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Synthesis of New Perhydroindole Derivatives and Their Evaluation in Ruthenium-Catalyzed Hydrogen Transfer Reduction

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New perhydroindole derivatives were synthesized with good yields and evaluated as chiral ligands in the Ru^{II}-catalyzed hydride transfer reduction of acetophenone.

Introduction

The development of new chiral ligands for catalytic asymmetric transformations is one of the most important issues in the search of efficient asymmetric syntheses.[1] Nitrogen-containing ligands are being used increasingly in asymmetric catalysis. They turn out to be suitable for many types of catalysis, especially for heterogeneous catalysis.[2] In particular, much emphasis has been placed on the role of nitrogen-containing compounds in transition-metal catalysis. Chiral amino acid based ligands are of significant importance due to their ready availability, low cost, and modular nature.

In contrast to the proline derivatives, which have been used in enantioselective C=C bond hydrogenation,[3] hydride transfer,[4] cyclopropanation,[5] selective oxidation of sulfides to sulfoxides,[6] cyanosilylation,[7] aldol reaction and organocatalytic transformations,[8–10] little has been reported on the related perhydroindole-based compounds. In the presence of perhydroindanylmethanol (**1**), diethylzinc reacted with benzaldehyde to provide 1-phenylpropan-1-ol with 90% *ee*,[11] and acetophenone was reduced by BH_3 with high *ee*.[12] Some perhydroindole derivatives were also used in enantioselective ring opening of *meso*-epoxides[13] and desymmetrization of cyclic carbamates.[14] After demonstrating the efficiency of perhydroindolic acid as an organocatalyst in the aldol reaction,[15] we now report the preparation of new perhydroindole amide derivatives **2**–**6** (Figure 1) and the evaluation of their catalytic activities as ligands in ketone reduction by hydride transfer. As the NH function within the molecule is crucial to carry out the metal-catalyzed asymmetric reduction of prochiral ketones,[16] we synthesized the amino alcohol **1**, the perhydroindole amides **2**,**3** and the C_2-symmetrical bis(perhydroindolic amides) **4**–**6** (Figure 1).

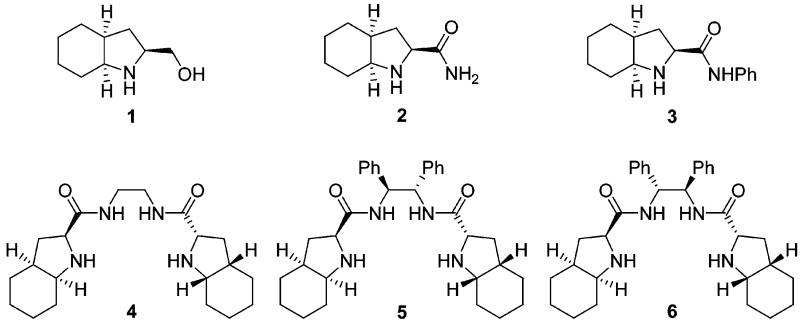

Figure 1. Perhydroindole derivatives **1**–**6**.

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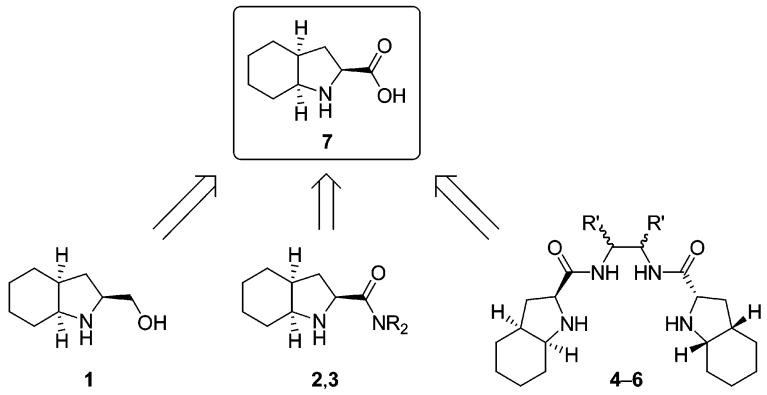
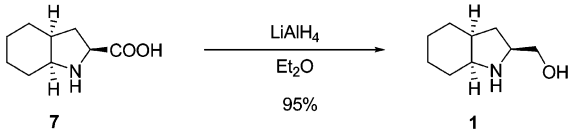
Results and Discussion

Compounds **1**–**6** were prepared from the (*S*,*S*,*S*)-perhydroindolic acid **7**, as outlined in Scheme 1.



Scheme 1. Retrosynthesis of perhydroindole derivatives.

The amino alcohol **1** was prepared by reduction of the amino acid **7** using lithium aluminium hydride in diethyl ether in excellent yield (Scheme 2).[11,12]



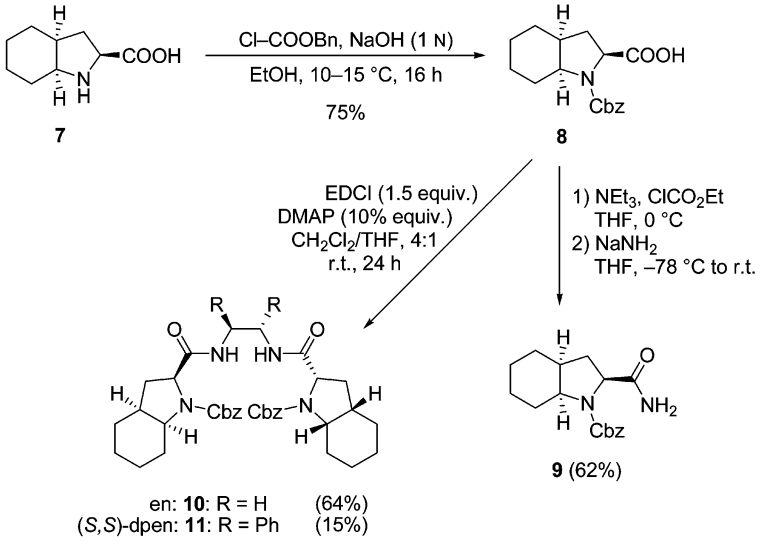
Scheme 2. Preparation of amino alcohol **1**.

We next turned our attention to the synthesis of the amides **2**–**6**. The protection of the amine was first performed using benzyl chloroformate to give **8** in 75% yield. Amide **9** was then prepared according to the procedure described by Sanchez et al.[17,18] An anhydride intermediate was first prepared by reaction of **8** with ethyl chloroformate in the presence of triethylamine in THF at 0 °C, and then directly treated with a substoichiometric amount of sodium amide at –78 °C to prevent epimerization, providing compound **9** in a moderate 62% yield. Peptide coupling of the protected amino acid **8** with ethylenediamine (en) or (*S*,*S*)-diphenylethylenediamine [(*S*,*S*)-dpen] in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 4-(dimethylamino)pyridine (4-DMAP) led to the bis(perhydroindolic amides) **10**,**11** in low to moderate yields (Scheme 3).

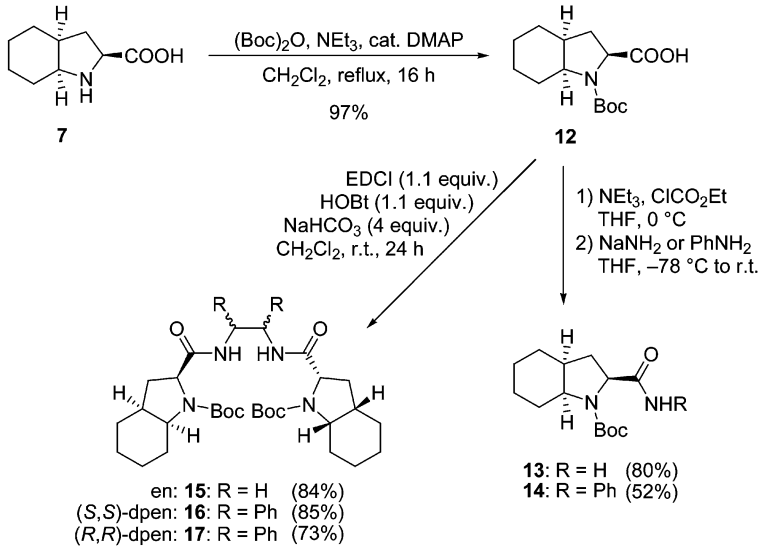
From the protected amino amide **9** and bis(amino amides) **10**,**11**, the last step towards amides **2**, **4**, and **5** was the removal of the protecting group from the indole nitrogen atom. The deprotection of these derivatives by hydrogenolysis using Pd/C as the catalyst resulted either in no reaction or in irreproducible reactions.

Thus, we envisioned an alternative protecting group which would be easier to cleave and would be removed under acidic conditions. The protection of the secondary amine **7** using $(Boc)_2O$ was performed to provide **12** in 97% yield. The diastereomerically pure amides **13** and **14** were isolated in moderate to good yields using the Sanchez procedure,[17] whereas the bis(perhydroindolic amides) **15**–**17** were obtained in good yields using the peptide coupling conditions previously described by Zhao (Scheme 4).[19]

The subsequent deprotection of the secondary amine derivatives was performed in the presence of trifluoroacetic acid in dichloromethane at 0 °C.[20] The resulting amino



Scheme 3. Synthesis of Cbz-protected perhydroindole amide **9** and bis(perhydroindole amides) **10**,**11**.



Scheme 4. Synthesis of Boc-protected perhydroindolic amides **13**,**14** and bis(perhydroindolic amides) **15**–**17**.

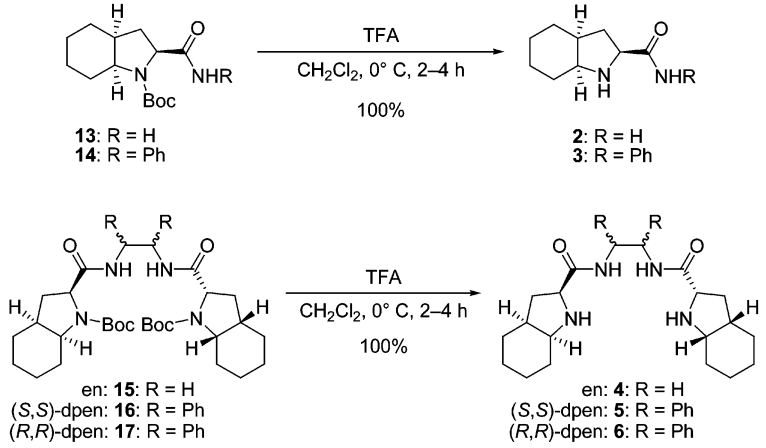
amides **2**,**3** and bis(amino amides) **4**–**6** were isolated in quantitative yields (Scheme 5).

The potential of these new optically pure perhydroindole derivatives was then evaluated by testing their efficiency as ligands in the Ru^{II}-catalyzed hydride transfer reduction of ketones.

Enantioselective transfer hydrogenation of ketones with no functional neighboring group represents a very useful method for the preparation of optically active alcohols.[21] Recently, Noyori and co-workers have shown that the NH function within the ligand molecule is crucial for the asymmetric transformation of prochiral ketones into chiral alcohols.[22] Among the ligands applied to this reaction, diamines[21a] and amino alcohols[23] have led to high catalytic activities and enantioselectivities. Proline amides have also been used and have shown potential.[4,18] In order to evaluate the perhydroindole derivatives **1**–**7**, we investigated the hydride transfer reaction with acetophenone and compared the results to those obtained with proline amides.

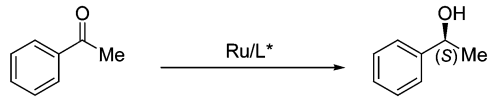
With ligands **1**–**7**, we first screened different reaction conditions using precatalyst $[RuCl_2(p\text{-cymene})]_2$ and either isopropyl alcohol/KOH or the azeotropic HCOOH/Et_3N mixture as the hydride source for the transfer hydrogenation (Table 1). The chiral ruthenium complexes were prepared in situ by heating a mixture of the ruthenium dimer and the chiral ligand in refluxing isopropyl aclohol. Catalytic reactions were carried out by adding acetophenone and either KOH to the previous isopropyl alcohol/catalyst solution (conditions A) or a mixture of HCOOH/Et_3N to the catalyst after removing isopropyl alcohol (conditions B). The mixture was allowed to react for a determined time, and then it was filtered through Celite (conditions A) or quenched with diluted HCl (conditions B).

In the first attempt using isopropyl alcohol as hydride source with the amino alcohol **1** (conditions A), we isolated 1-phenylethan-1-ol in high yield and good enantiomeric excess (Table 1, Entry 1). Under similar reaction conditions, the amino amides **2**,**3** did not provide any efficient catalysts



Scheme 5. Synthesis of perhydroindole derivatives **2**–**5**.

Table 1. Perhydroindole derivatives **1**–**7** as ligands in the hydride transfer reaction with acetophenone.



Entry	Ligand	Conditions[a]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1**	A	16	99	60
2	**1**	B	16	n.r.[d]	–
3	**2**	A	16	n.r.[d]	–
4	**2**	B′	20	32	10
5	**3**	A	16	n.r.[d]	–
6	**3**	B′	20	40	50
7	**4**	A′	48	60	52
8	**5**	A′	48	low yield	62

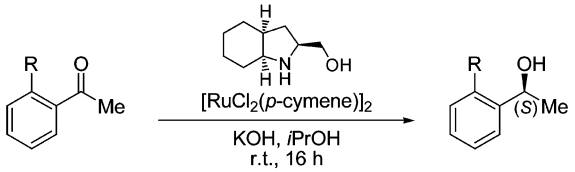
[a] A: acetophenone/KOH/L*/Ru, 100:5:2:1, *i*PrOH, room temp., 16 h. **A′**: acetophenone/KOH/L*/Ru, 100:5:2:1, *i*PrOH, room temp., 48 h. **B**: acetophenone/L*/Ru, 100:2:1, $HCOOH/NEt_3$, 5:2, room temp., 16 h. **B′**: acetophenone/L*/Ru, 100:2:1, $HCOOH/NEt_3$, 5:2, 45 °C, 20 h. [b] Isolated yield. [c] Determined by HPLC analysis, with Chiralcel OD-H chiral columns [(*S*) enantiomer as major product], after purification by flash chromatography. [d] No reaction.

(Entries 3 and 5), which contrasts with the results obtained with proline amide ligands.[4c] On the other hand, the bis(amino amide) **4** furnished the alcohol in moderate yield (60%) and *ee* (52%) (Entry 7).

We next investigated the hydride transfer reaction in the $HCOOH/Et_3N$ mixture (conditions B). The best result in terms of reactivity and enantioselectivity was obtained with ligand **3** (40% yield, 50% *ee*) (Table 1, Entry 6). However, this result is worse than the one obtained with the amino alcohol **1** in *i*PrOH in the presence of potassium hydroxide.

Thus, we decided to use ligand **1** to extend this reaction to several aromatic ketones (Table 2).

Table 2. (*S*,*S*,*S*)-Perhydroindolylmethanol **1** as ligand in the hydride transfer reaction with aromatic ketones.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	H	99	60
2	F	33	57
3	Cl	55	40
4	OMe	84	40

[a] Conditions: ketone/KOH/**1**/Ru, 100:5:2:1, *i*PrOH, room temp., 16 h. [b] Isolated yield. [c] Determined by HPLC analysis, with Chiralcel OD-H chiral columns [(*S*) enantiomer as major product], after purification by flash chromatography.

The scope of the hydride transfer reaction catalyzed by ruthenium complex/**1** in the presence of KOH in isopropyl alcohol with 1′-substituted aromatic ketones gave moderate to good yields and reasonable enantioselectivities (Table 2). The catalyst tolerated the presence of methoxy and halide substituents on the *ortho* position of the phenyl ring.

Conclusions

Very efficient methods for the synthesis of amides **2**,**3** and C_2-symmetrical bis(amides) **4**–**6** based on the (*S*,*S*,*S*)-perhydroindole skeleton have been disclosed. These compounds are the first members of a new class of perhydroindole compounds with potential properties as polydentate nitrogen ligands. They have been evaluated in the asymmetric transfer hydrogenation of *ortho*-substituted acetophenone (up to 62% *ee*). These C_1- and C_2-symmetrical aza derivatives provided encouraging results and will be tested in other enantioselective reactions.

Experimental Section

General Remarks: Most experiments were carried out under argon. Solvents were dried and purified in the usual manner. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance 200- or 300-DPX spectrometers. Chemical shifts are given in ppm, referenced to the residual proton resonance of the solvent. ^{13}C NMR multiplicity is reported with respect to proton (deduced from DEPT experiments; s, quaternary C; d, CH; t, CH_2; q, CH_3). High resolution mass spectra with electronic impact (HRMS-EI) or electrospray ionization (MS-ESI) were obtained with a Varian Mat 311 or a Micromass MS/MS ZABSpec TOF, respectively. TLC was performed on Merck $60F_{254}$ silica gel plates, and all compounds were purified by flash chromatography with Merck Si 60 silica gel (40–63 μm). HPLC analyses were carried out with a Waters 1515 chromatograph equipped with a Waters 2487 UV detector, using Daicel Chiralpack AS or Chiralcel OD-H chiral columns.

(2*S*,3a*S*,7a*S*)-Octahydro-1*H*-indole-2-carboxamide (2): To a solution of amide **13** (134 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TFA (2.5 mL). After 4 h at 0 °C, CH_2Cl_2 and TFA were removed under reduced pressure, and the crude material was purified by flash chromatography (CH_2Cl_2/MeOH) to afford 84 mg (100%) of **2** as a white solid. ^1H NMR (200 MHz, CD_3OD): δ = 3.89 (dd, J = 9.1, 7.2 Hz, 1 H), 3.29 (m, 1 H), 2.30–1.95 (m, 2 H), 1.75–1.10 (m, 9 H) ppm. HRMS-EI: calcd. 124.11262 [M – $CONH_2$]$^+$; found 124.1122.

(2*S*,3a*S*,7a*S*)-*N*-Phenyloctahydro-1*H*-indole-2-carboxamide (3): Compound **14** was subjected to the same procedure that produced compound **2** to yield **3** (100%). ^1H NMR (200 MHz, CD_3OD): δ = 7.63 (d, J = 8.1 Hz, 2 H), 7.35 (dd, J = 8.1, 7.4 Hz, 2 H), 7.15 (t, J = 7.4 Hz, 1 H), 4.51 (dd, apparent t, J = 8.5 Hz, 1 H), 3.80 (dt, J = 8.6, 5.6 Hz, 1 H), 2.63–2.42 (m, 2 H), 2.23–2.18 (m, 1 H), 2.05–1.88 (m, 1 H), 1.82–1.60 (m, 4 H), 1.54–1.36 (m, 3 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 167.4 (s), 138.2 (s), 129.0 (d), 124.9 (d), 120.3 (d), 59.8 (d), 59.6 (d), 37.9 (d), 33.1 (t), 25.1 (t), 24.8 (t), 22.5 (t), 20.8 (t) ppm.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-*N*,*N*′-(Ethane-1,2-diyl)bis(octahydro-1*H*-indole-2-carboxamide) (4): Compound **15** was subjected to the same procedure that produced compound **2** to yield **4** (100%). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.33 (dd, apparent t, J = 8.6 Hz, 2 H), 3.80 (dt, J = 8.9, 5.5 Hz, 2 H), 3.44 (ddd, J = 18.7, 11.4, 2.4 Hz, 4 H), 2.54–2.39 (m, 4 H), 2.13–2.0 (m, 2 H), 2.0–1.89 (m, 2 H),

1.78–1.57 (m, 8 H), 1.54–1.36 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2 (s), 59.2 (d), 58.6 (d), 39.1 (t), 37.5 (d), 32.4 (t), 24.7 (t), 24.3 (t), 22.0 (t), 20.4 (t) ppm. HRMS-ESI: calcd. 363.2760 $[M + H]^+$; found 363.2762.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-*N*,*N*′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis(octahydro-1*H*-indole-2-carboxamide) (5): Compound **16** was subjected to the same procedure that produced compound **2** to yield **5** (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.4 Hz, 4 H), 7.40–7.27 (m, 6 H), 5.91 (apparent s, 2 H), 4.44 (dd, apparent t, J = 8.7 Hz, 2 H), 3.62 (m, 2 H), 2.36–2.17 (m, 4 H), 1.80–1.70 (m, 2 H), 1.65–1.46 (m, 4 H), 1.44–1.22 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6 (s), 138.6 (s), 128.1 (d), 127.2 (d), 126.5 (d), 59.2 (d), 58.5 (d), 57.2 (d), 37.2 (d), 32.4 (t), 24.4 (t), 24.0 (t), 22.0 (t), 20.1 (t) ppm. HRMS-EI: calcd. 514.33078 $[M^+]$; found 514.3300.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-*N*,*N*′-[(1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl]bis(octahydro-1*H*-indole-2-carboxamide) (6): Compound **17** was subjected to the same procedure that produced compound **2** to yield **6** (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.4 Hz, 4 H), 7.40–7.27 (m, 6 H), 5.91 (apparent s, 2 H), 4.44 (dd, apparent t, J = 8.7 Hz, 2 H), 3.62 (m, 2 H), 2.36–2.17 (m, 4 H), 1.80–1.70 (m, 2 H), 1.65–1.46 (m, 4 H), 1.44–1.22 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6 (s), 138.6 (s), 128.1 (d), 127.2 (d), 126.5 (d), 59.2 (d), 58.5 (d), 57.2 (d), 37.2 (d), 32.4 (t), 24.4 (t), 24.0 (t), 22.0 (t), 20.1 (t) ppm. HRMS-EI: calcd. 514.33078 $[M^+]$; found 514.3305.

(2*S*,3a*S*,7a*S*)-1-(Benzyloxycarbonyl)octahydro-1*H*-indole-2-carboxylic Acid (8): To a solution of NaOH (2.64 g, 66 mmol, 1.1 equiv.) in a mixture of EtOH (150 mL) and H_2O (250 mL) at 10–15 °C was added the amino acid **7** (10.2 g, 60 mmol) in one portion followed by benzyl chloroformate (8.95 mL, 63 mmol, 1.05 equiv.) while keeping the solution at pH = 9–10 by adding a 1 N NaOH aqueous solution. After 16 h at room temp., the EtOH was removed under reduced pressure and the resulting aqueous solution was acidified to pH = 1 by adding a 6 N HCl aqueous solution. The white residue was dissolved and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (heptane/EtOAc gradient 30:70–0:100) to afford **8** (13.7 g, 75%) as a colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$, 2 rotamers): δ = 8.5 (s, 1 H), 7.40–7.26 (m, 5 H), 5.15 (d, J = 11.7 Hz, 2 H), 4.37 (m, 1 H), 3.90 (m, 1 H), 2.34 (m, 1 H), 2.20 (m, 2 H), 2.01 (m, 1 H), 1.80–1.58 (m, 3 H), 1.56–1.10 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 2 rotamers): δ = 178.1 (s), 177.7 (s), 155.5 (s), 154.6 (s), 137.0 (s), 136.9 (s), 128.9 (d), 128.8 (d), 128.4 (d), 128.2 (d), 127.9 (d), 67.5 (t), 59.6 (d), 59.3 (d), 58.4 (d), 58.0 (d), 37.4 (d), 36.9 (d), 33.0 (t), 31.8 (t), 28.3 (t), 27.7 (t), 26.1 (t), 24.1 (t), 20.8 (t) ppm.

(2*S*,3a*S*,7a*S*)-Benzyl 2-Carbamoyloctahydro-1*H*-indole-1-carboxylate (9): To a solution of amino acid **8** (303 mg, 1 mmol) in THF (10 mL) at 0 °C under argon were successively added triethylamine (135 μL, 0.95 mmol, 0.95 equiv.) and ethyl chloroformate (90 μL, 0.95 mmol, 0.95 equiv.). After 30 min at 0 °C, the solution was cooled to –78 °C, and $NaNH_2$ (35 mg, 0.9 mmol, 0.9 equiv.) was quickly added. The mixture was then warmed to 0 °C over 1 h, stirred at 0 °C during 1 h and then at room temperature overnight. The reaction was quenched by addition of water and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford **9** (187 mg, 62%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H), 5.14 (m, 2 H), 4.27 (m, 1 H), 3.92 (m, 1 H), 2.30–1.85 (m, 4 H), 1.75–1.10 (m, 7 H) ppm.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-Dibenzyl 2,2′-[Ethane-1,2-diylbis(azanediyl)]bis(oxomethylene)bis(octahydro-1*H*-indole-1-carboxylate) (10): To a solution of amino acid **8** (1.3 g, 4.3 mmol), EDCI (1.23 g, 6.4 mmol, 1.5 equiv.) and DMAP (52 mg, 0.43 mmol, 0.1 equiv.) in a mixture of CH_2Cl_2 (50 mL) and THF (15 mL) was added ethylenediamine (170 μL, 2.6 mmol, 0.6 equiv.). After 16 h at room temp., the reaction was quenched by addition of H_2O and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (heptane/EtOAc, 60:40) to afford **10** (600 mg, 64%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (m, 2 H), 7.40–7.30 (m, 10 H), 5.11 (dd, J = 17.4, 12.6 Hz, 4 H), 4.18 (m, 2 H), 3.84 (m, 2 H), 3.53 (m, 2 H), 3.21 (m, 2 H), 2.30–2.20 (m, 4 H), 2.10–1.95 (m, 4 H), 1.90–1.10 (m, 14 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7 (s), 155.4 (s), 137.1 (s), 128.9 (d), 128.4 (d), 128.2 (d), 67.4 (t), 61.7 (d), 58.2 (d), 38.0 (t), 37.4 (d), 31.7 (t), 28.3 (t), 26.3 (t), 24.2 (t), 20.8 (t) ppm.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-Dibenzyl 2,2′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis(azanediyl)bis(oxomethylene)bis(octahydro-1*H*-indole-1-carboxylate) (11): The same procedure was applied as for compound **10**, replacing ethylenediamine by (*S*,*S*)-diphenylethylenediamine to yield **11** (15%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 20 H), 5.26 (m, 2 H), 5.09 (m, 2 H), 4.36–4.24 (m, 4 H), 3.95 (m, 2 H), 2.30–1.85 (m, 8 H), 1.70–1.10 (m, 14 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.5 (s), 140.8 (s), 129.0 (d), 128.9 (d), 128.8 (d), 128.4 (d), 128.2 (d), 127.9 (d), 127.7 (d), 127.1 (d), 126.9 (d), 67.5 (t), 60.1 (d), 59.4 (d), 58.7 (d), 37.1 (d), 28.8 (t), 26.2 (t), 24.2 (t), 20.9 (t) ppm.

(2*S*,3a*S*,7a*S*)-1-(*tert*-Butoxycarbonyl)octahydro-1*H*-indole-2-carboxylic Acid (12): To a solution of amino acid **7** (3.38 g, 20 mmol), $(Boc)_2O$ (4.36 g, 20 mmol, 1 equiv.) and DMAP (244 mg, 2 mmol, 0.1 equiv.) in CH_2Cl_2 (40 mL) was added triethylamine (5.6 mL, 40 mmol, 2 equiv.). After 16 h at reflux, the mixture was cooled, the reaction quenched by addition of a 1 N HCl aqueous solution, and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to afford **12** (5.2 g, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 (m, 1 H), 3.82 (m, 1 H), 2.40–1.85 (m, 4 H), 1.80–1.60 (m, 3 H), 1.60–1.10 (m, 4 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0 (s), 154.7 (s), 79.9 (s), 59.4 (d), 57.9 (d), 37.0 (d), 28.8 (q), 28.2 (t), 28.0 (t), 26.2 (t), 24.1 (t), 20.9 (t) ppm. HRMS-EI: calcd. 224.16505 $[M – COOH]^+$; found 224.1643.

(2*S*,3a*S*,7a*S*)-*tert*-Butyl-2-carbamoyloctahydro-1*H*-indole-1-carboxylate (13): To a solution of amino acid **12** (269 mg, 1 mmol) in THF (10 mL) at 0 °C under argon were successively added triethylamine (135 μL, 0.95 mmol, 0.95 equiv.) and ethyl chloroformate (90 μL, 0.95 mmol, 0.95 equiv.). After 30 min at 0 °C, the solution was cooled to –78 °C, and $NaNH_2$ (35 mg, 0.9 mmol, 0.9 equiv.) was quickly added. The mixture was then warmed to 0 °C over 1 h, stirred at 0 °C for 1 h, and at room temperature overnight. The reaction was quenched by addition of H_2O and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford **13** (215 mg, 80%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.21 (m, 1 H), 3.82 (m, 1 H), 2.35–2.10 (m, 3 H), 1.95 (m, 1 H), 1.80–1.60 (m, 3 H), 1.58–1.15 (m, 4 H), 1.47 (s, 9 H) ppm.

(2*S*,3a*S*,7a*S*)-*tert*-Butyl-2-(phenylcarbamoyl)octahydro-1*H*-indole-1-carboxylate (14): The same procedure was applied as for compound **13**, replacing $NaNH_2$ with $PhNH_2$ to give **14** (52%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.0 Hz, 2 H), 7.30 (dd, apparent t, J = 7.8 Hz, 2 H), 7.07 (dd, apparent t, J = 7.3 Hz, 1 H), 4.39 (dd, apparent t, J = 8.1 Hz, 1 H), 3.91 (dt, J = 10.6, 5.4 Hz, 1 H), 2.45–2.25 (m, 2 H), 2.20–1.90 (m, 2 H), 1.80–1.60 (m, 3 H), 1.55–1.15 (m, 5 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1 (s), 138.6 (s), 129.3 (d), 124.4 (d), 120.0 (d), 81.0 (s), 58.6 (d), 53.9 (t), 37.1 (d), 30.2 (t), 28.9 (q), 26.4 (t), 24.3 (t), 20.9 (t) ppm.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-Di-*tert*-butyl 2,2′-[Ethane-1,2-diylbis(azanediyl)]bis(oxomethylene)bis(octahydro-1*H*-indole-1-carboxylate) (15): To a solution of amino acid **12** (269 mg, 1 mmol), EDCI (211 mg, 1.1 mmol, 1.1 equiv.), HOBt (149 mg, 1.1 mmol, 1.1 equiv.) and ethylene diamine (33 μL, 0.5 mmol, 0.5 equiv.) in CH_2Cl_2 (2 mL) was added $NaHCO_3$ (336 mg, 4 mmol, 4 equiv.). After 24 h at room temp., the reaction was quenched by addition of H_2O and the mixture extracted with CH_2Cl_2. The combined extracts were successively washed with a saturated aqueous solution of $NaHCO_3$, a 1 N HCl aqueous solution, and brine, then dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (heptane/EtOAc) to afford **15** (473 mg, 84%) as a white solid. ^{1}H NMR (MHz, $CDCl_3$): δ = 4.11 (dd, apparent t, J = 8.2 Hz, 2 H), 3.75 (m, 2 H), 3.47 (m, 2 H), 3.27 (m, 2 H), 2.34–2.10 (m, 6 H), 1.98 (m, 4 H), 1.76–1.54 (m, 6 H), 1.52–1.10 (m, 6 H), 1.43 (s, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7 (s), 154.5 (s), 79.8 (s), 61.1 (d), 57.8 (d), 36.8 (d), 36.8 (t), 31.4 (t), 28.5 (q), 26.0 (t), 23.9 (t), 20.5 (t) ppm. HMRS-ESI: calcd. 585.3628 $[M + Na]^+$; found 585.3630. HMRS-EI: calcd. 562.37304$[M]^+$; found 562.3713. HMRS-EI: calcd. 461.31278 $[M – Boc]^+$; found 461.3131.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-Di-*tert*-butyl 2,2′-[(1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl]bis(azanediyl)bis(oxomethylene)bis(octahydro-1*H*-indole-1-carboxylate) (16): The same procedure was applied as for compound **15**, replacing ethylenediamine by (*S*,*S*)-diphenylethylenediamine to yield **16** (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.09 (m, 10 H), 5.28 (br. d, J = 5.1 Hz, 2 H), 4.22 (m, 2 H), 3.78 (m, 2 H), 2.20 (m, 2 H), 1.93 (m, 2 H), 1.80–1.05 (m, 18 H), 1.32 (s, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8 (s), 155.1 (s), 138.5 (s), 128.3 (d), 127.5 (d), 80.1 (s), 60.1 (d), 58.7 (d), 58.0 (d), 36.5 (d), 28.3 (q), 28.1 (t), 25.9 (t), 23.7 (t), 20.5 (t) ppm. HRMS-ESI: calcd. 737.4254 $[M + Na]^+$; found 737.4251.

(2*S*,2′*S*,3a*S*,3a′*S*,7a*S*,7a′*S*)-Di-*tert*-butyl 2,2′-[(1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl]bis(azanediyl)bis(oxomethylene)bis(octahydro-1*H*-indole-1-carboxylate) (17): The same procedure was applied as for compound **15**, replacing ethylenediamine by (*R*,*R*)-diphenylethylenediamine (73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.09 (m, 10 H), 5.28 (br. d, J = 5.1 Hz, 2 H), 4.22 (m, 2 H), 3.78 (m, 2 H), 2.20 (m, 2 H), 1.93 (m, 2 H), 1.80–1.05 (m, 18 H), 1.32 (s, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8 (s), 155.1 (s), 138.5 (s), 128.3 (d), 127.5 (d), 80.1 (s), 60.1 (d), 58.7 (d), 58.0 (d), 36.5 (d), 28.3 (q), 28.1 (t), 25.9 (t), 23.7 (t), 20.5 (t) ppm.

General Hydride Transfer Procedure Using *i*PrOH: [(*p*-cymene)-$RuCl_2]_2$ (6 mg, 0.01 mmol, 0.5 mol-%) and the ligand (0.04 mmol, 2 mol-%) were stirred under argon in *i*PrOH (6 mL) at reflux for 20 min. The solution was cooled, and then *i*PrOH (14 mL), the ketone (2 mmol), and KOH (5 mol-%) were successively added. The mixture was stirred for the indicated time under argon at room temperature, filtered though Celite, rinsed with diethyl ether, and concentrated under reduced pressure. The crude product was purified by flash chromatography (heptane/ethyl acetate) to provide the desired alcohol.

General Hydride Transfer Procedure Using HCOOH/NEt_3: [(*p*-cymene)$RuCl_2]_2$ (6 mg, 0.01 mmol, 0.5 mol-%) and the ligand (0.04 mmol, 2 mol-%) were stirred under argon in *i*PrOH (6 mL) at reflux for 20 min. The solvent was removed under reduced pressure, and then CH_2Cl_2 (0.5 mL, if noted), NEt_3 (560 μL, 4 mmol, 2 equiv.), HCOOH (380 μL, 10 mmol, 5 equiv.) and the ketone (2 mmol) were successively added, and the solution was stirred for the indicated time under argon at room temperature (or at 45 °C if CH_2Cl_2 was used). CH_2Cl_2 was added, the reaction was quenched by addition of an aqueous solution of HCl (1 N), and the mixture extracted using CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (heptane/ethyl acetate) to provide the desired alcohol.

In both procedures, the absolute configuration of the major enantiomer, and the enantiomeric excesses were determined by HPLC on a Daicel Chiralcel OD-H chiral column.

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