Supplementary Material (ESI) for Chemical Communications

Regioselective access to 3^{I}-*O*-substituted-β-cyclodextrin derivatives

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Supporting Information available

Experimental procedures, ^{1}H and ^{13}C NMR data, identification of monosubstituted β-cyclodextrin regioisomers, NMR spectra for compounds **6a**, **6b**, **13a** and **13b** as specific and representative examples.

I) Experimental procedures and NMR data :

General: All solvents and reagents were purchased from commercial sources and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on a plate of silica gel 60 F_{254} (E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Columns chromatography were performed on silica gel 60 (0.063-0.200 mm, E. Merck).

LC-MS analyses were performed on a Waters 2695 Alliance coupled with a single quadripole mass spectrometer ZQ (Waters-Micromass, Manchester, UK) equipped with an electrospray ion source (ESI-MS). The composition of the mobile phase varied during the run according to a linear gradient as follows: A–B: 0 min (20:80, v/v), 0-50 min (50:50, v/v) at a flow rate of 1 mL/min. Compounds were loaded on a Alltech Carbohydrate ES 5u (5µm particle size, 250 mm x 4.6 mm) column using a sample injection volume of 20 µL (water solutions at 1 g/L for the compounds). The effluent was flow-split

via a peek tee with 1/5 of the flow directed toward the ESI source of the ZQ instrument and the residual 4/5 directed toward a PDA detector (Waters 2996). LC-ESI-MS data were recorded in the positive and negative ion mode. The source and desolvation temperatures were kept at 120 and 250°C, respectively. Nitrogen was used as a drying and nebulising gas at flow rates of 450 and 100 L/h, respectively. The capillary voltage was ±3.5 kV and a cone voltage range from ±20 to ±60 V was used (±ESI). Scanning was performed in the range 50–1950 Da at a scan rate of 1 s/scan. Data were collected in the continuum mode. Data acquisition and processing were performed with MassLynx V4.0 software.

The final purification by preparative HPLC was performed using a Waters HPLC system (Waters, France) equipped with a LC4000 pump and a 2487 UV–Vis detector (Waters, France). The separation was performed at room temperature on a Alltech Carbohydrate ES 5u (5 µm particle size, 250 mm x 10 mm). The mobile phase consisted of water (solvent A) and acetonitrile (solvent B). The composition of the mobile phase varied during the run according to a linear gradient as follows: A–B: 0 min (0:100, v/v), 0-50 min (50:50, v/v) at a flow rate of 4.7 ml/min. Detection was performed at 280 nm. Data acquisition and processing were performed with Empower.

NMR spectra were recorded on a Bruker DRX50 spectrometer equipped with a Z-gradient unit for pulsed-field gradient spectroscopy. All NMR experiments were performed (^{1}H at 500.13 MHz, ^{13}C at 125.7 MHz) in dimethylsulfoxide-d_6 at 300 K with careful temperature regulation. Me_4Si was used as an external standard and calibration was performed using the signal of the residual protons or of the carbon of the solvent as a secondary reference. The length of the 90° pulse was approximately 7 µs. 1D NMR data spectra were collected using 16K data points. 2D experiments were run using 1K data point and 256 or 512 time increments. The phase sensitive (TTPI) sequence was used and processing resulted in a 1K*1K (real-real) matrix.

Regioselective substitution at O-2: pure 2^I-*O*-benzyl-β-cyclodextrin **6a** and 2^I-*O*-(3-bromoprop-1-en)-β-cyclodextrin **13a** samples were prepared according to the literature procedure.[1]

2^I-*O*-benzyl-β-cyclodextrin 6a: is obtained in 23% yield (250 mg, pale yellow solid) using benzyl bromide **3** as electrophile reactant; HPLC retention time : 23.67 min. ^{1}H NMR (Me_2SO-d6): δ 7.38-7.30 (m, 5H, H-Ar), 4.87 (bs, 1H, H-1'), 4.85-4.79 (bs, 6H, H-1), 4.82 (1H, H-Bn), 4.74 (d, J= 12.3 Hz, 1H, H_{Bn}), 3.86 (t, J = 9.5 Hz, H-3'), 3.71-3.55 (m, 14H, H-6), 3.66-3.58 (m, 6H, H-3), 3.60-3.52 (m, 7H, H-5), 3.42-3.29 (m, 7H, H-4), 3.35-3.26 (m, 7H, H-2); ^{13}C NMR (Me_2SO-d6): δ 128.4, 128.3, 128.0, 127.9 (C-aro), 102.4-101.0 (6C, C-1) 100.2 (C-1'), 81.7-80.8 (7C, C-4), 79.3 (C-2'), 73.3-72.8 (6C, C-3), 73.0 (C-Bn), 72.6-71.7 (6C, C-2), 72.4 (C-3'), 71.5 (7C, C-5), 59.7 (7C, C-6). ESI-MS m/z 1247 $[M+Na]^+$.

2^I-*O*-(3-bromoprop-1-en)-β-cyclodextrin 13a: is obtained in 30% yield (340 mg, pale yellow solid) using 3-bromoprop-1-en **10** as electrophile reactant; HPLC retention time : 25.10 min. ^{1}H NMR (Me_2SO-d6): δ 6.68 (d, 1H, J = 13.7 Hz, H-alkene), 6.33-6.28 (dt, 1H, J = 13.7 Hz, J = 6.4 Hz, H-alkene), 4.97 (d, 1H, J = 3.7 Hz, H-1'), 4.84-4.82 (m, 6H, H-1), 4.28-4.18 (m, 2H, H-allyl), 3.79 (t, 1H, J = 9.2 Hz, H-3'), 3.66-3.51 (m, 14H, H-6), 3.65-3.59 (m, 6H, H-3), 3.58-3.51 (m, 7H, H-5), 3.37-3.26 (m, 14H, H-4, H-2); ^{13}C NMR (Me_2SO-d6): δ 134.2, 109.3 (C-alkene), 101.7 (6C, C-1), 101.5 (C-1'), 82.0-81.5 (7C, C-4), 79.7 (C-2'), 72.8-72.3 (7C, C-3), 72.3-71.7 (6C, C-2), 71.9-71.3 (7C, C-5), 70.5 (C-allyl), 59.7 (7C, C-6). ESI-MS m/z 1275 $[M+Na]^+$.

[1] N. Masurier, F. Estour, B. Lefèvre, B. Brasme, P. Masson, O. Lafont, *Carbohydr. Res.*, 2006, **341**, 935.

Regioselective substitution at O-3:

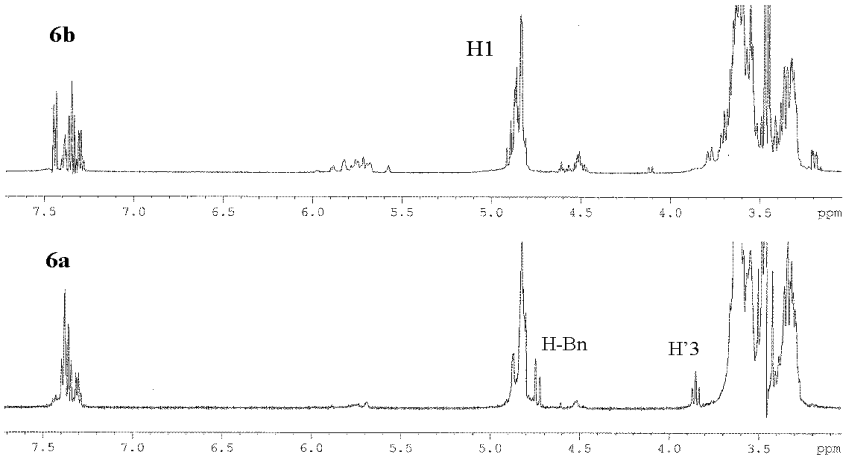
To a solution of β-CD (1 g, 0.88 mmol) in 44 mL of distilled water, were successively added dropwise a solution of $CuSO_4.5H_2O$ (660 mg, 2.64 mmol) in 44 mL of distilled water and a solution of NaOH (870 mg, 22 mmol) in 66 mL of distilled water. The mixture was stirred for 70 min, and a solution of electrophile reactant (7.3 mmol) in 10 mL of acetonitrile was added for 1 hour. The solution was stirred at 20°C for 10 hours (at 30°C for a complete dissolution of the reactant **10**). It was then neutralized with 10% aqueous HCl. After filtration, the solvent was evaporated under reduced pressure. The crude product was chromatographied (SiO_2, 12:7:4, ethyl acetate-isopropanol-water) and the compound obtained was recristallized in MeOH.

3^I-*O*-benzyl-β-cyclodextrin 6b: is obtained in 38% yield (410 mg, pale yellow solid) using benzyl bromide **3** as electrophile reactant; HPLC retention time : 23.77 min. ^{1}H NMR (Me_2SO-d6): δ 7.45-7.28 (m, 5H, H-Ar), 4.88-4.81 (bs, 6H, H-1), 4.87 (bs, 1H, H-1'), 4.90-4.85 (2H, H_{Bn}), 3.71 (1H, H-3'), 3.66-3.55 (m, 14H, H-6), 3.65-3.58 (m, 6H, H-3), 3.60-3.55 (m, 7H, H-5), 3.53 (bs, 1H, H-2') 3.40-3.27 (m, 7H, H-4), 3.34-3.30 (m, 5H, H-2), 3.19 (dd, 1H, J=9.5 Hz, J=3.5 Hz, H-2); ^{13}C NMR (Me_2SO-d6) δ 128.7, 128.2, 127.9, 127.5 (C-aro), 101.8 (6C, C-1), 100.9 (C-1'), 82.1-81.1 (7C, C-4), 79.8 (C-3'), 77.9 (C-2'), 73.6 (C-Bn), 73.4-72.8 (6C, C-3), 72.3-71.7 (5C, C-2), 72.1 (1C, C2), 71.8 (7C, C-5), 59.7 (7C, C-6). ESI-MS m/z 1247 $[M+Na]^+$.

3^I-*O*-(3-bromoprop-1-en)-β-cyclodextrin 13b: is obtained in 38% yield (420 mg, pale yellow solid) using 3-bromoprop-1-en **10** as electrophile reactant; HPLC retention time : 25.26 min. ^{1}H NMR (Me_2SO-d6): δ 6.61 (d, 1H, J = 13.7 Hz, H-alkene), 6.42-6.36 (dt, 1H, J = 13.7 Hz, J = 6.7 Hz, H-alkene), 5.02-4.99 (bs, 1H, H-1'), 4.83-4.81 (m, 6H, H-1), 4.29 (d, 2H, J = 6.7 Hz, H-allyl), 3.66-3.57 (m, 14H, H-6), 3.64-3.58 (m, 6H, H-3), 3.59-3.52 (m, 7H, H-5), 3.55 (1H, H-3'), 3.48 (bs, 1H, H-2'), 3.44-3.31 (m, 7H, H-4), 3.34-3.28 (m, 5H, H-2), 3.22 (dd, 1H, J = 9.7 Hz, J = 3.2 Hz, H-2); ^{13}C NMR (Me_2SO-d6): δ 134.6, 109.4 (C-alkene), 101.7 (6C, C-1), 101.0 (C-1'), 81.3-81.0 (7C, C-4), 80.4 (C-3'), 78.2 (C-2'), 72.8-72.2 (6C, C-3), 71.3-71.8 (6C, C-2), 71.1 (C-allyl), 71.6-70.7 (7C, C-5), 59.6 (7C, C-6). ESI-MS m/z 1275 $[M+Na]^+$.

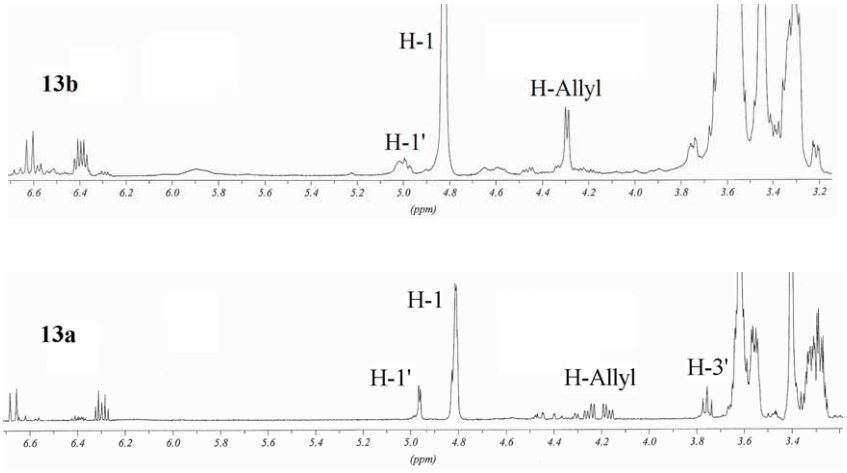
II) Identification of monosubstituted β-cyclodextrin regioisomers :

6a and **6b** derivatives have distinct NMR structural characteristics as illustrated on the following spectra



^{1}H-NMR spectra (500.13 MHz, d6-DMSO) of **6a** and **6b**

13a and **13b** derivatives have also distinct NMR structural characteristics as it is the case for compounds **6a** and **6b**.

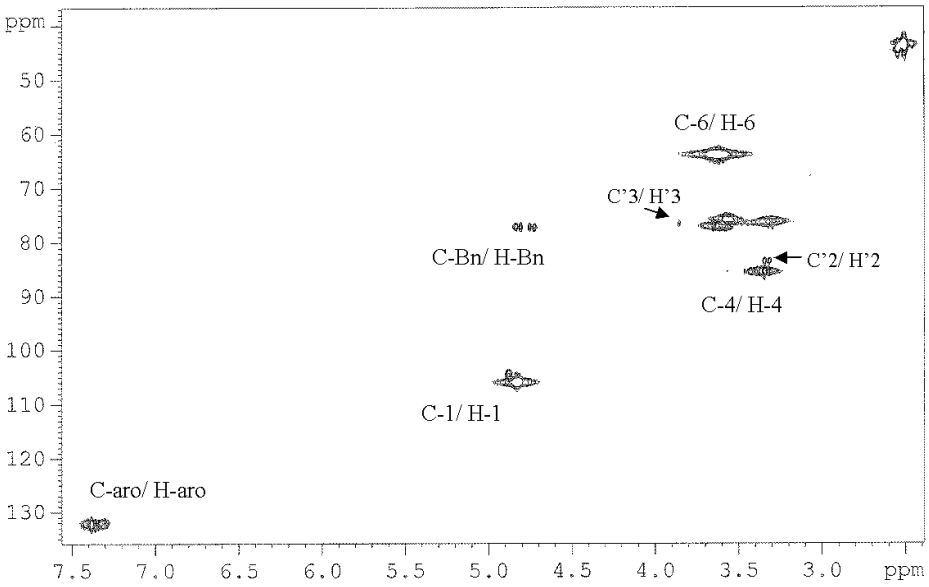


^{1}H-NMR spectra (500.13 MHz, d6-DMSO) of **13a** and **13b**

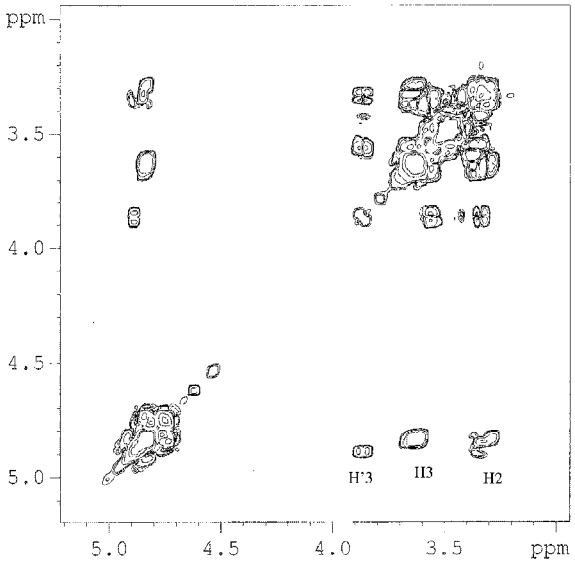
For any compound **6a**, **6b**, **13a** and **13b**, the single HMQC correlation between the carbon signal of C-6 and the corresponding proton signals established that no substitution occured at O-6.

2^{I}-O-substituted-β-cyclodextrin derivatives

In the case of the 2-monobenzylated β-cyclodextrin compound **6a**, the ^{1}H NMR and HMQC correlation revealed three relatively distinct signals at 3.86 ppm (H-3'), 4.74 ppm (benzylic proton) and 4.87 ppm (H-1'). The 2-O substitution in compound **6a** was proved by specific downshifted value of signal of C-2' (79.3 ppm). This specific signal was unambigously assigned using COSY, COSY RELAY and HMQC correlation.

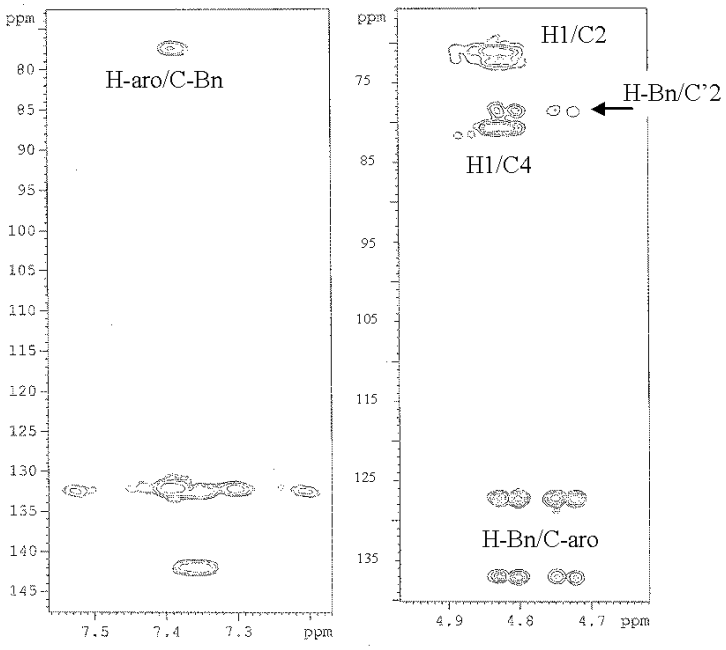


HMQC correlation experiment of **6a** (500.13 MHz, d6-DMSO)



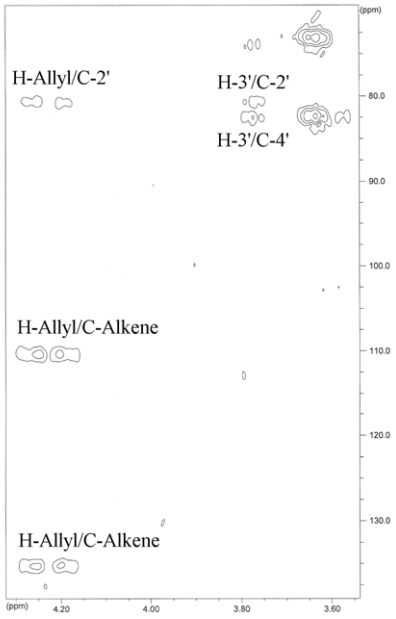
Partial contour plot of COSY RELAY experiments of **6a**

Moreover the presence of an HMBC correlation between the benzylic protons signal (4.82 and 4.74 ppm) and the same carbon signal C-2' proved the 2-O substitution in **6a**.



Partial contour plots of HMBC correlation of **6a** (area of aromatic and benzylic protons respectively)

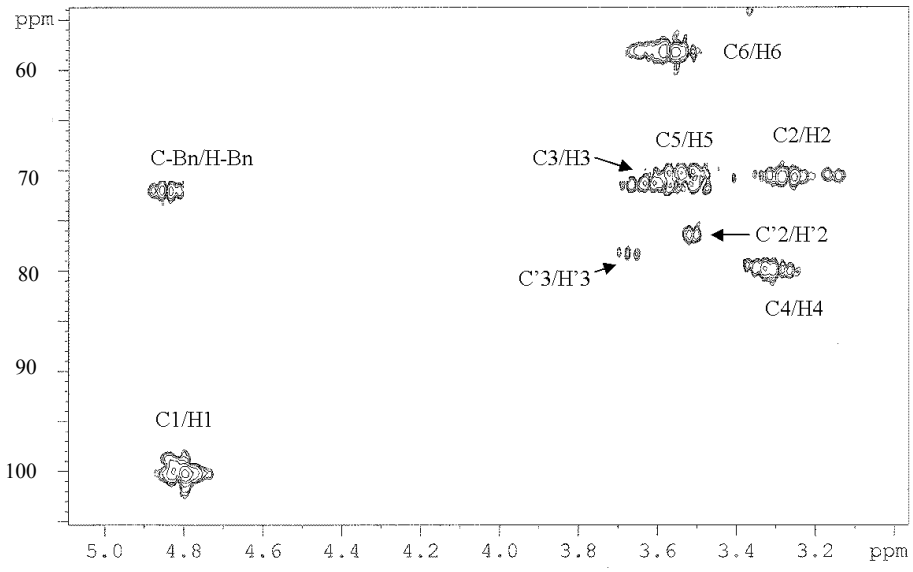
The same strategy has been applied for the structural determination of **13a**. In the case of the 2-monobromoallylated β-cyclodextrin compound **13a**, the ^{1}H NMR and HMQC correlation revealed three relatively distinct signals at 3.79 ppm (H-3'), 4.28-4.18 ppm (allylic protons) and 4.97 ppm (H-1'). The 2-O substitution in compound **13a** was proved by specific downshifted value of signal of C-2' (79.7 ppm). Moreover the presence of an HMBC correlation between the allylic protons signal (4.28 and 4.18 ppm) and the same carbon signal C-2' proved also the 2-O substitution in **13a**.



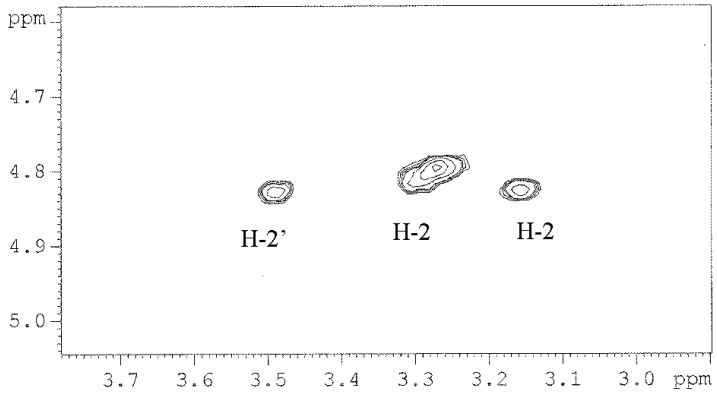
Partial contour plots of HMBC correlation of **13a** (500.13 MHz, d6-DMSO)

3[1]-O-substituted-β-cyclodextrin derivatives

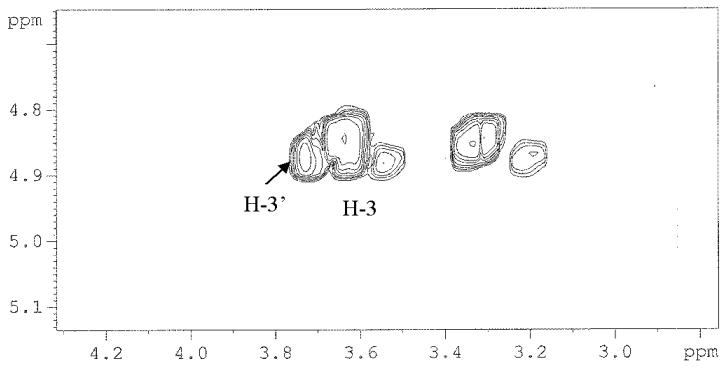
In the case of the 3-monobenzylated β-cyclodextrin compound **6b**, a downfield of the carbon signals C-2' (77.9 ppm) and C-3' (79.8 ppm) was observed. These specific signals were unambigously assigned using COSY and COSY RELAY experiments and characterized anomeric signals as starting-point.



HMQC correlation experiment of **6b** (500.13 MHz, d6-DMSO)

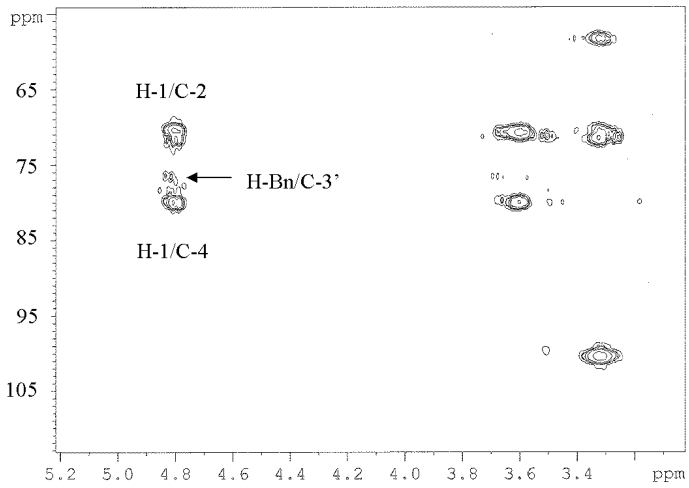


Partial contour plots of COSY experiment of **6b** (area of the anomeric protons)



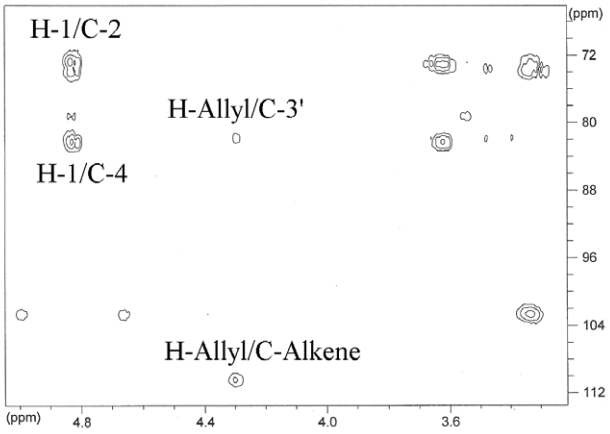
Partial contour plots of COSY RELAY experiment of **6b** (area of the anomeric protons)

Finaly, the presence of an HMBC correlation between the benzylic protons signal (4.90 and 4.85 ppm) and the carbon signal C-3' proved the 3-O substitution in **6b**.



Partial contour plot of HMBC correlation of **6b** (area of benzylic)

The same strategy has been applied for the structural determination of **13b**. In the case of the 3-monobromoallylated β-cyclodextrin compound **13b**, a downfield of the carbon signals C-2' (78.2 ppm) and C-3' (80.4 ppm) were observed. The presence of an HMBC correlation between the allylic protons signal (4.29 ppm) and the carbon signal C-3' proved the 3-O substitution in **13b**.



HMQC correlation experiment of **13b** (500.13 MHz, d6-DMSO)