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

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Received 18th February 2010, Accepted 23rd March 2010
First published as an Advance Article on the web 15th April 2010
DOI: 10.1039/c003228j

Three oxo-derivatives of bile acid methyl esters have been used as starting compounds in the preparation of novel bile acid monoketals with 1,2-benzenediol (catechol) and 2,3-naphthalenediol, as well as mono- and diketals with pentaerythritol. Monoketals of pentaerythritol showed a tendency to form thermoreversible gels in many aromatic solvents and the methyl lithocholate derivative proved to be a supergelator able to form a gel with *t*-butylbenzene at a concentration as low as 0.5% w/v. Whereas the naphthalenediol ketals formed film-type materials in the studied solvents, the catechol ketals underwent rapid crystallization into X-ray quality single crystals. Single crystal X-ray structures of the catechol ketals have been determined. The monoketal obtained from methyl-3,7,12-trioxo-5β-cholan-24-oate (dehydrocholate) revealed to have an unusual packing pattern in its solid state compared to other bile acid derivatives reported in the literature. The synthesis of diketals from pentaerythritol furnished a mixture of two diastereomers which, in the case of the methyl lithocholate derivative, have been separated and the X-ray crystal structure of one isomer resolved.

Introduction

The spontaneous self-assembly of organic molecules into well-defined molecular architectures has gained enormous interest in the field of supramolecular chemistry in recent years.[1] The cyclic ketal unit serves as a rigid scaffold coordinating the side chains in well-defined three-dimensional orientations. It is thus an attractive building unit towards the construction of supramolecular architectures, and in crystal engineering where the controllability plays a significant role. As a ketal-forming alcohol, pentaerythritol (PE) can form both mono- and diketals (spirocyclic systems), and rigid or flexible systems. Depending on the substituent, the ketals derived from PE may contain one or two flexible dioxane rings or they can be fully anancomeric. Grosu *et al.* have prepared different types of PE ketals with flexible or anancomeric ring systems and also studied the substituent effect on the magnetic properties of the protons in the 1,3-dioxane ring system.[2] Pentaerythritol ketals and acetals have been widely used as building blocks aimed for use in supramolecular chemistry, nanostructures and materials science. These include dendrimers,[3] macrocyclic structures,[4] polymers[5] and molecular rods.[6] Molecular rods are relatively rigid, linear and long molecules and they have gained growing interest in chemistry and biochemistry, as well as in materials science.[7] Wessig *et al.* have recently reported the synthesis of molecular rods with oligospiroketal backbones with different solubility-enhancing substituents and studied the use of these rods as hydrophobic membrane anchors.[6]

Our interest in bile acid chemistry led us to undertake a program towards novel conjugates of bile acids with ketal-functionality. Bile acids are endogenous steroids which form as end products of cholesterol metabolism in the liver. They are natural substrates of enterohepatic circulation, and their main role is the digestion of lipids and lipid-soluble vitamins.[8] Bile acids, their salts and their derivatives are found to have numerous applications in biology, medicine and physiology,[9] as well as in supramolecular chemistry and nanoscience.[10] Because of the unique facial amphiphilicity of the bile acids, we anticipated that this may lead to molecules with material properties like liquid crystals, organogels *etc*.

Herein, we report the synthesis of several novel bile acid-derived mono- and diketals and give detailed information of their structures in solution and in solid state, and further describe the preliminary studies of their self-assembling properties. Bile acid ketals do not exist widely in the literature and only a few reports were found.[11] Here, we have chosen three different methyl-3-oxy-cholanoate derivatives (**3a–c**) as enantiopure ketones in the preparation of the ketals. Three monoketals (**5a–c**) were prepared with pentaerythritol forming a conformationally flexible dioxane structure with two free hydroxymethyl extensions. Further, in order to decrease the flexibility of the 1,3-dioxane ring, cathechol and naphthol were introduced as the ketal-forming alcohols in **7a**,**c** and **8a**,**c**. Finally, three diketals (**10a–c**) with pentaerythritol (PE) were prepared and the influence of the bile acid substituent to the flexibility of the dioxane rings and the conformational preferences of these molecules in solution and in solid state were studied.

The monoketals **5a–c** were studied for their organogelling properties and **5a** proved to form gels in many aromatic solvents at 0.5–2% w/v concentrations. Low molecular mass organogelators (LMOGs) represent an active area of research not only for their organogelation properties but also for their numerous applications as new organic soft materials.[12] It is known that these organogelators self-assemble through highly specific noncovalent

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† Electronic supplementary information (ESI) available: Complete experimental part, supplementary and clarifying figures. CCDC reference numbers 766948–766950. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c003228j

interactions, such as hydrogen bonding, resulting in the formation of highly entangled fibrillar networks which encapsulate and immobilize the solvent. However, the gelation phenomena by the LMOGs still remain poorly understood. Bile acid derivatives, including *e.g.* amino acid alkyl ester derivatives,[13] bile acid amidoalcohols,[14] bile acid alkyl derivatives[15] and cationic bile salts[16] have been widely studied as organo- or hydrogelators. Recent reports from our laboratory have concentrated on unravelling the interactions and self-assembling properties in the gel and their comparison to those in the solid state.[17] The gels and the xerogels prepared here were further studied by electron microscopy and NMR spectroscopy.

The synthetic procedure for the preparation of diketals with PE produced a mixture of two isomers (**I** and **II**). In the case of methyl lithocholate derivative **10a**, the isomer **I** was isolated from the mixture and crystallized, thus enabling more detailed study of their structures. The molecular structure of **10aI** in crystalline state was determined by single crystal X-ray diffraction. Furthermore, whereas the naphthalenediol-derived ketals **9a** and **9c** formed film-type materials in the studied solvents, the catechol-derived ketals **7a** and **7c** were crystallized as single crystals, and their molecular structure and crystal packing were studied.

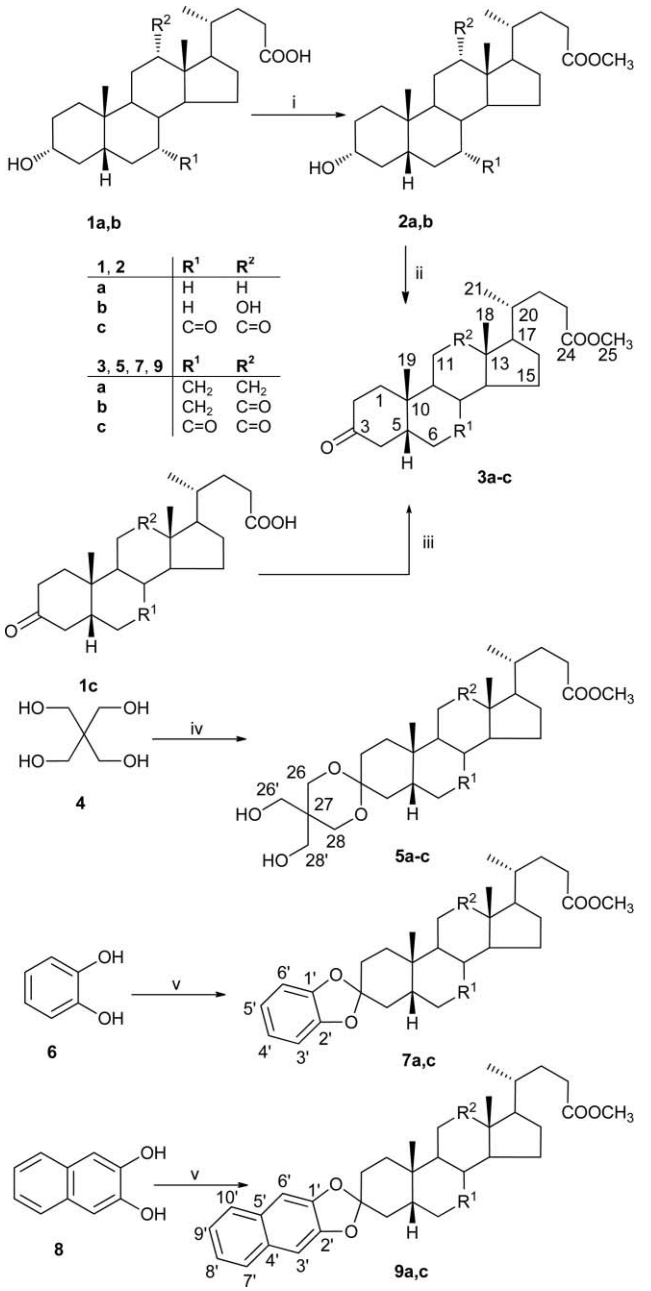
Dimeric bile acid derivatives have found applications in the fields of pharmaceutical and supramolecular chemistry.[18] Furthermore, the diketals prepared here might mimic the before mentioned oligospiroketals[6] and, in addition, introduce amphiphilicity and chirality into the structure. Bile acids are substrates for transporter proteins in the liver and the intestines, and they can thus be exploited in drug delivery and targeting.[19] On the other hand, acetals are promising candidates for the development of acid-sensitive linkages for hydroxyl groups.[20] Thus, the preparation of bile acid ketals may lead to novel prodrugs tailored for enhanced oral bioavailability or liver targeting of drugs; dihydroxy-containing drugs can be conjugated directly to bile acids using ketal linkage, or alternatively, pentaerythritol may be utilized as a spacer linking a ketone-drug to bile acid. Many drugs (such as catechins and catecholamines dopamine and epinephrine) are derivatives of catechol, and thus the catechol ketals prepared here are particularly interesting.

Results and discussion

Synthesis of bile acid-derived mono- and diketals of catechol, 2,3-naphthalenediol, and pentaerythritol

The synthetic route to the monoketals is presented in Scheme 1. Preparation of the ketals started by synthesis of methyl esters of the bile acids **1a** and **1b** using esterification methods described in the literature,[21] resulting in **2a** and **2b**. The next step was the oxidation of the hydroxyl group/groups in the steroidal part, and it was carried out by methods described in literature[22] to give **3a** and **3b**. In the case of **1c**, esterification was carried out by its reaction with *ca.* six-fold excess of methyl iodide using Cs_2CO_3 as a base at room temperature for 24 h. Pure product was gained by precipitation from water.

At first, the monoketals of PE (**4**) and three different bile acid methyl esters (**3a–c**) have been prepared. PE monoketals have a flexible 1,3-dioxane ring with two free hydroxymethyl substituents. The reactions were carried out in refluxing DMF–toluene (3 : 2 v/v) with *p*-toluene sulfonic acid (*p*-TSA) as a catalyst and using a Dean–Stark apparatus in order to remove the water from the reaction mixture by azeotropic distillation with toluene. In the reaction of **3a** with pentaerythritol, 1 : 2 ratio was used. In order to find out if only the keto-group at position 3 is reactive towards the ketalization in these conditions, four- and six-fold excess of pentaerythritol was used in the case of ketones **3b** and **3c**, respectively. It was discovered that the reaction took place selectively at position 3 while the other keto-groups remained intact. Yields of **3a–c** varied between 48 and 81% after purification.



Scheme 1 (i) MeOH, AcCl, reflux, 18 h or MeOH, HCl, 0–55 °C, 45 min; (ii) acetone, Jones reagent, 0 °C, 10 min or AcOH, $Na_2Cr_2O_7{\cdot}2H_2O/H_2SO_4$, rt, 24 h; (iii) MeI, Cs_2CO_3, DMF, rt, 24 h; (iv) *p*-TSA, DMF–toluene (3 : 2), reflux, 44 h; (v) Montmorillonite, toluene, reflux, 24 h.

Next, the idea was to decrease the flexibility of the dioxane ring and, therefore, vicinal aromatic diols were used (instead of PE) in ketal formation. Clay-catalyst in the ketalization reaction was selected since it has been used successfully in the preparation of benzodioxoles before.[23] Ketalization reactions between **3a**,**c** and aromatic diols, catechol (**6**) and 2,3-naphthalenediol (**8**), were carried out by refluxing equimolar amounts of ketone with diol using montmorrilonite as a catalyst in toluene with a Dean Stark–trap for 24 h. Yields of **7a**,**c** and **9a**,**c** varied between 48 and 74% after purification.

During the previous synthesis of PE-monoketals, the formation of diketals as side products was already observed. In optimizing the synthesis of diketals, it was found out that the use of ketone : PE ratio 5 : 3 minimized the formation of side products, and the main side product, namely monoketal, was easily removed by column chromatography or by washing the product carefully with EtOAc. Otherwise, reaction arrangements followed those for the preparation of monoketals **5a–c**. The synthesized diketals are presented in Scheme 2. The synthetic procedure always produces a mixture of two diastereomers, **I** and **II**, which cannot be interconverted to each other without breaking a bond (*i.e.* by conformational change in the 1,3-dioxane moieties). This was recognized by an appearance of two signals in the ^{13}C spectra for spiro-carbons C(3,3′) and C(27) as well as in some carbons of the steroidal skeleton. Yields of **10a** (mixture of two isomers), **10b** (mixture of two isomers) and **10c** (mixture of two isomers) were 66, 29 and 48%, respectively. A small amount of isomer **10a(I)** was isolated from the mixture of **10a(I)** and **10a(II)** based on its low solubility in ethylacetate, where the isomer **10a(II)** was soluble.

NMR spectroscopy

Bile acid-derived monoketals of PE have a flexible 1,3-dioxane ring to which two hydroxymethyl moieties are attached. ^1H NMR spectra of these compounds show different chemical shift values for all the protons of the 1,3-dioxane ring resulting from their diastereotopicity caused by the chiral bile acid backbone. Because the change in conformation is fast in the NMR time scale, the chemical shifts for different conformers are averaged. As a result, in the ^1H NMR spectrum of the monoketals **6a–c** there should be two AB-quartets in the subspectra of the 1,3-dioxane moiety resulting from the axial and equatorial protons 26-CH_2 and 28-CH_2, and two singlets for 26′-CH_2 and 28′-CH_2. The spectral resolution of the AB-quartets and singlets was highly dependent on the solvent used. For example, when **6b** was measured in CD_3OD (see the ESI† Fig. S1 for a copy of the spectrum), the AB-quartets and singlets were nicely resolved, thus emphasizing the significance of the solvent effects.

In the case of diketals **10**, unambiguous assignment of NMR chemical shifts for protons and carbons in the dioxane ring system is more complex. Grosu *et al.*[2] have studied the stereoisomerism of some trispiro-1,3-dioxanes obtained from substituted cyclohexanones and pentaerythritol, and their results have been the basis for the analysis of the diketal structures reported here. The isolation of the pure isomer **10a(I)** and the enrichment of the other isomer (**10a(II)**) enabled differentiation of the resonance lines originating from the different isomers. Based on the analysis of the ^1H and ^{13}C NMR spectra (Fig. 1) of the two isomers, we have concluded that both of the structures contain flexible dioxane rings and, as a result, four possible conformational isomers. Two of these conformers are C2-symmetric while the two others are unsymmetric. As in the case of monoketals, the conformational change is fast in the NMR time scale and only averaged chemical shifts are seen for different conformers. As a result, the carbons C(26) and C(26′) give one resonance, as do the carbons C(28) and C(28′), and because of the chiral bile acid substituent, carbons C(26) and C(28) as well as C(26′) and C(28′) remain magnetically different. Consequently, the protons in the dioxane ring system give two AB-quartets, which are overlapping in the spectrum measured in $CDCl_3$ in the case of the isomer **I**, while in the spectrum of isomer **II** they are well separated (see ESI† Fig. S2 and S3 for the spectra).

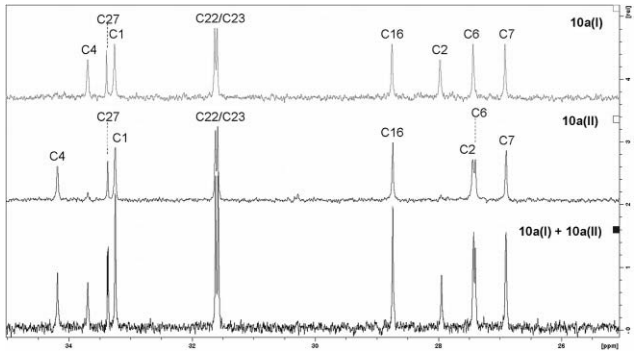


Fig. 1 Partial ^{13}C NMR spectra of **10a** in CD_2Cl_2 at 303 K showing the differences between the isomers **I** and **II**.

Table 1 Gelation studies with **5a–c**

Solvent	5a	5b	5c
Benzene	s, G (2%)	s, p (2%)	s, p (2%)
Toluene	s, G (2%)	s, pg (2%)	s, p (2%)
p-Xylene	s, G (1%)	s, pg (2%)	s, p (2%)
m-Xylene	s, G (1%)	s, pg (2%)	s, p (2%)
o-Xylene	s, G (2%)	s, p (2%)	s, p (2%)
Mesitylene	s, G (1%)	s, pg (2%)	s, p (2%)
Cumene	s, G (2%), g (1%)	s, pg (2%)	s, p (2%)
Ethylbenzene	s, G (2%), g (1%)	s, pg (2%)	s, p (2%)
t-Butylbenzene	s, G (0.5%)	s, pg (2%)	s, p (2%)
Chlorobenzene	s, p (2%)	s, p (2%)	s, p (2%)
Anisole	S, gf (2%)	S	S

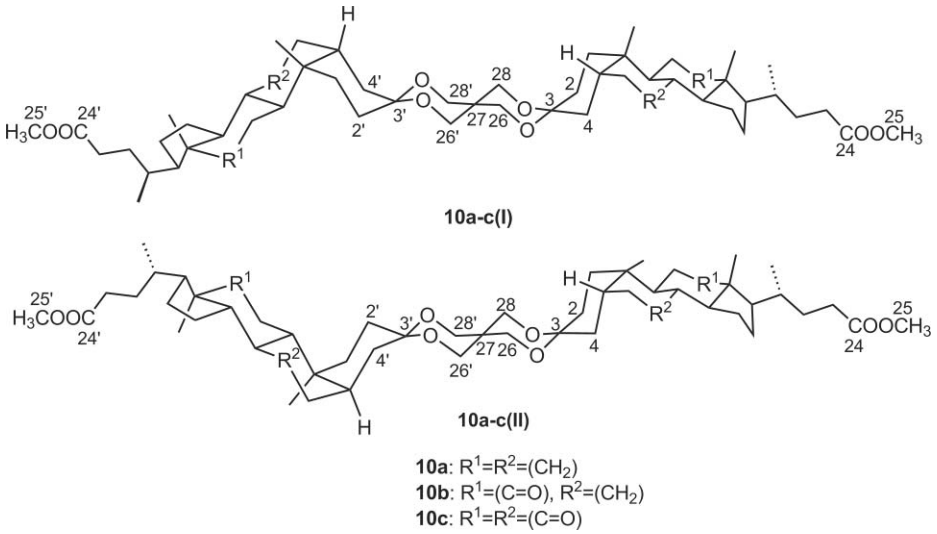
S = soluble at room temperature, s = soluble at boiling point, G = transparent gel at rt, g = opaque gel at rt, gf = gel at refrigerator temperature, pg = partly forms gel, p = precipitates, concentrations (% w/v) are given in parenthesis.

Self-assembly of bile acid ketals leading to organogelation

After successful synthesis and characterization, attempts were made towards the crystallization of the ketals from a variety of solvents. During the course of our investigation it was found that PE monoketals **5a–c** were able to immobilize a variety of aromatic solvents, leading to organogelation. Table 1 presents the results from the gelation tests.

Compound **5a** was found to form a transparent gel at room temperature with benzene, toluene, *o*-xylene, cumene, ethylbenzene and chlorobenzene in concentrations of 2% w/v,‡ and with

‡ All the concentrations given as % refer to % w/v (gelator/solvent).



Scheme 2 Prepared diketals.

p-xylene, *m*-xylene and mesitylene in concentrations of 1%. With cumene and ethylbenzene it formed a gel also in concentration of 1%, but the gel was already opaque indicating not so strong ability to gel these solvents. In the case of *t*-butylbenzene, the transparent gel was formed in 0.5% concentration. **5a** is soluble in anisole at room temperature; however, when the 2% solution of **5a** in anisole was cooled in a refrigerator, a transparent gel was formed. In the case of compounds **5b** and **5c**, the solubility to tested aromatic solvents was lower. **5b** formed an opaque gel-like material in concentrations of 2% with most of the tested solvents, but soon after gel-formation, the compound started to precipitate producing partly gelatinous and partly solid material. Compound **5c** was not able to form gels with any of the tested solvents in the concentration of 2% or below.

Maitra *et al.*[24] have prepared an ester from deoxycholic acid and PE, and studied its gelation ability; however, this ester did not show any tendency to gel the investigated solvents. On the other hand, the amide from deoxycholic acid and 2-amino-2-hydroxymethyl-1,3-propanediol formed stable, transparent, thermoreversible hydrogels in the presence of varying amounts of solvents such as MeOH, EtOH, DMSO, and DMF.[24] It is often deduced that the gel-formation by bile acid derivatives is due to the amide-functionality in the side chain.[14] However, a recent report,[25] together with the results presented here, show that stable gels may also be formed by another type of derivative, and even when the functionality is not in the side chain but conjugated to the steroidal part.

In order to have some insight into the morphology of the gels, the xerogels obtained from the toluene, *p*-xylene or *t*-butylbenzene gels of **5a** and from the toluene gel of **5b** were studied by scanning electron microscopy (SEM). Repeatable spherical fine structures were observed in the case of xerogels obtained from the gels derived from **5a** and **5b** with different solvents (see Fig. 2 and 3, see ESI† Fig. S4 for additional SEM images). Further, the spheres are quite uniform and have somewhat fibrous substructures, as may be seen in Fig. 3, representing the xerogel obtained from the *t*-butylbenzene gel of **5a**.

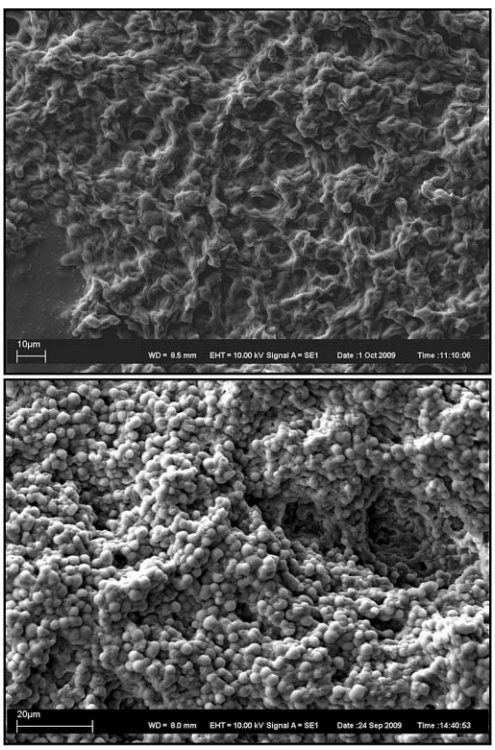


Fig. 2 SEM images of xerogels obtained from the gels of **5a** in toluene (2% w/v) (above) and **5b** in toluene (2% w/v) (below).

In order to study the formation and the thermoreversibility of the gels, ^{1}H NMR spectra were measured from the 3% toluene-d_8 gel of **5a** at variable temperatures. Fig. 4 shows the ^{1}H NMR spectra of the gel when it is heated up (Fig. 4a) and when the melted gel (sol) is cooled down (Fig. 4b). First, the gel was let to settle down over night, after which the spectra were measured. At 30 °C a significant line broadening of the proton signals was observed to the extent that they almost disappeared. With gradual increase in the temperature, recovery of the resonance lines was observed, indicating disruption of the self-organization

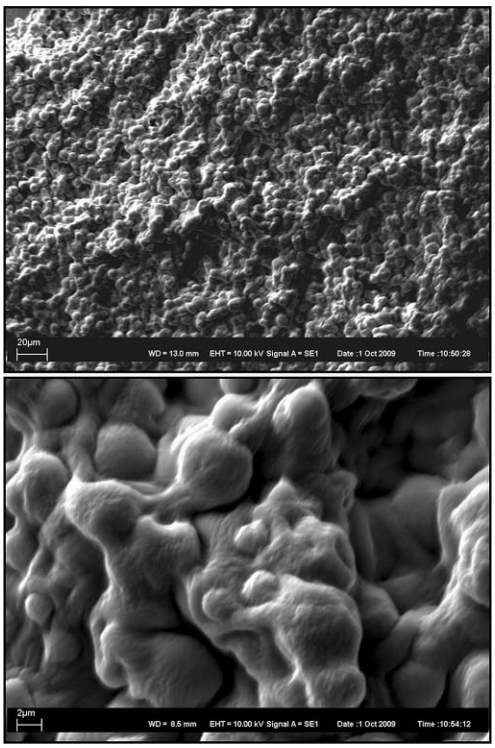


Fig. 3 SEM images of xerogel obtained from the gel of **5a** and *t*-butylbenzene (2% w/v).

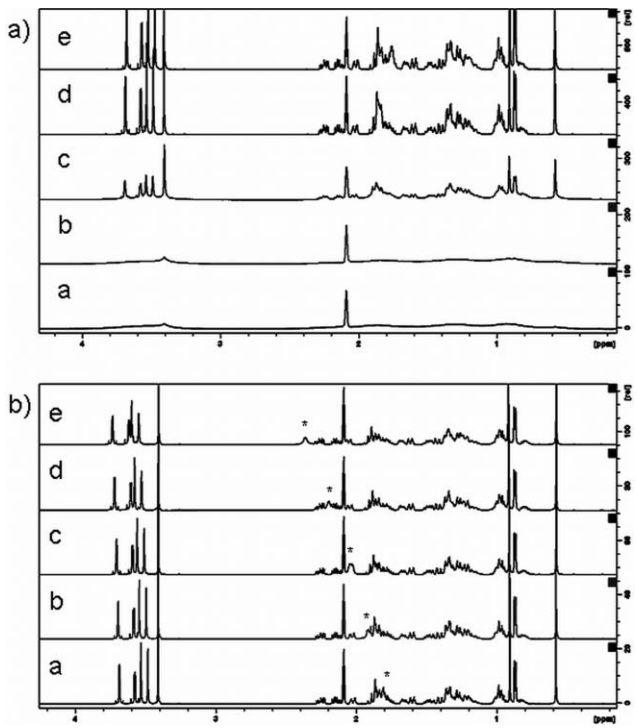


Fig. 4 (A) Heating up the gel of **5a** in toluene-d_8, ^{1}H NMR spectra at (a) 303 K, (b) 308 K, (c) 313 K, (d) 318 K, (e) 323 K and (B) cooling down the melted gel of **5a** in toluene-d_8, ^{1}H NMR spectra at (a) 323 K, (b) 318 K, (c) 313 K after 10 min, (d) 308 K, and (e) 303 K.

due to thermal motion of the moieties. The resonance lines started to become more visible at 40 °C, and at 45 °C there was a considerable sharpening of all the resonance lines upon complete gel melting. Following melting, the solution was again let to cool down gradually, and before each measurement the temperature was allowed to stabilize for 5 min and the ^{1}H NMR spectra were recorded. Upon cooling down the sample, there was a significant change in the chemical shifts originating from the protons in terminal hydroxyl groups of the PE-part of **5a** (marked with an asterisk in Fig. 4b). A small change in the chemical shift of the protons originating from the CH_2-protons in the the PE-part can also be observed.

Interestingly, upon aging the sample (see Fig. 5) there are again changes in the appearance of the spectra, but now they are independent of the temperature and, thus, probably reflect the changes in the structure when the gel starts to form. First of all, the resonance peak of the hydroxyl protons gets broader and becomes a bit more shielded. Another change is observed at the resonances originating from the CH_2-protons of the PE-part. While their peaks start to broaden, two forms appear (see Fig. 5 and ESI† Fig. S5) with different chemical shifts. The growing form has its resonances more shielded. Finally, everything is in one form. This is proposed to reflect the formation of hydrogen bonds which eventually lead to gel formation, and finally to disappearance of the resonances.

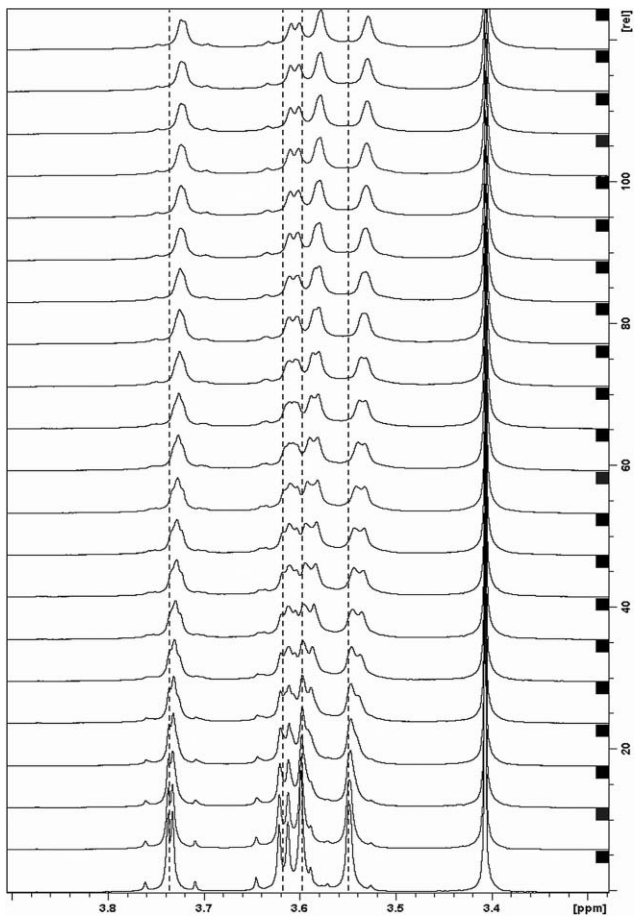


Fig. 5 ^{1}H NMR subspectra of **5a** in toluene-d_8 at 30 °C after aging for 0–60 min (sample measured every 3 min).

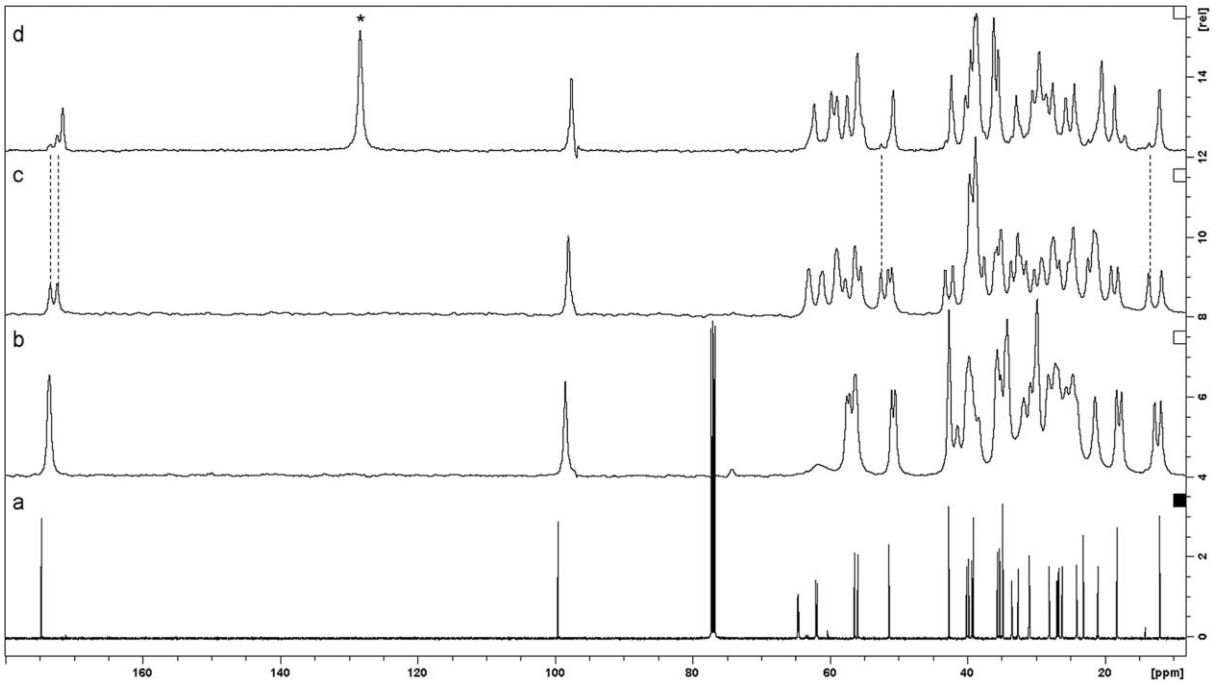


Fig. 6 ^{13}C NMR spectrum of **5a** in $CDCl_3$ (a) and ^{13}C CP/MAS NMR spectra of **5a** crystallized from acetonitrile (b), toluene (c), and benzene (d).

Studies in the solid state

Despite several attempts, we were not able to obtain single crystals from **5a–c** suitable for structure determination by single crystal X-ray diffraction. In the case of **5a**, the solids obtained by crystallization from various solvents (benzene, toluene, *p*-xylene, chlorobenzene, acetonitrile and acetone) were, however, highly crystalline, thus enabling its study in the solid state by CP/MAS NMR spectroscopy. In Fig. 6, the selected spectra are presented with comparison to the spectrum measured in liquid state (see ESI† Fig. S6 for more spectra). In the case of **5a** crystallized from toluene, *p*-xylene, and chlorobenzene, the spectra possess a doublet resonance pattern for most of the carbons, indicating the crystal structure of **5a** to have two crystallographically independent molecules per asymmetric unit.

In the case of solid crystallized from benzene, two different forms were observed, from which the minor one seems to be the same as the ones crystallized from other aromatic solvents and the major form seems to be a benzene solvate. Interestingly, when the same compound was crystallized from either acetonitrile or acetone (in which it is freely soluble and thus does not form gel), different spectra were obtained. In these spectra the doublet resonance was only observed in some of the carbons and not, for example, in the carbonyl carbon. Also, the signals originating from the carbons in the pentaerythritol part were not resolved, potentially resulting from severe disorder in that part of the molecule. Interestingly, in all of the spectra of **5a** crystallized from gel-forming solvents, the region from 50 to 64 ppm includes seven resonances (some of which are split to two) originating from the carbons C(25), C(14), C(17) and the four carbons in the pentaerythritol part. This reflects a highly ordered packing system in the solids obtained from the gelling solvents. However, in order to reveal whether this observation also reflects the same kind of high order in the packing in the gel-state, more experiments are needed.

Single crystals of catechol ketals **7a** and **7c** were obtained from ethyl acetate–hexane.§ Compound **7a** crystallizes in triclinic space group *P*1 with two crystallographically independent molecules in the asymmetric unit. The molecular structure of molecule A in the crystals of **7a** is illustrated in Fig. 7. The two molecules differ by the conformation of their side chains. Conformation of the bile acid side chain can be described using the value of the C17-C20-C22-C23 dihedral angle, or more comprehensively by examining all of the dihedral angles in the side chain using letters *t* (*trans*), *g* (*gauche*) or i (intermediate) for the combination of the four conformations, the first four in Table 2. Comparison of the two molecules in the asymmetric unit of **7a** reveals that they differ slightly by their side chain conformations, indicated by the dihedral angles. C17-C20-C22-C23 in B is 11.7° smaller and C22-C23-C24-O25 in B is 13.6° larger than the respective angles in the molecule A. Additionally, there are differences in the interactions between the molecules A and between the molecules B.

§ **Crystal data for 7a**. $C_{31}H_{44}O_4$, $M = 480.66$, triclinic, $a = 7.5708(2)$, $b = 11.1245(3)$, $c = 16.1074(5)$ Å, $\alpha = 80.080(2)$, $\beta = 85.635(2)$, $\gamma = 88.002(2)°$, $T = 123$ K, space group *P*1 (no. 1), $Z = 2$, $Z' = 2$, 10657 reflections measured, 6565 unique ($R_{int} = 0.055$) which were used in all calculations. The final R_1 and wR_2 were 0.073 and 0.134, respectively. **Crystal data for 7c**. $C_{31}H_{40}O_6$, $M = 508.63$, triclinic, $a = 7.5916(1)$, $b = 11.4074(2)$, $c = 16.0654(3)$ Å, $\alpha = 97.471(1)$, $\beta = 102.069(1)$, $\gamma = 95.081(1)°$, $T = 123$ K, space group *P*1 (no. 1), $Z = 2$, $Z' = 2$, 10685 reflections measured, 6588 unique ($R_{int} = 0.024$) which were used in all calculations. The final R_1 and wR_2 were 0.044 and 0.095, respectively. **Crystal data for 10a(I)**. $C_{55}H_{88}O_8$, $M = 877.25$, monoclinic, $a = 29.4843(5)$, $b = 6.4390(10)$, $c = 12.7626(2)$ Å, $\beta = 97.7664(9)°$, $T = 123$ K, space group *C*2 (no. 5), $Z = 2$, 9619 reflections measured, 3234 unique ($R_{int} = 0.035$) which were used in all calculations. The final R_1 and wR_2 were 0.046 and 0.108, respectively.

Table 2 Selected torsion angles (°) in the molecules **7a**, **7c**, and **10a(I)**

	7a(A)	**7a** (B)	**7c**(A)	**7c** (B)	**10a(I)**
C13-C17-C20-C22	176.8(4)	175.0(4)	173.4(2)	-56.5(3)	-178.5(2)
C17-C20-C22-C23	-176.8(4)	165.1(4)	-165.9(2)	-160.5(2)	-156.0(2)
C20-C22-C23-C24	174.8(4)	172.6(4)	-170.5(2)	-179.5(3)/ -157.5(6)	74.9(3)
C22-C23-C24-O25	-146.6(4)	-160.2(4)	-165.8(2)	39.7(5)/ 24.9(19)	11.1(4)
C23-C24-O24-C25	-175.9(4)	-176.5(5)	-178.5(3)	178.7(3)/ -176.9(11)	180(3)
C1′-O1′-C3-O2′	15.95	16.50	-3.02	-19.40	—
C2′-O2′-C3-O1′	-16.47	-15.84	3.72	19.00	—

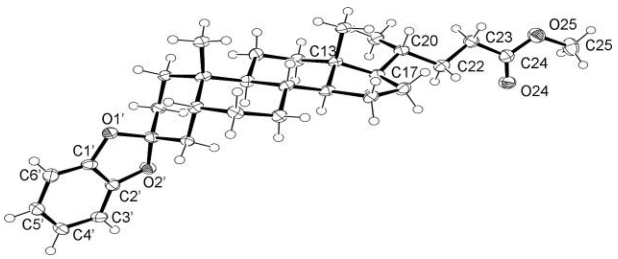


Fig. 7 Ortep drawing of **7a** showing ellipsoids with 50% probability.

There is a weak non-conventional intermolecular hydrogen bond between a proton attached to the aromatic ring of one molecule B and the carbonyl oxygen of another molecule B with 3.283 Å donor-to-acceptor distance and 166.20° bond angle (See ESI† Fig. S7 for the packing diagram of **7a**). On the contrary, molecules A do not form any intermolecular hydrogen bonds between each other. The methyl-carbon from the ester group in the side chain of molecule A lies above the plane of the phenyl ring of molecule B and, thus, there are probably weak CH–π hydrogen bonding interactions between the CH(sp^3) and the phenyl ring. The distance of the proton to the centroid of the phenyl ring is 2.795 Å and the hydrogen bonding angle is 152.08°. No interaction between the aromatic rings is observed.

Compound **7c** crystallizes in triclinic space group *P*1 with two crystallographically independent molecules in the asymmetric unit as well (see ESI† Fig. S8 for the molecular structure of **7c**). Again, the differences between the two independent molecules are found in the conformation of the side chain. Whereas the conformation of the side chain of molecule A verges on perfect zigzag (all-*trans*, *tttt*), the side chain in the molecule B is disordered between two conformations where two of the angles are in *gauche*- and two are in *trans*-conformation. The two molecules differ from each other also by the orientation of the ketal-part. While in molecule B the deviation of C3 from the plane of the aromatic ketal ring system is 0.274 Å, in molecule A it is 0.037 Å, making it almost flat while the other one is slightly distorted.

The packing in the crystals of **7c** is illustrated in Fig. 8. Interestingly, in its crystal, **7c** forms chiral entities in which all of the molecules are parallel oriented (see Fig. 6). The two independent molecules A and B are inclined to each other by 26.4°. This kind of packing, where all the bile acid backbones are oriented in (almost) parallel fashion, and with their α- and β-faces together, is very unusual for bile acid derivatives which usually form bilayered structures where the hydrophobic parts unite and hydrophilic parts are brought together. In fact, of the 532 bile acid-derived structures in the CSD-database,[26] only one structure was found to pack in quite a similar way.[27] It should be noted that certain cyclocholates have been reported to display unusual packing patterns (not bilayers) in their solid state, resulting from the intrinsic structure of the molecules.[28] Like in the case of **7a**, in the crystals of **7c** the methyl carbon of the ester group of one molecule B lies above the plane of the phenyl ring of another molecule of B. The distance between the CH(sp^3)-proton and the centroid of the phenyl ring is 2.688 Å, and the angle between the ring plane and the methyl carbon is 119.99° and, thus, there may be weak CH–π hydrogen bonding interaction between them. Centroid-to-centroid distance between the aromatic rings is 4.510 Å and the angle between the plane of the aromatic rings is 25.92°.

Attempts to crystallize the naphthalenediol ketals (**9a** and **9c**) using different solvent systems resulted in thin film-type materials. A thin film of compound **9a** in $CHCl_3$ was placed over a glass slide and observed under polarizing optical microscope. The compound turned isotropic at 210 °C. Upon cooling to 90 °C, birefringent textures were observed (for photographs see ESI† Fig. S9), but no liquid crystalline phases were observed.

Single crystals of **10a(I)** were obtained from CH_2Cl_2.§ Compound **10a(I)** crystallizes in monoclinic space group C2 and, as pointed out earlier, this molecule has rotational symmetry over the spirocarbon C27 and, thus, only half of the molecule is present in an asymmetric unit of its crystal. The molecular structure of **10a(I)** is illustrated in Fig. 9. Both of the 1,3-dioxane rings are in chair conformation, as can be expected. The bile acid side chain is in *ttgg*-conformation. The molecule is quite linear and its length is approximately 3.3 nm, thus it resembles a molecular rod. The linearity of this kind of steroidal molecular rod could be enhanced by using, for example, allobile acid (with *trans*-fusion of the A and B rings) or cholesterol as the steroidal part, since the ring junction

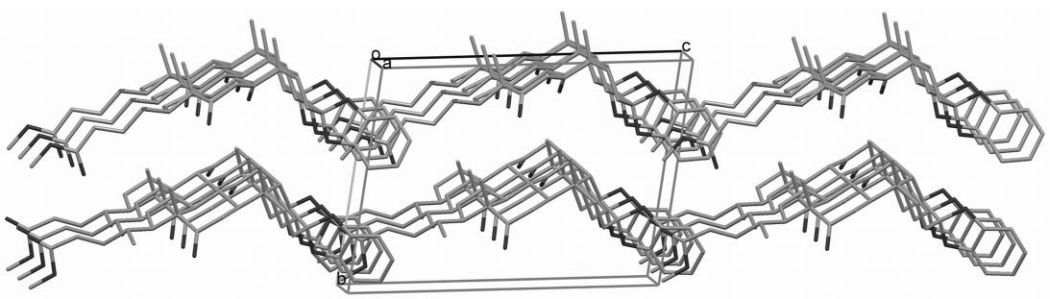


Fig. 8 Packing in the crystal of **7c**. The disorder in the side chain and the hydrogen atoms are omitted for clarity.

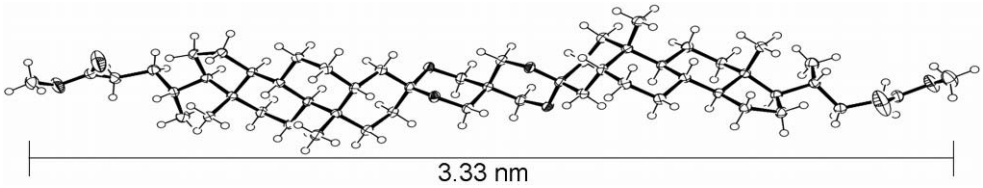


Fig. 9 Ortep drawing of **10a(I)** showing the ellipsoids with 50% probability. Only half of the molecule is found in an asymmetric unit.

between the A and B rings of these are *cis* instead of *trans*, as in bile acids. The crystal packing of **10a(I)** is driven by the close-packing forces.

Experimental

Typical experimental procedures and representative examples of characterization of compounds are given below. Complete detailed experimental part including full characterization data for all compounds is in the ESI.†

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 spectra were 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 were referenced to the solvent signals ($\delta = 7.26$ ($CDCl_3$) and $\delta =$ 2.09 (toluene-d_8) for ^{1}H and $\delta = 77.0$ ppm for ^{13}C from int. TMS). Molecular masses of the compounds were confirmed either by using a 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-analyser.

^{13}C CP/MAS NMR

For 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. 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 transients 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 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-Kα radiation. COLLECT[29] data collection software was utilized and data was processed with DENZO-SMN.[30] The reflections were corrected for Lorenz polarization effects but absorption correction was not used. The structures were solved by direct methods (SIR2002[31]) and refined anisotropically (SHELXL-97[32]) 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[33] and Mercury.[34] CCDC 766948–766950 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Gelation tests

For each experiment, a weighed amount of compound (**5a–c**) was placed in a 5 mL test tube and the tested solvent was added. The mixture was heated to reflux 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. The state of the sample was defined as a gel when it was stable to inversion. When the gel formation or precipitation did not occur at room temperature, the sample was allowed to cool down to ~6 °C in a refrigerator 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 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.[21] Methyl 3,7,12-trioxo-5β-cholan-24-oate (**3c**)[35] was prepared from **1c** by esterification reaction described in the literature for other bile acid esters.[15b]

Methyl-3-oxo-5β-cholan-24-oate (3a)[22]

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 × 80 mL). The crude product was dissolved in dichloromethane (200 mL) and washed with water (3 × 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 a colorless solid.

Method B. A solution of **2a** (7.86 g, 20.0 mmol) in 200 mL of acetone was cooled on an 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. The oxidizing reagent was added until the orange color was persistent in the mixture. Stirring of the mixture was continued for another 10 min on ice, after which the reaction was ceased by addition of a 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. The 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 a 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*-toluenesulfonic acid (0.18 g, 5% w/w of ketone) were added to 60 mL DMF–toluene (3 : 2 v/v). The 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). The reaction mixture was refluxed for 44 h. Precipitated crude product obtained by addition of ice-water was filtered and dissolved in 200 mL of ethyl acetate. The 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 a colorless solid. δ_H (500.13 MHz; $CDCl_3$): 0.62 (3H, s, 18-CH_3), 0.88 (3H, d, 6.4 Hz, 21-CH_3), 0.91 (3H, s, 19-CH_3), 2.36-0.62 (m, 23-CH_2, steroidal-CH_2 and -CH), 2.97 (2H, br. s, 26′-CH_2OH, 28′-CH_2OH), 3.64 (3H,s, 25-CH_3), 3.72-3.65 (8H, 4 × s, 26-CH_2, 28-CH_2, 26′-CH_2, 28′-CH_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 benzene-1,2-diol ketal of methyl-3-oxo-5β-cholan-24-oate (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** (1.77 g, 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-CH_3), 0.92 (3H, d, J = 6.5 Hz, 21-CH_3), 1.01 (3H, s, 19-CH_3), 2.40-1.00 (m, 23-CH_2, steroidal -CH_2 and -CH), 3.66 (3H, s, 25-CH_3), 6.77-6.71 (4H, m, 3′-CH, 4′-CH, 5′-CH, 6′-CH); 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, 1072, 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 naphthalene-2,3-diol ketal of 3,7,12-trioxo-5β-cholan-24-oate (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 -CH), 7.01 (2H, br. t, 3′-CH, 6′-CH), 7.30-7.27 (2H, m, 8′-CH, 9′-CH), 7.63-7.60 (2H, m, 7′-CH, 10′-CH); 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). The 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). The reaction mixture was refluxed for 64 h. Precipitated crude product obtained by addition of ice-water was filtered and dissolved in 50 mL of EtOAc–DCM (1 : 2). The 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 a 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 -CH), 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 -CH), 3.66 (6H, s, 25-CH_3), 3.82-3.62 (8H, $2 \times q_{AB}$, 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; $C_{30}H_{46}O_8 \cdot \frac{1}{2}H_2O$ requires C 74.53, H 10.12%.

Conclusions

Novel bile acid-derived monoketals with 1,2-benzenediol (catechol) and 2,3-naphthalenediol as well as mono- and diketals with pentaerythritol have been prepared and characterized. Monoketals of pentaerythritol showed a tendency to form thermoreversible gels in many aromatic solvents and the methyl lithocholate derivative proved to be a supergelator able to form a gel in *t*-butylbenzene at a concentration of 0.5% w/v. While most of the bile acid-derived organogelators have the amide functionality in their side chain, the type of organogelators presented here are rare. It is thus interesting to further study the interactions and the nucleation process required for the formation of the gel by these and other similar LMOGs. Because of the biocompatibility of the bile acid moiety, the gels derived from their derivatives may find applications in the fields of supramolecular biochemistry or biomedicinal chemistry. Furthermore, these monoketals may serve as model compounds for a wide variety of similar bile acid derivatives with organogelling fuctionality. Whereas the naphthalenediol ketal **9a** formed film-type materials in the studied solvents, the catechol ketals underwent rapid crystallization to X-ray quality single crystals and their crystal structures were determined. Interestingly, very small changes in the steroidal part induced completely different kinds of packing in the crystals of **7a** and **7c**. The monoketal **7c**, obtained from methyl-3,7,12-trioxocholanoate (cholic acid derivative), revealed to have a packing pattern which is very unusual for bile acid derivatives. Formation of diketals of pentaerythritol always produced a mixture of two diastereomers which, in the case of the methyl lithocholate derivative, have been separated and the X-ray crystal structure of one isomer resolved. The bile acid substituent in the dioxane ring seems to not disable the conformational changes in the flexibility of the dioxane rings. In the future it will be interesting to study whether the diketals could be crystallized also in the other conformations and to compare the properties of these crystals. Finally, the bile acid-derived acetals may serve as model structures for preparation of novel prodrugs with the bile acid moiety aimed for enhanced drug uptake or liver targeting.

Acknowledgements

The authors wish to thank Spec. Lab. Tech. Reijo Kauppinen for his help in running the NMR spectra, and Lab. Tech. Elina Hautakangas for elemental analysis. Financial support from the Finnish Ministry of Education, National Graduate School of Organic Chemistry and Chemical Biology (S. Ikonen) and from the Academy of Finland (project no. 121805, Nonappa) is gratefully acknowledged.

Notes and references

1 (*a*) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, Germany, 1995; (*b*) *Molecular Self-Assembly, Structure and Bonding*, ed. M. Fujita, Springer, Berlin, 2000, vol. 96; (*c*) The Crystal as a Supramolecular Entity, *Perspectives in Supramolecular Chemistry*, ed. G. R. Desiraju, Wiley, Chichester, U.K., 1995, vol. 2; (*d*) M. D. Hollingsworth, *Science*, 2002, **295**, 2410–2413.
2 (*a*) I. Grosu, S. Mager and G. Ple, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1351–1357; (*b*) I. Grosu, S. Mager, G. Ple, I. Turos, E. Mesaros and I. Schirger, *Monatsch. Chem.*, 1998, **129**, 59–68; (*c*) A. Mihis, E. Condamine, E. Bogdan, A. Terec, T. Kurtan and I. Grosu, *Molecules*, 2008, **13**, 2848–2858.
3 N. G. Lemcoff and B. Fuchs, *Org. Lett.*, 2002, **4**, 731–734.
4 (*a*) I. Grosu, E. Bogdan, G. Ple, L. Toupet, Y. Ramondenc, E. Condamine, V. Peulon-Agasse and M. Balog, *Eur. J. Org. Chem.*, 2003, 3153–3161; (*b*) M. Balog, I. Grosu, G. Ple, Y. Ramondenc, L. Toupet, E. Condamine, C. Lange, C. Loutelier-Bourhis, V. Peulon-Agasse and E. Bogdan, *Tetrahedron*, 2004, **60**, 4789–4799.
5 (*a*) H. A. Stanbury, and H. R. Guest, *US Patent*, US19570716, 1962.; (*b*) D. B. Capps, *US Patent*, US2889290, 1959; (*c*) E. H. Pryde, R. A. Awl, H. M. Teeter and J. C. Cowan, *J. Org. Chem.*, 1960, **25**, 2260–2261; (*d*) S. M. Cohen and E. Lavin, *J. Appl. Polym. Sci.*, 1962, **6**, 503–507; (*e*) M. S. Cohen, C. F. Hunt, R. E. Kass and A. H. Markhart, *J. Appl. Polym. Sci.*, 1962, **6**, 508–517; (*f*) S. M. Cohen, and E. Lavin, *US Patent*, US19570610, 1962.; (*g*) A. H. Markhart, C. F. Hunt, and E. Lavin, *US Patent*, US19580811, 1962.; (*h*) W. J. Bailey and A. A. Volpe, *J. Polym. Sci., Part A-1*, 1970, **8**, 2109–2122; (*i*) F. V. Zalar, *Macromolecules*, 1972, **5**, 539–541; (*j*) S. Makhseed and N. B. McKeown, *Chem. Commun.*, 1999, 255–256.
6 (*a*) P. Wessig, K. Möllnitz and C. Eiserbeck, *Chem.–Eur. J.*, 2007, **13**, 4859–4872; (*b*) P. Wessig and K. Möllnitz, *J. Org. Chem.*, 2008, **73**, 4452–4457; (*c*) P. Mueller, J. Nikolaus, S. Schiller, A. Herrmann, K. Moellnitz, S. Czapla and P. Wessig, *Angew. Chem., Int. Ed.*, 2009, **48**, 4433–4435.
7 (*a*) P. F. H. Schwab, J. R. Smith and J. Michl, *Chem. Rev.*, 2005, **105**, 1197–1280; (*b*) P. F. H. Schwab, M. D. Levin and J. Michl, *Chem. Rev.*, 1999, **99**, 1863–1934.
8 H. Danielsson, in *The Bile Acids: Chemistry, Physiology and Metabolism*, ed. P. P. Nair and D. Kritchevsky, Plenum Press, New York, 1973, vol. 2, pp. 1-32.
9 (*a*) A. Enhsen, W. Kramer and G. Wess, *Drug Discovery Today*, 1998, **3**, 409–418; (*b*) S. Mukhopadhyay and U. Maitra, *Curr. Sci.*, 2004, **87**, 1666–1683; (*c*) A. F. Hofmann and L. R. Hagey, *Cell. Mol. Life Sci.*, 2008, **65**, 2461–2483.
10 (*a*) J. Tamminen and E. Kolehmainen, *Molecules*, 2001, **6**, 21–46; (*b*) E. Virtanen and E. Kolehmainen, *Eur. J. Org. Chem.*, 2004, 3385–3399; (*c*) A. P. Davis, *Molecules*, 2007, **12**, 2106–2122; (*d*) Nonappa and U. Maitra, *Org. Biomol. Chem.*, 2008, **6**, 657–669.

11 (*a*) E. Bartoli, B. Palmieri, and A. Medici, *European Patent*, EP2003095462, 2003.; (*b*) V. Bertolasi, V. Ferretti, G. Fantin and M. Fogagnolo, *Z. Kristallogr.*, 2008, **223**, 515–523; (*c*) G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini and U. Cova, *Steroids*, 1993, **58**, 524–526.

12 (*a*) P. Terech and R. G. Weiss, *Chem. Rev.*, 1997, **97**, 3133–3159; (*b*) N. M. Sangeetha and U. Maitra, *Chem. Soc. Rev.*, 2005, **34**, 821–836; (*c*) M. George and R. G. Weiss, *Acc. Chem. Res.*, 2006, **39**, 489–497; (*d*) S. Banerjee, R. K. Das and U. Maitra, *J. Mater. Chem.*, 2009, **19**, 6649–6687; (*e*) D. K. Smith, *Chem. Soc. Rev.*, 2009, **38**, 684–694; (*f*) A. R. Hirst, B. Escuder, J. F. Miravet and D. K. Smith, *Angew. Chem., Int. Ed.*, 2008, **47**, 8002–8018.

13 H. M. Willemen, T. Vermonden, A. T. M. Marcelis and E. J. R. Sudholter, *Eur. J. Org. Chem.*, 2001, 2329–2335.

14 A. Valkonen, M. Lahtinen, E. Virtanen, S. Kaikkonen and E. Kolehmainen, *Biosens. Bioelectron.*, 2004, **20**, 1233–1241.

15 (*a*) H. M. Willemen, T. Vermonden, A. T. M. Marcelis and E. J. R. Sudhoelter, *Langmuir*, 2002, **18**, 7102–7106; (*b*) Nonappa and U. Maitra, *Soft Matter*, 2007, **3**, 1428–1433.

16 (*a*) K. Nakano, Y. Hishikawa, K. Sada, M. Miyata and K. Hanabusa, *Chem. Lett.*, 2000, 1170–1171; (*b*) S. Bhat and U. Maitra, *Tetrahedron*, 2007, **63**, 7309–7320.

17 (*a*) V. Noponen, Nonappa, M. Lahtinen, H. Salo, and E. Sievänen, *Soft Matter*, under revision; (*b*) Nonappa, M. Lahtinen, B. Behera, E. Kolehmainen and U. Maitra, *Soft Matter*, 2010, **6**, 1748–1757.

18 For recent examples see: (*a*) L. Ma, M. Melegari, M. Colombini and J. T. Davis, *J. Am. Chem. Soc.*, 2008, **130**, 2938–2939; (*b*) Y. Li, G. Li, X. Wang, W. Li, Z. Su, Y. Zhang and Y. Ju, *Chem.–Eur. J.*, 2009, **15**, 6399–6407; (*c*) J. Koivukorpi and E. Kolehmainen, *J. Mol. Struct.*, 2008, **875**, 63–67; (*d*) N. G. Aher, V. S. Pore and S. P. Patil, *Tetrahedron*, 2007, **63**, 12927–12934.

19 For reviews see: (*a*) E. Sievänen, *Molecules*, 2007, **12**, 1859–1889; (*b*) A. Balakrishnan and J. E. Polli, *Mol. Pharmaceutics*, 2006, **3**, 223–230; (*c*) P. W. Swaan, F. C. Szoka, Jr. and Ø. Svein, *Adv. Drug Delivery Rev.*, 1996, **20**, 59–82.

20 E. R. Gillies, A. P. Goodwin and J. M. J. Fréchet, *Bioconjugate Chem.*, 2004, **15**, 1254–1263.

21 L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 1950, **72**, 5530–5536.

22 G. P. Tochtrop, G. T. DeKoster, D. P. Cistola and D. F. Covey, *J. Org. Chem.*, 2002, **67**, 6764–6771.

23 T. Li, L. Li, B. Lu and F. Yang, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3561–3564.

24 N. M. Sangeetha, R. Balasubramanian, U. Maitra, S. Ghosh and A. R. Raju, *Langmuir*, 2002, **18**, 7154–7157.

25 P. Terech, N. M. Sangeetha and U. Maitra, *J. Phys. Chem. B*, 2006, **110**, 15224–15233.

26 Cambridge Structural Database (CSD) search was performed using the structure of cholic acid excluding the hydroxyl-groups and gave 532 hits as a result including bile acids and their derivatives.

27 U. Rychlewska, B. Warzajtis, R. Joachimiak and Z. Paryzek, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2008, **64**, 383–392.

28 J. R. Dias, R. A. Pascal, Jr., J. Morrill, A. J. Holder, H. Gao and C. Barnes, *J. Am. Chem. Soc.*, 2002, **124**, 4647–4652.

29 *COLLECT*, Bruker AXS Inc., W. I. Madison, 2004.

30 C. W. Carter, Jr. and R. M. Sweet, in *Methods in enzymology. Macromolecular crystallography, Part A*, Academic Press, New York, 1997, vol. 276.

31 M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 2003, **36**, 1103.

32 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.

33 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.

34 C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Crystallogr.*, 2006, **39**, 453–457.

35 A. J. Pearson, Y. S. Chen, G. R. Han, S. Y. Hsu and T. Ray, *J. Chem. Soc., Perkin Trans. 1*, 1985, 267–273.

