. The excess of thionyl chloride was removed under reduced pressure and the residue was dissolved in CHCl₃ (100 mL). To a stirred solution of homoveratrylamine (4.9 g, 27 mmol) and triethylamine (7 mL) in CHCl₃ (200 mL), a solution of γ -phthalimidobutyryl chloride 6 was added for 20 min. The mixture was stirred at room temperature for 2 h, treated with aqueous Na₂CO₃ solution, and then extracted with chloroform $(2 \times 50 \text{ mL})$. The organic phase was washed with brine $(2 \times 50 \text{ mL})$, dried over MgSO₄, and the solvent was evaporated in vacuo. The residue was purified by crystallization from ethyl acetate to give 8.4 g of product 18 (79%) as white solid, mp 141–143 °C. ¹H NMR (500 MHz, CDCl₃): δ=2.01 (quintet, J=6.5 Hz, 2H), 2.17 (t, J=7 Hz, 2H), 2.78 (t, J=7 Hz, 2H), 3.50 (q, J=6.5 Hz, 2H), 3.69 (t, J=6.5 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.02 (t, J=5.2 Hz, 1H), 6.73-6.81 (m, 3H), 7.72-7.74 (m, 2H), 7.82-7.84(m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ =25.0, 33.8, 35.2, 37.2, 40.7, 55.8, 55.9, 111.3, 111.9, 120.6, 123.3, 131.4, 132.0, 134.1, 147.6, 149.0, 168.6, 171.8. HRMS (ESI) calcd for $C_{22}H_{24}N_2O_5Na$ ([M+Na]⁺) *m*/*z* 419.1583, found 419.1576.

3.8. 2-[3-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)propyl]-1H-isoindole-1,3(2H)-dione (19)

To a stirred solution of **18** (2.8 g, 7.1 mmol) in CH₂Cl₂ (28 mL), POCl₃ (10 mL) was added and the reaction mixture refluxed for 1 h. It was next poured onto crushed ice and the mixture was made neutral with NaHCO₃ solution. The aqueous layer was subsequently extracted with CH₂Cl₂ (3×30 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was crystallized from CH₂Cl₂/ether to give 2.4 g (91%) of compound **19** as white solid, mp 116–117 °C. ¹H NMR (500 MHz, CDCl₃): δ =2.10 (quintet, *J*=7.5 Hz, 2H), 2.58 (t, *J*=7.5 Hz, 2H), 2.77 (t, *J*=7.5 Hz, 2H), 3.59 (t, *J*=7.5 Hz, 2H), 3.82 (t, *J*=7.5 Hz,

2H), 3.89 (s, 3H), 3.91 (s, 3H), 6.67 (s, 1H), 6.95 (s, 1H), 7.68–7.72 (m, 2H), 7.80–7.84(m, 2H). 13 C NMR (125 MHz, CDCl₃): δ =25.8, 32.9, 37.8, 46.8, 55.9, 56.2, 108.4, 110.3, 121.7, 123.1, 131.5, 132.1, 133.9, 147.5, 150.8, 165.4, 168.4. HRMS (ESI) calcd for C₂₂H₂₃N₂O₄ ([M+H]⁺) *m/z* 379.1658, found 379.1668.

3.9. 2-[3-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propyl]-1H-isoindole-1,3(2H)-dione (**20**)

The catalyst (R,R)-12 was pre-formed from $[RuCl_2(p-cym$ ene)]₂ (3.7 mg, 6 μ mol) and (1R,2R)-1,2-diphenyl-N-(p-toluoylsulfonyl)ethylenediamine (4.4 mg, 12 µmol) in 4 mL of CH₃CN. To a solution of imine 19 (491 mg, 1.3 mmol) in CH₃CN (5 mL), a 5:2 formic acid/triethylamine mixture (1.5 mL) was introduced, followed by the addition of the preformed catalyst. The mixture was then stirred at room temperature for 3 h and after evaporation of the solvents, the residue was basified by the addition of aqueous Na₂CO₃ and extracted with chloroform. The organic phase was washed with brine (2×10 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using chloroform/methanol 30:1 to afford 444 mg (90% yield) of compound (+)-(R)-20 as white solid, mp 108–109 °C, $[\alpha]_D^{23}$ +25.7 (c 1, CHCl₃) (89% ee). Recrystallization from ethyl acetate mixture gave pure enantiomer $\left[\alpha\right]_{D}^{23}$ +28.9 (c 1, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ =1.71-1.94 (m, 4H), 2.61–2.74 (m, 2H), 2.92–2.97 (m, 1H), 3.15– 3.20 (m, 1H), 3.75-3.80 (m, 2H), 3.84 (s, 6H), 3.94-3.98 (m, 1H), 6.55 (s, 1H), 6.61 (s, 1H), 7.69–7.73 (m, 2H), 7.82– 7.85 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ =25.3, 29.5, 33.5, 37.9, 40.8, 54.8, 55.8, 56.0, 109.1, 111.7, 123.2, 127.2, 131.2, 132.1, 133.9, 147.2, 147.3, 168.4. HRMS (ESI) calcd for C₂₂H₂₅N₂O₄ ([M+H]⁺) *m/z* 381.1814, found 381.1815.

3.10. N-[3-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1yl)propyl]-N',N"-bis(Boc)guanidine (21)

To a solution of (1*R*)-(+)-**20** (1.37 g, 3.6 mmol) $[\alpha]_{D}^{23}$ +28.9 (c 1, CHCl₃) in 35 mL of ethanol 0.3 mL (8.19 mmol) of anhydrous hydrazine in ethanol (1.5 mL) was added. The mixture was refluxed for 1.5 h, cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in (20 mL) then N,N'-bis(Boc)-S-methylisothiourea DMF (1.57 g, 5.4 mmol) and DMAP (8.8 mg, 0.072 mmol) were added. The mixture was stirred at room temperature for 3 h and after evaporation of the solvents, the residue was purified by column chromatography on silica gel using chloroform/ methanol 25:1 to afford 903 mg (51% yield) of compound (+)-(*R*)-21 as yellow solid, mp 108–109 °C, $[\alpha]_{D}^{23}$ +13.7 (*c* 1, CHCl₃). ¹H NMR (500 MHz, CDCl₃): $\delta = 1.49$ (s, 9H), 1.51 (s, 9H), 1.75-1.89 (m, 4H), 2.62-2.67 (m, 1H), 2.72-2.78 (m, 1H), 2.95–2.99 (m, 1H), 3.18–3.23 (m, 1H), 3.45–3.54 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.94-3.96 (m, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 8.42 (t, J=4.5 Hz, 1H), 11.51 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ =25.6, 28.1, 28.3, 29.5, 33.5, 40.8, 41.1, 54.9, 55.8, 56.0, 79.3, 83.0, 109.0, 111.8, 127.2,

131.0, 147.3, 147.3, 153.3, 156.2, 163.6. HRMS (ESI) calcd for $C_{25}H_{41}N_4O_6$ ([M+H]⁺) *m*/*z* 493.3026, found 493.3027.

3.11. (R)-(+)-Crispine E(3)

To a solution of **21** (370 mg, 0.75 mmol) in 20 mL of CH₂Cl₂ was added 4 mL of TFA. The mixture was then stirred at room temperature for 1 h, and concentrated under reduced pressure. The residue was treated with MeOH/HCl and after evaporation to give product **3** as white solid, mp 132–134 °C (lit.^{21a} mp 130–133 °C), $[\alpha]_D^{23} + 22.6$ (*c* 1, MeOH). ¹H NMR (500 MHz, CD₃OD): δ =1.82–1.86 (m, 2H), 2.01–2.09 (m, 1H), 2.17–2.26 (m, 1H), 2.98–3.04 (m, 1H), 3.09–3.15 (m, 1H), 3.30–3.39 (m, 3H), 3.56–3.61 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 4.51–4.57 (m, 1H), 6.80 (s, 1H), 6.87 (s, 1H). ¹³C NMR (125 MHz, CD₃OD): δ =25.8, 26.2, 32.3, 40.7, 42.0, 56.2, 56.5, 56.9, 111.1, 113.0, 125.1, 125.3, 149.8, 150.5, 158.6. IR (KBr, cm⁻¹): 3378, 3161, 2939, 1665, 1650, 1519, 1261. HRMS (ESI) calcd for C₁₅H₂₅N₄O₂ ([M+H]⁺) *m/z* 293.1978, found 293.1974.

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