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Nucleophilic substitution on α-mesyloxy-O-alkyloximes — II. Enantiospecific synthesis of 2-(imidazol-1-yl)-1-cyclohexyl-3-phenylpropan-1-one O-alkyloximes

Antonio Giordani,[a,*] Alberto Carera,[b] Vittorio Pinciroli[b] and Paolo Cozzi[c]

[a] CNS Research Med. Chem. Dept., Pharmacia and Upjohn, Preclinical Research, Viale Pasteur 10, 20014 Nerviano Milan, Italy

[b] R and D Pharmaceuticals, Pharmacia and Upjohn, Preclinical Research, Viale Pasteur 10, 20014 Nerviano Milan, Italy

[c] Therapeutic Area Oncology, Chem. Dept.; Pharmacia and Upjohn, Preclinical Research, Viale Pasteur 10, 20014 Nerviano Milan, Italy

Abstract: An enantiospecific synthesis of (S)- and (R)-(E)-5-[1-cyclohexyl-3-phenyl-2-(imidazol-1-yl)propylidene]aminooxypentanoic acids **2** using homochiral phenylalanines as starting material is described. Protected α-hydroxy-N,O-dimethylamides **4**, obtained from α-hydroxyacids **3** were coupled with 1-cyclohexenyllithium to afford α,β-enones **5**, which were in turn converted to α-hydroxyketones **6**. Configurational liability of compound **11**, prompted us to attempt imidazole introduction on the α-hydroxy-O-alkyloxymes **12** which proved to be configurationally more stable. Thus nucleophilic substitution on α-mesyloxy-O-alkyloxymes **14** led, after ester removal, to homochiral compounds **2**. The use of hydrogenolysis for **14b** deblocking provided **2a** with 97% ee. Considerations on the stereochemical outcome of this hitherto undescribed nucleophilic substitution on α-mesyloxy-O-alkyloxymes are reported. © 1997 Elsevier Science Ltd. All rights reserved.

In a previous paper[1] we described the enantiospecific synthesis of enantiomers of (±)-(E)-5-[1,3-diphenyl-2-(imidazol-1-yl)propylidene]aminooxypentanoic acid **1**, a compound endowed with combined thromboxane A_2 (TxA_2) synthase inhibition and TxA_2 receptor antagonism. An optimization of the pharmacological profile of **1** and congeners led to the selection of (±)-(E)-5-[1-cyclohexyl-3-phenyl-2-(imidazol-1-yl)propylidene] aminooxypentanoic acid **2**, as a possible drug candidate[2]. Here too, the dual mechanism required deep insight on the possible enantioselectivity of action. Since compounds **1** and **2** are structurally closely related, we decided to extend to the synthesis of enantiomers of **2**, the enantiospecific approach starting from phenylalanine, previously reported for enantiomers of **1**[1].

N-methyl-N-methoxyamides (S)-**3a** and (R)-**3b** (Scheme 1) were prepared by a two-step synthesis, starting from homochiral phenylalanine as previously described[1]. However, in contrast to the enantiospecific synthesis of **1**, the direct condensation of cyclohexylmagnesium halide with Weinreb's amide **3** was not feasible in this case. Although there are several examples of Weinreb's ketone synthesis involve primary aliphatic organolithium or Grignard reagents[3], only one example dealing with an N-methoxy-N-methylurea concerns the use of the secondary cyclohexylmagnesium chloride[4a]. In addition negligible yields have been reported for the reaction of secondary lithium alkyls and specifically with N,N-dimethylpropionamide[4b]. Conversely, the condensation of 1-cyclohexenyllithium **10** with the α-benzyloxyamide **4** is expected to provide the protected α-hydroxyketone **5** without racemization (Scheme 1), according to the results reported by Evans in the synthesis of

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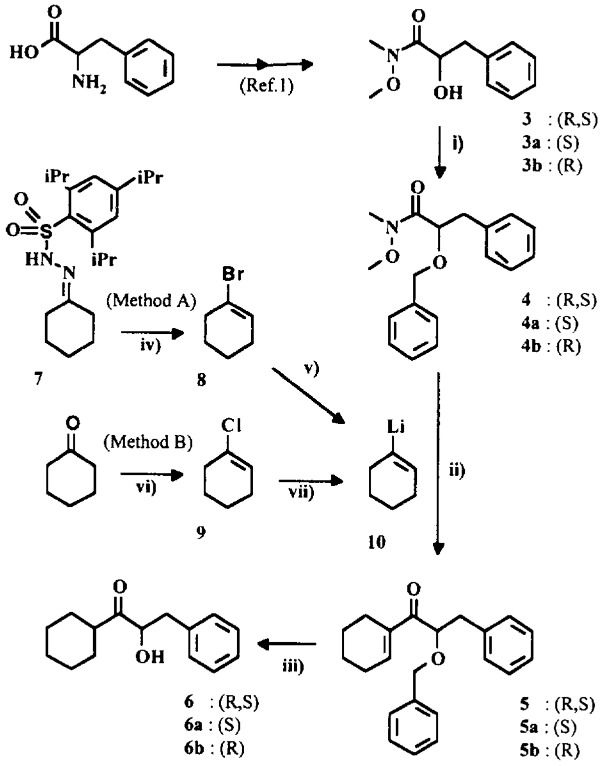
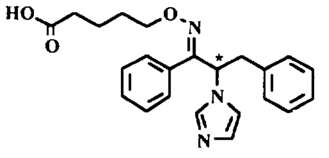
[*] Corresponding author. Email: Antonio.Giordani@eu.phu.com



Scheme 1. (i) NaH, DMF, 0°C, then $PhCH_2Br$; (ii) THF, **10**, −40°C→r.t.; (iii) H_2, EtOH, Pd/C; (iv) n-BuLi, TMDA, then $BrCH_2CH_2Br$; (v) t-BuLi, THF, −78°C; (vi) PCl_5; (vii) Li, Et_2O.

polyether antibiotic X-206[5], for the reaction of a secondary alkenyl-lithium with chiral α-benzyloxy-N-methoxy-N-methylamides.



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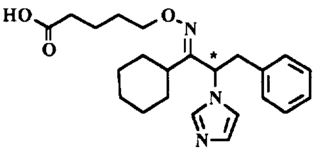


2

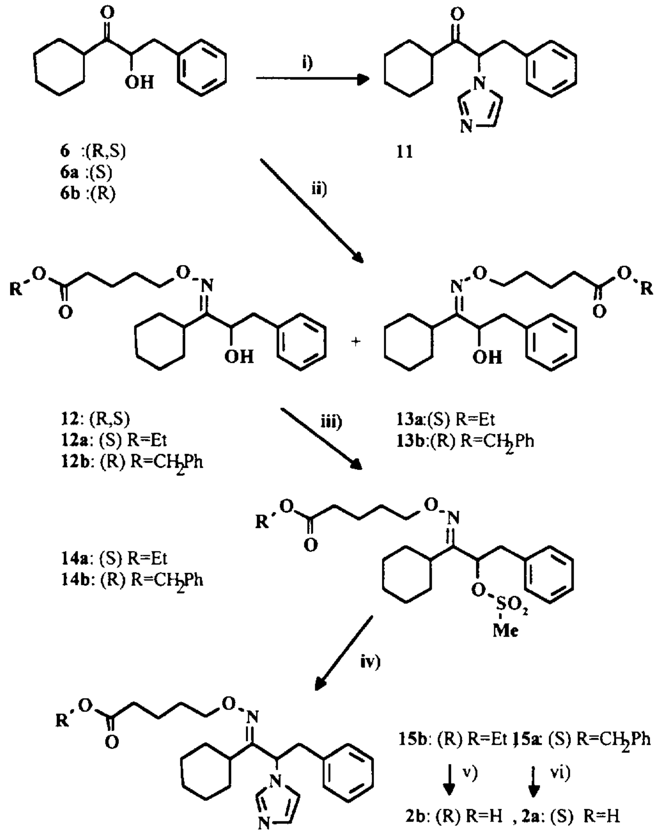
Amides **4** were prepared by reaction of **3a** or **3b** with benzyl bromide (NaH/DMF). Back hydrogenation of **4a** to **3a** demonstrated that the stereogenic centre was not affected during the benzylation, as proved by unchanged optical properties of the obtained starting compound. 1-Cyclohexenyl-lithium **10** was cleanly obtained from 1-bromocyclohexene **8**, which was in turn prepared from cyclohexanone-(2,4,6-triisopropylphenylsulfonyl) hydrazone (trisylhydrazone)[6] **7**, according to the two-step procedure reported by Paquette[11]. An attempt at direct decomposition of trisylhydrazone **7** to the corresponding vinyl carbanion **10** (Shapiro Reaction)[7], followed by *in situ* reaction with the electrophile **4**, as previously reported for the analogous reaction with alkylbromides, ketones and aldehydes[8,9], provided the α,β-enone **5** in low yield and after a tedious purification procedure.

Thus 1-bromocyclohexene **8**[11] was prepared by treating **7** (Scheme 1) (Method A) with n-BuLi in TMDA at −78°C. Subsequent quenching of the alkenyllithium with 1,2-dibromoethane provided **8** in 58% yield after column chromatography. Further metallation of **8** with tert-BuLi (−78°C)[15], followed by alkenyllithium trapping with Weinreb's amide **4** (from −40°C to r.t.), afforded the protected α-hydroxyketone **5** in 86% yield. Although this method gave rise to a clean reaction mixture and satisfactory yields, the preparation of **8** proved to be rather expensive. In addition the use of tert-BuLi in the following step further discouraged this reaction scale-up. A recent methodology[13] that allowed to overcome metal deactivation occuring during halogen–metal exchange of vinyl halides with lithium chips, prompted us to attempt the direct preparation of 1-cyclohexenyllithium **10** from the easily available 1-chloro-cyclohexene[12] **9**. As reported[13], **10** was almost quantitatively prepared by reaction of **9** (Scheme 1)(Method B) in diethyl ether, with lithium metal. Addition an ether solution of **10** to a cooled (−40°C) solution of **4** in THF, afforded the protected α-hydroxyketone **5** in 94% yield. Analogously, the chiral α-hydroxyketones **5a** and **5b** (Scheme 1) were prepared starting from (S)-**4a** and (R)-**4b**, in 91% and 86% yield, respectively. Catalytical hydrogenation (Pd/C 5%; H_2, 50 Psi; r.t.) of the α,β-enones (S)-**5a** and (R)-**5b** led to the α-hydroxyketones **6a** and **b** in 76–78% yields, with concomitant double-bond reduction and hydroxyl deprotection.

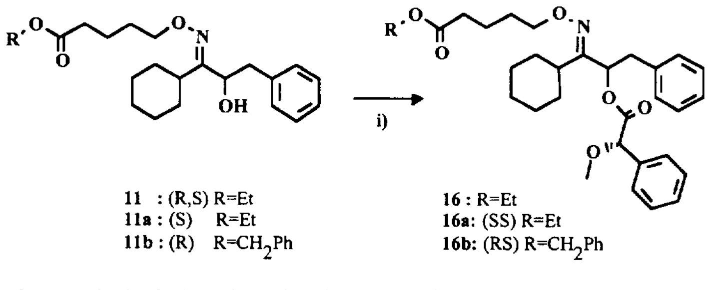
Reaction of the racemic α-hydroxyketone **6** with methanesulfonyl chloride (Et_3N, CH_2Cl_2)(Scheme 2) afforded the corresponding mesylate, which underwent nucleophilic substitution (imidazole, DMF) providing the ketone **11**[2] in 56% overall yield. However, as previously reported[1], here too, the configurational instability for **11** was proved either during its reaction with 5-aminooxypentanoic acid to afford **2** (25% deuterium uptake at the methine bearing the imidazolyl group was observed by running the reaction in the presence of D_2O)[14], or during its synthesis from **6** (50% deuterium uptake). Analogously to the previously reported results[1], no deuterium uptake was revealed on oximation of **6** either with aminoxypentanoic acid or its esters. Reaction of (S)-α-hydroxy ketone **6a** with ethyl 5-aminooxypentanoate hydrochloride, afforded the corresponding E/Z regioisomeric mixture (60:40) of the (S)-oximes **12a** and **13a** (Scheme 2), which were separated by column chromatography. As previously discussed[1], the oximes' geometric configuration was assigned by ^1H NMR spectroscopy[10].

^1H NMR analysis of the (S,S)-diastereoisomeric ester **16a**[17](Scheme 3) proved the enantiomeric purity of the E-oxime **12a**. Comparison of the spectra of **16a** with the diester **16**, obtained by reaction of the (RS)-α-hydroxyoxime **12** with (S)-2-methoxyphenylacetyl chloride (CH_2Cl_2, K_2CO_3), indicated for **12a** an enantiomeric excess greater than 98%, the signals of the corresponding (RS)-diester, well recognizable in the spectrum of the diastereoisomeric mixture **16**, being undetectable in the spectrum of **16a**.

Reaction of the α-hydroxyoxime **12a** with mesyl chloride (Et_3N, CH_2Cl_2) afforded the mesylate **14a**, which was found pure enough to be used as such in the following step. Reaction of **14a** with imidazole (DMF, 50°C, 10 hours) afforded the optically active ester **15b** in 87% yield. Finally, hydrolysis (LiOH, THF, H_2O) of **15b** led to the (R)-acid **2b** in 70% yield. Though nucleophilic substitution on α-halo or mesyloxy O-alkyl oximes has not been yet reported[1], the maintenance of enantiomeric purity in the step **12a**→**15b** would be accounted for by a pure SN_2 mechanism, conversely the lost of enantiomeric excess would indicate a mixed SN_1/SN_2 or a pure SN_1 mechanism. HPLC analysis on chiral stationary phase (Ultron-ES-OVM)[10], for the product **2b** (Rt. 6.0 min) in comparison with the racemic mixture **2** (peaks at Rt 6.2 and 12.0 min), indicated the presence of a second peak integrating 13.6% of the total area, and corresponding to the (S)-enantiomer, as proved either by the retention time or by adding amounts of the racemic mixture to **2b**. In order to assess whether this racemization was to be ascribed to the step **12**→**15** or to the following hydrolysis, the corresponding benzyl-esters **12b** and **13b** (Scheme 2) were prepared by reaction of the α-hydroxyketone **6b** with benzyl 5-aminooxypentanoate. Chromatographic separation of the regioisomeric E/Z oximes mixture afforded the pure E-oxime **12b**. Enantiomeric excess of this product was assessed by ^1H NMR analysis of its diastereoisomeric ester **16b** and found greater than 98%[10]. Reaction of **12b** with mesyl chloride led to the mesylate **14b** which was isolated and characterized. Subsequent reaction with imidazole provided the benzylester **15a** in 73% yield. Catalytic (Pd/C 5%) hydrogenolysis of the **15a** was



Scheme 2. (i)$MeSO_2Cl$, Et_3N, CH_2Cl_2, then imidazole, DMF; (ii) Ethyl 5-aminoxypentanoate·HCl, pyridine; (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (iv) imidazole, DMF; (v) LiOH, THF, H_2O; (vi) H_2, Pd/C, EtOH.



Scheme 3. (i) (S)-2-Methoxyphenylacetyl chloride, K_2CO_3, DMAP, CH_2Cl_2.

smoothly carried out in ethanol (H_2, 15 psi), leading to the corresponding acid **2a** in 85% yield, without affecting the oxime double bond. HPLC evaluation of **2a**, as reported above, revealed an optical purity of 96.5%, the peak corresponding to the R-enantiomer being only 1.7% of the total area. This negligible racemization proved that the previously observed lost of optical purity has to be ascribed mainly to the alkaline conditions used for the ester hydrolysis, thus indicating that a pure SN_2 mechanism occurs during the nucleophilic displacement. In conclusion in this paper we report a wider application of the previously reported[1] enantiospecific route to α-(imidazol-1-yl)-O-alkyloximes, based on an hitherto undescribed nucleophilic substitution on α-mesyloxy-O-alkyloximes. In this case the synthesis of the required α-hydroxyketone, involved the reaction of an alkenyl-lithium with the Weinreb amide **4**. The presence of an aliphatic moiety instead of a phenyl ring did not alter the reactivity and the configurational stability of the corresponding α-hydroxy-O-alkyl oxime, either during its preparation or in the following nucleophilic displacement. The satisfactory enantiomeric purity displayed by **2a**, suggested that this reaction of nucleophilic substitution on α-mesyloxy-O-alkyloximes could be used as a possible promising method for the functionalization of homochiral α-hydroxy ketones, given the widely reported mild methods for oxime–ketone conversion[19].

Experimental

Melting points were determined in open glass capillaries, with a Buchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR-200, VXR-400 or a Bruker WP-80 SY spectrometer, using the solvent as internal standard; chemical shifts are expressed in δ (ppm), coupling constants (J) are expressed in Hertz. Field desorption (FD) or electron impact (EI) mass spectra (MS) were obtained on Varian MAT 311A and Varian MAT CH7 instruments. Specific rotations were taken with a Jasco DIP 140 polarimeter operating at 25°C (λ=589 nm). Products, where applicable, were routinely dried over anhydrous Na_2SO_4 and evaporated using an Heidolph VV 2000 rotary evaporator at 15 mmHg. Flash column chromatographic separations were carried out according to the method of Still[18], on 40/60 μm silica gel (Carlo Erba). Thin-layer chromatography was performed on Whatman silica gel 60 plates coated with 250 μm layer, with fluorescent indicator. Components were visualized by UV light (λ:254 nm), or by spraying with suitable reagents: 2,4-dinitrophenylhydrazine was used to detect ketones, Druggendorff's reagent was used to detect compounds containing imidazole, other compounds were detected by ceriumsulfate-ammonium molybdate spray reagent. Dichloromethane was distilled from P_2O_5 and stored over 4Å molsieves. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried over sodium benzophenone, then distilled and stored over 4Å molsieves. Reactions dealing with air or moisture-sensitive materials were performed in flame dried glassware under argon or dry nitrogen atmosphere. Air and moisture-sensitve solutions were transferred with hypodermic syringes or doubled-ended needles.

(RS)-N-Methyl-N-methoxy-O-benzyl-2-hydroxy-3-phenylpropionamide 4

A solution of **3**[1] (6.8 g, 32.5 mmol) in DMF (30 mL) was slowly added to a suspension of hexane-washed NaH (1.7 g, 55% dispersion in mineral oil, 35.7 mmol) in dry DMF (60 mL), cooled at −10°C, while stirring under N_2 atmosphere. The resulting suspension was stirred at −10°C over 30 min, then a solution of benzylbromide (4.24 mL, 35.7 mmol) in DMF (10 mL) was added dropwise at −10°C. The reaction mixture was stirred at −10°C for 2 h (TLC, hexane/EtOAc 70:30). The resulting solution was poured into ice/water and extracted with EtOAc. Drying of the combined extracts, evaporation of the solvent and column chromatography (hexane/EtOAc 20%) of the residue afforded pure compound **4** (7.1 g, 73%), colorless needles, mp. 74–75°C (Et_2O/hexane). ^{1}H NMR (80 MHz; $CDCl_3$) δ: 3.05 (m, 2H, CH_2CH); 3.20 (s, 3H, N-CH_3); 3.48 (s, 3H, O-CH_3); 4.35 (d, J=12,1H, OCH_{2A} Ph); 4.45 (dd, J=6, J=1.5, 2H, $CH2$CH); 4.65 (d, J=12, 1H, $OCH_{2B}Ph$) 7.2–7.5 (m, 10 H, Phenyls). MS (EI) m/z: 211 $(M-CO(NCH_3)OCH_3)^{+\cdot}$; 193 $(M-PhCHO)^{+\cdot}$; 109 (C_6H_9O); 91 $(C_7H_7)^{+\cdot}$.

(S)-N-Methyl-N-methoxy-O-benzyl-2-hydroxy-3-phenylpropionamide 4a

The title compound was prepared as described above in 67% yield after two recrystallisation from Et_2O/hexane, mp. 77–78°C, $[\alpha]_D=-54.80$ (c=0.93, Acetone).

(R)-N-Methyl-N-methoxy-O-benzyl-2-hydroxy-3-phenylpropionamide 4b

The title compound was prepared as described above in 70% yield, mp. 77–78°C (Et_2O/hexane), $[\alpha]_D=+55.06$ (c=1.39, Acetone).

(S)-O-Benzyl-2-hydroxy-1-cyclohexenyl-3-phenylpropanone ***5a*** *(Method A)*

Compound **8** was prepared from **7** in 58% yield, as described[11]. 1.4 M tert-butyllithium[15] in pentane (11.4 mL, 16 mmol) was added dropwise over 20 min, under argon atmosphere, to a stirred solution of 1-bromocyclohexene (**8**)(1.3 g, 8 mmol) in dry THF (60 mL), cooled at −78°C. The resulting solution was stirred at −78°C for 20 min, then **4a** (2 g, 6.7 mmol) in dry THF (20 mL) was added over 10 min at −78°C. The reaction mixture was stirred at −78°C for 30 min, then allowed to warm to −20°C, and poured into a 20% NH_4Cl solution. Et_2O was added, the phases were separated and the aqueous layer extracted with Et_2O, the combined organic extracts were washed with water, dried and concentrated to a yellow oil (2.2 g). Column chromatography (hexane/Et_2O 80:20) afforded pure ketone **5a** (1.8 g, 86%), colorless prisms, mp. 89–90°C (Et_2O/hexane), $[\alpha]_D$=−5.50 (c=0.98, Acetone). ^1H NMR (200 MHz; $CDCl_3$) δ: 1.6 (m, 4H, $CH_{cyclohexyl}$); 2.0–2.4 (m, 4H, allylic $CH_{cyclohexyl}$); 3.0 (m, 2H, CH_2CH); 4.29 (d, J=12.0, 2H, O-$CH_{2A}Ph$); 4.56 (d, J=12, 1H, O-$CH_{2B}Ph$); 4.65 (dd, J=5.6, J=7.9, 1H, CH_2CH); 6.95 (m, 1H, CH vinyl); 7.10–7.30 (m, 10 H, Phenyls). MS (EI) m/z: 213 $(M-OCH_2Ph)^{+\cdot}$; 210 $(M-C_6H_9CHO)^{+\cdot}$; 109 $(C_6H_6CO)^{+\cdot}$; 91 $(C_7H_7)^{+\cdot}$.

(RS)-O-Benzyl-2-hydroxy-1-cyclohexenyl-3-phenylpropanone ***5*** *(Method B)*

Crushed capillaries[13] were added to a well stirred supension of lithium metal (0.6 g, 86.4 mmol) in dry Et_2O (30 mL). After 10 min stirring the surface of the metal was perfectly clean. A solution of 1-chlorocyclohexene (**9**)(3.6 g, 30.9 mmol) in Et_2O (30 mL) was added dropwise at r.t. under dry N_2 atmosphere. Within a few minutes the reaction mixture temperature rose to the reflux temperature. The solution of **9** was then added in one hour at a rate able to maintain a gentle reflux. The reaction mixture was then heated to 40°C and stirred until almost all the metal was consumed (5 h). The above prepared solution of **10** was then decanted and transferred *via cannula* into a stirred solution of **4** (2.5 g, 7.67 mmol) in dry THF (120 mL), cooled at −60°C, over 30 min. The resulting solution was stirred at −60°C for 30 min, then allowed to rise to r.t., and poured into 20% NH_4Cl solution. Et_2O was added, the organic layer separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with water, dried and concentrated to a colorless oil (2.8 g). Column chromatography (hexane/Et_2O 80:20) afforded pure ketone **5a** (2.3 g, 94%), colorless prisms mp. 89–90°C (Et_2O/hexane). ^1H NMR (400 MHz; $CDCl_3$) δ: 1.6 (m, 4H, $CH_{cyclohexyl}$); 2.05–2.45 (m, 4H, allylic $CH_{cyclohexyl}$); 3.0 (m, 2H, CH_2CH); 4.28 (d, J=11.7, 1H, O-$CH_{2A}Ph$); 4.58 (d, J=11.7, 1H, O-$CH_{2B}Ph$); 4.68 (dd, J=7.9, J=5.6, 1H, CH_2CH); 6.93 (m, 1H, CH vinyl); 7.10–7.30 (m, 10 H, Phenyls).

(S)-O-Benzyl-2-hydroxy-1-cyclohexenyl-3-phenylpropanone ***5a*** *(Method B)*

The title compound was prepared in a 5 g scale (91% yield), using the above described method. Colorless prisms, mp. 89–90°C, $[\alpha]_D$=−5.41 (c=1, Acetone).

(R)-O-Benzyl-2-hydroxy-1-cyclohexenyl-3-phenylpropanone ***5b***

The title compound was prepared in a 10 g scale (86% yield), using the above described method B. Colorless prisms, mp. 89–90°C, $[\alpha]_D$=+5.07 (c=0.7, Acetone).

(RS)-2-Hydroxy-1-cyclohexyl-3-phenylpropanone ***6***

Pd/C 5% (300 mg) was added to a solution of **5** (2 g, 6.3 mmol) in absolute EtOH (200 mL), the resulting suspension was hydrogenated, at room temperature and at 50 p.s.i. Both the deblocking step and the olefine reduction may be monitored by TLC (Et_2O/hexane 80:20), since the benzyl hydrogenolysis is the faster one (20 min). After 6 hours the olefine reduction was completed, the catalyst was filtered and the filtrate concentrated under reduced pressure to a colorless solid. Recrystallisation from isopropyl ether provided pure **6** (1 g, 71%), colorless needles, mp. 52–54°C. ^1H NMR (400 MHz; $CDCl_3$) δ: 1.20–1.95 (m, 10H, $CH_{2\ cyclohexyl}$); 2.55 (m, 1H, $CH_{cyclohexyl}$); 2.83 (dd, J=14.1, J=7.6, 2H, $CH_{2A}CH$); 3.12 (dd, J=14.1, J=4.4, 2H, $CH_{2B}CH$); 4.54 (m, 1H, CH_2CH);

7.20–7.33 (m, 5 H, Phenyl). MS (EI) m/z: 232 $(M)^{+\cdot}$; 214 $(M\text{-}H_2O)^{+\cdot}$; 121 $(M\text{-}C_6H_{12}CO)^{+\cdot}$; 83 $(C_6H_{11})^{+\cdot}$.

*(S)-2-Hydroxy-1-cyclohexyl-3-phenylpropanone **6a***

The title compound was prepared analogously from **5a** in 76% yield, colorless needles, mp. 58–59°C, $[\alpha]_D$=+16.9 (c=3.14, Acetone).

*(R)-2-Hydroxy-1-cyclohexyl-3-phenylpropanone **6b***

The title compound was prepared analogously from **5b** in 78% yield, colorless needles, mp. 58–59°C, $[\alpha]_D$=− 17.3 (c=1.09, Acetone).

(RS)-2-(imidazol-1-yl)-1-cyclohexyl-3-phenylpropan-1-one (11)[2].

CH_3SO_2Cl (0.74 mL, 9.6 mmol) was added, under N_2 atmosphere, to a stirred ice-cooled solution of **6** (0.75 g, 3.2 mmol) in dry CH_2Cl_2 (60 mL), followed by addition of triethylamine (1.35 mL, 9.6 mmol). The reaction was completed by stirring at 0°C over 40 min (TLC: hexane/EtOAc 80:20). The mixture was then poured into 0.5 N HCl/ice, the organic layer separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried and evaporated (30°C), to afford the crude mesylate (0.8 g). This crude product was dissolved in DMF (50 mL), and imidazole (2.1 g, 32 mmol) was added while stirring at r.t. The resulting solution was stirred at r.t. over 32 h (TLC: CH_2Cl_2/methanol 95:5). The mixture was poured into water and extracted with EtOAc. The combined organic extracts were washed with water, dried and concentrated to an oil. Chromatography (CH_2Cl_2/methanol 95:5) provided pure compound **11** , as a colorless viscous oil (441 mg, 56%). ^1H NMR (80 MHz; $CDCl_3$) δ: 1.0–1.9 (m, 10 H, CH_2 $_{\text{cyclohexyl}}$); 2.5 (m, 1H, $CH_{\text{cyclohexyl}}$); 3.1–3.7 (m, 2H, CH_2CH); 4.85 (dd, J=6 Hz, J=10 Hz, 1H, CH_2CH); 6.88–7.80 (m, 8H, phenyl+imidazole).

Reaction of 11 with 5-aminoxypentanoic acid in pyridine, in the presence of D_2O

To an ice-cooled solution of **11** (150 mg, 0.53 mmol) in pyridine (5 mL) and D_2O (0.5 mL), 5-aminooxypentanoic acid hydrochloride[2] (180 mg, 1.06 mmol) was added while stirring. The resulting reaction mixture was stirred at r.t. overnight, then the solvents were evaporated, the residue taken up with water and the pH of the resulting mixture was adjusted to 5 by adding AcOH. Extraction with $CHCl_3$, after drying and evaporation of the solvent, afforded an oily material (164 mg, 78%) consisting of the oximes E/Z mixture. This crude material was pure enough (TLC: CH_2Cl_2/MeOH 95:5) to be analyzed by ^1H NMR spectroscopy without further purification. The spectrum (400 MHz, $CDCl_3$) identified the obtained compound as a (75:25) mixture of E/Z oximes (see below for the assesment of the E/Z oxime regioisomers), the chemical shifts for the O-N=CCHCH$_2$ signal being at 4.82 δ for the E oxime and at 5.60 δ for the Z oxime, in agreement with our previous findings[1,2]. However, the integrals of these two signals quantified only 0.75 H (instead of 1H), by comparison with the integrals of the other signals of the spectrum. This did not occur when D_2O was not present in the reaction medium, suggesting partial deuteration at position 2. The full 200 MHz spectra for the above described E and Z oximes, have been previously reported[2].

Reaction of 11 with imidazole in DMF, in the presence of D_2O

D_2O (0.3 mL) was added to a solution of compound **11** (100 mg, 0.35 mmol) in DMF (3 mL), followed by imidazole (119 mg, 1.75 mmol). The resulting solution was stirred at r.t. for 12 h. The reaction mixture was then poured into water, and extracted with EtOAc, the combined organic extracts were washed with water, dried and evaporated. The product obtained (76 mg) was analyzed by 400 MHz ^1H NMR spectroscopy. Inspection of the $CH\text{-}CH_2$ signal at 4.85 δ showed integration only of 0.5H in comparison with the other signals of the spectrum.

*Ethyl (S)-(E)-5-[[[1-cyclohexyl-2-hydroxy-3-phenylpropylidene]amino]oxy]pentanoate **13a** and ethyl (S)-(Z)-5-[[[1-cyclohexyl-2-hydroxy-3-phenylpropylidene]amino] oxy] pentanoate **12a***

Ethyl 5-aminooxypentanoate hydrochloride (4.9 g, 25 mmol) was added to a solution of **6a** (2.3 g, 10 mmol) in pyridine (100 mL), cooled at 0°C, while stirring. The resulting solution was allowed to react at r.t. for 12 h. The solvent was then evaporated under reduced pressure (30°C), and the residue partitioned between 0.5N HCl and EtOAc, the organic layer was separated and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with water, dried and concentrated to a viscous oil (4 g). The two regioisomeric oximes were detectable by TLC (hexane/Et_2O 80:20), the Z isomer being the faster moving (Rf=0.32) and the E isomer slower moving (Rf=0.18). The crude mixture was separated by column chromatography; elution with hexane–Et_2O 15% afforded the pure Z isomer **13a** (1.25 g, 38%), as a colorless oil, $[\alpha]_D=-4.13$ (c=8.0, Acetone). ^1H NMR (400 MHz; $CDCl_3$) δ: 1.10–1.38 (m, 7H, CH_2 $_{cyclohexyl}$+$COOCH_2CH_3$); 1.60–1.82 (m, 10H, CH_2 $_{cyclohexyl}$+O-$CH_2CH_2CH_2$); 1.98 (m, 1H, CH $_{cyclohexyl}$); 2.36 (m, 2H, CH_2COO); 2.95 (dd, J=13.5, J=8.5, 1H, CH_ACH); 3.05 (dd, J=13.5, J=5.0, 1H, CH_BCH); 3.24 (d, J=8.8,1H, OH); 4.05 (m, 2H, O-$CH_2CH_2CH_2$); 4.13 (q, J=7.0, 2H, $COOCH_2CH_3$); 4.53 (m, 1H, CH_2CH); 7.20–7.30 (m, 5 H, Phenyl). MS (EI) m/z: 284 $(M\text{-}C_7H_7)^+$; 230 $(M\text{-}O\text{-}C_4H_8COOC_2H_5)^+$; 101 $(C_5H_9O_2)^+$. Further elution with hexane–ethyl ether 30% afforded the pure E isomer **12a** (1.86 g, 56%), as a colorless oil, $[\alpha]_D=+7.77$ (c=6.3, Acetone).

^1H NMR (400 MHz; $CDCl_3$) δ: 1.10–1.35 (m, 5H, CH_2 $_{cyclohexyl}$+$COOCH_2CH_3$); 1.45–1.80 (m, 12H, CH_2 $_{cyclohexyl}$+O-$CH_2CH_2CH_2$); 2.34 (m, 2H, CH_2COO); 2.70 (m, 1H, CH $_{cyclohexyl}$); 2.74 (dd, J=14.0, J=8.5, 1H, CH_ACH); 2.83 (d, J=6.4, 1H, OH); 3.08 (dd, J=14.0, J=3.8, 1H,CH_BCH); 4.04 (m, 2H, NO-CH_2); 4.14 (q, J=7.3, 2H, $COOCH_2CH_3$); 4.42 (m, 1H, CH_2CH); 7.20–7.33 (m, 5 H, Phenyl). MS (EI) m/z: 330 $(M\text{-}OC_2H5)^+$; 284 $(M^-\ C_7H_7)^+$; 101 $(M\text{-}C_5H_9O_2)^+$. The Z or E configurations for the above reported oximes, like those previously decribed[1,2], were assessed by ^1H NMR spectroscopy. According to the assignments reported in literature[16] it was possible, on the basis of the deshielding effect (N–O group) or shielding effect (N lone pair) exerted by the oxime moiety on the adjacent protons, to establish the oxime configuration. In the Z isomer **13** the H-2 chemical shift is down-field (≈0.2 ppm) in comparison with the corresponding H-2 chemical shift for the E isomer **12**. Conversely the cyclohexyl-methine is more shielded (≈0.7 ppm) in the Z isomer than the corresponding signal in the E isomer.

*Reaction of **6** with ethyl 5-aminoxypentanoate in pyridine, in the presence of D_2O*

The reaction was run as described above, but using a 1:10 (v/v) mixture of D_2O:pyridine as solvent. After the usual work up, the isolated E/Z mixture of the oximes was analyzed by ^1H NMR (400 MHz) spectroscopy without chromatographic purification. The spectrum did not show any detectable deuterium uptake.

*Reaction of **12** with (S)-2-methoxyphenylacetyl chloride*

Anhydrous K_2CO_3 (300 mg) was added to a solution of **12** (90 mg, 0.26 mmol) in dry CH_2Cl_2 (10 mL), followed by DMAP (4 mg). A solution of (S)-2-methoxyphenylacetyl chloride (96 mg, 0.52 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise at r.t., to the resulting stirred suspension, under N_2 atmosphere. The reaction was then completed while stirring at r.t. for 3 h, TLC (hexane/Et_2O 80:20). The reaction mixture was diluted with CH_2Cl_2, filtered and the filtrate washed sequentially with: 1N HCl, saturated $NaHCO_3$ and water. Concentration of the dried organic solution afforded the diester **16** (102 mg, 83%) as a pale yellow oil. ^1H NMR spectrum (400 MHz, $CDCl_3$) of this product showed significant chemical shift differences between the corresponding proton resonances of the two diastereoisomers. The more significant ones were: δ: 2.50 (m, 0.5H, SR $CH_{cyclohexyl}$), 2.73 (m, 0.5H, SS $CH_{cyclohexyl}$); 3.25 (s, 1.5H, SS OCH_3), 3.33 (s, 1.5H, SR OCH_3); 4.63 (s, 0.5H, SS $CHOCH_3$), 4.73 (s, 0.5H, SR $CHOCH_3$); 5.55 (dd, J=5.6, J=8.2, 0.5H, SR $CHCH_2$), 5.61 (dd, J=6.4, J=7.9, 0.5H, SS $CHCH_2$).

*Reaction of **12a** with (S)-2-methoxyphenylacetyl chloride*

The reaction and the work-up were carried out as described above, starting from **12a** the SS-diester **16a** was obtained in 76% yield as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80–1.20 (m, 6H, $CH_{2\,\mathrm{cyclohexyl}}$); 1.23 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.40–1.70 (m, 8H, $CH_{2\,\mathrm{cyclohexyl}}+OCH_2CH_2CH_2$); 2.31 (m, 2H, CH_2COO); 2.51 (m, 1H, $CH_{\mathrm{cyclohexyl}}$); 3.0 (dd, J=13.6, J=7.9, 1H, CH_ACH); 3.16 (dd, J=13.6, J=6.4, 1H, CH_BCH); 3.25 (s, 3H, OCH_3); 3.98 (m, 2H, $NOCH_2$); 4.14 (q, J=7.0, 2H, $COOCH_2CH_3$); 4.63 (s, 1H, $CHOCH_3$); 5.61 (dd, J=6.4, J=7.9, 1H, $CHCH_2$); 7.18–7.40 (m, 10H, Phenyls). The signals corresponding to the RS diastereoisomer were not detectable in this spectrum.

Benzyl 5-aminooxypentanoate hydrochloride

5M HCl in isopropanol (7 mL) was added to a well stirred suspension of 5-aminooxypentanoic acid hydrochloride^2 (16.8 g, 0.1 mol) in benzyl alchool (160 mL). The resulting suspension was stirred at r.t. for 12 h, then heated at 70°C for further 3 h. The solution obtained was cooled to r.t. High vacuum evaporation of the solvent afforded a colorless solid which was recrystallized from EtOAc/hexane to lead to benzyl 5-aminooxypentanoate hydrochloride (23.6 g, 91%) as colorless prisms, mp. 124–126°C. ^{1}H NMR (80 MHz, d_6-DMSO) δ: 1.4–1.7 (m, 4H, $NOCH_2CH_2CH_2$); 2.2–2.45 (m, 2H, CH_2COO); 3.8–4.0 (m, 2H, $NOCH_2CH_2$); 5.0 (s, 2H, CH_2Ph); 7.2–7.35 (s, 5H, Phenyl).

*Benzyl-(R)-(E)-5-[[[1-cyclohexyl-2-hydroxy-3-phenylpropylidene]amino]oxy]pentanoate **12b** and benzyl-(R)-(Z)-5-[[[1-cyclohexyl-2-hydroxy-3-phenylpropylidene]amino]oxy]pentanoate **13b***

Benzyl 5-aminooxypentanoate hydrochloride (14 g, 54 mmol) was added portionwise over 30 min to a stirred solution of **6b** (5 g, 21.5 mmol) in pyridine (80 mL), cooled at 0°C. The resulting solution was stirred at 0°C for 2 h and then at r.t. overnight. Concentration under reduced pressure afforded an oily material, which was partitioned between 1N HCl and Et_2O, the organic layer was washed with water, dried and concentrated to an oil, E/Z diastereoisomeric mixture of oximes, TLC (hexane/Et_2O 70:30): Z oxime Rf=0.47; E oxime Rf=0.28 (starting material Rf=0.4). The mixture was separated by column chromatography, elution with hexane/Et_2O (70:30) afforded the Z oxime **13b** (3.57 g, 38%) as colorless oil, $[\alpha]_D$=+4.10 (c=2.49, acetone). ^{1}H NMR (400 MHz; $CDCl_3$) δ: 1.12–1.40 (m, 4H, $CH_{2\,\mathrm{cyclohexyl}}$); 1.60–1.90 (m, 10H, $CH_{2\,\mathrm{cyclohexyl}}+O\text{-}CH_2CH_2CH_2$); 2.0 (m, 1H, $CH_{\mathrm{cyclohexyl}}$); 2.43 (m, 2H, CH_2COO); 2.95 (dd, J=13.6, J=8.5, 1H, CH_ACH); 3.05 (dd, J=13.6, J=5.0, 1H, CH_BCH); 3.23 (d, J=8.5, 1H, OH); 4.08 (m, 2H, NO-CH_2); 4.55 (m, 1H, CH_2CH); 5.12 (s, 2H, OCH_2Ph); 7.20–7.40 (m, 10 H, Phenyl). MS (EI) m/z: 346 $(M\text{-}C_7H_7)^+$; 230 $(M\text{-}OC_4H_8COOC_7H_7)^+$; 101 $(C_5H_5O_2)^+$; 91 $(C_7H_7)^+$. Further column elution with hexane/Et_2O (60:40) provided the E oxime **12b** (5.2 g, 56%), as colorless oil, $[\alpha]_D$=−7.0 (c=2.2, acetone). ^{1}H NMR (400 MHz; $CDCl_3$) δ: 1.10–1.34 (m, 4H, $CH_{2\,\mathrm{cyclohexyl}}$); 1.46–1.80 (m, 10H, $CH_{2\,\mathrm{cyclohexyl}}+O\text{-}CH_2CH_2CH_2$); 2.40 (m, 2H, CH_2COO); 2.70 (m, 1H, $CH_{\mathrm{cyclohexyl}}$); 2.74 (dd, J=13.8 Hz, J=8.8, 1H, CH_ACH); 2.81 (d, J=6.4, 1H, OH); 3.06 (dd, J=13.8, J=3.8, 1H, CH_BCH); 4.0 (m, 2H, NO-CH_2); 4.42 (m, 1H, CH_2CH); 5.12 (s, 2H, OCH_2Ph); 7.20–7.40 (m, 10 H, Phenyl). 11281. FD m/z: 438 $(M+H)^+$; 437 $(M)^+$; 346 $(M\text{-}C_7H_7)^+$.

*Reaction of **12b** with (S)-2-methoxyphenylacetyl chloride*

The reaction and the work-up were carried out as described above; starting from the chiral alcohol **12b**, reaction with (S)-2-methoxyphenylacetyl chloride using K_2CO_3 as base and DMAP as catalyst, led to the RS-diester **16b**, in 96% yield (1 h at r.t). ^{1}H NMR (400 MHz, $CDCl_3$)δ: 1.08–1.78 (m, 14H, $CH_{2\,\mathrm{cyclohexyl}}+OCH_2CH_2CH_2$); 2.40 (t, 2H, CH_2COO); 2.75 (m, 1H, $CH_{\mathrm{cyclohexyl}}$); 2.84 (dd, J=13.9, J=8.3Hz, 1H, CH_ACH); 3.06 (dd, J=13.9, J=5.6Hz, 1H, CH_BCH); 3.35 (s, 3H, OCH_3); 4.00 (t, 2H, $NOCH_2$); 4.74 (s, 1H, $CHOCH_3$); 5.12 (s, 2H, OCH_2Ph); 5.56 (t, J=5.6Hz, 1H, $CHCH_2$); 7.08–7.40 (m, 15H, Phenyls). In this case, signals corresponding to the SS diastereoisomer were detectable at ppm: 3.25 (-OCH_3), 4.62 ($CHOCH_3$) within the spectrum of **16b**, however their integrals were evaluated less than 5% of the corresponding signals of the RS diastereoisomer.

Ethyl (R)-(E)-5-[[[1-cyclohexyl-2-(1H-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoate ***15b***

Mesyl chloride (0.39 mL, 5 mmol) was added, under N_2 atmosphere, to a stirred solution of **12a** (561 mg, 1.64 mmol) in dry CH_2Cl_2 (40 mL), cooled at 0°C,. Then triethylamine (0.70 mL, 5 mmol) was slowly added dropwise. The resulting reaction mixture was stirred at 0°C for 40 min, then poured into ice cooled 1N HCl, and stirred for a few minutes. The phases were separated, the aqueous layer extracted with CH_2Cl_2, and the combined organic extracts washed with water, dried and concentrated to the crude mesylate **14a** (680 mg), pure enough (TLC:hexane/Et_2O, 80:20) for the subsequent step. Imidazole (0.560 g, 8 mmol) was added at r.t. to a solution of compound **14a** (680 mg) in dry DMF (50 mL), and the resulting solution was heated at 50°C for 10 h. The reaction mixture was then cooled to r.t., and poured into 1N HCl. Extraction with EtOAc and washing with 0.5N HCl of the combined organic extracts, after drying and concentration, afforded an oily residue (1.22 g). Column chromatography (CH_2Cl_2/MeOH, 95:5) provided pure compound **14b**, as a pale yellow oil (606 mg, 87%), $[\alpha]_D=+26.37$ (c=2.81, acetone). Spectroscopic characteristics are identical to those previously reported[2].

Benzyl (S)-(E)-5-[[[1-cyclohexyl-2-(1H-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoate ***14a***

The reaction was carried out as described above, starting from the benzylester **12b** (2 g, 4.6 mmol) the corresponding crude mesylate **14b** was obtained as a pale yellow oil (3.05 g). In this run, an amount (230 mg) of the crude mesylate was chromatographed over SiO_2 (hexane/Et_2O 60:40) to lead to the pure mesylate (192.6 mg) as a colorless oil $[\alpha]_D=+18.70$ (c=1.55, acetone). ^1H NMR (80 MHz, $CDCl_3$)δ: 1.10–1.83 (m, 14H, CH_2 $_{cyclohexyl}$+O-$CH_2CH_2CH_2$); 2.10–2.50 (m, 2H, CH_2COO); 2.48 (s, 3H, SO_2CH_3); 2.54–2.88 (m, 1H, $CH_{cyclohexyl}$); 3.05 (d, J=7, 2H, CH_2CH); 3.95 (m,2H, NO-CH_2); 5.02 (s, 2H, OCH_2Ph); 5.20 (t, J=7, 1H, CH_2CH); 7.0–7.5 (m, 10 H, 2-Phenyls). MS (FD) m/z: 516 $(M+H)^+$; 515 $(M)^{+\cdot}$; 419 $(M-HOSO_2CH_3)^{+\cdot}$.

Further reaction of the crude **14b** (2.82 g) with imidazole (23 mmol) in DMF (50°C, 10 h) after usual work up and column chromatography over SiO_2 (CH_2Cl_2/MeOH, 95:5), afforded the pure ester **15a** (1.6 g, 73%), as a colorless viscous oil, $[\alpha]_D=-47.37$ (c=0.99, acetone). ^1H NMR (80 MHz, $CDCl_3$)δ: 0.80–1.80 (m, 14H, CH_2 $_{cyclohexyl}$+O-$CH_2CH_2CH_2$); 2.10–2.40 (m, 2H, CH_2COO); 2.50–2.82 (m, 1H, $CH_{cyclohexyl}$); 2.90–3.32 (m, 2H, CH_2CH); 3.90–4.10 (m,2H, NO-CH_2); 4.68 (dd, J=6 Hz, J=9 Hz, 1H, CH_2CH); 5.0 (s, 2H,-OCH_2Ph); 6.70–7.30 (m, 13 H,Phenyls+imidazole). MS (FD) m/z: 488 $(M+H)^+$.

(R)-(E)-5-[[[1-Cyclohexyl-2-(1H-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic acid ***2b***

1N LiOH (1.3 mL, 1.3 mmol) was added to a solution of **15b** (400 mg, 0.94 mmol) in THF (6 mL) and water (2 mL), cooled at 0°C. The resulting solution was stirred at 0°C over 4 h. Further stirring at r.t. for 1 h completed the hydrolysis. The reaction mixture was then diluted with water, and the pH adjusted to 5 by adding AcOH. Extraction of the resulting mixture with EtOAc, after drying and evaporation of the solvents, afforded the crude acid which was chromatographed (SiO_2; CH_2Cl_2/MeOH, 95:5). Concentration of the fractions positive to the Druggendorff spray provided the pure acid, as a pale yellow oil (302 mg) which crystallized from isopropyl ether/hexane leading to **2a** (263 mg, 70%), as colorless plates, mp. 112–113°C, $[\alpha]_D=+60.19$ (c=2.09, acetone). ^1H NMR (400 MHz, $CDCl_3$)δ: 0.8–1.50 (m, 8H, CH_2 $_{cyclohexyl}$); 1.58–83 (m, 6H, CH_2 $_{cyclohexyl}$+O-$CH_2CH_2CH_2$); 2.40 (m, 2H, CH_2COO); 2.94 (m, 1H, $CH_{cyclohexyl}$); 3.14 (dd, J=13.8, J=9.1, 1H, CH_ACH); 3.33 (dd, J=13.8, J=5.9, 1H, CH_BCH); 4.18 (m,2H, NO-CH_2); 4.82 (dd, J=9.1, J=5.9, 1H, CH_2CH); 6.82–7.22 (m, 7H, Phenyl+H_4+H_5 imidazole); 7.53 (s, 1H, H_2 imidazole). MS (EI) m/z: 397 $(M)^{+\cdot}$; 353 $(M-CO_2)^{+\cdot}$; 329 $(M-C_3H_3N_2)^{+\cdot}$; 306 $(M-C_7H_7)^+$. Calcd. for $C_{23}H_{31}N_3O_3$: C 69.49; H7.86; N 10.57. Found: C 69.46; H 7.96; N 10.42. HPLC separation of the racemic compound **2** was achieved by means of an Ulton-ES OVM column (15 cm×4.6 mm), using as eluant phosphate buffer 0.01M (pH=7.0)/methanol 78:22, and operating at a flow of 0.8 mL/min. UV detection at 210 nm was used. According to this condition racemic **2** was separated in two peaks, integrating 49.1 and 49.1%, corresponding to the R-enantiomer (Rt=6.2 min) and the S-enantiomer (Rt=12.0 min) respectively. Using the same conditions, the above obtained compound **2b** consisted of a major peak at Rt=6.0 (84.8%) and a peak at Rt=12.5 (13.6%) corresponding to the S-enantiomer as assessed by injecting mixtures containing increasing amounts of the racemic mixture. The enantiomeric excess for compound **2b** was then found to be 73%.

*(S)-(E)-5-[[[1-Cyclohexyl-2-(1H-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic acid **2a***

Pd/C 5% (120 mg) was added to a solution of **15b** (1.2 g, 2.5 mmol) in absolute ethanol (90 mL), the resulting suspension was hydrogenated at 15 p.s.i. and r.t. After 10 min the reaction was complete. The catalyst was filtered and the filtrate concentrated under reduced pressure to a colorless oil (900 mg). Crystallization from Et_2O/hexane afforded the pure **2a** (843 mg, 85%) as colorless plates, mp. 112–113°C, $[\alpha]_D=-69.6$ (c=2.09, acetone). Calcd. for $C_{23}H_{31}N_3O_3$: C 69.49; H 7.86; N 10.57. Found: C 68.98; H 8.06; N 10.17. According to the above reported conditions, enantiomeric excess for compound **2a** was assessed by HPLC. Analysis of the above obtained **2a** resulted in a major peak at Rt=10.51 (95.4%) and a peak at Rt=6.5 (1.7%) corresponding to the R-enantiomer as assessed by injecting mixtures of the two enantiomers. The enantiomeric excess for compound **2a** was then found to be 96.5%.

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