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Dynamic Kinetic Resolution of 2-Oxocycloalkanecarbonitriles: Chemoenzymatic Syntheses of Optically Active Cyclic β- and γ-Amino Alcohols

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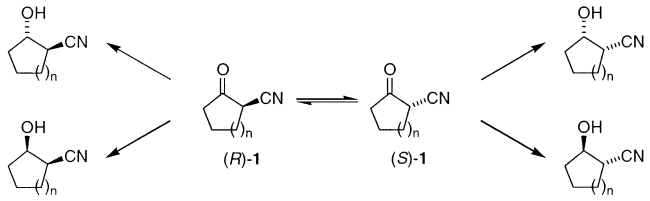
Abstract: A series of fungi and yeasts have been tested for the stereoselective bioreduction of 2-oxocycloalkanecarbonitriles, **1**. The yeast *Saccharomyces montanus* CBS 6772 yielded the corresponding *cis*-hydroxy nitriles, **2**, in >90% ee and de and in high chemical yields. Through simple and efficient procedures, they were transformed into optically active 2-amino and 2-aminomethyl cycloalkanols.

The preparation of optically active amino alcohols has received considerable attention in recent years due to their importance in both medicinal chemistry[1] and asymmetric synthesis.[2] In this context, cyclic compounds are of the utmost importance because of their conformational restrictions.

To date, several enzymatic procedures for the kinetic resolution of racemic mixtures of 2-aminocycloalkanols[3,4] and 2-aminomethylcycloalkanols[5] have been described. However, they suffer from the main disadvantage of this kind of resolutions: the theoretical impossibility of reaching 100% of both chemical yield and enantiomeric excess. To overcome this limitation, a great effort has been devoted to create processes that afford the product with the same high enantiomeric purity but in significantly improved yield.[6]

We have been interested in the bioreduction of α-unsubstituted β-keto nitriles by whole cells[7] as potential precursors of optically active γ-amino alcohols. In this study, we also found and optimized a competing reaction, which introduced an alkyl chain at the α-position, therefore yielding β-hydroxy nitriles with two contiguous chiral centers.[8,9]

SCHEME 1



Continuing this study and encouraged by the high enantio- and diastereoselectivity of these processes, we decided to extend the methodology to 2-oxocycloalkanecarbonitriles, **1**, as suitable precursors of cyclic amino alcohols. The high acidity of the α-hydrogen[10] would cause racemization of the substrate in water and allow for a dynamic kinetic resolution (see Scheme 1), as has been previously described for β-keto esters,[11,12] β-keto amides,[13] and β-diketones.[14]

The importance of this acidic α-hydrogen must be emphasized, since β-keto nitriles fully substituted at the α-position do not racemize under the biotransformation conditions and are reduced through a parallel kinetic resolution, therefore yielding both enantioenriched diastereomers of the corresponding β-hydroxy nitriles containing a quaternary stereocenter.[15]

The bioreduction of α-monosubstituted β-keto nitriles has been scarcely reported in the literature: Itoh described that baker's yeast-mediated bioreduction of acyclic substrates resulted in a nearly equimolar mixture of diastereomers in most cases.[16] On the other hand, Azerad studied the microbial reduction of a couple of 2-cyano-1-tetralones.[17]

The selection of compounds **1** was made on the basis of its ready availability from inexpensive alkanedinitriles through a Thorpe−Ziegler reaction,[18] which would make this a good strategy for the preparation of the abovementioned amino alcohols.

To confirm our hypothesis of easy racemization of the substrates, the pK_a of compound **1a** was measured by potentiometry, in a 0.1 mol/L NMe_4Cl solution at 298 K, obtaining a value as low as 7.84. This high acidity of β-keto nitriles (considerably higher than that of the analogous β-keto esters) had been previously reported.[10]

The results obtained in the bioreduction of **1a** with several fungal and yeast strains at an analytical scale are summarized in Table 1. With fungi, a low stereoselectivity was observed. In contrast, when yeasts were

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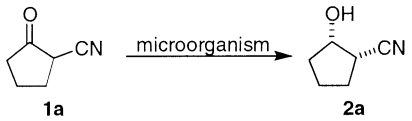
TABLE 1. Bioreduction of 1a by Several Microbial Strains at an Analytical Scale[a]

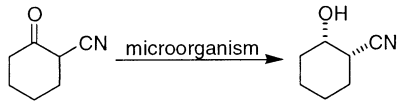


1a **2a**

microorganism	cis:trans[b,c]	ee_{cis} (%)[b]	absolute configuration
baker's yeast	95:5	90	1*S*,2*S*
Saccharomyces montanus NRRL 6772	96:4	93	1*S*,2*S*
Curlvularia lunata CECT 2130	53:47	41	1*R*,2*R*
Mortierella isabellina NRRL 1757	65:35	48	1*S*,2*S*
Beauveria bassiana ATCC 7159	50:50	21	1*S*,2*S*

[a] Typically, the substrate (35 mg) and ethanol (350 μL) were added to a 35 mL culture. [b] Determined by chiral GC. [c] The ee and the absolute configuration of the trans isomer have not been determined.

TABLE 2. Bioreduction of 1b by Several Microbial Strains at an Analytical Scale[a]



1b **2b**

microorganism	cis:trans[b]	ee_{cis} (%)[b]	absolute configuration	ee_{trans} (%)[b,c]
baker's yeast	87:13	65	1*S*,2*S*	26
S. montanus NRRL 6772	95:5	87	1*S*,2*S*	8
C. lunata CECT 2130	70:30	17	1*S*,2*S*	46
M. isabellina NRRL 1757	71:29	71	1*S*,2*S*	60
B. bassiana ATCC 7159	30:70	72	1*S*,2*S*	89

[a] Typically, the substrate (35 mg) and ethanol (350 μL) were added to a 35 mL culture. [b] Determined by chiral GC. [c] Absolute configuration of the trans isomer has not been determined.

used, a very high stereoselectivity occurred: with both strains, *cis*-**2a** was obtained as the major diastereomer and in high enantiomeric excess.

With *Saccharomyces montanus*, the most promising strain, some modifications of the reaction conditions were made to optimize the process for an efficient preparative scale: the use of resting cells instead of growing cells resulted in a sharp decrease in the stereoselectivity. On the contrary, the addition of the substrate at an early stage of the culture growth (8 h after inoculation) resulted in a higher cis:trans ratio (99:1) as well as ee_{cis} (97%). However, and despite our efforts, substrate concentrations higher than 1 g/L resulted in incomplete conversions.

When this was repeated at the gram scale, using 1 g of **1a**, 10 mL of ethanol, and 1 L of culture, we obtained **2a** in 89% chemical yield and 97% ee after removing the traces of the trans isomer by column chromatography.

The same screening for a suitable biocatalyst was carried out for the bioreduction of the six-membered ring (see Table 2).

Again, the best results were obtained with the yeast *S. montanus*. In this case, the use of resting cells instead of growing cells resulted in a slight increase in the ee_{cis} (up to 93%). Cells were resuspended in distilled water instead of phosphate buffer to facilitate the downstream processing of a hypothetical industrial application.[19] Once again, substrate concentrations higher than 1 g/L led to incomplete conversion. An insufficient ratio of biocatalyst to substrate rather than inhibition by substrate or product was invoked, since a 10-fold concentration of the cells allowed us to carry out the biotransformation at 10 g/L of **1b**.

We carried out the gram-scale bioreduction under the following conditions: 1 g of **1b** and 1 mL of ethanol were added to cells grown in 1 L of medium and resuspended in 100 mL of distilled water. After 1 day, **2b** was obtained in 85% chemical yield and 93% ee. A space−time yield of 8.6 g L^{-1} day^{-1} was calculated.

The fact that the β-hydroxy nitriles, **2**, obtained in the bioreductions had a cis configuration and very high ee values made them very tempting building blocks for the preparation of amino alcohols. It must be emphasized that, whereas for the preparation the *trans*-hydroxy nitriles many strategies have been developed,[20,21] very few examples have been described for the cis isomers.[22,23]

Furthermore, the bioreduction of structurally related 2-oxocyclopentanecarboxamide with *Mortierella isabellina* yielded mainly the trans isomer, and with *B. bassiana*, the cis isomer only with low ee.[13] In the course of our work, a synthesis of cis amino alcohols from the corresponding β-hydroxy esters obtained by baker's yeast-mediated reduction has been described.[24] It must be also mentioned that the bioreduction of analogous β-keto esters by *S. montanus* yielded mainly the cis diastereomers, but in lower diastereomeric excess (ca. 60%).[11]

The pathway followed for the preparation of 2-aminocycloalkanols, **5**, is outlined in Scheme 2. Acidic hydrolysis of the nitrile group at 50 °C yielded the corresponding carboxylic amide, **3**, in nearly quantitative yield. Hofmann rearrangement with iodobenzene diacetate[25,26] at room temperature yielded the oxazolidinones **4**. Epimerization at the stereogenic center α to the amide group was excluded by the high yield (over 90%), together with NMR and TLC analysis of the crude product, and the ee was confirmed by chiral GC. Finally, hydrolysis of **4** by LiOH in a mixture of water and MeOH yielded the β-amino alcohols, which were isolated as their *N*-Cbz derivatives, **5**, in 65−70% global yield.

On the other hand, the reduction of the nitrile group by $LiAlH_4$ in anhydrous Et_2O yielded the corresponding γ-amino alcohols in excellent yields, which were also isolated as their *N*-Cbz derivatives, **6** (Scheme 3). As for compounds **5**, neither by TLC nor by NMR of the crude reaction was the other diastereomer detected.

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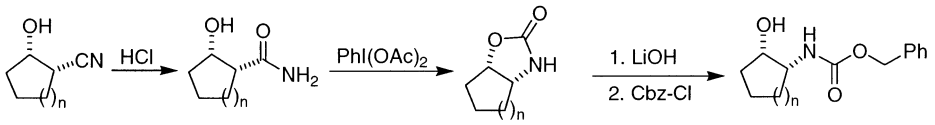
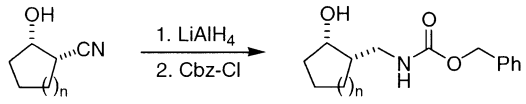
SCHEME 2



2 3 4 5

SCHEME 3



2 6

Although Kanerva and co-workers have recently developed a method for the enzymatic resolution of both *cis*-2-hydroxycycloalkanenitriles, they noticed an impurity affecting the value of the optical rotations, as well as the spectral data. However, the values reported for the trans isomers were incompatible with those obtained in this work.[23] The cis relative configuration of **2b** was confirmed by comparison of its ^{1}H NMR spectral data with those already published for the compound obtained by *syn*-cyanohydroxylation of cyclohexene.[22]

Optically active **3a** and **4a** have also been described, but in only 51% ee.[13] On the other hand, β-amino alcohols, **5**, have been obtained in high ee values.[4] Taken all together, and after discarding epimerization throughout the processes (see above), we could unambiguously assign the configuration of all the products reported herein.

In summary, the enantio- and diastereoselective bioreduction of 2-oxocycloalcanecarbonitriles, **1**, has been accomplished by whole cells of the yeast *S. montanus*. In the case of **1b**, resting cells have been concentrated to work at a higher substrate concentration. The optically active β-hydroxy nitriles have been shown to be suitable building blocks for the preparation of β- and γ-amino alcohols through very efficient procedures. Due to their cis relative configuration, this methodology complements our previously reported procedure for the synthesis of *trans*-2-aminomethyl and 2-aminocyclopentanol.

Experimental Section

General. Fungi and yeasts were obtained from the corresponding culture collections, except baker's yeast type II, which was acquired from Sigma. THF and Et_2O were distilled over sodium and stored under nitrogen. Precoated TLC plates of silica gel 60 F254 were used, while for column chromatography silica gel 60/230−400 mesh was applied. ^{1}H and ^{13}C NMR spectra were carried out in $CDCl_3$, unless otherwise stated. Mass spectra were recorded using electrospray (40 V) as an ionization source. Diastereomeric ratios and ee values were determined by GC analyses using a Rt-βDEXse (30 m × 0.25 mm, Restek) capillary column and nitrogen as the carrier gas (15 psia).

Potentriometric Titration. A Metrohm 702 titrimeter was used, and the reference electrode was an Ag/AgCl electrode in saturated aqueous KCl. The cell was thermostated at 298 ± 0.1 K and the solution stirred, and the measurements were performed under nitrogen. The pK_a value was determined by titration with 0.1 N NaOH of a solution containing 10^{-3} M of compound **1a** in the presence of Me_4NCl (0.1 M). The measurements were carried out twice, and the data analysis was performed with the computer program SUPERQUAD.[27]

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Syntheses of the 2-Oxocycloalkanecarbonitriles, 1. To a suspension of NaH (1.3 g, 55 mmol) in 100 mL of THF was added 50 mmol of the corresponding alkanedinitrile, and the mixture was refluxed until the substrate disappeared (TLC monitoring, eluent 2:1 hexane/AcOEt). Then, the reaction mixture was allowed to reach room temperature; the reaction was quenched with 30 mL of water, and the mixture was extracted with Et_2O. After drying and elimination of the solvent, the enamine formed was hydrolyzed at room temperature with 50 mL of 3 N H_2SO_4, extracted again with Et_2O, and dried and the solvent removed on a rotovapor. The residual oil was further purified by bulb-to-bulb distillation.

Synthesis of Stereoisomeric Mixtures of 2-Hydroxycycloalkanecarbonitriles. To a solution of 1 mmol of **1** in 5 mL of EtOH was added 25 mg (0.7 mmol) of $NaBH_4$, and the mixture was shaken at room temperature overnight. After partial elimination of the solvent, addition of water, and extraction with Et_2O, a pale yellowish oil was obtained, which was used without further purification as a standard for chiral GC analyses (conditions: 100 °C, 15 min; 1 °C/min until 170 °C). t_R (min): (1*S*,2*S*)-**2a**, 34.9; (1*R*,2*R*)-**2a**, 36.9; *trans*-**2a**, 42.4 (both enantiomers); (1*S*,2*S*)-**2b**, 46.6; (1*R*,2*R*)-**2b**, 47.5; *trans*-**2b**, 49.2 and 50.9.

General Procedure for Cultures of *S. montanus* CBS 6772. A loop of a solid culture of *S. montanus* from an agar plate was sown into 35 mL of liquid medium [composed of yeast extract (0.3%), malt extract (0.3%), D-glucose (1%), and bactopeptone (0.5%) in distilled water]. After the culture had grown for over 60 h (rotatory shaker, 28 °C, 200 rpm), 5 mL of it were used to inoculate 1 L of fresh medium, which was cultured under the same conditions.

Bioreduction with Growing Cells. 2-Oxocyclopentanecarbonitrile (1 g), **1a**, and 10 mL of EtOH were added to growing cells of *S. montanus* (grown for 8 h in 1 L of medium), and the biotransformation was carried out at 28 °C and 200 rpm. After 4 days, no more substrate was left (TLC monitoring), and the culture was continuously extracted with CH_2Cl_2 over 12 h. Flash chromatography (3:1 eluent hexane/Et_2O) of the crude reaction yielded 0.91 g of (1*S*,2*S*)-**2a**.

(1*S*,2*S*)-2-Hydroxycyclopentanecarbonitrile, 2a: yield 89%, colorless oil; $[\alpha]_D^{20}$ +6.0 (*c* 1.0, CH_2Cl_2); ee 97%; IR ν (cm^{-1}) 2245, 3426; ^{1}H NMR δ (ppm) 1.55−2.25 (m, 6H), 2.74 (m, 1H, CH−CN), 3.0 (bs, 1H, OH), 4.4 (m, 1H, CH−O); ^{13}C NMR δ (ppm) 21.8, 27.8, 33.4 (CH_2), 36.4 (*C*H−CN), 73.4 (CH−O), 120.4 (CN); ESIMS *m*/*z* 134 (M + Na)$^+$. Anal. Calcd for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.59; H, 8.25; N, 12.51.

Bioreduction with Resting Cells. 2-Oxocyclohexanecarbonitrile (1 g), **1b**, and 1 mL of EtOH were added to cells of *S. montanus* (grown for 36 h in 1 L of medium, centrifuged, and resuspended in 100 mL of distilled water), and the biotransformation was carried out at 28 °C and 200 rpm. After 48 h, no more substrate was left (TLC monitoring), and the culture was continuously extracted with CH_2Cl_2 over 12 h. Flash chromatography (eluent 3:1 hexane/Et_2O) of the crude reaction yielded 0.86 g of (1*S*,2*S*)-**2b**.

(1*S*,2*S*)-2-Hydroxycyclohexanecarbonitrile, 2b: yield 85%, colorless oil; $[\alpha]_D^{20}$ −26.9 (*c* 1.0, CH_2Cl_2); ee 93%; IR ν (cm^{-1}) 2244, 3425; ^{1}H NMR δ (ppm) 1.25−1.4 (m, 1H), 1.5−1.9 (m, 6H), 1.95−2.1 (m, 1H), 2.43 (bs, 1H, OH), 3.0 (m, 1H, CH−CN), 3.8 (m, 1H, CH−O); ^{13}C NMR δ (ppm) 21.8, 22.5, 26.4, 31.6 (CH_2), 36.0 (CH−CN), 68.4 (CH−O), 120.2 (CN); ESIMS *m*/*z* 148 (M + Na)$^+$. Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.01; H, 9.02; N, 11.07.

General Procedure for Hydrolyses of the β-Hydroxy Nitriles 2. The corresponding nitrile **2** (1 mmol) was solved in

2 mL of concentrated HCl and the solution shaken at 50 °C for 2 h. The solution was placed on an ice bath, and 0.7 g NaOH was added and then $NaHCO_3$ until neutralization. Then, the solution was continuously extracted with AcOEt for 6 h, and after purification by flash chromatography (1:3 eluent hexane/AcOEt), the corresponding amide **3** was obtained.

(1*R*,2*S*)-2-Hydroxycyclopentanecarboxamide, 3a: yield 96%, white solid; mp 100−101 °C; $[\alpha]_D^{20}$ +29.3 (*c* 1.7, EtOH); ee 97%; IR ν (cm^{-1}) 1673; ^1H NMR (CD_3OD) δ (ppm) 1.75−2.25 (m, 6H), 2.78 (m, 1H, CH−CO), 4.57 (m, 1H, CH−O); ^{13}C NMR (CD_3OD) δ (ppm) 23.6, 28.4, 36.2 (CH_2), 52.0 (*C*H−CO), 76.1 (CH−O), 180.3 (CO); ESIMS *m*/*z* 152 $(M + Na)^+$. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.52; H, 8.78; N, 10.70.

(1*R*,2*S*)-2-Hydroxycyclohexanecarboxamide, 3b: yield 94%, white solid; mp 121−122 °C; $[\alpha]_D^{20}$ +24.1 (*c* 1.0, EtOH); ee 93%; IR ν (cm^{-1}) 1670; ^1H NMR (CD_3OD) δ (ppm) 1.45−2.2 (m, 8H), 2.54 (ddd, 1H, CH−CO, J = 2.6, 3.7, 11.6 Hz), 4.33 (m, 1H, CH−O); ^{13}C NMR (CD_3OD) δ (ppm) 20.9, 25.2, 26.0, 33.3 (CH_2), 48.4 (CH−CO), 68.2 (CH−O), 181.0 (CO); ESIMS *m*/*z* 166 $(M + Na)^+$. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.68; H, 9.31; N, 9.65.

Hofmann Rearrangement of the Amides 3. Iodobenzene diacetate (1.3 mmol) was added to a solution of the corresponding amide **3** (1 mmol) in 2.5:1 THF/MeOH (5 mL). The mixture was stirred at room temperature until the substrate disappeared (TLC monitoring, 2 h). Then, the solvents were removed under vacuum, and the resulting residue was purified by flash chromatography (3:2 eluent hexane/AcOEt).

(3a*R*,6a*S*)-Perhydrocyclopenta[*d*]oxazol-2-one, 4a: yield 93%, white solid; mp 129−130 °C; $[\alpha]_D^{20}$ −44.4 (*c* 1.1, $CHCl_3$); ee 97%; IR ν (cm^{-1}) 1753, 3459; ^1H NMR δ (ppm) 1.5−1.85 (m, 5H), 2.05−2.1 (m, 1H), 4.26 (m, 1H, CH−N), 5.04 (m, 1H, CH−O), 6.39 (bs, 1H, NH); ^{13}C NMR δ (ppm) 21.9, 33.8, 34.4 (CH_2), 56.7 (CH−N), 82.3 (CH−O), 160.3 (CO); ESIMS *m*/*z* 150 $(M + Na)^+$. Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.50; H, 7.22; N, 10.91. GC conditions: 170 °C, 10 min; 2 °C/min until 200 °C. t_R (min): (3a*S*,6a*R*)-**4a**, 14.8; (3a*R*,6a*S*)-**4a**, 15.1.

(3a*R*,7a*S*)-Perhydrobenzo[*d*]oxazol-2-one, 4b: yield 94%, white solid; mp 92−93 °C; $[\alpha]_D^{20}$ −28.8 (*c* 1.4, $CHCl_3$); ee 93%; IR ν (cm^{-1}) 1757; ^1H NMR δ (ppm) 1.2−1.35 (m, 1H), 1.35−1.65 (m, 4H), 1.65−1.85 (m, 2H), 1.9−2.0 (m, 1H), 3.72 (m, 1H, CH−N), 4.55 (m, 1H, CH−O), 6.40 (bs, 1H, NH); ^{13}C NMR δ (ppm) 19.3, 19.6, 26.5, 28.4 (CH_2), 51.5 (CH−N), 75.8 (CH−O), 160.8 (CO); ESIMS *m*/*z* 164 $(M + Na)^+$. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.24; H, 8.01; N, 9.80. GC conditions: 170 °C, 10 min; 2 °C/min until 200 °C. t_R (min): (3a*S*,7a*R*)-**4b**, 18.2; (3a*R*,7a*S*)-**4b**, 18.5.

Hydrolyses of the Oxazolidinones 4. The corresponding compound **4** (0.5 mmol) was added to a solution of LiOH (100 mg) in 2.5 mL of an 8:1 water/methanol mixture. After the mixture was refluxed for 2 h, solvents were evaporated, and the residue was solved in Et_2O, filtered, and concentrated again. To the oil obtained were added Na_2CO_3 (0.6 mmol), water (1 mL), and benzyl chloroformate (1 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and shaken overnight. After extraction with CH_2Cl_2, the product was isolated by column chromatography (eluent 2:1 hexane/AcOEt).

Benzyl (1*R*,2*S*)-*N*-(2-Hydroxycyclopentyl)carbamate, 5a: yield 76%, white solid; mp 55−56 °C; $[\alpha]_D^{20}$ +35.0 (*c* 1.3, EtOH); ee 97%; IR ν (cm^{-1}) 1717; ^1H NMR δ (ppm) 1.45−1.7 (m, 3H), 1.7−2.0 (m, 3H), 2.17 (bs, 1H, OH), 3.86 (m, 1H, CH−N), 4.15 (m, 1H, CH−O), 5.09 (s, 2H, CH_2−O), 5.27 (m, 1H, NH), 7.37 (m, 5H, arom); ^{13}C NMR δ (ppm) 20.0, 28.9, 32.4 (CH_2), 55.7 (CH−N), 66.7 (CH_2−O), 72.5 (CH−O), 128.0, 128.4 (CH_{arom}), 136.3 (C_{arom}), 156.2 (CO); ESIMS *m*/*z* 258 $(M + Na)^+$. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.33; H, 7.35; N, 5.81.

Benzyl (1*R*,2*S*)-*N*-(2-Hydroxycyclohexyl)carbamate, 5b: yield 73%, white solid; mp 51−52 °C; $[\alpha]_D^{20}$ +32.5 (*c* 1.7, EtOH); ee 93%; IR ν (cm^{-1}) 1715; ^1H NMR δ (ppm) 1.3−1.75 (m, 8H), 2.16 (bs, 1H, OH), 3.65 (m, 1H, CH−N), 3.94 (m, 1H, CH−O), 5.08 (s, 2H, CH_2−O), 5.25 (m, 1H, NH), 7.35 (m, 5H, arom); ^{13}C NMR δ (ppm) 19.7, 23.6, 27.2, 31.5 (CH_2), 52.4 (CH−N), 66.6 (CH_2−O), 68.9 (CH−O), 128.0, 128.1, 128.4 (CH_{arom}), 136.3 (C_{arom}), 156.1 (CO); ESIMS *m*/*z* 272 $(M + Na)^+$. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.28; H, 7.89; N, 5.49.

Reduction of Nitriles 2. To a solution of the corresponding nitrile **2** (1 mmol) in anhydrous THF (5 mL) at 0 °C was added an excess of $LiAlH_4$ (5 mmol), and the suspension was allowed to reach room temperature with stirring. After 1 h, the reaction was quenched with water (1 mL) and the mixture extracted several times with Et_2O. Solvent was removed on a rotovapor, and to the residual oil were added Na_2CO_3 (1.2 mmol), water (2 mL), and benzyl chloroformate (1.2 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and shaken overnight. After extraction with CH_2Cl_2, the product was isolated by column chromatography (eluent 2:1 hexane/AcOEt).

Benzyl (1*S*,2*S*)-*N*-[(2-Hydroxycyclopentyl)methyl]carbamate, 6a: yield 91%, white solid; mp 54−55 °C; $[\alpha]_D^{20}$ +7.3 (*c* 1.2, $CHCl_3$); ee 97%; IR ν (cm^{-1}) 1703; ^1H NMR δ (ppm) 1.3−1.9 (m, 7H), 3.1 (m, 1H, C*H*H−N), 3.3−3.7 (m, 2H, CH*H*−N and OH), 4.12 (m, 1H, CH−O), 5.10 (s, 2H, CH_2−O), 5.25 (bs, 1H, NH), 7.34 (m, 5H, arom); ^{13}C NMR δ (ppm) 21.8, 26.2, 33.8 (CH_2), 40.3 (CH_2−N), 47.6 (CH), 66.9 (CH_2−O), 72.3 (CH−O), 128.0, 128.1, 128.4 (CH_{arom}), 136.2 (C_{arom}), 157.6 (CO); ESIMS *m*/*z* 272 $(M + Na)^+$. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.21; H, 7.75; N, 5.52.

Benzyl (1*S*,2*S*)-*N*-[(2-Hydroxycyclohexyl)methyl]carbamate, 6b: yield 90%, colorless oil; $[\alpha]_D^{20}$ +6.4 (*c* 2.9, $CHCl_3$); ee 93%; IR ν (cm^{-1}) 1715; ^1H NMR δ (ppm) 1.15−1.85 (m, 9H), 2.92 (m, 1H, C*H*H−N), 3.31 (m, 1H, CH*H*−N), 2.3−3.5 (bs, 1H, OH), 3.88 (m, 1H, CH−O), 5.09 (s, 2H, CH_2−O), 5.28 (bs, 1H, NH), 7.33 (m, 5H, arom); ^{13}C NMR δ (ppm) 20.0, 24.2, 25.1, 32.3 (CH_2), 42.1 (CH), 43.1 (CH_2−N), 65.7 (CH−O), 66.8 (CH_2−O), 127.9, 128.0, 128.4 (CH_{arom}), 136.2 (C_{arom}), 157.6 (CO); ESIMS *m*/*z* 286 $(M + Na)^+$. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.20; H, 8.18; N, 5.16.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **2a**,**b**, **3a**,**b**, **4a**,**b**, **5a**,**b**, and **6a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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