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Synthesis and spectroscopic studies of new quasi podands from bile acid derivatives

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ABSTRACT

A new method for the synthesis of esters of bile acid derivatives is described. These new compounds are characterized by spectroscopic and PM5 methods. Estimation of the pharmacotherapeutic potential has been accomplished for the compounds synthesized on the basis of prediction of activity spectra for substances (PASS).

Steroids are a large class of natural compounds, many of which display very important roles in plants and animals. Steroids are not only constituents of the cell membrane in eukaryotes (e.g., cholesterol and ergosterol), but they are also the main sex hormones in mammals (e.g., testosterone and estrogens) and plants (e.g., brassinosteroids). They also play important roles in regulating metabolism (e.g., bile acids and vitamin D).[1] Bile acids (e.g., lithocholic, deoxycholic and cholic) and their derivatives are attractive for synthetic chemists because they have a large, rigid, and curved skeleton. Moreover, they possess chemically different polar hydroxy groups (3α,3α,7α and 3α,7α,12α) and amphiphilic properties. As a result of the unique structural elements, bile acids are very prominent in the study of molecular recognition, host–guest chemistry, and biomimetic chemistry.[2] They play important roles in supramolecular chemistry and as drugs in pharmacology.[2] Bile acids themselves have been used as building blocks for the design and construction of new molecular receptors that are able to recognize guest molecules of diverse chemical nature.[3] Bile acid dimers can be used for the synthesis of macrocyclic compounds as artificial receptors[4] and some derivatives of bile acids are very good organogelators.[5]

On the other hand, classical podands have acyclic structures, in which polyether chains are linked to the same binding center, which can be different atoms, for example, N, P, or S. In view of their specific properties, these simple compounds are so-called open-chain simple analogues of crown ethers and cryptands.[6] Similar to the above compounds, podand hosts are generally able to form stable complexes with monovalent cations.[7] Podands show relatively low cation selectivity during complex formation as well as limited capacity to recognize selectively chiral compounds as a result of their geometry.[7,8] For this reason, semi-synthetic dipodands and tripodands have been obtained from the naturally occurring polyether ionophores, lasalocid acid, monensin A, and 1,6-dibromohexane, or 1,3,5-tris(bromomethyl)benzene.[9] Furthermore, bile acid derivatives based on the structure of 1,3,5-benzenetricarboxylic acid form a hydrophilic cavity and can recognize hydrophilic hosts in organic solvents. These molecules bind nitrophenols, triethanolamine, amino acids, and octyl-glucosides.[10] A large group of anion receptors based on the structure of cholesterol and bile acids belongs to the cholapods.[6] Satyanarayana and Maitra have previously described the synthesis of steroid dendrimers.[11] Oligomers have been obtained from reactions of sodium salts of bile acids with 1,3,5-tris(bromomethyl)benzene in DMF. These oligomers facilitate the transport of molecules of different sizes and structures, and with various functional groups, into nonpolar solvents.[11]

However, to the best of our knowledge, no work has been published on the synthesis or the physicochemical properties of bile esters of 1,3,5-tris(bromomethyl)benzene or 1,2,4,5-tetrakis(bromomethyl)benzene and 3α-acetoxy-5β-cholanic acid, 3α,12α-diacetoxy-5β-cholanic acid, and 3α,7α,12α-triacetoxy-5β-cholanic acid. Connection of acetate groups to bile acids can increase the probability of formation of complex compounds.

This Letter reports the synthesis and physicochemical properties of new esters of bile acid derivatives and 1,3,5-tris(bromomethyl)benzene or 1,2,4,5-tetrakis(bromomethyl)benzene. The

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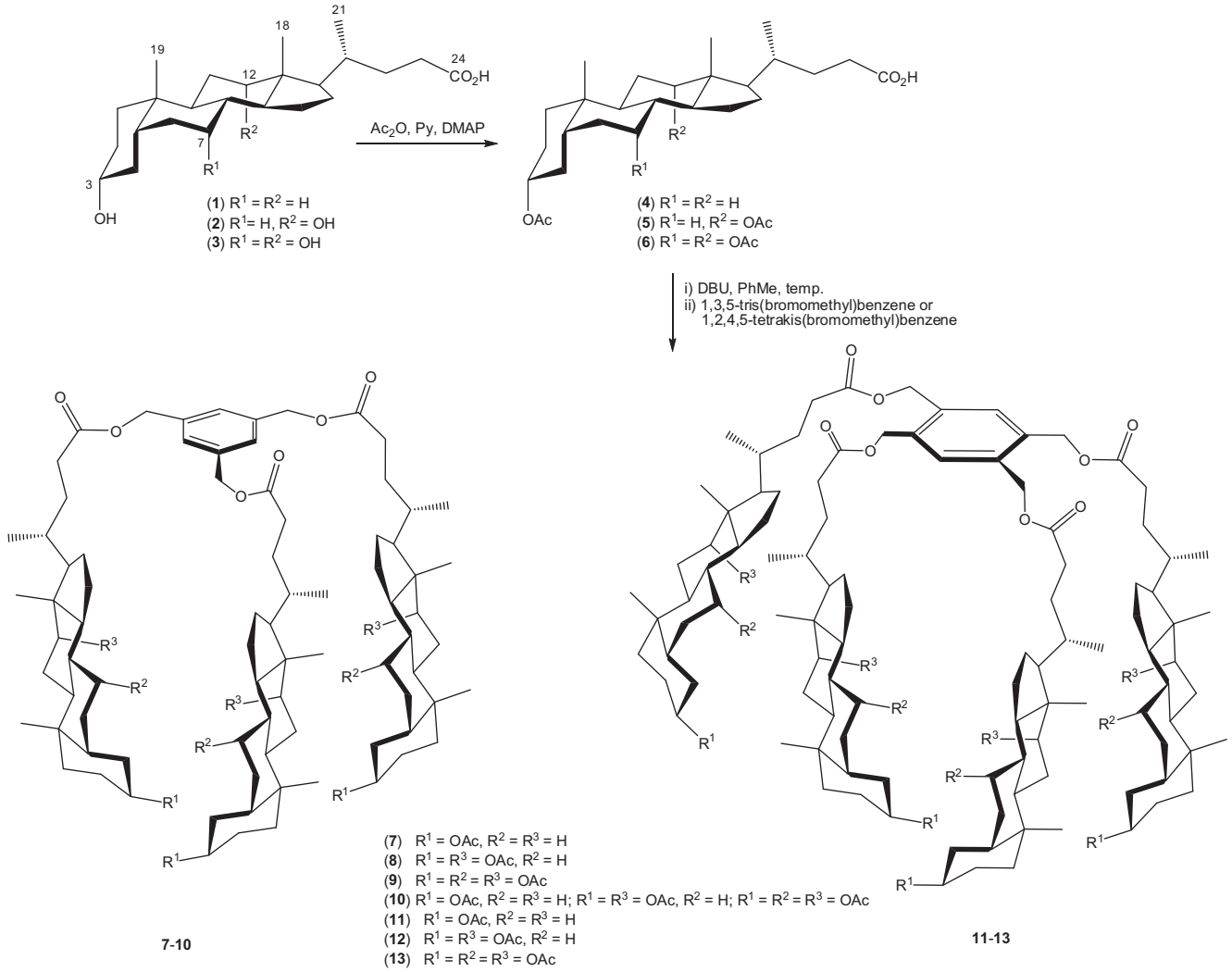
syntheses of compounds **7**–**13** are shown in Scheme 1. We used the direct alkylation reaction of the carboxylate ions of bile acids with 1,3,5-tris(bromomethyl)benzene or 1,2,4,5-tetrakis(bromomethyl)benzene using a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry toluene.[12] DBU is a strong base and a weak nucleophile (nonnucleophilic base), and therefore generates carboxylate ions easily. This esterification method shows, however, a remarkable solvent dependence. The highest yields of the respective esters were obtained in nonpolar solvents such as toluene. This is probably due to the very good solubility of the substrates and products in solvents with low electrical permittivity.

The potential pharmacological activity of the synthesized compounds was investigated using computer-aided drug discovery ap-



Scheme 1. Synthesis of quasi podands of bile acid derivatives **7**–**13**. Reagents and conditions: (**1** or **2** or **3**), anhydrous Py, Ac_2O, catalytic DMAP, 25 °C, 72 h, yields: **4** (87%), **5** (91%), **6** (89%); (**4** or **5** or **6**) (1.0 equiv), DBU (1.3 equiv), 1,3,5-tris(bromomethyl)benzene (0.35 equiv), toluene, 90 °C, 24 h, yields: **7** (56%), **8** (46%), **9** (45%); (mixture of **4** and **5** and **6**) (1.0 equiv), DBU (1.3 equiv), 1,3,5-tris(bromomethyl)benzene (0.35 equiv), toluene, 90 °C, 24 h, yields: **10** (54%); (**4** or **5** or **6**) (1.0 equiv), DBU (1.3 equiv), 1,2,4,5-tetrakis(bromomethyl)benzene (0.25 equiv), toluene, 90 °C, 24 h, yields: **11** (60%), **12** (41%), **13** (32%).

Table 1
PA (probability 'to be active') values for predicted biological activities of compounds **7**–**13**

Focal predicted activity (PA >0.85)	Compound						
	7	**8**	**9**	**10**	**11**	**12**	**13**
Conjunctivitis	0.954	0.946	0.940	0.946	0.948	0.940	0.933
Antihypercholesterolemic	0.917	0.893	0.914	0.893	0.934	0.916	0.932
Respiratory analeptic	0.911	–	–	–	0.911	–	–
Hypercholesterolemic	0.906	0.881	0.890	0.881	0.906	0.881	0.890
Ocular toxicity	0.886	0.871	0.888	0.871	0.871	0.855	0.874
Hypolipemic	0.872	0.876	0.914	0.876	0.891	0.894	0.926
Analeptic	0.869	0.855	–	0.855	0.858	–	–
Teratogen	0.867	–	–	–	0.877	0.862	–
Behavioral disturbance	0.861	–	–	–	0.869	–	–
Embryotoxic	0.857	–	–	–	0.866	–	–
Hepatoprotectant	0.853	–	–	–	–	–	–
Cholestasis	–	0.870	–	0.870	–	0.870	–

proaches with the prediction of activity spectra for substances (PASS) program. It is based on a robust analysis of structure–activity relationships in a heterogeneous training set, currently including about 60,000 biologically active compounds from different chemical series with about 4500 types of biological activity. Since only the structural formula of the chemical compound is necessary to obtain a PASS prediction, this approach can be used at the earliest stage of an investigation. There are many examples of

Table 2
Heat of formation (HOF) (kcal/mol) of compounds **7**–**13**

Compound	Heat of formation (kcal/mol)
7	−790.2419
8	−1056.5849
9	−1307.3404
10	−1049.0739
11	−1060.0673
12	−1407.2389
13	−1739.4799

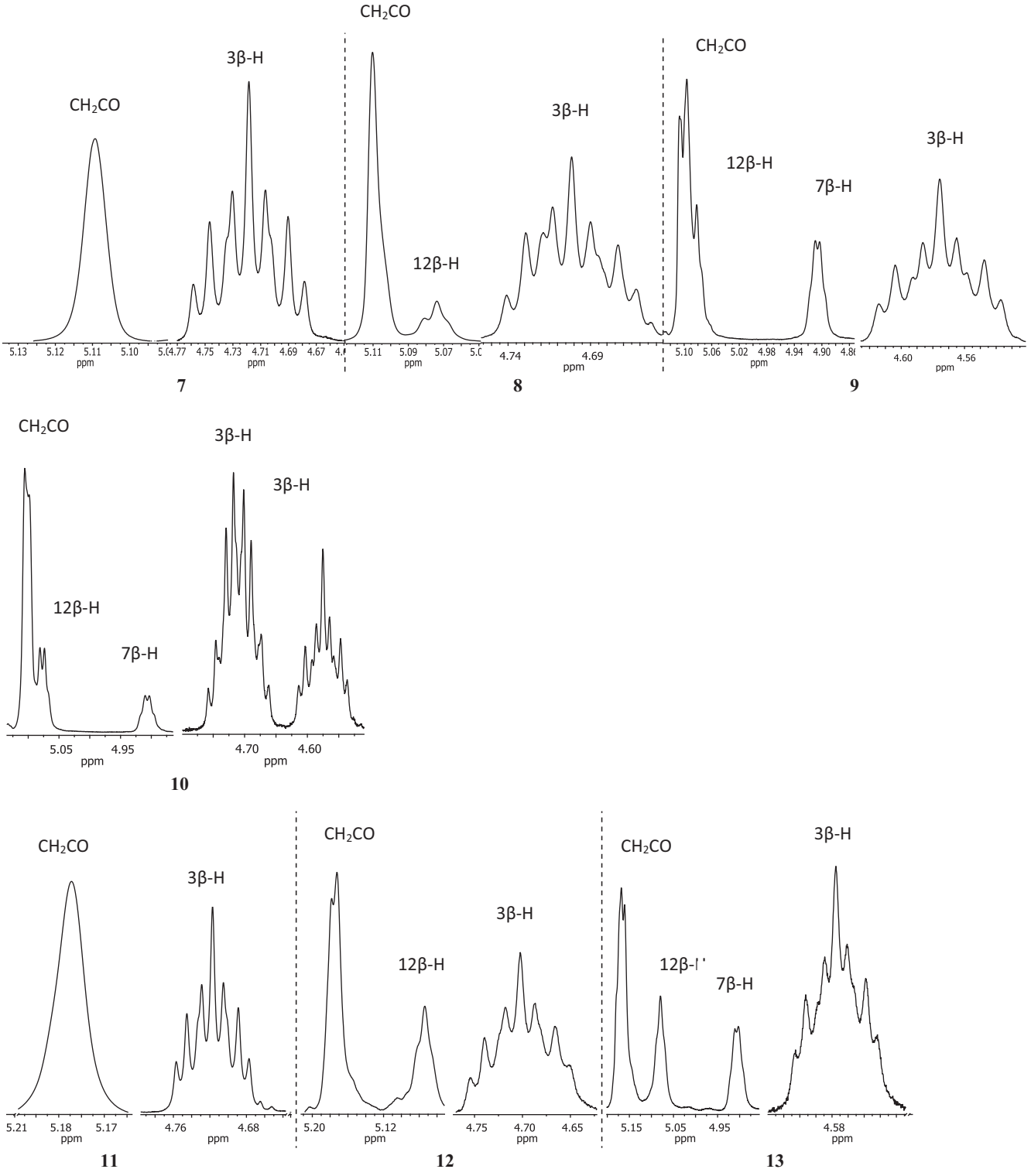


Figure 1. ^{1}H NMR spectra in the region (5.20–4.30 ppm) of the most characteristic signals of compounds **7**–**13**.

the successful use of the PASS approach leading to new pharmacological agents.[13]

The structures of all the synthesized compounds were determined from their ^{1}H and ^{13}C NMR, FT-IR, and ESI-MS spectra. Moreover, PM5 calculations were performed on all the products.[14] Additionally, analyses of the biological prediction activity spectra for the new esters prepared herein are good examples of in silico studies of chemical compounds. The biological activity spectra were predicted with PASS for compounds **7**–**13**. We also selected the types of activity that were predicted for a potential compound with the highest probability (focal activities) (Table 1). According to these data the most frequently predicted types of biological activity are: conjunctivitis, antihypercholesterolemic, hypercholesterolemic, ocular toxicity, and hypolipemic.

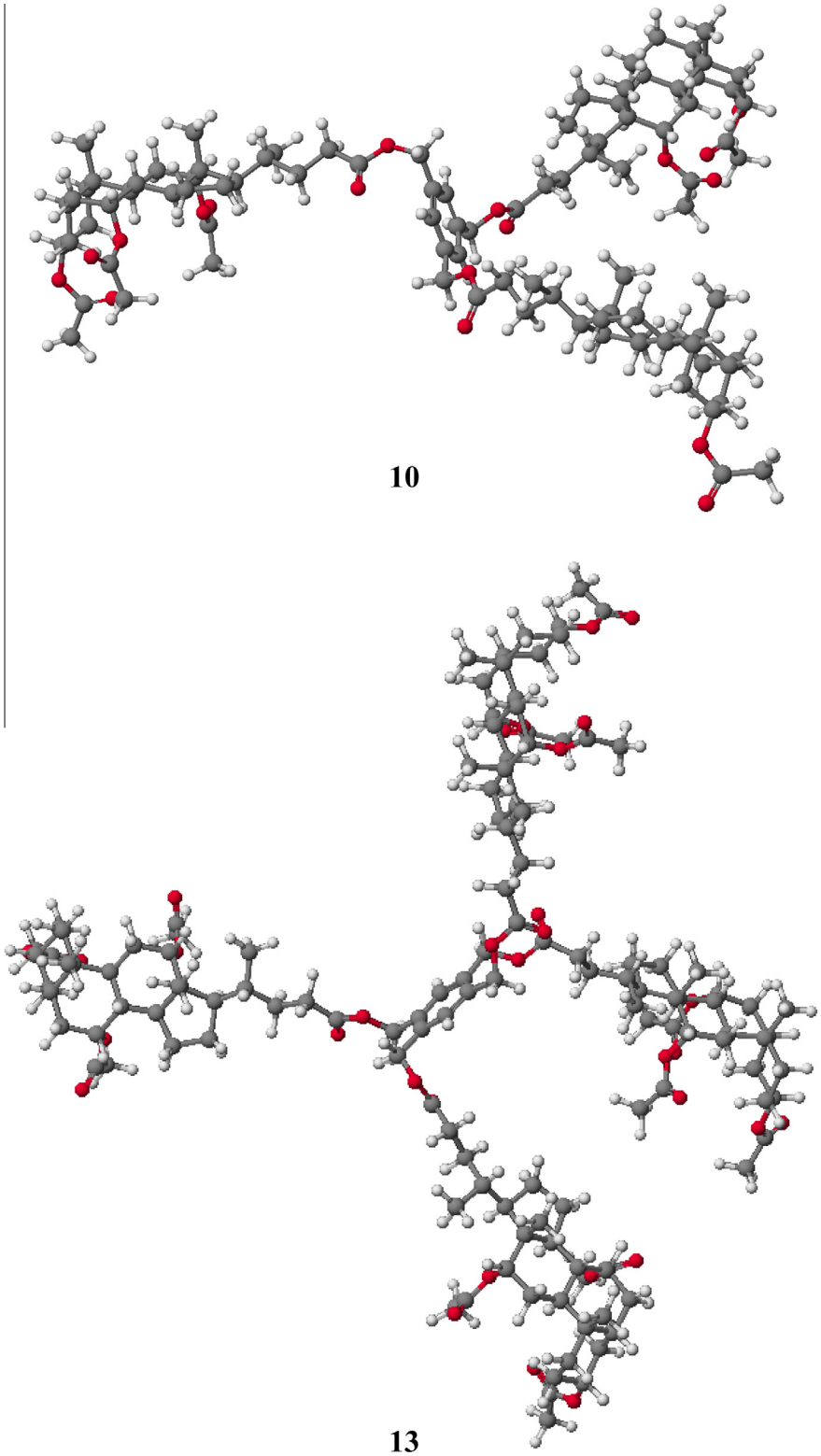


Figure 2. Molecular models of representative compounds **10** and **13** calculated using the PM5 method.

The ^{1}H NMR spectra of compounds **7**–**10** and **11**–**13** in $CDCl_3$ show characteristic multiplets in the range of 4.77–4.52 ppm assigned to the C3β-H protons of the steroid skeleton, and two hydrogen singlets ranging from 0.72–0.63 to 0.93–0.91, and characteristic doublets at 0.91–0.81 ppm assigned to CH_3-18, CH_3-19, and CH_3-21, respectively. In the spectra of compounds **8**, **12**, **9,** and **13** characteristic broad singlets in the range of 5.10–5.08 ppm due to the C12β-H protons and doublets at 4.90 ppm for the C7β-H protons (**9** and **13**) were observed (Fig. 1). Of particular interest is compound **10** where two multiplets at 4.76–4.66 and 4.60–4.54 ppm are assigned to the three C3β-H protons, and three signals due to CH_3-18 at 0.72, 0.71, and 0.63 ppm were present. Two signals were present at 0.93 and 0.92 ppm due to CH_3-19, and a doublet at 0.91 ppm and a doublet of doublets at 0.81 ppm were assigned to CH_3-21. Moreover, the spectrum of compound **10** showed two broad singlets due to C12β-H at 5.08 and 5.07 ppm, and also two singlets for C7β-H at 4.91 and 4.90 ppm (Fig. 1). In the ^{1}H NMR spectra of compounds **7**–**13** the most characteristic signals were observed for the aromatic protons of 1,3,5-trisubstituted benzene **7**–**10** and 1,2,4,5-tetrasubstituted benzene **11**–**13** units. These appeared as singlets at 7.30–7.29 and 7.43–7.42 ppm for **7**–**10** and **11**–**13**, respectively. The signals for two methylene protons of the Ph–CH_2–CO group occurred as broad singlets in the range of 5.18–5.07 ppm.

The ^{13}C NMR spectra of compounds **7**–**13** in $CDCl_3$ showed characteristic signals 12.4–12.0 ppm, 23.4–22.8 ppm, and 18.3–17.5 ppm, which were assigned to CH_3-18, CH_3-19, and CH_3-21, respectively. The carbon atoms of the CO_2–CH_2–Ph unit resonated in the range of 173.9–173.6 ppm and 65.7–63.1 ppm, assigned to CO_2 and CH_2, respectively. The signals due to the acetate C=O group at the 3α or 3α,7α and 3α,7α,12α positions gave signals in the range of 170.6–170.3 ppm.

The FT-IR spectra of all the compounds ($CHCl_3$) revealed two strong characteristic bands in the regions 1736–1734 cm^{-1} and 1249–1243 cm^{-1}, assigned to ν(C=O) and ν(C–O), respectively.

PM5 semi–empirical calculations were performed using the WinMopac 2003 program. The final heats of formation (HOF) for compounds **7**–**13** are presented in Table 2. Representative compounds **10** and **13** are shown in Figure 2. The lowest HOF values were observed for cholic acid derivatives **9** and **13**. In general the HOF values of 1,2,4,5-tetrasubstituted benzene derivatives were lower than those of 1,3,5-trisubstituted benzene derivatives. This fact can be explained by an alternating arrangement of the steroid in the structure, and thus reduction of electrostatic and steric interactions between the steroid skeletons. This spatial arrangement of bile acids can facilitate the formation of stable host–guest complexes.

In conclusion, seven new bile acid esters **7**–**13** were prepared from 3α-acetoxy-5β-cholanic acid, 3α,12α-diacetoxy-5β-cholanic acid, 3α,7α,12α-triacetoxy-5β-cholanic acid, and 1,3,5-tris(bromomethyl)benzene or 1,2,4,5-tetrakis(bromomethyl)benzene in dry toluene in the presence of DBU at 95 °C for 24 h. These new compounds were characterized by spectroscopic and molecular structure methods. These bile acid esters may find applications in molecular recognition, supramolecular chemistry, and in pharmacology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.m096.

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12. Example procedure for the synthesis of compound **7**: 3α-acetoxy-5β-cholanic acid (200 mg, 0.48 mmol) was dissolved in anhydrous toluene (5 mL), the mixture heated for 1 h, and DBU (0.1 mL, 0.62 mmol) was added. The mixture was heated at reflux for 1 h, followed by the addition of 1,3,5-tris(bromomethyl)benzene (Aldrich) (60 mg, 0.168 mmol) and heating for an additional 24 h. The mixture was poured onto ice, extracted with toluene (10 mL), and washed with H_2O (15 mL) and brine (15 mL), and then dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification of the residue over silica gel ($CHCl_3$/EtOAc, 50:1) gave 123 mg of product **7** (56%).
General procedure for the synthesis of compound **10**: 3α-acetoxy-5β-cholanic acid (50 mg, 0.12 mmol), 3α,12α-diacetoxy-5β-cholanic acid (56.9 mg, 0.12 mmol) and 3α,7α,12α-triacetoxy-5β-cholanic acid (63.9 mg, 0.12 mmol) were dissolved in anhydrous toluene (5 mL). The mixture was heated for 1 h, DBU (3.6 mmol, 0.069 ml) was added and the solution heated under reflux for 1 h. 1,3,5-Tris(bromomethyl)benzene (Aldrich) (42.8 mg, 0.12 mmol) was added, and the mixture heated for 24 h, then poured onto ice. The mixture was extracted with toluene (10 mL), and washed with H_2O (15 mL) and brine (15 mL), and then dried over anhydrous $MgSO_4$, then evaporation of the solvent and purification of the residue over silica gel ($CHCl_3$/EtOAc, 30:1) gave 100 mg of **10** (54%).
Compound (**7**): ^{1}H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ_H 7.30 (s, 3H, ArH), 5.11 (br s, 6H, CH_2CO), 4.75–4.69 (m, 3H, 3β-H), 2.03 (s, 9H, 3α-CH_3COO), 0.93 (s, 9H, CH_3-19), 0.91 (d, J = 6.5 Hz, 9H, CH_3-21), 0.63 (s, 9H, CH_3-18). ^{13}C NMR (75 MHz, $CDCl_3$, TMS, ppm): δ_C 174.31, 173.95, 170.61, 136.92, 127.6, 74.37, 65.72, 65.50, 56.46, 55.97, 42.70, 41.85, 40.37, 40.11, 35.75, 35.33, 35.00, 34.55, 32.22, 31.30, 31.21, 30.97, 30.92, 28.18, 26.99, 26.60, 26.29, 24.16, 23.31, 21.47, 20.80, 18.25, 12.01. FT-IR ($CHCl_3$, film) ν_{max}: 1736, 1448, 1379, 1362, 1243, 756. ESI-MS (m/z): 1392 $[C_{87}H_{132}O_{12}+Na]^+$, 1408 $[C_{87}H_{132}O_{12}+K]^+$.
Compound (**10**): ^{1}H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ_H 7.29 (s, 3H, ArH), 5.11 and 5.10 (br s, 6H, CH_2CO), 5.08 and 5.07 (2s, 2H, 12β-H), 4.91 (s, 1H, 7β-H), 4.76–4.66 (m, 2H, 3β-H), 4.60–4.54 (m, 1H, 3β-H), 2.13 and 2.12 (2s, 6H, 12α-CH_3COO), 2.08 (s, 3H, 7α-CH_3COO), 2.05, 2.04 and 2.03 (3s, 9H, 3α-CH_3COO), 0.93 and 0.92, (2s, 9H, CH_3-19), 0.91 (d, J = 6.3 Hz, 3H, CH_3-21) and 0.81 (dd, J = 6.3 Hz, 6H, CH_3-21), 0.72, 0.71 and 0.63 (s, 9H, CH_3-18). ^{13}C NMR (75 MHz, $CDCl_3$, TMS, ppm): δ_C 173.90, 173.78, 173.72, 170.63, 170.51, 170,46, 170.42, 170.40, 170.29, 136.92, 136.90, 136.83, 127.69, 75.84, 75.34, 74.35, 74.16, 74.05, 70.66, 65.60, 56.46, 56.00, 49.41, 47.63, 47.42, 45.05, 45.00, 43.37, 42.72, 41.86, 41.80, 40.93, 40.39, 40.13, 37.74, 35.77, 35.66, 35.32, 35.01, 34.69, 34.58, 34.38, 34.32, 34.02, 33.72, 32.24, 31.23, 31.07, 30.94, 30.77, 30.70, 28.87, 28.18, 27.33, 27.17, 27.00, 26.87, 26.62, 26.30, 25.86, 25.63, 25.56, 24.16, 23.42, 23.31, 23.06, 22.80, 22.55, 21.60, 21.45, 21.41, 20.81, 18.26, 17.51, 12.39, 12.22, 12.01. FT-IR ($CHCl_3$, film) ν_{max}: 1734, 1448, 1378, 1363, 1246, 753. ESI-MS (m/z): 1566 $[C_{93}H_{138}O_{18}+Na]^+$, 1582 $[C_{93}H_{138}O_{18}+K]^+$.
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