

Synthesis and crystal structure of a salen-type copper(II) complex derived from 3,5'-*O*-dimethyl-2',3'-diamino-2',3'-dideoxy- β -D-xylo-uridine†

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We report the synthesis of the first 2',3'-diamino substituted uridine derivative with *xylo*-configuration, its use as starting material for the synthesis of salen-type ligands and the first structurally characterised copper(II) complex thereof.

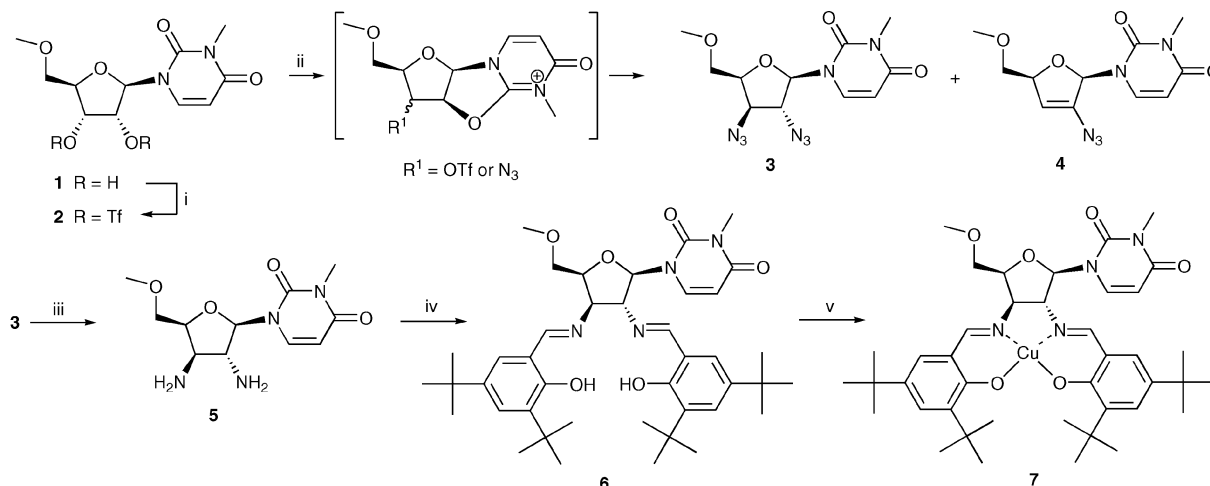
Many of the catalysts used today are transition metal complexes of ligands with chiral 1,2-diamino ethane based structures¹ often derived from natural products as a chiral source. Numerous papers have been published determining the interaction of nucleosides and nucleobases with metal ions² but only a very few examples contain the binding of a metal ion onto the functionalised chiral sugar moiety³ although this would give access to a new class of catalyst. Beside this the introduction of azido and amino groups into nucleosides and nucleotides has gained increasing attention due to the bioactivity of the resulting derivatives.⁴ For both their use as catalysts and as bioactive substances the position of the functional groups and the configuration of the resulting products are decisive. In contrast to the easy introduction of azido groups into the 3',5'-position⁵ in 2'-deoxynucleosides, a substitution in the 2',3'-position is reported in only one case to the *ribo*-configured diamino adenosine.³

To explore the possibility of introducing amino groups into the 2'- and 3'-position of nucleosides, uridine was protected to give 3,5'-*O*-dimethyluridine **1** by isopropylideneation at the 2',3'-position using dimethoxypropane and *p*-toluene sulfonic acid in DMF, subsequent methylation with MeI/NaH in DMF

and deprotection by an acidic DOWEX resin in MeOH/H₂O according to the literature.⁶ Compound **1** is reacted with trifluoromethanesulfonic anhydride and pyridine in CH₂Cl₂ obtaining the 3,5'-*O*-dimethyluridine-2',3'-bistrifluoromethanesulfonate **2** as a white powder in quantitative yield, which is stable for several hours at room temperature. Azidation with NaN₃ in DMF leads to two major products which were separated chromatographically and identified to be 3,5'-*O*-dimethyl-2',3'-diazido-2',3'-dideoxy- β -D-xylo-uridine **3**† and 3-methyl-1-(3-azido-5-methoxymethyl-2(*R*),5(*S*)-dihydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione **4**‡ (Scheme 1) by NMR spectroscopy. The formation of the isolated *xylo* isomer **3** (instead of the expected *lyxo*, with all the substituents in a pseudo-axial position) could only be assumed from the difference of the coupling constants $J_{1'-2'} = 3.0$ Hz, $J_{2'-3'} = 3.1$ Hz and $J_{3'-4'} = 4.8$ Hz of the corresponding protons. The result can be explained by a double S_N2 reaction at the C-2' of the sugar ring. Firstly an intramolecular attack of the carbonyl oxygen of the uracil residue occurs leading to a resonance stabilised cation followed by a second nucleophilic substitution by the azide anion (Scheme 1). The formation of the unsaturated product **4** is caused by the easy elimination of the proton at C-2' which is adjoining the glucosidic carbon. The final structure of **4** could be assigned by ¹³C-¹³C correlation NMR spectroscopy.

Subsequent reduction of the diazide **3** with RANEY nickel to the diamine **5**, followed by condensation with 3,5-di-*tert*-butylsalicyl aldehyde leads to the salen-type ligand **6** in quantitative yield, which was in a first attempt reacted with copper(II) ions to give the title compound **7**. Recrystallisation from methanol-THF results in crystals suitable for single crystal X-ray structure

† Electronic supplementary information (ESI) available: Experimental details. See <http://www.rsc.org/suppdata/ob/b5/b500785b/>



Scheme 1 Reagents and conditions: i) Tf₂O, pyridine, CH₂Cl₂, 0 °C, 15 min, 95%; ii) NaN₃, DMF, 50 °C, 12 h, 25% **3**, 50% **4**; iii) RANEY-Ni, N₂H₄-H₂O, MeOH, 50 °C, 80%; iv) 2,4-di-*tert*-butylsalicyl aldehyde, EtOH, reflux, 95%; v) CuCl₂, THF, rt, 90%.

Table 1 Selected bond lengths [Å] and angles [°] of **7**

Cu–O1	1.894(2)	O1–Cu–O2	90.20(10)
Cu–O2	1.900(2)	O1–Cu–N1	91.34(11)
Cu–N1	1.950(3)	O2–Cu–N2	93.72(11)
Cu–N2	1.960(3)	N1–Cu–N2	86.34(11)
N2–C33	1.460(4)	N2–C33–C32	106.6(3)
N1–C32	1.462(4)	C33–C32–N1	106.9(3)
C32–C33	1.526(5)	Cu–N1–C32	107.2(2)

analysis⁷ (Fig. 1, ¶). The coordination sphere of the copper ion is distorted square pyramidal (Table 1). The obtained data confirm the *trans*-position of the substituents at C-2' (C32) and C-3' (C33) of the sugar residue (*xylo*-configuration). O6 of the uracil residue is turned away and does not coordinate the copper centre. O5 binds intermolecularly to the copper ion of the next molecule to form a chain like arrangement of the molecules in the crystal.

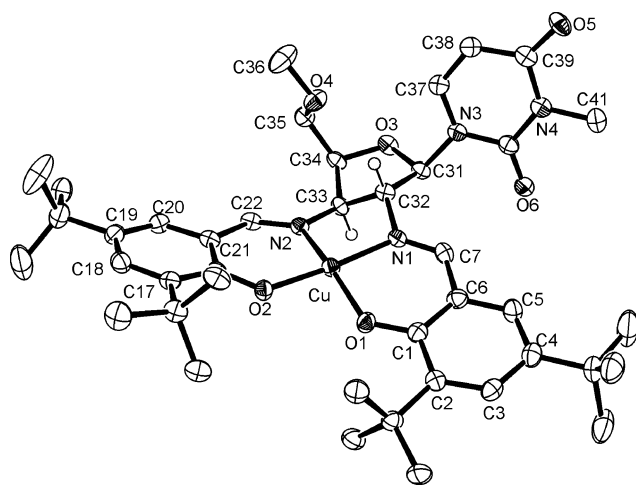


Fig. 1 X-Ray crystal structure of the copper(II) complex **7** (with used crystallographic numbering, including only the H-atoms at C32 and C33). Atomic displacement parameters are drawn at the 50% probability level.

In summary, the simultaneous introduction of azido groups in the 2',3'-position of uridine could be shown. Due to the influence of the carbonyl group of the uracil residue after reduction a new *trans*-configured chiral diamine could be obtained which is similar to the diamines used for Jacobson and Katsuki catalysts. The resulting copper(II) complex shows the anticipated coordination behaviour and accents the potential of nucleoside derivatives as chiral ligands for transition metal ions.

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Notes and references

‡ 3,5'-*O*-Dimethyl-2',3'-diazido-2',3'-dideoxy- β -D-*xylo*-uridine (**3**). δ_{H} (CDCl₃) 7.52 (d, $J_{5-6} = 8.2$ Hz, H-5), 5.84 (d, $J_{1'-2'} = 3.0$ Hz, H-1'), 5.75 (d, H-6), 4.35 (dd, $J_{4-5'} = 5.1$ Hz, H-4'), 4.14 (t, $J_{2-3'} = 3.1$ Hz, H-2'), 4.02 (dd, $J_{3'-4'} = 4.8$ Hz, H-3'), 3.65 (d, $2 \times$ H-5'), 3.38 (s, CH₃), 3.28 (s, CH₃). MS (DEI) m/z 323 ([M + 1]⁺).

§ 3-Methyl-1-(3-azido-5-methoxymethyl-2(*R*),5(*S*)-dihydro-furan-2-yl)-1*H*-pyrimidine-2,4-dione (**4**). δ_{H} (CDCl₃) 7.65 (d, $J_{5-6} = 8.1$ Hz, H-5), 6.80 (m, H-3'), 5.71 (m, H-1'), 5.50 (d, H-6), 4.93 (m, H-4'), 3.52 (m, $2 \times$ H-5') 3.38 (s, CH₃), 3.31 (s, CH₃). MS (DEI) m/z 280 ([M + 1]⁺).

¶ X-Ray crystal structure of **7**. The intensity data for the compound were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects.^{8,9} The structures were solved by direct methods (SHELXS¹⁰) and refined by full-matrix least squares techniques against Fo² (SHELXL-97¹¹). The hydrogen atoms were included at calculated positions with fixed thermal parameters. All non hydrogen atoms were refined anisotropically.¹¹ ORTEP and POV-Ray were used for structure representation. C₄₁H₅₆CuN₄O₆, $M_r = 764.44$ g mol⁻¹, green prism, size 0.03 \times 0.02 \times 0.02 mm³, orthorhombic, space group *P*2₁2₁2₁, $a = 11.4800(3)$, $b = 12.8012(4)$, $c = 28.1994(8)$ Å, $V = 4144.1(2)$ Å³, $T = -90$ °C, $Z = 4$, $\rho_{\text{calcd.}} = 1.225$ g cm⁻³, μ (Mo-K α) = 5.75 cm⁻¹, $F(000) = 1628$, 8961 reflections in $h(-14/14)$, $k(-16/16)$, $l(-36/36)$, measured in the range $1.92^\circ \leq \theta \leq 27.47^\circ$, completeness $\theta_{\text{max}} = 98.5\%$, 8961 independent reflections, 7311 reflections with $F_o > 4\sigma(F_o)$, 469 parameters, 0 restraints, $R1_{\text{obs}} = 0.053$, $wR2_{\text{obs}} = 0.103$, $R1_{\text{all}} = 0.077$, $wR2_{\text{all}} = 0.115$, GOOF = 1.065, Flack-parameter $-0.01(1)$, largest difference peak and hole: 0.397/ -0.417 e Å⁻³.

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