Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting information for

Syntheses of bifunctional 2,3-diamino propionic acid based chelators as small and strong tripod ligands for the labelling of biomolecules with ^{99m}Tc

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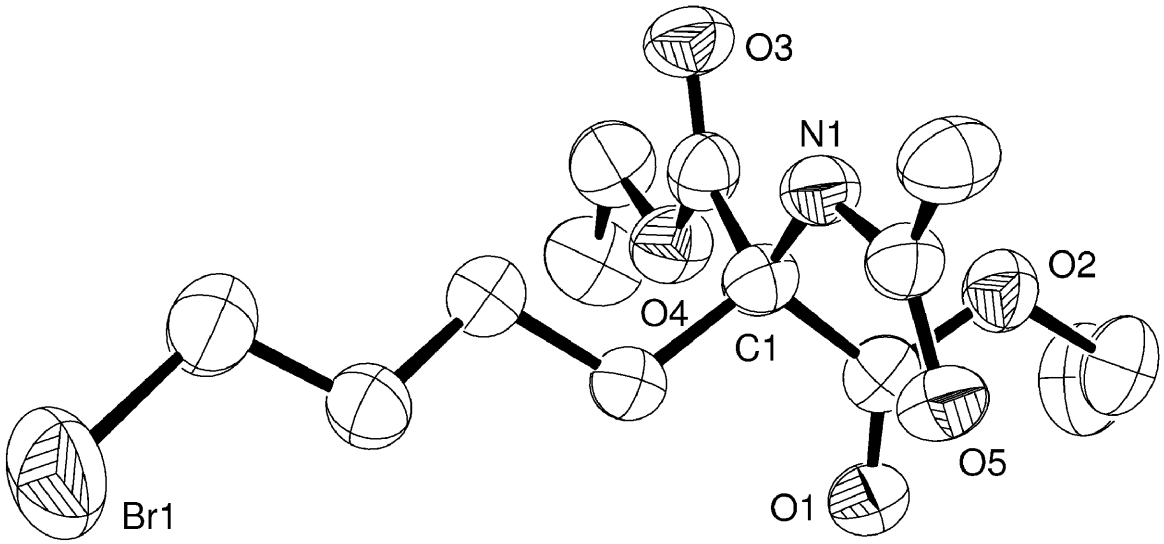
Table S1. Crystal data and structure refinement for **4**.

Empirical formula	$C_{13}H_{22}BrNO_5$	
Formula weight	352.23	
Temperature	183(2) K	
Wavelength	1.54186 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 17.996(3) Å	α= 90°.
	b = 10.0702(11) Å	β= 95.477(13)°.
	c = 9.3258(15) Å	γ = 90°.
Volume	1682.4(4) $Å^3$	
Z	4	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	3.489 mm^{-1}	
F(000)	728	
Crystal size	0.28 x 0.23 x 0.02 mm^3	
Crystal description	colourless plate	
Theta range for data collection	2.47 to 58.91°.	
Index ranges	-19<=h<=19, -10<=k<=10, -10<=l<=8	
Reflections collected	10736	
Independent reflections	2353 [R(int) = 0.0855]	
Reflections observed	1867	
Criterion for observation	>2sigma(I)	
Completeness to theta = 58.91°	97.6 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9321 and 0.4310	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2353 / 0 / 185	
Goodness-of-fit on F^2	1.215	
Final R indices [I>2sigma(I)]	R1 = 0.0744, wR2 = 0.2050	
R indices (all data)	R1 = 0.0901, wR2 = 0.2413	
Extinction coefficient	0.019(3)	
Largest diff. peak and hole	0.467 and -0.670 $e.Å^{-3}$	

Compound **4** was isolated as a colorless gel from EtOAc. Recrystallization from EtOAc/hexane did not yield single crystals. Finally, the solution in EtOAc was concentrated to an oil and put into a small Erlenmeyer flask fitted with rubber stopper. The rubber stopper was changed with new ones from time to time to make sure the residual solvent was absorbed by the rubber. The crystals appeared from the semi-solid at last.

ORTEP presentation (50% probability) of **4** (all hydrogen atoms were omitted for clarity):



Labelling yields with compounds **20** and **25** as a function of concentration and temperature. All labelling reactions at pH = 7.4

Radiochemical yields of *fac*-[^{99m}Tc(**20**)$(CO)_3$] and *fac*-[^{99m}Tc(**25**)$(CO)_3$].

[conc mM]	100 °C	75 °C		100°C	75°C
0.1	98 % (30 min)	98 % (30 min)		98 % (30 min)	79 % (30 min) 91 % (60 min)
0.08	96 % (30 min)	87 % (30 min) 85 % (60 min)		86 % (30 min) 96 % (60 min)	72 % (30 min) 89 % (60 min)
0.008	56 % (30 min) 60 % (60 min)	65 % (30 min)		29 % (30 min) 33 % (60 min)	10 % (30 min) 15 % (60 min)

^{13}C NMR data of the described compounds

Ethyl 2-acetamido 3-(tert-butoxycarbonylamine) propanoate 3

^{13}C-NMR (75 MHz, $CDCl_3$, ppm) δ_C 170.6 (***C***O), 170.5 (***C***O), 156.7 (***C***O), 79.8 (***C***$(CH_3)_3$), 62.0 (***C***H_2CH_3), 53.9, 42.4, 28.4, 23.5, 14.3.

Triethyl 1,6-diacetamido 6-cyanohexane 1,1,6-tricarboxylate 5

^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ_C 169.6 (***C***O), 169.4 (***C***O), 168.3 (***C***O), 66.7, 62.9, 62.8, 33.6, 32.2, 23.5, 23.4, 23.3, 14.2, 14.1.

Triethyl 1,6-diacetamido 7-(tert-butoxycarbonylamino)heptane 1,1,6-tricarboxylate 6

^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ_C 172.7 (***C***O), 169.9 (***C***O), 169.2 (***C***O), 168.3 (***C***O), 156.0 (***C***O), 79.7 (-***C***$(CH_3)_3$), 66.7, 65.2, 62.8, 62.7, 62.6, 45.1, 32.5, 32.3, 28.5 (-C(***C***$H_3)_3$), 24.3, 24.0, 23.9, 23.3, 14.3(-OCH_2***C***H_3), 14.2 (-OCH_2***C***H_3).

(S)-2-Benzyloxycarbonylamino 6-methanesulfonyloxy-hexanoic acid ethyl ester 11.

^{13}C-NMR (125 MHz, $CDCl_3$, ppm): δ_C 172.3 (***C***O), 156.1 (***C***O), 136.4 (Cbz), 128.7 (Cbz), 128.4(cbz), 128.3(Cbz), 69.6, 67.2, 61.8, 53.7, 37.5, 32.3, 28.8, 21.4, 14.4.

Benzyl *N*-(3-bromopropyl)carbamate 15.

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 156.4, 136.3, 128.4, 128.0, 127.9, 66.6, 39.2, 32.3, 30.6.

Ethyl 2-acetamido-5-(benzyloxycarbonylamino)-2-cyanopentanoate 16.

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 171.2 (***C***O), 166.8 (***C***O), 157.5 (***C***O), 136.5 (Cbz), 128.8 (Cbz), 128.5 (Cbz), 128.3 (Cbz), 116.9 (N≡***C***-), 67.2 (Cbz), 64.1 (-O***C***H_2CH_3), 57.5 (-C^b-), 40.0 (-C^f-), 32.8 (-C^d-), 25.6 (-C^e-), 22.3 (-CO***C***H_3), 14.2 (-OCH_2***C***H_3).

Ethyl 2-acetamido-5-(benzyloxycarbonylamino)-2-((tert-butoxycarbonylamino)-methyl)pentanoate 17.

Isomer a: ^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 172.6 (***C***O), 170.1 (***C***O), 156.6 (***C***O), 156.2 (***C***O), 136.8 (Cbz), 128.8 (Cbz), 128.4 (Cbz), 128.3 (Cbz), 79.9 (-***C***$(CH_3)_3$), 66.9, 64.7, 62.6 (-O***C***H_2CH_3), 44.6, 41.0, 28.5 (-C(***C***$H_3)_3$), 24.5, 24.1, 14.3 (-OCH_2***C***H_3).

Isomer b: ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ_c 172.8 (***C***O), 170.4 (***C***O), 156.9 (***C***O), 156.2 (***C***O), 136.4 (Cbz), 128.8 (Cbz), 128.4 (Cbz), 128.3 (Cbz), 79.9 (-***C***$(CH_3)_3$), 67.4, 63.9, 62.6 (-O***C***H_2CH_3), 40.0, 32.6, 29.8 (-C(***C***$H_3)_3$), 25.9, 22.5, 14.3 (-OCH_2***C***H_3).

Ethyl 2-acetamido-5-amino-2-((tert-butoxycarbonylamino)methyl)pentanoate 18.

^{13}C-NMR (75.5 MHz, CD_3OD, ppm) δ_c 171.9 (***C***O), 171.8 (***C***O), 157.5 (***C***O), 79.1 (-***C***$(CH_3)_3$), 62.5, 61.4, 42.0, 39.5, 29.3, 27.5 (-C(***C***$H_3)_3$), 21.9, 21.5, 13.2 (-OCH_2***C***H_3).

Compound 19:

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 172.4 (***C***O), 170.5 (***C***O), 157.6 (***C***O), 80.4 (-***C***$(CH_3)_3$), 59.1, 46.6, 42.5, 30.0, 28.5 (-C(***C***$H_3)_3$), 23.6, 20.5.

2,5-diamino-2-(aminomethyl)pentanoic acid 20.

^{13}C-NMR (75.5 MHz, D_2O, ppm) δ_c 171.2 (***C***O), 60.2, 42.5, 39.8, 30.5, 21.3.

***tert*-butyl acetamidocyanoacetate 21.**

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 169.5 (***C***O), 162.1 (***C***O), 114.3 (N≡***C***-), 86.4 (-***C***$(CH_3)_3$), 43.3 (-***C***H-), 27.3 (-C(***C***$H_3)_3$), 22.6 (-***C***H_3).

1-tert-butyl 6-ethyl 2-acetamido-2-cyanohexanedioate 22.

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 173.4 (***C***O), 169.7 (***C***O), 164.9 (***C***O), 116.6 (N≡***C***-), 86.4 (-***C***$(CH_3)_3$), 61.8, 57.1, 34.9, 32.9, 27.8 (-C(***C***$H_3)_3$), 22.7, 18.9, 14.3.

1-tert-butyl 6-ethyl 2-acetamido-2-((tert-butoxycarbonylamino)methyl)hexanedioate 23.

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 173.1 (***C***O), 171.4 (***C***O), 169.7 (***C***O), 155.6 (***C***O), 85.3 (-***C***$(CH_3)_3$), 83.2 (-***C***$(CH_3)_3$), 65.0, 60.4, 44.7, 33.8, 31.8, 28.3 (-C(***C***$H_3)_3$), 27.6 (-C(***C***$H_3)_3$, 24.1, 19.1, 14.2.

5-acetamido-6-tert-butoxy-5-((tert-butoxycarbonylamino)methyl)-6-oxohexanoic acid 24.

^{13}C-NMR (75.5 MHz, $CDCl_3$, ppm) δ_c 177.9 (***C***O), 171.3 (***C***O), 170.6 (***C***O), 155.7 (***C***O), 85.7 (-***C***$(CH_3)_3$), 79.4 (-***C***$(CH_3)_3$), 65.1, 44.7, 33.8, 31.8, 28.3 (-C(***C***$H_3)_3$), 27.7 (-C(***C***$H_3)_3$, 23.9, 19.1.

2-amino-2-(aminomethyl)hexanedioic acid 25.

^{13}C-NMR (75.5 MHz, D_2O, ppm) δ_c 177.0 (***C***O), 176.6 (***C***O), 173.9 (***C***O), 169.9 (***C***O), 60.7 (-C^b-, **26**), 60.2 (-C^b-, **25**), 44.2 (-C^a-, **26**), 42.0 (-C^a-, **25**), 32.6 (-C^f-, **25**), 32.3 (-C^d-, **25**), 29.6 (-C^f-, **26**), 27.3 (-C^d-, **26**), 17.8 (-C^e-, **25**), 16.4 (-C^e-, **26**)

Compound 26.

^{13}C-NMR (75.5 MHz, D_2O, ppm) δ_c 174.6 (***C***^{c}), 172.7 (***C***^{g}), 59.0 (***C***H^b), 42.5 (-***C***^{a}-), 27.9 (-***C***^{f}-), 25.6 (-***C***^{d}-), 14.7 (-***C***^{e}-).

Re complexes 27

^{13}C-NMR (75.5 MHz, CD_3OD, ppm) δ_c 197.3 (***C***≡O), 195.9 (***C***≡O), 181.0 (C^c), 163.3 (q, CF_3***C***OO^-), 116.4 (q, ***C***F_3COO^-), 67.3 (-C^b-), 45.1 (-C^a-), 39.4 (-C^f-), 30.4 (-C^d-), 21.4 (-C^e-).

***fac*-[Re(κ^3-25)$(CO)_3$] (28)**

^{13}C-NMR (75.5 MHz, CD_3OD, ppm) δ_c 198.3 (***C***≡O), 197.1 (***C***≡O), 181.2 (C^c), 177.2 (C^g), 67.0 (-C^b-), 46.6 (-C^a-), 35.0 (-C^f-), 34.8 (-C^d-), 19.9 (-C^e-).

***fac*-[Re(26)$(CO)_3$]**

^{13}C-NMR (75.5 MHz, CD_3OD, ppm) δ_c 199.2 (***C***≡O), 199.0 (***C***≡O), 197.8 (***C***≡O), 181.6 (C^c), 172.6 (C^g), 70.5 (-C^b-), 49.0 (-C^a-; overlapped with CD_3OD peak, assigned from HSQC spectrum), 28.9 (-C^f-), 26.7 (-C^d-), 18.3 (-C^e-).