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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 406–413

Enantioselective synthesis of some tetrahydroisoquinoline and tetrahydro-β-carboline alkaloids

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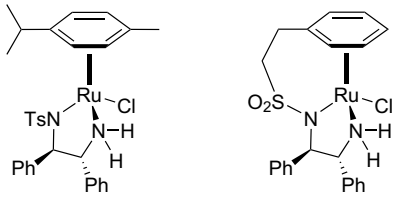
Received 22 December 2006; accepted 8 January 2007
Available online 21 February 2007

Abstract—Four alkaloids: (*R*)-(+)-cryspine A **5**, (*R*)-(+)-octahydroindolo[2,3-*a*]quinolizidine **8**, (*R*)-(+)-harmicine **19** and (*R*)-(+)-desbromoarborescidine **22** were prepared via the asymmetric transfer hydrogenation reaction of a prochiral enamine (iminium salt). The enantiomeric excesses of the isolated alkaloids were determined from their ^{1}H NMR spectra measured in the presence of (+)-(*R*)-*tert*-butylphenylphosphinothio(seleno)ic acids as chiral solvating agents. The absolute configurations at the newly created stereogenic carbon atoms were confirmed, in all cases, by X-ray crystallography.

1. Introduction

The asymmetric transfer hydrogenation (ATH) has become, over the last decade, a highly powerful, versatile and practical tool for the stereoselective synthesis of non-racemic secondary alcohols and amines from prochiral ketones or imines (iminium salts).[1–4]

Due to the use of 2-propanol or formic acid (usually in the presence of triethylamine) as a hydrogen source, dangerous manipulation with molecular hydrogen can be avoided in this reaction. Several effective ligands have already been introduced, including a variety of β-amino alcohols and 1,2-diamino compounds.[5–12] These ligands, when reacted with a ruthenium pre-catalyst, such as $[RuCl_2(\eta^6\text{-mesitylene})]_2$, form chiral, coordinatively saturated 18-electron Ru(II) complexes [such as (*R*,*R*)-**1** (Fig. 1)] that serve as promotors for a stereoselective reduction of prochiral ketones. In comparison with ketones, imines are far less popular substrates and a limited number of successful examples of effective chirality transfer have been published so far.[2,4,13–26]



(*R*,*R*)-**1** (*R*,*R*)-**2**

Figure 1. Selected chiral catalysts for ATH.

In the mid 1990s, Noyori reported that Ru(II) complexes of monotosylosulfonated 1,2-diamines, such as *N*-tosyl-(1*R*,2*R*)-diphenylethylenediamine (TsDPEN) or its enantiomer, were able to effectively stabilize the transition state through hydrogen bonding, which allowed an efficient chirality transfer as a result of the apparent simultaneous protonation by the NH group and hydride ion attack from the Ru–H onto the imine. Since that time several modifications of the original procedure have been proposed, including variations of the central atom from Ru(II) to Rh(III),[27] and the nature of the ligands. The most effective and promising seems to be the 'tethered' Ru(II) catalyst (*R*,*R*)-**2** introduced by Wills et al.[14,28]

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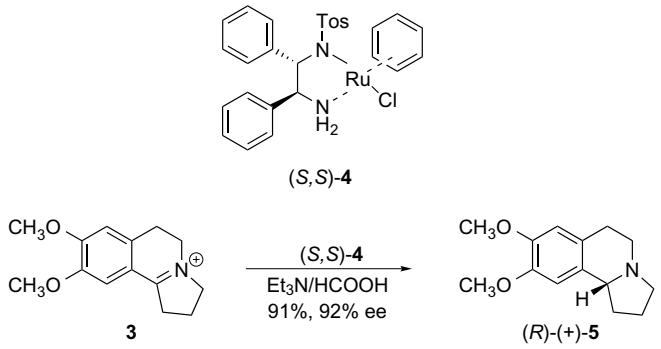
doi:10.1016/j.tetasy.2007.01.014

We have recently communicated that the asymmetric hydrogen transfer protocol is very effective in the enantioselective synthesis of various fatty acid 1-substituted-tetrahydro-β-carbolines,[29] the antihelminitic drug Praziquantel[30] and the isoquinoline alkaloid crispine A.[31] Herein, we report our recent results, which show the synthetic utility of the ATH methodology for the preparation of analogous heterocyclic systems and present structural assignments performed for the alkaloids products, including the determination of their absolute configurations.

2. Results and discussion

2.1. Enantioselective synthesis of (+)-crispine A 5

The title alkaloid has been isolated from *Carduus crispus* Linn. (welted thistle), the plant intensively studied for its promising pharmacological activity.[32,33] Our approach for its preparation in its enantiomerically pure form (already described in our preliminary communication[31]) is based on the ATH procedure applied to iminium salt **3** (Scheme 1). This allows the chirality induction in the last step of the synthetic sequence, which maximizes the atom economy.[34]



Scheme 1. The synthesis of (*R*)-(+)-**5**.

The wanted, desired crispine A (*R*)-(+)-**5** was isolated in 96% yield and 92% ee. Even better results (90% chemical yield, ee >99%) were obtained when the enamine corresponding to **3** was subjected to the reduction. The (*R*)-absolute configuration at the newly created stereogenic carbon atom in (+)-**5** was finally confirmed on the basis of the X-ray analysis of its picrate salt (Fig. 2).

2.2. Enantioselective synthesis of benzo[*a*]quinolizidine ring system

The title heterocyclic moiety is abundant in several types of isoquinoline alkaloids, including emetine-related bases, known as *Ipecac* alkaloids. The medicinal value of the extracts derived from *Cephaelis ipecacuanha* (Brot.) A. Richard and *Cephaelis accuminata* Carsten (Rubiaceae) rests mainly on emetine and cephaeline,[35] but is not limited to their emetic and expectorant properties, and includes also their antiamoebic[36] and anti-tumour activity.[37]

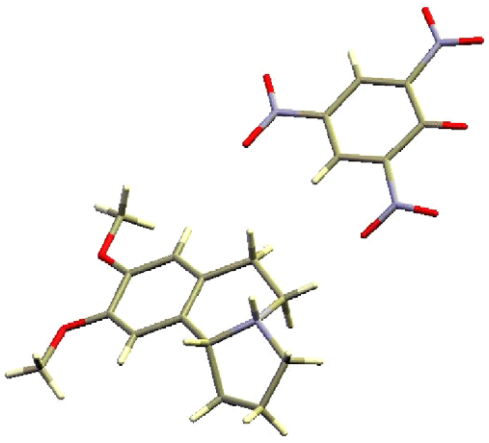
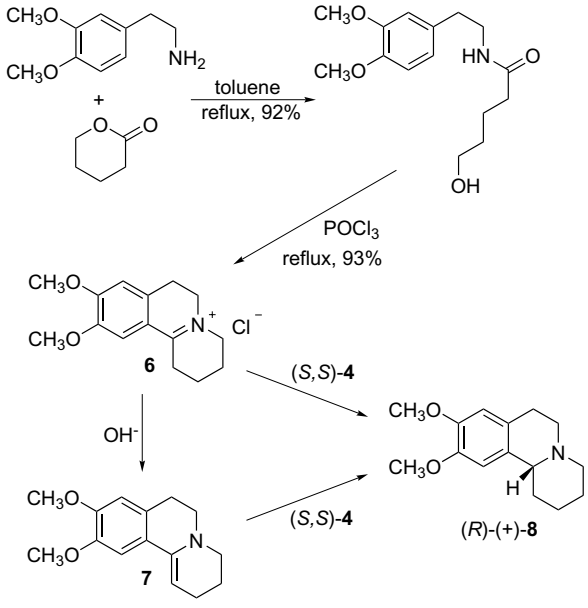


Figure 2. The absolute stereochemistry of the picrate salt of (*R*)-(+)-**5**.

In recent years, considerable efforts have been devoted to the stereoselective construction of emetine alkaloids and their synthetic congeners.[38] Having been encouraged by the positive results of our catalytic approach to crispine A, we considered a similar reaction sequence for the enantioselective synthesis of benzo[*a*]quinolizidine ring system. Thus, simple condensation of 3,4-dimethoxyphenylethylamine with δ-valerolactone in boiling toluene afforded, after crystallization, *N*-homoveratryl-ω-hydroxyvaleramide[39] in 92% yield. Its subsequent treatment with $POCl_3$ in toluene gave, after a careful basification, the iminium salt **6**[39] in 93% yield.

It is interesting to note that the isolation of the hydroxyamide intermediate was not necessary and when the whole process was performed as a one-pot sequential operation, only a slight loss in the chemical yield of **6** (69%) was observed (Scheme 2).



Scheme 2. Chemical transformations leading to (*R*)-(+)-**8**.

The iminium salt **6** was then subjected to a series of hydrogen transfer reductions (Scheme 2) with ruthenium catalysts modified with various ligands **9**–**12** (Fig. 3), according to the protocol optimized for the synthesis of crispine A.[31]

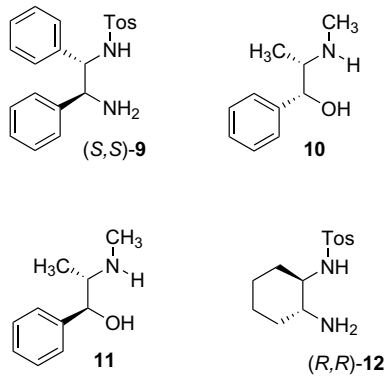


Figure 3. The structure of chiral ligands.

In all cases, the reduction proceeded smoothly, giving good to excellent yields of benzo[*a*]quinolizidine **8**. The enantiomeric excesses for the isolated samples of the product were determined based on the NMR measurements described already[31] with (+)-(*R*)-*tert*-butylphenylphosphinothioic acid **13** (Fig. 4) as a chiral solvating agent.

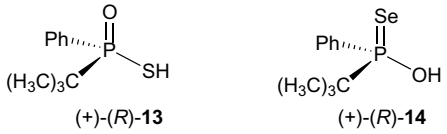


Figure 4. Chiral solvating agents.

In sharp contrast to the previous findings, there was no temperature influence on asymmetric induction and the 'classical' Noyori ligand (*S*,*S*)-**9** was again the most effective, albeit only 87% ee was achieved, even after optimization efforts. Moreover, the experiments realized on the corresponding enamine **7** did not afford a product with higher enantiomeric excess (Table 1).

Table 1. Enantioselective synthesis of benzo[*a*]quinolizidine **8**

Entry	Substrate	Ligand	*T* (°C)	Yield (%)	Configuration	ee (%)
1	**6**	**9**	22	97	(*R*)-(+)-	87.0
2	**6**	**9**	0	83	(*R*)-(+)-	85.8
3	**6**	**10**	22	97	(*R*)-(+)-	1.0
4	**6**	**11**	22	65	(*R*)-(+)-	5.2
5	**6**	**12**	22	82	(*S*)-(−)-	84.3
6	**7**	**9**	22	80	(*R*)-(+)-	68.7
7	**7**	**9**	0	89	(*R*)-(+)-	82.7

Our attempts to obtain good quality crystals for enantiomers of **8** (or their salts) were unsuccessful. Therefore, in order to establish the absolute configuration, we transformed the dextrorotary enantiomer of **8** into the diastereomeric mixture of its *N*-oxides **15** and **16** (MCPBA, 78% chemical yield, **15**:**16** = 6:1, Fig. 5). An anomalous X-ray scattering analysis proved the (*R*)-absolute configuration at the stereogenic carbon atom in the *trans*-*N*-oxide **15**. This means also that in the parent amine, the stereogenic carbon atom has the (*R*) absolute configuration (Fig. 5).

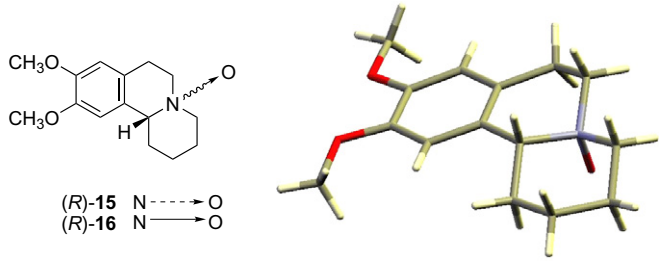


Figure 5. The structure of *N*-oxides **15** and **16** and the absolute configuration at the stereogenic carbon in (*R*)-(−)-**15**.

The *cis*-stereochemistry of the quinolizidine moiety in (*R*)-**16** was fully supported by the NMR data. Interestingly, phosphinothioic acid **13** was also found to behave as a good chiral solvating agent in ^{1}H NMR experiments with *N*-oxide **15**. It probably results from the presence of a basic oxygen atom in this compound (Fig. 6).

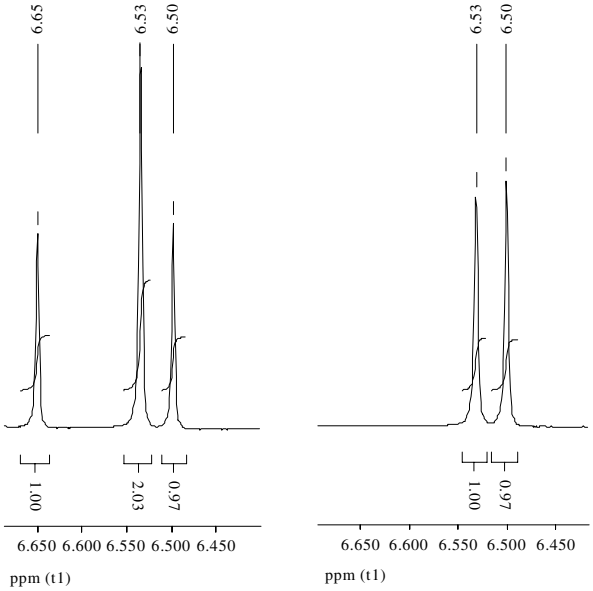
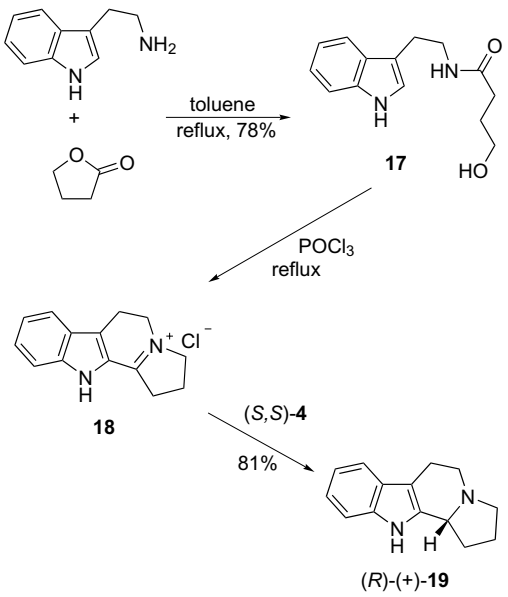


Figure 6. ^{1}H NMR spectra of **15** (aromatic region) (a) racemic; (b) enantiopure (*R*)-(−)-**15** $[\alpha]_D^{23} = -14.3$ (*c* 1, $CHCl_3$) {both measured in the presence of (+)-(*R*)-**13**}.

2.3. Enantioselective synthesis of (*R*)-(+)-harmicine 19

A basic fraction of an ethanolic extract from the leaves of Malaysian plant *Kopsia griffithii* exhibits a profound antileishmania activity.[40] Among several nitrogen bases found in this extract, (*R*)-(+)-harmicine (+)-**19** is suspected to be responsible for a pharmacological profile of the plant. An elegant synthesis of the racemic harmicine has recently been published.[41] Also, (*S*)-(−)-harmicine (−)-**19** was prepared using optically active 1-allyl-1,2,3,4-tetrahydro-β-carboline as a substrate.[42]

From a synthetic point of view, the preparation of optically active harmicine should be possible by an analogous route applied for the synthesis of crispine A, (*R*)-(+)-**5**.[31] Thus, the condensation of γ-butyrolactone with tryptamine afforded hydroxyamide **17**[43] in 78% yield. Its subsequent treatment with $POCl_3$ was found to be most effective when the reaction was carried out without the solvent. We were not able to obtain good analytical data for the prepared iminium salt **18** (except acceptable MS spectrum) due to its strong tendency to decomposition. A similar behaviour of analogous compounds was observed by other authors.[44–48] The asymmetric transfer hydrogenation carried out on the crude samples of **18** under standard conditions using (*S*,*S*)-**4** as the catalyst gave (+)-harmicine (+)-**19** in 81% chemical yield (Scheme 3).



Scheme 3. The synthesis of (*R*)-(+)-**19**.

The highest enantiomeric excess (determined on the basis of ^{1}H NMR experiments with phosphinothioic acid **13**) was only 79% despite our optimization efforts. Fortunately, after a single crystallization, an almost enantiopure alkaloid could be obtained. Again, the absolute configuration at the stereogenic carbon was established by the X-ray crystallographic analysis (Fig. 7) thus concluding the discussion[42] on this subject.

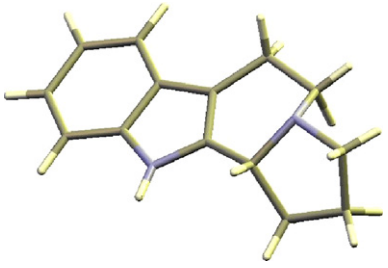
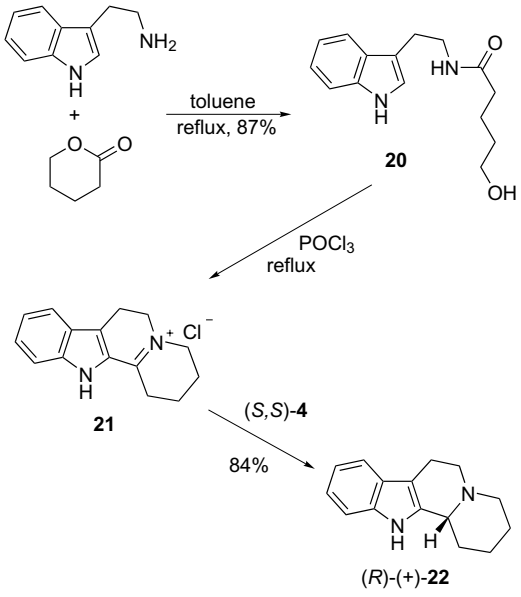


Figure 7. The absolute stereochemistry of (*R*)-(+)-**19**.

2.4. Enantioselective synthesis of (+)-desbromoarborescidine A 22

The indolo[2,3-*a*]quinolizine heterocyclic ring system, present also in (+)-desbromoarborescidine A **22**, is of particular interest for the pharmacological chemistry of tryptophan-derived alkaloids, since it is a common structural motif in many highly bioactive secondary metabolites, including *Rauwolfia* family bases (ajmaline, ajmalicine, reserpine)[49] along with newly characterized brominated β-carbolines from marine tunicate *Pseudodistoma arborescens*[50] or desbromoarborescidine **22**, isolated from the bark of *Dracontomelum mangiferum*.[42,51]

Our attempts to enantioselectively synthesize desbromoarborescidine A **22** were based on the reaction sequence already discussed in this paper. Again, the condensation of tryptamine with δ-valerolactone in refluxing toluene gave known hydroxyamide **20**[47] in 87% yield. It should be noted here that the use of tetralin as a solvent[47] caused further transformation of **20** into the lactam derivative and lowered the yield. Its subsequent Bischler–Napieralski cyclization in neat $POCl_3$ gave, after a short work-up, unstable iminium salt 21.[44,45,47] Its immediate reduction under standard conditions using (*S*,*S*)-**4** afforded (+)-desbromoarborescidine A (+)-**22** in 84% chemical yield (Scheme 4).



Scheme 4. Synthesis of (*R*)-(+)-**22**.

Comparison of the specific rotation ($[\alpha]_D^{23} = +74.4$), of the isolated product with the reported value[42] indicated that it had an enantiomeric excess of 90.5%. Again, a single crystallization afforded almost enantiopure material. In contrast to the determination of the enantiomeric excesses discussed above, the ^{1}H NMR differentiation using phosphinothioic acid **13** was unsuccessful for (+)-**22**. However, using its selenium analogue, (*R*)-(+)-**14**, we were able to observe a very good separation of the signals of the formed dynamic diastereomeric associates (Fig. 8).

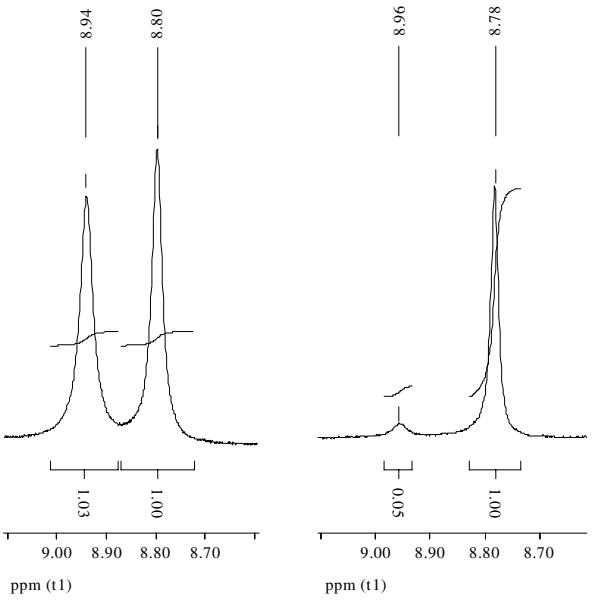


Figure 8. ^{1}H NMR spectra of **22** (indole N–H region): (a) racemic mixture; (b) sample (*R*)-(+)-**22** $[\alpha]_{D}^{23} = +74.4$ (*c* 1, CH_3OH) {both measured in the presence of (+)-(*R*)-**14**}.

Crystallization of the enantiopure (+)-**22** gave a monocrystal that was used for X-ray analysis (Fig. 9), which indicated the (*R*) absolute configuration at the stereogenic carbon atom. This is in accordance with the data collected for an analogous heterocyclic system.[52]

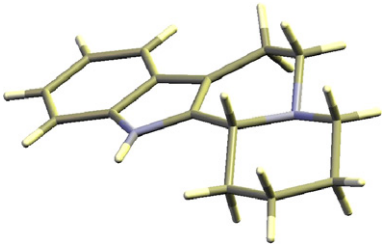


Figure 9. The absolute stereochemistry of (*R*)-(+)-**22**.

3. Conclusion

In conclusion, we used asymmetric transfer hydrogenation for the enantioselective synthesis of four alkaloids: (*R*)-(+)-cryspine A **5**, (*R*)-(+)-octahydroindolo[2,3-*a*]quinolizidine **8**, (*R*)-(+)-harmicine **19** and (*R*)-(+)-desbromoarborescidine **22**. The enantiomeric excesses of the alkaloids prepared were determined from their ^{1}H NMR spectra measured in the presence of (+)-(*R*)-*tert*-butylphenylphosphinothio(seleno)ic acids as chiral solvating agents. The absolute configurations at the newly created stereogenic carbon atoms were established in all cases by the X-ray analysis.

4. Experimental

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR or at 200 MHz for ^{1}H NMR and at 50 MHz for ^{13}C NMR. The spectra were measured in $CDCl_3$ or CD_3OD and are given as δ values (in ppm) elative to TMS. 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 Kiesegel GF254) 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 of chloroform/methanol as eluents. 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 **15**, **19** and **22**) or on Enraf Nonius TurboCAD4 κ-axis diffractometer with a point scintillation counter (crystal of **5**). In all cases, Cu Kα characteristic radiation was applied. After the initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine the structures. SHELXS97[53] and SHELXL97[54] programs were used for these tasks. The absolute structures were estimated by applying Flack parameter[55] values calculated using Friedel pair reflections for each structure.

4.1. General procedure for the synthesis of ω-hydroxyamides

To a stirred solution of homoveratrylamine or tryptamine (20.0 mmol) in toluene (30 mL), an appropriate lactone (22.0 mmol) and a catalytic quantity of *p*-toluenesulfonic acid were added. The mixture was refluxed for 7 h under argon. The solvent was evaporated, and the residue was crystallized from AcOEt to afford ω-hydroxyamides as white solids.

Data for *N*-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxypentanamide (Scheme 2): yield 92%; mp 65–65.5 °C; ESMS (positive ion mode) *m*/*z* 282.2 $[M+H]^+$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.69–6.83 (m, 3H), 6.03 (br s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.60 (t, 2H, $J = 6$ Hz), 3.48 (q, 2H, $J_1 = 7$ Hz, $J_2 = 6$ Hz), 3.02 (br s, 1H), 2.75 (t, 2H, $J = 7$ Hz), 2.18 (t, 2H, $J = 7$ Hz), 1.45–1.77 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.19, 148.87, 147.53, 131.28, 120.52, 111.81, 111.23, 61.78, 55.79, 55.75, 40.58, 35.92, 35.10, 31.81, 21.65.

Data for compound **17**: yield 78%; mp 71–73 °C; ESMS (negative ion mode) *m*/*z* 245.2 $[M-H]^+$; ^{1}H NMR (200 MHz, CD_3OD): δ 1.77 (quintet, 2H, $J = 6.8$ Hz), 2.22 (t, 2H, $J = 7.4$ Hz), 2.93 (t, 2H, $J = 7.4$ Hz), 3.43–5.56 (m, 4H), 6.95–7.12 (m, 3H), 7.31 (d, 1H, $J = 8.3$ Hz), 7.53 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (50 MHz, CD_3OD): δ 26.27, 29.82, 33.71, 41.43, 62.29, 112.23, 113.26, 119.28, 119.58, 122.29, 123.39, 128.79, 138.15, 175.85.

Data for compound **20**: yield 87%; mp 75–77 °C; ^{1}H NMR (200 MHz, CD_3OD): δ 1.44–1.67 (m, 4H), 2.16 (t, 2H, $J = 7.2$ Hz), 2.93 (t, 2H, $J = 6.8$ Hz), 3.43–5.55 (m, 4H), 6.95–7.12 (m, 3H), 7.32 (d, 1H, $J = 8.2$ Hz), 7.55 (d, 1H,

$J = 7.6$ Hz); ^{13}C NMR (50 MHz, CD_3OD): δ 23.38, 26.27, 33.01, 36.81, 41.36, 62.49, 112.21, 113.23, 119.23, 119.56, 122.29, 123.39, 128.78, 138.12, 176.00.

4.2. Preparation of iminium salt 6

To a stirred solution of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxypentanamide (5.0 g, 17.8 mmol) in toluene (50 mL), $POCl_3$ (16 mL, 175.3 mmol) was added and the reaction mixture refluxed for 2 h. Next it was poured onto crushed ice and the mixture was made basic with NH_{3aq}. The aqueous layer was subsequently extracted with chloroform (3×30 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized from ethanol/ether to give 4.7 g (93%) of compound **6** as white needles. Mp 162–165 °C; ESMS (positive ion mode) *m*/*z* 246.1 [M^+−Cl]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.89 (s, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 3.89 (t, 2H, $J = 7$ Hz), 3.67 (t, 2H, $J = 6$ Hz), 3.35 (t, 2H, $J = 7$ Hz), 3.07 (t, 2H, $J = 8$ Hz), 1.99–2.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.85, 156.55, 149.07, 133.67, 117.01, 111.29, 111.26, 56.76, 56.67, 44.34, 40.77, 31.38, 31.27, 25.83, 25.50.

4.3. General procedure for the preparation of iminium salts 18 and 21

The solution of ω-hydroxyamides **17** or **20** (6.0 mmol) and freshly distilled $POCl_3$ (15 mL) was refluxed for 3 h under argon. The excess of $POCl_3$ was removed in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with 25% NH_{3aq}, saturated solution of $NaHCO_3$ and brine, and finally evaporated (after drying over $MgSO_4$). The crude salts were reduced in the presence of catalyst (*S*,*S*)-**4** as described below.

Data for compound **18**: ESMS (positive ion mode) *m*/*z* 247.1 [M+H]$^+$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (quintet, 2H, $J = 7.3$ Hz), 3.17 (t, 2H, $J = 8.5$ Hz), 3.35–3.59 (m, 4H), 3.91 (t, 2H, $J = 8.5$ Hz), 7.16 (t, 1H, $J = 7.5$ Hz), 7.39 (t, 1H, $J = 7.5$ Hz), 7.58 (d, 1H, $J = 8.5$ Hz), 7.71 (d, 1H, $J = 8.5$ Hz), 12.73 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.46, 30.42, 31.16, 42.10, 43.99, 114.28, 121.25, 121.94, 124.14, 125.55, 129.15, 142.20, 169.22.

Data for compound **21**: MS *m*/*z* (%) 224 ($M^{+\cdot}$, 91), 223 (100), 209 (26), 195 (19), 167 (21), 154 (7), 104 (11); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85–2.09 (m, 4H), 3.23 (t, 2H, $J = 8.3$ Hz), 3.47–3.64 (m, 4H), 3.99 (t, 2H, $J = 8.3$ Hz), 7.19 (t, 1H, $J = 7.3$ Hz), 7.43 (t, 1H, $J = 7.3$ Hz), 7.62 (d, 1H, $J = 8$ Hz), 7.73 (d, 1H, $J = 8$ Hz), 12.29 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.76, 26.06, 31.95, 32.20, 42.37, 44.53, 107.17, 114.37, 121.54, 122.18, 124.38, 125.65, 129.39, 142.20, 170.24.

4.4. General procedure for the asymmetric transfer hydrogenation

The catalyst (*S*,*S*)-**4** formed independently from $[RuCl_2(C_6H_6)]_2$ (6 mg, 24 μmol) and (1*S*,2*S*)-1,2-diphenyl-*N*-(p-toluoylsulfonyl)ethylenediamine **9** (7.3 mg, 20 μmol) in 4 mL CH_3CN was introduced at 0 °C to a stirred solution of iminium salts **3**, **6**, **18** or **21** in CH_3CN (10 mL) containing also a 5:2 formic acid–triethylamine mixture (2.5 mL). Stirring was continued for 10 h at 0 °C and then the reaction mixture was made basic by the addition of aqueous Na_2CO_3 (or NH_{3aq} in the case of **19** and **22**) and extracted with diethyl ether (or chloroform). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using chloroform/methanol as a solvent system to afford amines **5**, **8**, **19** or **22**.

Data for compound (*R*)-(+)-**5**: 79.3 mg (96% yield); all the spectral data were the same as already described.[31] The picrate salt was obtained by mixing hot solutions of equimolar amounts of amine **5** and picric acid in ethanol.

Crystallographic data: $C_{20}H_{22}N_4O_9$, $M_r = 462.42$, $T = 293(2)$ K, monoclinic crystals, $P2_1$ space group with $a = 9.2228(5)$, $b = 10.5363(7)$ and $c = 11.3660(7)$ Å, $\beta = 105.724(8)°$, $V = 1063.15(11)$ Å^3, $Z = 2$, $F(000) = 484$, $\rho = 1.445$ Mg/m^3, μ(Cu Kα) = 0.986 mm^{-1}, $R1 = 0.0534$ and $wR2 = 0.1195$ for 2122 reflections with $I \geqslant 2\sigma(I)$. Absolute structure parameter $x = -0.2(4)$. In the crystal structure, strong N(4)–H(4)···O(1′) hydrogen bonds between crispine cation and picric acid anion were observed. The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 630264.

Data for compound (*R*)-(+)-**8**: yields 83–97% depending on the temperature of the reduction; mp 57–59 °C [lit.[56] 58–60 °C]; $[\alpha]_D^{23} = +94.0$ (*c* 1.0, $CHCl_3$) (87% ee); ESMS (positive ion mode) *m*/*z* 248.1 [M+H]$^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.56 (s, 1H), 3.84 (2s, 6H), 3.04–3.14 (m, 2H), 2.91–2.99 (m, 2H), 2.58–2.62 (m, 1H), 2.47–2.52 (m, 1H), 2.24–2.33 (m, 2H), 1.90–1.93 (m, 1H), 1.70–1.75 (m, 2H), 1.38–1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.38, 147.14, 130.51, 126.83, 111.52, 108.22, 63.28, 56.94, 56.00, 55.85, 52.93, 31.58, 29.17, 25.52, 25.15.

Data for compound (*R*)-(+)-**19**: 81% yield; mp 171–172 °C [lit.[57] 164–167 °C]; $[\alpha]_D^{23} = +94.0$ (*c* 1, $CHCl_3$) (79% ee) [lit.[40] $[\alpha]_D^{23} = +119$ (*c* 0.086, $CHCl_3$)]; after recrystallization from ethanol: mp 171–172 °C; $[\alpha]_D^{23} = +109.5$ (*c* 0.99, $CHCl_3$) (92% ee); ESMS (negative ion mode) *m*/*z* 211.2 [M−H]$^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81–1.95 (m, 3H), 2.23–2.32 (m, 1H), 2.62–2.67 (m, 1H), 2.84–2.99 (m, 3H), 3.05–3.11 (m, 1H), 3.31–3.35 (m, 1H), 4.22–4.24 (m, 1H), 7.08–7.15 (m, 2H), 7.29 (d, 1H, $J = 8$ Hz), 7.49 (d, 1H, $J = 7.5$ Hz), 7.86 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.78, 23.44, 29.43, 45.93, 49.26, 56.91, 107.77, 110.70, 118.09, 119.93, 121.36, 127.32, 135.44, 135.95.

Crystallographic data: $C_{14}H_{16}N_2$, $M_r = 212.29$, $T = 293(2)$ K, orthorhombic, $P2_12_12_1$ space group, $a = 7.3217(6)$, $b = 9.1999(9)$, $c = 17.495(4)$ Å, $V = 1178.4(3)$ Å^3, $Z = 4$, $\rho = 1.197$ Mg/m^3, $F(000) = 456$, μ(Cu Kα) = 0.548 mm^{-1}, $R1 = 0.0367$ and $wR2 = 0.1000$ for 2066 independent reflections with $I \geqslant 2\sigma(I)$. Absolute

structure parameter $x = -0.2(5)$. In the crystal structure, strong N(11)–H(11)···N(4) hydrogen bonds between adjacent symmetry related molecules were observed. The detailed structural parameters have been deposited with Cambridge Crystallographic Data Centre under the number CCDC 630266.

Data for compound (*R*)-(+)-**22**: 84% yield; mp 148–149 °C [lit.[42] 149–152 °C]; $[\alpha]_D^{23} = +74.4$ (*c* 1, MeOH) (90.5% ee); after recrystallization from propanol/H_2O mp 148–149 °C; $[\alpha]_D^{23} = +82.7$ (*c* 0.96, MeOH); MS *m*/*z* (%) 226 ($M^{+\cdot}$, 68), 225 (100), 197 (27), 169 (30), 156 (9), 115 (7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43–1.63 (m, 2H), 1.71–1.82 (m, 2H), 1.90 (d, 1H, $J = 12.5$ Hz), 2.06 (dd, 1H, $J = 12.5$, 2.5 Hz), 2.39 (td, 1H, $J = 11.3$, 3.4 Hz), 2.61–2.72 (m, 2H), 2.98–3.09 (m, 3H), 3.23 (d, 1H, $J = 10.5$ Hz), 7.07–7.14 (m, 2H), 7.29 (d, 1H, $J = 8$ Hz), 7.47 (d, 1H, $J = 8$ Hz), 7.78 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.58, 24.31, 25.73, 29.98, 53.55, 55.74, 60.22, 108.09, 110.68, 118.08, 119.31, 121.22, 127.46, 135.10, 135.89.

Crystallographic data: $C_{15}H_{18}N_2 \cdot 1/2H_2O$, $M_r = 235.32$, $T = 293(2)$ K, monoclinic, *C*2, $a = 19.297(4)$, $b = 6.5192(13)$, $c = 10.423(2)$ Å, $\beta = 91.71(3)°$, $V = 1310.7(5)$ Å^3, $Z = 4$, $\rho = 1.193$ Mg/m^3, $F(000) = 508$, μ(Cu Kα) = 0.567 mm^{-1}, $R1 = 0.0386$ and $wR2 = 0.0956$ for 2003 independent reflections with $I \geqslant 2\sigma(I)$. Absolute structure parameter $x = -0.2(4)$. The crystal structure is a hydrate structure with water molecules occupying special positions on twofold axes. Strong hydrogen bonds N(12)–H(12)···O(1S) and O(1S)–H(1S)···N(5) between **22** and water molecules are observed. The detailed structural parameters have been deposited with Cambridge Crystallographic Data Centre under the number CCDC 630267.

4.5. Preparation of *N*-oxides 15 and 16

To a stirred solution of amine (+)-**8** (643 mg, 2.6 mmol) in dichloromethane (50 mL) was added *m*-chloroperbenzoic acid (494 mg, 2.9 mmol) and the solution stirred for 2 h at room temperature. The mixture was then washed with 10% $NaHCO_3$ and 10% Na_2SO_3 solutions. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford crude *N*-oxides (**15**:**16** ca. 6:1) that were separated with column chromatography (Al_2O_3 activity II, Brockmann, chloroform/methanol) giving compounds **15** and **16**. Both compounds formed monohydrates.

Data for compound **15**: mp 187–192 °C; $[\alpha]_D^{23} = -14.3$ (*c* 1, $CHCl_3$); ESMS (positive ion mode) *m*/*z* 264.1 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ 6.66 (s, 1H), 6.62 (s, 1H), 4.13 (d, 1H, $J = 11.7$ Hz), 3.85 (s, 3H), 3.82 (s, 3H), 3.38–3.51 (m, 3H), 3.23 (ddd, 1H, $J_1 = 14.6$, $J_2 = 12.7$, $J_3 = 2.9$ Hz), 2.64–2.73 (m, 4H; 2H after exchange with D_2O) 2.36 (qd, 1H, $J_1 = 12.7$, $J_2 = 3.9$ Hz), 2.23 (dq, 1H, $J_1 = 13.7$, $J_2 = 2.9$ Hz), 2.04 (distorted d, 1H, $J = 2$ Hz), 1.66 (d, 1H, $J = 14.6$ Hz), 1.55 (qd, 1H, $J_1 = 13.7$, $J_2 = 3.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ 148.34, 147.71, 124.77, 124.38, 111.57, 108.68, 71.58, 68.64, 65.00, 56.18, 55.95, 24.71, 24.19, 23.41, 20.10.

Crystallographic data: $C_{15}H_{21}NO_3 \cdot H_2O$, $M_r = 281.34$, $T = 173(2)$ K, orthorhombic, $P2_12_12_1$, $a = 9.987(6)$, $b = 14.074(11)$, $c = 20.786(8)$ Å, $V = 2922(3)$ Å^3, $Z = 8$, $\rho = 1.279$ Mg/m^3, $F(000) = 1216$, μ(Cu Kα) = 0.754 mm^{-1}, $R1 = 0.0308$, $wR2 = 0.0671$ for 4361 independent reflections with $I \geqslant 2\sigma(I)$. Absolute structure parameter $x = 0.05(13)$. The crystal structure of **15** is a hydrate structure where compound molecules are linked together via strong intermolecular water–compound and water–water O–H···O hydrogen bonds. Two molecules of **15**, slightly differing in geometry, and two water molecules form independent part of the unit cell. The detailed structural parameters have been deposited with Cambridge Crystallographic Data Centre under the number CCDC 630265.

Data for compound **16**: colourless oil; $[\alpha]_D^{23} = +9.1$ (*c* 1, $CHCl_3$); ESMS (positive ion mode) *m*/*z* 264.1 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ 6.65 (s, 1H), 6.58 (s, 1H), 4.61 (br s, 1H), 4.34 (d, 1H, $J_1 = 9.8$, $J_2 = 2.8$ Hz), 3.86 (s, 3H), 3.84 (s, 3H), 3.78–3.95 (m, 8H), 3.70 (m, 1H), 3.60 (m, 1H), 3.49 (m, 1H), 3.37 (m, 1H), 2.89 (br d, 1H, $J = 16.6$ Hz) 2.39 (m, 1H), 2.06 (m, 1H), 1.65–1.85 (m, 4H:2H after exchange with D_2O); ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ 148.63, 148.29, 125.88, 122.32, 111.45, 109.91, 77.43, 73.78, 56.32, 56.11, 29.69, 25.03, 22.63, 21.52, 19.00.

Acknowledgement

Financial support from Grants PBZ-KBN-126/T09/2004/13, KBN-3/T09A/073/28 and 288/FNiTP/624/2005 is gratefully acknowledged.

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