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Optically active imidazoles derived from enantiomerically pure *trans*-1,2-diaminocyclohexane[1]

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Dedicated to Professor Janusz Jurczak (Warsaw) on the occasion of his 70th birthday

ABSTRACT

A new exploration of monoprotected derivatives of *trans*-1,2-diaminocyclohexane as a platform for the synthesis of enantiomerically pure imidazole derivatives is described. The primary amino group ($-NH_2$), present in the *mono*-imine derivative of salicylic aldehyde (hemi-salen derivative) **5** was used for sequential reactions with formaldehyde and the corresponding α-(hydroxyimino)ketone. (*S*)-(−)-1-Phenylethylamine was also used as starting material for the preparation of new imidazole *N*-oxides **7c** and **10a**–**c**, bearing a chiral *N*-(1-phenylethyl)carboxamido function at C(4). Imidazole *N*-oxides **10a**,**b** possessing either a Me or *i*-Pr group at N(1), respectively, follow the known sulfur-transfer pathway to afford the corresponding imidazole-2-thiones **13a**,**b**. However, in the case of imidazole *N*-oxide **10c** with a bulky adamantan-1-yl substituent at N(1), the attempted 'sulfur-transfer reaction' led to the deoxygenated imidazole derivative **14**. Finally, the same reaction with **7c**, which bears an electron-withdrawing *N*-(1-phenylethyl)carboxamide residue at C(4) of the imidazole ring, yielded a mixture of deoxygenated imidazole **16** and imidazole-2-thione **15c**.

1. Introduction

Chiral 1,2-diamines are widely applied as easily available starting materials for the preparation of optically active heterocycles.[2] Of particular note is *trans*-1,2-diaminocyclohexane **1a**, which can be isolated as a pure enantiomer by resolution via diastereomeric tartrates.[3] In recent papers we reported the efficient synthesis of bis-imidazoles starting with enantiomerically pure **1a**.[4,5] The initially obtained *N*,*N*′-dioxides **2** were deoxygenated to give the bis-imidazoles **3**, which were subsequently alkylated to yield the corresponding bis-imidazolium salts **4** (Fig. 1).[4b] Some of the optically active *N*,*N*′-dioxides as well as the deoxygenated bis-imidazoles were successfully applied as organocatalysts for the asymmetric allylation of aromatic aldehydes[5] and for asymmetric cyclopropanations.[6]

Herein our goal was the synthesis of a novel series of optically active imidazole *N*-oxides using some monoprotected derivatives of **1a**. Furthermore, the obtained *N*-oxides should be converted into the corresponding imidazole-2-thiones. Both imidazole *N*-oxides and imidazole-2-thiones are potentially attractive as new ligands for asymmetric synthesis or as organocatalysts. In numerous recent papers, some optically active aza-aromatic *N*-oxides were demonstrated to be efficient ligands.[7a] Moreover, it is well established that many thiourea derivatives, which can be considered as structural analogs of imidazole-2-thiones, act efficiently as organocatalysts and ligands for asymmetric synthesis.[7b–e] Nevertheless, to the best of our knowledge, no reports on the synthesis of optically active imidazole-2-thiones, potentially useful in asymmetric synthesis, have been published.

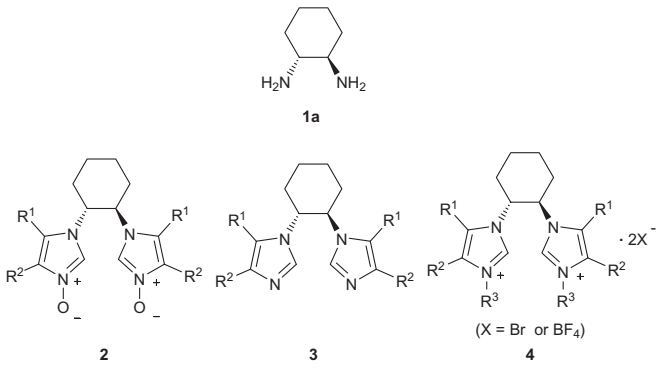

Figure 1. *trans*-1,2-Diaminocyclohexane **1a** (DACH) as a substrate for preparation of C_2-symmetrical bis-imidazole derivatives **2**,[4a] **3**[4a] and **4**.[4b]

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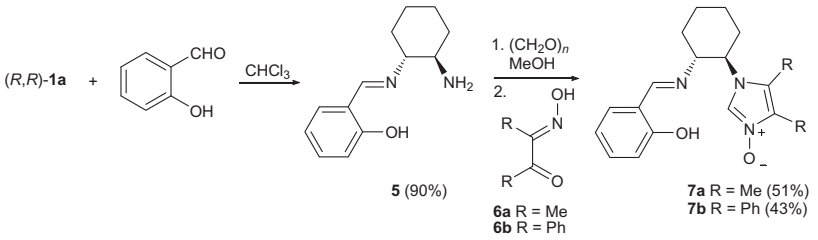


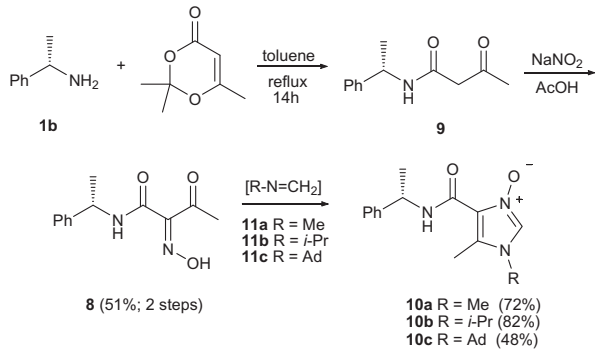
Scheme 1.

2. Results and discussion

Several methods for the monoprotection of **1a** are known; the most frequently applied are *N*,*N*-dialkylation,[8] *N*-acetylation,[9] and *N*-Boc-protection.[10] In addition to these methods, the conversion to a monoimine with aldehydes or ketones is also described, and this type of monoprotection with salicylic aldehydes is of special importance (hemi-salen-type ligands).[11]

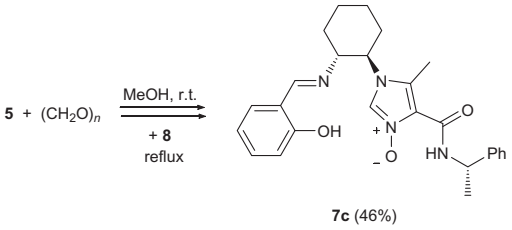
Based on literature protocol, the desired monoimine **5** was prepared in high yield and, without purification, it was reacted with paraformaldehyde (Scheme 1). The crude product obtained was used for a condensation with α-hydroxyimino ketones **6** to yield, after heating for 8 h in ethanol, the desired imidazole 3-oxides **7** as crystalline materials. The enantiomeric purity of these products was proven by recording the ^{1}H NMR spectra with equimolar amounts of (*S*)-(−)-(*tert*-butyl)(phenyl)phosphinothioic acid.[4a] In both cases, there was only one set of the diagnostic signals for H-C(2) and HC=N. For example, in the spectrum of **7a**, these signals appeared at 9.70 and 8.13 ppm, respectively, and were significantly downfield shifted in comparison with the parent structure (7.82 and 8.00 ppm, respectively).

Recently, we described an efficient method for the preparation of 3-oxidoimidazole-4-carboxamides using 2-(hydroxyimino)-3-oxoamides in the reaction with *N*-methylidene amines.[12] For the purposes of this study, (*S*)-(−)-*N*-(1-phenylethyl)-2-hydroxyimino-3-oxobutyramide **8** was prepared by trapping the in situ generated acetylketene[13] with (*S*)-(−)-1-phenylethylamine **1b** and subsequent nitrosation of the β-oxoamide **9** (Scheme 2). In order to check the utility of **8** in the synthesis of enantiomerically pure 3-oxidoimidazole-4-carboxamides **10**, compound **8** was successfully employed in the reaction with *N*-methylidene amines **11** (R = Me, *i*-Pr, Ad). Even in the case of the bulky *N*-(adamant-1-yl)formaldimine **11c**, the product **10c** was obtained in fair yield.



Scheme 2.

The successful synthesis of *N*-oxides **10** prompted us to use **8** for the reaction with **5** in order to prepare the more complex hemi-salen-like imidazole 3-oxide **7c**, which possess three stereogenic centers (Scheme 3).

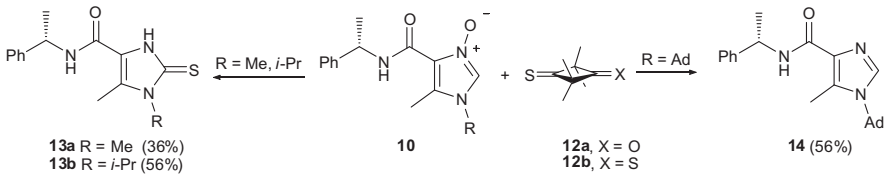


Scheme 3.

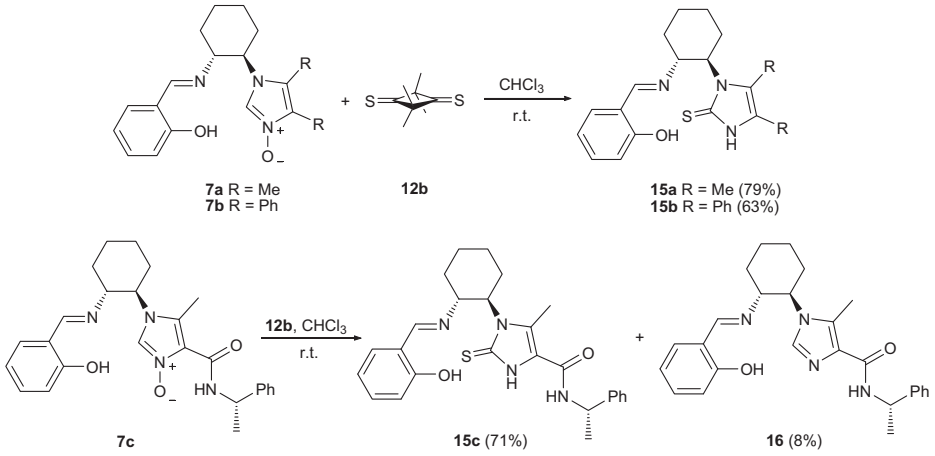
As evidenced in a series of papers, 2-unsubstituted imidazole 3-oxides can be easily converted into the corresponding imidazole-2-thiones via a sulfur-transfer reaction by treatment with 2,2,4,4-tetramethyl-3-thioxocyclobutanone **12a** or the corresponding dithione **12b**.[14] The reaction mechanism involves a [2+3] cycloaddition reaction as an initiating step. Both thioketones **12a** and **12b** are easily available and in contrast to other representatives of this class of sulfur-containing substances, can be stored for a longer time without decomposition.[14a] Earlier studies indicated that they act as efficient dipolarophiles and superior 'sulfur transferring agents' in reactions with 2-unsubstituted imidazole 3-oxides. With these 1,3-dipoles, the reactions of **12a** and **12b**, used as dipolarophiles are more efficient than those of other popular thioketones, such as thiobenzophenone or adamantanethione.[14b] According to the general 'sulfur transfer' protocol, the new imidazole 3-oxides were treated with **12b** in chloroform at room temperature. In the case of **10a**,**b**, the reactions occurred smoothly to yield, as expected, imidazole-2-thiones **13a**,**b** as the sole products (Scheme 4). However, in the case of **10c**, bearing the bulky adamantyl substituent at N(1), the deoxygenated imidazole **14** was obtained as the only product.[15] A stepwise mechanism of the [2+3]-cycloaddition reaction leading to deoxygenation of the starting imidazole *N*-oxide, reacting as a 'nitrone-like' 1,3-dipole, was extensively discussed in a previous paper[15] and an elusive oxathiirane, derived from **12b**, was evidenced as an intermediate. In order to confirm the structure of the isolated product, imidazole 3-oxide **10c** was reacted with freshly prepared *Raney*-nickel and imidazole **14** was isolated as the sole product in 61% yield.

The reaction of dithione **12b** with 'hemi-salen derived' imidazole 3-oxides **7a**,**b** led to the expected imidazole-2-thiones **15a**,**b** in good yields (Scheme 5). The presence of the electron-withdrawing carboxamide group at C(4) in **7c** slightly influenced the reaction course,[15] and along with imidazole-2-thione **15c**, the deoxygenated imidazole **16** was formed. Both products were separated by column chromatograph and obtained in 71% and 8% yield, respectively.

In the ^{1}H NMR spectrum of **15c** recorded in $CDCl_3$, two sets of diagnostic signals (in ca. 4:1 ratio) were observed. An analogous doubled-signal pattern was observed in CD_3OD (ca. 3:1 ratio) as well as in DMSO-d_6 (ca. 5:3 ratio). The dynamic nature of **15c** was proven by the registration of a series of ^{1}H NMR spectra in DMSO-d_6 at increased temperatures (the diagnostic part is shown



Scheme 4.



Scheme 5.

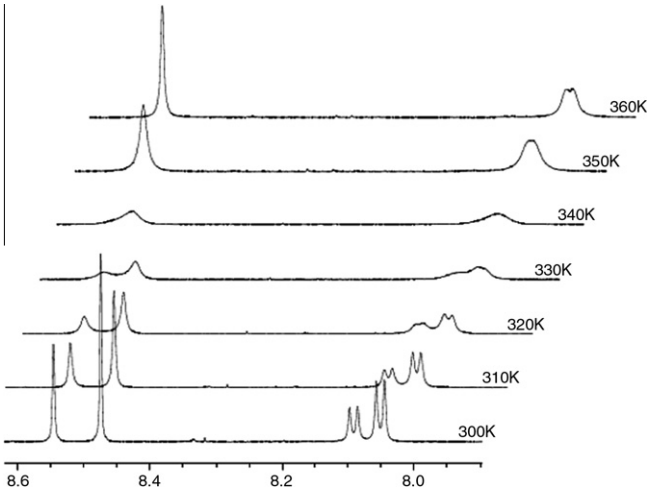
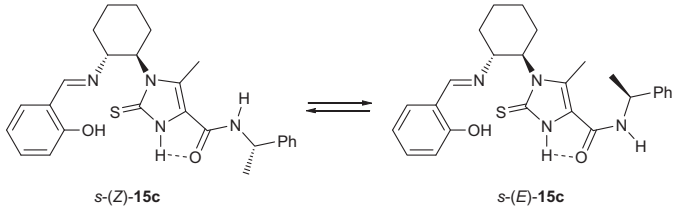


Figure 2. The diagnostic part of ^{1}H NMR spectra (DMSO-d_6, 600 MHz) of **15c** at variable temperatures.



Scheme 6.

in Figure 2). A likely explanation of the observed phenomena is the formation of two rotamers [*s*-(*Z*)-**15c** and *s*-(*E*)-**15c**] stabilized by strong intramolecular hydrogen bonding of the amide function (Scheme 6). The IR spectrum of **15c** supports this assumption; in contrast to the corresponding imidazole *N*-oxide **7c** ($\nu_{C=O}$ 1660 cm^{-1}) and the deoxygenated derivative **16** ($\nu_{C=O}$ 1653 cm^{-1}), in the case of **15c** a significant shift of the amide C=O to 1629 cm^{-1} was observed.

In addition, the synthesis of imidazole derivatives of **1**, analogous to **7**, was attempted, starting with *mono*-Boc and *mono*-acetyl protected *trans*-1,2-diaminocyclohexane **1a** and α-(hydroxyimino)ketone **6a**. In both cases, none of the expected imidazole N-oxides was obtained.

3. Conclusions

The results presented herein show that the mono-imine **5**, derived from *trans*-1,2-diaminocyclohexane and salicylaldehyde, is a suitable substrate for the preparation of non-symmetrical, enantiomerically pure imidazole *N*-oxides **7**. On the other hand, optically active imidazole *N*-oxides with a carboxamide function at C(4) can be prepared using 2-hydroxyimino-3-oxobutyramide **8**, easily accessible from (*S*)-(−)-1-phenylethylamine **1b** and in situ generated acetylketene. Examples of both classes of *N*-oxides can be converted into the corresponding imidazole-2-thiones **13** and **15**. However, in the cases of **10c** and **7c**, bearing an electron-withdrawing carboxamido group at C(4) and a bulky substituent at N(1), the deoxygenation of the imidazole *N*-oxide was observed. The enantiomerically pure imidazole derivatives described are potentially attractive ligands for asymmetric syntheses.

4. Experimental

4.1. General

Melting points were determined in a capillary using a MEL-TEMP II apparatus (*Aldrich*) and are uncorrected. IR Spectra were

recorded with a NEXUS FT-IR instrument as KBr pellets or as films; absorptions (ν) are given in cm^{-1}. ^1H NMR and ^{13}C NMR Spectra were recorded on a BRUKER AVANCE III (^1H at 600 and ^{13}C at 150 MHz) instrument in $CDCl_3$, CD_3OD or DMSO-d_6 solutions; chemical shifts (δ) in ppm; coupling constants (J) in Hz. The multiplicity of the ^{13}C signals was deduced from DEPT, supported by ^1H–^{13}C HMQC spectra. Optical rotations were determined on a PERKIN-ELMER 241 MC polarimeter. ESI mass spectra were measured on a Finnigan MAT-95 instrument.

4.2. Starting materials

Applied reagents such as racemic *trans*-1,2-diaminocyclohexane (technical grade), L-(+)-tartaric acid, salicylaldehyde, (*S*)-(−)-1-phenylethylamine, acetylacetone, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, other ketones, alkyl amines, paraformaldehyde, and solvents are commercially available and were used as received. Enantiomerically pure (*R*,*R*)-*trans*-1,2-diaminocyclohexane was prepared by the resolution of racemic DACH using natural tartaric acid.[3] Formaldimines derived from methylamine, isopropylamine, and 1-adamantaneamine were prepared according to literature protocols.[16] α-(Hydroxyimino)ketones were obtained according to known procedures: butane-2,3-dione monooxime by nitrosation of butanone using isoamyl nitrite;[17a] 1,2-diphenylethane-1,2-dione monooxime (benzil monooxime) from dibenzoyl and hydroxylamine.[17b] Monoimine **5**[11a] was obtained in 90% yield (95% purity) and used in the next step without further purification.

4.3. Synthesis of imidazole 3-oxides 7a–c

To the magnetically stirred solution of monoimine **5** (10.0 mmol, 2.2 g) in dry ethanol (30 mL), containing freshly activated molecular sieves 4 Å, paraformaldehyde (11.0 mmol, 0.33 g) was added in one portion at 0 °C. The resulting mixture was allowed to reach rt and stirred overnight. Next, the respective α-(hydroxyimino)ketone (11.0 mmol; 1.11 g of **6a**, 2.48 g of **6b**, or 2.57 g of **8**) was added and the mixture refluxed for 8 h. After the solution was cooled and filtered, the solvent was removed in vacuo, the oily residue was purified by column chromatography to give the product of type **7** as a yellow solid.

4.3.1. Imidazole 3-oxide 7a

Yield after column chromatography (SiO_2, AcOEt then AcOEt/MeOH 1:1, R_f = 0.36): 1.60 g (51%). Yellow solid. Mp 139–141 °C. IR (KBr): 3420vs (br), 2935s, 2860 m, 1629vs, 1579 m, 1497 m, 1452 m, 1413 m, 1339 m, 1275 m, 1208 m, 1197 m, 759 m. ^1H NMR ($CDCl_3$): 12.70 (s, 1H, OH); 8.00 (s, 1H, –N=CH–); 7.82 (s, 1H, HC(2)); 7.32–7.29 (m, 1 arom. H); 7.14 (dd, J = 7.8, J = 1.8, 1 arom. H); 6.90 (dd, J = 8.4, J = 1.2, 1 arom. H); 6.86 (dt, J = 7.8, J = 1.2, 1 arom. H); 4.03–3.99 (m, 1H, *c*Hex); 3.23–3.19 (m, 1H, *c*Hex); 2.19–2.12 (m, 2H, *c*Hex); 2.07, 2.03 (2s, 6H, 2Me); 2.01–1.47 (m, 6H, *c*Hex). ^{13}C NMR ($CDCl_3$): 165.7 (s, –N=CH–); 160.5 (s, (Ph)C–OH); 132.8, 132.0, 119.0, 116.7 (4d, 4CH(Ph)); 125.8, 121.8, 118.2 (3s, C(Ph), C(4), C(5)); 121.4 (d, C(2)); 73.9, 59.3 (2d, CH(*c*Hex)); 34.1, 32.4, 25.1, 23.8 (4t, $4CH_2$(*c*Hex)); 8.9, 7.0 (2q, 2Me). ESI-HRMS: 314.1862 (calcd 314.1863 for $C_{18}H_{24}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25} = -387.3$ (*c* 1.10, $CHCl_3$), $[\alpha]_D^{25} = -386.9$ (*c* 0.50, $CHCl_3$), $[\alpha]_D^{25} = -388.0$ (*c* 0.25, $CHCl_3$).

4.3.2. Imidazole 3-oxide 7b

Yield after column chromatography (SiO_2, AcOEt then AcOEt/MeOH 1:1, R_f = 0.74): 1.88 mg (43%). Yellow solid. Mp 117–120 °C. IR (KBr): 3420vs (br), 3060 m, 2934s, 2858 m, 1671 m, 1628vs, 1578 m, 1497 m, 1446 m, 1406 m, 1340 m, 1279 m, 765 m, 712 m. ^1H NMR ($CDCl_3$): 12.33 (s, 1H, OH); 8.22 (s, 1H, HC(2)); 8.21 (s, 1H, –N=CH–); 7.45–7.36 (m, 5 arom. H); 7.31–7.28 (m, 1 arom. H); 7.23 (dd, J = 7.2, J = 1.2, 1 arom. H); 7.19–7.16 (m, 3 arom. H); 7.11–7.09 (m, 2 arom. H); 6.93–6.89 (m, 1 arom. H); 6.86 (dt, J = 7.5, J = 1.2, 1 arom. H); 4.03–3.98 (m, 1H, *c*Hex); 3.40–3.36 (m, 1H, *c*Hex); 2.20–2.16 (m, 1H, *c*Hex); 1.96–1.74 (m, 4H, *c*Hex); 1.63–1.56 (m, 1H, *c*Hex); 1.49–1.41 (m, 1H, *c*Hex); 1.37–1.30 (m, 1H, *c*Hex). ^{13}C NMR ($CDCl_3$): 165.7 (s, –N=CH–); 160.5 (s, (Ph)C–OH); 132.8, 132.0, 130.9 (2C), 129.6, 129.5 (2C), 129.1 (2C), 128.0, 127.9 (2C), 119.0, 116.7 (10d, 14CH(Ph)); 128.1, 127.1, 126.5, 125.6, 118.3 (5s, 3C(Ph), C(4), C(5)); 123.2 (d, C(2)); 72.9, 59.9 (2d, CH(*c*Hex)); 34.0, 33.3, 24.9, 23.6 (4t, $4CH_2$(*c*Hex)). ESI-HRMS: 438.2174 (calcd 438.2176 for $C_{28}H_{28}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25} = -81.0$ (*c* 1.05, $CHCl_3$).

4.3.3. Imidazole 3-oxide 7c

Yield after column chromatography (SiO_2, AcOEt then AcOEt/MeOH 6:1, R_f = 0.54): 2.05 g (46%). Yellow solid. Mp 99–102 °C. IR (KBr): 3427*s* (br), 2935s (br), 2862 m, 1660s, 1629s, 1598s, 1546s (br), 1495 m, 1449 m, 1416 m, 1279s, 758 m, 700 m. ^1H NMR ($CDCl_3$): 12.45 (s, 1H, OH); 11.00 (d, J = 7.8, 1H, NH); 8.09 (s, 1H, –N=CH–); 7.97 (s, 1H, HC(2)); 7.34–7.30 (m, 2 arom. H); 7.27–7.25 (m, 3 arom. H); 7.19–7.17 (m, 1 arom. H); 7.10 (dd, J = 7.8, J = 1.8, 1 arom. H); 6.89–6.85 (m, 1 arom. H); 6.80 (dt, J = 7.5, J = 1.2, 1 arom. H); 5.20 (quint, J = 7.1, 1H); 4.22–4.18 (m, 1H, *c*Hex); 3.29 (dt, J = 10.5, J = 4.3, 1H, *c*Hex); 2.58 (s, 3H, Me); 2.12–1.91 (m, 4H, *c*Hex); 1.80–1.72 (m, 3H, *c*Hex); 1.56–1.46 (m, 1H, *c*Hex); 1.52 (d, J = 7.1, 3H, Me). ^{13}C NMR ($CDCl_3$): 166.0 (s, –N=CH–); 160.6 (s, (Ph)C–OH); 158.6 (s, CONH); 143.7, 131.3, 121.4, 118.0 (4s, 2C(Ph), C(4), C(5)); 133.1, 131.9, 128.5 (2C), 126.9, 126.0 (2C), 119.0, 117.1 (7d, 9CH(Ph)); 122.5 (d, C(2)); 72.9, 59.4, 48.1 (3d, 3CH); 34.4, 32.6, 25.0, 23.7 (4t, $4CH_2$(*c*Hex)); 22.9, 9.7 (2q, 2Me). ESI-HRMS: 447.2387 (calcd 447.2391 for $C_{26}H_{31}N_4O_3$, $[M+1]^+$). $[\alpha]_D^{25} = -195.0$ (*c* 1.00, $CHCl_3$).

4.4. Synthesis of (*S*)-(−)-*N*-(1-phenylethyl)-2-hydroxyimino-3-oxobutyramide 8

A mixture of (*S*)-(−)-1-phenylethylamine **1b** (6.61 g, 54.6 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (9.09 g, 64.1 mmol) in dry toluene (150 mL) was refluxed for 16 h. After the solvent was removed under reduced pressure, the residue was flash chromatographed (SiO_2, AcOEt/$CHCl_3$ 1:2, R_f = 0.37) to give crude β-oxoamide **9** (10.82 g, 96%) as a pale orange oil, which was used in the next step without purification. The amide **9** (10.82 g, 52.8 mmol) was dissolved in glacial AcOH (25.0 mL), the resulting mixture was magnetically stirred while cooling (water/ice bath), and a solution of sodium nitrite (4.9 g, 71.0 mmol) in H_2O (7.0 mL) was added dropwise. After ca. 2.5 h, the mixture was diluted with H_2O (90 mL) and extracted with three portions of CH_2Cl_2 (70 mL each). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, then with water, dried over $MgSO_4$, and the solvent removed. The crude product was flash chromatographed (SiO_2, CH_2Cl_2) and purified by column chromatography (SiO_2, petroleum ether/Et_2O 9:1, R_f = 0.25) to give **8** (6.52 g) as a pale yellow oil in 51% overall yield. IR: 3281vs (br), 2980s, 1686vs, 1648vs, 1551vs, 1496 m, 1451 m, 1416 m, 1363 m, 1107 m, 1019 m, 700 m. ^1H NMR ($CDCl_3$): 9.39 (br s, 1H, NH); 7.38–7.35 (m, 2 arom. H); 7.32–7.28 (m, 3 arom. H); 5.15 (quint, J = 7.2, 1H); 2.50 (s, 3H, Me); 1.57 (d, J = 7.2, Me). ^{13}C NMR ($CDCl_3$): 199.6 (s, C=O); 162.6 (s, CONH); 143.4 (s, C=N); 141.6 (s, C(Ph)); 128.9, 127.8, 126.0 (3d, 5CH(Ph)); 48.7 (d, CH); 26.2, 21.9 (2q, 2 Me). ESI-HRMS: 257.0894 (calcd 257.0896 for $C_{12}H_{14}N_2NaO_3$, $[M+Na]^+$). $[\alpha]_D^{22} = -98.3$ (*c* 1.05, MeOH).

4.5. Synthesis of imidazole 3-oxides 10a and 10b

A solution of (*S*)-*N*-(1-phenylethyl)-2-hydroxyimino-3-oxobutyramide **8** (2.34 g, 10.0 mmol) and the respective formaldimine **11** (12.0 mmol) in ethanol (30 mL) was refluxed for 5 h. After the solvent was removed, the residue was washed with Et_2O (three portions of ca. 20 mL) and purified by recrystallization of **10a** or chromatography of **10b**.

4.5.1. (*S*)-*N*-(Phenylethyl)-1,5-dimethyl-3-oxido-1*H*-imidazole-4-carboxamide 10a

Yield: 1.86 g (72%). Colorless solid. Mp 170–171 °C ($CHCl_3$/Et_2O). IR (KBr): 3442vs, 3152 m, 1655vs, 1604s, 1558 m, 1448 m, 1290 m, 766 m, 704 m. ^{1}H NMR ($CDCl_3$): 11.15 (br d, J = 6.6, 1H, CONH); 7.74 (s, 1H, HC(2)); 7.40–7.39 (m, 2 arom. H); 7.33–7.30 (m, 2 arom. H); 7.22–7.20 (m, 1 arom. H); 5.27 (quint, J = 7.2, 1H); 3.55 (s, 3H, MeN); 2.59 (s, 3H, Me); 1.57 (d, J = 7.2, 3H, Me). ^{13}C NMR ($CDCl_3$): 158.6 (s, C=O); 143.8, 130.6, 125.2 (3s, C(Ph), C(4), C(5)); 128.3, 126.7, 125.8, 121.9 (4d, 5CH(Ph), C(2)); 48.0 (d, CH); 31.7, 22.8, 9.2 (3q, 3 Me). ESI-HRMS: 282.1212 (calcd 282.1213 for $C_{14}H_{17}N_3NaO_2$, $[M+Na]^+$), 260.1392 (calcd 260.1393 for $C_{14}H_{18}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25} = -12.5$ (c 1.03, $CHCl_3$).

4.5.2. (*S*)-*N*-(Phenylethyl)-1-isopropyl-5-methyl-3-oxido-1*H*-imidazole-4-carboxamide 10b

Yield after column chromatography (SiO_2, AcOEt/MeOH 1:1, R_f = 0.51): 2.36 g (82%). Colorless solid. Mp 124–126 °C. IR (KBr): 3432s, 3100–2850s (br), 1659vs, 1603s, 1551s, 1495 m, 1452 m, 1284s, 705 m, 700 m. ^{1}H NMR ($CDCl_3$): 11.23 (br s, 1H, CONH); 7.87 (s, 1H, HC(2)); 7.41–7.40 (m, 2 arom. H); 7.32–7.30 (m, 2 arom. H); 7.23–7.20 (m, 1 arom. H); 5.27 (quint, J = 7.2, 1H); 4.40–4.33 (m, 1H, *i*Pr); 2.63 (s, 3H, Me); 1.57 (d, J = 7.2, 3H, Me); 1.45 (dd, J = 10.8, J = 6.6, 6H, *i*Pr). ^{13}C NMR ($CDCl_3$): 158.9 (s, C=O); 143.9, 129.6, 121.8 (3s, C(Ph), C(4), C(5)); 128.4, 126.8, 126.0, 122.3 (4d, 5CH(Ph), C(2)); 48.1, 47.8 (2d, 2CH); 22.9, 22.7, 9.3 (3q, 4 Me). ESI-HRMS: 310.1527 (calcd 310.1526 for $C_{16}H_{21}N_3NaO_2$, $[M+Na]^+$), 288.1706 (calcd 288.1706 for $C_{16}H_{22}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25} = -12.3$ (c 10.0, $CHCl_3$).

4.6. Synthesis of (*S*)-*N*-(phenylethyl)-1-adamantyl-5-methyl-3-oxido-1*H*-imidazole-4-carboxamide 10c

A solution of 1-adamantaneformaldimine **11c** (1.96 g, 12.0 mmol) and α-(hydroxyimino)ketone **8** (2.34 g, 10.0 mmol) in glacial AcOH (30 mL) was stirred for two days at rt. Then, a stream of dry HCl gas was bubbled through the mixture for 1.5 h, and the solvents were removed under reduced pressure. The resulting yellow oil was triturated with Et_2O, decanted, dried under vacuum, and dissolved in a 4:1 mixture of $CHCl_3$ and methanol. After excess solid $NaHCO_3$ was added, vigorous stirring was continued for 2 h. Then, the mixture was filtered, the solvents were removed, and the resulting solid was recrystallized from CH_2Cl_2/Et_2O to give 1.81 g (48%) of **10c** as colorless crystals. Mp 257–260 °C. IR (KBr): 3432vs (br), 3135 m, 1916vs, 1663vs, 1589vs, 1551s, 1495 m, 1452 m, 1409 m, 1388 m, 1374 m, 1278s, 1212 m, 1152 m, 1103 m, 763 m, 747 m, 698 m. ^{1}H NMR ($CDCl_3$): 11.24 (br s, 1H, CONH); 7.93 (s, 1H, HC(2)); 7.41–7.39 (m, 2 arom. H); 7.32–7.30 (m, 2 arom. H); 7.23–7.20 (m, 1 arom. H); 5.25 (quint, J = 7.2, 1H); 2.88 (s, 3H, Me); 2.28 (br s, 3H, CH, Ad); 2.19 (d, J = 2.4, 6H, CH_2, Ad); 1.80–1.73 (m, 6H, CH_2, Ad); 1.56 (d, J = 7.2, 3H, Me). ^{13}C NMR ($CDCl_3$): 159.2 (s, C=O); 144.1, 130.8, 123.4 (3s, C(Ph), C(4), C(5)); 128.5, 126.8, 126.1, 1228 (4d, 5CH(Ph), C(2)); 60.6 (s, N–C(Ad)); 48.3 (d, CH); 41.9, 29.6 (2t, 6CH_2, Ad); 35.5 (d, 3CH, Ad); 23.0, 13.2 (2q, 2Me). ESI-HRMS: 402.2152 (calcd 402.2152 for $C_{23}H_{29}N_3NaO_2$, $[M+Na]^+$), 380.2331 (calcd 380.2332 for $C_{23}H_{30}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25} = -6.4$ (c 5.00, $CHCl_3$).

4.7. Reactions of imidazole 3-oxides of type 7 and 10 with 2,2,4,4-tetramethylcyclobutane-1,3-dithione 12b

To the magnetically stirred solution of an imidazole *N*-oxide **7a**–**c** or **10a**–**c** (1.0 mmol) in $CHCl_3$ (5 mL), excess 2,2,4,4-tetramethylcyclobutane-1,3-dithione **12b** (1.8 mmol, 309 mg) in $CHCl_3$ (3 mL) was added dropwise at 0 °C, and stirring was continued overnight at rt. Then, the solvent was removed under reduced pressure, the resulting material was purified and identified as the corresponding imidazole-2-thione (**13** or **15**) and/or as an imidazole (**14** and **16**).

4.7.1. (*S*)-*N*-(1-Phenylethyl)-1,3-dihydro-1,5-dimethyl-2-thioxoimidazole-4-carboxamide 13a

Yield: 98 mg (36%). Colorless crystals. Mp 221–223 °C (EtOH). IR (KBr): 3312vs, 3166vs (br), 1661s, 1626 m, 1537 m, 1487 m, 1475 m, 1450 m, 1425 m, 1395 m, 1368 m, 763 m, 702 m. ^{1}H NMR ($CDCl_3$): 12.83 (br s, 1H, NH); 7.48 (br d, J = 7.8, 1H, NH); 7.30–7.28 (m, 2 arom. H); 7.23–7.20 (m, 2 arom. H); 7.16–7.13 (m, 1 arom. H); 5.16 (quint, J = 7.2, 1H); 3.41 (s, 3H, NMe); 2.42 (s, 3H, Me); 1.51 (d, J = 6.6, 3H, Me). ^{13}C NMR ($CDCl_3$): 158.9, 157.5 (2s, C=O, C=S); 143.2, 134.1, 118.7 (3s, C(Ph), C(4), C(5)); 128.5, 127.2, 126.4 (3d, 5CH(Ph)); 49.3 (d, CH); 31.0, 22.1, 10.2 (3q, 3 Me). ESI-HRMS: 298.0986 (calcd 298.0984 for $C_{14}H_{28}N_3NaOS$, $[M+Na]^+$). $[\alpha]_D^{25} = +326.3$ (c 0.80, $CHCl_3$).

4.7.2. (*S*)-*N*-(1-Phenylethyl)-1,3-dihydro-1-isopropyl-5-methyl-2-thioxoimidazole-4-carboxamide 13b

Yield after column chromatography (SiO_2, AcOEt/$CHCl_3$ 1:2, R_f = 0.65): 173 mg (56%). Colorless solid. Mp 107–110 °C. IR (KBr): 3304s (br), 3061 m, 2973 m, 2933 m, 1656 m, 1626s, 1540 m, 1494s, 1451 m, 1416 m, 1370 m, 1282 m, 1197 m, 763 m, 700 m. ^{1}H NMR ($CDCl_3$): 13.11 (br s, 1H, NH); 7.62 (br d, J = 7.2, 1H, NH); 7.38–7.37 (m, 2 arom. H); 7.30–7.28 (m, 2 arom. H); 7.23–7.20 (m, 1 arom. H); 5.30 (br s, 1H, *i*Pr); 5.23 (quint, J = 7.2, 1H); 2.64 (s, 3H, Me); 1.57 (d, J = 7.2, 3H, Me); 1.52–1.49 (m, 6H, *i*Pr). ^{13}C NMR ($CDCl_3$): 158.0 157.7 (2s, C=O, C=S); 143.4, 134.0, 119.3 (3s, C(Ph), C(4), C(5)); 128.5, 127.2, 126.3 (3d, 5CH(Ph)); 49.5, 49.2 (2d, 2CH); 22.1, 20.4, 11.1 (3q, 4 Me). ESI-HRMS: 326.1299 (calcd 326.1297 for $C_{16}H_{21}N_3NaOS$, $[M+Na]^+$). $[\alpha]_D^{25} = +149.0$ (c 1.00, $CHCl_3$).

4.7.3. (*S*)-*N*-(Phenylethyl)-1-adamantyl-5-methyl-1H-imidazole-4-carboxamide 14

Yield after column chromatography (SiO_2, AcOEt/$CHCl_3$ 1:2, R_f = 0.70): 203 mg (56%). Colorless solid. Mp 132–134 °C. IR (KBr): 3407 m, 2910s, 2856 m, 1660vs, 1578s, 1494vs, 1452 m, 1235 m, 697 m. ^{1}H NMR ($CDCl_3$): 7.59 (br s, 1H, NH); 7.51 (s, 1H, HC(2)); 7.40–7.38 (m, 2 arom. H); 7.33–7.29 (m, 2 arom. H); 7.23–7.20 (m, 1 arom. H); 5.25 (quint, J = 7.2, 1H); 2.86 (s, 3H, Me); 2.25 (br s, 3H, 3CH, Ad); 2.21 (d, J = 2.4, 6H, 3CH_2, Ad); 1.80–1.74 (m, 6H, 3CH_2, Ad); 1.56 (d, J = 7.2, 3H, Me). ^{13}C NMR (DMSO-d_6): 162.9 (s, C=O); 145.1, 132.2, 131.5 (3s, C(Ph), C(4), C(5)); 133.6 (d, C(2)); 128.4 (2C), 126.7, 126.2 (2C) (3d, 5CH(Ph)); 57.9 (s, N–C(Ad)); 47.4 (d, CH); 41.5, 29.2 (2t, 6CH_2, Ad); 35.4 (d, 3CH, Ad); 22.4, 12.8 (2q, 2Me). ESI-HRMS: 386.2200 (calcd 386.2203 for $C_{23}H_{29}N_3NaO$, $[M+Na]^+$), 364.2384 (calcd 364.2383 for $C_{23}H_{30}N_3O$, $[M+1]^+$). $[\alpha]_D^{25} = -33.0$ (c 1.00, $CHCl_3$).

4.7.4. Imidazole-2-thione 15a

Yield after column chromatography (SiO_2, AcOEt/$CHCl_3$ 1:1, R_f = 0.74): 259 mg (79%). Yellow solid. Mp 89–92 °C. IR (KBr): 3423s (br), 3166 m, 3069s, 2929vs, 2857s, 1629vs, 1497 m, 1450 m, 1388 m, 1370 m, 1353 m, 1278 m, 756 m. ^{1}H NMR ($CDCl_3$): 13.30 (s, 1H, OH); 10.30 (br s, 1H, NH); 8.34 (s, 1H, –N=CH–); 7.18–7.15 (m, 1 arom. H); 7.12 (d, J = 7.2, 1 arom. H);

6.81 (d, J = 8.4, 1 arom. H); 6.75 (t, J = 7.2, 1 arom. H); 5.19–5.16 (m, 1H, *c*Hex); 3.86–3.81 (m, 1H, *c*Hex); 3.31–3.24 (m, 1H, *c*Hex); 1.91, 1.85 (2s, 6H, 2Me); 1.76–1.51 (m, 6H, *c*Hex); 1.36–1.28 (m, 1H, *c*Hex). ^{13}C NMR ($CDCl_3$): 165.7 (s, –N=CH–); 161.1 (s, (Ph)C–OH); 157.2 (s, C=S); 132.1, 131.7, 118.5, 116.7 (4d, 4CH(Ph)); 122.8, 119.4, 118.8 (3s, C(Ph), C(4), C(5)); 64.9, 61.6 (2d, 2CH(*c*Hex)); 34.5, 27.2, 25.6, 23.7 (4t, $4CH_2$(*c*Hex)); 9.2, 9.0 (2q, 2Me). ESI-HRMS: 330.1632 (calcd 330.1635 for $C_{18}H_{24}N_3OS$, $[M+1]^+$). $[\alpha]_D^{25} = -294.0$ (c 1.00, $CHCl_3$).

4.7.5. Imidazole-2-thione 15b

Yield after column chromatography (SiO_2, AcOEt/$CHCl_3$ 1:8, R_f = 0.54): 285 mg (63%). Yellow solid. Mp 278–281 °C. IR (KBr): 3427vs (br), 3058vs (br), 2936vs, 2853 m, 1627s, 1579 m, 1495s, 1446 m, 1384 m, 1355 m, 1274 m, 1261 m, 1237 m, 754 m, 695 m. ^{1}H NMR ($CDCl_3$): 13.08 (s, 1H, OH); 9.86 (br s, 1H, NH); 8.56 (s, 1H, –N=CH–); 7.53–7.50 (m, 3 arom. H); 7.27–7.24 (m, 3 arom. H); 7.20 (d, J = 7.8, 1 arom. H); 7.16–7.15 (m, 3 arom. H); 7.03–6.99 (m, 2 arom. H); 6.91 (d, J = 8.4, 1 arom. H); 6.18 (t, J = 7.5, 1 arom. H); 5.47–5.43 (m, 1H, *c*Hex); 3.79–3.75 (m, 1H, *c*Hex); 3.23–3.17 (m, 1H, *c*Hex); 1.87–1.63 (m, 4H, *c*Hex); 1.54–1.38 (m, 2H, *c*Hex); 1.28–1.25 (m, 1H, *c*Hex). ^{13}C NMR ($CDCl_3$): 166.0 (s, –N=CH–); 161.0 (s, (Ph)C–OH); 159.7 (s, C=S); 137.0, 133.7, 124.6, 119.8, 118.8 (5s, 3C(Ph), C(4), C(5)); 132.2, 131.8, 129.8, 129.4, 129.3, 128.7 (2C), 128.1, 128.0, 127.7, 125.9 (2C), 118.6, 116.8 (12d, 14CH(Ph)); 64.8, 62.1 (2d, CH(*c*Hex)); 34.4, 27.7, 25.3, 23.7 (4t, $4CH_2$(*c*Hex)). ESI-HRMS: 454.1949 (calcd 454.1948 for $C_{28}H_{28}N_3OS$, $[M+1]^+$). $[\alpha]_D^{25} = -69.0$ (c 1.00, $CHCl_3$).

4.7.6. Imidazole-2-thione 15c

Yield after column chromatography (SiO_2, AcOEt/$CHCl_3$ 1:1, isolated as a less polar fraction, R_f = 0.79): 328 mg (71%). Pale yellow solid. Mp 138–140 °C. IR (KBr): 3432vs (br), 2931s, 1629vs (br), 1533 m, 1494s, 1452 m, 1384 m, 1348 m, 1278s, 1135 m, 759 m, 699 m. ^{1}H NMR for major isomer ($CDCl_3$): 13.03, 12.77 (2br s, 2H, OH, NH); 8.27 (s, 1H, –N=CH–); 7.34–7.20 (m, 6 arom. H); 7.12 (d, J = 7.8, 1 arom. H); 6.85 (d, J = 8.4, 1 arom. H); 6.81–6.79 (m, 1 arom. H); 5.20 (quint, J = 7.2, 1H); 5.14–5.10 (m, 1H, *c*Hex); 4.14–4.09 (m, 1H, *c*Hex); 3.26–3.19 (m, 1H, *c*Hex); 2.51 (s, 3H, Me); 1.98–1.41 (m, 7H, *c*Hex); 1.54 (d, J = 7.2, 3H, Me). ^{13}C NMR for major isomer ($CDCl_3$): 165.9 (s, –N=CH–); 161.0 (s, (Ph)C–OH); 157.5, 157.4 (2s, CONH, C=S); 143.0, 134.7, 118.9, 118.6 (4s, 2C(Ph), C(4), C(5)); 132.4, 131.7, 128.6 (2C), 127.2, 126.3 (2C), 118.4, 117.0 (7d, 9CH(Ph)); 65.1, 61.6, 49.1 (3d, 3CH); 34.6, 27.3, 25.3, 23.7 (4t, $4CH_2$(*c*Hex)); 21.9, 9.9 (2q, 2Me). ESI-HRMS: 485.1985 (calcd 485.1982 for $C_{26}H_{30}N_4NaO_2S$, $[M+Na]^+$), 463.2166 (calcd 463.2162 for $C_{26}H_{31}N_4O_2S$, $[M+1]^+$). $[\alpha]_D^{25} = -305.0$ (c 1.00, $CHCl_3$).

4.7.7. Imidazole 16

Yield after column chromatography (SiO_2, AcOEt/$CHCl_3$ 1:1, isolated as more polar fraction, R_f = 0.44): 34 mg (8%). Yellow semi-solid. IR (KBr): 3400 m (br), 2932s (br), 2860 m, 1653s, 1630s, 1582s, 1494s, 1449 m, 1278 m, 1229 m, 758 m, 700 m. ^{1}H NMR ($CDCl_3$): 12.65 (s, 1H, OH); 7.91 (s, 1H, –N=CH–); 7.40 (s, 1H, HC(2)); 7.33–7.28 (m, 2 arom. H); 7.26–7.24 (m, 3 arom. H); 7.21–7.18 (m, 1 arom. H); 7.01 (dd, J = 7.6, J = 1.6, 1 arom. H); 6.87 (d, J = 8.1, 1 arom. H); 6.76 (dt, J = 7.4, J = 1.1, 1 arom. H); 5.19 (quint, J = 7.1, 1H); 4.06–4.01 (m, 1H, *c*Hex); 3.36 (dt, J = 10.5, J = 4.4, 1H, *c*Hex); 2.51 (s, 3H, Me); 2.14–2.11 (m, 1H, *c*Hex); 2.02–1.75 (m, 6H, *c*Hex); 1.54–1.49 (m, 1H, *c*Hex); 1.51 (d, J = 7.1, 3H, Me). ^{13}C NMR ($CDCl_3$): 165.1 (s, –N=CH–); 162.8 (s, (Ph)C–OH); 160.6 (s, CONH); 143.8, 132.6, 130.7, 118.1 (4s, 2C(Ph), C(4), C(5)); 132.7, 131.5, 128.4 (2C), 126.9, 126.1 (2C), 118.7, 117.0 (7d, 9CH(Ph)); 132.1 (d, C(2)); 73.4, 58.7, 47.9 (3d, 3CH); 34.2, 32.8, 25.2, 23.9 (4t, $4CH_2$(*c*Hex)); 22.2, 9.6 (2q, 2Me). ESI-HRMS: 453.2260 (calcd 453.2261 for $C_{26}H_{30}N_4NaO_2$, $[M+Na]^+$), 431.2439 (calcd 431.2442 for $C_{26}H_{31}N_4O_2$, $[M+1]^+$). $[\alpha]_D^{25} = -174.8$ (c 0.48, $CHCl_3$).

4.8. Deoxygenation of 10c with Raney-nickel

To the solution of **10c** (101 mg, 0.26 mmol) in methanol (8.0 mL) a suspension of freshly prepared Raney-Ni in methanol was added in small portions at rt, until the starting material was fully consumed (TLC monitoring). The crude mixture was filtered through a Celite® pad, washed with MeOH, and the solvent was removed from the filtrate. The resulting residue was purified on preparative TLC plates (SiO_2) using $CHCl_3$/AcOEt mixture (2:1) to give 58 mg (61%) of **14** as a colorless solid.

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