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Synthesis of a new family of protected 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid derivatives with thioctic acid pending arms

Arnaud de la Reberdière, Fabien Lachaud, Françoise Chuburu, Cyril Cadiou, Gilles Lemercier *

Université de Reims Champagne-Ardenne, ICMR, UMR CNRS n° 7312, C²POM team, BP 1039, 51687 Reims cedex 2, France

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ABSTRACT

The synthesis and characterization of a new family of ester protected N-substituted [1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (H3DO3A) derivatives containing a pendant thioctic acid (α lipoic acid, LA) are reported. These compounds (**DO3A^{t}Bu-NLA**, **DO3A^{t}Bu-NMeNLA**, and **DO3A^{t}Bu-NEtNLA**) are suitable for the functionalization of gold surfaces with rare-earth complexes.

The coordination of lanthanide ionic centers by chelating,[1] and macrocyclic ligands such as substituted triazacyclononane (TACN),[2] is an important topic in fundamental research and photonic applications.[3] In this field, macrocyclic derivatives based on 1,4,7,10-tetraazacyclododecane (cyclen), and more particularly 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid (DOTA) analogues,[4] are among the most widely studied and used ligands for efficient complexation of Ln^{3+} ions, and especially stability and relative inertness[5,6] in water.

These lanthanide complexes are archetypal targets, and used as contrast agents for magnetic resonance imaging (MRI),[7] (including pH mapping method[8]), as radiopharmaceuticals for diagnosis and therapy,[9] and as one-[10] and two-photon[11] excited luminescent tags in biological systems. Some recent papers have reported the grafting of Cu^{2+} complexes of 1,4,8,11-tetraazacyclotetradecane (cyclam)[12] macrocycles on porous and mesoporous silica substrates, and C-substituted-1,4,7,10-tetraazacyclotridecane monolayers on glass surfaces.[13] These new N- or C-substituted macrocyclic platforms are also of interest in the emerging field of nanosciences for example as chelates in delivery systems for therapy,[14] or in nano-objects for imagery,[15] multimodal imaging,[16] and in multifunctional systems (theragnostic).[17] To the best of our knowledge, only a few linear ligands for rare-earth, involving a thiol function, have been reported (for instance dithiolated diethylenetriaminepentaacetic acid, that is, DTDTPA[18]). Even less examples involving a macrocyclic unit,[19] can be found in the literature, for example in order to obtain redox-sensitive contrast agents.[20] Therefore, we report herein a convenient route for the preparation of DOTA analogues as candidates for the functionalization of gold surfaces such as nanoparticles. **DO3A^{t}Bu-NLA**, **DO3A^{t}Bu-NMeNLA**, and **DO3A^{t}Bu-NEtNLA** are shown in Figure 1. The new family of protected 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid derivatives (DO3A^{t}Bu) contains a terminal dithiol linker (thioctic or α lipoic acid, LA).

Ligand **DO3A^{t}Bu-NEtNLA** has been synthesized according to the route depicted in Scheme 1a after the N-alkylation of 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**DO3A^{t}Bu**) with bromoethylphthalimide and conversion into the primary amine via hydrazinolysis according to Ing-Manske procedure,[21] a peptidic coupling using *N*-hydroxysuccinimide/1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide hydrochloride (NHS/EDC) with the activated ester **LA-NHS** (prepared according to a slightly modified reported procedure[22] Scheme 1b). The crude was concentrated and purified over a short column of silica using dichloromethane as eluent led to **DO3A^{t}Bu-NEtNLA**. Due to the instability of the aminal formed via hydrazinolysis, this approach was not applicable to the synthesis of **DO3A^{t}Bu-NMeNLA** and gave exclusively the parent compound **DO3A^{t}Bu** (Scheme 1). To overcome this reactivity, the benzotriazole way developed by Katritzky et al. revealed that a pertinent methodology being an efficient access to *N*-acylaminals.[23] The *N*-(benzotriazol-1-ylmethyl) lipoic amide obtained by condensation of 1-hydroxymethylbenzotriazole with lipoic amide (Scheme 1b) reacted with **DO3A^{t}Bu** to give **DO3A^{t}Bu-NMeNLA**. The well-documented polymerization of lipoic derivatives[24] never occurred when coupling the lipoic moiety to the macrocyclic unit, even if the high temperature and the acidic conditions of the condensation with 1-hydroxymethylbenzotriazole

* Corresponding author. Tel.: +33 032 691 3240; fax: +33 032 691 3243.
E-mail address: gilles.lemercier@univ-reims.fr (G. Lemercier).

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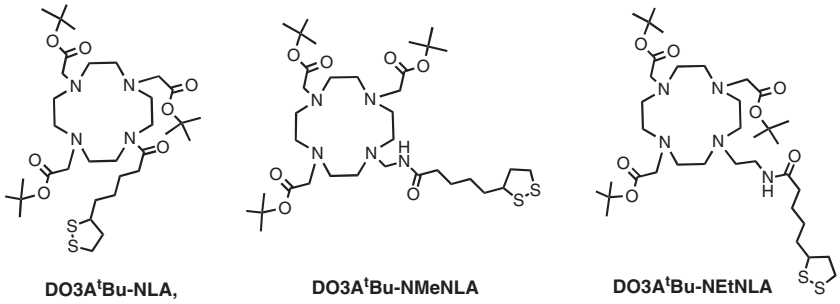
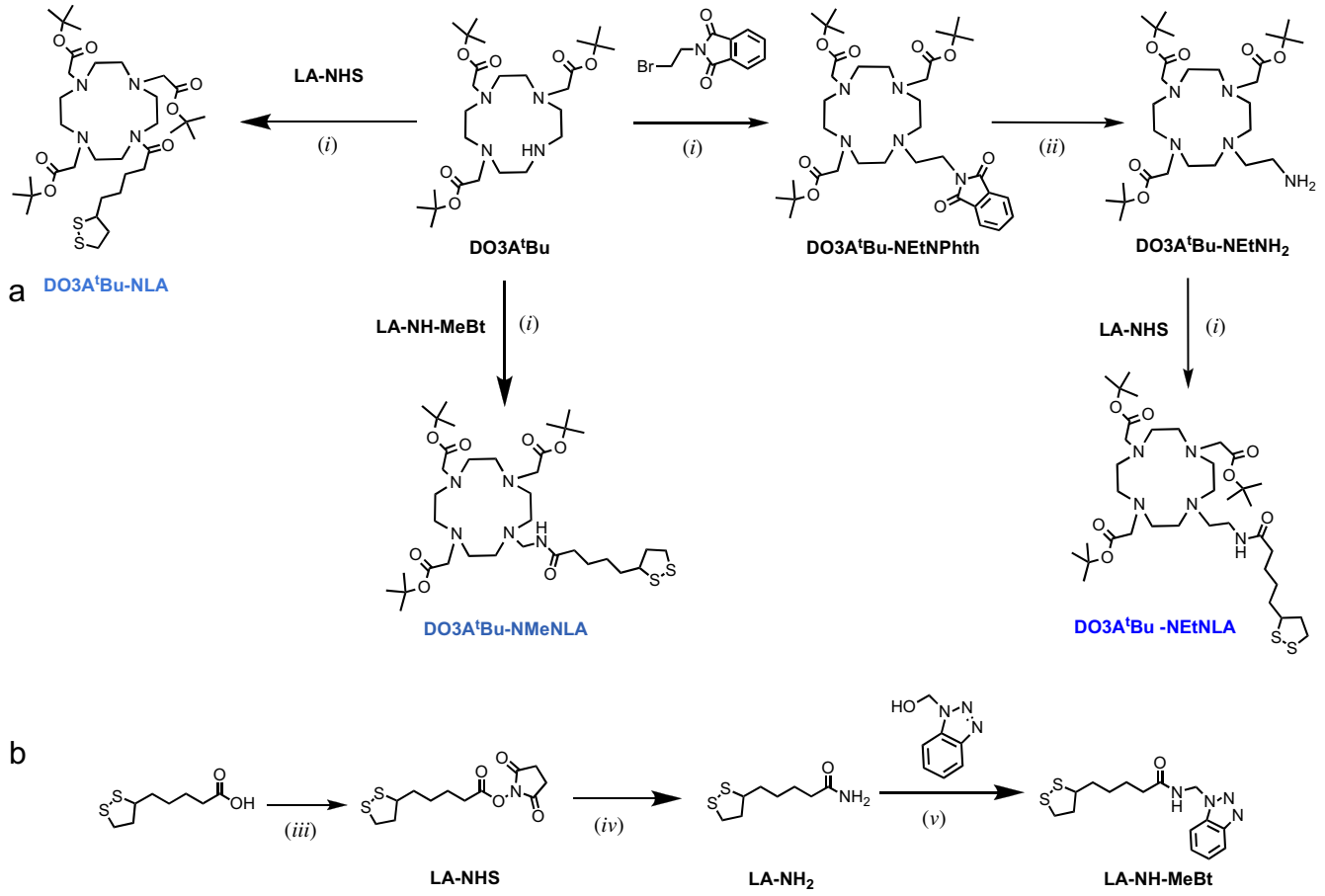


Figure 1. Molecular structures of macrocyclic ligands **DO3A^{t}Bu-NLA**, **DO3A^{t}Bu-NMeNLA**, and **DO3A^{t}Bu-NEtNLA**.



Scheme 1. Reagents and conditions: (i) Cs_2CO_3, CH_3CN, 80 °C; (ii) N_2H_4, MeOH, 65 °C; (iii) NHS/EDC, CH_2Cl_2, rt; (iv) NH_3, 30% in H_2O, CH_3CN, CH_2Cl_2, rt; (v) *p*-toluene–sulfonic acid (cat), toluene, 100 °C.

could have favored this undesirable side-reaction. Direct use of the rubbery polymer gave exact results in accordance with the recognized reversibility of the polymerization.[25] Ligand **DO3A^{t}Bu-NLA** was obtained by the nucleophilic attack of **DO3A^{t}Bu** on the activated ester **LA-NHS**. General procedure and main characterizations are reported in the notes.[26] Compounds were fully characterized by ^{1}H, ^{13}C NMR, mass spectrometry, and elemental analysis.

Starting material is **DO3A^{t}Bu**, obtained with 70–80% yield according to an already published procedure.[27] The strategy used for compound **DO3A^{t}Bu-NEtNLA**, can be generalized to other bromoalkylphthalimide in order to increase the length of the alkyl chain. Synthesis of the versatile DO3A^{t}Bu-ethylamine intermediate compound (**DO3A^{t}Bu-NEtNH$_2$**) bearing a free amine group readily reactive towards most electrophiles, has already been a part of several other synthetic schemes using for example *tert*-butyloxycarbonyl (BOC)[28] or carbobenzyloxy (Cbz)[29,19a] as protecting group and in the substitution of bis(aminal)-protected cyclen-based bis-macrocycles,[30] and using cyclen and other electrophiles such as *N*-chloroacetyl-aza-15-crown-5,[31] alkyl-bromides,[32] or bromoacetonitrile.[33] A convenient synthesis of **DO3A^{t}Bu-NEtNH$_2$** (EtO-ester analogue) and the corresponding cyclam-based macrocycle was also reported by Mishra and Chatal.[34]

A new family of monosubstituted macrocyclic ligands (**DO3A^{t}Bu**) with anchored thioctic acid moieties as pendant arms, have been reported. Work is in progress to involve these ligands in new Ln(III) complexes (Gd^{3+}, Eu^{3+}, Tb^{3+}, Yb^{3+}). This study opens the route to the functionalization of gold surfaces, allowing a fine-tuning of the distance between the complex and the metallic surface. It gives also the opportunity of obtaining Au nanoparticles, especially for applications in therapy and/or biological imaging.

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References and notes

1. (a) Sabbatini, N.; Guardigli, M.; Lehn, J.-M. *Coord. Chem. Rev.* **1993**, *123*, 201; (b) Bretonniere, Y.; Mazzanti, M.; Pecaut, J.; Olmstead, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 9012; (c) Comby, S.; Imbert, D.; Chauvin, A. S.; Bunzli, J. C. G.; Charbonniere, L. J.; Ziessel, R. F. *J. Biol. Inorg. Chem.* **2004**, *43*, 7369; (d) Bunzli, J. C. G. *Acc. Chem. Res.* **2006**, *39*, 53.
2. Charbonniere, L.; Ziessel, R.; Guardigli, M.; Roda, A.; Sabbatini, N.; Cesario, M. *J. Am. Chem. Soc.* **2001**, *123*, 2436.
3. (a) Bünzli, J.-C. G. *Chem. Rev.* **2010**, *110*, 2729; (b) Bünzli, J.-C. G.; Chauvin, A.-S.; Kim, H. K.; Deiters, E.; Eliseeva, S. V. *Coord. Chem. Rev.* **2010**, *254*, 2623; (c) Bünzli, J. C. G.; Piguet, C. *Chem. Rev.* **2002**, *102*, 1897.
4. Wai-Yan Chan, K.; Wong, W.-T. *Coord. Chem. Rev.* **2007**, *251*, 2428.
5. Toth, E.; Brücher, E.; Lazar, I.; Toth, I. *J. Biol. Inorg. Chem.* **1994**, *33*, 4070.
6. Parker, D.; Dickins, R. S.; Puschmann, H.; Crossland, C.; Howard, J. A. K. *Chem. Rev.* **2002**, *102*, 1977.
7. (a) Aime, S.; Geninatti Crich, S.; Gianolio, E.; Giovenzana, G. B.; Tei, L.; Terreno, E. *Coord. Chem. Rev.* **2006**, *250*, 1562; (b) Caravan, P.; Ellison, J. J.; Mc Murry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293.
8. Gianolio, E.; Napolitano, R.; Fedeli, F.; Arena, F.; Aime, S. *Chem. Commun.* **2009**, 6044.
9. (a) Liu, S. *Chem. Soc. Rev.* **2004**, *33*, 445; (b) Anderson, C. J.; Welch, M. J. *Chem. Rev.* **1999**, *99*, 2219; (c) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269.
10. (a) Montgomery, C. P.; Murray, B. S.; New, E. J.; Pal, R.; Parker, D. *Acc. Chem. Res.* **2009**, *42*, 925; (b) Law, G.-L.; Pal, R.; Palsson, L. O.; Parker, D.; Wong, K.-L. *Chem. Commun.* **2009**, 7321.
11. (a) Palsson, L.-O.; Pal, R.; Murray, B.-S.; Parker, D.; Beeby, A. *Dalton Trans.* **2007**, 5726; (b) Kielar, F.; Congreve, A.; Law, G.-L.; New, E. J.; Parker, D.; Wong, K.-L.; Castreno, P.; de Mondoza, J. *Chem. Commun.* **2008**, 2435; (c) Kong, H.-K.; Chadbourne, F. L.; Law, G.-L.; Li, H.; Tam, H.-L.; Cobb, S. L.; Lau, C.-K.; Lee, C.-S.; Wong, K.-L. *Chem. Commun.* **2011**, *47*, 8052.
12. (a) Etienne, M.; Goubert-Renaudin, S.; Rousselin, Y.; Marichal, C.; Denat, F.; Lebeau, B.; Walcarius, A. *Langmuir* **2009**, *25*, 3137; (b) Corriu, R. J. P.; Embert, F.; Guari, Y.; Reyé, C.; Guilard, R. *Chem. Eur. J.* **2002**, *8*, 5732.
13. Pallavicini, P.; Dacarro, G.; Cucca, L.; Denat, F.; Grisoli, P.; Patrini, M.; Sok, N.; Taglietti, A. *New J. Chem.* **2011**, *35*, 1198.
14. Kuruppuarachchi, M.; Savoie, H.; Lowry, A.; Alonso, C.; Boyle, R. W. *Mol. Pharm.* **2011**, *8*, 920.
15. (a) Kielar, F.; Tei, L.; Terreno, E.; Botta, M. *J. Am. Chem. Soc.* **2010**, *132*, 7836; (b) Courant, T.; Roullin, V. G.; Cadiou, C.; Delavoie, F.; Molinari, M.; Andry, M. C.; Gafa, V.; Chuburu, F. *Nanotechnology* **2010**, *21*, 165101; (c) Ratzinger, G.; Agrawal, P.; Körner, W.; Lonkai, J.; Sanders, H. M. H. F.; Terreno, E.; Wirth, M.; Strjkers, G. J.; Nicolay, K.; Gabor, F. *Biomaterials* **2010**, *31*, 8716; (d) Chen, K.-J.; Wolahan, S. M.; Wang, H.; Hsu, C.-H.; Chang, H.-W.; Durazo, A.; Hwang, L.-P.; Garcia, M. A.; Jiang, Z. K.; Wu, L.; Lin, Y.-Y.; Tseng, H.-R. *Biomaterials* **2011**, *32*, 2160.
16. (a) Kim, J. S.; Rieter, W. J.; Taylor, K. M. L.; An, H.; Lin, W.; Lin, W. *J. Am. Chem. Soc.* **2007**, *129*, 8962; (b) Patel, D.; Kell, A.; Simard, B.; Xiang, B.; Lin, H. Y.; Tian, G. *Biomaterials* **2011**, *32*, 1167.
17. Li, X.; Qian, Y.; Liu, T.; Hu, X.; Zhang, G.; You, Y.; Liu, S. *Biomaterials* **2011**, *32*, 6595.
18. (a) Debouttière, P.-J.; Roux, S.; Vocanson, F.; Billotey, C.; Beuf, O.; Favre-Réguillon, A.; Lin, Y.; Pellet-Rostaing, S.; Lamartine, R.; Perriat, P.; Tillement, O. *Adv. Funct. Mater.* **2006**, *16*, 2330; (b) Alric, C.; Taleb, J.; Le Duc, G.; Mandon, C.; Billotey, C.; Le Meur-Herland, A.; Brochard, T.; Vocanson, F.; Janier, M.; Perriat, P.; Roux, S.; Tillement, O. *J. Am. Chem. Soc.* **2008**, *130*, 5908; (c) Park, J.-A.; Reddy, P. A. N.; Kim, H.-K.; Kim, I.-S.; Kim, G.-C.; Chang, Y.; Kim, T.-J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6135; (d) Moriggi, L.; Cannizzo, C.; Dumas, E.; Mayer, C. R.; Ulianov, A.; Helm, L. *J. Am. Chem. Soc.* **2009**, *131*, 10828; (e) Warsi, M. F.; Adams, R. W.; Duckett, S. B.; Chechik, V. *Chem. Commun.* **2010**, 451; (f) Kim, H.-K.; Jung, H.-Y.; Park, J.-A.; Huh, M.-I.; Jung, J.-C.; Chang, Y.; Kim, T.-J. *J. Mater. Chem.* **2010**, *20*, 5411.
19. (a) Stasiuk, G. J.; Tamang, S.; Imbert, D.; Poillot, C.; Giardiello, M.; Tisseyre, C.; Barbier, E. L.; Fries, P. H.; de Waard, M.; Reiss, P.; Mazzanti, M. *ACS Nano* **2011**, *5*, 8193; (b) Digilio, G.; Menchise, V.; Gianolio, E.; Catanzaro, V.; Carrera, C.; Napolitano, R.; Fedeli, F.; Aime, S. *J. Med. Chem.* **2010**, *53*, 4877; (c) Lacerda, S.; Campello, M. P.; Marques, F.; Gano, L.; Kubicek, V.; Fouskova, P.; Toth, E.; Santos, I. *Dalton Trans.* **2009**, 4509.
20. Raghunand, N.; Guntle, G. P.; Gokhale, V.; Nichol, G. S.; Mash, E. A.; Jagadish, B. *J. Med. Chem.* **2010**, *53*, 6747.
21. Manske, R. H. F. *J. Am. Chem. Soc.* **1926**, *129*, 2348.
22. Stokes, R. J.; Macaskill, A.; Dougan, J. A.; Hargreaves, P. G.; Stanford, H. M.; Smith, W. E.; Faulds, K.; Graham, D. *Chem. Commun.* **2007**, *27*, 2811. Purification was done by precipitation with diethylether and filtration on silica.
23. Katritzky, A. R.; Fali, C. N.; Bao, W.; Qi, M. *Synthesis* **1998**, 1421.
24. Thomas, R. C.; Reed, L. J. *J. Am. Chem. Soc.* **1956**, *78*, 6148.
25. (a) US Patent Application 20070055070-novel esters of lipoic acid.; Kisanuki, A.; Kimpara, Y.; Oikado, Y.; Kado, N.; Matsumoto, M.; Endo, K. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 5247.
26. *Materials and methods*: All reactions were performed under an argon atmosphere using standard Schlenk techniques. ^{1}H NMR spectra were recorded in $CDCl_3$, on a Bruker 250 DPX. Chemical shifts are reported in delta (δ units, expressed in parts per million (ppm). Coupling constants are given in hertz (Hz), and multiplicity expressed as follows: s for singlet, d for doublet, t for triplet, b for broad signal and m for a multiplet. High-resolution mass spectra (HRMS) were obtained with a Micromass Q-TOF electrospray positive ionization. Typical experimental procedure for:
Compound ***DO3A^{t}Bu-NEtNPhth***: Bromoethylphtalimide (158 mg, 0.65 mmol), and cesium carbonate (360 mg, 1.10 mmol) were added to a solution of DO3A^{t}Bu under argon atmosphere (285 mg, 0.55 mmol) in freshly distilled acetonitrile (5 mL). The suspension was heated to reflux for 24 h, before being filtered at room temperature. The yellow filtrate was evaporated under reduced pressure and 10 mL chloroform was added in order to precipitate residual inorganic impurities. Evaporation of the solvent afforded **DO3A^{t}Bu-NEtNPhth** as a clear yellow oil (429 mg, quantitative yield), which was used without further purification. An analytical sample was obtained after purification over a short column of silica using dichloromethane/methanol (92:8) as eluant. ^{1}H NMR ($CDCl_3$) δ: 7.73–7.55 (m, 4H), 3.61 (bt, J = 6.0 Hz, 2H), 3.06 (s, 6H), 2.62, 2.53 (m, 18H), 1.30 n (s, 27H); ^{13}C NMR ($CDCl_3$) δ: 170.86, 170.82, 168.08, 134.36, 133.61, 132.05, 122.88, 80.36, 56.43, 56.21, 52.61, 52.16, 51.78, 35.66, 28.03. ESI-MS Calcd for $C_{36}H_{58}N_5O_8$: m/z = 688.4 (M+H$^+$), obsd 688.5 (M+H$^+$) and 710.5 (M+Na$^+$); **DO3A^{t}Bu-NMeNPhth.** Bromomethylphtalimide (85 mg, 0.35 mmol), sodium iodide (53 mg, 0.56 mmol) and cesium carbonate (177 mg, 0.54 mmol) were added to a solution of DO3A^{t}Bu under argon atmosphere (172 mg, 0.33 mmol) in freshly distilled acetonitrile (5 mL). The suspension was heated to reflux for 24 h, before being filtered at room temperature. The yellow filtrate was evaporated under reduced pressure and 10 mL chloroform was added in order to precipitate residual inorganic impurities. Evaporation of the solvent and addition of 20 mL of ether led to precipitation of a yellow powder corresponding to the sodium adduct $C_{35}H_{55}N_5O_8$.NaI.H_2O (191 mg, 67% yield). ^{1}H NMR ($CDCl_3$) δ: 7.82–7.71 (m, 4H), 4.66 (s, 2H), 3.27–2,34 (broad signals overlapping, 22H), 1.48–1,40 (two signals overlapping, 27H); ^{13}C NMR ($CDCl_3$) δ: 173.91, 173.30, 169.70, 134.58, 131.69, 123.59, 83.03, 82.73, 57.62, 56.48, 55.69, 53.55, 51.77, 51.15, 48.34, 28.06, 27.88. Anal. Calcd for $C_{35}H_{55}N_5O_8$.NaI.H_2O: C, 49.94; H, 6.83; N, 8.32. Found: C, 50.13; H, 6.67; N, 8.49.
Compound ***DO3A^{t}Bu-NEtNH$_2$***: To the crude oil of **DO3A^{t}Bu-NEtNPhth** (429 mg) dissolved in 7 mL MeOH was added hydrazine monohydrate (55 μL, 1.13 mmol). The solution was heated at reflux for 4 h, and the solvent was evaporated. 20 mL CH_2Cl_2 was added to the resulting solids and the insoluble phtalhydrazide impurities were filtered out. The filtrate was washed first with distilled water (4 × 10 mL), then with 5 mL of an aqueous solution of KOH 20% and the organic layer was dried under $MgSO_4$. Evaporation of the solvent under reduced pressure yielded an amber oil (281 mg, 91%). ^{1}H NMR ($CDCl_3$) δ: 3.32–3.29 (two signals overlapping, 6H), 2.81–2.57 (m, 20H), 1.44 (s, 27H). ^{13}C NMR ($CDCl_3$) δ: 170.98, 80.57, 80.48, 56.28, 52.53, 51.90, 51.75, 39.58, 28.11. Anal. Calcd for $C_{28}H_{55}N_5O_6$.0.25 $CHCl_3$: C, 57.74; H, 9.48; N, 11.92. Found: C, 57.46; H, 9.45; N, 11.95. ESI-MS: obsd m/z = 558.3 (M+H$^+$).
Compound ***DO3A^{t}Bu-NEtNLA***: Under argon atmosphere potassium carbonate (143 mg, 1.04 mmol) and **LA-NHS** (189 mg, 0.62 mmol) were added to a solution of **DO3A^{t}Bu-NEtNH$_2$** (290 mg, 0.52 mmol) in anhydrous acetonitrile (10 ml). The solution was kept at reflux for 24 h. Then the reaction mixture was allowed to cool at room temperature and was filtered. The filtrate was evaporated and purified over a short column of alumina deactivated with water (5%) using dichloromethane: ethyl acetate as eluent (100:0 to 0:100). Evaporation of the solvent afforded **DO3A^{t}Bu-NEtNLA** as a clear yellow oil (322 mg, 83%). ^{1}H NMR ($CDCl_3$) δ 3.55(m, 1H), 3.27–3.02 (signals overlapped, 10H), 2.82–2.39 (signals overlapped, 18H) 2.15 (t, J = 7.3 Hz, 2H), 1.89 (m, 1H), 1.65–1.41 (signals overlapped, 33H) ^{13}C NMR ($CDCl_3$) δ: 172.88, 170.88, 170.65, 80.99, 57.61, 56.51, 56.13, 52.74, 52.45, 51.94, 40.28, 38.51, 36.23, 34.89, 29.26, 28.30, 25.57. ESI-MS: m/z = 746.46 (M+H$^+$). Anal. Calcd for $C_{15}H_{20}N_4O_5S_2$: C, 53.54; H, 5.99; N, 16.65; S, 19.06. Found: C, 53.66; H, 6.10; N, 16.16; S, 19.39.
Compound ***LA-NH$_2$***: The activated ester **LA-NHS** (707 mg, 2.53 mmol) was dissolved in a chloroform/acetonitrile mixture (1:2, 15 mL). Then, ammonia (30% in water) was added until the appearance of two phases. The heterogeneous solution was left under vigorous stirring for one hour. After addition of chloroform (15 mL) the crude product was extracted with water (2 × 15 mL) and aqueous solution of KOH (20%). The organic layer was dried under $MgSO_4$. Subsequent evaporation led to a yellow solid which was oven-dried. (485 mg, 93%). ^{1}H NMR ($CDCl_3$) δ: 5.53 (broad singlet,2H–NH), 3.63–3.52 (m, 1H), 3.24–3.06 (m, 2H), 2,52–2.40 (m, 1H), 2.24 (t, J = 7.4 Hz, 2H), 1.97–1.84 (m, 1H), 1.77–1.41 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 175.21, 56.52, 40.38, 38.62, 35.69, 34.77, 28.97, 25.27. ESI-MS: m/z = 228.0 (M+Na$^+$).
Compound ***LA-NH-MeBt***: (100 mg, 0.49 mmol), benzotriazolemethanol (72 mg, 0.49 mmol) and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) were stirred for 6 h at the reflux in 10 mL toluene. The crude product was washed with an aqueous KOH solution (10%, 5 mL), dried under $MgSO_4$ and, then, cooled overnight. Filtration and the consecutive solvent evaporation led to 146 mg of the yellow desired product (89% yield). ^{1}H NMR ($CDCl_3$) δ: 8.05–7.35 (m, 4H), 6.11 (d, J = 6.9 Hz, 2H), 3.53–3.42 (m, 1H), 3.18–3.01 (m, 2H), 2.43–2.31 (m, 1H), 2.25 (t, J = 7.4 Hz, 2H), 1.87–1.30 m, 7H. ^{13}C NMR ($CDCl_3$) δ: 173.39, 128.20, 124.56, 119.69, 111.07, 56.35, 50.90, 40.26, 38.60, 36.09, 34.62, 28.76, 24.96.. Anal. Calcd for $C_{15}H_{20}N_4O_5S_2$: C, 53.54; H, 5.99; N, 16.65; S, 19.06. Found: C, 53.66; H, 6.10; N, 16.16; S, 19.39; ESI-MS: m/z = 337.1 (M+H$^+$); m/z = 359.1 (M+Na$^+$); m/z = 695.3 (2M+Na$^+$).

Compound ***DO3A^{t}Bu-NMeNLA***: **DO3A^{t}Bu** (103 mg, 0.2 mmol), potassium carbonate (82 mg, 0.6 mmol) and **LA-NH-MeBt** (100 mg, 0.3 mmol) were stirred in freshly distilled acetonitrile at reflux for 48 h. Then, after evaporation, ether (30 mL) was added to the crude which was filtered after standing around 6 °C overnight. The filtrate was washed with 10% aqueous KOH solution (30 mL) and dried under $MgSO_4$. Evaporation of the ethereal phase led to a yellow oil corresponding to the desired product (with an estimated molar purity of 85% in mixture with reactant LA-NH-MeBt) ^{1}H NMR ($CDCl_3$) δ: 4.09 (d, J = 5 Hz, 2H) 3.55 (m, 1H), 3.32–3.03 (signals overlapped, 8H) 2.88–2.65 (signals overlapped, 16H) 2.45 (m, 1H), 2.19 (t, J = 7.6 Hz, 2H), 1.90 (m, 1H), 1.69–1.43 (signals overlapped, 33H). ^{13}C NMR ($CDCl_3$) δ: 171.36, 171.14, 81.09, 81.01, 80.95, 60.20, 57.49, 57.03, 56.57, 56.52, 52.64, 52.51, 52.35, 52.12, 51.84, 50.96, 47.63, 40.33, 38.57, 36.53, 34.82, 29.14, 28.35, 25.56. ESI-MS: m/z = 732.2 ($M+H^+$).

Compound ***DO3A^{t}Bu-NLA***: A mixture of **DO3A^{t}Bu** (438 mg, 0.85 mmol), potassium carbonate (235 mg, 1.71 mmol), and **LA-NHS** (309 mg, 1.02 mmol) in 15 mL of anhydrous acetonitrile was stirred at room temperature for 24 h. Then the crude was allowed to cool at room temperature, filtered, and purified by chromatography over an alumina column using ether/methanol (96:4). Evaporation of the solvent afforded **DO3A^{t}Bu-NLA** as a clear yellow oil (526 mg, 88%). ^{1}H NMR ($CDCl_3$) δ 3.63–3.46 (signals overlapped, 5H), 3.26–3.21 (signals overlapped, 6H), 3.07 (m, 2H), 2.95–2.66 (signals overlapped, 12H) 2.41 (m, 1H), 2.25 (t, J = 7.3 Hz, 2H), 1.86 (m, 1H), 1.67–1.37 (signals overlapped, 33H). ^{13}C NMR ($CDCl_3$) δ 172.90, 170.95, 170.85, 81.14, 81.03, 80.93, 58.55, 57.24, 56.56, 54.97, 54.64, 53.26, 52.72, 52.64, 52.30, 51.59, 48.03, 45.72, 38.55, 34.91, 32.90, 29.25, 28.31, 25.33. ESI-MS: m/z = 703.5 ($M+H^+$). Anal. Calcd for $C_{34}H_{62}N_4O_7S_2$. 0.66 $CHCl_3$: C, 53.20; H, 8.07; N, 7.16; S, 8.19. Found: C, 53.36; H, 8.28; N, 7.30; S, 8.16.

27. Jagadish, B.; Brickert-Albrecht, G. L.; Nichol, G. S.; Mash, E. A.; Raghunand, N. *Tetrahedron Lett.* **2011**, *52*, 2058.
28. Mishra, A.; Pfeuffer, J.; Mishra, R.; Engelmann, J. R.; Mishra, A. K.; Ugurbil, K.; Logothetis, N. K. *Bioconjugate Chem.* **2006**, *17*, 773.
29. Dhingra, K.; Fousková, P.; Angelovski, G.; Maier, M. E.; Logothetis, N. K.; Tóth, E. *J. Biol. Inorg. Chem.* **2008**, *13*, 35.
30. (a) Anda, C.; Bencini, A.; Berni, E.; Ciattini, S.; Chuburu, F.; Danesi, A.; Giorgi, C.; Handel, H.; Le Baccon, M.; Paoletti, P.; Tripier, R.; Turcry, V.; Valtancoli, B. *Eur. J. Inorg. Chem.* **2005**, 2044; (b) Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Patent EP1637524 A1, 2006.
31. (a) Li, C.; Wong, W.-T. *Tetrahedron Lett.* **2004**, *45*, 6055; (b) Li, C.; Li, Y.-X.; Law, G.-L.; Man, K.; Wong, W.-T.; Lei, H. *Bioconjugate Chem.* **2006**, *17*, 571.
32. (a) Li, C.; Wong, W.-T. *Tetrahedron Lett.* **2002**, *43*, 3217; (b) Duimstra, J. A.; Femia, F. J.; Maede, T. J. *J. Am. Chem. Soc.* **2005**, *127*, 12847.
33. Mishra, A.; Fousková, P.; Angelovski, G.; Balogh, E.; Mishra, A. K.; Logothetis, N. K.; Tóth, E. *J. Biol. Inorg. Chem.* **2008**, *47*, 1370.
34. Mishra, A. K.; Chatal, J.-F. *New J. Chem.* **2001**, *25*, 336.