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Efficient synthesis of calix[4]resorcinol *rccc* diastereoisomers using high amount of trifluoroacetic acid in the chloroform medium

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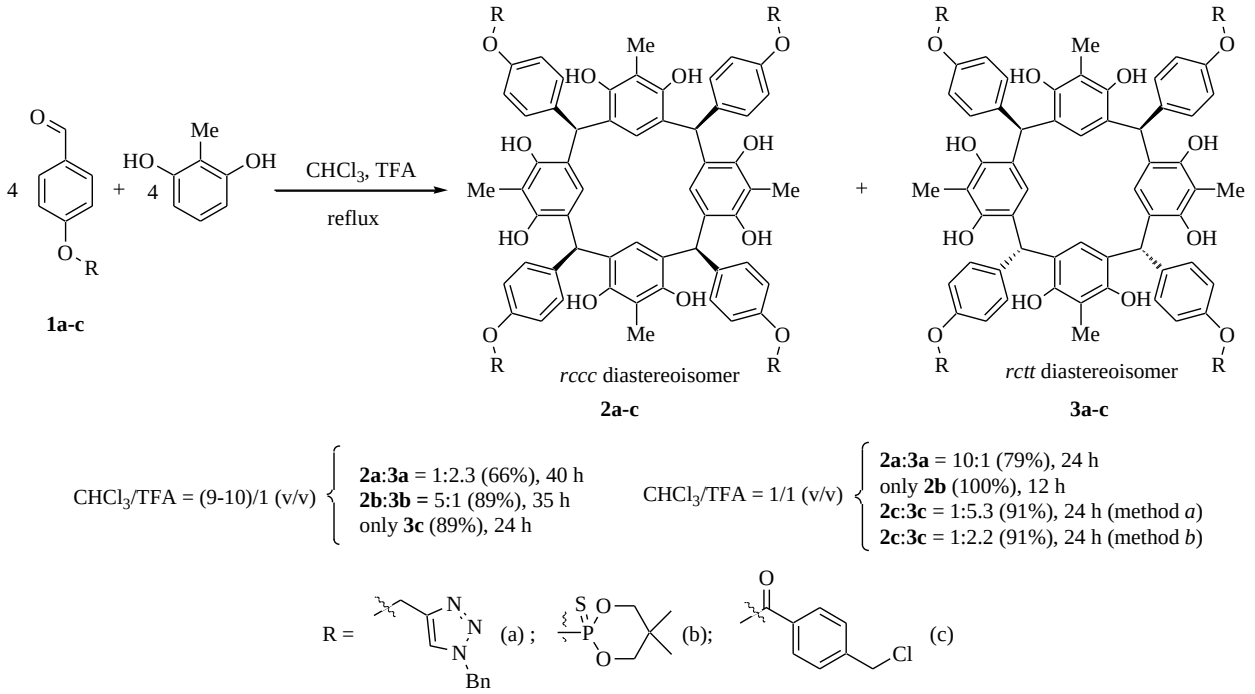
General

NMR experiments were performed on a Bruker AVANCE-600 spectrometer at 303 K equipped with 5 mm broadband probehead working at 500 MHz in ^{1}H and 150.9 MHz in ^{13}C. Chemical shifts were reported relative to residual signal of deuterated solvents. IR spectra of solid compounds have been registered using Bruker Vector-27 FTIR spectrometer in the 400–4000 cm^{-1} range (optical resolution 4 cm^{-1}). The samples were prepared as KBr pellets. The MALDI mass spectra were recorded on an Ultraflex III TOF/TOF mass spectrometer (Bruker Daltonic GmbH, Bremen, Germany) operated in the linear mode with the registration of positively charged ions or negatively charged ions. A Nd:YAG laser (λ = 355 nm, repetition rate 100 Hz) was used. The mass spectra were obtained with an accelerating voltage of 25 kV and an ion extraction delay time of 30 ns. The resulting mass spectra were formed due to multiple laser irradiation of the crystal (50 shots). The metal target MTP AnchorChipTM was used. Portions (0.5 μl) of a 1% matrix solution in acetonitrile and of a 0.1% sample solution in methanol were consecutively applied onto the target and evaporated. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix. The polyethylene glycol was used to calibrate the mass scale of the device. The data were obtained using the FlexControl program (Bruker Daltonik GmbH, Germany) and processed using the FlexAnalysis 3.0 program (Bruker Daltonik GmbH, Germany). The elemental analysis was carried out on a CHNS analyzer EuroEA3028-HT-OM (Eurovector SpA, Italy).



Scheme S1

General procedure for synthesis of calix[4]resorcinols 2a, 3a, 2b: A mixture of 2-methylresorcinol (1.82 mmol) and aldehyde **1a-c** (1.82 mmol) in $CHCl_3$ (25 ml) and TFA (25 ml) was stirred under reflux for 12-24 h under an argon atmosphere. Then the solvent was evaporated to dryness, and the residue was sequentially recrystallized from acetone and ethanol gaving the corresponding pure *rccc* and/or *rctt* isomers. The characteristics of compounds **2a**, **3a**, **2b** are identical to those obtained earlier.[S1,S2]

***Experimental procedure for preparation and spectroscopic data of compounds* 2c *and* 3c (method *a*)**. Calix[4]resorcinols **2c** and **3c** in a 1:5.3 ratio with overall yield 0.63 g (91%) were obtained according to the general procedure by treatment of 2-methylresorcinol (0.23 g, 1.82 mmol) with aldehyde **1c** (0.50 g, 1.82 mmol) for 24 h. The precipitate formed was filtered off, washed sequentially with $CHCl_3$ and Et_2O, the washing procedure was repeated until a colorless filtrate was observed. After drying *in vacuo* at 40 ºC and 0.06 Torr, pure *rctt* isomer **3c** in the *chair* conformation was obtained as a white powder, yield 0.49 g (71%). The filtrate was evaporated, and the crude residue was subjected to flash chromatography with CH_2Cl_2–MeOH (15:0.5) affording additional amount of pure *rctt* diastereoisomer **3c** (0.04 g, 6%); total yield 0.53 g, (77%), R_f =0.53) and pure *rccc* diastereoisomer **2c** in the *cone* conformation as a white powder (0.10 g , 14.5%, R_f=0.07).

***Experimental procedure for preparation and spectroscopic data of compounds* 2c *and* 3c (method *b*)**. Calix[4]resorcinols **2c** and **3c** in a 1:2.2 ratio with overall yield 0.63 g (91%) were obtained upon condensation of 2-methylresorcinol (0.23 g, 1.82 mmol) with aldehyde **1c** (0.50 g, 1.82 mmol) in $CHCl_3$ (40 ml) and TFA (40 ml). The mixture was stirred under reflux for 24 h under an argon atmosphere. Isomer *rctt*-**3c** (yield 0.42 g, 61%) and isomer *rccc*-**2c** (yield 0.21 g, 30%) were isolated as described above. The characteristics of compound **3c** are identical to those obtained earlier.[S3]

***Calix[4]resorcinol rccc diastereoisomer 2c*:** mp > 200 ºC (dec). ^{1}H NMR (DMSO-d_6): δ 1.99 (s, 12H, CH_3), 4.75 (s, 8H, CH_2Cl), 5.91 (s, 4H, CH), 6.14 (s, 4H, CH_{ar}), 6.82 (d, $^3J_{HH}$ 8.58 Hz, 8H, CH_{ar}), 7.00 (d, $^3J_{HH}$ 8.58 Hz, 8H, CH_{ar}), 7.33 (d, $^3J_{HH}$ 8.32 Hz, 8H, CH_{ar}), 7.62 (s, 8H, OH), 7.88 (d, $^3J_{HH}$ 8.25 Hz, 8H, CH_{ar}) ppm. ^{13}C NMR (DMSO-d_6): δ 10.1 (s, $\underline{C}H_3$), 42.3 (s, $\underline{C}H$), 45.1 (s, $\underline{C}H_2Cl$), 111.6 (s, $\underline{C}_{ar}$-CH_3), 120.5 (s, $\underline{C}H_{ar}$), 122.1 (s, $\underline{C}_{ar}$-CH), 127.6 (s, $\underline{C}_{ar}$), 128.7 (s, $\underline{C}_{ar}$-C(=O)-), 128.8 (s, $\underline{C}H_{ar}$), 129.4 (s, $\underline{C}_{ar}$), 142.9 (s, $\underline{C}_{ar}$-CH, $\underline{C}_{ar}$-CH_2Cl), 147.9 (s, $\underline{C}_{ar}$-O-), 150.7 (s, $\underline{C}_{ar}$-OH), 163.9 (s, $\underline{C}$=O) ppm. IR ν_{max} (KBr): 1723 cm^{-1} (C=O), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{88}H_{68}Cl_4O_{16}$ (%): C, 69.39; H, 4.50; Cl, 9.31. Found: C, 69.10; H, 4.51; Cl, 9.41. MALDI-MS, *m/z*: 1524 $[M+H]^+$ (calcd. M = 1523).

References

S1. I. R. Knyazeva, V. I. Sokolova, M. Gruner, W. D. Habicher, V. V. Syakaev, V. V. Khrizanforova, B. M. Gabidullin, A. T. Gubaidullin, Yu. H. Budnikova, A. R. Burilov and M. A. Pudovik, *Tetrahedron Lett.*, 2013, **54**, 3538.

S2. I. R. Knyazeva, K. M. Mukhamedyanova, V. V. Syakaev, A. T. Gubaidullin, W. D. Habicher and A. R. Burilov, *Tetrahedron Lett.*, 2018, **59**, 1683.

S3. I. R. Knyazeva, V. V. Syakaev, O. A. Lodochnikova and A. R. Burilov, *Mendeleev Commun.*, 2019, **29**, 700.

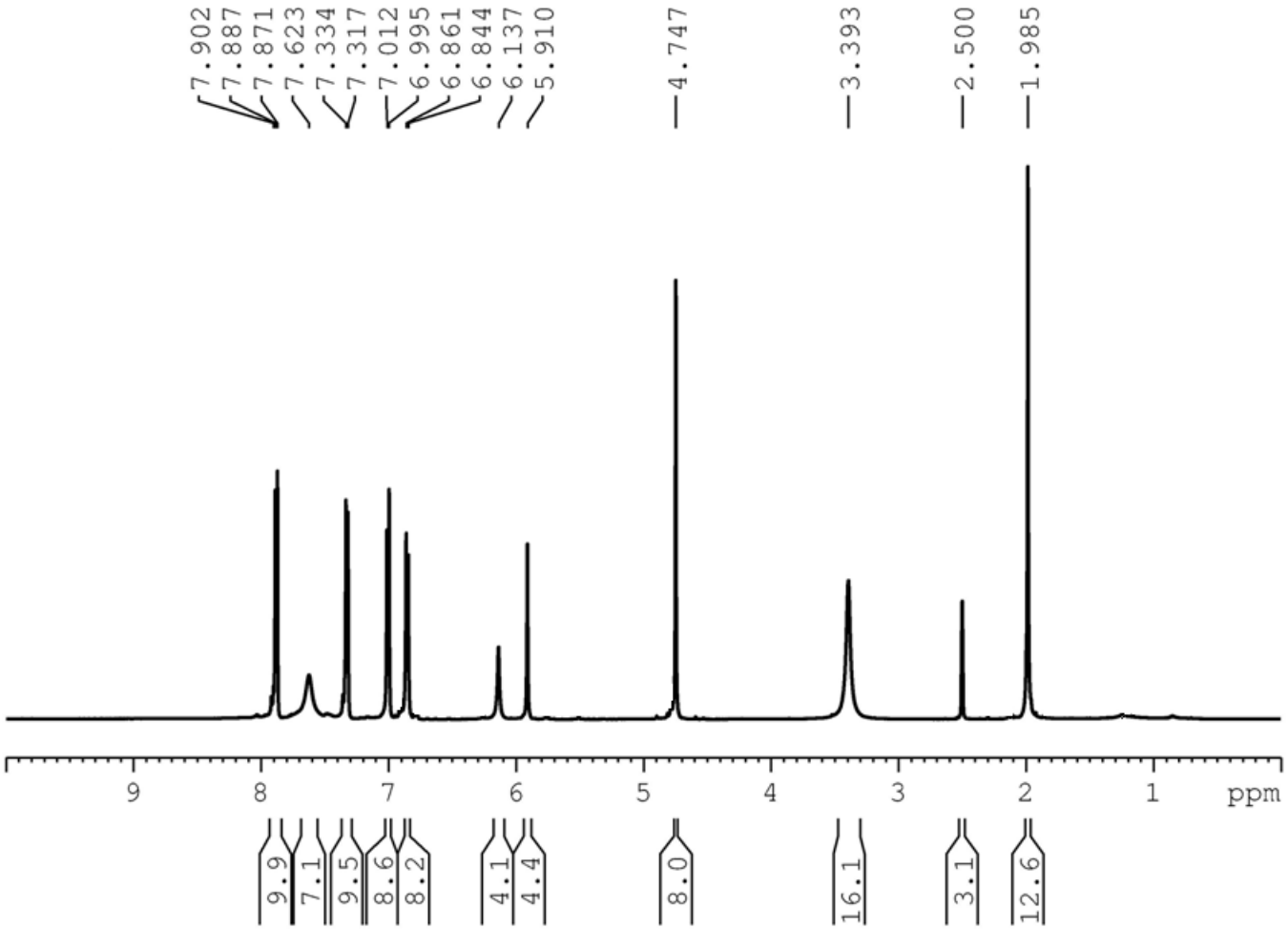


Figure S1. ^{1}H NMR spectrum of calix[4]resorcinol **2c** (*rccc* isomer in *cone* conformation) in DMSO-d_6 (T=303 K)

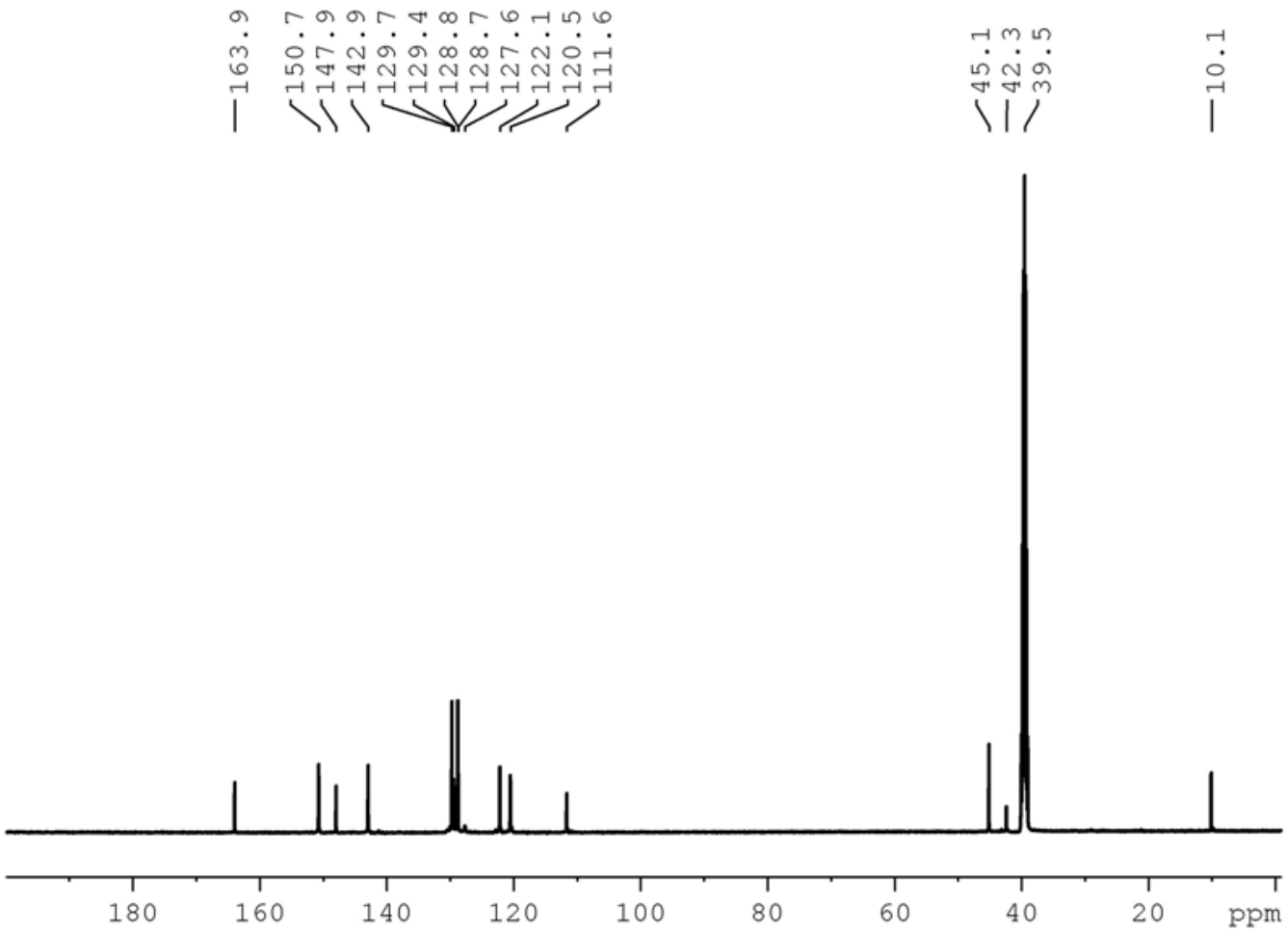


Figure S2. ^{13}C NMR spectrum of calix[4]resorcinol **2c** (*rccc* isomer in *cone* conformation) in DMSO-d_6 (T=303 K)

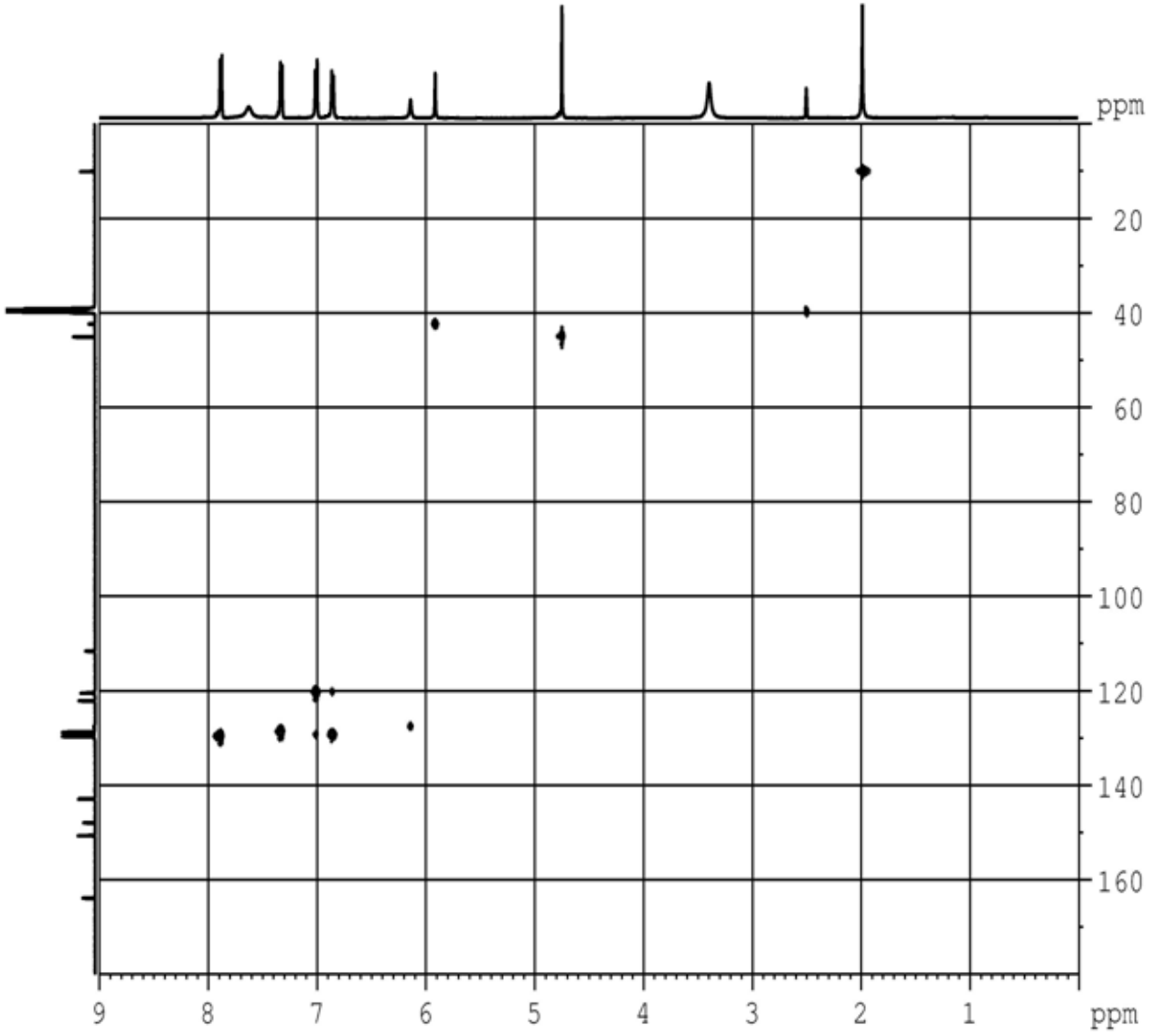


Figure S3. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol **2c** (*rccc* isomer in *cone* conformation) in DMSO-d_6 (T=303 K)

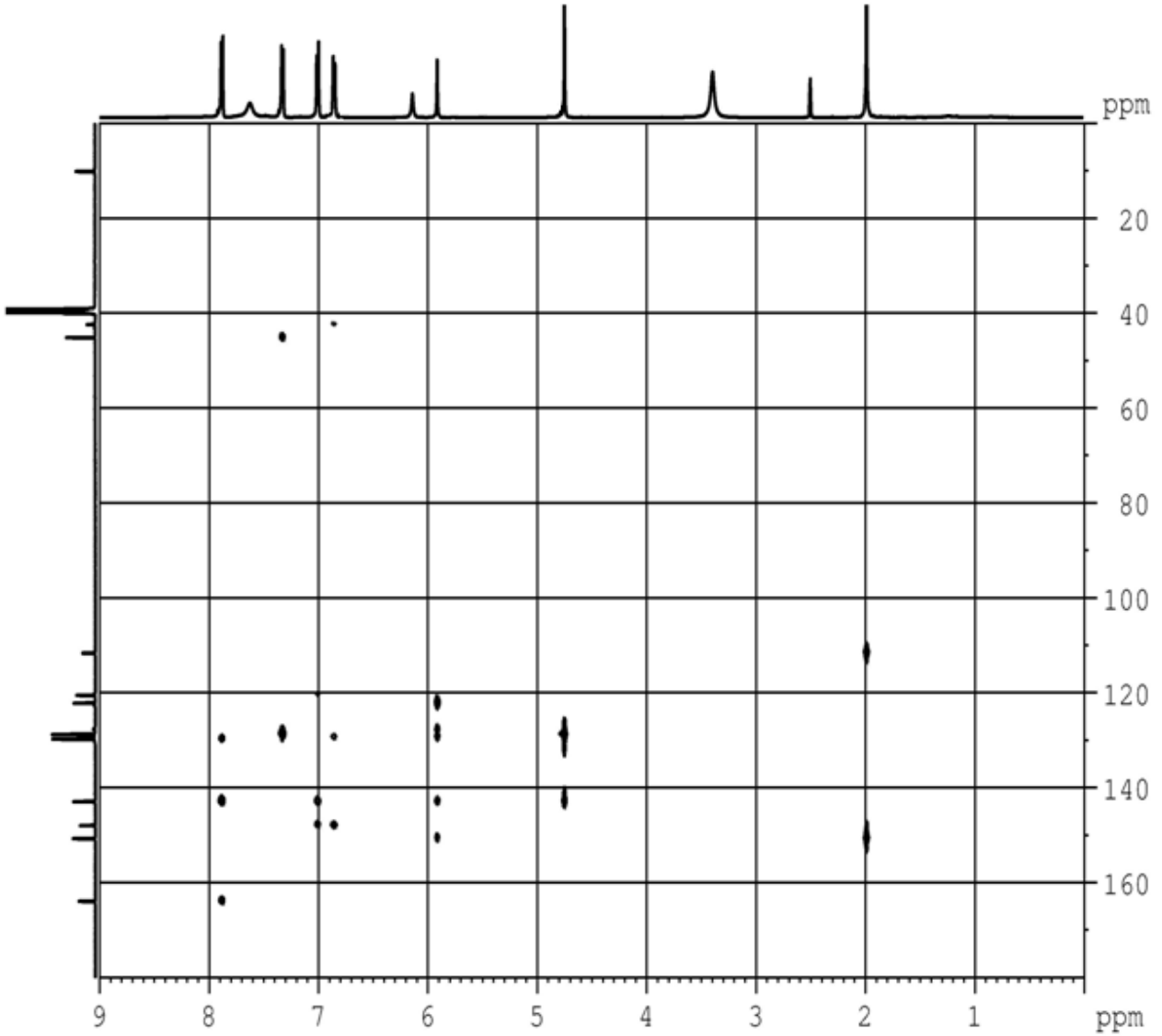


Figure S4. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol **2c** (*rccc* isomer in *cone* conformation) in DMSO-d_6 (T=303 K)

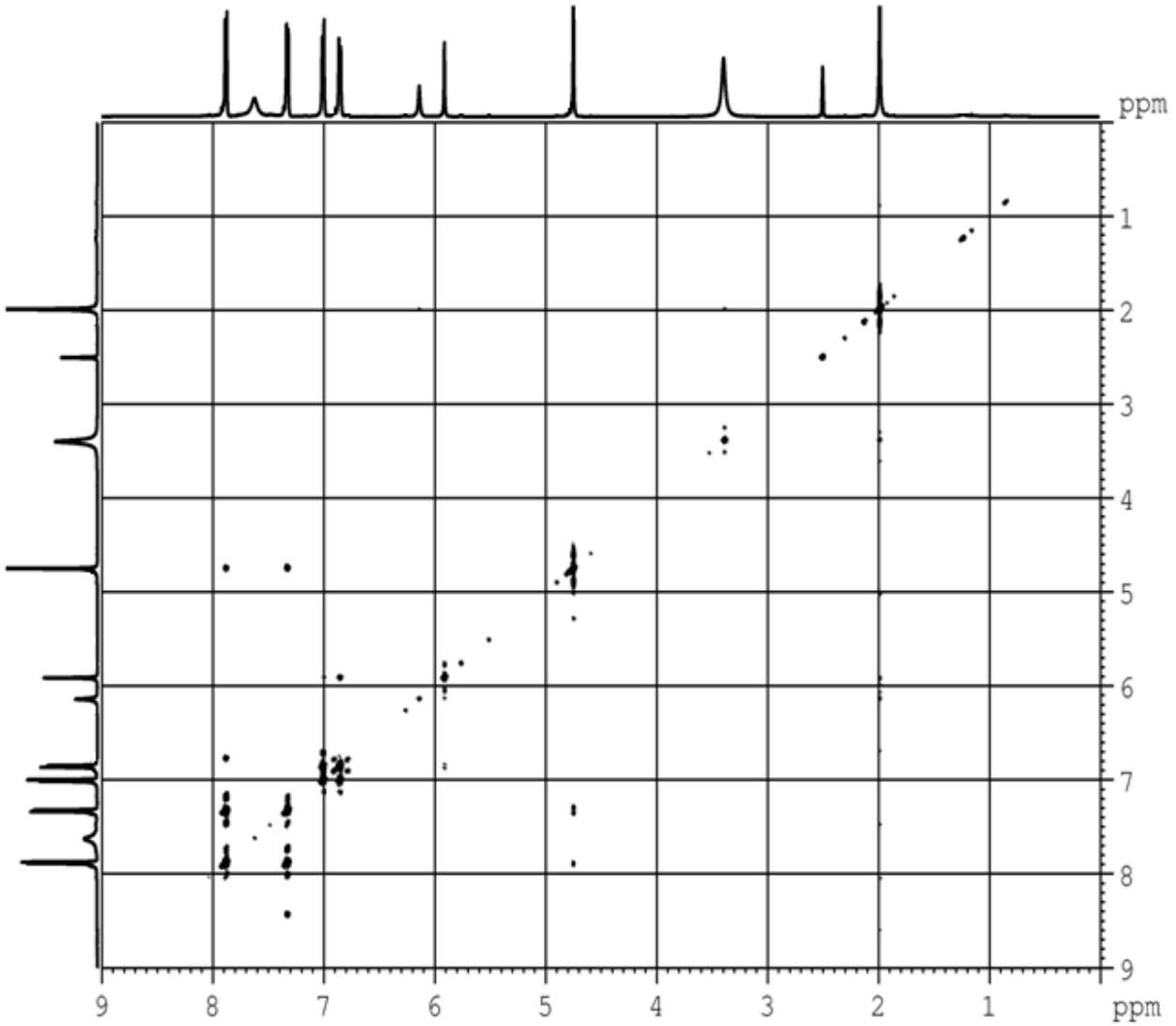


Figure S5. COSY NMR spectrum of calix[4]resorcinol **2c** (*rccc* isomer in *cone* conformation) in DMSO-d_6 (T=303 K)

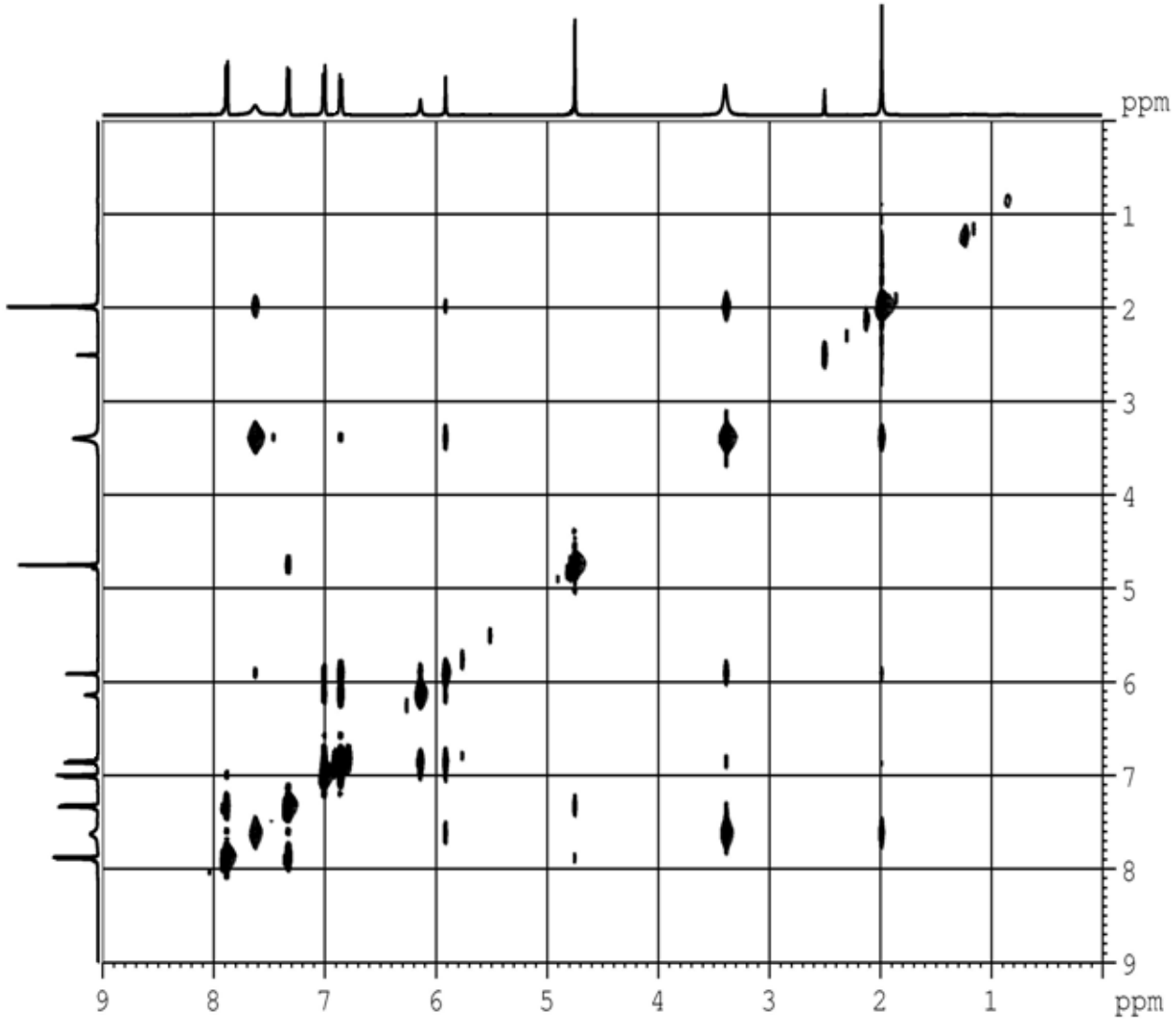


Figure S6. 2D NOESY spectrum of calix[4]resorcinol **2c** (*rccc* isomer in *cone* conformation) in DMSO-d_6 (T=303 K)