Synthesis and coordination ability of tartrate-derived *N*-alkyl dicarbohydrazides towards Cu²⁺ ions

Jana Kousalová, Oldřich Pytela and Filip Bureš*

Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, Studentská 573, Pardubice, CZ-532 10, Czech Republic
E-mail: filip.bures@upce.cz

Abstract

Starting from (R,R)-tartaric acid we have synthesized eight *N*- and *N*,*N*-(di-)alkyl dicarbohydrazides **3** and **4**, by two general methods, which were able to form two M_2L and ML complexes. These target compounds were further used as model nitrogen ligands coordinating Cu²⁺ ions. Whereas the formation of the first type of complexes is linearly dependent on the increasing electron-donating ability of the appended alkyls, the ML complexes were significantly affected by both electronic and steric effects of the alkyl groups used. These observations were supported by theoretical calculations of both complex types. The target compounds were also employed as chiral nitrogen ligands in the asymmetric version of the Henry reaction. Modest chemical yields and low enantioselectivities were attained for ligand **3a** bearing one methyl group on each terminal nitrogen atom. Structure-property relationships were also evaluated to gain useful guidelines for ligand design targeting catalysts for asymmetric reactions.

Keywords: Tartaric acid, carbohydrazide, *N*-alkylation, coordination ability, stability constants

Introduction

Tartaric acid, with its C_2-symmetric backbone, represents an unique, chiral, and readily available building block used for the construction of many optically active compounds.[1] Since the pioneering work of Frankland[2] and later Seebach's studies,[3] α,α,α',α'-tetra-aryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) became one of the most widely known and studied tartaric acid derivatives that catalyze numerous asymmetric reactions. Also well-known[1] are TADDOLs, nitrogen-containing tartaric acid derivatives such as amines, amides, imides, and nitriles. Such compounds should possess higher coordination abilities towards transition metals, owing to the

presence of nitrogen atoms.[4] Hence, in our previous studies, we focused on the synthesis of *N*-containing α-amino acid-[5-11] or tartaric acid-derived[12] compounds and their Cu^{2+} complexes.

Hydrazine,[13] although it has a deceptively simple structure, represents a unique and interesting molecule, with many applications in organic chemistry.[14] Its derivatives are also indispensable for the preparation of azides, isocyanates, ureas, and amides, and are also widely employed as reducing agents. Moreover, the hydrazine derivatives are well-suited for the construction of a great variety of heterocyclic rings such as diazoles, diazines and triazines.[15-17] Hydrazine and hydrazide derivatives possess interesting biological activity and many of them been showed to be effective for treatment of various diseases.[18-19] We now report the synthesis of 2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazides, their subsequent *N*-alkylation, and their coordination abilities towards Cu^{2+} ions. The general structure of the studied dicarbohydrazides **3** and **4** is shown in Scheme 1. Whereas the first series of compound **3a-c** possess mono-alkylated terminal hydrazide nitrogens (except cyclic derivative **3c**), the second series of dicarbohydrazides **4a-e** was dialkylated on each of the terminal nitrogens. Related organic compounds featuring the tartaric dicarbohydrazide pattern were studied as chiral compounds,[20] as HIV protease inhibitors,[21] testolactone derivatives,[22] calix[4](aza)crown based receptors for α-amino acids,[23] NLO-active compounds,[24] organocatalysts for catalytic asymmetric phase-transfer reactions,[25] and precursors used for the construction of various heterocycles.[26-28]
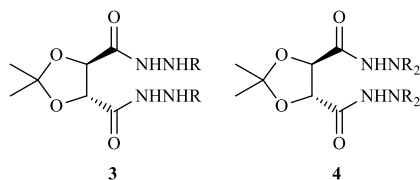

Scheme 1. General structure of the studied tartrate-derived dicarbohydrazides **3** and **4**.

Results and Discussion

Synthesis. The synthesis of target compounds started from the (*R*,*R*)-tartaric acid and its one-pot protection and esterification by reaction with 2,2-dimethoxypropane and methanol in the presence of *p*-toluenesulfonic acid.[25] The resulting (4*R*,5*R*)-dimethyl-2,2-dimethyl-1,3-dioxolan-4,5-dicarboxylate (**1**) is also commercially available. Subsequent treatment of the diester **1** with aqueous solution of hydrazine resulted in the formation of desired dicarbohydrazide **2**, however attempts to isolate this product always resulted in polycondensation and mixture of products. The same result was achieved when THF was used as solvent. Finally, the synthesis and isolation of **2** was successfully carried out in *i*-PrOH. The main advantage of this solvent is that the di-carbohydrazide **2** slowly separates from the reaction media as a viscous oily product within one week. This procedure assures partial separation/purification of **2** from the unreacted starting material, solvents, and side products. In this way, the attained yields ranged from 70-81% and

the synthesis was well-reproducible. However, the dicarbohydrazide **2** is unstable and polymerizes spontaneously if heated, dried or stored.
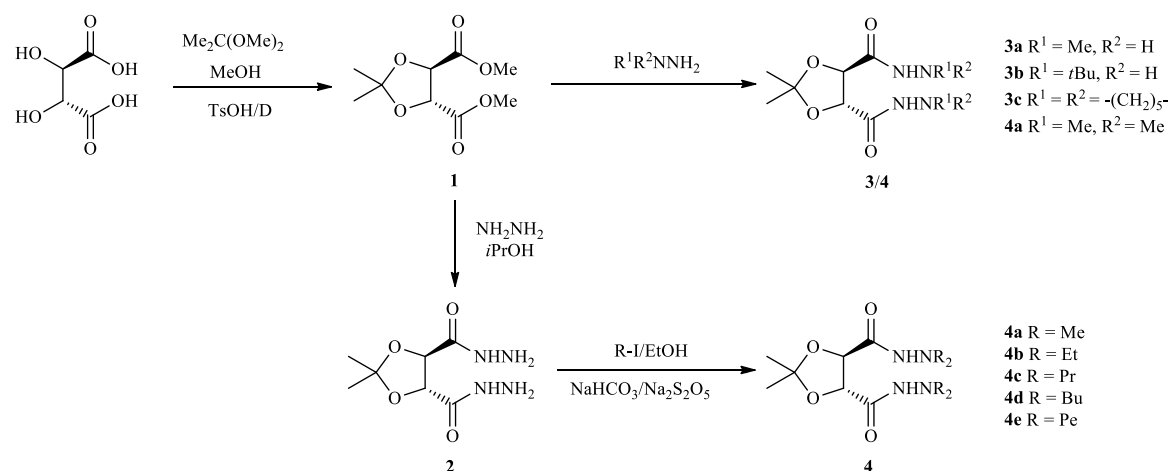
Scheme 2. Synthesis of target *N*-alkyl and *N,N*-dialkyl dicarbohydrazides.

Table 1. Structure, yields, reaction conditions, and properties of compounds **3-4**

Compd.	R	Yields [%] GC/isolated	Reaction conditions	Mp [°C]	$[\alpha]_D^{20}$ (*c* 1, MeOH)
3a	Me	88/36	*i*-PrOH, 5 days, 25°C	107-109	-32.5
3b	*t*-Bu	70/31	H$_2$O, 10 days, 25 °C	82-84	-19.2
3c	-(CH$_2$)$_5$-	82/13	no solvent, 30 days, 25 °C	84-86	-17.5
4a	Me	83/31(25)[a]	EtOH, 12 h, 25 °C	35-38	-30.1
4b	Et	90/11	EtOH, 4 days (25°C), 7 days (reflux)	65-68	-31.0
4c	Pr	89/10	EtOH, 10 days (25 °C), 20 days (reflux)	66-69	-13.2
4d	Bu	91/20	EtOH, 30 days (reflux)	70-71	-21.5
4e	Pe	84/23	EtOH, 30 days (reflux)	74-75	-22.1

[a] The yield of **4a** prepared via *N*-methylation is shown in parentheses.

The syntheses of target *N*-alkylated dicarbohydrazides were carried out in two ways. Whereas the first reaction path involves the reaction of the diester **1** with *N*-alkylhydrazines, the second path utilizes *N*-alkylation of dicarbohydrazide **2**. The first reaction path is limited by the availability of corresponding *N*-alkylhydrazides. From the number of commercially available hydrazines such as *N*-methylhydrazine, *N,N*-dimethylhydrazine, 1-aminopiperidine,

2-hydroxyethylhydrazine, methyl carbazate, phenylhydrazine, *N*-methyl-*N*-phenylhydrazine, and *tert*-butylhydrazine hydrochloride, the S$_N$ reaction on **1** was successful only with *N,N*-(di)-methylhydrazine, *tert*-butylhydrazine, and 1-aminopiperidine. The reaction of **1** with *N*-methylhydrazine furnished **3a** in 36%. Similar reaction with *N,N*-dimethylhydrazine afforded compound **4a** in 31% yield, which, however, can be synthesized also by *N*-methylation of **2** (see below) in the slightly lower yield of 25%. In contrast, the reaction of **1** with *N,N*-dimethylhydrazine was very sluggish (30 days). The desired dicarbohydrazide of the reaction between **1** and 2-hydroxyethylhydrazine was not detected at all, while the reaction with methyl carbazate was very slow and only traces of the corresponding dicarbohydrazide were detected after 10 weeks. The reactions with *tert*-butylhydrazine and 1-aminopiperidine were successful and dicarbohydrazides **3b** and **3c** were isolated in 31 and 13% yields (Scheme 1). It should be noted that similar reactions with aromatic hydrazines always afforded a black mixture of inseparable products. All the afore-mentioned reactions were carried out as solvent-free or in solvents such as MeOH and CH$_2$Cl$_2$. The detailed procedures are shown in Table 1 and the Experimental Section.

Because of the sluggish and problematic preparation of *N,N*-disubstituted dicarbohydrazides by S$_N$ reactions on **1**, we turned our attention to modification of dicarbohydrazide **2**. Although some new methods for *N*-modification of hydrazine derivatives have recently been developed by Mäeorg *et al*.,[29-31] we have used simple *N*-alkylation. Thus, treatment of freshly-prepared labile dicarbohydrazide **2** with excess of alkyl iodides in the presence of NaHCO$_3$ and Na$_2$S$_2$O$_5$ afforded *N,N*-dialkyl dicarbohydrazides **4a**-**e** (Scheme 2). The reaction course was strongly affected by the length of the used alkyl iodide. Whereas the reaction with methyl iodide required 12 h at 25 °C, the reaction with ethyl iodide took 4 days at 25 °C and 7 days at reflux. The butyl- and pentyl- derivatives **4d** and **4e** were alkylated for 30 days at reflux (Table 1). The alkylation with higher alkyl iodides or branched alkyl iodides/bromides was unsuccessful. These reactions afforded most often inseparable mixture of products. This methodology was operationally very simple, however the purification of target compounds, especially those with short alkyls, was rather tricky owing to their solubility in water as well as in organic solvents. The isolated yields of pure compounds are thus generally lower than those determined by GC analysis of the crude reaction mixture (Table 1; Experimental Section).

Complexation. The formation of coordination compounds between metal ions M and ligand L can be in the solution described by the following reaction

$$m\mathrm{M} + n\mathrm{L} \rightleftharpoons \mathrm{M}_m\mathrm{L}_n$$

where *m* is the number of metal ions and *n* means the number of ligand molecules in the complex M$_m$L$_n$. The particular equilibrium is described by the stability constant of the complex defined by equation (1)

$$\beta_{mn} = \frac{[\mathrm{M_mL_n}]}{[\mathrm{M}]^m \times [\mathrm{L}]^n} \tag{1}$$

where β_{mn} is the stability constant of the complex M_mL_n. Spectrophotometric titration is a common technique used for the determination of the stability constants β_{mn}. Thus, such titration of ligands **3a-3c, 4a-4e** and Cu^{2+} ions in methanol has been employed to determine the stability constants β_{mn}. Factor analysis of the matrix of absorbencies during titration[12] indicated approximately four species with different absorption spectra. This implies that in the solution two complexes are being formed. The detailed analysis through the EFA profiles revealed that ligands form with Cu^{2+} ions 2:1 and 1:1 complexes (metal:ligand). The calculation using the model, which comprises the formation of M_2L and ML complexes provided the corresponding stability constants which are listed in Table 2.

Table 2. Calculated stability constants β for **3-4**, their standard deviations, and residual standard deviations of the non-linear regression, s

Compd.	R	$\log \beta$ (M$_2$L)	$\log \beta$ (ML)	s
3a	Me	a	3.983±0.022	2.50×10^{-2}
3b	*t*-Bu	4.974±0.018	2.668±0.021	4.83×10^{-3}
3c	-(CH$_2$)$_5$-	6.673±0.034	3.409±0.101	9.60×10^{-3}
4a	Me	5.521±0.003	3.644±0.002	9.62×10^{-3}
4b	Et	6.484±0.002	4.650±0.152	9.86×10^{-3}
4c	Pr	6.896±0.009	4.810±0.008	1.21×10^{-2}
4d	Bu	7.773±0.032	4.635±0.036	7.95×10^{-3}
4e	Me	7.626±0.026	4.372±0.032	1.05×10^{-2}

[a] Statistically non-significant.

The substituent effects on the stability constants were evaluated through the substituent constants σ^i proposed within the AISE theory.[32] These constants describe the inductive effect of the alkyl substituents appended to terminal nitrogen atoms of the hydrazido group. The inductive effect primarily affects the electron density of nitrogen atoms coordinated to Cu^{2+} ion(s). A dependence of the $\log \beta_{21}$ values (complex M_2L) on the substituent constant σ^i is shown in Figure 1. This picture clearly shows that the complex stability is approximately linearly dependent on the extent of the inductive effect of the substituents appended to nitrogen atoms of the hydrazido group. This relationship can be described by the following regression equation (2)

$$\log \beta_{21} = (0.30 \pm 0.94) - (61.4 \pm 9.1)\ \sigma^i, \tag{2}$$
$$n = 7,\ s = 0.355,\ r = 0.949.$$

The high slope value implies that the ligand coordination ability towards metal ions is unexpectedly strongly dependent on the electron density change of the coordinating atoms. The equation (2) also explains the experimental unavailability of the log β_{21} value for ligand **3a** (R = Me). The value of this constant is probably small showing that this particular complex is not being formed. However, the predicted log β_{21} value for **3a** is shown in Figure 1. Although the alkyl substituents appended to nitrogen atoms are sterically different, the dependence is linear. This implies that steric effects do not play significant role in the formation of M$_2$L complex. This is in accordance with the theoretically calculated spatial arrangement of the M$_2$L complex as shown in Figure 2. In this complex, two Cu^{2+} ions are peripherally coordinated by the carbonyl oxygens and terminal nitrogens of the each hydrazido group.
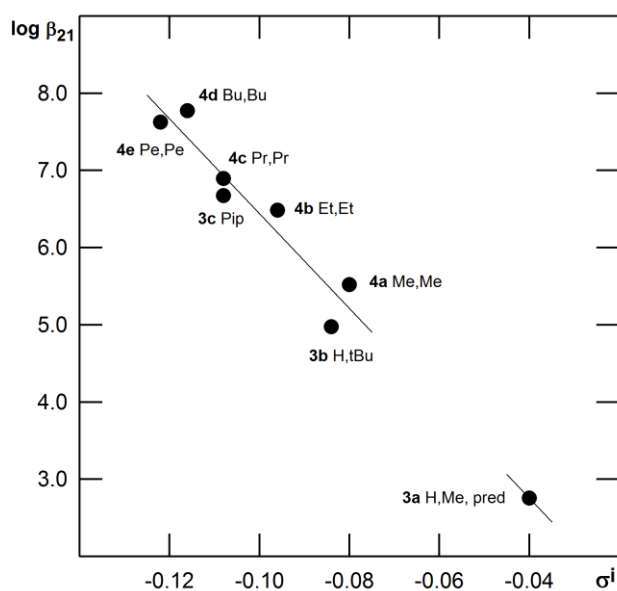

Figure 1. Dependence of the log β_{21} values (complex M$_2$L) on the substituent constants σ^i (AISE theory). The points were fitted with a regression line according to equation (2). The value for **3a** (R = Me) was predicted from this equation.

A dependence of the log β_{11} values (ML complex) on the substituent constants σ^i is shown in Figure 3. In this case, the dependence is not linear any more. However, Figure 3 shows a clear trend within the series of tetra-alkylated carbohydrazides **4a**-**4e**. The complex stability raises with the increasing donating ability of the appended alkyl substituents (similar to M$_2$L), passes through the maxima, and subsequently decreases for bulkier substituents. This is most probably caused by the higher steric demands of the particular substituents (Pr, Bu, and Pe), which hinder formation of stable complex. This situation is even more pronounced for ligands **3a** (R = Me) and **3b** (R = *t*-Bu). Similarly, the steric effects affect the coordination ability of ligand **3c** (R = -(CH$_2$)$_5$-), which possesses the electron density of the coordinating atoms comparable to ligand **4c** (R = Pr), but is formed by a rigid six-membered ring (piperidine). From these

observations we can deduce that the formation of ML complex is significantly affected by both electronic and steric effects. This is in accordance with the calculated structure of the ML complex as shown in Figure 2. In this complex, one Cu^{2+} ion is centrally coordinated by the two terminal nitrogens of the hydrazido groups. Moreover, in this case other coordinating ligands such as methanol (solvent) may sterically affect the formation of the ML complex.
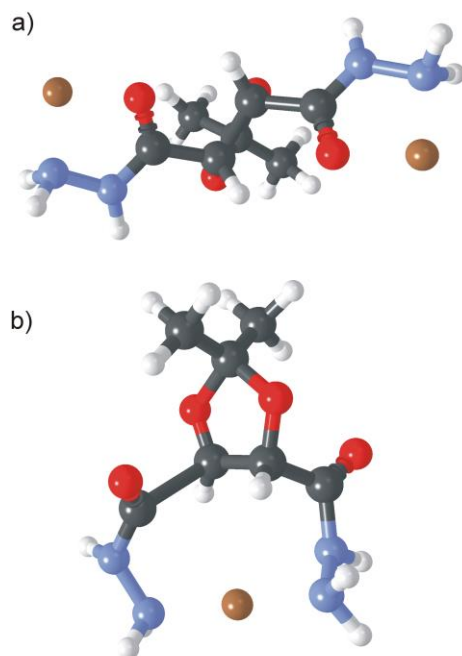

Figure 2. Complex structure of tartrate dicarbohydrazide **2** with a) two (M₂L) and b) one (ML) Cu^{2+} ion(s) calculated by PM6 method (MOPAC 2009).
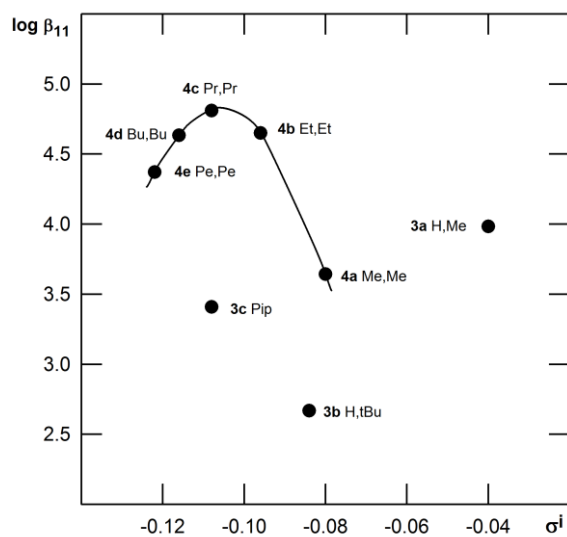

Figure 3. Dependence of the log β_{11} values (complex ML) on the substituent constants σ^i (AISE theory). The points for ligands **4a**-**4e** were fitted with an empirical curve for better illustration.

Conclusions

Starting from (*R,R*)-tartaric acid, we have synthesized the diester **1** and dicarbohydrazide **2**. Both intermediates were used for the construction of *N*- and *N,N*-(di)-alkylated dicarbohydrazides **3** and **4**. Whereas the synthesis of compounds **3** involved the reaction of diester **1** with *N*-alkyl hydrazines (R = Me, Bu, -(CH$_2$)$_5$-), derivatives **4** were synthesized by tetra-fold *N*-alkylation of dicarbohydrazide **2** (R = Me, Et, Pr, Bu, Pe). The reaction course of *N*-alkylation was strongly affected by the length of the used alkyl iodides.

All well-purified target compounds **3a**-**c** and **4a**-**e** were further used as model nitrogen ligands coordinating Cu^{2+} ions and some important features were revealed. In general, both ligands **3** and **4** form two complex types with the ratio metal:ligand of 2:1 and 1:1. Whereas the formation of the M$_2$L complex is linearly dependent on the increasing electron-donating nature of the appended alkyl substituents, the steric effects are engaged only negligible. On the other hand, the formation of ML complexes was affected by both electronic and steric effects. These observations are in accordance with the theoretical PM3/PM6 calculations of both complex types. Whereas M$_2$L complex possesses two Cu^{2+} ions coordinated peripherally to each carbohydrazide group, one Cu^{2+} ion in the complex ML is bound centrally employing both dicarbohydrazide moieties.

According to our previous studies,[6,10-11] we have attempted to employ Cu^{2+} complexes of chiral ligands **3a**-**c** and **4a**-**e** as catalysts of the asymmetric Henry reaction. Using 4-nitrobenzaldehyde and nitromethane as reagents under standard condition,[6] the best results were achieved with ligand **3a** (62% yield, 15% *ee*; R = Me). All other ligands provided the corresponding nitro-aldol but the enantiomeric excesses were almost zero. However, such behavior reflects the above discussed complexation ability. Compared to our previous TADDOL-like derivatives,[12] the stability constants of ligands **3** and **4** with Cu^{2+} ions are generally lower. Considering ML type of the complex as an active catalyst of the Henry reaction, the stability constants of M$_2$L complexes of **3-4** are higher (Table 2). It is anticipated that in the M$_2$L complex, the asymmetric induction will be generally lower. Moreover, the investigation of ML complexes (Figure 3) showed clearly a steric repulsion caused by the increasing alkyl chain length. Hence, only the ligand **3a** which feature very low log β_{21} value (see Figure 1) and less sterically demanding methyl substituent showed some asymmetric induction.

From the aforementioned discussion we can conclude the following structural features affecting the complexation ability and enantioselectivity of ligands **3** and **4**:

- Complexes of ligands **3** and **4** with Cu^{2+} ions are weaker than other TADDOL-like derivatives.
- Ligands **3** and **4** form stable M$_2$L rather than ML complexes.
- Low concentration of the active catalyst – ML complex.
- Sterically hindered complexes ML.

We believe that this structure-property relationships study employing model tartrate-derived *N*-alkyl dicarbohydrazide ligands **3** and **4** and their coordination ability towards copper(II)

acetate would serve as a useful guideline for ligand design targeting catalysts of asymmetric reactions.

Experimental Section

General. Reagents and solvents were reagent-grade, purchased from Penta, Aldrich and Acros and used as received. The starting dicarboxylate **1** was synthesized according to literature procedure.[25] Column chromatography was carried out with silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminum sheets coated with silica gel 60 F254 obtained from Merck, with visualization by UV lamp (254 or 360 nm). ^{1}H- and ^{13}C-NMR (APT) spectra were recorded at 400 MHz and 100 MHz, respectively, with a Bruker AVANCE 400 instrument at 25 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. The residual solvent signal in the ^{1}H- and ^{13}C-NMR spectra was used as an internal reference ($CDCl_3$ – 7.25 and 77.23 ppm, CD_3OD – 3.31 and 49.15 ppm). Apparent resonance multiplicities are described as s (singlet), *br* s (broad singlet), d (doublet) and m (multiplet). The compound **3b** (R = *t*-Bu) showed in $CDCl_3$ strongly hindered rotation in the carbohydrazide moiety, which resulted in a set of broad signals. Therefore, ^{1}H- and ^{13}C-NMR spectra of **3b** were measured in CD_3OD.[6] Mass spectra were measured on a GC/MS configuration comprised of an Agilent Technologies – 6890N gas chromatograph equipped with a 5973 Network MS detector (EI 70 eV, mass range 33−550 Da). IR spectra were recorded on a Perkin Elmer FT-IR Spectrum BX spectrometer. Optical rotations were measured on a Perkin Elmer 341 polarimeter using the sodium D line (589 nm), specific rotations [α] are given in units of deg cm^2 g^{-1} and concentration *c* is 1.0 g/100 cm^3 in MeOH. Elemental analyses were performed on an EA 1108 Fisons instrument.

(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (2). To a solution of hydrazine (2.49 mL; 40.0 mmol; 50% aq. solution) in *i*-PrOH (50 mL), was added the diester **1** (4.2 g; 20.0 mmol) and the resulting mixture stood at 25 °C for 7 days. The solvent was carefully decanted off and the oily product was kept in an open flask to remove residual solvent. The crude product was used directly in the next step. Compound **2:** yellowish viscous oil, yields 70-81 %. $[\alpha]_D^{20}$ = -10.2 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 3309, 2987, 2937, 1662 (C=O), 1508, 1375, 1209, 1147, 1086, 989, 870, 557; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 1.15 (6H, s, 2×CH_3), 4.33 ppm (2H, s, 2×CH); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 25.65 (CH_3), 76.68 (CH), 112.48 (C), 168.87 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 218 ([M]$^+$, 5), 187 (65), 160 (32), 129 (27), 113 (24), 101 (55), 85 (61), 71 (100), 59 (73%).

(4*R*,5*R*)-*N*,*N'*-Dimethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (3a). Into a vigorously stirred solution of the diester **1** (3.6 g; 16.5 mmol) in propan-2-ol (50 mL), methylhydrazine (3.7 g; 80.0 mmol) was added and the resulting solution was stirred at 25 °C for

5 days. The solvent was evaporated *in vacuo* and the crude product purified by crystallization from dichloromethane and subsequently suspended in THF and decanted to give the title compound **3a**. White solid, yield 36%, 1.48 g, mp 107-109 °C; $[\alpha]_D^{20}$ = -32.5 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 3314, 2353, 1658 (C=O), 1534, 1477, 1206, 1143, 1081, 1062, 958, 846, 718, 534; ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 1.47 (6H, s, 2×CH$_3$), 2.63 (6H, s, 2×NCH$_3$), 4.21 (2H, br s, 2×NH), 4.59 (2H, s, 2×CH), 8.22 ppm (2H, br s, 2×NH); ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ_C 26.29 (CH$_3$), 39.44 (CH$_3$), 77.00 (CH), 113.03 (C), 168.66 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 246 ([M]$^+$, 12), 201 (41), 127 (35), 115 (100), 99 (65), 85 (56), 71 (70), 59 (38%); Anal. Calcd for C$_9$H$_{18}$N$_4$O$_4$ (246.26): C, 43.86; H, 7.37; N, 22.75%. Found: C, 42.64; H, 7.40; N, 22.46%.

(4R,5R)-N,N'-Bis-(*tert*-butyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (3b). To a flask containing *tert*-butylhydrazine hydrochloride (25.0 g; 200.0 mmol), solution of NaOH (15.0 g; 375.0 mmol) in H$_2$O (35 mL) was added dropwise at 25 °C and the resulting mixture was subjected to distillation. A fraction containing aqueous *tert*-butylhydrazine distilling at 100-110 °C was collected. The accurate concentration of *tert*-butylhydrazine solution was determined by titration with 1 *M* HCl on Tashiro's indicator.

A mixture of the diester **1** (6.0 g; 27.5 mmol) and a solution of *tert*-butylhydrazine (20 mL; 120.0 mmol; 6*M* solution) was stirred at 25 °C for 10 days. The resulting white suspension was filtered off. The crude product was dried in air, dissolved in ethanol (200-300 mL) and refluxed with activated charcoal and Al$_2$O$_3$. The solution was filtered while hot, and the solvent evaporated *in vacuo* to give **3b**. White solid, yield 31%, 2.82 g, mp 82-84 °C; $[\alpha]_D^{20}$ = -19.2 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 2421, 1641 (C=O), 1572, 1534, 1392, 1368, 1313, 1243, 1215, 1148, 1102, 1087, 945, 853, 696. ^{1}H-NMR (400 MHz, CD$_3$OD, 25 °C): δ_H 1.27 (s, 18H, 6×CH), 1.45 (s, 6H, 2×CH$_3$), 4.53 ppm (s, 2H, 2×CH). ^{13}C-NMR (100 MHz, CD$_3$OD, 25 °C): δ 24.95 (CH$_3$), 27.27 (CH$_3$), 58.51 (C), 81.62 (CH), 112.41 (C), 178.57 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 331 ([M]$^+$, 5), 207 (22), 160 (21), 144 (48), 113 (26), 101 (21), 85 (42), 73 (18), 57 (100); Anal. Calcd for C$_{15}$H$_{30}$N$_4$O$_4$ (330.42): C, 54.52; H, 9.15; N, 16.96 Found: C, 53.97; H, 8.78; N, 15.98%.

(4R,5R)-N,N'-Bis-(piperidin-1-yl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboamide (3c). A mixture of the diester **1** (2.0 g; 9.2 mmol) and *N*-aminopiperidine (2.9 mL; 0.027 mmol) was stirred at 25 °C for 30 days and followed by GC/MS. The resulting crystals were filtered off and taken up in dichloromethane (100-200 mL). The solution was refluxed with activated charcoal and Al$_2$O$_3$, filtered while hot, and the solvent evaporated *in vacuo*. The product was purified by column chromatography (SiO$_2$; MeOH/EtOAc 4:1) to give **3c** as a white solid, 0.4 g, yield 13%, mp 84-86 °C; $[\alpha]_D^{20}$ = -17.5 (*c* 1, MeOH). IR (ν_{max}, cm^{-1}): 3219, 2953, 2927, 2858, 1659 (C=O), 1547, 1456, 1367, 1221, 1147, 1093, 989, 856, 680. ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 1.39-1.42 (4H, m, 2×CH$_2$), 1.48 (6H, s, 2×CH$_3$), 1.68-1.74 (8H, m, 4×CH$_2$), 2.65-2.76 (8H, m, 2×NCH$_2$), 4.48 (2H, s, 2×CH), 7.73 ppm (2H, br s, 2×NH). ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ 23.37 (CH$_2$), 25.31 (CH$_2$), 26.11 (CH$_3$), 57.24 (NCH$_2$), 76.97 (CH), 112.88 (C), 166.66 ppm (CO). EI-MS (eV) *m/z* (rel. int.): 354 ([M]$^+$, 9), 272 (15), 197 (23), 169 (31), 127 (22), 99 (100),

84 (61), 55 (49), 42 (24%); Anal. Calcd for $C_{17}H_{30}N_4O_4$ (354.44): C, 57.61; H, 8.53; N, 15.81%. Found: C, 57.48; H, 8.71; N, 15.67%.

(4*R*,5*R*)-*N*,*N*,*N'*,*N'*-Tetramethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (4a). Into a stirred solution of diester **1** (4.4 g; 20.2 mmol) in methanol (25 mL), *N*,*N*-dimethylhydrazine (3.8 ml; 50.0 mmol) was added and the resulting solution was stirred at 25 °C for 30 days, and followed by GC/MS. The solvent was evaporated *in vacuo* and the crude product taken up in dichloromethane (200-300 mL), the solution was refluxed with activated charcoal and Al_2O_3, filtered while hot, and the solvent evaporated *in vacuo*. The product was purified by column chromatography (SiO$_2$; EtOAc to CH$_2$Cl$_2$/Et$_3$N) to give the title compound **4a,** as a. white amorphous and hygroscopic solid, yield 1.7 g, 31%, mp 35-38 °C; $[\alpha]_D^{20}$ = -30.1 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 3213, 2989, 2953, 2864, 2782, 1668 (C=O), 1530, 1445, 1374, 1249, 1211, 1160, 1093, 1017, 883, 812, 659 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 1.40 (6H, s, 2×CH$_3$), 2.52 (12H, s, 4×NCH$_3$), 4.42 (2H, s, 2×CH), 7.72 ppm (2H, br s, 2×NH); ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ 25.96 (CH$_3$), 47.58 (NCH$_3$), 76.61 (CH), 112.58 (C), 166.75 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 274 ([M]$^+$, 18), 157 (19), 129 (24), 86 (27), 59 (100), 43 (32%); Anal. Calcd for $C_{11}H_{22}N_4O_4$ (274.32): C, 48.16; H, 8.08; N, 20.42. Found: C, 46.78; H, 7.55; N, 19.68%.

General method for the alkylation of 2 (synthesis of compounds 4a–e)
Into a solution of dicarbohydrazide **2** (12.5-15.8 mmol) in EtOH (25 mL), alkyl iodide (100.0 mmol), NaHCO$_3$ (8.4 g; 100.0 mmol), and Na$_2$S$_2$O$_3$ (0.2 g; 1.3 mmol) were added. The reaction mixture was stirred at 25 °C until complete disappearance of starting dicarbohydrazide (monitored by GC/MS). The reaction was then heated at reflux until complete conversion to the tetra-alkyl derivatives **4a**-**e** (monitored by GC/MS). The reaction mixture was cooled to 25 °C, filtered, and the solvent was evaporated *in vacuo*. The crude products were purified by various methods.

(4*R*,5*R*)-*N*,*N*,*N'*,*N'*-Tetramethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (4a). The title compound was synthesized from **2** (2.72 g; 12.5 mmol) and methyl iodide (6.2 mL; 100.0 mmol) following the general method. The reaction was stirred at 25 °C for 12 h. The crude product was taken up in dichloromethane (200-300 mL), the solution refluxed with activated charcoal and Al_2O_3, filtered while hot, and the solvent evaporated *in vacuo*. The product was purified by column chromatography (SiO$_2$; EtOAc to CH$_2$Cl$_2$/Et$_3$N) to give the title compound. **4a**, as a white amorphous and hygroscopic solid, yield 25%, 0.85g. For the spectroscopic characterization see above.

(4*R*,5*R*)-*N*,*N*,*N'*,*N'*-Tetraethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (4b). The title compound was synthesized from **2** (3.07 g; 14.1 mmol) and ethyl iodide (8.04 mL; 100.0 mmol) following the general method as for (4a), but with stirring at 25 °C for 4 days and then refluxed for 7 days. The crude product was taken up in dichloromethane (200-300 mL), then the solution was refluxed with activated charcoal and Al_2O_3, filtered while hot, and the solvent was evaporated *in vacuo*. The product was purified by column chromatography (SiO$_2$; EtOAc to CH$_2$Cl$_2$/Et$_3$N) to give the title compound **4b**, as a white solid, yield 11%, 0.51 g, mp 65-68 °C;

$[\alpha]_D^{20}$ = -31.0 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 3213, 2975, 1683, 1658 (C=O), 1540, 1382, 1252, 1210, 1160, 1053, 966, 884, 667; ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 1.07 (12H, t, *J* 7.2 Hz, 4×CH$_3$), 1.50 (6H, s, 2×CH$_3$), 2.74 (8H, q, *J* 7.2 Hz, 4×NCH$_2$), 4.52 (2H, s, 2×CH), 7.43 ppm (2H, br s, 2×NH); ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ 11.95 (CH$_3$), 26.14 (CH$_3$), 52.32 (CH$_2$), 76.96 (CH), 112.72 (C), 168.32 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 330 ([M]$^+$, 17), 260 (19), 185 (22), 157 (25), 115 (28), 87 (100), 72 (27), 59 (28%); Anal. Calcd for C$_{15}$H$_{30}$N$_4$O$_4$ (330.42): C, 54.52; H, 9.15; N, 16.96%. Found: C, 53.56; H, 9.39; N, 16.27%.

(4*R*,5*R*)-*N*,*N*,*N'*,*N'*-Tetrapropyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (4c). The title compound was synthesized from **2** (2.93 g; 13.4 mmol) and propyl iodide (9.75 mL; 100.0 mmol) following the general method. The reaction was stirred at 25 °C for 10 days and refluxed for 20 days. The crude product was taken up in dichloromethane (200-300 mL), the solution heated at reflux with activated charcoal and Al$_2$O$_3$, filtered while hot, and the solvent was evaporated *in vacuo*. The product was purified by column chromatography (SiO$_2$; EtOAc to CH$_2$Cl$_2$/Et$_3$N) to give the title compound **4c**. White solid, yield 10%, 0.52 g, mp 66-69 °C; $[\alpha]_D^{20}$ = -13.2 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 3240, 2954, 2933, 2864, 1674 (C=O), 1531, 1466, 1369, 1219, 1147, 1093, 850, 730, 617, 576; ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 0.787 (12H, t, *J* 7.6 Hz, 4×CH$_3$), 1.34-1.44 (8H, m, 4×CH$_2$), 1.38 (6H, s, 2×CH$_3$), 2.56 (8H, t, *J* 7.6 Hz, 4×NCH$_2$), 4.38 (2H, s, 2×CH), 7.37 ppm (2H, br s, 2×NH); ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ 11.52 (CH$_3$), 20.00 (CH$_2$), 25.85 (CH$_3$), 60.09 (NCH$_2$), 76.70 (CH), 112.44 (C), 167.81 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 386 ([M]$^+$, 15), 288 (17), 213 (27), 185 (26), 157 (58), 143 (59), 115 (100), 100 (60), 87 (97), 70 (61%); Anal. Calcd for C$_{19}$H$_{38}$N$_4$O$_4$ (386.53): C, 59.04; H, 9.91; N, 14.49%. Found: C, 57.66; H, 9.41; N, 14.16%.

(4*R*,5*R*)-*N*,*N*,*N'*,*N'*-Tetrabutyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (4d). The title compound was synthesized from **2** (3.45 g; 15.8 mmol) and butyl iodide (11.38 mL; 100.0 mmol) following the general method. The reaction mixture was heated at reflux for 30 days. The crude product was taken up in dichloromethane (200-300 mL), the solution refluxed with activated charcoal and Al$_2$O$_3$, filtered while hot, and the solvent was evaporated *in vacuo* to give the title compound **4d**. White solid, yield 20%, 1.40 g, mp 70-71 °C; $[\alpha]_D^{20}$ = -21.5 (*c* 1, MeOH); IR (ν_{max}, cm^{-1}): 3230, 2954, 2930, 2867, 1675 (C=O), 1528, 1465, 1367, 1217, 1147, 1074, 847, 730. ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 0.83 (12H, t, *J* 7.2 Hz, 4×CH$_3$), 1.23-1.32 (6H, m, 4×CH$_2$), 1.39-1.43 (8H, m, 4×CH$_2$), 1.45 (6H, s, 2×CH$_3$), 2.65 (8H, t, *J* 7.2 Hz, 4×NCH$_2$), 4.45 (2H, s, 2×CH), 7.40 ppm (2H, br s, 2×NH); ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ 14.06 (CH$_3$), 20.39 (CH$_2$), 26.01 (CH$_3$), 28.98 (CH$_2$), 58.22 (CH$_2$), 76.82 (CH), 112.60 (C), 167.93 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 442 ([M]$^+$, 16), 316 (32), 241 (33), 171 (78), 144 (88), 128 (76), 101 (100), 84 (68), 57 (64%); Anal. Calcd for C$_{23}$H$_{46}$N$_4$O$_4$ (442.64): C, 62.41; H, 10.47; N, 12.66%. Found: C, 61.87; H, 10.45; N, 12.67%.

(4*R*,5*R*)-*N*,*N*,*N'*,*N'*-Tetrapentyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide (4e). The title compound was synthesized from **2** (3.10 g; 14.2 mmol) and pentyl iodide (13.05 mL; 100.0 mmol) following the general method. The reaction was heated at reflux for 30 days. The crude product was taken up in dichloromethane (200-300 mL), then the solution was refluxed with

activated charcoal and Al_2O_3, filtered while hot, and the solvent was evaporated *in vacuo* to give the title compound **4e**. White solid, yield 1.63 g, 23%, mp 74-75 °C; $[\alpha]_D^{20}$ = -22.1 (*c* 1, MeOH); IR (v_{max}, cm^{-1}): 3216, 2951, 2926, 2856, 1666 (C=O), 1545, 1457, 1378, 1214, 1147, 1095, 990, 922, 851, 684. ^{1}H-NMR (400 MHz, CDCl$_3$, 25 °C): δ_H 0.84 (12H, t, *J* 6.8 Hz, 4×CH$_3$), 1.24-1.27 (16H, m, 8×CH$_2$), 1.42-1.47 (8H, m, 4×CH$_2$), 1.49 (6H, s, 2×CH$_3$), 2.67 (8H, t, *J* 6.8 Hz, 4×NCH$_2$), 4.48 (2H, s, 2×CH), 7.43 ppm (2H, br s, 2×NH); ^{13}C-NMR (100 MHz, CDCl$_3$, 25 °C): δ 14.17 (CH$_3$), 22.72 (CH$_2$), 26.11 (CH$_3$), 26.65 (CH$_2$), 29.48 (CH$_2$), 58.65 (CH$_2$), 76.92 (CH), 112.71 (C), 168.02 ppm (CO); EI-MS (eV) *m/z* (rel. int.): 498 ([M]$^+$, 14), 344 (48), 269 (34), 199 (31), 172 (86), 156 (85), 115 (100), 98 (98), 71 (36%); Anal. Calcd for $C_{27}H_{54}N_4O_4$ (498.74): C, 65.02; H, 10.91; N, 11.23%. Found: C, 64.71; H, 10.04; N, 11.56%.

Stability constants β determination. The stability constants of the complexes prepared from ligands **3a-3c, 4a-4e** and Cu^{2+} ions were determined by spectrophotometric titration at 25 °C. A 1 cm wide quartz cuvette was filled with 3 cm^3 of ligand solution in methanol (*c* = 1 × 10^{-5} mol/dm^3) and the absorption spectrum was measured in the range of wavelengths λ from 220 to 320 nm. A 745 μl of solution of copper(II) acetate in methanol (*c* = 1 × 10^{-3} mol/dm^3, the accurate concentration was determined by ICP) was added gradually in 2–50 μl portions. The additions were optimized with respect to the molar ratio of ligand:metal (15:1 at the beginning, 1:25 at the end, 40 additions overall). The absorption spectra were recorded upon each Cu^{2+} addition. The absorption spectrum of 745 μl aforementioned copper(II) acetate solution in 3 cm^3 of methanol was measured at the end. The stability constants β and molar absorption coefficients $\varepsilon(\lambda)$ of the complexes were calculated from the matrix of measured absorbancies (row – concentrations, columns – wavelengths) employing the program OPchem.[33] The same program was used for the determination of the number of particles in the solution and for the indication of the complexes with the given ratio of metal:ligand.

Calculations. The optimized geometries of unsubstituted tartrate dicarbohydrazide **2** and its complexes with Cu^{2+} ions were calculated by the PM3 (ArgusLab)[34] and, subsequently, the PM6 methods (MOPAC2009).[35]

Acknowledgements

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