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Synthesis of 1*S*,5*R*- and 1*R*,5*S*-glycoluriles by diastereospecific α-ureidoalkylation of (*S*)/(*R*)-*N*-carbamoyl-α-amino acids with 4,5-dihydroxyimidazolidin-2-one

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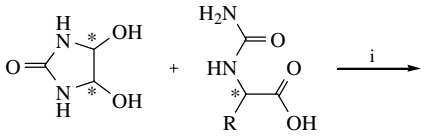
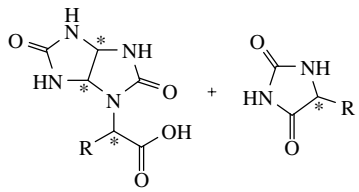
A diastereospecific method for the synthesis of individual enantiomers of 1*S*,5*R*- and 1*R*,5*S*-glycoluriles has been developed based on the α-ureidoalkylation of (*S*)/(*R*)-*N*-carbamoyl-α-amino acids with 4,5-dihydroxyimidazolidin-2-one.

We have shown previously[1–3] that glycoluriles are a new promising class of psychotropic compounds. It was found later that they also have other types of biological activity. In particular, they have cancer-control activity[4] and influence the cytochrome P-450 dependent monooxygenase function of liver.[5] The synthesis of enantiomerically pure glycoluriles as potential pharmaceuticals is of considerable interest. One of the most popular methods for the synthesis of glycoluriles is based on the α-ureidoalkylation of N-mono- and N,N′-disubstituted ureas with 4,5-dihydroxyimidazolidin-2-ones as the ureidoalkylating reagents.[6–10] Based on this approach, we studied the α-ureidoalkylation of achiral and enantiomerically pure *N*-carbamoylamino acids with 4,5-dihydroxyimidazolidin-2-ones. We obtained racemic glycoluriles;[7–9] of these, conditions for the isolation of enantiomers by spontaneous crystallisation from water were found for 4-[(3,7-dioxo-2-(3-carboxypropyl)-6,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]butanoic acid.[7] A similar reaction with enantiomerically pure *N*-carbamoylamino acids occurs diastereoselectively;[10] the ratio between the major and minor products ranges from 3:1 to 15:1. Individual diastereomers were isolated from the mixtures by fractional crystallisation.

We report here on a simple approach to the synthesis of individual enantiomers of glycoluriles by the diastereospecific α-ureidoalkylation of corresponding enantiomers of (*S*)/(*R*)-*N*-carbamoyl-α-amino acids **2a**–**f**, *viz.*, (*S*)/(*R*)-*N*-carbamoylmethionine



1 **2a–f**



3a–f **4a–g**

a R = CH_2CH_2SMe (*S*)
b R = CH_2CH_2SMe (*R*)
c R = $CHMe_2$ (*S*)
d R = $CHMe_2$ (*R*)
e R = CH_2Ph (*S*)
f R = CHEtMe (*S*)
g R = H

Scheme 1 *Reagents and conditions*: i, 1 mol **2** : 2 mol HCl, H_2O or H_2O + Pr^iOH, 80 °C, 2.5 h.

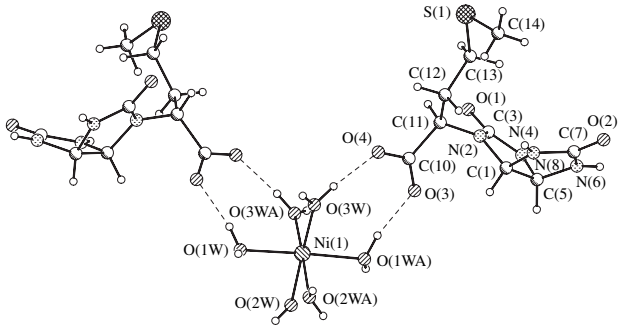


Figure 1 The cation and anion in a crystal of compound **1**.

2a,**b**, (*S*)/(*R*)-*N*-carbamoylvaline **2c**,**d**, (*S*)-*N*-carbamoylphenylalanine **2e** and (*S*)-*N*-carbamoylisoleucine **2f** with 4,5-dihydroxyimidazolidin-2-one **1**.

In order to reveal the conditions required for the reactions of 4,5-dihydroxyimidazolidin-2-one **1** with (*S*)/(*R*)-*N*-carbamoylamino acids **2** to occur diastereospecifically, we studied the effect of the process parameters, such as the medium pH from 0 to 6, temperature from 40 to 90 °C and duration of the reaction from 0.5 to 4 h, for the reaction of compound **1** with (*S*)/(*R*)-*N*-carbamoylmethionines **2a**,**b** as an example. We found that a diastereospecific synthesis requires the following conditions: 2 mol of HCl per mole of the ureidoacid; the temperature should be 80 °C; and the reaction time should be 2.5 h. (Scheme 1). The physico-chemical characteristics of individual enantiomers **3a**,**b** obtained under these conditions are consistent with data reported previously; the structure and absolute configuration of compound **3a** were proved by X-ray diffraction analysis.[10]

These conditions were used in reactions of **1** with other (*S*)/(*R*)-*N*-carbamoyl-α-amino acids **2c**–**f**. In all cases, the target individual enantiomers of glycoluriles **3a**–**f** were obtained in preparative yields of 30–40%.†

The diastereospecific reactions of compound **1** with (*S*)- and (*R*)-*N*-carbamoylvaline **2c** and **2d** give enantiomers **3c** and **3d**, which, like compounds **3a**,**b**, have identical melting points, as well as IR and ^{1}H NMR spectra, whereas their $[\alpha]_D^{20}$ have the same absolute values but opposite signs: $[\alpha]_D^{20}$ +1.21° for **3c**; $[\alpha]_D^{20}$ –1.21° for **3d**. The ureidoalkylation of (*S*)-*N*-carbamoylphenylalanine **2e** and (*S*)-*N*-carbamoylisoleucine **2f** also occurs diastereoselectively to give enantiomerically pure glycoluriles **3e**,**f**.

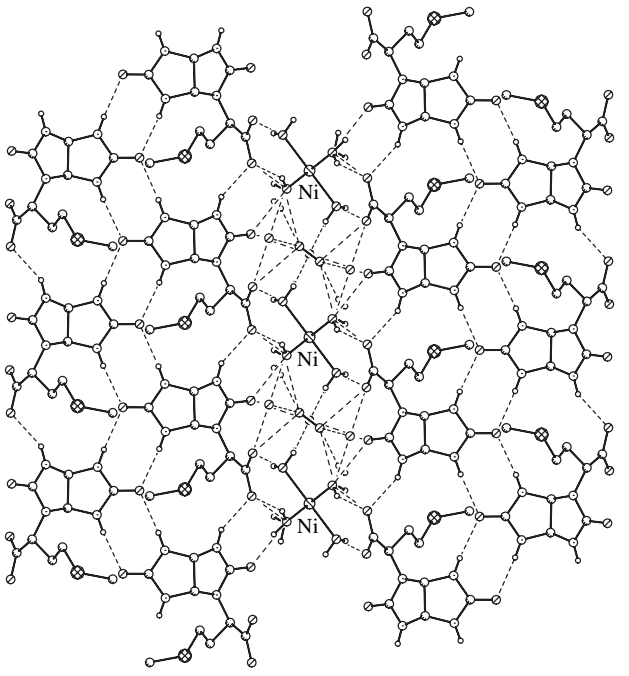


Figure 2 A projection of crystal packing that demonstrates alternating cationic layers and anionic chains.

The absence of the second diastereomer after the isolation of compounds **3a**–**f** was established by the ^{1}H NMR spectroscopy of mother liquors evaporated to dryness. Analysis of the ^{1}H NMR spectra of the residues (in the region of signals corresponding to the CH protons of the amino acid fragment at 3.7–4.5 ppm) suggests that all the products give signals due to CH_2 and CH protons, as well as NH protons (~8 and ~10.5 ppm) of hydantoins **4a**–**f**,[11] which are formed as a result of the self-cyclisation of *N*-carbamoyl-α-amino acids **3a**–**f**, and hydantoin **4g**, which results from a rearrangement of 4,5-dihydroxyimidazolidin-2-one **1**. Furthermore, according to ^{1}H NMR data, the test mixtures contained minor amounts of target glycoluriles **3**. The signals of the second diastereomer were absent.

A comparison of the results of X-ray diffraction analysis and spectral characteristics of compound **3a**[10] and spectral data for compounds **3c** and **3e**,**f** allowed us to state that the bridging carbon atoms in these glycoluriles have the (1*R*,5*S*) configuration. In the case of compounds **3b**,**d**, it can be assumed with a higher probability that the CH–CH moieties have an opposite configuration, *i.e.*, (1*S*,5*R*).

For a conclusive confirmation of the configurations of asymmetric atoms C(1) and C(5) in glycoluriles **3b**,**d**, we obtained coordination compound **5** by ligand exchange between glycolurile **3b** and nickel acetate in an aqueous solution with heating. An X-ray diffraction study of single crystals grown by crystallisation from water was carried out.‡

It was shown that the nickel atom in compound **5** did not participate directly in the coordination with the functional groups of the ligand. In a crystal, the nickel atom arranged on axis 2 is surrounded by six water molecules. In addition to the water molecules involved in the coordination of nickel, the crystal also contains four solvate water molecules. The ligand (L) is in the deprotonated form [the bond lengths C(10)–O(3) and

† All new compounds exhibited satisfactory elemental analyses, and their structures were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H and ^{13}C spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively. Chemical shifts were measured with reference to the residual protons of a [$^2H_6$]DMSO solvent (δ 2.50 ppm).

Initial 4,5-dihydroxyimidazolin-2-one **2** was synthesised according to the known method from urea and glyoxal;[12] *N*-carbamoyl-α-amino acids **3a**–**d** were synthesised by analogy to published methods from α-amino acids and KOCN.[13,14]

(+)-2-[(1R,5S)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]-2(S)-4-methylthiobutanoic acid **3a**: yield 37%, mp 256–258 °C (decomp.), $[\alpha]_D^{20}$ +18.50° (*c* 2, 1 N NaOH), see ref. 10.

(–)-2-[(1S,5R)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]-2(R)-4-methylthiobutanoic acid **3b**: yield 37%, mp 256–258°C (decomp.), $[\alpha]_D^{20}$ –18.50° (*c* 2, 1 N NaOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.05–2.17 (m, 5H, Me + CH_2), 2.36–2.64 (m, 2H, CH_2), 4.47 (dd, 1H, CH, ^3J 9.4 Hz, ^3J 6.3 Hz), 5.29 [dd, 1H, C(1)H, ^3J 8.44±0.04 Hz, ^3J 1.7 Hz], 5.41 [dd, 1H, C(5)H, ^3J 8.44±0.04 Hz, ^3J 2.4 Hz], 7.25 (br. s, 2H, 2NH), 7.48 (br. s, 1H, NH), 12.81 (br. s, 1H, OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 14.64 (Me), 28.79 (CH_2), 30.28 (CH_2), 53.18 (CH), 62.99 (CH), 67.48 (CH), 160.02 (CO), 161.53 (CO), 173.01 (COOH).

(+)-2-[(1R,5S)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]-2(S)-3(S)-3-methylbutanoic acid **3c**: yield 30.5%, mp 158–159 °C (decomp.), $[\alpha]_D^{20}$ +1.21°. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.9 (m, 2Me), 2.19 (m, CH), 3.9 (d, 1H, CH, ^3J 10.7 Hz), 5.27 [br. dd, 1H, C(1)H, ^3J 8.4 Hz], 5.51 [dd, 1H, C(5)H, ^3J 2.3 Hz, ^3J 8.4 Hz], 7.32 (s, NH), 7.40 (s, NH), 7.55 (s, NH), 12,79 (br. s, COOH).

(–)-2-[(1R,5S)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]-2(S)-3(S)-3-methylbutanoic acid **3d**: yield 30.5%, mp 158–159 °C (decomp.), $[\alpha]_D^{20}$ –1.21°. ^{1}H NMR ([$^2H_6$]DMSO) δ: (see **3c**).

(+)-2-[(1R,5S)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]-2(S)-3-phenylpropanoic acid **3e**: yield 35%, mp 170–172 °C (decomp.), $[\alpha]_D^{20}$ +19.34°. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.07–3.23 (m, 2H, CH_2), 4.47–4.55 (m, 1H, CH), 5.20 (br. s, 2H, CH–CH), 7.15–7.27 (m, 6H, Ph + NH), 7.35 (s, 1H, NH), 7.44 (s, 1H, NH).

(+)-2-[(1R,5S)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)]-2(S)-3(S)-3-methylpentanoic acid **3f**: yield 35.5%, mp 244–246 °C (decomp.), $[\alpha]_D^{20}$ +7.12°. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.80–0.88 (m, 6H, 2Me), 1.02–1.19 (m, 1H, CH), 1.43–1.62 (m, 2H, CH_2), 1.94–2.12 (m, 2H, CH_2), 4.01 (d, 1H, CH, ^3J 10.3 Hz), 5.26 [br. d, 1H, C(1)H, ^3J 8.1 Hz], 5.51 [dd, 1H, C(5)H, ^3J 2.2 Hz, ^3J 8.1 Hz], 7.32 (s, 1H, NH), 7.37 (s, 1H, NH), 7.55 (s, 1H, NH).

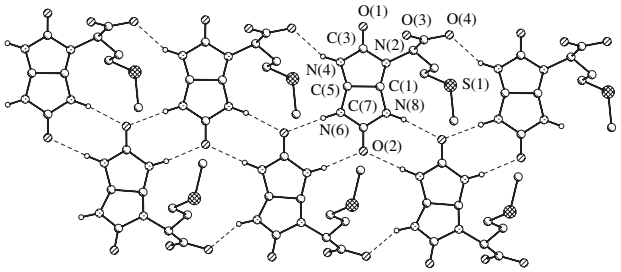


Figure 3 Double chains combined through the N–H···O bonds in a crystal of compound **5**.

C(10)–O(4) equal 1.247(3) and 1.255(4) Å, respectively]; hence, the overall composition of the crystal can be represented as $Ni(H_2O)_6L_2(H_2O)_4$ (Figure 1).

The existence of a large number of proton donors and acceptors in a crystal of compound **5** results in a complex supramolecular organisation. Alternating inorganic (cationic) and organic (anionic) parts can be distinguished in a crystal (Figure 2).

The cationic part is a hexaaqua nickel complex. The cations are combined into layers parallel to the *ac* crystallographic plane through hydrogen bonds with solvate water molecules.

The anions are combined through the N–H···O bonds to form double chains (Figure 3).

Note that the previous[10] X-ray diffraction study of glycolurile **3a** showed that molecules in the crystal were combined through hydrogen bonds into a three-dimensional H-bonded framework.

The main geometric parameters in compounds **3a** and **3b** are similar. In all the molecules, the bridging hydrogen atoms are characterised by the *cis* configuration. It was found that the C(1) and C(5) atoms in compound **5** have the (1*S*,5*R*) absolute configuration, which suggests that compound **3b** has a similar configuration of the bridging carbon atoms. This fact confirms our assumption on the opposite configuration of the C(1)–C(5) atoms in the enantiomer pairs.

Thus, we were the first to develop diastereospecific syntheses of (1*S*,5*R*)- and (1*R*,5*S*)-glycoluriles, including enantiomeric pairs, by the α-ureidoalkylation of (*S*)/(*R*)-*N*-carbamoyl-α-amino acids with 4,5-dihydroxyimidazolidin-2-one as a ureidoalkylating reagent. The absolute configurations of the resulting compounds were established by X-ray diffraction analysis.

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‡ *X-ray diffraction analysis*: at 120 K, the crystals of **5** ($C_{18}H_{46}N_8NiO_{18}S_2$) are orthorhombic, space group $P2_12_12$, $a = 7.664(1)$, $b = 32.849(5)$ and $c = 6.722(1)$ Å, $V = 1692.3(5)$ Å^3, $Z = 2$ ($Z' = 0.5$), $M = 785.46$, $d_{calc} = 1.541$ g cm^{-3}, $(MoK\alpha) = 7.81$ cm^{-1}, $F(000) = 828$. The intensities of 11714 reflections were measured with a Smart 1000 CCD diffractometer at 120 K [$\lambda(MoK\alpha) = 0.71072$ Å, $2\theta < 58°$], and 4025 independent reflections ($R_{int} = 0.0409$) were used in the further refinement. The structure was solved by the direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Analysis of the Fourier density synthesis revealed that one of solvate water molecules is disordered by centre of symmetry and the other one is disordered by two positions with occupancies of 0.4 and 0.6. The hydrogen atoms were located from the Fourier density synthesis with the only exception of disordered water molecules for which the positions of hydrogen atoms were not found. The absolute configuration was determined by means of the Flack parameter,[15] the value of which in the case of the 1*S*,5*R* configuration of the C(1) and C(5) atoms was 0.00(2). The refinement converged to $wR_2 = 0.1052$ and GOF = 1.084 for all independent reflections [$R_1 = 0.0480$ was calculated against F for 29658 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 257433. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.