Experimental

Materials and methods

1,2-dicarba-*closo*-dodecaborane was purchased from Katchem Ltd. (Prague, Czech Republic). All other reagents and anhydrous solvents, stored over 4 Å molecular sieves, were purchased from Aldrich Chemical Co. (Madrid, Spain) and used without further purification. HPLC grade ethanol, methanol, and acetonitrile were purchased from Scharlab (Sentmenat, Barcelona, Spain).

All reactions were performed under inert atmosphere. Flash chromatography was performed using silica gel 60 (Scharlab, Spain). Analytical thin layer chromatography (TLC) measurements were conducted with silica gel 60 F_{254} plates (Macherey-Nagel); for the visualization of carboranes, TLC plates were treated with an acidic solution of 1% $PdCl_2$ in methanol. NMR spectra were recorded on a 500-MHz Avance III Bruker spectrometer.

UPLC/ESI-MS analyses were performed using an AQUITY UPLC separation module coupled to a LCT TOF Premier XE mass spectrometer (Waters, Manchester, UK). An Acquity BEH C18 column (1.7 µm, 5 mm, 2.1 mm) was used as stationary phase. The elution buffers were A (water and 0.1% formic acid) and B (Methanol and 0.1% formic acid). The column was eluted with a gradient: t=0 min, 95% A, 5% B; t=0.5 min, 95% A, 5% B; t=7.5 min, 1% A, 99% B; t=10min, 1% A, 99% B. Total run was 10 min, injection volume was 5 µL and the flow rate 300 µL/min. The detection was carried out in negative ion mode, monitoring the most abundant isotope peaks from the mass spectra.

Synthesis of 9-I-1,2-dicarba-*closo*-dodecaborane (2)

The synthesis of the 9-I-1,2-dicarba-*closo*-dodecaborane (**2**) was based on a previously reported method.[1] Iodine monochloride (1.16 g, 7.1 mmol) and $AlCl_3$ (100 mg) were added to a cooled (0°C) solution of 1,2-dicarba-*closo*-dodecaborane (1.04 g, 7.1 mmol) in 25 mL of methylene chloride and the resulting mixture was refluxed for 4 h. The reaction mixture was then poured into 25 mL of ice-cold water, shaken and the organic phase was separated from the mixture. The aqueous phase was extracted twice with 25mL of CH_2Cl_2. The combined organic layer was sequentially washed with 10% aqueous $Na_2S_2O_3$ solution and water, and finally dried over Na_2SO_4. The mixture was concentrated and the crude product was purified using column chromatography (Silica gel 60, Hexane/Ethyl acetate = 90/10) to yield **2** as as powdered white solid (1.4 g, 74%).

Synthesis of *p*-tolyl-(9-*o*-carboranyl) iodonium bromide (3)

The synthesis of **3** was based on a previously reported method.[2] $NaBO_3.H_2O$ (576 mg, 5.7 mmol) was suspended in Ac_2O (2.6 mL) and stirred at 25°C for 90 min; 9-I-1,2-dicarba-*closo*-dodecaborane (500 mg, 1.9 mmol) was added and the resulting mixture was further stirred at the same temperature for another 90 min. Toluene (1 mL, 9.6 mmol) was added, the reaction mixture was cooled to 0°C and concentrated H_2SO_4 (0.4 mL) was added dropwise while the internal temperature was maintained below 10 °C. The resulting mixture was allowed to stir at room temperature for 16 h, poured into 25 mL of cold water and stirred for 30 min. The aqueous phase was washed twice with Et_2O (20 mL) to remove any unreacted organic substrates and the ethereal extracts were discarded. To the cooled aqueous phase, aqueous KBr solution (920 mg in 5 mL of water) was added with stirring. This mixture was allowed to stand in the fridge overnight. The precipitate formed was filtered, washed with water and Et_2O and dried under vacuum to yield **3** as a yellow solid (240 mg, 30 %).

Synthesis of 9-[^{18}F]fluoro-1,2-dicarba-*closo*-dodecaborane ([^{18}F]4)

[^{18}F]fluorine was produced by irradiation of [^{18}O]H_2O with 18MeV protons using an IBA Cyclone 18/9 cyclotron. [^{18}F]F^- was trapped in an Accell™ Plus QMA anion exchange resin (Waters) and pushed into a V-shaped vial with 15 mg of Kryptofix 2.2.2 in 1 mL of MeCN and 0.5 mL of aqueous

solution containing 3 mg of K_2CO_3. The vial was heated at 80°C for 10 min under nitrogen flow to remove the MeCN-H_2O azeotrope; the temperature was increased to 100°C under vacuum for another 5min to remove any traces of water residues. To the dry potassium-[^{18}F]fluoride-Kryptofix$_{2.2.2}$ complex, *p*-tolyl-(9-*o*-carboranyl) iodonium bromide (10 mg dissolved in a mixture of 900 µL of 2-methyl 2-butanol and 100 µL of MeCN) was added. The mixture was heated at 100°C for 20 min. After cooling, the reaction crude was diluted with acetonitrile (1 mL) and water (1 mL) and the resulting mixture was passed through a Sep-Pak Alumina Plus cartridge (Waters) and loaded into an HPLC system for purification. A Mediterranean Sea18 column (10 x 250 mm, 5 µm) was used as stationary phase and MeCN/0.1M AMF (pH adjusted to 3.9 with HCOOH) (60/40) as mobile phase at a flow rate of 8 mL/min. The desired fraction (retention time ~ 10 min) was collected, diluted with water (50 mL) and reformulated by trapping in a Sep-Pak C18 Plus Short Cartridge (waters) and further eluting with dichloromethane (1 mL). The radiochemical yield (decay corrected) was 44%. The radiochemical purity was determined by HPLC, using an Agilent 1200 Series HPLC system with a multiple wavelength UV detector (λ = 254 nm) and a radiometric detector (Raytest). A RP-C18 column (Eclipse XDB C18, 4.6x150 mm, 5 µm particle size) was used as stationary phase and water/MeCN 50/50 as a mobile phase with a flow rate of 2mL/min (retention time = 5.5 min). Total synthesis time was approximately 60 min from the end of irradiation (EOB).

Synthesis of non radioactive (9-fluoro-*o*-carboranyl) (4-methoxyphenyl) methanol (5)

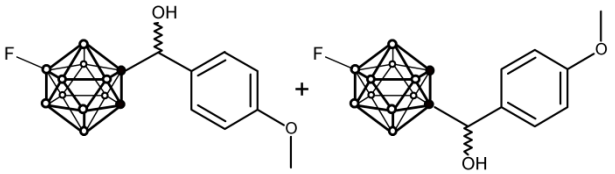
To 10 mg of 9-fluoro-*o*-carborane (0.062 mmol) in 500 µL of ice cold THF, *n*-BuLi 2.6M solution in THF (71 µL, 0.186 mmol) was added and the mixture was heated at 50°C for 5 min. After cooling to 0-5°C, 4-methoxybenzaldehyde (MBA, 0.186 mmol) dissolved in TFH (500 µL) was added and the mixture was heated again at 50°C for 10 min. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum and the crude was purified by column chromatography (silica gel, 10% Ethyl acetate/Hexane) to yield **5** as yellow solid (240 mg, 30 %).

Synthesis of (9-[^{18}F]fluoro-*o*-carboranyl) (4-methoxyphenyl) methanol ([^{18}F]5)

The precursor 9-[^{18}F]fluoro-*o*-carborane, obtained in 1 mL of dichloromethane, was dried over Na_2SO_4, decanted and mixed with 10 mg of non radioactive 9-fluoro-*o*-carborane (0.062 mmol). This mixture was dried under nitrogen flow at 50°C for 10 min. After complete evaporation, the residue was cooled to 0°C and 2.6M *n*-BuLi (71 µL, 0.186 mmol) in 500 µL of THF was added. The mixture was heated at 50°C for 5 min, cooled again back to 0-5°C and a solution of MBA (0.186 mmol) in TFH (500 µL) was added. After heating at 50ºC for 10 min, the reaction was cooled to room temperature and quenched with 1M HCl. The radiochemical conversion was determined by radio-HPLC. A RP-C18 column (Eclipse XDB C18, 4.6x150 mm, 5 µm particle size) was used as stationary phase and water/MeCN 50/50 as a mobile phase with flow rate of 2 mL/min (retention time = 9.5 min). A fraction of the reaction crude was purified under identical chromatographic conditions and the purified fraction was analyzed by radio HPLC; a chiral column (ULTRON ES-OVM chiral analytical, 4.6x150mm) was used as stationary phase. The column was eluted with A (water) and B (Ethanol) using a gradient: t=0 min, 95% A, 5% B; t=1min, 95% A, 5% B; t=20 min, 60% A, 40% B; t=32 min, 60% A, 40% B; t=40 min, 95% A, 5% B. The retention times of the four isomers were 17.5, 18, 20 and 21 min, respectively.

Spectroscopic data

(9-fluoro-*o*-carboranyl) (4-methoxyphenyl) methanol (**5**)



$^{1}H\{^{11}B\}$ NMR (500 MHz, $CDCl_3$): δ 7.28 ($C_{ar}H$-C_{ar}-OCH_3, 2 H, dd, *J* 8.5, 4.5), 6.93 ($C_{ar}H$-C_{ar}-CH-, 2 H, d, *J* 8.6), 5.39 (C*H*-OH, 0.38 H, s), 5.19 (C*H*-OH, 0.59 H, s), 3.85 (O-CH_3, 3 H, s), 3.74 (C_cH, 0.37 H, s), 3.63 (C_cH, 0.62 H, s), 2.73 (O*H*, 1 H, s), 2.98 – 1.36 (B*H*, 10 H).

$^{11}B\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 15.32 (*B*F), -5.08, -6.41, -10.44, -11.05, -13.08, -14.36, -15.68, -16.57, -17.53.

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.57 (C_{ar}-OCH_3), 130.30 (C_{ar}-CH-), 127.89 (C_{ar}H-C_{ar}-OCH_3), 114.16 (C_{ar}H-C_{ar}-CH-), 74.72 (*C*H-OH), 73.46 (*C*H-OH), 55.35 (CH_3O-), 54.29 (C_cH), 42.94 (C_cH).

^{19}F NMR (471 MHz, $CDCl_3$): δ -184.37 (B*F,* 1F, *q*), -189.97(B*F,* 0.58F, *q*).

LCMS (ESI) Experimental $[M+HCOO]^-$ m/z = 343.35.

Elemental analysis: Measured: 40.1% C, 6.3% H; calculated: 40.26% C, 6.42% H.

References

[1] Z. Zheng, W. Jiang, A. A. Zinn, C. B. Knobler and M. F. Hawthorne, *Inorg. Chem.*, 1995, **34**, 2095.

[2] A. Kryska and L. Skulski, *Molecules*, 2001, **6**, 875.