Synthesis of Chiral Imidazole Derivatives as Purine Precursors

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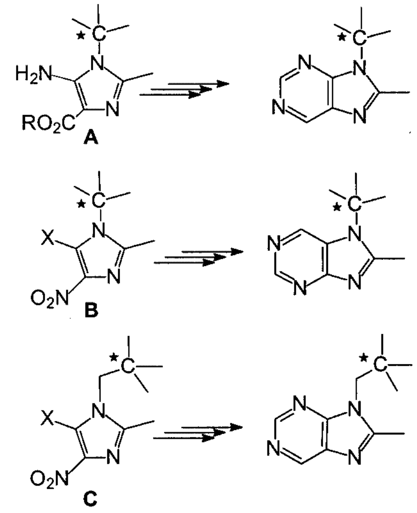
From commercially available chiral building blocks, we have developed methods for the syntheses of imidazole derivatives that contain a chiral alkyl substituent at ring atom. These compounds are suitable for further transformation into *N*-alkyl purine derivatives.

Introduction

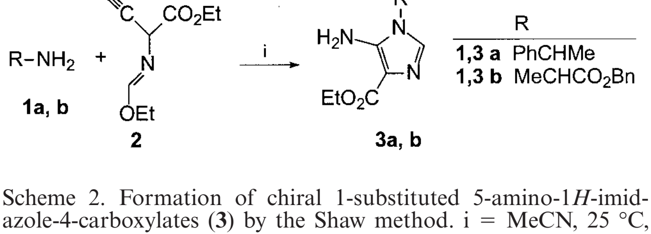
As parts of nucleic acids, purines have been under investigation for over 100 years. Some of the more useful methods of purine synthesis involve constructing the pyrimidine ring starting from imidazole derivatives.[1] The aim of this work was to synthesize such imidazole derivatives containing chiral substituents at one of the ring nitrogen atoms. These types of compounds have gathered increasing interest recently as either potential antiviral agents or their precursors.[2] Since compounds containing only one chiral center can be tested biologically both as single enantiomers and as racemates, we have attempted to develop synthetic methods useful for the preparation of all three forms. Additionally, we were interested in methods that would afford products that could be transformed readily by known methods to the corresponding purine derivatives containing chiral substituents attached either to N-7 or N-9 (Scheme 1). As sources of chiral fragments we used commercially available natural α-amino acids, amines corresponding to α-amino acids, substituted oxiranes, and sugar derivatives. Three different approaches have been applied to achieve the targets (**A**, **B** or **C**).



Scheme 1 . General concepts for the formation of chiral purine derivatives substituted at the position 7 or 9, starting from imidazole precursors **A**, **B**, or **C**.

Results and Discussion

To synthesize compounds **A**, we adapted the method invented by Shaw et al. for the preparation of nucleosides.[3] Thus, we condensed natural α-amino acid esters and chiral primary amines with cyano[(1-ethoxymethylene)amino]acetates (**2**) (Scheme 2).[4] The results are disclosed in Table 1. Yields of products obtained from amines were higher than those obtained from amino acid esters. Surprisingly, the yield of racemic product **13b** was lower than those of the corresponding single enantiomers. Judging from optical activity measurements, no racemization was observed during the reaction or its workup.



Scheme 2. Formation of chiral 1-substituted 5-amino-1*H*-imidazole-4-carboxylates (**3**) by the Shaw method. i = MeCN, 25 °C, 18 h.

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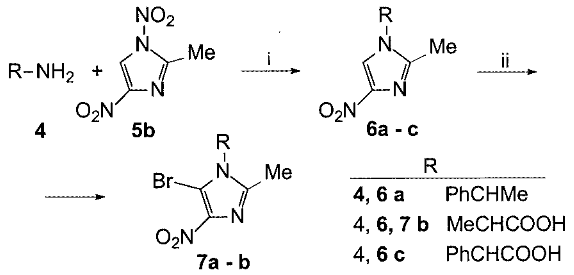
Table 1. Yields and properties of chiral imidazole derivatives **3a** and **3b** (compounds of type **A**) obtained by the Shaw method

Compound	Configuration of the chiral center	Yield [%][a]	M.p. [°C]	Solvent for crystallization	$[\alpha]^{25}_{546}$ (c = 0.5, methanol)
3a	*RS*	59	179−180	acetone	−
	R	51	145−146	acetone/Et_2O	+37.5
	S	44	147−148	acetone/Et_2O	−39.7
3b	*RS*	6.5	129−130	methanol/Et_2O	−
	R	29	157−159	methanol	+21.9
	S	17	158−159	methanol	−27.1

[a] ^1H NMR and MS data are given in the Exp. Sect.

For the synthesis of compounds **B**, we used a method that we had developed previously.[5,6] The method consists of treating a compound containing a primary amino group with 2-methyl-1,4-dinitro-1*H*-imidazole (**5b**) in aqueous solution at room temperature (Scheme 3). Under the conditions, a so-called degenerate ring transformation occurs after nucleophilic attack at C-5 of the imidazole derivative by the amino compound. The ring formation is then followed by elimination of a nitroamide. The results are listed in Table 2. When we used chiral amino acids or amines, we brominated the products of this reaction with either bromine or *N*-bromosuccinimide (Scheme 3). It should be mentioned that, until now, the bromination could be applied successfully only to imidazole derivatives containing an alkyl substituent at C-2 of the ring.



Scheme 3. Formation of chiral 1-substituted 2-methyl-4-nitroimidazoles (**6**) and 5-bromo-2-methyl-4-nitro-1*H*-imidazole (**7b**) from chiral amino compounds **4** and 2-methyl-1,4-dinitro-1*H*-imidazole (**5b**). i = water, 25 °C, 30 min, ii = Br_2 or NBS, water (see also Table 3).

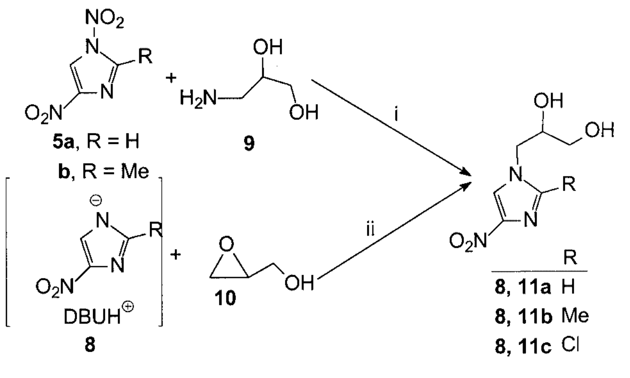
Compounds **C** were prepared using two independent methods shown in Scheme 4. The first one is based on the reaction of 1,4-dinitro-1*H*-imidazoles with 3-amino-1,2-propandiol[5,6] and the second on a nucleophilic addition[7,8] of 1-*H*-4(5)-nitroimidazole to (hydroxymethyl)oxirane. Both methods led to chiral products with very similar properties, suggesting the preservation of the configuration of the asymmetric carbon atom when using chiral starting materials (Table 4).

Table 2. Yields of chiral imidazole derivatives **6a**−**c** (compounds of type **B**) obtained in the reaction of 2-methyl-1,4-dinitro-1*H*-imidazole with amines or amino acids

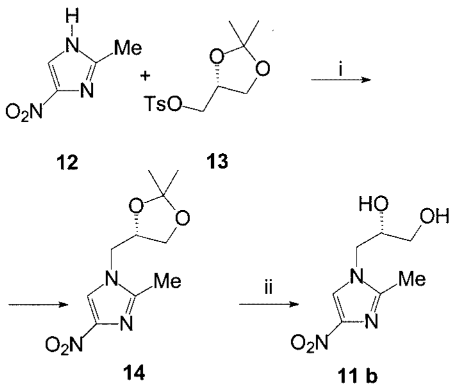
Compound	Configuration of the chiral center	Yield [%]	M.p. [°C]	Solvent for crystallization	$[\alpha]^{25}_{546}$ (c = 1, methanol)
6a	*RS*	83	110−111	methanol	−
	R	85	glass	−	+13.9
	S	87	glass	−	−14.0
6b	*RS*	81	108−110	water	−
	R	84	99−101	water	+44.5
	S	86	98−100	water	−49.8
6c	*RS*	36	glass	−	−
	R	81	glass	−	+15.6
	S	51	glass	−	−18.8

Table 3. Yields and physicochemical properties of 1-substituted 5-bromo-2-methyl-4-nitro-1*H*-imidazoles **7b**.

Compound	Configuration of the chiral center	Yield [%]	M.p. [°C]	$[\alpha]^{25}_{D}$ (c = 1, MeCN)
	RS	94	180 (dec.)	−
7b	*R*	60	182 (dec.).	+51.0
	S	53	185 (dec.).	−50.0



Scheme 4. Two routes to chiral 1-(2,3-dihydroxypropyl)-4-nitroimidazoles (**11**). i = water/1,4-dioxane (1:1), 25 °C, 1 h; ii = MeCN, reflux, 3−5 h.



Scheme 5. Synthesis of chiral **11b** by reaction of imidazole **12** with 1,3-dioxolane derivative **13** followed by cleavage of the dioxolane ring in **14** under acidic conditions. i = K_2CO_3, DMF; ii = 80% AcOH.

Racemic 3-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)propane-1,2-diol and its (*S*) enantiomer were obtained also by the reaction of 2-(*RS*) or 2-(*S*)-3-tosyloxy-1,2-*O*-isopropylidenepropanediol,[9,10] respectively, with 2-methyl-4(5)-nitro-1*H*-imidazole in the presence of anhydrous potassium carbonate, followed by a cleavage of the isopropylidene unit using 80% acetic acid (Scheme 5). Spectroscopic and optical properties of (*S*)-**11b** obtained this way were very similar to those described above.

Conclusions

Three general methods have been used for the successful syntheses of the desired inmidazole derivatives containing a chiral center in their *N*-alkyl substituents. Condensation of ethyl cyano[(1-ethoxymethylene)amino]acetate with chiral primary amines or chiral amino acid esters has afforded 1-substituted ethyl 5-amino-1*H*-imidazole-4-carboxylates, albeit in moderate yields. Reaction of 1,4-dinitro-1*H*-imidazoles with chiral primary amines or amino acid esters has given 1-substituted 4-nitroimidazoles in high yields. Bromination of one of the latter compounds, containing a methyl group at position 2 on the ring, produced the corresponding 5-bromo derivative that is suitable for further transformations. 3-(4-Nitro-1*H*-imidazol-1-yl)propane-1,2-diols have been obtained by two parallel routes: by reaction of 1,4-dinitro-1*H*-imidazoles with 3-amino-1,2-propanediols, and by alkylation of 4(5)-nitroimidazoles with (hydroxymethyl)oxiranes. The 1,2-dihydroxypropanediol derivatives can be used in syntheses of oligonucleotides containing nitroimidazole building blocks. In all the reactions studied, we have obtained both racemic and enantiomerically enriched products; the optical purity of the single enantiomers depended on the optical purity of the starting amines, amino acids, and oxiranes. We have not observed racemization during any of these syntheses.

Experimental Section

General Remarks: Elemental analyses were obtained using a Perkin−Elmer 240C apparatus. NMR spectra were recorded on a Varian spectrometer at 300 MHz for ^1H and 75.5 MHz for ^{13}C

Table 4. Yields and properties of chiral imidazole derivatives **11** obtained in the reactions of 1,4-dinitro-1*H*-imidazoles with 3-amino-1,2-propanediol (method A) or 1*H*-4(5)-nitroimidazoles with (hydroxymethyl)oxirane (method B)

Compound	Configuration of the chiral center	Method	Yield [%]	M.p. [°C]; from methanol	$[\alpha]^{25}_{546}$ (c = 1, methanol)
11a	*RS*	A	74	123−124	−
	RS	B	60	124−125	−
	R	A	77	136−137	+40.0
	R	B	55	139−140	+38.6
	S	A	67	135−136	−37.8
	S	B	53	136−137	−38.9
11b	RS	A	84	125−126	−
	RS	B	43	124−126	−
	R	A	78	130−131	+32.0
	R	B	53	130−131	+31.9
	S	A	83	129−130	−32.0
	S	B	78	130−131	−29.3
11c	RS	B	72	108−109	−
	R	B	80	106−107	+34.0
	S	B	64	105−106	−33.0

NMR; δ values are in ppm relative to tetramethylsilane as internal standard. GC-Mass spectra (EI, 70 eV) were taken with a Shimadzu QP 2000 apparatus. Column chromatography was performed on SiO_2 column (230−400 mesh, Merck). TLC plates (Merck, silica gel $60F_{254}$) were used for monitoring the progress of reactions. The aminodiols and (hydroxymethyl)oxiranes were purchased from Sigma−Aldrich.

Synthesis of 1-Substituted 4-Alkoxycarbonyl-5-aminoimidazoles 3a,b: A saturated aqueous solution of sodium hydrogen carbonate (30 mL) was added to a solution of ethyl α-hydroxyimino-α-cyanoacetate (5 g, 35.2 mmol) in water (60 mL), followed by gradual, careful (evolution of gas) addition of sodium dithionate (20 g of 86% purity). The resulting solution was stirred for 30 min at 25 °C and then extracted with dichloromethane (4 × 30 mL). The combined extracts were dried over anhydrous magnesium sulfate, the solid was filtered off, and the filtrate was condensed under reduced pressure. The weighed residue was treated with an equimolar amount of triethyl orthoformate and then heated under reflux for 45 min. The resulting solution was cooled down to room temperature and then treated with 0.83 molar equiv. of an amino compound (amine, α-amino acid or its ester) in acetonitrile (20 mL). The solution was left overnight at room temperature and then the solvents were evaporated under reduced pressure. The oily residues were dissolved in chloroform (100 mL), washed with aqueous sodium hydroxide solution (10%, 3 × 20 mL) followed by saturated aqueous sodium chloride solution (20 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and then the solvent was evaporated under reduced pressure. A solid residue was recrystallized from a suitable solvent. Spectra (^1H NMR and MS) of 1-substituted 5-amino-1*H*-imidazole-4-carboxylates (*RS*-, *R*-, and *S*-**3a,b**) were identical.

Ethyl 5-Amino-1-(1-phenylethyl)-1*H*-imidazole-4-carboxylate (3a): $C_{14}H_{17}N_3O_2$ (259.3): calcd. C 64.84, H 6.61, N 16.29; found C 64.90, H 6.57, N 16.10. ^1H NMR ($CDCl_3$): δ = 1.38 (t, *J* = 6.9 Hz, 3 H, CH_3CH_2O), 1.88 (d, *J* = 7.2 Hz, 3 H, CH_3), 4.33 (q, *J* = 6.9 Hz, 2 H, CH_3CH_2O), 4.71 (br. s, 2 H, NH_2), 5.23 (q, *J* = 7.2 Hz, 1 H, CH), 7.14−7.19 (m, 2 H, from C_6H_5), 7.33−7.43 (m, 4 H, from C_6H_5 and 2-H, imid.) ppm. MS: *m*/*z* (%) = 259 (6) [M^+], 214 (2) [M^+ − EtO], 155 (28), [M^+ − Ph-CH=CH_2], 127 (8), 105 (100) [$PhC_2H_4^+$].

Ethyl 5-Amino-1-[2-(benzyloxy)-1-methyl-2-oxoethyl]-1*H*-imidazole-4-carboxylate (3b): $C_{16}H_{19}N_3O_4$ (317.34): calcd. C 60.55, H 6.04, N 13.24; found C 60.52, H 6.02, N 13.30. ^1H NMR ($CDCl_3$): δ = 1.39 (t, *J* = 6.9 Hz, 3 H, CH_3CH_2O), 1.79 (d, *J* = 7.2 Hz, 3 H, CH_3), 4.35 (q, *J* = 6.9 Hz, 2 H, CH_3CH_2O), 4.88 (q, *J* = 7.2 Hz, 1 H, CH), 5.14 (br. s, 2 H, NH_2), 5.18 (d, *J* = 12 Hz, 1 H, CH_2Ph), 5.23 (d, *J* = 12 Hz, 1 H, CH_2Ph), 7.22 (s, 1 H, 2-H, imid.), 7.29−7.40 (m, 5 H, Ph) ppm. MS: *m*/*z* (%) = 317 (15.3) [M^+], 272 (4.2) [M^+ − EtO], 163 (1.4) [$CH_3CHCOOCH_2Ph^+$], 155 (4.7) [M^+ − CH_2=$CHCOOCH_2Ph$], 91 (100) [$PhCH_2^+$].

Synthesis of 1-Substituted 4-Nitroimidazoles 6a−c: The products **6a−c** were obtained by the reaction of 2-methyl-1,4-dinitro-1*H*-imidazole with amines or amino acids according to the method described earlier.[5,6]

(*RS*)-2-Methyl-4-nitro-1-(1-phenylethyl)-1*H*-imidazole (*RS*-6a): $C_{12}H_{13}N_3O_2$ (231.25): calcd. C 62.33, H 5.67; N 18.17; found C 62.31, H 5.68; N 18.10. ^1H NMR ($CDCl_3$): δ = 1.88 (d, *J* = 7.2 Hz, 3 H, CH_3, aliph.), 2.34 (s, 3 H, CH_3, imid.), 5.33 (q, *J* = 7.2 Hz, 1 H, CH, aliph.), 7.01−7.13 (m, 2 H, *o*- and *o*′-Ph), 7.27−7.43 (m, 3 H, *m*-, *m*′-, and *p*-Ph), 7.85 (s, 1 H, H, imid.) ppm. MS: *m*/*z* (%) = 231 (3) [M^+], 105 (100), 79 (12), 77 (15). The NMR and mass spectra of the individually prepared (*R*) and (*S*) enantiomers of **6a** were identical to those described above.

(*RS*, *R*, and *S*)-2-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)propanoic Acids (*RS*-, *R*-, and *S*-6b): The syntheses of these compounds have been described earlier.[5]

(*RS*)-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)phenylacetic Acid (*RS*-6c): Yield 40%. M.p. 110−112 °C. $C_{12}H_{11}N_3O_4$ (261.2): calcd. C 55.17, H 4.24, N 16.09; found C 55.32, H 4.01, N 15.89. ^1H NMR (CD_3OD): δ = 2.44 (s, 3 H, CH_3, imid.), 6.30 (s, 1 H, CH, aliph.), 7.49 (m, 5 H, Ph), 7.75 (s, 1 H, H, imid.) ppm. MS: *m*/*z* (%) = 261 (35) [M^+], 217 (6), 184 (2), 135 (100), 117 (11), 116 (12), 107 (38), 106 (13), 105 (31), 91 (46), 90 (18), 89 (20), 79 (51), 78 (10), 77 (55), 65(11), 63 (13), 53 (12), 52 (23), 51 (13), 46 (93), 45 (95), 44 (22), 43 (10), 42 (10), 41 (24), 40 (10). The NMR and mass spectra of the individually prepared *R* and *S* enantiomers were identical to those described above.

Synthesis of 2-(5-Bromo-2-methyl-4-nitro-1*H*-imidazolylo)propanoic Acid (7b): Bromination of 1-substituted 2-methyl-4-nitro-1*H*-imidazoles was carried out as follows: *N*-Bromosuccinimide (0.89 g, 5 mmol) was added to a suspension of (*R*)-, (*S*)-, or (*RS*)-**6b** (5 mmol) in water (20 mL) and the resulting mixture was heated at 60 °C with stirring for 2 h. A second portion of succinimide (0.89 g, 5 mmol) was then added and heating was continued for another 2 h. After cooling, a white precipitation was collected, rinsed with water, dried, and recrystallized from an appropriate solvent.

(*RS*)-7b: Recrystallized from aqueous dimethylformamide. $C_7H_8BrN_3O_4$ (278.06): calcd. C 30.24, H 2.90, N 15.11; found C 30.19, H 2.78, N 15.01. ^1H NMR ([D_7]DMF): δ = 1.81 (d, *J* = 7.5 Hz, 3 H, CH_3), 2.53 (s, 3 H, CH_3, imid.), 5.58 (q, *J* = 7.5 Hz, 1 H, CH) ppm. MS: *m*/*z* (%) = 277 (12) [M^+ + 2], 275 (11) [M^+], 198 (2), 95 (10), 47 (11), 45 (100), 44 (26). The NMR and mass spectra of the individually prepared (*R*) and (*S*) enantiomers were identical to those described above.

Synthesis of 3-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)propane-1,2-diols (11). Method A: 1,4-Dinitro-1*H*-imidazole **5a** (1.58 g, 0.01 mol) or 2-methyl-1,4-dinitro-1*H*-imidazole (**5b**) (1.72 g, 0.01 mol) was added gradually to a solution of 3-amino-1,2-propanediol (**9**) (0.91 g, 0.01 mol) in water/1,4-dioxane (1:1, 40 mL). Evolution of gas, which caused foam to form, was observed during the addition. The resulting reddish-yellow solution was left overnight at 25 °C and then evaporated under reduced pressure. An oily residue was chromatographed on silica gel using methanol/chloroform (1:5) as eluent. Products were recrystallized from methanol.

Synthesis of 3-(4-Nitro-1*H*-imidazol-1-yl)propane-1,2-diols (11). Method B: Stable salts (**8a−c**) formed[11,12] from nitroimidazoles and DBU (2 mmol) were dissolved individually in anhydrous acetonitrile (10 mL) and heated to reflux. (Hydroxymethyl)oxirane (**10**) (3 mmol) was added gradually over 20 min to the boiling solutions and heating was continued for 2−5 h until disappearance of the substrates occurred (TLC). The solutions were cooled to room temperature, carefully neutralized to pH 7 with hydrochloric acid (5%), evaporated under reduced pressure, and the residues purified as in method A.

(*RS*)-11a: $C_6H_9N_3O_4$ (187.16): calcd. C 38.51, H 4.85, N 22.45; found C 38.65, H 4.86, N 22.31. ^1H NMR ([D_6]DMSO): δ = 3.22 (dd, 1 H, *J* = 6.6, 11.1 Hz, CH_aHOH), 3.39 (dd, 1 H, *J* = 5.1, 11.1 Hz, CHH_bOH), 3.74−3.80 (m, 1 H, CH, aliph.), 3.98 (dd, 1 H, *J* = 7.8, 13.8 Hz, NCH_aH), 4.20 (dd, 1 H, *J* = 3.0, 13.8 Hz, $NCHH_b$), 4.86 (br. s, 1 H, CH_2OH), 5.18 (br. s, 1 H, CHO*H*), 7.77, (d, *J* = 1.5 Hz, 1 H, 2-H, imid.), 8.28 (d, *J* = 1.5 Hz, 1 H, 5-H, imid.) ppm.

(*R*)-11a: MS: *m*/*z* (%) = 187 (8) [M$^+$], 171 (2), 157 (20) [M − NO]$^+$, 127 (100), 114 (78), 110 (15), 97 (16), 81 (18), 67 (18), 61 (49), 55 (30), 53 (28), 43 (65), 41 (44).

(*S*)-11a: ^{1}H NMR ([D$_6$]DMSO): δ = 3.27−3.44 (m, 2 H, C*H*$_2$OH), 3.70−3.78 (m, 1 H, CH, aliph.), 4.01 (dd, 1 H, *J* = 7.8, 13.8 Hz, NC*H*$_a$H), 4.21 (dd, 1 H, *J* = 3.0, 13.8 Hz, NCH*H*$_b$), 4.88 (t, *J* = 5.1 Hz, 1 H, CH$_2$O*H*), 5.21 (d, *J* = 5.1 Hz, 1 H, CHO*H*), 7.84, (d, *J* = 1.5 Hz, 1 H, 2-H, imid.), 8.30 (d, *J* = 1.5 Hz, 1 H, 5-H, imid.) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 50.59 (CH$_2$OH), 62.08 (CHOH), 70.02 (N−CH$_2$), 122.17 (C-5, imid.), 137.88 (C-2, imid.), 146.66 (C-4, imid.) ppm.

3-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)propane-1,2-diol (11b)

(*RS*)-11b: $C_7H_{11}N_3O_4$ (201.18): calcd. C 41.79, H 5.51, N 20.89; found C 41.88, H 5.49, N 20.95. ^{1}H NMR ([D$_6$]DMSO): δ = 2.38 (s, 3 H, Me), 3.28−3.34 (m, 1 H, C*H*$_a$HOH), 3.41−3.43 (m, 1 H, CH*H*$_b$OH), 3.77−3.80 (m, 1 H, CH, aliph.), 3.93 (dd, 1 H, *J* = 7.8, 14.1 Hz, NC*H*$_a$H), 4.16 (dd, 1 H, *J* = 3.3, 14.1 Hz, NCH*H*$_b$), 4.92 (t, *J* = 5.4 Hz, 1 H, CH$_2$O*H*), 5.21 (d, *J* = 5.4 Hz, 1 H, CHO*H*), 8.19 (s, 1 H, 5-H, imid.) ppm.

(*R*)-11b: ^{13}C NMR ([D$_6$]DMSO): δ = 12.83 (2-CH$_3$), 49.64 (CH$_2$OH), 62.93 (CHOH), 70.24 (CH$_2$N), 122.83 (C-5, imid.), 145.12 (C-2, imid.), 145.62 (C-4, imid.) ppm. MS: *m*/*z* (%) = 201 (10) [M$^+$], 171 (2, [M − NO]$^+$), 154 (3), 141 (24), 128 (36), 124 (6), 95 (2), 81 (10) 74 (2), 69 (12), 61 (13), 43 (100), 41 (12).

(*S*)-11b: ^{1}H NMR ([D$_6$]DMSO): δ = 2.39 (s, 3 H, Me), 3.29−3.30 (m, 1 H, C*H*$_a$HOH), 3.38−3.45 (m, 1 H, CH*H*$_b$OH), 3.70−3.78 (m, 1 H, CH, aliph.), 3.91 (dd, 1 H, *J* = 8.1, 14.1 Hz, NC*H*$_a$H), 4.12 (dd, 1 H, *J* = 3.0, 14.1 Hz, NCH*H*$_b$), 4.87 (t, *J* = 5.1 Hz, 1 H, CH$_2$-O*H*), 5.16 (d, *J* = 5.4 Hz, 1 H, CHO*H*), 8.17 (s, 1 H, 5-H, imid.) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 49.53 (CH$_2$OH), 62.82 (CHOH), 70.15 (NCH$_2$), 122.68 (C-5, imid.), 145.05 (C-2, imid.), 145.48 (C-4, imid.) ppm.

3-(2-Chloro-4-nitro-1*H*-imidazol-1-yl)propane-1,2-diol (11b)

(*RS*)-11c: $C_6H_8ClN_3O_4$ (221.60): calcd. C 32.52; H 3.64; N 18.96; found C 32.72; H 3.70; N 18.81. ^{1}H NMR ([D$_6$]DMSO): δ = 3.28−3.32 (m, 1 H, C*H*$_a$HOH), 3.41−3.45 (m, 1 H, CH*H*$_b$OH), 3.78−3.84 (m, 1 H, CH, aliph.), 3.98 (dd, 1 H, *J* = 8.4, 14.1 Hz, NC*H*$_a$H), 4.18 (dd, 1 H, *J* = 3.3, 14.1 Hz, NCH*H*$_b$), 4.90 (t, *J* = 5.5 Hz, 1 H, CH$_2$O*H*), 5.23 (d, *J* = 5.4 Hz, 1 H, CHO*H*), 8.42 (s, 1 H, 5-H, imid.) ppm.

(*R*)-11c: ^{1}H NMR ([D$_6$]DMSO): δ = 3.34−3.46 (m, 2 H, C*H*$_2$OH), 3.79−3.85 (m, 1 H, C*H*OH), 3.96 (dd, 1 H, *J* = 8.4, 14.0 Hz, NC*H*$_a$H), 4.20 (dd, *J* = 3.0, 14.0 Hz, NCH*H*$_b$), 4.92 (br. s, 1 H, CH$_2$O*H*), 5.25 (br. s, 1 H, CHO*H*), 8.42 (s, 1 H, 5-H, imid.) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 50.75 (CH$_2$OH), 63.05 (CHOH), 69.50 (NCH$_2$), 124.28 (C-5, imid.), 132.02 (C-2, imid.), 144.32 (C-4, imid.) ppm.

Synthesis of 3-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)propane-1,2-diols (11). Method C: (*R*)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl tosylate[9,10] **13** (0.43 g, 1.5 mmol) was added to a suspension of 2-methyl-4(5)-nitroimidazole **12** (0.23 g, 1.8 mmol) and anhydrous K_2CO_3 (0.21 g, 1.5 mmol) in anhydrous DMF (4 mL), and then the mixture was heated at 80 °C for 1 h. TLC (MeOH/CHCl$_3$, 3:97, v/v) indicated disappearance of the starting tosylate. The reaction solvent was evaporated to dryness and purified on a silica gel-packed column (3% MeOH/CHCl$_3$). The oily intermediate (*S*)-{1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-methyl-4-nitro-1*H*-imidazole} (**14**) was isolated (0.31 g, 86%). ^{1}H NMR (CDCl$_3$): δ = 1.34 (s, 3 H, Me, diox.), 1.41 (s, 3 H, Me, diox.), 2.47 (s, 3 H, Me, imid.), 3.75 (dd, 1 H, *J* = 6.5, 8.6 Hz, NC*H*$_a$H), 4.02 (dd, 1 H, *J* = 7.3, 14.7 Hz, C*H*$_a$H, diox.), 4.19 (dd, 1 H, *J* = 6.3, 8.6 Hz, NCH*H*$_b$), 4.20 (dd, 1 H, *J* = 2.6, 14.7 Hz, CH*H*$_b$, diox.), 4.46−4.39 (m, 1 H, CH, diox.), 7.89 (s, 1 H, 5-H, imid.) ppm.

(*S*)-(11b): Compound **14** (0.19 g, 0.8 mmol) was heated under reflux in 80% AcOH (10 mL) for 2 h. Evaporation of the volatiles and purification of the residue on a silica gel column gave the product (0.09 g, 63%). M.p. 127−129 °C. $[\alpha]_D^{25} = -33.0$ (*c* = 1, MeOH).

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