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Bioreduction of 2-oxocyclopentanecarboxamides: syntheses of optically active 2-aminomethyl- and 2-aminocyclopentanols

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Abstract

The fungus *Mortierella isabellina* NRRL 1757 catalyzes the reduction of 2-oxocyclopentanecarboxamides with very high enantioselectivity giving, in most cases, the corresponding enantiopure 2-hydroxycyclopentanecarboxamides. The presence or absence of a substituent on the amidic nitrogen has a strong influence on the diastereoselectivity achieved in these processes. Optically active hydroxyamides prepared in these microbial reductions are used as starting materials for the preparation of optically active 2-aminomethyl- and 2-aminocyclopentanols.

1. Introduction

Preparation of chiral building blocks by means of the asymmetric reduction of carbonyl compounds is a subject of current interest in organic chemistry.[1] In this context, isolated enzymes and microorganisms, baker's yeast in particular, have been extensively used to enantioselectively reduce the prochiral ketone group of a great variety of compounds of synthetic usefulness.[2] Thus, baker's yeast mediated reduction of β-ketoesters is, at the present time, a well-established methodology for the preparation of optically active β-hydroxyesters.[2d,3] However, despite the broad variety of substrates reduced by microorganisms, bioconversions of β-ketoamides into β-hydroxyamides are rarely reported, and only some specific β-ketoamides have been reduced by baker's yeast.[4]

Interest in this kind of process is obvious because optically active β-hydroxyamides are precursors of other interesting compounds such as 1,3- and 1,2-amino alcohols, which are usually used as chiral auxiliaries in asymmetric syntheses.[5] Moreover, 1,2-amino alcohols are structural elements of biologically active compounds[6] (β-blockers, antidepressants, adrenergic drugs, etc.).

Recently, we have demonstrated that the fungus *Mortierella isabellina* is an excellent catalyst for the asymmetric reduction of different 3-oxo-3-phenylpropanamides and 3-oxobutyramides, the

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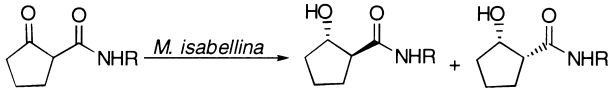
corresponding (*S*)-3-hydroxyamides being obtained with high chemical yields and enantiomeric excesses.[7] These good results encouraged us to investigate the microbial reduction of racemic cyclic β-ketoamides, 2-oxocyclopentanecarboxamide and some of their *N*-alkyl derivatives. The reduction of these substrates would allow us to investigate both diastereoselective and enantioselective activity of the fungus *Mortierella isabellina*. In addition, derivatives of the resulting optically active 2-hydroxycyclopentanecarboxamides are present in a great variety of biologically important molecules,[8] and they have interesting applications as stereochemical control elements due to their conformational restrictions.[9]

2. Results and discussion

In order to optimize the stereoselectivity of the process, 2-oxocyclopentanecarboxamide **1a** was chosen as a model substrate. Firstly, we carried out the reaction under the same conditions previously reported for the bioreduction of acyclic β-ketoamides.[7] Thus, when submitted to a culture of *Mortierella isabellina* (NRRL 1757) grown for 24 h, **1a** was converted (85% conversion after 5 days)† into a mixture of *trans*- and *cis*-2-hydroxycyclopentanecarboxamides **2a** and **3a** (see Table 1) in a ratio of 70:30, both diastereomers being easily separated by flash chromatography. The major isomer was identified as *trans*-(1*S*,2*S*)-**2a** and its enantiomeric purity was >99%. The minor isomer proved to be *cis*-(1*R*,2*S*)-**3a**, obtained with low enantiomeric excess (47%). Assignment of the absolute configurations for these compounds will be discussed later.

Table 1
Microbial reduction of **1a–c**



1a, R= H
1b, R= Allyl
1c, R= Bn

(1*S*,2*S*)-**2a-c** (1*R*,2*S*)-**3a-c**

1	R	Microorganism	t, h	*c*,[a] %	*trans*:*cis* 2:3 ratio[b]	ee,[c] % (1*S*,2*S*)-**2**	ee,[c] % (1*R*,2*S*)-**3**
1a	H	*M. isabellina*[d]	120	85	70 : 30	>99	47
1a	H	*M. isabellina*[e]	96	92	72 : 28	>99	49
1a	H	*B. bassiana*[e]	120	97	2 : 98	—	51
1b	Allyl	*M. isabellina*[e]	96	95	14 : 86	98	>98
1c	Bn	*M. isabellina*[e]	24	100	4 : 96	>99	>99

[a] Determined by ^{1}H NMR. [b] Determined by GC and ^{1}H NMR. [c] Determined by chiral HPLC analysis (see in the text). [d] growth time: 24 h. [e] growth time: 38 h.

Because of the good result obtained for the major isomer **2a**, we decided to modify the reduction conditions in an attempt to improve the *trans* diastereoselectivity of the process. It is well known that in the reduction of a carbonyl group by whole cells, unsatisfactory stereoselectivity is often the result of the simultaneous action of several dehydrogenase systems displaying both different kinetic

† No more progress of the reaction was observed after this time.

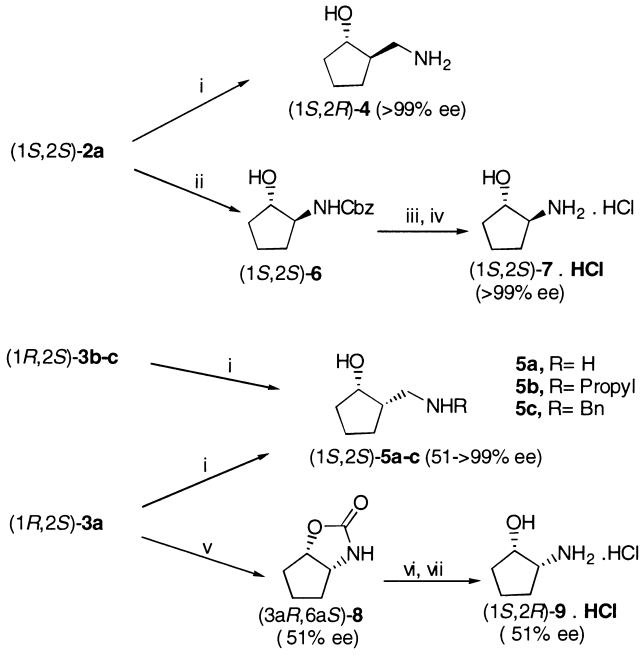
and different selectivity towards the same substrate.[10] Therefore, based on reported findings concerning the stereocontrol of the microbial reductions, the following experiments were carried out: (a) use of different *Mortierella isabellina* cultures after growing times ranging from 14 to 86 h,[7] (b) addition of dehydrogenase inhibitors such as methyl vinyl ketone and ethyl chloroacetate,[11] and (c) treatments of the mycelium prior to substrate addition[12] (ageing of the mycelium, resuspension in 0.1 M phosphate buffer pH=7, addition of an inorganic salt, and heating at 40–50°C[11b]). However, all our efforts were disheartening since the results of these experiments revealed that no significant changes in the *trans–cis* ratio were produced. Nevertheless, improvement in the activity of the microorganism was observed in the culture grown for 38 h, obtaining a similar percentage of conversion (92%) after a shorter reaction time (see Table 1).

On the other hand, we have also investigated the activity of the fungus *Beauveria bassiana* (ATCC 7159) in the reduction of **1a**. This microorganism has been employed in the reduction of β-ketoesters.[6e,13] Thus, when ketoamide **1a** was submitted to different cultures of the fungus *Beauveria bassiana* after growing times ranging from 14 to 86 h, the *cis*-2-hydroxycyclopentanecarboxamide **3a** was isolated as the only product of reduction with 51% ee. Although the remarkable feature of this bioreduction is its diastereoselectivity — higher and opposite to that shown by *Mortierella isabellina* — the enantioselectivity achieved was low.

In the light of these experiments, we decided to continue our studies with the fungus *Mortierella isabellina* and carry out the bioreduction of other *N*-substituted 2-oxocyclopentanecarboxamides such as *N*-allyl **1b** and *N*-benzyl **1c** (Table 1). In both cases, conversions and diastereoselectivities achieved were higher than in the reduction of **1a**, the reaction with **1c** being remarkable. This substrate **1c** was completely reduced after 24 h of incubation and the corresponding hydroxyamides **2c** and **3c** were obtained with a very high diastereomeric ratio (4:96), both isomers being enantiopure. Also of note, is the effect the presence of the *N*-substituent had on the stereocontrol of the bioreduction; in this case, the diastereoselectivity was reversed and *cis*-(1*R*,2*S*)-**2b**,**c** was obtained as the major isomer. This change of diastereoselection could be due to the action of different dehydrogenases possessing different specificities. Moreover, an enhancement of diastereoselectivity was obtained when the *N*-substituent increased in size (compare reductions of **1b** and **1c**, Table 1). This fact is similar to that observed in other microbial reductions, for which the stereoselectivity is usually driven by the steric difference between the substituents that flank the carbonyl function. So the more different they are, the greater the stereoselectivity.[10b,d,14]

However, it is noteworthy that in all cases the major diastereomer **2a** or **3b**,**c** is obtained enantiomerically pure. This is an interesting result from the viewpoint of obtaining enantiomerically pure cyclic 1,3- and 1,2-amino alcohols whose importance has already been mentioned. Thus, treatment of hydroxyamides (1*S*,2*S*)-**2a** and (1*R*,2*S*)-**3a**–**c** with lithium aluminum hydride afforded the corresponding 2-(aminomethyl)cyclopentanols (1*S*,2*R*)-**4** and (1*S*,2*S*)-**5a**–**c** (Scheme 1) in 75–87% yield. In the case of **3b** a reduction of the allyl group and the corresponding *N*-propyl derivative (1*S*,2*S*)-**5b** was obtained. These reduction processes took place without racemization because in the ^{1}H NMR spectra of **4** and **5a**–**c** only the presence of a diastereomer was detected.

On the other hand, (1*S*,2*S*)-2-aminocyclopentanol was obtained from enantiopure *N*-unsubstituted hydroxyamide (1*S*,2*S*)-**2a** by a Hofmann rearrangement (Scheme 1), which was accomplished with $Hg(OAc)_2$ and NBS[15] in the presence of benzyl alcohol. Thus, the alcoholysis of the isocyanate intermediate was achieved, and the rearranged product was easily isolated as its benzyl carbamate (1*S*,2*S*)-**6**. The hydrogenolysis of **6** yielded the enantiomerically pure (1*S*,2*S*)-2-aminocyclopentanol, which was isolated as its hydrochloride (1*S*,2*S*)-**7**·HCl after treatment with 6 M HCl. In addition, hydroxyamide (1*R*,2*S*)-**3a** (ee=51%) was also submitted to a Hofmann rearrangement through a recently



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, 1,4-dioxane, reflux, 24 h; (ii) $Hg(OAc)_2$, NBS, BnOH, DMF, 50°C, 17 h; (iii) Pd–C, 1,4-cyclohexadiene; (iv) 6 M HCl; (v) $PhI(OAc)_2$, THF, MeOH; (vi) LiOH, H_2O/MeOH reflux; (vii) CH_2Cl_2/3 M HCl

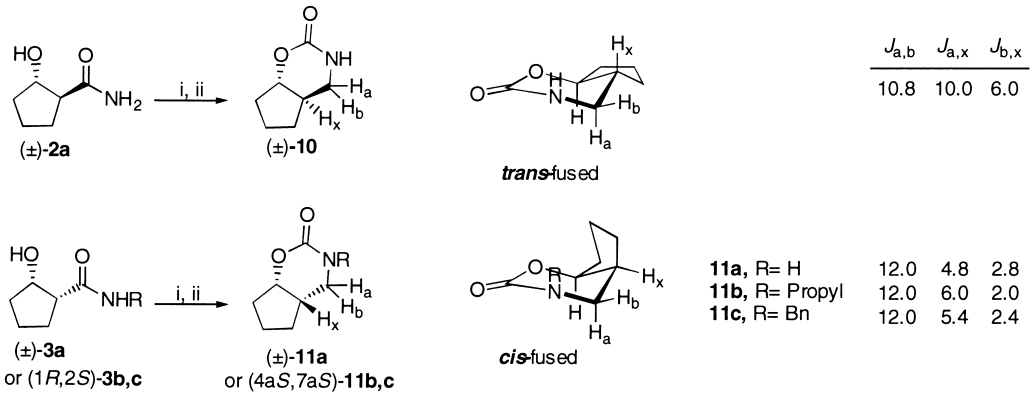
described procedure involving the use of an iodine reagent.[16] Treatment of (1*R*,2*S*)-**3a** with $PhI(OAc)_2$ in a mixture of THF–MeOH led to the oxazolidinone **8**. In this case, the formation of the oxazolidinone was favoured because both rings are *cis*-fused. Basic hydrolysis[17] of **8** and subsequent treatment with 6 M HCl afforded (1*S*,2*R*)-**9**·HCl in a 68% overall yield.

To assign the *cis*:*trans* configuration of the hydroxyamides **2a** and **3a** obtained in the microbial reductions, the analogous racemic mixtures *trans*-(±)-**2a** and *cis*-(±)-**3a** were prepared[‡] and their ^1H NMR spectra compared. $LiAlH_4$ reduction of *trans*-(±)-**2a** and *cis*-(±)-**3a** and subsequent carbonylation (*N*,*N*′-carbonyldiimidazole, NaH) of the resulting racemic amino alcohols (±)-**4** and (±)-**5a** afforded the corresponding racemic perhydrocyclopentano[*e*]-1,3-oxazine-2-ones (±)-**10** and (±)-**11a**, which were analyzed by ^1H NMR (Scheme 2). Similarly, to establish the *cis*-configuration of (1*R*,2*S*)-**3b**,**c** their aminoalcohol derivatives (1*S*,2*S*)-**5b** and (1*S*,2*S*)-**5c** were converted into (4a*S*,7a*S*)-**11b** and (4a*S*,7a*S*)-**11c**, respectively. Because of the bicyclic system present in these compounds, it is possible to assign the configuration through the coupling constant values of the diastereotopic protons H_a and H_b with H_x. The results of the ^1H NMR analyses of ABX systems[18] of compounds **10** and **11a**–**c**[§] are shown in Scheme 2. Compound **10** showed coupling constant values of 10.8, 10.0 and 6.0 Hz. These values are in agreement with geminal, axial–axial and axial–equatorial couplings, respectively, and they are consistent with a *trans*-relationship of the hydrogen atoms at the stereogenic centres. The same analysis for the compounds **11a**–**c** showed coupling constant values corresponding to geminal (12.0 Hz), equatorial–equatorial

[‡] $NaBH_4$ reduction of methyl 2-oxocyclopentanecarboxylate gave a 1:1 mixture of methyl *trans*-(±):*cis*-(±)-2-hydroxycyclopentanecarboxylates. This mixture was submitted to conventional ammonolysis (ammonia in methanol) yielding the corresponding mixture of *trans*-(±):*cis*-(±)-2-hydroxycyclopentanecarboxamides **2a**:**3a**, which was separated by flash chromatography (firstly AcOEt:hexane 1.5:1 to isolate (±)-**3a** and then, AcOEt to isolate (±)-**2a**).

[§] In order to simplify the spin system, the NH signal was irradiated in **10** and **11a**.

(2.0–2.8 Hz) and axial–equatorial (4.8–6.0 Hz) couplings, which are consistent with a *cis*-relationship of the hydrogen atoms at the stereogenic centres, and with the conformation shown in the Scheme 2.



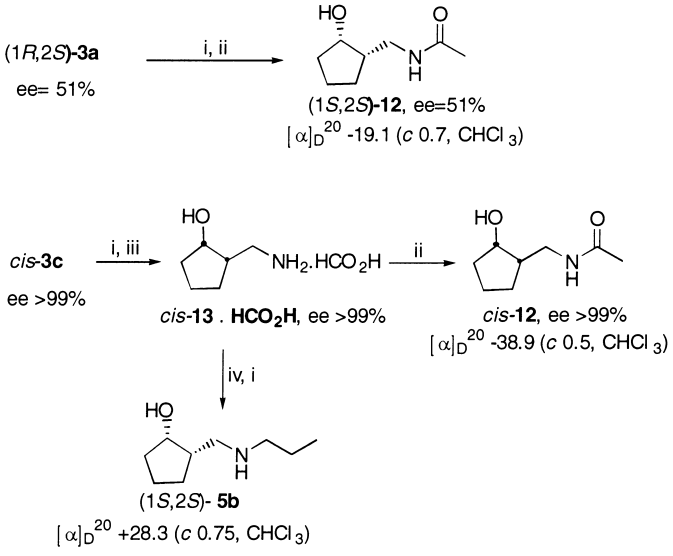
Scheme 2. Reagents and conditions: (i) $LiAlH_4$, 1,4-dioxane, reflux, 24 h (see Scheme 1); (ii) CDI, NaH, THF, reflux

On the other hand, the results obtained in the Hofmann rearrangement of (1*S*,2*S*)-**2a** and (1*R*,2*S*)-**3a** (see Scheme 1) corroborate the *cis*:*trans* assignment. Whereas the *cis*-isomer **3a** yielded the oxazolidinone **8**, the *trans*-isomer **2a** could not undergo intramolecular alcoholysis because this would involve the formation of two strained *trans*-fused 5-membered rings. That is why intermolecular alcoholysis product **6** is the only one isolated.[¶] On the basis of these arguments, the *cis*:*trans* configuration of the obtained diastereomeric hydroxyamides has been unambiguously established.

The absolute configurations of these compounds were assigned as follows. For (1*S*,2*S*)-**2a** by comparison of the sign for the specific rotations of its derivatives (1*S*,2*S*)-**6** and (1*S*,2*S*)-**7**·HCl (see Scheme 1) with the reported values.[19] Similarly, configuration (1*R*,2*S*) for **3a** was assigned by comparison of the sign for the specific rotations of its derivatives (3a*R*,6a*S*)-**8** and (1*S*,2*R*)-**9**·HCl (see Scheme 1) with those published for (3a*R*,6a*S*)-**8**[9a] and (1*R*,2*S*)-**9**,[19b] respectively.

In the case of hydroxyamides **3b** and **3c**, the absolute configuration (1*R*,2*S*) was established on the basis of the configuration for the hydroxyamide (1*R*,2*S*)-**3a** before being assigned. The strategy, outlined in Scheme 3, firstly involved the preparation of the same derivative, *N*-acetylated 2-(aminomethyl)cyclopentanol (1*S*,2*S*)-**12**, from the stereochemically well-defined (1*R*,2*S*)-**3a** and from the enantiopure *cis*-**3c**. To obtain enantiopure *cis*-**12** from *cis*-**3c**, the latter was transformed into *N*-(benzylaminomethyl)cyclopentanol *cis*-**5c** (see Scheme 1) and the benzyl group was removed by hydrogenolysis yielding the corresponding *cis*-2-(aminomethyl)cyclopentanol, which was isolated as its formic salt *cis*-**13**·HCO_2H. Conventional acetylation of *cis*-**13** led to *N*-acetylated amino alcohol *cis*-**12**. Comparison of the signs for the optical rotations of both compounds *cis*-**12** obtained from **3a** and **3c** establishes the (1*R*,2*S*) configuration for **3c**. To assign the configuration of enantiopure *cis*-**3b**, compound *cis*-**13**·HCO_2H prepared from (1*R*,2*S*)-**3c** was treated with propanoic anhydride (Scheme 3) and the resulting propanamide was reduced with $LiAlH_4$ yielding (1*S*,2*S*)-*N*-(propylaminomethyl)cyclopentanol (1*S*,2*S*)-**5b**. Comparison of the signs for the optical rotations of both compounds **5b** obtained according to Schemes 1 and 3 clearly establishes the (1*R*,2*S*) configuration for *cis*-**3b**.

[¶] The same results were obtained when racemic (±)-**2a** and (±)-**3a** were subjected to Hofmann rearrangement in the same reaction conditions, that is, $Hg(OAc)_2$, DMF and methanol. From (±)-**3a** the oxazolidinone was obtained, but (±)-**2a** gave the corresponding methyl carbamate.



Scheme 3. Reagents and conditions: (i) $LiAlH_4$ (see Scheme 1); (ii) Ac_2O, CH_2Cl_2, Et_3N; (iii) Pd–C, HCO_2H/MeOH; (iv) $(EtCO)_2O$, THF, Et_3N

Reductions with *Mortierella isabellina* have usually been reported to fit[13b,20] to Prelog's rule.[14a] In this context, the absolute configuration of hydroxyamides **2a** and **3a**–**c** obtained in this work are in accordance with this rule. For this, taking into account the results obtained and by application of the Prelog's rule, we have tentatively assigned the (1*S*,2*S*) configuration to the minor diastereomers **2b** and **2c**.

Enantiomeric excesses of the obtained hydroxyamides were determined as follows. For compounds (1*S*,2*S*)-**2a**–**c** and (1*R*,2*S*)-**3a**,**c** they were determined by chiral HPLC analysis: (1*S*,2*S*)-**2c** and (1*R*,2*S*)-**3c** as the compounds themselves; (1*S*,2*S*)-**2a** after conversion into its *O*-acetyl derivative; (1*S*,2*S*)-**2b** and (1*R*,2*S*)-**3a** after transformation into their *O*-*tert*-butyldiphenylsilyl derivatives. In the case of hydroxyamide (1*R*,2*S*)-**3b** it was transformed with (*R*)-MTPA-Cl into its MTPA-ester derivative,[21] which was subsequently analyzed by ^{19}F NMR (see the Experimental section for details).

3. Conclusion

We have shown that the fungus *Mortierella isabellina* (NRRL 1757) is an effective biocatalyst for the reduction of 2-oxocyclopentanecarboxamides **1**. Reactions proceeded with very high enantioselectivities and with moderate to excellent diastereoselectivities. Although the *N*-substituent of substrate **1** has a great influence on the *cis*:*trans* diastereoselection of the fungus, in all cases the major diastereomer of the product was enantiopure. This is of great importance since such optically active 2-hydroxycyclopentanecarboxamides **2** and **3** can be valuable chiral synthons. Thus, through very simple procedures, enantiopure 2-(aminomethyl)cyclopentanols (1*S*,2*R*)-**4** and (1*S*,2*S*)-**5b**,**c** and (1*S*,2*S*)-2-aminocyclopentanol were obtained from the microbial products. In our opinion, this microbial process contributes to broaden the range of applicability of biotransformations in organic synthesis.

4. Experimental

4.1. General

The fungi *Mortierella isabellina* and *Beauveria bassiana* were purchased from NRRL and ATCC culture collections, respectively. All reagents were purchased from Aldrich Chemie. Substrates **1** were prepared by enzymatic ammonolysis of the corresponding β-ketoesters as previously described.[22] Solvents were distilled over an adequate desiccant and stored under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). For chiral HPLC analyses, a Chiralcel-OD column (Daicel) was used. Solvents were distilled over an adequate desiccant and stored under nitrogen. Melting points were taken using a Gallenkamp apparatus and are uncorrected. Mass spectra were recorded on a Finnigan MAT/95 spectrometer. Elemental analyses were performed on a Perkin–Elmer analyzer 2400. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 1720-X FT Infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were carried out using a Bruker AC-200 (200.13 MHz for ^{1}H and 50.3 MHz for ^{13}C) or Bruker AC-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) spectrometer.

4.2. Culture conditions

The experimental procedure was as follows. *Mortierella isabellina* (NRRL1757) was precultured and cultured as previously described,[23] in a growing medium prepared by dissolving of tryptic soy broth (Difco, 30 g) and D-glucose (17.5 g) in 1 L of distilled water. After 38 h of culture (350 mL, in a 1 L Erlenmeyer flask), the mycelium was harvested by filtration and resuspended in distilled water (350 mL) and then substrate was added. In the case of reductions by *Beauveria bassiana* (ATCC 7159) the general procedure was the same except that the composition of the growing medium was: D-glucose (30 g), peptone (10 g), K_2HPO_4 (1 g), $MgSO_4$ (0.5 g), KCl (0.5 g), $ZnSO_4$ (0.3 g) and $FeSO_4 \cdot 7H_2O$ (0.01 g) in distilled water (1 L).

4.3. Biotransformation of *1*

4.3.1. General procedure

The corresponding 2-oxocyclopentanecarboxamide **1** was added to the culture as an ethanolic solution (100 mg/mL of ethanol) to reach a concentration of 1 mg/mL. Incubation was then carried out (rotary shaker, 200 rpm, 28°C) until no more progress of the reaction was observed (TLC monitoring). The mycelium was filtered out, washed with distilled water, and the combined aqueous phases continuously extracted with AcOEt (24 h). After drying and elimination of the solvent, a mixture of the corresponding diastereomeric 2-hydroxycyclopentanecarboxamides **2** and **3** was obtained. Flash column chromatography (the eluent is indicated in every case) of the mixture yielded pure **2** and **3**.

4.3.2. *(1*S*,2*S*)*-trans-*2-Hydroxycyclopentanecarboxamide **2a***

Eluent, AcOEt (once **3a** was isolated); white solid; yield, 51%; mp 122–123°C; $[\alpha]_D^{20}$ +78.0 (*c* 0.61, EtOH; ee >99%); IR (KBr) 1663 cm^{-1}; ^{1}H NMR (CD_3OD) δ (ppm) 1.72–2.00 (m, 4H, CH_2), 2.08–2.20 (m, 2H, CH_2), 2.73 (m, 1H, C*H*$CONH_2$), 4.46 (m, 1H, C*H*OH); ^{13}C NMR (CD_3OD) δ (ppm) 23.78 (CH_2), 29.67 (CH_2), 36.11 (CH_2), 54.80 (CH), 77.81 (CH), 180.66 (C=O); MS (70 eV) *m/z* (relative intensity) 129 (M^+, 3), 101 (34), 85 (15), 72 (100). Anal. calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.73; H, 8.69; N, 10.83. For the chiral HPLC analysis, (1*S*, 2*S*)-**2a** was conventionally

(Ac_2O, Et_3N, THF) converted into its *O*-acetylderivative: t_R 15.81 min. For the *O*-acetylderivative of (±)-**2a** two peaks at t_R 13.72 and 16.40 min; R_S=2.4 (hexane:propan-2-ol, 90:10; 0.8 mL/min).

*4.3.3. (1*R,*2*S*)*-cis-*2-Hydroxycyclopentanecarboxamide **3a***

Eluent, AcOEt:hexane (1.5:1); white solid; yield, 20%; mp 95–96°C; $[\alpha]_D^{20}$ +15.7 (*c* 0.62, EtOH; ee 51%); IR (KBr) 1678 cm^{-1}; ^1H NMR (CD_3OD) δ (ppm) 1.75–2.25 (m, 6H, CH_2), 2.77 (m, 1H, C*H*$CONH_2$), 4.56 (m, 1H, C*H*OH); ^{13}C NMR (CD_3OD) δ (ppm) 23.04 (CH_2), 27.84 (CH_2), 35.65 (CH_2), 51.41 (CH), 75.51 (CH), 179.70 (C=O); MS (70 eV) *m/z* (relative intensity) 129 (M^+, 3), 101 (16), 85 (5), 72 (100). Anal. calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.92; H, 8.70; N, 10.46. For the chiral HPLC analysis, (1*R*, 2*S*)-**3a** was transformed (TBDPSCl, imidazol, THF)[24] into its *O-tert*-butyldiphenylsilyl derivative: t_R 9.67 min. For the *O-tert*-butyldiphenylsilyl derivative of (±)-**3a** two peaks at t_R 9.27 and 11.15 min; R_S=1.85 (hexane:propan-2-ol, 95:5; 0.8 mL/min).

*4.3.4. (1*S,*2*S*)*-trans-N-*Allyl 2-hydroxycyclopentanecarboxamide **2b***

Eluent, AcOEt:hexane (1:1); white solid; yield, 15%; mp 78–79°C; $[\alpha]_D^{20}$ +49.3 (*c* 0.80, $CHCl_3$; ee 98%); IR (KBr) 1640, 1549 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.49–2.08 (m, 6H, CH_2), 2.46 (m, 1H, C*H*CONHR), 3.33 (bs, 1H, OH), 3.86 (m, 2H, CH_2N), 4.24 (m, 1H, C*H*OH), 5.08–5.21 (m, 2H, $=CH_2$), 5.72–5.88 (m, 1H, =CH), 6.28 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.46 (CH_2), 26.39 (CH_2), 34.36 (CH_2), 41.68 (CH_2), 53.11 (CH), 76.52 (CH), 115.99 (CH_2), 134.07 (CH), 174.56 (C=O); MS (70 eV) *m/z* (relative intensity) 169 (M^+, 14), 128 (29), 112 (68), 57 (100), 41 (66). Anal. calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.85; H, 9.25; N, 8.16. For the chiral HPLC analysis, (1*S*, 2*S*)-**2b** was transformed (TBDPSCl, imidazol, THF) into its *O-tert*-butyldiphenylsilyl derivative: t_R 4.63 min. For the *O-tert*-butyldiphenylsilyl derivative of (±)-**2b** two peaks at t_R 4.84 and 5.98 min; R_S=2.4 (hexane:propan-2-ol, 97:3; 0.8 mL/min).

*4.3.5. (1*R,*2*S*)*-cis-N-*Allyl-2-hydroxycyclopentanecarboxamide **3b***

Eluent, AcOEt:hexane (1:1); white solid; yield, 71%; mp 93–94°C; $[\alpha]_D^{20}$ +4.8 (*c* 0.76, $CHCl_3$; ee >98%); IR (KBr) 1655, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.58–2.12 (m, 6H, CH_2), 2.45 (m, 1H, C*H*CONHR), 3.90 (m, 2H, CH_2N), 4.20 (bs, 1H, OH), 4.44 (m, 1H, C*H*OH), 5.10–5.28 (m, 2H, $=CH_2$), 5.73–6.05 (m, 2H, =CH and NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.87 (CH_2), 27.53 (CH_2), 34.17 (CH_2), 41.51 (CH_2), 49.48 (CH), 73.90 (CH), 116.23 (CH_2), 133.72 (CH), 175.07 (C=O); MS (70 eV) *m/z* (relative intensity) 169 (M^+, 10), 128 (11), 112 (100), 57 (97), 41 (55). Anal. calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.74; H, 8.85; N, 7.90. ^{19}F NMR data for the diastereomeric MPTA-esters derived from (±)-**3b**, δ −72.17 and −72.24 ppm ($CFCl_3/CDCl_3$ as an external standard). For the MPTA-ester derived from (1*R*,2*S*)-**3b** only one signal to −72.17 ppm.

*4.3.6. (1*S,*2*S*)*-trans-N-*Benzyl-2-hydroxycyclopentanecarboxamide **2c***

Eluent, AcOEt:hexane (1:1); white solid; yield, 3%; mp 141–142°C; $[\alpha]_D^{20}$ +53.6 (*c* 0.53, EtOH; ee >99%); IR (KBr) 1634 cm^{-1}; ^1H NMR (CD_3OD) δ (ppm) 1.74–1.95 (m, 4H, CH_2), 2.14–2.25 (m, 2H, CH_2), 2.76 (m, 1H, C*H*CONH), 4.51 (m, 1H, C*H*OH), 4.57 (s, 2H, CH_2Ph), 7.35–7.53 (m, 5H, Ph); ^{13}C NMR (CD_3OD) δ (ppm) 23.82 (CH_2), 29.73 (CH_2), 36.16 (CH_2), 44.36 (CH_2), 55.35 (CH), 77.80 (CH), 128.40 (CH), 128.74 (CH), 129.78 (CH), 140.36 (C), 177.65 (C=O); MS (70 eV) *m/z* (relative intensity) 219 (M^+, 52), 128 (13), 106 (55), 91 (100). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.87; H, 8.01; N, 6.30. Chiral HPLC analysis: (1*S*, 2*S*)-**2a**, t_R 11.63 min; (±)-**2a**, t_R 6.47 and 11.33 min; R_S=3.6 (hexane:propan-2-ol, 90:10; 0.8 mL/min).

*4.3.7. (1*R,*2*S*)*-cis-N-Benzyl-2-hydroxycyclopentanecarboxamide **3c***

Eluent, AcOEt:hexane (1:1); white solid; yield, 85%; mp 83–84°C; $[\alpha]_D^{20}$ +5.0 (*c* 0.75, $CHCl_3$; ee >99%); IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.52–2.10 (m, 6H, CH_2), 2.42 (m, 1H, C*H*CONH), 4.41 (m, 4H, C*H*OH, OH and CH_2Ph), 6.65 (bs, 1H, NH), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.87 (CH_2), 27.47 (CH_2), 34.16 (CH_2), 43.13 (CH_2), 49.55 (CH), 73.90 (CH), 127.40 (CH), 127.46 (CH), 128.60 (CH), 137.82 (C), 175.04 (C=O); MS (70 eV) *m/z* (relative intensity) 219 (M^+, 72), 106 (80), 91 (100). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.11; H, 8.10; N, 6.48. Chiral HPLC analysis: (1*R*, 2*S*)-**3c**, t_R 14.15 min; (±)-**3c**, t_R 14.14 and 18.09 min; R_S=2.4 (hexane:propan-2-ol, 90:10; 0.8 mL/min).

4.4. Reduction of 2-hydroxycyclopentanecarboxamides by lithium aluminum hydride

4.4.1. General procedure

A suspension of the corresponding hydroxyamide **2a**, **3a**–**c** (0.5 mmol) in anhydrous 1,4-dioxan (2 mL) was added dropwise with stirring to a slurry of $LiAlH_4$ (5 mmol) in anhydrous 1,4-dioxane (7 mL) under nitrogen. The mixture was refluxed for 24 h and then cooled to 0–5°C and water (0.8 mL) was added dropwise with stirring. After 1 h, the mixture was treated with hot MeOH and filtered through a thin pad of Celite. The filtrates were combined and the solvents were removed in vacuum. The solid residue was extracted with hot $CHCl_3$ and the resulting organic solution evaporated to give the corresponding product, which was pure in most cases. For analytical purposes it was purified by flash chromatography using as eluents: propan-2-ol:CH_2Cl_2:(30% NH_4OH) (2:2:0.1) for **4** and **5a**,**b** and CH_2Cl_2:MeOH (10:1) for **5c**.

*4.4.2. (1*S,*2*R*)*-trans-2-*(Aminomethyl)cyclopentanol **4***

Prepared from (1*S*,2*S*)-**2a**. Oil; yield, 84%; $[\alpha]_D^{20}$ +9.5 (*c* 0.83, $CHCl_3$; ee >99%); ^1H NMR ($CDCl_3$) δ (ppm) 1.20–1.18 (m, 1H, C*H*H), 1.45–2.00 (m, 6H, CH_2, CH*H* and CH), 2.24 (bs, 3H, NH_2 and OH), 2.60 (dd, 1H, C*H*HNH_2, *J*=12.0, *J*=9.0), 2.97 (dd, 1H, CH*H*NH_2, *J*=12.0, *J*=3.0), 3.85 (q, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.13 (CH_2), 27.35 (CH_2), 34.02 (CH_2), 45.73 (CH), 49.41 (CH_2), 77.95 (CH); MS (70 eV) *m/z* (relative intensity) 115 (M^+, 3), 98 (94), 68 (100), 67 (80). Anal. calcd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.81; H, 11.40; N, 11.91.

*4.4.3. (1*S,*2*S*)*-cis-*2-(Aminomethyl)cyclopentanol **5a***

Prepared from (1*R*,2*S*)-**3a**. Oil; yield, 80%; $[\alpha]_D^{20}$ +14.3 (*c* 0.87, $CHCl_3$, ee 51%); ^1H NMR ($CDCl_3$) δ (ppm) 1.30–1.90 (m, 7H, CH_2 and CH), 2.75–2.95 (m, 2H, CH_2NH_2), 3.33 (bs, 3H, NH_2 and OH), 4.25 (m, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.93 (CH_2), 26.62 (CH_2), 34.66 (CH_2), 41.66 (CH), 45.08 (CH_2), 75.16 (CH); MS (70 eV) *m/z* (relative intensity) 115 (M^+, 5), 98 (19), 68 (100), 67 (88). Anal. calcd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.47; H, 11.29; N, 12.28.

*4.4.4. (1*S,*2*S*)*-cis-*2-(*N-*Propylaminomethyl)cyclopentanol **5b***

Prepared from (1*R*,2*S*)-**3b**. Oil; yield, 75%; $[\alpha]_D^{20}$ +27.0 (*c* 1.07, $CHCl_3$; ee >98%); IR (neat) 3293, 2959, 2874, 1466 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.91 (t, 3H, CH_3, *J*=7.3), 1.35–2.02 (m, 9H, CH_2, CH and $CH_3CH_2CH_2N$), 2.46–2.66 (m, 2H, $CH_3CH_2CH_2N$), 2.76–3.92 (m, 2H, $CHCH_2N$), 3.44 (bs, 2H, NH and OH), 4.29 (m, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.58 (CH_3), 22.29 (CH_2), 22.80 (CH_2), 27.32 (CH_2), 34.54 (CH_2), 42.00 (CH), 50.44 (CH_2), 51.61 (CH_2), 75.47 (CH); MS (70 eV) *m/z* (relative intensity) 157 (M^+, 3), 128 (35), 72 (100). Anal. calcd for $C_9H_{19}NO$: C, 68.74; H, 12.1; N, 8.91. Found: C, 68.51; H, 12.30; N, 8.80.

*4.4.5. (1*S*,2*S*)*-cis-*2-(*N-*Benzylaminomethyl)cyclopentanol* ***5c***

Prepared from (1*R*,2*S*)-**3c**. White solid; yield, 87%; mp 83–85°C; $[\alpha]_D^{20}$ +26.4 (*c* 0.76, $CHCl_3$; ee >99%); IR (KBr) 3430, 2953, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.35–1.85 (m, 6H, CH_2), 2.02 (m, 1H, C*H*CH_2NH), 2.81–2.93 (m, 2H, C*H*$_2$NH–), 3.47 (bs, 2H, NH and OH), 3.71–3.85 (m, 2H, CH_2Ph), 4.32 (m, 1H, C*H*OH), 7.25–7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm) 22.29 (CH_2), 27.41 (CH_2), 34.51 (CH_2), 42.26 (CH), 49.62 (CH_2), 53.74 (CH_2), 74.95 (CH), 127.28 (CH), 128.23 (CH), 128.44 (CH), 138.58 (C); MS (70 eV) *m/z* (relative intensity) 205 (M^+, 5.2), 120 (91), 106 (71), 91 (100). Anal. calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.11; H, 9.21; N, 7,05.

*4.5. Benzyl (1*S*,2*S*)*-trans-N-*(2-hydroxycyclopentyl)carbamate* ***6***

A solution of NBS (0.5 g, 2.8 mmol) in DMF (1.6 mL) was added under nitrogen to a solution of (1*S*,2*S*)-**2a** (0.26 g, 2 mmol) and $Hg(OAc)_2$ (0.96 g, 3 mmol) in DMF (2.8 mL) and benzyl alcohol (2.8 mL). The reaction was stirred at 50°C and once completed the white precipitate was removed by filtration. The solution was evaporated and the solid residue extracted with CH_2Cl_2. The organic solution was successively washed with 10% NH_4OH. After the aqueous layer was continuously extracted (24 h) with more CH_2Cl_2, both organic solutions were combined, dried and concentrated. Compound **6** was purified by flash chromatography using AcOEt:hexane as eluent; firstly in a ratio 1:4 in order to remove the BnOH in excess and then 1:2. White solid; yield, 70%; mp 57–59°C; $[\alpha]_D^{20}$ −10.7 (*c* 0.71, $CHCl_3$; ee >99%); IR (KBr) 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.29–1.47 (m, 1H, CH_2), 1.59–2.18 (m, 5H, CH_2), 3.64–3.78 (m, 1H,C*H*OH), 3.90 (bs, 1H, OH), 4.00–4.07 (m, 1H, C*H*NH), 5.05 (bs, 1H, NH), 5.11 (s, 2H, CH_2Ph), 7.30–7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm) 20.74 (CH_2), 30.24 (CH_2), 32.14 (CH_2), 60.52 (CH), 66.89 (CH_2), 79.14 (CH), 128.04 (CH), 128.14 (CH), 128.47 (CH), 136.07 (C), 157.28 (C=O); MS (70 eV) *m/z* (relative intensity) 235 (M^+, 7.5), 144 (76), 91 (100). Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.34; H, 7,53; N, 5.88.

*4.6. (1*S*,2*S*)*-trans-*2-Aminocyclopentanol hydrochloride* ***7***·*HCl*

Palladium hydroxide on carbon (90 mg) and 1,4-cyclohexadiene (0.36 mL; 3.8 mmol) was added to a solution of (1*S*,2*S*)-**6** (90 mg; 0.38 mmol) in ethanol (3 mL) the mixture then stirred at room temperature for 4 h. Catalyst was filtered off on a pad of Celite and washed with ethanol. HCl 6 M was added to the resulting ethanolic solution and after stirring for 1 h, solvents were evaporated to give the corresponding hydrochloride, which was purified by recrystallization from CH_2Cl_2–MeOH. White solid; yield, 91%; mp 180–182°C; $[\alpha]_D^{20}$ +30.1 (*c* 0.65, EtOH; ee >99%); ^1H NMR (CD_3OD) δ (ppm) 1.70–2.10 (m, 4H, CH_2), 2.12–2.46 (m, 2H, CH_2), 3.46 (m, 1H, CHN), 4.28 (m, 1H, C*H*OH); ^{13}C NMR (CD_3OD) δ (ppm) 21.48 (CH_2), 29.08 (CH_2), 33.56 (CH_2), 59.96 (CH), 76.94 (CH); MS (FAB^+, NBA matrix) *m/z* (relative intensity) 101 (M^+, 15), 84 (7), 56 (100). Anal. calcd for $C_5H_{11}NO$·HCl: C, 43.64; H, 8.79; N, 10.18. Found: C, 43.35; H, 8.76; N, 10.00.

*4.7. (3a*R*,6a*S*)*-cis-*Perhydrocyclopenta[*d*]oxazol-2-one* ***8***

$PhI(OAc)_2$ (0.8 g, 2.5 mmol) was added under nitrogen to a solution of (1*R*,2*S*)-**3a** (0.25 g, 1.9 mmol) in a mixture of THF (13 mL) and methanol (5 mL). The mixture was stirred at room temperature until disappearance of the starting material (TLC monitoring, 90 min) and then it was heated at 50°C for 30 min. At this point solvents were removed under vacuum and the resulting residue was submitted to flash chromatography (AcOEt:hexane, 1:1.5) to afford compound **8** as a white solid. Yield, 85%; mp

98–100°C; $[\alpha]_D^{20}$ −19.6 (*c* 0.70, $CHCl_3$; ee 51%); IR (KBr) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.45–1.85 (m, 5H, CH_2, C*H*H), 2.01–2.12 (m, 1H, CH*H*), 4.24 (m, 1H, CHN), 5.03 (m, 1H, CHO), 6.66 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.71 (CH_2), 33.61 (CH_2), 34.13 (CH_2), 56.63 (CH), 82.14 (CH), 160.44 (C=O); MS (70 eV) *m/z* (relative intensity) 127 (M^+, 100), 98 (80). Anal. calcd for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.72; H, 6.91; N, 10.82.

*4.8. (1*S*,2*R*)*-cis-*2-Aminocyclopentanol hydrochloride **9**·HCl*

Compound **8** (0.048 g, 0.38 mmol) was added to a solution of LiOH (0.028 g, 2 mmol) in a water:methanol (8:1, 0.7 mL) mixture. After heating at reflux for 3 h, solvents were removed under vacuum and the solid residue extracted with dichloromethane. The organic solution was evaporated to give the corresponding crude aminoalcohol **9**, which was immediately treated with CH_2Cl_2:6 M HCl giving the hydrochloride as a white solid, which was purified by recrystallization from CH_2Cl_2:MeOH. Yield, 80%; mp 219–221°C; $[\alpha]_D^{20}$ +10.0 (*c* 0.5, EtOH; ee 51%); ^1H NMR (CD_3OD) δ (ppm) 1.75–2.30 (m, 6H, CH_2), 3.62 (m, 1H, CHN), 4.43 (m, 1H, C*H*OH); ^{13}C NMR (CD_3OD) δ (ppm) 21.61 (CH_2), 28.77 (CH_2), 33.89 (CH_2), 55.86 (CH), 72.08 (CH); MS (FAB^+, NBA matrix) *m/z* (relative intensity) 102 [$(M+1)^+$, 100]. Anal. calcd for $C_5H_{11}NO\cdot HCl$: C, 43.64; H, 8.79; N, 10.18. Found: C, 43.82; H, 8.51; N, 10.25.

4.9. (±)-trans-*Perhydrocyclopenta[*e*]-1,3-oxazin-2-one (±)-**10***

Prepared from (±)-*trans*-2-(aminomethyl)cyclopentanol [(±)-**4**], which was previously obtained from (±)-**2a**[19] as described for enantiopure (1*S*,2*R*)-**4**. A solution of (±)-**4** (0.023 g, 0.2 mmol) in dry THF (1.5 mL) was added under nitrogen, to a suspension of NaH (0.009 g, 0.39 mmol) in dry THF (1.5 mL). Then *N*,*N*′-carbonyldiimidazole (CDI) (0.063 g, 0.39 mmol) was added and the resulting mixture stirred and heated at reflux for 16 h. After being cooled, the mixture was treated with a saturated NH_4Cl solution. Solvents were evaporated and the residue was dissolved in distilled water and extracted with CH_2Cl_2. The organic layer were dried and concentrated under reduced pressure to give crude (±)-**10**, which was purified by flash chromatography (AcOEt:hexane, 2:1). White solid; yield, 45%; mp 131–133°C; IR (KBr) 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.10–1.40 (m, 1H, C*H*H), 1.55–2.20 (m, 6H, CH_2, CH*H*, CH), 3.09 (m, 1H, C*H*HNH, *J*=10.8, *J*=10.0), 3.46 (ddd, 1H, CH*H*NH, *J*=10.8, *J*=6.0), 4.07 (m, 1H, CHO), 6.39 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 20.21 (CH_2), 24.01 (CH_2), 28.25 (CH_2), 38.24 (CH), 45.20 (CH_2), 82.00 (CH), 155.81 (C=O); MS (70 eV) *m/z* (relative intensity) 141 (M^+, 64), 96 (100), 80 (44). Anal. calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.60; H, 7.71; N, 10.11.

4.10. (±)-cis-*Perhydrocyclopenta[*e*]-1,3-oxazin-2-one (±)-**11a***

Prepared from (±)-*cis*-2-(aminomethyl)cyclopentanol [(±)-**5a**] (0.023 g, 0.2 mmol) as described for (±)-**10**. Yield, 43%; IR (KBr) 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.60–2.01 (m, 6H, CH_2), 2.25 (m, 1H, CH), 3.21 (ddd, C*H*HNH, *J*=12.0, *J*=2.8), 3.54 (ddd, CH*H*NH, *J*=12.0, *J*=4.8), 4.69 (m, 1H, CHO), 6.46 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.80 (CH_2), 26.39 (CH_2), 33.23 (CH_2), 35.54 (CH), 40,58 (CH_2), 82.44 (CH), 154.85 (C=O); MS (70 eV) *m/z* (relative intensity) 141 (M^+, 28), 96 (22), 80 (100). Anal. calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.31; H, 7.94; N, 9.68.

4.11. (4aS,7aS)-cis-3-Propylperhydrocyclopenta[e]-1,3-oxazin-2-one **11b**

Prepared from (1*S*,2*S*)-**5b** (0.068 g, 0.43 mmol) as described for (±)-**10**. In this case, AcOEt:hexane (1:1.5) was used as an eluent. Oil; yield, 72%; $[\alpha]_D^{20}$ −51.2 (*c* 0.57, $CHCl_3$; ee >98%); IR (neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.92 (t, 3H, CH_3, *J*=7.4), 1.50–2.10 (m, 8H, CH_2 and C*H*$_2$CH$_3$), 2.34 (m, 1H, C*H*CH$_2$N, *J*=2.0, *J*=6.0), 3.13 (dd, 1H, C*H*HN, *J*=12.0, *J*=2.0), 3.29 (t, 2H, CH$_2$C*H*$_2$N, *J*=6.0), 3.55 (dd, 1H, CH*H*N, *J*=12.0, *J*=6.0), 4.67 (m, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.03 (CH_3), 20.31 (CH_2), 22.01 (CH_2), 27.10 (CH_2), 33.46 (CH_2), 36.93 (CH), 46.43 (CH_2), 50.75 (CH_2), 81.87 (CH), 153.80 (C=O); MS (70 eV) *m/z* (relative intensity) 183 (M^+, 100), 154 (62), 110 (83), 81 (99). Anal. calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.60; H, 9.58; N, 7.91.

4.12. (4aS,7aS)-cis-3-Benzylperhydrocyclopenta[e]-1,3-oxazin-2-one **11c**

Prepared from (1*S*,2*S*)-**5c** (0.040 g, 0.2 mmol) as described for (±)-**10**. In this case, AcOEt:hexane (1:1.5) was used as eluent. White solid; yield, 71%; mp 103–105°C; $[\alpha]_D^{20}$ −73.9 (*c* 0.57, $CHCl_3$; ee >99%); IR (KBr) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.49–2.10 (m, 6H, CH_2), 2.28 (m, 1H, C*H*CH$_2$N, *J*=2.4, *J*=5.4), 3.05 (dd, 1H, C*H*HN, *J*=12.0, *J*=2.4), 3.41 (dd, 1H, CH*H*N, *J*=12.0, *J*=5.4), 4.57 (q, 2H, CH_2Ph, *J*=14.6), 4.71 (m, 1H, CHO), 7.15–7.49 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.92 (CH_2), 26.98 (CH_2), 33.40 (CH_2), 36.72 (CH), 45.59 (CH_2), 52.34 (CH_2), 82.11 (CH), 127.56 (CH), 128.11 (CH), 128.55 (CH), 136.73 (C), 154.22 (C=O); MS (70 eV) *m/z* (relative intensity) 231 (M^+, 76), 186 (61), 162 (80), 91 (100). Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.81; H, 7.25; N, 6.21.

4.13. (1S,2S)-cis-2-(N-Acetylaminomethyl)cyclopentanol **12**

A solution of (1*S*,2*S*)-**5a** (0.060 g, 0.52 mmol) in dry CH_2Cl_2 (0.8 mL) was cooled at 0°C and treated with Et_3N (0.04 mL, 0.58 mmol) and acetic anhydride (0.032 mL, 0.58 mmol). After stirring at room temperature for 90 min, the solvents were evaporated. The residue was dissolved in distilled water and extracted with a mixture of $CHCl_3$:propan-2-ol (9:1). The organic solution was dried and concentrated to afford **12** as a crude product, which was purified by recrystallization from ether:hexane. White solid; yield, 90%; mp 97–98°C; $[\alpha]_D^{20}$ −38.9 (*c* 0.50, $CHCl_3$; ee 51%); IR (KBr) 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.30–1.85 (m, 7H, CH_2 and CH), 1.98 (s, 3H, CH_3), 2.98–3.06 (m, 1H, C*H*HN), 3.43–3.58 (m, 1H, CH*H*N), 4.02 (m, 1H, C*H*OH), 4.45 (bs, 1H, OH), 6.73 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 21.82 (CH_2), 22.91 (CH_3), 26.28 (CH_2), 33.40 (CH_2), 39.15 (CH_2), 47.47 (CH), 72.01 (CH), 171.75 (C=O); MS (70 eV) *m/z* (relative intensity) 157 (M^+, 15), 129 (41), 114 (19), 100 (47), 72 (67), 43 (100). Anal. calcd for $C_8H_{15}NO_2$: C, 61.11; H, 9.62; N, 8.91. Found: C, 61.24; H, 9.58; N, 8.63.

4.14. (1S,2S)-cis-2-(Aminomethyl)cyclopentanol formic salt **13**·HCO_2H

(1*S*,2*S*)-**5c** (0.6 g, 2.9 mmol) was dissolved in a methanolic solution of formic acid (4.4%, 30 mL) and the solution added to a suspension of palladium black catalyst (0.6 g) in the same formic acid methanolic solution (30 mL). The mixture was continuously stirred under nitrogen atmosphere until disappearance of the starting material (TLC monitoring, 120 min), and then the catalyst was filtered off onto a pad of Celite and washed with methanol. Solvents were removed in vacuum, and the resulting crude (1*S*,2*S*)-**13**·HCO_2H (97% yield) was employed without further purification in the reactions shown in the Scheme 3. The ^1H and ^{13}C NMR data of the crude product are as follows: ^1H NMR (CD_3OD) δ

(ppm) 1.60–2.35 (m, 7H, CH_2 and CH), 3.05–3.50 (m, 2H, CH_2N), 4.45 (m, 1H, C*H*OH), 8.63 (s, 1H, *H*COOH); ^{13}C NMR (CD_3OD) δ (ppm) 23.14 (CH_2), 28.28 (CH_2), 35.99 (CH_2), 41.29 (CH_2), 43.87 (CH), 74.28 (CH), 167.49 (C=O).

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