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Bile acid derived mono- and diketals - synthesis, structural characterization and self-assembling properties

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1. Complete experimental part

General

Analytical grade reagents and solvents were used for the synthesis, purification, crystallization and gelation studies. Bile acids were purchased from Sigma Aldrich. Silica 0.043-0.060 Å was used in column chromatographic purifications. ^{1}H and ^{13}C NMR experiments were run with a Bruker Avance DRX 500 NMR spectrometer equipped with a 5 mm diameter broad band inverse probehead working at 500.13 MHz for ^{1}H and at 125.76 MHz for ^{13}C. The $^{13}C\{^{1}H\}$ NMR spectrum was measured in standard way using composite pulse, waltz16, decoupling. NMR spectra were measured in $CDCl_3$ and toluene-d_8 ^{1}H and ^{13}C chemical shifts referenced to the solvent signals (δ=7.26 ($CDCl_3$) and δ=2.09 (toluene-d_8) for ^{1}H and δ =77.0 ppm for ^{13}C from int. TMS). Molecular masses of the compounds were confirmed either by using Micromass LCT ESI-TOF mass spectrometer in positive ion mode or by VG AutoSpec 3500 HR-MS EI/CI high resolution mass spectrometer. IR spectra were recorded on Bruker Tensor 27 FT-IR using Pike GladiATR attenuated total reflectance (ATR) cell equipped with a diamond crystal plate. Elemental analyses were carried out using Elementar Vario EL III -analysator.

^{13}C CP/MAS NMR

For ^{13}C CP/MAS NMR spectroscopy compound **5a** was crystallized from various solvents. The $^{13}C\{^{1}H\}$CP/MAS spectra were recorded on a Bruker AV 400 spectrometer equipped with a 4 mm standard bore CP/MAS probehead whose X channel was tuned to 100.62 MHz for ^{13}C. The other channel was tuned to 400.13 MHz for broad band ^{1}H decoupling. Approximately 100 mg of dried and finely powdered samples were packed in the ZrO_2 rotor closed with Kel-F cap and spun at 10 kHz rate. The $^{13}C\{^{1}H\}$CP/MAS NMR was carried out for all samples under Hartmann–Hahn conditions with TPPM decoupling. The $\pi/2$ pulse for proton and carbons were found to be 4.0 and 5 μs at power levels of −5.0 and −4.0 dB, respectively. The experiments were conducted at contact time of 2 ms. A total of 10,000 scans were recorded with 4 s recycle delay for each sample. All FIDs were processed by exponential apodization function with line broadening of 20–40 Hz prior to FT. The ^{13}C CPMAS chemical shifts were referenced with those of glycine standard measured before the each sample.

X-ray crystallography

Single crystals of compounds **7a** and **7c** were grown from EtOAc/hexane (10:90 v/v) and those of compound **10aI** from CD_2Cl_2, respectively. Data were collected at 123(2) K on a Nonius KappaCCD diffractometer with graphite monochromated Mo-K_α radiation. COLLECT[1] data collection software was utilized and data was processed with DENZO-SMN[2]. The reflections were corrected for Lorenz polarization effects but absorption correction was not used. The structures were solved by direct methods (SIR2002[3]) and refined anisotropically (SHELXL-97[4]) by full matrix least squares on F^2 values. Hydrogen atoms were located from the expected geometry and were refined only isotropically. Figures were drawn with Ortep-3 for Windows[5] and Mercury[6].

Gelation tests

For each experiment weighed amount of compound (**5a**-**c**) were put into 5 mL test tube and the tested solvent was added. The mixture was heated to reflux until until it turned into a clear solution (if soluble) after which the sample was sonicated for ca. 10-60 s. Upon cooling down the formation of transparent gel (G), opaque gel (g), precipitate (P), or solution (S), or something between these was detected. State of the sample was defined as a gel, when when it was stable to inversion. When the gel formation or precipitation did not occur at the room temperature, the sample was allowed to cool down to ~6 ^oC in a refridgerator and its appearance was studied.

SEM

Scanning electron micrographs were taken with Bruker Quantax400 EDS microscope equipped with a digital camera. Samples of the xerogels were prepared by placing a hot, clear 2 wt-% solution of the gelator in toluene on carbon tape placed over a sample stub, and after evaporation of the solvent, coated with gold in a JEOL Fine Coat Ion Sputter JFC-1100.

Synthesis and characterization

Methyl 3α-hydroxy-5β-cholan-24-oate (**2a**) and Methyl 3α,12α-dihydroxy-5β-cholan-24-oate (**2b**) were prepared following the known procedures[7]. Methyl 3,7,12-trioxo-5β-

cholan-24-oate (**3c**)[8] was prepared from **1c** by esterification reaction described in the literature for other bile acid esters[9].

Methyl 3-oxo-5β-cholan-24-oate (3a)[10]

Method A: A solution of **2a** (6.06 g, 15.51 mmol) in hot glacial acetic acid (150 mL) was added dropwise over a period of 60 min to a stirred solution of sodium dichromate dihydrate (7.12 g, 23.89 mmol) in water (17 mL) containing conc. H_2SO_4 (1.8 mL) and stirred at room temperature for 24 h. The precipitate obtained after adding water (150 mL) was filtered and washed with water (3 x 80 mL). The crude product was dissolved in dichloromethane (200 mL) and washed with water (3 x 80 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure and column purified using 10-25% ethyl acetate in hexane to yield 4.82 g (80%) of **3a** as colorless solid.

Method B: A solution of **2a** (7.86 g, 20.0 mmol) in 200 mL of acetone was cooled on ice-bath, and to the cooled solution, Jones reagent (prepared by dissolving 3 g of CrO_3 in conc. H_2SO_4 (3 mL) and water (9 mL) with powerful stirring) was added dropwise with vigorous stirring. Oxidizing reagent was added until the orange color was persistent in the mixture. Stirring of the mixture was continued for another 10 minutes on ice, after which the reaction was ceased by an addition of 6 mL portion of 2-propanol. Acetone was removed by evaporation under reduced pressure and the residue stirred vigorously with 250 mL of ethyl acetate. Organic solution was washed three times with 10 mL of water and once with 20 mL of brine and dried over anhydrous Na_2SO_4. Volatiles were removed by evaporation under reduced pressure and the resulting solid dried *in vacuo* to yield 7.05 g (91 %) of **3a** as colorless solid.

Methyl 3,12-dioxo-5β-cholan-24-oate (3b) [10]

Prepared by following the method B from **2b** (8.13 g, 20.0 mmol). Yield 7.50 g (93%) of **3b** as colorless solid.

Methyl 3,7,12-trioxo-5β-cholan-24-oate (3c)[8]

Methyl Iodide (8.6 g, 60.58 mmol) was added to a previously stirred mixture of dehydrocholic acid **1c** (4.26g, 10.58 mmol) and Cs_2CO_3 (4.28g, 13.13 mmol) in DMF (25

mL) and the mixture was stirred at room temperature for 24 h. The precipitate obtained after the addition of water (40 mL) was filtered and dried to yield (4.14 g; 94%) of **3c** as colorless solid.

Cyclic 3-ketal of methyl 3-oxo-5β-cholan-24-oate with pentaerythritol (5a)

Method C: In a two-necked 250 mL flask fitted with a dropping funnel and Dean-Stark – trap pentaerythritol, **4**, (2.45 g, 18.0 mmol) and *p*-toluenesulphonic acid (0.18 g, 5 % w/w of ketone) were added to 60 mL DMF/toluene (3:2 v/v). Mixture was heated until dissolution of all of the solids followed by dropwise addition of **3a (**3.50 g, 9.0 mmol) dissolved in 40 mL of DMF/toluene (3:2 v/v). Reaction mixture was refluxed for 44 hours. Precipitated crude product obtained by addition of ice-water was filtered and dissolved in 200 mL of ethyl acetate. Organic solution was washed with 20 mL of water and with 20 mL of brine and dried over Na_2SO_4. Removal of volatiles followed by column chromatography with ethyl acetate as an eluent gave 3.00 g (66%) of **5a** as colorless solid. δ_H (500.13 MHz; $CDCl_3$): 0.62 (3H, s, 18-C*H*$_3$), 0.88 (3H, d, 6.4 Hz, 21-C*H*$_3$), 0.91 (3H, s, 19-C*H*$_3$), 2.36-0.62 (m, 23-C*H*$_2$, steroidal -C*H*$_2$ and -C*H*), 2.97 (2H, br. s, 26'-CH$_2$O*H*, 28'-CH$_2$O*H*), 3.64 (3H,s, 25-C*H*$_3$), 3.72-3.65 (8H, 4 x s, 26-C*H*$_2$, 28-C*H*$_2$, 26'-C*H*$_2$, 28'-C*H*$_2$); δ_C (125.7 MHz; $CDCl_3$): 12.0 (C18), 18.2 (C21), 21.0 (C11), 23.1 (C19), 24.1 (C15), 26.2 (C7), 26.7 (C2), 27.0 (C6), 28.1 (C16), 31.0 (C22, C23), 32.6 (C1), 33.5 (C4), 35.0 (C10), 35.3 (C20), 35.5 (C8), 39.1 (C27), 39.3 (C9), 39.8 (C5), 40.1 (C12), 42.7 (C13), 51.4 (C25), 55.9 (C17), 56.4 (C14), 61.9, 62.1 (C26, C28), 64.7, 64.7 (C26', C28'), 99.6 (C3),174.8 (C24). ν_{max}/cm^{-1}: 3336, 2927, 2864, 1738, 1446, 1366, 1250, 1167, 1143, 1099, 1035, 870, 700; MS (ES$^+$), found m/z: 529.3 ([M+Na]$^+$), 545.3 ([M+K]$^+$), 570.4 ([M+C_2H_3N+Na]$^+$); Found: C 70.94, H 10.04; $C_{30}H_{50}O_6$ requires C 71.11, H 9.95%.

Cyclic 3-ketal of methyl 3,12-dioxo-5β-cholan-24-oate with pentaerythritol (5b)

Prepared by the method C from **4** (2.72 g, 20.0 mmol), **3b** (2.01 g, 5.0 mmol) and *p*-toluenesulphonic acid (0.104 g, 5 % w/w of ketone). Crude product was finely grind and washed by stirring with water for 4 h. Solid was filtered and dried *in vacuo* to give (2.12 g, 81%) **5b** as colorless solid. δ_H (500.13 MHz; $CDCl_3$): 0.85 (3H, d, 6.5 Hz, 21-C*H*$_3$), 1.01 (3H, s, 19-C*H*$_3$), 1.02 (3H, s, 18-C*H*$_3$), 2.89-1.15 (m, 23-C*H*$_2$, steroidal -C*H*$_2$ and -

C*H*), 2.94 (2H, br. s, 26'-CH_2OH, 28'-CH_2OH), 3.66 (3H, s, 25-CH_3), 3.85-3.65 (8H, 4 x s, 26-CH_2, 28-CH_2, 26'-CH_2, 28'-CH_2); δ_C (125.7 MHz; $CDCl_3$): 11.7 (C18), 18.6 (C21), 22.6 (C19), 24.3 (C15), 26.0 (C7), 26.2 (C6), 26.7 (C2), 27.5 (C16), 30.5 (C22), 31.3 (C23), 32.6 (C1), 34.1 (C4), 35.6 (C8), 35.7 (C20), 35.7 (C10), 38.3 (C11), 38.9 (C5), 39.2 (C27), 43.6 (C9), 46.5 (C17), 51.4 (C25), 57.5 (C13), 58.7 (C14), 61.9, 62.1 (C26, C28), 65.2, 65.4 (C26', C28'), 99.2 (C3), 174.7 (C24), 214. 6 (C12); ν_{max}/cm^{-1}: 3421, 2929, 2868, 1732, 1698, 1446, 1380, 1245, 1100, 1027, 872, 616, 526; MS (ES^+), found m/z: 521.3 ($[M+H]^+$), 543.3 ($[M+Na]^+$), 559.2 ($[M+K]^+$); Found: C 68.02, H 9.32; $C_{30}H_{48}O_7 \cdot ½H_2O$ requires C 67.94, H 9.23%.

Cyclic 3-ketal of methyl 3,7,12-trioxo-5β-cholan-24-oate with pentaerythritol (5c)

Prepared by the method C from **4** (4.08 g, 30.0 mmol), **3c** (2.08 g, 5.0 mmol), and *p*-TSA (0.104 g, 5 % w/w of ketone). Crude product was finely grind and washed by stirring with water for 3 h and filtered. Water-washing was repeated and the solids dried *in vacuo* to give 1.29 g (48%) **5c** colorless solid. δ_H (500.13 MHz; $CDCl_3$): 0.88 (3H, d, 6.5 Hz, 21-CH_3), 1.02 (3H, s, 18-CH_3), 1.29 (3H, s, 19-CH_3), 2.50-0.90 (m, 23-CH_2, steroidal -CH_2 and -C*H*), 2.52 (2H, br. s, 26'-CO*H*, 28'-CO*H*), 3.65 (3H, s, 25-CH_3), 3.70-3.66 (8H, 4 x s, 26-CH_2, 28-CH_2, 26'-CH_2, 28'-CH_2); δ_C (125.7 MHz; $CDCl_3$): 11.8 (C18), 18.6 (C21), 22.3 (C19), 25.1 (C15), 26.7 (C2), 27.6 (C16), 30.5 (C22), 31.3 (C23), 31.6 (C1), 34.4 (C4), 35.5 (C20), 36.1 (C10), 38.6 (C11), 39.2 (C27), 43.0 (C5), 45.0 (C6), 45.2 (C9), 45.6 (C17), 49.0 (C8), 51.4 (C25), 51.8 (C14), 56.8 (C13), 62.0, 62.0 (C26, C28), 65.2, 65.4 (C26', C28'), 98.2 (C3), 174.6 (C24), 209.7 (C7), 212.6, (C12); ν_{max}/cm^{-1}: 3333, 2939, 2879, 1730, 1702, 1446, 1380, 1251, 1170, 1100, 1035, 895, 624; MS (ES^+), found m/z: 557.2 ($[M+Na]^+$), 573.2 ($[M+K]^+$); Found: C 66.25, H 8.71; $C_{30}H_{46}O_8 \cdot ½H_2O$ requires C66.27, H 8.71%.

Cyclic 3-ketal of methyl 3-oxo-5β-cholan-24-oate with benzene-1,2-diol (7a)

Method D: Montmorillonite (1.50 g) was added to a solution of benzene-1,2-diol, **6**, (1.50 g, 13.62 mmol) and **3a** (1.77g, 4.54 mmol) in 30 mL toluene. After stirring the reaction mixture under reflux conditions for 24 h using Dean-Stark apparatus, it was cooled and filtered. Removal of volatiles followed by column purification using ethyl acetate/hexane (10:90-30:70 v/v) resulted in a colorless solid which upon recrystallization from ethyl

acetate/hexane (10:90 v/v) yielded 1.48 g (68%) of **7a** as colorless X-ray quality crystals. δ_H (500.13 MHz; $CDCl_3$): 0.67 (s, 3H, 18-C*H*$_3$), 0.92 (3H, d, *J*=6.5 Hz, 21-C*H*$_3$), 1.01 (3H, s, 19-C*H*$_3$), 2.40-1.00 (m, 23-C*H*$_2$, steroidal -C*H*$_2$ and -C*H*), 3.66 (3H, s, 25-C*H*$_3$), 6.77-6.71 (4H, m, 3'-C*H*, 4'-C*H*, 5'-C*H*, 6'-C*H*); δ_C (125.7 MHz; $CDCl_3$): 12.1 (C18), 18.3 (C21), 21.1 (C11), 23.0 (C19), 24.2 (C15), 26.1 (C7), 26.4 (C6), 28.2 (C16), 30.3 (C2), 31.0 (C23), 31.1 (C22), 33.3 (C1), 34.4 (C10), 35.4 (C20), 35.6 (C4), 35.6 (C8), 40.0 (C9), 40.2 (C12), 40.2 (C5), 42.8 (C13), 51.4 (C25), 56.0 (C17), 56.5 (C14), 119.2 (C3), 108.3, 108.5 (C3', C6'), 120.9, 120.9 (C4',C5'), 147.3, 147.4 (C1', C2'), 174.7 (C24); ν_{max}/cm^{-1}: 2929, 2884, 2864, 1731, 1488, 1452, 1438, 1376, 1362, 1241, 1206, 1169, m1072, 907, 733, 620, 532, 417; MS (ES$^+$), found m/z: 503.25 ([M+Na]$^+$); Found: C 77.50, H 9.46; $C_{31}H_{44}O_4$ requires C 77.46, H 9.23%.

Cyclic 3-ketal of 3,7,12-trioxo-5β-cholan-24-oate with benzene-1,2-diol (7c)

Prepared by method D from **6** (1.72 g, 15.61 mmol), **3c** (1.42g, 3.40 mmol) and montmorillonite (1.72 g). Purification by column chromatography using ethyl acetate/hexane (40:60-50:50 v/v) resulted in a colorless solid which upon recrystallization from ethyl acetate/hexane (10:90 v/v) yielded 1.21 g (70%) of **7c** as colorless X-ray quality crystals. δ_H (500.13 MHz; $CDCl_3$): 0.85 (d, *J*=6.5 Hz, 3H, 21-C*H*$_3$), 1.05 (3H, s, 18-C*H*$_3$), 1.38 (3H, s, 19-C*H*$_3$), 2.93-1.20 (m, 23-C*H*$_2$, steroidal -C*H*$_2$ and -C*H*), 3.67 (3H, s, 25-C*H*$_3$), 6.77-6.71 (4H, m, 3'-C*H*, 4'-C*H*, 5'-C*H*, 6'-C*H*),; δ_C (125.7 MHz; $CDCl_3$): 11.8 (C18), 18.6 (C21), 22.2 (C19), 25.2 (C15), 27.6 (C16), 29.7 (C2), 30.5 (C22), 31.3 (C23), 32.2 (C1), 35.5 (C4), 35.7 (C10), 36.6 (C20), 38.6 (C11), 43.6 (C5), 44.8 (C9), 44.8 (C6), 45.6 (C17), 49.0 (C8), 51.4 (C25), 51.8 (C14), 56.9 (C13), 108.5, 108.7 (C3', C6'), 117.1 (C3), 121.1, 121.3 (C4', C5'), 146.7, 147.1 (C1', C2'), 174.5 (C24), 209.0 (C7), 212.2 (C12); ν_{max}/cm^{-1}: 2955, 2882, 1732, 1711, 1696, 1488, 1435, 1240, 1071, 736, 623; MS (ES$^+$), found m/z: 531.21 ([M+Na]$^+$); Found: C 73.21, H 8.20; $C_{31}H_{40}O_6$ requires C 73.20, H 7.93%.

Cyclic 3-ketal of methyl 3-oxo-5β-cholan-24-oate with naphthalene-2,3-diol (9a)

Prepared by method D from naphthalene-2,3-diol, **8**, (1.45 g, 13.62 mmol), **3a** (1.01 g, 2.59 mmol) and montmorillonite (1.12 g). Purification by column chromatography using ethyl acetate/hexane (15:85-30:70 v/v) yielded 1.00 g (74%) of **9a** colorless solid. δ_H

(500.13 MHz; $CDCl_3$): 0.67 (s, 3H, 18-CH_3), 0.93 (3H, d, *J*=6.5 Hz, 21-CH_3), 1.03 (3H, s, 19-CH_3), 2.40-1.00 (m, 23-CH_2, steroidal -CH_2 and -C*H*), 3.66 (3H, s, 25-CH_3), 7.01 (2H, d, *J*=4.25 Hz, 3'-C*H*, 6'-C*H*), 7.28-7.27 (2H, m, 8'-C*H*, 9'-C*H*), 7.64-7.60 (2H, m, 7'-C*H*, 10'-C*H*); δ_C (125.7 MHz; $CDCl_3$): 12.1 (C18), 18.3 (C21), 21.1 (C11), 23.0 (C19), 24.2 (C15), 26.1 (C7), 26.4 (C6), 28.2 (C16), 30.5 (C2), 31.0 (C23), 31.1 (C22), 33.4 (C1), 34.4 (C10), 35.4 (C20), 35.7 (C4), 35.8 (C8), 40.1 (C9), 40.2 (C12), 40.3 (C5), 42.8 (C13), 51.4 (C25), 56.0 (C17), 56.6 (C14), 103.4, 103.6 (C3', C6'), 119.8 (C3), 123.9, 123.9 (C8', C9'), 126.7, 126.8 (C7', C10'), 130.4, 130.4 (C4', C5'), 147.8, 147.9 (C1', C2'), 174.7 (C24); ν_{max}/cm^{-1}: 2929, 2859, 1736, 1472, 1251, 1162, 1069, 851, 744, 619, 480; MS (ES^+), found m/z: 553.29 ($[M+Na]^+$). Found: C 78.85, H 8.81; $C_{35}H_{46}O_4$ requires C 79.21, H8.74%.

Cyclic 3-ketal of 3,7,12-trioxo-5β-cholan-24-oate with naphthalene-2,3-diol (9c).

Prepared by method D from **8** (0.89 g, 5.56 mmol), **3c** (1.45 g, 3.48 mmol) and montmorillonite (1.52 g). Purification by column chromatography using ethyl acetate/hexane (30:70-50:50 v/v) yielded 0.89 g (47%) of **9c**. δ_H (500.13 MHz; $CDCl_3$): 0.86 (3H, d, *J*=6.5 Hz, 21-CH_3), 1.06 (3H, s, 18-CH_3), 1.34 (3H, s, 19-CH_3), 2.96-1.20 (m, 23-CH_2, steroidal -CH_2 and -C*H*), 7.01 (2H, br. t, 3'-C*H*, 6'-C*H*), 7.30-7.27 (2H, m, 8'-C*H*, 9'-C*H*), 7.63-7.60 (2H, m, 7'-C*H*, 10'-C*H*); δ_C (125.7 MHz; $CDCl_3$): 11.8 (C18), 18.6 (C21), 22.2 (C19), 25.2 (C15), 27.6 (C16), 29.9 (C2), 30.5 (C22), 31.3 (C23), 32.2 (C1), 35.6 (C4), 35.7 (C10), 36.7 (C20), 38.6 (C11), 43.6 (C5), 44.8 (C6), 45.3 (C9), 45.7 (C17), 49.0 (C8), 51.5 (C25), 51.8 (C14), 56.9 (C13), 103.7, 103.9 (C3', C5'), 117.6 (C3), 124.1, 124.1 (C8', C9'), 126.8, 126.9 (C7', C10'), 130.3, 130.4 (C4', C5'), 147.2, 147.4 (C1', C2'), 174.5 (C24), 209.0 (C7), 212.1 (C12); ν_{max}/cm^{-1}: 2964, 2871, 1737, 1706, 1471, 1250, 1166,1069, 857, 751, 621, 482; MS (ES^+), found m/z: 581.20 ($[M+Na]^+$); Found C 72.97, H 7.73; $C_{35}H_{42}O_6 \cdot H_2O$ requires C 72.89, H 7.69%.

Cyclic diketal of methyl 3-oxo-5β-cholan-24-oate with pentaerythritol (10a)

Method E: Pentaerythritol, **4**, (0.74 g, 5.4 mmol) and *p*-TSA (0.18 g, 5 % w/w ketone) were added to 60 mL of toluene-DMF (2:3). Mixture was heated until dissolution of all of the solids were followed by dropwise addition of **3a (**3.50 g, 9.0 mmol) dissolved in 40 mL of DMF/toluene (3:2). Reaction mixture was refluxed for 64 hours. Precipitated crude

product obtained by addition of ice-water was filtered and dissolved in 50 mL of EtOAc/DCM (1:2). Organic solution was washed with 20 mL of H_2O and 20 mL of brine and dried over anhydrous Na_2SO_4. Removal of volatiles followed by column chromatography using EtOAc-DCM (1:2) as an eluent gave 2.61 g (66%) of **7a** as white solid consisting of isomers **10a(I)** and **10a(II)**. **10a(I)**: δ_H (500.13 MHz; $CDCl_3$): 0.64 (3H, s, 18-CH_3), 0.90 (3H, d, *J*=6.5 Hz, 21-CH_3), 0.92 (3H, s, 19-CH_3), 2.38-1.00 (m, 23-CH_2, steroidal -CH_2 and -C*H*), 3.66 (s, 6H, 25-CH_3), 3.80-3.65 (m, 8H, 26-CH_2, 28-CH_2, 26'-CH_2, 28'-CH_2); δ_C (125.7 MHz; $CDCl_3$): 12.0 (C18), 18.3 (C21), 21.1 (C11), 23.2 (C19), 24.2 (C15), 26.3 (C7), 26.8 (C6), 27.1 (C2), 28.2 (C16), 31.0, 31.1 (C22, C23), 32.6 (C1), 33.0 (C27), 33.3 (C4), 35.4 (C20), 35.7 (C8), 39.4 (C9), 39.8 (C5), 35.0 (C10), 40.2 (C12), 42.8 (C13), 51.4 (C25), 56.0 (C17), 56.5 (C14), 63.6, 63.3 (C26, C28, C26', C28'), 100.1 (C3), 174.7 (C24); ν_{max}/cm^{-1}: 2923, 2850, 1734, 1439, 1365, 1177, 1150, 1081, 1028, 998, 873, 732, 606, 423; MS (ES^+), found m/z: 899.67 ($[M+Na]^+$) and 915.61 ($[M+K]^+$). Found: C 73.41, H 9.84; $C_{55}H_{88}O_8 \cdot H_2O$ requires C 73.79, H 10.13%.
10a(II): δ_H (500.13 MHz; $CDCl_3$): 0.64 (3H, s, 18-CH_3), 0.90 (3H, d, *J*=6.5 Hz, 21-CH_3), 0.92 (3H, s, 19-CH_3), 2.38-1.00 (m, 23-CH_2, steroidal -CH_2 and -C*H*), 3.66 (6H, s, 25-CH_3), 3.82-3.62 (8H, 2 x q_{AB}, 26-CH_2, 28-CH_2, 26'-CH_2, 28'-CH_2, H_b=3.80 H_a=3.79 *J*=13.7 Hz, H_b=3.66, H_a=3.64 *J*=11.6 Hz); δ_C (125.7 MHz; $CDCl_3$): 12.0 (C18), 18.3 (C21), 21.1 (C11), 23.1 (C19), 24.2 (C15), 26.2 (C7), 26.7 (C2, C6), 28.2 (C16), 31.1, 31.0 (C23, C22), 32.6 (C1), 33.7 (C4), 35.0 (C10), 35.4 (C20), 35.7 (C8), 39.4 (C9), 40.2 (C12), 40.2 (C5), 42.8 (C13), 51.4 (C25), 56.0 (C17), 56.5 (C14), 63.6, 63.3 (C26, C28, C26', C28'), 99.7 (C3), 174.7 (C24); ν_{max}/cm^{-1}: 2928, 2853, 1737, 1447, 1377, 1166, 1078, 1022, 873, 608, 527, 423; Found: C 74.37, H 9.94; $C_{30}H_{46}O_8 \cdot ½H_2O$ requires C 74.53, H 10.12%.

Cyclic 3-diketal of methyl 3,12-dioxo-5β-cholan-24-oate with pentaerythritol (10b)

Prepared by the method E from **4** (0.41 g, 3.0 mmol), **3b** (2.01 g, 5.0 mmol), and *p*-TSA (0.104 g, 5 % w/w of ketone) by refluxing for 44 hours. Crude product was finely grind and washed by stirring with EtOAc for 3 hours. Washing was repeated twice with 1 hour stirring and the product was dried in *vacuo* to give 0.66 g (29%) of **7b** as white solid consisting of isomers **10b(I)** and **10b(II)**. δ_H (500.13 MHz; $CDCl_3$): 0.82 (6H, d, *J*=6.5 Hz, 21-CH_3), 0.98 (6H, s, 18-CH_3), 0.99 (6H, s, 19-CH_3), 2.50-0.95 (m, 23-CH_2, steroidal

-C*H*$_2$ and -C*H*), 3.64 (6H, s, 25-C*H*$_3$), 3.85-3.60 (8H, m, 26-C*H*$_2$, 28-C*H*$_2$, 26'-C*H*$_2$, 28'-C*H*$_2$); δ_C (125.7 MHz; $CDCl_3$): 11.6 (C18), 18.5 (C21), 22.2 (C19), 24.2 (C15), 25.9 (C7), 26.2 and 25.8 (C2(I) and C2(II)), 26.6 (C6), 27.5 (C16), 30.5 (C22), 31.3 (C23), 32.5 (C1), 32.9 and 32.8 (C27(I) and C27(II)), 34.3 and 33.8 (C4(I) and C4(II)), 35.6, 35.5 (C20, C8), 35.7 (C10), 38.3 (C11), 38.8 (C5), 43.5 (C9), 46.4 (C17), 51.4 (C25), 57.4 (C13), 58.6 (C14), 63.2, 63.3, 63.4, 63.4 (C26, C28, C26', C28'), 99.2 (C3), 174.5 (C24), 214.5 (C12); ν_{max}/cm^{-1}: 2929, 2868, 1734, 1699, 1449, 1433, 1185, 1084, 1026, 873, 613, 524; MS (ES$^+$), found m/z: 899.67 ([M+Na]$^+$), 915.61 ([M+K]$^+$); Found: C 72.09, H 9.21; $C_{55}H_{84}O_{10}\cdot½H_2O$ requires C 72.25, H 9.37%.

Cyclic 3-diketal of methyl 3,7,12-trioxo-5β-cholan-24-oate with pentaerythritol (10c)
Prepared by the method E from **4** (0.41 g, 3.0 mmol), **3c** (2.08 g, 5.0 mmol) and *p*-TSA (0.104 g, 5 % w/w of ketone) by refluxing for 44 hours. Crude product was finely grind and washed by stirring with EtOAc for 19 hours. Product was dried in *vacuo* to give 1.10 g (47%) of **7c** as white solid consisting of isomers **10c(I)** and **10c(II)**. δ_H (500.13 MHz; $CDCl_3$): 0.82 (6H, d, *J*=6.5 Hz, 21-C*H*$_3$), 1.00 (6H, s, 19-C*H*$_3$), 1.27 (6H, s, 18-C*H*$_3$), 2.90-1.10 (m, 23-C*H*$_2$, steroidal -C*H*$_2$ and -C*H*), 3.64 (6H, s, 25-C*H*$_3$), 3.75-3.55 (8H, m, 26-C*H*$_2$, 28-C*H*$_2$, 26'-C*H*$_2$, 28'-C*H*$_2$); δ_C (125.7 MHz; $CDCl_3$): 11.8 (C18), 18.6 (C21), 22.2 and 22.2 (C19(I) and C19(II)), 25.1 (C15), 27.2 and 25.9 (C2(I) and C2(II)), 27.6 (C16), 30.5 (C22), 31.3 (C23), 31.5 (C1), 32.9 and 32.9 (C27(I) and C27(II)), 34.9 and 33.7 (C4(I) and C4(II)), 35.5 (C20), 36.1 (C10), 38.5 (C11), 42.9 (C5), 45.0 (C6), 45.2 (C9), 45.6 (C17), 48.9 (C8), 51.4 (C25), 51.8 (C14), 56.8 (C13), 63.3, 63.3 (C26, C28, C26', C28'), 98.3 and 98.3 (C3(I) and C3(II)), 174.5 (C24), 209.5 and 209.4 (C7(I) and C7(II)), 212.4 and 212.3 (C12(I) and C12(II)); ν_{max}/cm^{-1}: 2952, 2874, 1733, 1701, 1435, 1168, 1086, 1033, 894, 622; MS (ES$^+$), found m/z: 899.67 ([M+Na]$^+$), 915.61 ([M+K]$^+$). Found: C 69.90, H 8.58; $C_{55}H_{80}O_{12}\cdot½H_2O$ requires C 70.11, H 8.66%.

2. Copies of selected NMR spectra.

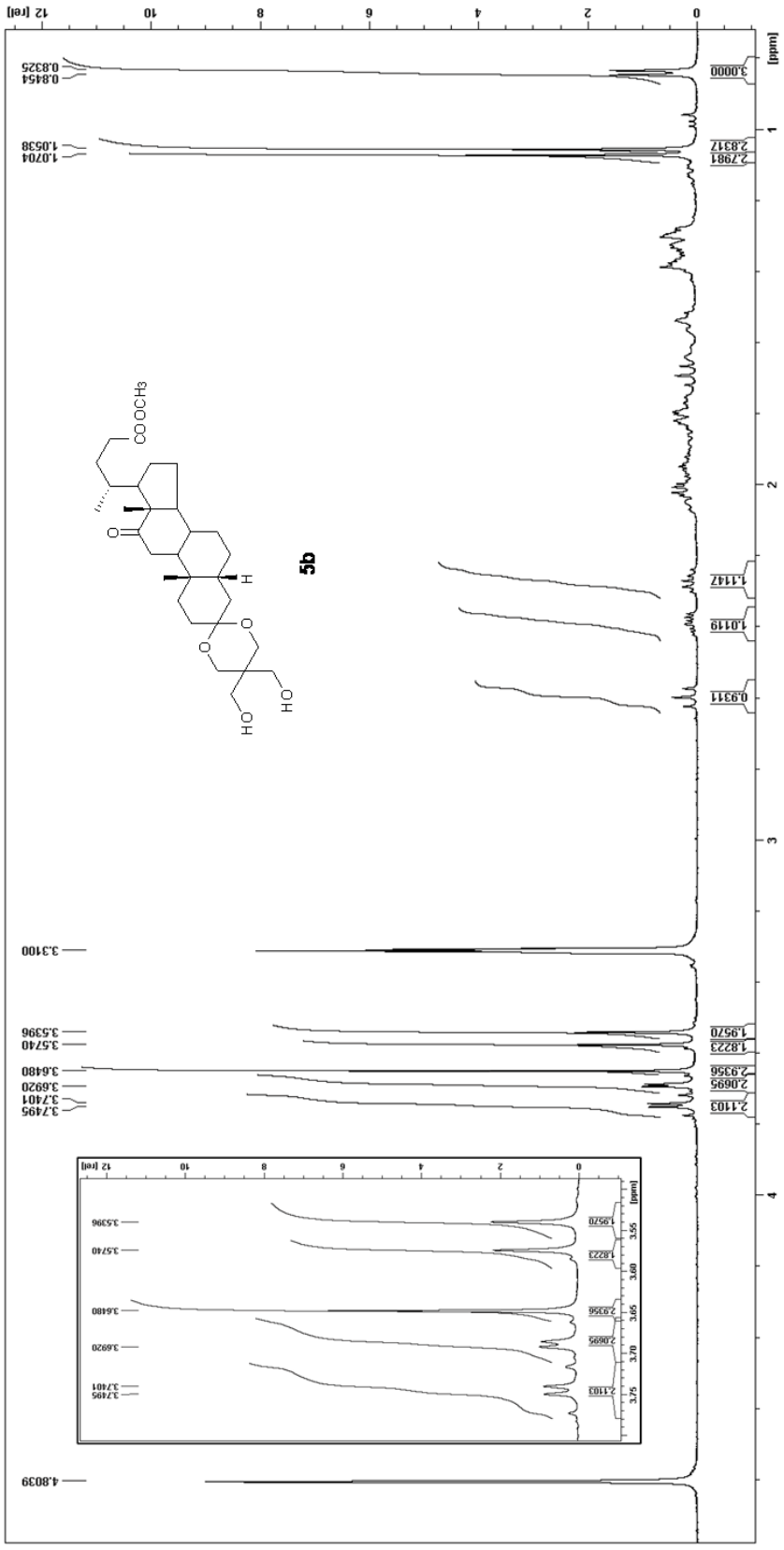

Fig. S1 ^{1}H specrum of **5b** in CD_3OD at 303K.

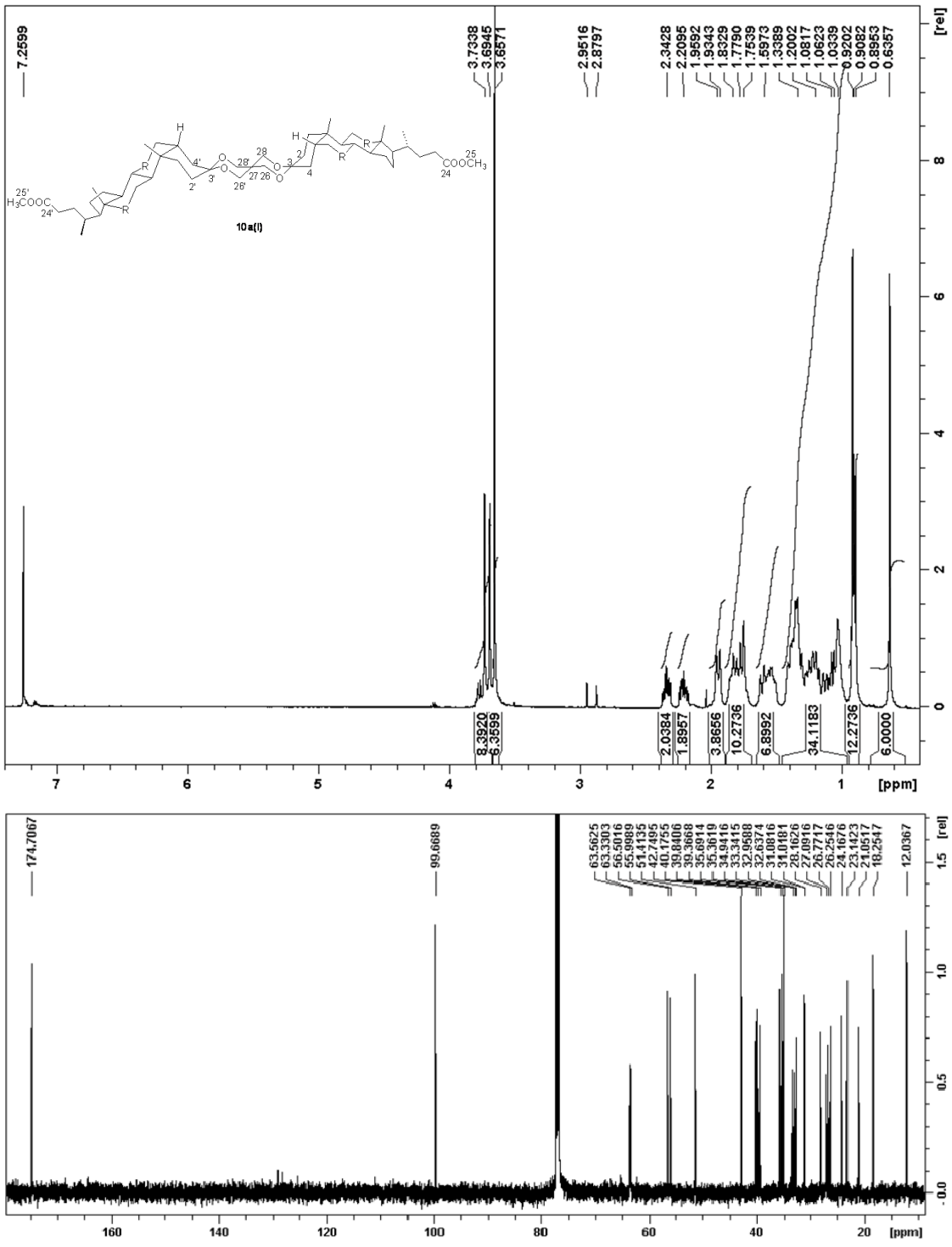

Fig. S2. ^{1}H and ^{13}C NMR spectra of **10a(I)** in $CDCl_3$ at 303K.

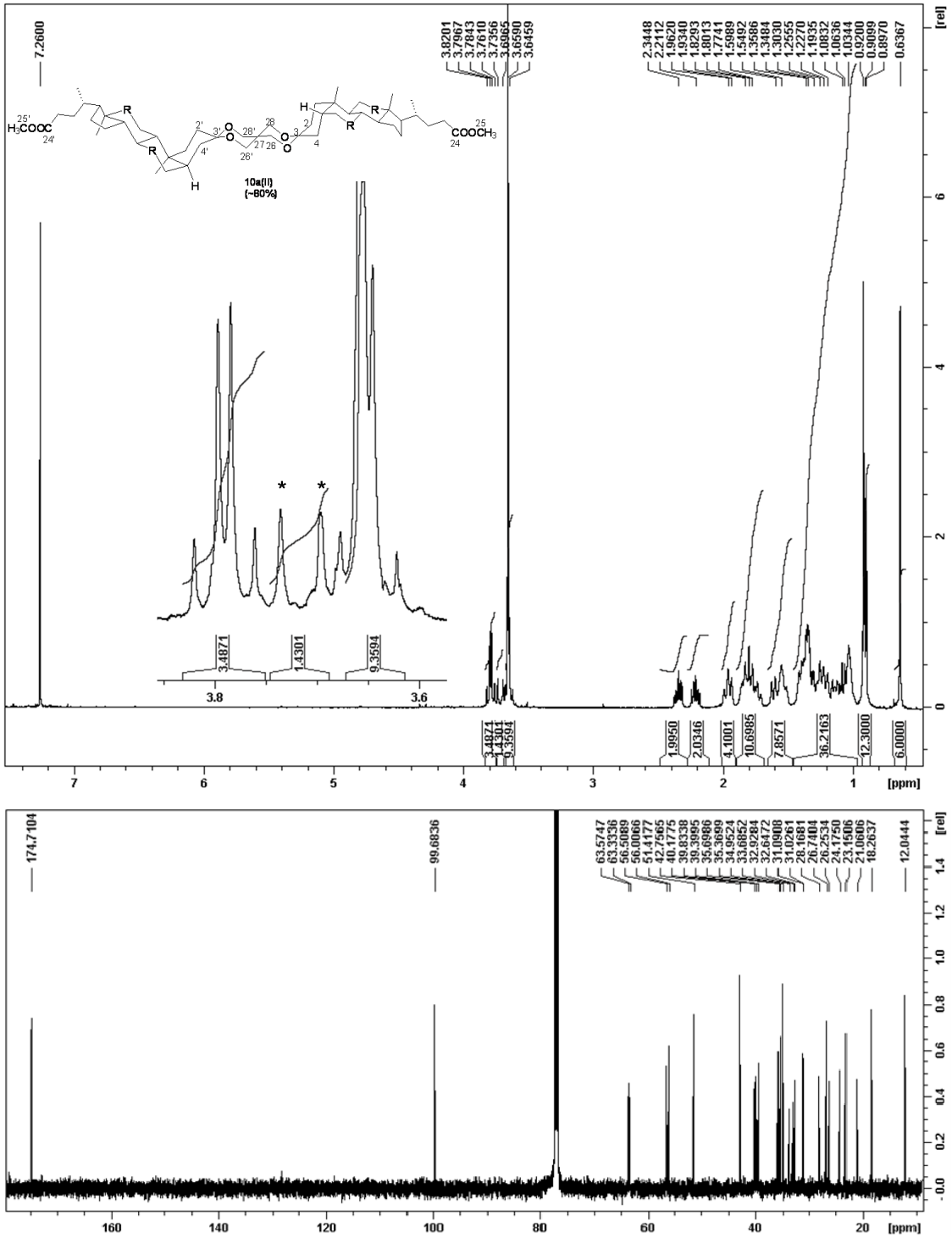

Fig. S3. ^{1}H and ^{13}C NMR spectra of **10a(I)** in $CDCl_3$ at 303K.

3. Supplementary SEM images of xerogels

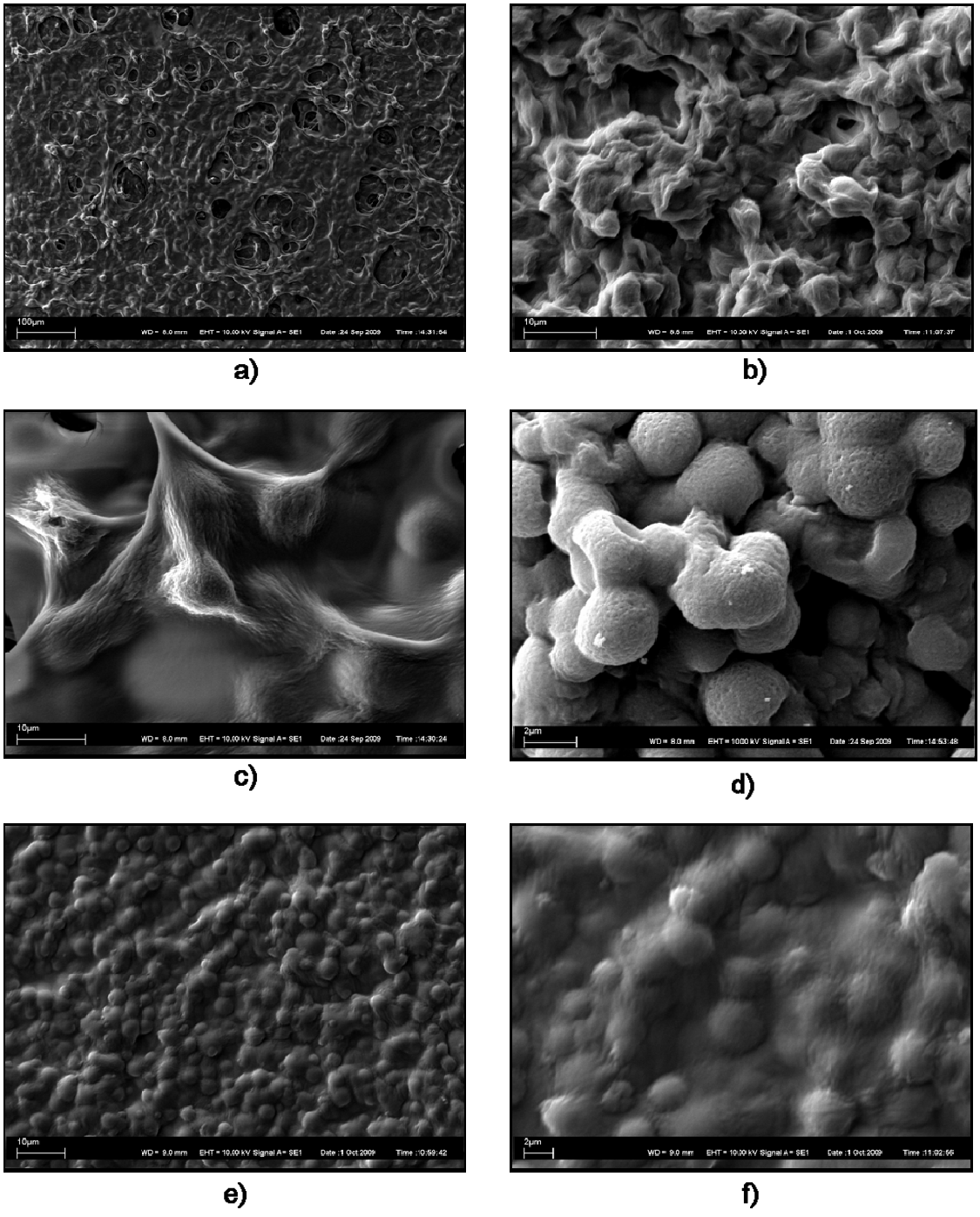

Fig. S4. SEM images of xerogels obtained from gel of **5a** in toluene (2 wt-%) (a-c), **5b** in toluene (2 wt-%) (d) and **5a** in *p*-xylene (2 wt-%)(e-f).

4. Supplementary ^{1}H NMR spectra of **5a** in toluene-d_8.

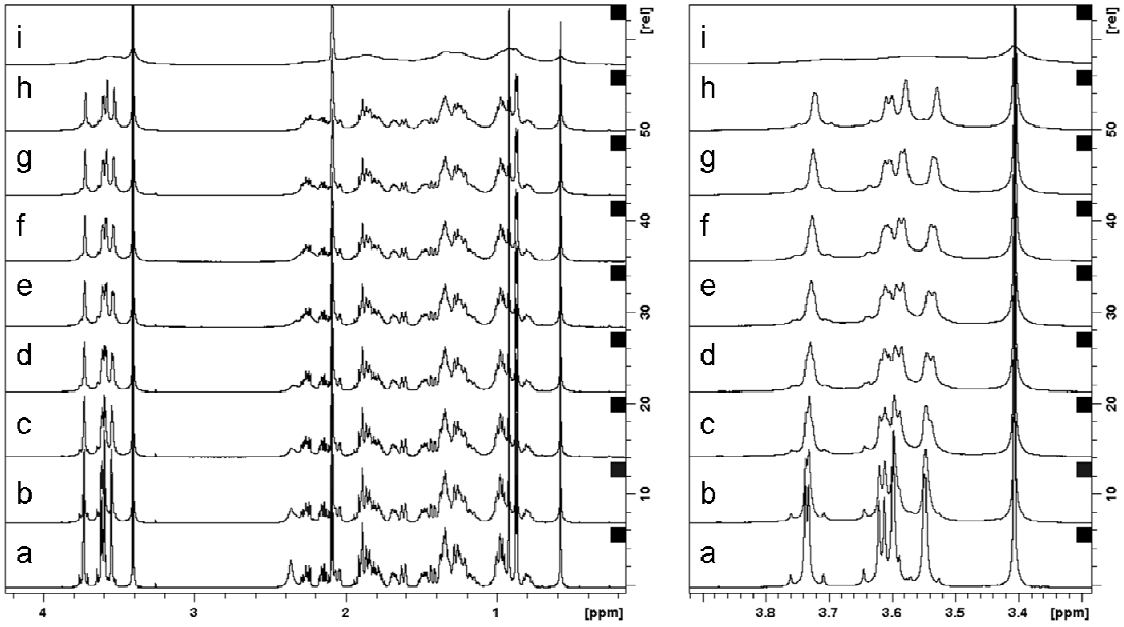

Fig. S5. ^{1}H NMR spectra and subspectra of **5a** in toluene-d_8 at 30 ^{o}C after aging for a) 0 min, b) 6 min, c) 12 min, d) 18 min, e) 24 min, f) 30 min, g) 36 min, h) 60 min, and i) 210 min.

5. ^{13}C CP/MAS NMR spectra

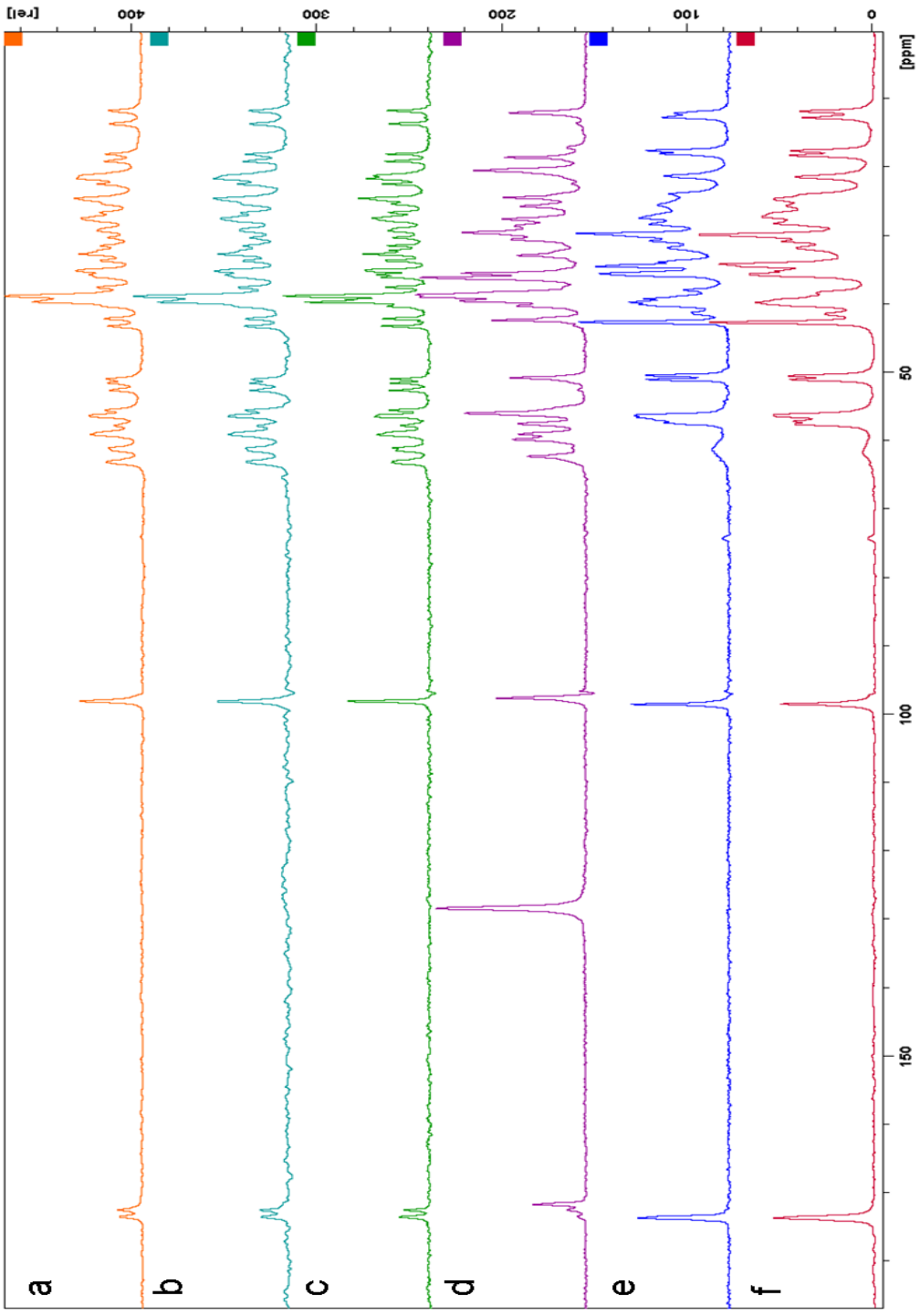

Fig. S6. ^{13}C CP/MAS spectra of **5a** crystallized from a) toluene, b) p-xylene, c) chlorobenzene, d) benzene, e) acetonitrile, and f) acetone.

6. Supplementary figures of the crystal structures of **7a** and **7c**

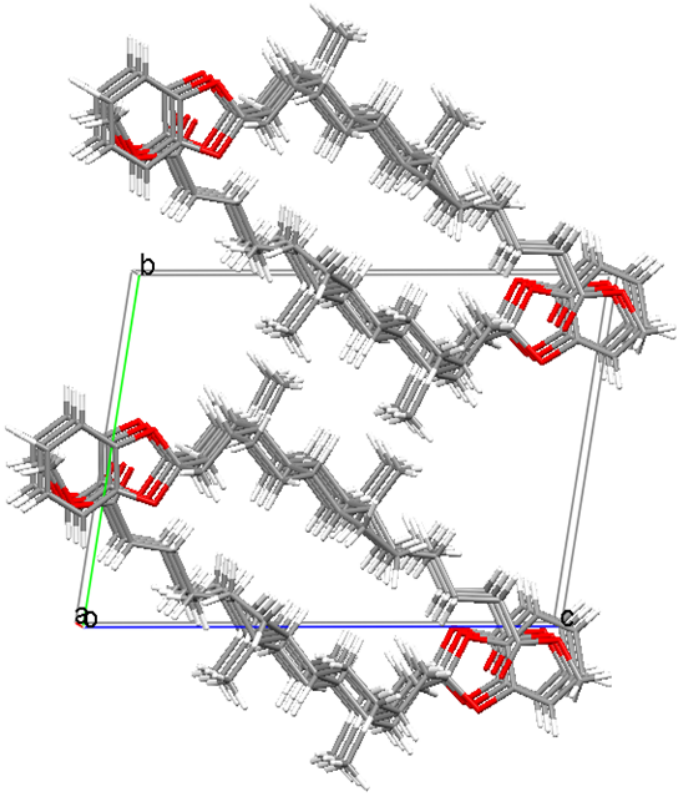

Fig. S7. Crystal packing of **7a**.

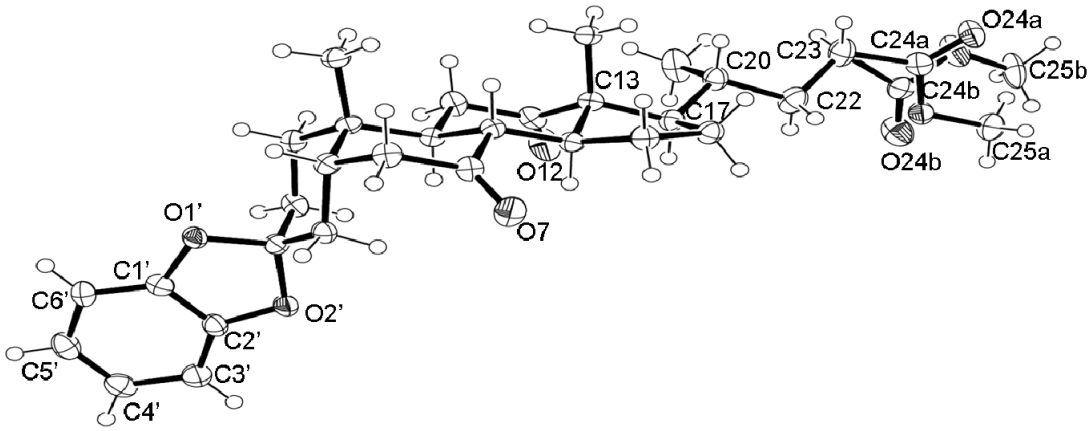

Fig. S8. Molecular structure the molecule A in the crystals of of 7c showing the disorder in the side chain.

7. Polarizing microscope images of **9a**.

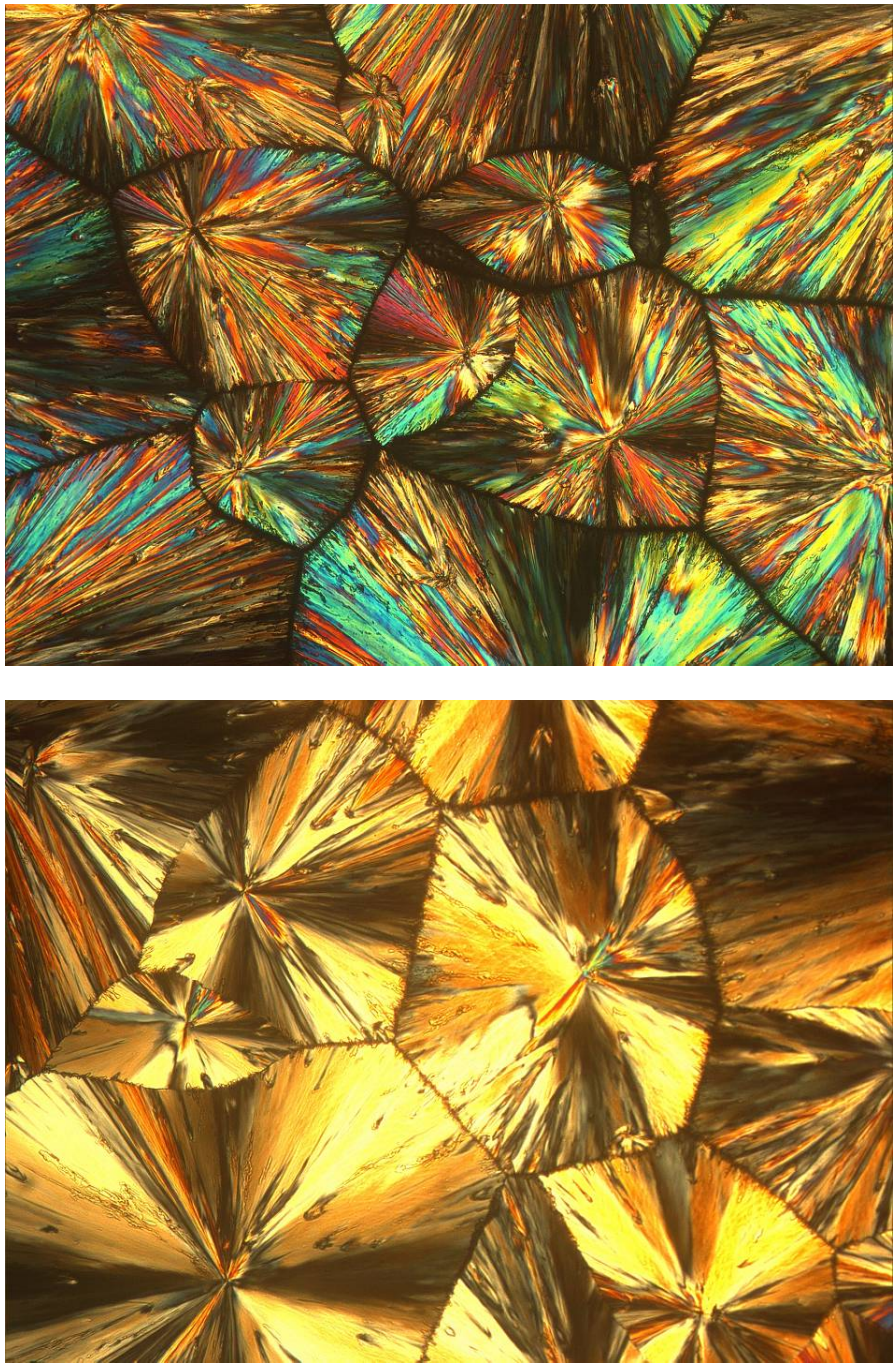

Fig. S9. Polarizing microscope images of **9a** upon cooling to 90 ^{o}C from isotropic liquid.

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