New Synthetic Strategy of MRI/BNCT Agents Based on Hydroboration Reaction

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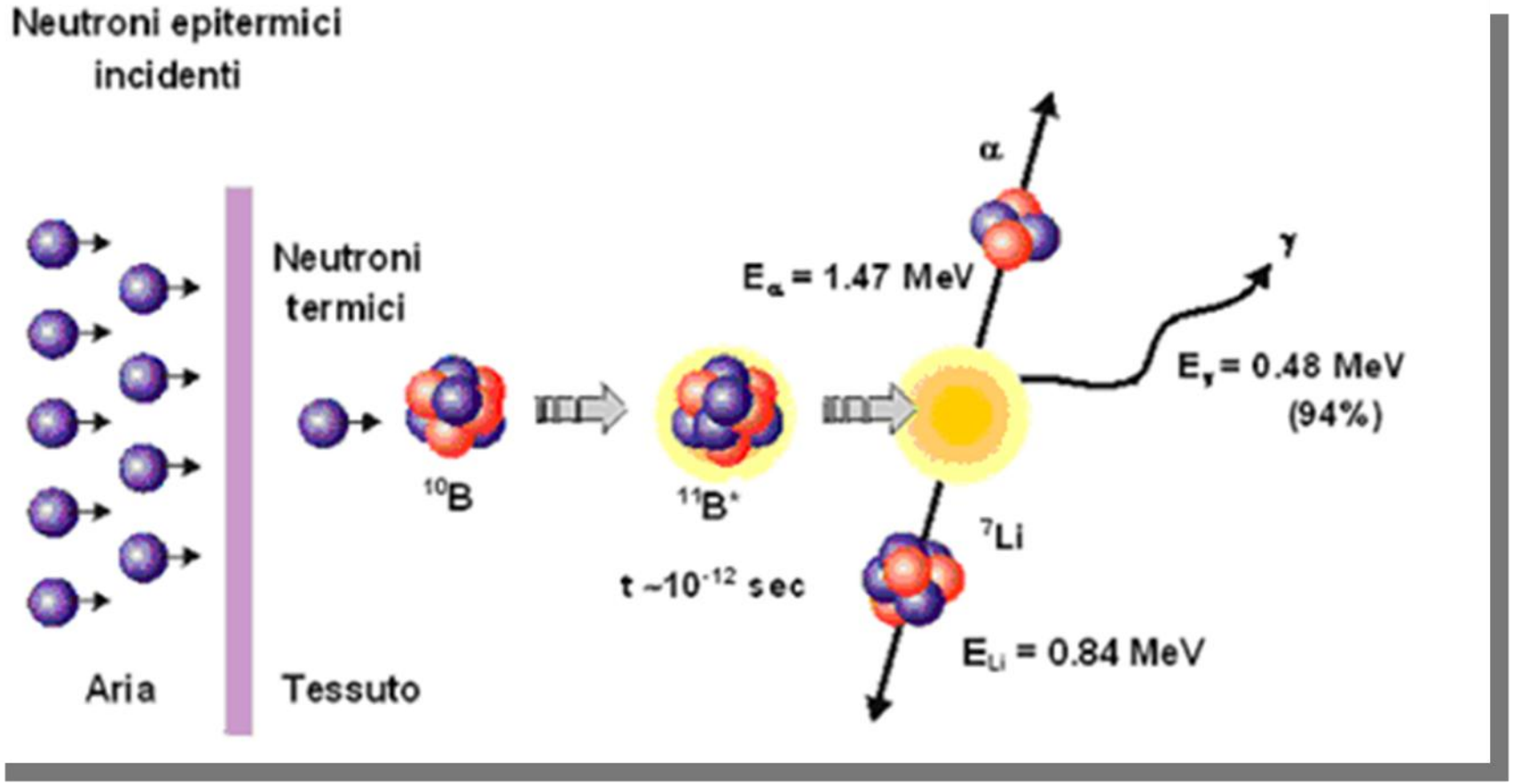
Boron Neutron Capture Therapy



A. H. Soloway, W. Tjarks, B. A. Barnum, F. G. Rong, R. F. Barth, I. M. Codogni and J. G. Wilson, *Chem. Rev.* 1998, *98*, 1515.

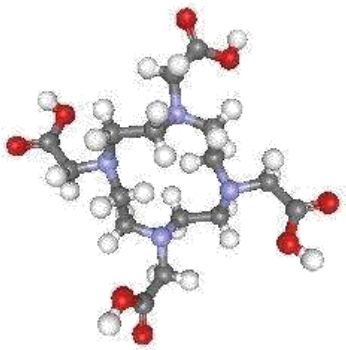
Properties for BNCT agents

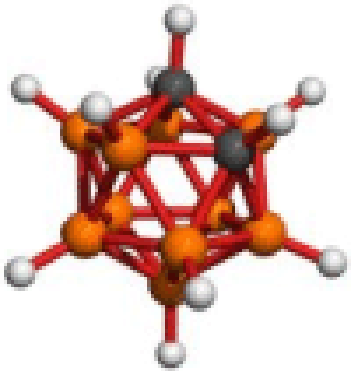
- Low toxicity
- Good stability in biological enviroment
- Persistence inside target cells
- High boron introduction in tumor tissue:
  20 – 35 μg ^{10}B /1 gr cancer cells
- Concentration ratio cancer tissue/healthy tissue : 3 – 5 / 1
- Concentration ratio cancer tissue/blood : 5 / 1
- Efficient body scanning

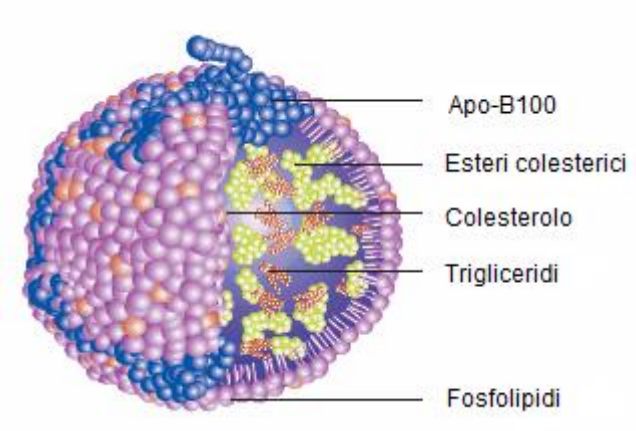
R. F. Barth, J. A. Coderre, M. G. H. Vicente, T. E. Blue, *Clin.Cancer Res.*, 2005, *11*, 3987

MRI/BNCT dual agent: general structure

MOLECULAR PROBE → **CARBORANE** → **BIOLOGICAL VECTOR**

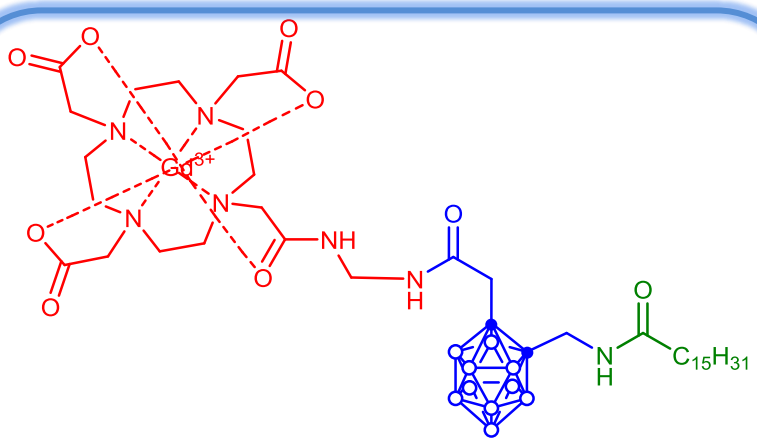




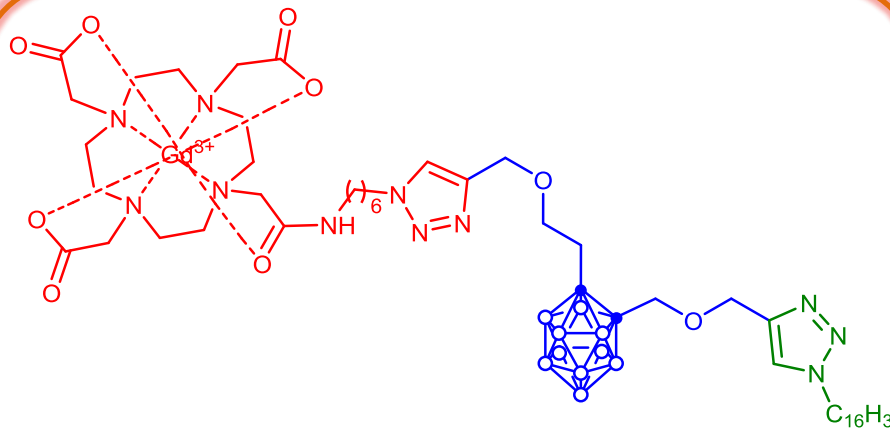


[Gd-DOTA]$^-$ **Dicarba-*closo*-dodecaborane** **Lipoprotein**

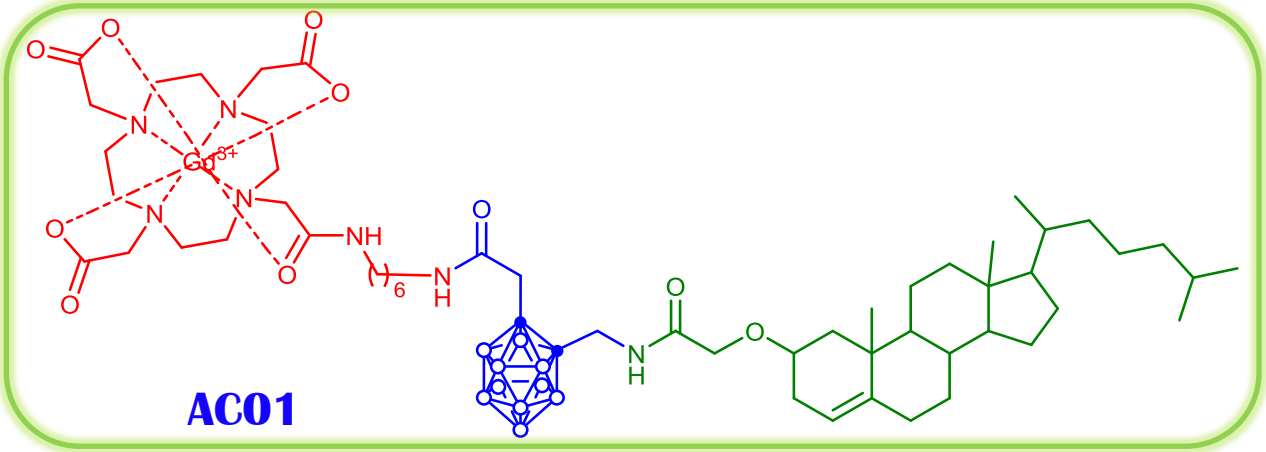
Examples of MRI/BNCT agents



AT101



MEA01



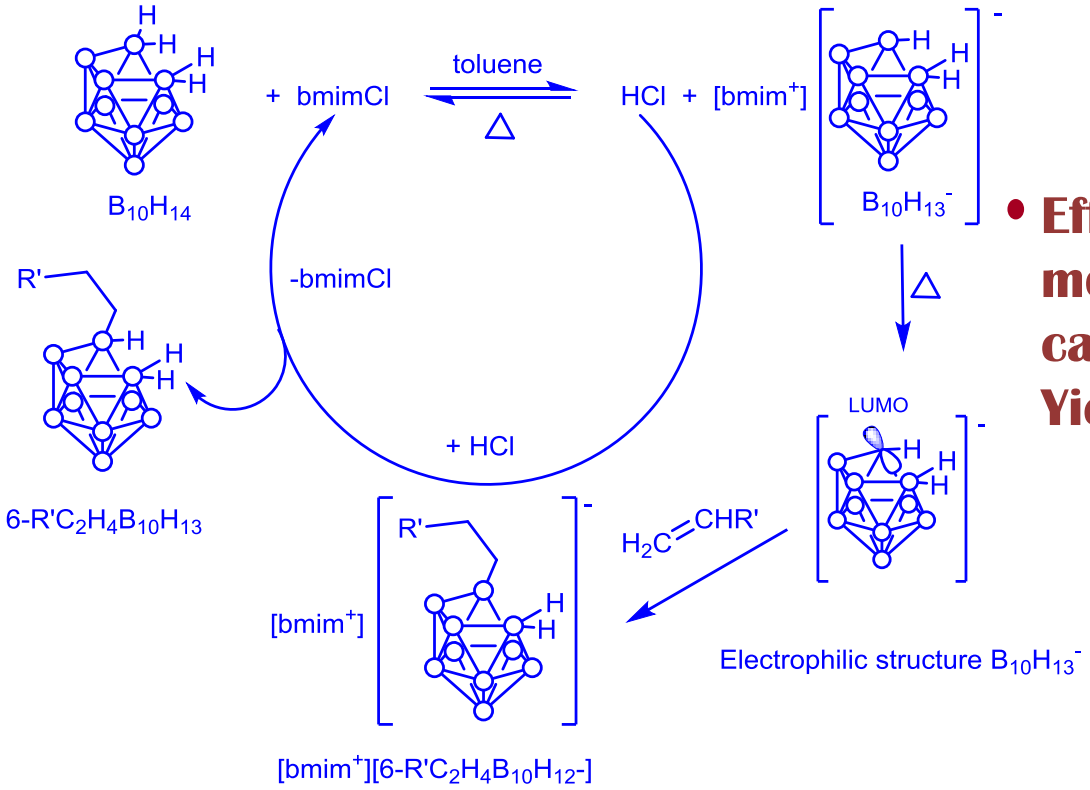
AC01

Org. Biomol. Chem., **2008**, **6**, 4460

Chem. Eur. J., **2013**, **19**, 721 – 728

Org. Biomol. Chem., **2014**, **12**, 2457-2467

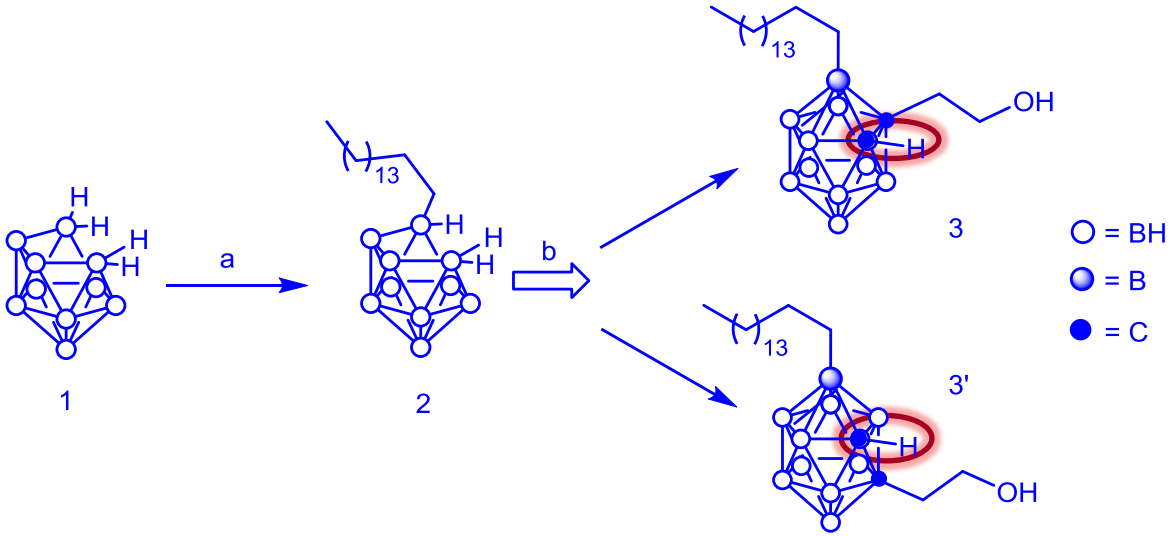
New decaborane functionalization strategy: Hydroboration reaction



- **Efficient strategy for lipophilic moiety introduction on boron cage:**
  Yield product: 55 – 92 %

U. Kusari, P. J. Carrol, L. G. Sneddon; *Inorg. Chem.*, 2008, 47, 9203-9215

New dual agent synthesis: PB01



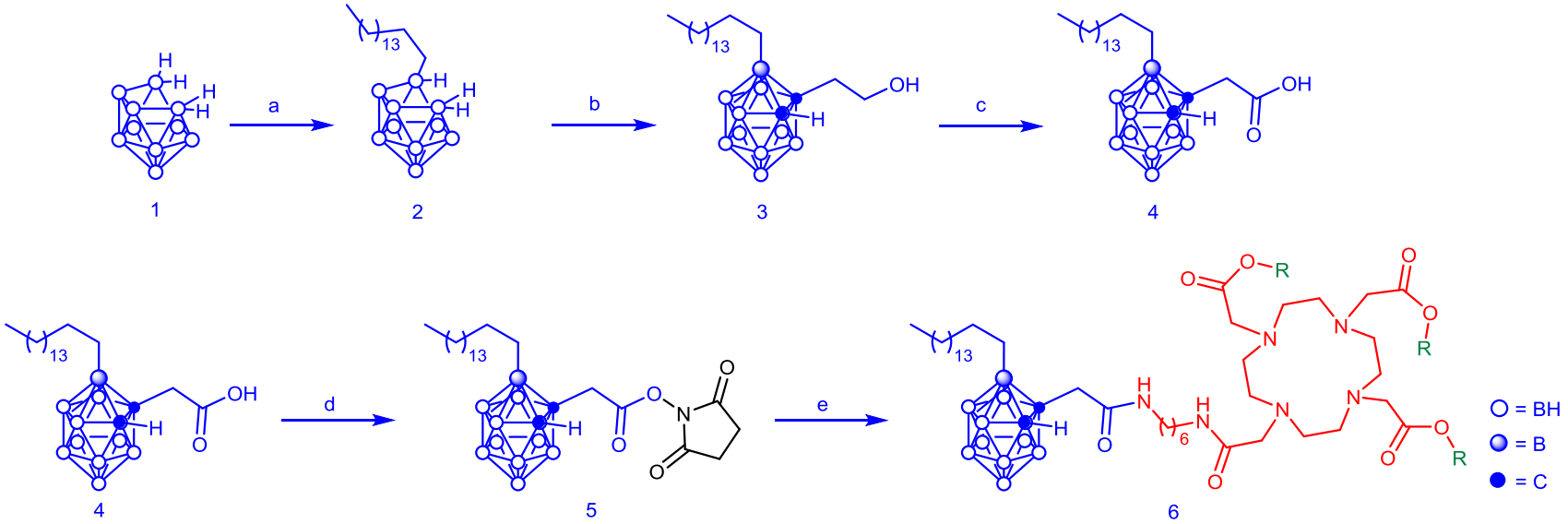
Synthesis of *C*-(2-hydroxy)-ethyl-*C*'-H-6-(hexadecil)-*o*-carborane (3)
a) 1-hexadecene (3.5 eq), bmimCl (0.3 eq), toluene, 125°C, yield 43%; b) 3-butyn-1-ol (4 eq), bmimCl (0.3 eq), toluene, 100°C, yield 40%

Structure 3 : Isomer 1[a]
Chemical shift for C-H
^{1}H: 4.1 ppm
^{13}C: 60.35 ppm

Structure 3' : Isomer 2
Chemical shift for C-H
^{1}H: 3.8 ppm
^{13}C: 61.47 ppm

[a] Molecular structure defined by X-ray diffrattometric study
Structure acquired by Dott.ssa Domenica Marabello

New dual agent synthesis: PB01



General procedure:

Synthesis of *C*-[R_3-DOTAMA-C_6]-acetamide-*C'*-H-6-(hexadecil)-*o*-carborane (6)

a) 1-hexadecene (3.5 eq), bmimCl (0.3 eq), toluene, 125°C, yield 43%; b) 3-butyn-1-ol (4 eq), bmimCl (0.3 eq), toluene, 100°C, yield 40%; c) CrO_3 (4 eq), H_2SO_4 (3M), acetone, room temperature, yield 77%

d) *N*-hydroxysuccinimide [NHS] (1.15 eq), dicyclohexilcarbodiimide [DCC] (1.2 eq), CH_2Cl_2, room temperature;

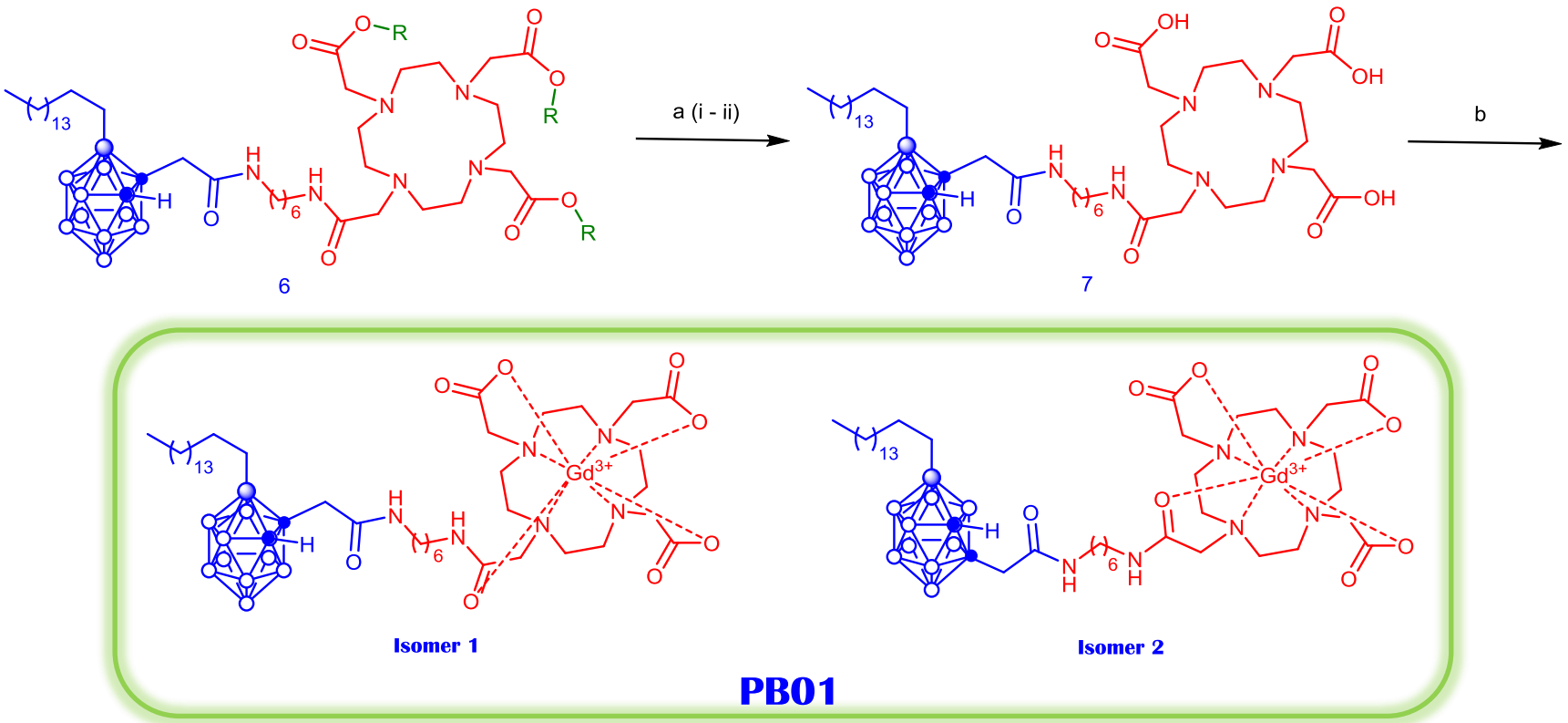
e) R_3-DOTAMA-C_6 (0.95 eq), diisopropylethylamine [DIEA] (0.95 eq), CH_2Cl_2, room temperature, yield: 13 – 42%

Protecting groups

R' = *ter*-Butyl

R" = Benzyl

New dual agent synthesis: PB01



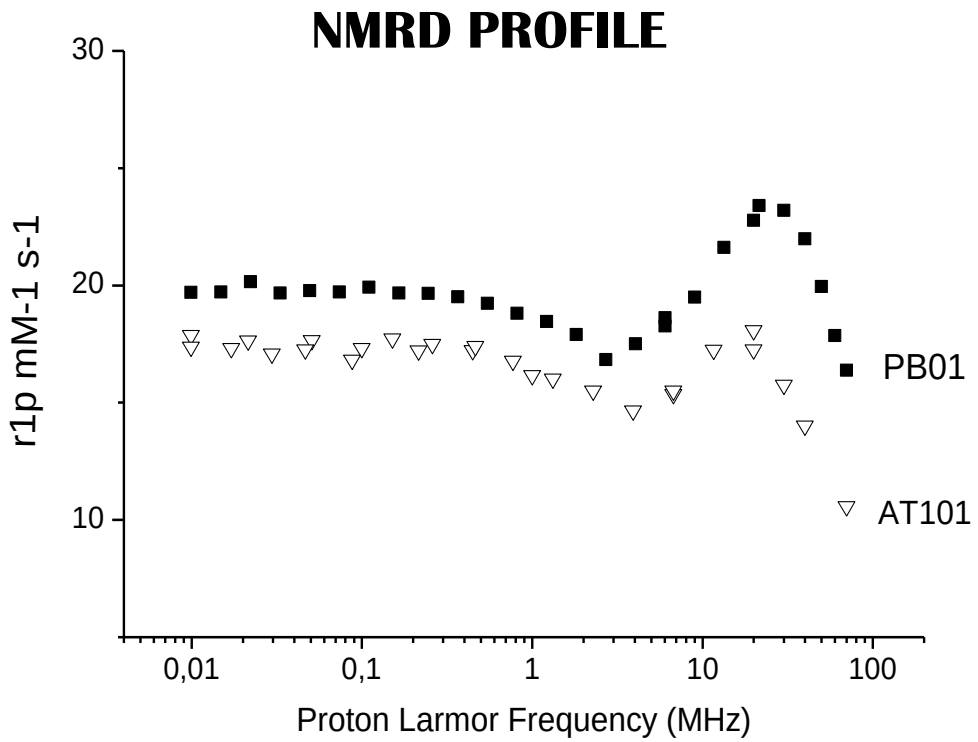
Synthesis of PB01:

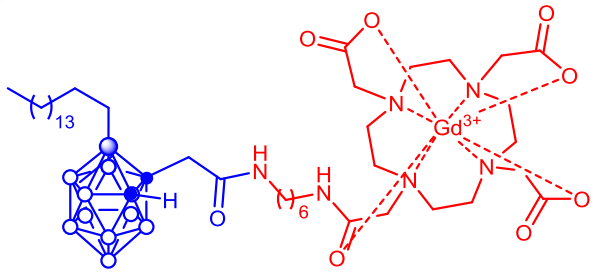
a) i R = *ter*-(Butyl) CF_3COOH (2 ml), CH_2Cl_2, room temperature, yield: > 99%

ii R = Benzyl H_2, Pd on carbon (20% w/w), CH_2Cl_2/CH_3OH (1/1), room temperature ,yield: > 99%

b) $GdCl_3$, H_2O, t. amb., pH. 7

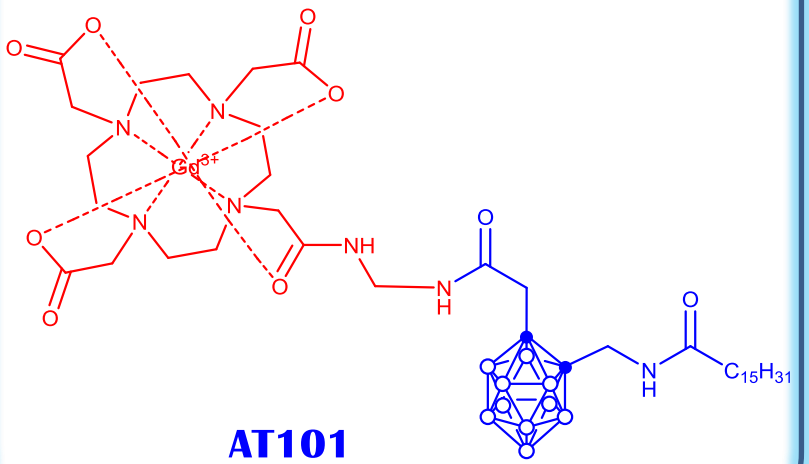
Comparison PB01-AT101





PB01

Synthetic steps required: 6



AT101

Synthetic steps required: 14

Dott.ssa Simonetta Geninatti Crich
Dott. Diego Alberti

Conclusions

Synthesis of MRI/BNCT dual agent based on hydroboration reaction:

- **efficient strategy for lipophilic moiety introduction on boron cage**
- **reduction of synthetic steps required**

Experimental evidence for molecular structure of precursor (3): X-ray diffractometric study

Preliminary relaxometric tests on PB01 interaction with LDLs show a Nuclear Magnetic Relaxation Dispersion (NMRP) profile superior in comparison with AT101

Aknowledgments

Dott.ssa Domenica Marabello — **X-ray diffractometric study**

Prof. Claudio Medana — **Mass spectra**