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Lipase-catalyzed resolution of both enantiomers of Ornidazole and some analogues

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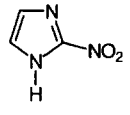
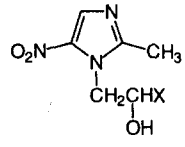
Abstract: The resolution of the enantiomers of the chemotherapeutic Ornidazole (*Tiberal*®) **1a** was achieved by acetylation of the racemic compound with vinylacetate in the presence of lipase Amano PS (from *Pseudomonas cepacia*). The halogen analogues **4a–6a** and the corresponding 4-nitro-derivatives **1b** and **4b–6b** were also synthesized and the enantiomers were separated by kinetic enzymatic resolution. The absolute configuration of two compounds was determined by X-ray crystallography. © 1997 Elsevier Science Ltd

Introduction

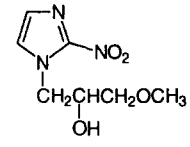
The constant interest in nitroimidazoles was originally caused by the discovery of the naturally occurring antibiotic Azomycin **I** (2-nitroimidazole).[1] Concerning their activity against pathogenic microorganisms, several investigations towards structure–activity relationships of this substance class were accomplished and led to 1-alkylated 4- and 5-nitroimidazoles, which showed the 5-nitro-compounds were more effective than their 4-nitro isomers. [2]The screening of several substitution patterns of the nitroimidazoles elicited Metronidazole **II** (*Flagyl*®, *Clont*®) and Ornidazole **1a** (*Tiberal*®), to name but two, as very potent compounds against anaerobic microbial infections, i.e. *Amoebiasis* or *Trichomoniasis*. [3]Some 2- and 4(5)-nitroimidazoles were tested as radiosensitizing agents in hypoxic cells (esp. Misonidazole (**III**)) and their potential in cancer chemotherapy was the subject of many reports.[4]



I



X=H **II**
X=CH_2Cl **1a**



III

The latest developments in this field of research show that the nitroimidazole moiety is used as a substructure in pharmacologically relevant compounds, i.e. bis(nitroimidazolyl)alkane-carboxamides as hypoxia-selective antitumor agents [5]or as ligands in organometallic complexes, i.e. in osmium(III) complexes $[Os^{III}(L)_3]$ as antiparasitic agents.[6]

Ornidazole itself and several analogues are still subject of research as antifertility agents in male animals,[7] possibly due to the release of the chlorinated side-chain during metabolism.[8] It is well known since 1969 that chlorinated C3-subunits like α-chlorohydrin or epichlorohydrin cause reversible antifertility effects in male animals.[9] The active compound was considered to be (*S*)-

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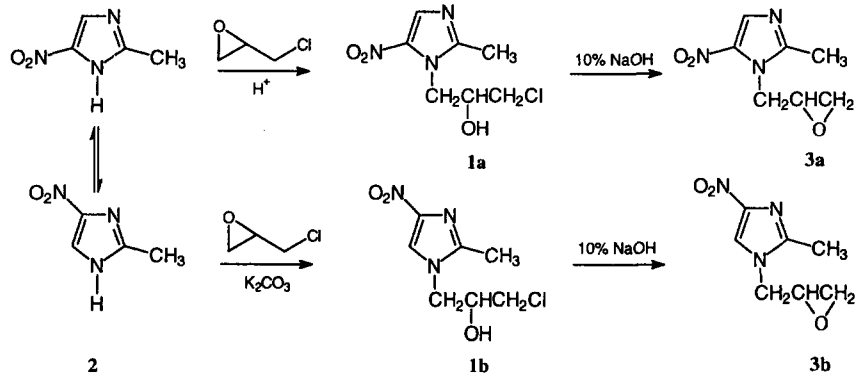
† X-Ray analyses.

chlorolactaldehyde, a metabolite of α-chlorohydrin, which is able to inhibit the activity of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase and therefore the synthesis of ATP in sperm.[10] Latest reports show that the corresponding bromo-compounds are also able to inhibit the glycolytic pathway.[11] In this special case the inhibition of the enzyme is strongly related to the stereochemistry of the applied compounds. As the mode of action of Ornidazole is comparable to α-chlorohydrin and similar compounds, the necessity of gaining the pure enantiomers of Ornidazole and its analogues is quite obvious.

Results and discussion

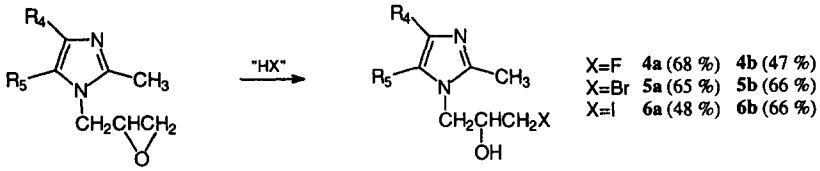
Ornidazole is a racemic chlorohydrin with the halogen in the terminal position. There are some examples in the literature in which racemic halohydrins were separated into their optical antipodes by lipase-catalyzed acylation in order to obtain optically active epoxides after alkaline treatment.[12] Some biotransformations of acyclic α-chlorohydrins were used as a key-step to obtain enantiomerically pure precursors of pharmacologically relevant compounds like β-adrenergic blockers (i.e. Atenolol or Propanolol) from (±)-(1-chloro-2-hydroxy)-3-aryloxy compounds. [13]The screening of several enzymes showed that the lipase from *Pseudomonas sp.* was the enzyme of choice to perform these reactions in high yields and enantiomeric purities.[14] In order to achieve this aim the substrates employed have to correspond with certain structural properties. If the substituents of the secondary alcohol differ in size and bear a carbocyclic, quite unpolar, aromatic system as the largest group, the enantioselectivity of *Pseudomonas sp.* was very good.[15] In this paper we want to show that it is also possible to apply lipase-catalyzed enantioselective esterifications to several α-halohydrins of classical heteroaromatic compounds which has not been mentioned before as a general pathway except for rare examples.[16]

The starting material **1a** and **1b** can be synthesized by known alkylation of 2-methyl-4(5)-nitroimidazole **2** with epichlorohydrin, which represents a tautomeric equilibrium of the 4- and 5-nitro-isomers. Depending on the pH, it is possible to control the regiochemistry of the alkylation of the imidazole ring. Acidic catalysis affords the 5-nitro compound **1a** whereas the corresponding 4-nitro compound **1b** is obtained under basic conditions.[3]



The epoxides **3a** and **3b** were synthesized by elimination of HCl in a moderately alkaline medium.[3a] The different halogen compounds were prepared by acid catalyzed cleavage of the oxirane ring with the corresponding hydrohalogenic acids. Concerning the fluorinated compounds Olah's reagent (pyridine·9HF) was used instead since liquid hydrogen fluoride is not a useful reagent, especially for the hydrofluorination of acyclic epoxides which proceeds poorly.[17] The yields were moderate due to the polar, hydrophilic character of the products, which led to problems in isolating them from the aqueous media. On the other hand, the addition of HX was definite and yielded the desired regioisomers. Concerning the fluorohydrins this result was quite unexpected in the sense that the 'wrong' regioisomer was formed. The regioselectivity of the ring opening of terminal oxiranes is directed by the fluorinating reagent which influences the mechanism of the reaction.[18] As pyridine·9HF is a quite acidic reagent

one would have expected the secondary fluorohydrin derived from the secondary carbeniumion center (S_N1-like mechanism). On the other hand, by using a less acidic, but more nucleophilic reagent like $Et_3N \cdot 3HF$, the nucleophilic attack of fluoride at the less hindered terminal carbon atom had been expected (S_N2-like mechanism). However, this reagent did not react at all with **3a** or **3b**. Only with pyridine·9HF the cleavage of the oxirane ring was possible, providing exclusively **4a** or **4b** in moderate yield. The intermediate formation of a secondary cationic center seems to be disfavoured by the strong electron withdrawing effect of the nitro-substituted heterocycle.

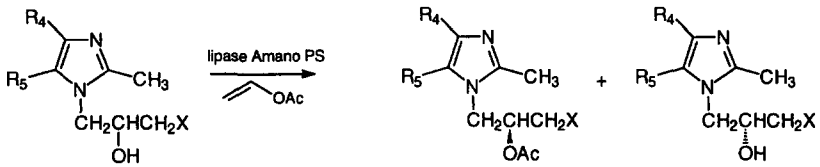


3a
3b

4a-6a
4b-6b

a) $R_4 = H$ $R_5 = NO_2$
b) $R_4 = NO_2$ $R_4 = H$

The halohydrins were esterified in the presence of lipase Amano PS (from *Pseudomonas cepacia*) with vinylacetate acting as acyl donor. The lipase from *Pseudomonas cepacia* was formerly categorized with other lipases from this family as *Pseudomonas sp.* Lipase Amano PS was formerly known as lipase P (classified as *Pseudomonas fluorescens*, until 1989).[19] First trials gave rise to the problem that the reaction became too slow if solvents were applied, and therefore vinylacetate had to act as a solvent as well. This fact should confirm the advantages of using enol esters as acetylating agents (acyl donors) in general, to ensure on the one hand the irreversibility of the reaction, and therefore the most probable enantioselectivity, and on the other hand, the enhancement of the reaction rate by using a great excess of the reagent. However, all reactions remained quite slow. Even the fastest reaction lasted 5 days (Table 1).



***rac*-1a, 4a-6a**
***rac*-1b, 4b-6b**

(*S*)-7a-10a
(*S*)-7b-10b

(*R*)-1a, 4a-6a
(*R*)-1b, 4b-6b

Comparing the different halogen compounds with each other, the best result was achieved with the fluorohydrin **4a** with respect to velocity, enantioselectivity and yield of the reaction, which was not completely reached with the corresponding 4-nitroisomer **4b**. Generally the 5-nitro compounds **1a**, **4a–6a** reacted faster than their 4-nitro counterparts. The very satisfying result of the acylation of Ornidazole **1a** corresponds with that of its 4-nitro isomer. The conversion of the bromohydrins **5a** and **5b** was quite difficult and only the enantiomeric excess of **5a** was satisfactory, whereas with the iodohydrins **6a** and **6b** no significant reaction was visible under the described conditions after 50 days. Such marked dependence from the halogen of an enzymatic acylation of halohydrins has never been obtained before.

In this case the observed reaction time was obviously determined by the electronic and steric nature of the halogen atom. Apparently the size of the halogen seems not to be very important, because no significant decrease in the enantioselectivity of the formation of the acetates was observed. On the other hand, the different halogen atoms have a very different electronic effect to the vicinal halohydrins As the large electronegativity of fluorine causes the biggest polarization to the neighbouring hydroxy function this could explain an enhanced reaction rate only by intramolecular electronic effects. But this is in contrast to other enzymatic esterifications mentioned in the literature[20] at which vicinal chloro- and bromohydrins of one family for instance had almost the same reaction rate. With our fluoro, chloro and

Table 1. Enzymatic esterification of 1-(3-halo-2-hydroxypropyl)-2-methyl-4(5)-nitroimidazole **1**, **4–6a,b** with vinylacetate and lipase from *Pseudomonas cepacia* (Amano PS)

Comp.	R_4	R_5	X	time [d]	conversion [%]	product	yield [%]	ee [%]	E val.[21]
rac-**1a**	H	NO_2	Cl	16	51	**S-(−)-7a**	41	95	201
						R-(+)-1a	43	89	30.2
rac-**4a**	H	NO_2	F	5	50	**S-(−)-8a**	41	>98	458
						R-(+)-4a	43	95	146
rac-**5a**	H	NO_2	Br	40	30	**S-(−)-9a**	21	94	29.8
						R-(+)-5a	45	39	31.1
rac-**1b**[a)]	NO_2	H	Cl	17	51	**S-(−)-7b**	36	92	93.0
						R-(+)-1b	43	95	81.5
rac-**4b**	NO_2	H	F	16	47	**S-(−)-8b**	34	96	134
						R-(+)-4b	45	48	5.3
rac-**5b**	NO_2	H	Br	89	31	**S-(−)-9b**	15	b)	
						R-(+)-5b	24	61	c)

[a)] performed with a different lot of lipase Amano PS. Thus, the reaction time is not comparable with the other experiments; [b)] pure compound could not be isolated; [c)] at 31% conversion no further reaction occurred

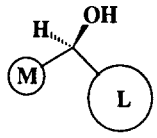


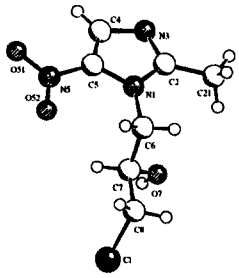
Figure 1. Kazlauskas' rule for the enantiopreference of lipase from *Pseudomonas cepacia* towards secondary alcohols.

bromohydrins nearly equal rate was observed for the chemical esterification (halohydrin/Ac_2O/pyridine 1:1:1 in CH_2Cl_2). For the enzymatic acetylation, however, with the polar character of the imidazole ring the conformation of the active site of the enzyme seems to be changed by the nature of the terminal halogen atom and causes therefore the different reaction rate.

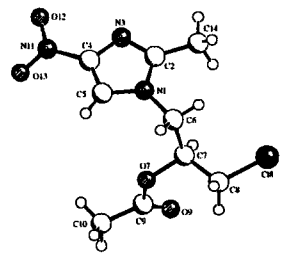
The supposed configuration of all enantiomerically enriched compounds (Table 1) is provisional until it is proved by X-ray crystallography or CD-spectroscopy. If the halohydrins are considered secondary alcohols, Kazlauskas *et al.* gave a survey of the enantioselectivity for the esterification of secondary alcohols with lipases, among others *Pseudomonas cepacia*.[22] The derived empirical rule predicts that the enantiomer shown in Figure 1 reacts faster than the other.

M, L are considered large and medium substituents, i.e. M=CH_3 and L=Ph. Concerning only alkyl substituents the conversion of the (*R*)-enantiomer is preferred. With compounds **1**, **4**, and **5** at which M=CH_2X and L=CH_2Het, the conversion of the (*S*)-enantiomer should be preferred according to the formalism of the sequence rule by Cahn, Ingold and Prelog. If the Kazlauskas rule is applicable to the nitroimidazole derivatives, the concluded configuration of the acetates formed would be (*S*), showing a negative specific rotation and (*R*) for the remaining alcohols.

In order to determine the absolute configuration compounds *R*-(+)-**1a** and *S*-(−)-**7b** were recrystallized from toluene and single crystals of the enantiopure compounds were grown. Since the anomalous X-ray (copper) scattering of chlorine renders the direct determination of the absolute structure,[23] there was no need to esterify the alcohols, for instance with chiral acids (i.e. Mosher's acid). The crystal structures of compounds *R*-(+)-**1a** [98% ee][24] and *S*-(−)-**7b** [96% ee] are shown below.



R-(+)-1a



S-(−)-7b

The Flack parameter (enantiopol parameter) for compound *R*-(+)-**1a** was −0.07(2) and −0.02(2) for compound *S*-(−)-**7b**, so that the shown structures represent the absolute configurations directly. Thus the expected absolute configurations derived from the empirical rule by Kazlauskas were confirmed by X-ray crystallography and can be generalized for all the mentioned nitroimidazoles. This result confirms, that this rule is also useful for secondary halohydrins bearing a heterocyclic aromatic substituent despite their non-uniform electronic structure.

Experimental

Melting points are uncorrected. ^{1}H NMR (300.13 MHz, ^{13}C NMR (75.5 MHz) and ^{19}F NMR (282.3 MHz) were recorded on a Bruker WM 300. Chemical shifts for ^{1}H NMR are reported as δ-values in ppm relative to TMS as internal standard in $CDCl_3$, ^{13}C NMR spectra were calibrated to 77.0 ppm of the $CDCl_3$ triplet, multiplicity was determined by the DEPT operation, and for ^{19}F NMR spectra $CFCl_3$ (δ=0 ppm) was used as internal standard in $CDCl_3$. Silica gel (Merck 60, 70–230 mesh) was used for column chromatography, thin layer chromatography was performed with Merck silica gel DC 60 F254 plates, detection UV (λ=254 nm). Microanalyses were carried out by the "Mikroanalytisches Laboratorium", OC, University of Münster. Optical rotations: Perkin Elmer 241 polarimeter (Na-D-line: λ=589 nm).

The conversion of the enzymatic esterifications were monitored with HPLC, analytical silica gel column Nucleosil 50-7, detection with differential refractometer (all from Knauer). Acetonitrile p.a. was used as mobile phase. 1:1 mixtures of the esterifying alcohol and its corresponding acetate were used as calibration constants for the HPLC measurement, which was determined for each compound. The value of conversion in Table 1 is the corrected one. The integration of the peaks was made manually so the total error for the corrected value is amounted to ±1%. Retention times (5.0 ml/min, 6 MPa) of the 5-nitro compounds: 2.7 min (acetates) and 3.3 min (alcohols); 4-nitro compounds: 2.1 min (acetates) and 2.3 min (alcohols).

The enantiomeric excesses of the acetates were determined by addition of 70 mol% $Eu(hfc)_3$ (5-nitro compounds) or 30 mol% $Pr(hfc)_3$ (4-nitro compounds). The protons of the methyl group of the acetoxy-functionality were shifted. The halohydrins were esterified chemically (Ac_2O, pyridine) and then shifted. The shift experiments were performed directly after chromatographic separation of the halohydrins from acetates without any further purification.

Olah's reagent (pyridine·9HF) was obtained from Aldrich; lipase Amano PS was a gift from Amano Pharmaceuticals Co. Ornidazole was partly taken from Sigma and partly provided by Hoffmann–La Roche. Vinylacetate was obtained from Acros and dried over molecular sieves (0.4 nm). Acetonitrile p.a. was obtained from Baker. All other starting materials and applied reagents were obtained from Acros (Janssen) and Fluka.

1-(3-Chloro-2-hydroxypropyl)-2-methyl-4-nitroimidazole ***1b***

The synthesis was carried out according to Ref.[3a] Batch size 15 g (0.12 mol) of 2-methyl-4(5)-nitroimidazole (**2**), 100 mL (0.9 mol) of epichlorohydrin and 0.5 g (3.6 mmol) of K_2CO_3. Yield 15.7

g, (60%), slightly yellow solid, which was recrystallized from ethanol; mp 151°C (Lit.[3a]: 151°C); ^{1}H NMR δ 2.13 (s, 3H, -C*H*$_3$), 3.12 (dd, 1H, -C*H*$_2$Cl, $^2J_{H,H}$=11.2 Hz, $^3J_{H,H}$=6.8 Hz), 3.29 (dd, 1H, -C*H*$_2$Cl, $^2J_{H,H}$=11.4 Hz, $^3J_{H,H}$=4.1 Hz), 3.60–4.00 (m, 3H, -NC*H*$_2$, -C*H*OH), 5.36 (d, 1H, -CHO*H*, $^3J_{H,H}$=4.8 Hz), 7.63 (s, 1H, arom. H); ^{13}C NMR δ 12.5 (q, -*C*H$_3$), 44.6 (t, -*C*H$_2$Cl), 49.1 (t, -N*C*H$_2$-), 69.2 (d, -*C*HOH), 120.7 (d, C-5), 144.8 (s, C-2), 145.4 (s, C-4).

General procedure for the synthesis of the epoxides

4 g (18 mmol) of the chlorohydrin were added in portions to 25 mL of a sodium hydroxide solution (10%) and the suspension was stirred vigorously for 15 minutes. After cooling to 0°C the white solid was filtered and washed with cold water (3×10 mL) and pentane (3×10 mL). The obtained powder can be employed directly for the following syntheses.

1-(2,3-Epoxypropyl)-2-methyl-5-nitroimidazole ***3a***

According to the general procedure 2.71 g (82%) were obtained as a colorless solid, mp 113°C (Lit.[3a]: mp 111°C); ^{1}H NMR δ 2.43 (s, 3H, C*H*$_3$), 2.48 (dd, 1H, -C*H*$_2$O, $^2J_{H,H}$=4.5 Hz, $^3J_{H,H}$=2.6 Hz) 2.82 (dd, 1H, -C*H*$_2$-O, $^2J_{H,H}$=4.5 Hz, $^3J_{H,H}$=4.1 Hz), 3.29–3.36 (m, 1H, -C*H*-), 4.17 (dd, 1H, -NC*H*$_2$, $^2J_{H,H}$=15.1 Hz, $^3J_{H,H}$=5.7 Hz), 4.82 (dd, 1H, -NC*H*$_2$, $^2J_{H,H}$=15.1 Hz, $^3J_{H,H}$=2.3 Hz) 7.88 (s, 1H, H-4); ^{13}C NMR δ 14.2 (q, -*C*H$_3$), 45.0, (t, -CH$_2$O), 47.4 (t, N*C*H$_2$), 50.2 (d, -*C*H-), 132.7 (d, C-4), 138.4 (s, C-5), 151.3 (s, C-2).

1-(2,3-Epoxypropyl)-2-methyl-4-nitroimidazole ***3b***

According to the general procedure 1.43 g (43%) were obtained as a colourless solid, mp 89.5°C; ^{1}H NMR δ 2.40 (s, 3H, -C*H*$_3$), 2.45 (dd, 1H, -C*H*$_2$O, $^2J_{H,H}$=4.5 Hz, $^3J_{H,H}$=2.6 Hz), 2.80 (dd, 1H, -C*H*$_2$O, $^2J_{H,H}$=4.5 Hz, $^3J_{H,H}$=4.1 Hz), 3.15–3.22 (m, 1H, -C*H*O), 3.85 (dd, 1H, -NC*H*$_2$, $^2J_{H,H}$=15.3 Hz, $^3J_{H,H}$=6.2 Hz), 4.36 (dd, 1H, -NC*H*$_2$-, $^2J_{H,H}$=15.0 Hz, $^3J_{H,H}$=2.4 Hz), 7.77 (s, 1H, H-5); ^{13}C NMR δ 13.0 (q, -*C*H$_3$), 44.8 (t, -*C*H$_2$O), 48.5 (t, -N*C*H$_2$-), 49.2 (d, -*C*HO), 120.2 (d, C-5), 145.2 (s, C-2), 146.6 (s, C-4).

General procedure for the synthesis of the fluorohydrins

1.83 g (10 mmol) of the epoxide is weighed in a dry 100 mL Erlenmeyer flask of polypropylene. The flask was cooled to 0°C and 5 mL of Olah's reagent (pyridine·9HF) was added. After removing from the ice bath the solution is stirred over a period of 3 h at room temperature. Finally the solution is poured into 50 mL of ice water, neutralized with ammonia solution (conc.) and extracted 3 times with ethylacetate (10 mL). The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product had to be purified by column chromatography, using isopropanol as eluent.

1-(3-Fluoro-2-hydroxypropyl)-2-methyl-5-nitroimidazole ***4a***

According to the general procedure 1.38 g, (68%) were obtained as a colorless solid, mp 92°C; ^{1}H NMR δ 2.57 (s, 3H, -C*H*), 4.32–4.82 (br, several multiplets, 6H, -C*H*$_2$-C*H*(O*H*)-C*H*$_2$F, 7.98 (s, 1H, H-4); ^{13}C NMR δ 14.7 (q, -*C*H$_3$), 48.9 (dt, -NCH$_2$, $^3J_{C,F}$=7.5 Hz), 68.9 (dd, *C*H-OH, $^2J_{C,F}$=20.3 Hz), 85.0 (dt, -*C*H$_2$F, $1J_{C,F}$=172.1 Hz), 133.0 (d, C-4), 138.9 (very weak, s, C-5), 152.2 (s, C-2); ^{19}F NMR δ −230.62 (dt, -CH(OH)CH$_2$*F*, $^2J_{H,F}$=47.7 Hz, $^3J_{H,F}$=21.0 Hz); microanalysis calcd. for $C_7H_{10}FN_3O_3$ (203.07), C 41.38, H 4.96, N 20.68, found C 41.35, H 4.80, N 20.06.

1-(3-Fluoro-2-hydroxypropyl)-2-methyl-4-nitroimidazole ***4b***

According to the general procedure 0.95 g (47%) were obtained as a colourless solid, mp 169°C; ^{1}H NMR δ 2.00 (s, 3H, -C*H*$_3$), 3.53–4.09 (br, several multiplets, 5H, -NC*H*$_2$-, -C*H*$_2$F, -C*H*OH), 5.15 (s, 1H, -CHO*H*), 7.55 (s, 1H, H-5); ^{13}C NMR δ 12.5 (q, -*C*H$_3$), 48.1 (dt, -N*C*H$_2$-, $^3J_{C,F}$=5.09 Hz), 67.3 (dd, -*C*HOH, $^2J_{C,F}$=20.35 Hz), 82.7 (dt, -*C*H$_2$F, $^1J_{C,F}$=172.96 Hz), 120.7 (d, C-5), 145.0 (s, C-4),

144.6 (s, C-2); ^{19}F NMR δ −230.00 (dt, -CH_2F, $^2J_{H,F}$=47.7 Hz, $^3J_{H,F}$=17.2 Hz) microanalysis calcd. for $C_7H_{10}FN_3O_3$ (203.07), C 41.38, H 4.96, N 20.68, found C 41.25, H 4.94, N 20.18.

General procedure for the synthesis of the bromohydrins

1.83 g (10 mmol) of the epoxide was introduced in portions to 11.3 mL of an aqueous solution of hydrobromic acid (48%, 0.1 mol). The solution was stirred for 3 h and then poured into 50 mL of ice water. After neutralizing with aqueous ammonia (conc.) to pH 7–8 the solution was extracted 3 times with ethylacetate (10 mL). The organic layer was dried with magnesium sulfate and then the solvent evaporated under reduced pressure. No more purifying was necessary.

1-(3-Bromo-2-hydroxypropyl)-2-methyl-5-nitroimidazole ***5a***

According to the general procedure 1.7 g (65%) were obtained as a colorless solid, mp 75°C; ^{1}H NMR δ 2.48 (s, 3H, -CH_3), 3.52 (dd, 1H, -CH_2Br $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=4.8 Hz), 3.6 (dd, 1H, -CH_2Br $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=4.1 Hz) 4.10–4.30 (br, m, 3H, -NCH_2 (1H!) -CHOH), 4.58–4.70 (m, 1H, -NCH_2), 7.80 (s, 1H, H-4); ^{13}C NMR δ 14.5 (q, -CH_3), 35.6 (t, -CH_2Br) 50.4 (t, -NCH_2), 69.6 (d, -CHOH), 132.5 (d, C-4), 138.3 (s, C-5), 151.8 (s, C-2).

1-(3-Bromo-2-hydroxypropyl)-2-methyl-4-nitroimidazole ***5b***

Deviating from the general procedure 7 mmol of the educt **3b** were employed. 1.3 g (66%) of **5b** was obtained as a slightly green solid, mp 135°C; ^{1}H NMR δ 2.17 (s, 3H, -CH_3), 3.05 (dd, 1H, -CH_2Br, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=7.5 Hz), 3.19 (dd, 1H, -CH_2Br, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=4.1 Hz), 3.65–3.80 (m, 2H,-CHOH, -NCH_2 (1H!)), 3.92–3.98 (m, 1H, -NCH_2), 5.43 (d, 1H, -CHOH, $^3J_{H,H}$=5.0 Hz), 7.64 (s, 1H, H-5); ^{13}C NMR δ 12.6 (q, -CH_3), 33.3 (t, -CH_2Br), 49.9 (t, -N-CH_2-), 69.0 (d, -CH-OH), 120.7 (d, C-5), 144.9 (s, C-2), 145.4 (s, C-4); microanalysis calcd. for $C_7H_{10}BrN_3O_3$ (262.99), C 31.84, H 3.82, N 15.91, found C 32.03, H 3.91, N 15.56.

General procedure for the synthesis of the iodohydrins

7.6 mL (20 mmol) hydrogen iodide solution was diluted with 7.6 mL water and cooled to 0°C. 10 mmol of the epoxide were added in portions and finally stirred at room temperature for 3 h. After completion of the reaction the solution was poured into 50 mL of ice water and neutralized with aqueous ammonia (conc.) to pH 7–8 and the solution was extracted 3 times with ethylacetate (10 mL). The organic layer was washed with 15 mL of a saturated solution of $Na_2S_2O_3$ (1×) and then dried with magnesium sulfate. After removing the solvent, the products were obtained which need not be purified further.

1-(2-Hydroxypropyl-3-iodo)-2-methyl-5-nitroimidazole ***6a***

According to the general procedure 1.48 g (48%) were obtained as a yellowish oil, which crystallized after treatment with toluene and storing several weeks in the refrigerator; mp 84°C; ^{1}H NMR δ 2.47 (s, 3H, -CH_3), 3.33 (dd, 1H, -CH_2I, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=6.0 Hz), 3.39 (dd, 1H, -CH_2I, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=4.5 Hz), 3.5–3.7 (br, m, 1H, -CHOH), 3.82–3.95 (m, 1H, -CHOH), 4.00–4.16 (m, 1H, -NCH_2), 4.52–4.67 (m, 1H, -NCH_2) 7.78 (s, 1H, H-4); ^{13}C NMR δ 9.8 (t, -CH_2I), 14.7 (q, -CH_3), 51.5 (t, -NCH_2), 69.5 (d, -CHOH), 132.6 (d, C-4), 138.3 (s, C-5), 151.8 (s, C-2); microanalysis calcd. for $C_7H_{10}IN_3O_3$ (310.98), C 27.03, H 3.24, N 13.51, found C 27.28, H 3.31, N 13.49.

1-(2-Hydroxypropyl-3-iodo)-2-methyl-4-nitroimidazole ***6b***

Deviating from the general procedure 56 mmol HI and 5.6 mmol of the epoxide **3b** were used. 1.2 g (66%) of **6b** were obtained as a yellowish solid, mp 109°C; ^{1}H NMR δ 2.18 (s, 3H, -CH_3), 2.95 (dd, 1H, -CH_2I, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=6.9 Hz), 3.00 (dd, 1H, -CH_2I, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=4.8 Hz), 3.50–3.80 (m, 2H,-CHOH, -NCH_2 (1H!)), 3.96 (dd, 1H, -NCH_2; $^2J_{H,H}$=13.8 Hz, $^3J_{H,H}$=2.6 Hz), 7.66 (s, 1H, H-5); ^{13}C NMR δ 7.8 (t, -CH_2I), 12.7 (q, -CH_3), 51.0 (t, -NCH_2-), 69.1 (d, -CHOH), 120.7

(d, C-5), 144.9 (s, C-2), 145.4 (s, C-4); microanalysis calcd. for $C_7H_{10}IN_3O_3$ (310.98), C 27.03, H 3.24, N 13.51, found C 27.48, H 3.27, N 13.21.

General procedure for the synthesis of the acetates

Method A. 5-Nitro compounds. 3.7 mmol of the halohydrin was suspended in 37 mmol (3.5 mL) acetic anhydride. After addition of 3.7 mmol (0.3 mL) dry pyridine the solid was dissolved and stirred for 1 h at room temperature. The solution was poured into 25 mL ice water. The product precipitates as a white solid, which was filtered and washed with cold water (3×10 mL).

Method B. 4-Nitro compounds. 4 mmol of the halohydrin was dissolved in 15 mL acetic anhydride and 4.8 mmol (1.2 eq.) dry pyridine. The solution was stirred for 1 h at room temperature and finally poured into 5 mL of ice water. The mixture was extracted with dichloromethane (3×2 mL) and the organic layer was washed with diluted hydrochloric acid (2 N, 1×2 mL), saturated $NaHCO_3$ solution (1×2 mL) and distilled water (1×2 mL). The products were obtained as oils which crystallize in the refrigerator.

1-(2-Acetoxypropyl-3-chloro)-2-methyl-5-nitroimidazole ***7a***

Deviating from method A 50 mmol of **1a** and pyridine, 0.4 mol of acetic anhydride were used instead; 10.1 g (84%) of **7a** was obtained as a colorless solid, mp 112°C) ^{1}H NMR δ 2.0 (s, 3H, -C*H*$_3$), 2.55 (s, 3H, -CO_2C*H*$_3$), 3.87 (dd, 1H, -C*H*$_2$Cl, $^2J_{H,H}$=12.4 Hz, $^3J_{H,H}$=3.8 Hz), 3.93 (dd, 1H, -C*H*$_2$Cl, $^2J_{H,H}$=12.4 Hz, $^3J_{H,H}$=4.5 Hz), 4.49 (dd, 1H, -NC*H*$_2$-, $^2J_{H,H}$=14.8 Hz, $^3J_{H,H}$=9.5 Hz), 4.76 (dd, 1H, -NC*H*$_2$-, $^2J_{H,H}$=14.8 Hz, $^3J_{H,H}$=2.9 Hz), 5.32–5.42 (m, 1H, -C*H*OAc), 7.93 (s, 1H, H-5); ^{13}C NMR δ 14.3 (q, -*C*H$_3$), 20.4 (q, -CO_2*C*H$_3$), 43.3 (t, -*C*H$_2$Cl), 46.9 (t, -N*C*H$_2$-), 70.7 (d, -*C*HOAc), 133.1 (d, C-4), 138.6 (s, C-2), 150.9 (s, C-5), 169,9 (s, -*C*O$_2$-); microanalysis calcd. for $C_9H_{12}ClN_3O_4$ (261.05), C 41.31, H 4.62, N 16.06, found C 41.40, H 4.63, N 15.93.

1-(2-Acetoxypropyl-3-chloro)-2-methyl-4-nitroimidazole ***7b***

According to method B 1.02 g (98%) of **7b** were obtained as a yellowish solid, mp 88°C; ^{1}H NMR δ 2.05 (s, 3H, -C*H*3), 2.45 (s, 3H, -CO_2C*H*$_3$), 3.55 (dd, 1H, -C*H*$_2$Cl, $^2J_{H,H}$=12.2 Hz, $^3J_{H,H}$=6.2 Hz), 3.62 (dd, 1H, -C*H*$_2$Cl, $^2J_{H,H}$=12.2 Hz, $^3J_{H,H}$=4.3 Hz), 4.16–4.32 (m, 2H, -NC*H*$_2$-), 5.14–5.28 (m, 1H, -C*H*OAc), 7.71 (s, 1H, H-5); ^{13}C NMR δ 13.0 (q, -*C*H$_3$), 20.6 (q, -CO_2*C*H$_3$), 41.7 (t, -*C*H$_2$-Cl), 46.9 (t, -N*C*H$_2$-), 70.6 (d, -*C*HOAc), 119.9 (d, C-5), 145.4 (s, C-2), 146.8 (s, C-4), 169.3 (s, -*C*O$_2$-); microanalysis calcd. for $C_9H_{12}ClN_3O_4$ (261.05), C 41.31, H 4.62, N 16.06, found C 41.43, H 4.50, N 15.95.

1-(2-Acetoxypropyl-3-fluoro)-2-methyl-5-nitroimidazole ***8a***

According to method A 0.40 g (44%) of **8a** were obtained as a colorless solid, mp 85°C; ^{1}H NMR δ 1.97 (s, 3H, -C*H*$_3$), 2.49 (s, 3H, -CO_2C*H*$_3$), 4.42–4.81 (m, 4H, -NC*H*$_2$, -C*H*$_2$F), 5.18–5.36, 5.37–5.43 (dm, 1H, -C*H*OAc, $^3J_{H,F}$=26.4 Hz), 7.90 (s, 1H, H-4); ^{13}C NMR δ 14.2 (q, -*C*H$_3$), 20.5 (q, -CO_2*C*H$_3$), 45.6 (dt, -N*C*H$_2$-, $^3J_{C,F}$=7.6 Hz), 70.8 (dd, -*C*HOAc, $^2J_{C,F}$=20.4 Hz), 81.7 (dt, -*C*H$_2$F, $1J_{C,F}$=175.5 Hz), 133.1 (d, C-4), 138.5 (s, C-2), 150.9 (s, C-5), 169.4 (s, -*C*O$_2$-); ^{19}F NMR δ −236.2 (dt,-CH$_2$*F*, $^2J_{H,F}$=47.7 Hz, $^3J_{H,F}$=26.7 Hz); microanalysis calcd. for $C_9H_{12}FN_3O_4$ (245.08), C 44.08, H 4.93, N 17.14, found C 44.45, H 5.07, N 16.72.

1-(2-Acetoxypropyl-3-fluoro)-2-methyl-4-nitroimidazole ***8b***

Deviating from method B 0.8 mmol of **4b**, 0.96 mmol of pyridine and 2.8 mL (30 mmol) of acetic anhydride were used instead. 0.18 g (74%) of **8b** were obtained as a colorless solid, mp 84°C; ^{1}H NMR δ 2.06 (s, 3H, -C*H*$_3$), 2.43 (s, 3H, -CO_2-C*H*$_3$), 4.23 (m, 2H, -NC*H*$_2$-), 4.48 (dd, 2H, -C*H*$_2$F, $^2J_{H,F}$=46,7 Hz, $^2J_{H,H}$=$^3J_{H,H}$=3.6 Hz), 5.15–5.28 (m, 1H, -C*H*OAc), 7.70 (s, 1H, H-5); ^{13}C NMR δ 12.9 (q, -*C*H$_3$), 20.5 (q, -CO_2*C*H$_3$), 45.7 (dt, -N*C*H$_2$-, $^3J_{C,F}$=5.09 Hz), 69.8 (dd, -*C*HOAc, $^2J_{C,F}$=20.35

Hz), 80.3 (dt, -CH_2F, $1J_{C,F}$=172.95 Hz), 120.0 (d, C-5), 145.4 (s, C-2), 146.8 (s, C-4), 169.5 (s, -CO_2-); ^{19}F NMR δ −233.68 (dt,-CH_2F, $^2J_{H,F}$=45.77 Hz, $^3J_{H,F}$=20.98 Hz); microanalysis calcd. for $C_9H_{12}FN_3O_4$ (245.08) C 44.08, H 4.93, N 17.14, found C 44.00, H 5.10, N 16.35.

1-(2-Acetoxypropyl-3-bromo)-2-methyl-5-nitroimidazole ***9a***

According to method A 0.97 g (80%) of **9a** were obtained as a colorless solid, mp 118.5°C; ^{1}H NMR δ 1.98 (s, 3H, -CH_3), 2.53 (s, 3H, -CO_2CH_3), 3.58 (dd, 1H, -CH_2Br, $^2J_{H,H}$=11.4 Hz, $^3J_{H,H}$=3.8 Hz), 3.65 (dd, 1H, -CH_2Br, $^2J_{H,H}$=11.4 Hz, $^3J_{H,H}$=4.5 Hz), 4.45 (dd, 1H, -NCH_2-, $^2J_{H,H}$=14.8 Hz, $^3J_{H,H}$=9.5 Hz), 4.74 (dd, 1H, -NCH_2-, $^2J_{H,H'}$=14.6 Hz, $^3J_{H,H}$=2.9 Hz), 5.22–5.38 (m, 1H, -CHOAc), 7.90 (s, 1H, H-4); ^{13}C NMR δ 14.3 (q, -CH_3), 20.4 (q, -CO_2CH_3), 31.0 (t, -CH_2Br), 48.1 (t, –NCH_2–), 70.2 (d, -CHOAc), 133.0 (d, C-4), 139.8 (s, C-2), 150.9 (s, C-5), 169.2 (s, -CO_2-); microanalysis calcd. for $C_9H_{12}BrN_3O_4$ (305.00), C 35.31, H 3.95, N 13.73, found C 35.29, H 3.97, N 13.45.

1-(2-Acetoxypropyl-3-bromo)-2-methyl-4-nitroimidazole ***9b***

According to method B 0.66 g (53%) of **9b** were obtained as a colorless solid, mp 96°C; ^{1}H NMR δ 2.04 (s, 3H, -CH_3), 2.45 (s, 3H, -CO_2CH_3), 3.45 (dd, 1H, -CH_2-Br, $^2J_{H,H}$=11.2 Hz, $^3J_{H,H}$=6.8 Hz), 3.52 (dd, 1H, -CH_2Br, $^2J_{H,H}$=11.2 Hz, $^3J_{H,H}$=4.1 Hz), 4.27 (dd, 1H, -NCH_2-, $^2J_{H,H}$=14.8 Hz, $^3J_{H,H}$=7.2 Hz), 4.35 (dd, 1H, -NCH_2-, $^2J_{H,H}$=14.8 Hz, $^3J_{H,H}$=4.3 Hz), 5.17–5.27 (m, 1H, -CHOAc), 7.72 (s, 1H, H-5); ^{13}C NMR δ 13.1 (q, -CH_3), 20.6 (q, -CO_2CH_3), 29.3 (t, -CH_2Br), 47.9 (t, -NCH_2), 70.3 (d, -CH-OAc), 119.9 (d, C-5), 145.4 (s, C-2), 146.8 (s, C-4), 169.3 (s, -CO_2-); microanalysis calcd. for $C_9H_{12}BrN_3O_4$ (305.00), C 35.31, H 3.95, N 13.73, found C 35.61, H 3.91, N 13.57.

1-(2-Acetoxypropyl-3-iodo)-2-methyl-5-nitroimidazole ***10a***

Deviating from method A 4.8 mmol of **6a** and pyridine, 74 mmol of acetic anhydride were used instead. 1.46 g (87%) of **10a** were obtained as a brown solid, mp 112°C; ^{1}H NMR δ 1.99 (s, 3H, -CH_3), 2.54 (s, 3H, -CO_2CH_3), 3.41 (dd, 1H, -CH_2I, $^2J_{H,H}$=11.2 Hz, $^3J_{H,H}$=4.3 Hz), 3.48 (dd, 1H, -CH_2I, $^2J_{H,H}$=11.2 Hz, $^3J_{H,H}$=5.0 Hz), 4.38 (dd, 1H, -NCH_2-, $^2J_{H,H}$=14.6 Hz, $^3J_{H,H}$=9.5 Hz), 4.74 (dd, 1H, -NCH_2-, $^2J_{H,H}$=14.6 Hz, $^3J_{H,H}$=2.9 Hz), 4.97–5.04 (m, 1H, -CHOAc), 7.93 (s, 1H, H-4); ^{13}C NMR δ 3.4 (t, -CH_2I), 14.4 (q, -CH_3), 20.5 (q, -CO_2CH_3), 49.8 (t, -NCH_2-), 70.0 (d, -CHOAc), 133.0 (d, C-4), 139.9 (s, C-2), 150.9 (s, C-5), 169.1 (s, -CO_2-).

1-(2-Acetoxypropyl-3-iodo)-2-methyl-4-nitroimidazole ***10b***

Deviating from the general procedure the batch size was only half that described in method B and 8 mL of acetic anhydride were used as solvent. 0.39 g (63%) of **10b** were obtained as a colorless solid, mp 119°C; ^{1}H NMR δ 2.18 (s, 3H, -CH_3), 2.46 (s, 3H, -CO_2CH_3), 3.24 (dd, 1H, -CH_2I, $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=6.7 Hz), 3.29 (dd, 1H, -CH_2I, $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=4.5 Hz), 4.19 (dd, 1H, -NCH_2-, $^2J_{H,H}$=14.8 Hz, $^3J_{H,H}$=7.6 Hz), 4.29 (dd, 1H, -NCH_2-, $^2J_{H,H}$=15.0 Hz, $^3J_{H,H}$=4.1 Hz) 4.90–5.00 (m, 1H, -CHOAc), 7.72 (s, 1H, H-5); ^{13}C NMR δ 1.8 (t, -CH_2I), 13.2 (q, -CH_3), 20.3 (q, -CO_2CH_3), 49.3 (t, -NCH_2-), 70.6 (d, -CH-OAc), 119.8 (d, C-5), 145.4 (s, C-2), 146.8 (s, C-4), 169.3 (s, -CO_2-); microanalysis calcd. for $C_9H_{12}IN_3O_4$ (352.99), C 30.61, H 3.43, N 11.90, found C 30.96, H 3.38, N 11.69.

General procedure for the enzymatic resolution of the halohydrins

The suspension of 3.7 mmol of the halohydrin, 0.75 g of pure lipase Amano PS and 10 mL vinylacetate was stirred at room temperature. For reaction control 0.1 mL of the suspension was filtered over silica gel (addition of 2 mL acetonitrile as eluent) and submitted to HPLC analysis. The whole reaction was stopped when almost 50% conversion was reached; the workup of the reaction followed in the same manner (10–20 mL acetonitrile). The solution was evaporated under reduced pressure. Subsequent column chromatography (eluent dichloromethane/acetone=1:1 (5-nitro compounds), resp. 2:1 (4-nitro compounds) provided the *S*-acetates and the *R*-alcohols.

S-(−)-1-(2-Acetoxypropyl-3-chloro)-2-methyl-5-nitroimidazole S-(−)-**7a**

Yield: 0.40 g (1.5 mmol, 41%); $[\alpha]_D^{20}$: −69.3 (c=1.01, CH_2Cl_2), 95% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

R-(+)-1-(3-Chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole R-(+)-**1a**

Yield: 0.35 g (1.6 mmol, 43%); $[\alpha]_D^{20}$: +58.5 (c=1.00, CH_2Cl_2), 89% ee (^{1}H NMR); recrystallization from toluene afforded *R*-(+)-**1a** (0.25 g, 1.2 mmol, 31%) with $[\alpha]_D^{20}$: +65.5 (c=1.0, CH_2Cl_2), 98% ee (^{1}H NMR). *R*-(+)-**1a** was obtained as colorless crystals, mp 92°C.[25] ^{1}H NMR δ 2.44 (s, 3H, -CH_3), 3.63 (dd, 1H, -CH_2Cl, $^2J_{H,H}$=11.6 Hz, $^3J_{H,H}$=5.0 Hz), 3.69 (dd, 1H, -CH_2Cl, $^2J_{H,H}$=11.6 Hz, $^3J_{H,H}$=3.9 Hz), 4.10–4.22 (br, m, 2H, -NCH_2 (1H!) -C*H*OH), 4.52–4.68 (m, 1H, -NCH_2), 4.85 (s, 1H, CHO*H*), 7.71 (s, 1H, H-4); ^{13}C NMR δ 14.3 (q, -*C*H$_3$), 46.8 (t, -*C*H$_2$Cl), 49.6 (t, -N*C*H$_2$), 69.8 (d, -*C*HOH), 132.2 (d, C-4), 138.2 (s, C-5), 151.8 (s, C-2).

S-(−)-1-(3-Chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole S-(−)-**1a**

0.08 g of *S*-(−)-**7a** are dissolved in 7 mL concentrated HCl. After 5 h the reaction mixture was poured into 25 mL water and neutralized with aqueous ammonia to exactly pH 7. The solution was extracted 3 times with ethylacetate (5 mL), dried with magnesium sulfate and finally the solvent was evaporated under reduced pressure. Recrystallization from toluene provided *S*-(−)-**1a** in 60% yield (0.04 g); $[\alpha]_D^{20}$: −67.8 (c=0.99, CH_2Cl_2), >98% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

S-(−)-1-(2-Acetoxypropyl-3-chloro)-2-methyl-4-nitroimidazole S-(−)-**7b**

Deviating from the general procedure, 1.7 mmol of *rac*-**1b** were used instead. The enzymatic esterification was performed with a different lot of lipase Amano PS.

Yield: 0.16 g (0.73 mmol, 36%); $[\alpha]_D^{20}$: −25.6 (c=0.52, ethanol), 92% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

R-(+)-1-(3-Chloro-2-hydroxypropyl)-2-methyl-4-nitroimidazole R-(+)-**1b**

Yield: 0.12 g (0.73 mmol, 43%); $[\alpha]_D^{20}$: +29.2 (c=1.01, ethanol), 95% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

S-(−)-1-(2-Acetoxypropyl-3-fluoro)-2-methyl-5-nitroimidazole S-(−)-**8a**

Yield: 0.37 g (1.5 mmol, 41%); $[\alpha]_D^{20}$: −40.2 (c=1.01, CH_2Cl_2), >98% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

R-(+)-1-(3-Fluoro-2-hydroxypropyl)-2-methyl-5-nitroimidazole R-(+)-**4a**

Yield: 0.32 g (1.6 mmol, 43%); $[\alpha]_D^{20}$: +50.0 (c=1.00, CH_2Cl_2), 95% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

S-(−)-1-(2-Acetoxypropyl-3-fluoro)-2-methyl-4-nitroimidazole S-(−)-**8b**

Yield: 0.31 g (1.3 mmol, 34%); $[\alpha]_D^{20}$: −13.3 (c=0.99, ethanol), 96% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

R-(+)-1-(3-Fluoro-2-hydroxypropyl)-2-methyl-4-nitroimidazole R-(+)-**4b**

Yield: 0.34 g (1.7 mmol, 45%); $[\alpha]_D^{20}$: +17.9 (c=1.00, ethanol), 48% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

S-*(−)-1-(2-Acetoxypropyl-3-bromo)-2-methyl-5-nitroimidazole* S-*(−)-**9a***

Yield: 0.24 g (0.8 mmol, 21%); $[\alpha]_D^{20}$: −58.2 (c=1.01, CH_2Cl_2), 94% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

R-*(+)-1-(3-Bromo-2-hydroxypropyl)-2-methyl-5-nitroimidazole* R-*(+)-**5a***

Yield: 0.44 g (1.7 mmol, 45%); $[\alpha]_D^{20}$: +20.1 (c=0.99, CH_2Cl_2), 39% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

R-*(+)-1-(3-Bromo-2-hydroxypropyl)-2-methyl-4-nitroimidazole* R-*(+)-**5b***

Yield: 0.23 g (0.9 mmol, 24%); $[\alpha]_D^{20}$: +12.7 (c=0.94, ethanol), 61% ee (^{1}H NMR). All other spectroscopic and physical data as described above.

X-Ray analyses

Crystallographic data for *R*-(+)-**1a**: formula $C_7H_{10}N_3O_3Cl$, formula weight 219.63, colorless blocks (0.7×0.4×0.2 mm), orthorhombic, space group $P2_12_12_1$ (No. 19), a=7.455(1), b=10.497(1), c=12.812(1) Å, V=1002.6(2) Å^3, Z=4, F(000)=456, T=20°C, ρ_{calc}=1.455 g cm^{-3}, μ=33.14 cm^{-1}, empirical absorption correction via ψ-scan data ($0.861 \le C \le 0.998$), Enraf-Nonius CAD4 diffractometer, λ(CuKα_1)=1.54178 Å, ω/2θ scans, 1200 independent reflections (+h, +k, +l), $2\theta_{max}$=148.5°, 1160 observed reflections [$I \ge 2\sigma(I)$], 130 refined parameters, $R_{(obs/all)}$=0.033/0.034, $wR^2_{(obs/all)}$=0.096/0.097, goodness-of-fit on F^2 1.047, extinction correction 0.077(4), Flack parameter −0.07(2), residual electron density 0.17/−0.31 e Å^{-3}.

Crystallographic data for *S*-(−)-**7b**: formula $C_9H_{12}N_3O_4Cl$, formula weight 261.67, colorless blocks (0.25×0.20×0.15 mm), tetragonal, space group $P4_3$ (No. 78), a=8.384(1), c=35.96(3) Å, V=2466.9(5) Å^3, Z=8, F(000)=1088, T=−50°C, ρ_{calc}=1.409 g cm^{-3}, μ=28.51 cm^{-1}, empirical absorption correction via ψ-scan data ($0.936 \le C \le 0.999$), Enraf-Nonius CAD4 diffractometer, λ(CuKα_1)=1.54178 Å, ω/2θ scans, 2563 independent reflections (+h, +k, −l), $2\theta_{max}$=148.7°, 2233 observed reflections [$I \ge 2\sigma(I)$], 312 refined parameters, $R_{(obs/all)}$=0.036/0.049, $wR^2_{(obs/all)}$=0.097/0.102, goodness-of-fit on F^2 1.014, extinction correction 0.022(3), Flack parameter −0.02(2), residual electron density 0.21/−0.30 e Å^{-3}. The asymmetric unit contains two rotating isomers, characterised by the dihedral angles O7-C7-C8-Cl8/O57-C57-C56-Cl58 164.9(2)/70.9(3) and C6-C7-C8-Cl8/C56-C57-C58-Cl58 −78.5(3)/−171.3(2).

Both structures were solved with SHELXS-86[26] and refined against F^2 with SHELXL-93,[27] the hydrogen atoms were placed in calculated positions and refined as riding atoms. The figures were drawn with the SCHAKAL-92 program.[28] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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