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Rapid communication

Synthesis of spiroannulated oligopyrrole macrocycles derived from lithocholic acid

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ABSTRACT

Two new steroidal spiroannulated calix[4]pyrroles **5** and **10**, derived from bile acids (lithocholate), were prepared by the acid catalyzed condensation of methyl-3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3** with carbonyl compounds and with 2,2′-propane-2,2-diylbis(1*H*-pyrrole), respectively. The new compounds were fully characterized by physicochemical methods.

1. Introduction

In the last years, steroidal constructs have been attracting the interest of many research groups in many branches of science and technology, such as the medical and pharmacological fields, supramolecular chemistry and nanotechnology [1–4]. In fact, the inclusion of steroid residues in the molecular structure of certain molecular species could ascribe them with new physicochemical and biological features, as well as new morphological features related to their self-assembly. Upon the inclusion of spiroanulated steroidal substituents in tetrapyrrole macrocycles we can expect new and interesting properties in their association capability with different compounds, new selective molecular interactions, changes in fluorescence spectra and electrochemical properties, as well as different and chiral sensitive changes in excited triplet states. Moreover, this new class of compounds may also bear interesting stereochemical features, which would definitely serve as a new tool in molecular recognition, ion channel building-up, membrane penetration and even photodynamic therapy (PDT). A very important feature is the solvent assisted amplification of chirality studied in similar compounds (cf. [5] and papers cited therein). A nice example of similar interesting compounds is the steroidal calix[4]pyrroles [6], where similar structural features are exploited in enantioselective recognition. The estradiol porphyrin conjugate was synthesized as a targeted photodynamic drug [7]. Despite the fact that the structural type of compounds described is new their properties could be compared with "steroidal dimers", which may be rather simple [8] or more complex, as described in recent reviews [9,10].

In a recent study we provided data on the synthesis of a new type of steroidal oligopyrrole macrocycles and their synthons [11–15]. We focused our interest also towards the improvement of some already used chemical reactions, by means of microwave chemistry, as used in contemporary literature [16]; for example, part of the experimental descriptions on this communication has appeared in the patented literature, in a foreign language [11–13].

2. Experimental

2.1. Materials and methods

TLC was performed on either HF_{254} plates (Merck) with detection by UV light or on plates made from MP Biomedicals SilicaGel G with detection by spraying with a solution of 5 g of $Ce(SO_4)_2(H_2O)_4$ in 500 ml 10% H_2SO_4 and subsequent heating. Flash column chromatography was performed on silica gel (Merck, 100–160 μm) with solvents distilled prior to use. ^1H and ^{13}C NMR spectra were taken on a Bruker AVANCE 500/300 (500.1/300.13 MHz for ^1H and

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125.8/75 MHz for ^{13}C), Varian Gemini 300 HC (300 MHz for ^{1}H and 75 MHz for ^{13}C) NMR spectrometer at 300 K if not stated otherwise. The internal signal of tetramethylsilane (δ 0.0) for ^{1}H and the central line of solvent (δ 77.0) for ^{13}C spectra were used as standards. Chemical shifts are presented in ppm (δ), coupling constants in Hz (J). UV spectra were taken on a Carey-300 UV-VIS spectrophotometer, CD spectra were taken on a Jasco spectropolarimeter J-715 using quartz cuvettes (path length l = 0.5 cm). Mass spectra were taken on a Q TOF (Micromass) spectrometer with direct inlet (ESI), on a ZAB-EQ (VG Analytical) instrument (FAB) with Xe ionization, or Autospec Ultima (Micromass) by EI technique. As the source of microwave (MW) irradiation a microwave microprocessor controlled chemical reactor Plasmatronika M REOS with electromagnetic stirring, MW generator of 2.45 GHz and temperature regulation was used.

2.2. Chemical synthesis

2.2.1. Esterification and subsequent oxidation of lithocholic acid 1 under microwave irradiation

A mixture of lithocholic acid (**1**, 1.27 g, 3.4 mmol) and *p*-toluene sulphonyl acid monohydrate (281 mg, 1.5 mmol) in methanol (80 ml) was irradiated by MW for 6 min at 50% of maximum intensity (i.e. at 375 W). After the evaporation of methanol, water was added (30 ml) and the crude product was filtered and washed with water. Recrystallization from ether yielded 1.27 g (97%) of methyl lithocholate, identical to the product described in the literature, however, with m.p. 71–73 °C where literature mostly gives different melting points [17] between 115 and 157 °C.

Fresh distilled pyridine (5.6 ml, 69 mmol) was added to the mixture of dry chromium (VI) oxide (2.3 g, 23 mmol) and dichloromethane (10 ml) at 0 °C, and the mixture was stirred until a suspension was formed. Then methylester of lithocholic acid (1.5 g, 3.85 mmol) dissolved in dichloromethane (40 ml) was added. The mixture was irradiated by MW for 6 min at 50% of maximum intensity (i.e. at 375 W). Dichloromethane was distilled and the residue was diluted by diethyl ether (20 ml), filtered through a layer of alumina (30 g) and the filtrate was evaporated and co-evaporated with toluene (3 × 10 ml). The product was recrystallized from diethyl ether providing 1.45 g (97%) of methyl 5β*H*-3-oxocholan-24-oate **2** with similar properties to those reported in the literature [18,19].

2.2.2. Methyl-3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3**

2.2.2.1. Condensation with pyrrole and $BF_3{\cdot}OEt_2$. $BF_3{\cdot}OEt_2$ (0.61 ml, 6.6 mmol) was slowly added to the mixture of methyl 5β*H*-3-oxocholan-24-oate (**3**, 1.3 g, 3.4 mmol) and pyrrole (5 ml) under Ar and stirring. Stirring was continued for 3.5 h at room temperature [20]. The mixture was evaporated and co-evaporated with toluene (4 ml). The residue was dissolved in dichloromethane (20 ml) and filtered through a small column of silica (10 g). The column was then washed with dichloromethane (120 ml). Collected filtrates were evaporated and then chromatographed on a column of silica in cyclohexane:diethyl ether 9:1. It yielded 462 mg (27%) of product **3** and 123 mg (7%) of its isomer **4** as an amorphous powder. Product **3** was identical to the compound described in the literature [20].

Product **4** was characterized by ^{1}H NMR ($CDCl_3$; 400 MHz): 0.64 s, 3 H, (18-CH_3); 0.84 s, 3 H, (19-CH_3); 0.93 d, $^{2}J_{H\text{-}H}$ = 4.0, 3 H, (21-CH_3); 1.05–2.46 m, steroidal skeleton; 3.67 s, 3 H, (1″; 24-$COOCH_3$); 6.02 m 1 H (18′; pyrrole); 6.13 m, 2 H (2′ + 17′; pyrrole); 6.50 m, 1 H (16′; pyrrole); 6.68 m, 1 H (3′; pyrrole); 6.78 m, 1 H (4′; pyrrole); 7.68 bs, 1 H (N1H; pyrrole); 8.13 bs, 1 H (N4H; pyrrole). ^{13}C NMR (75.44 MHz, $CDCl_3$): 175.12, 24; 137.64, 19′; 129.42, 1′; 118.40, 16′; 115.89, 4′; 115.31, 3′; 108.15, 17′; 107.82, 18′; 56.74, 14; 56.15, 17; 51.75, 1″; 50.39, 9; 42.99, 5; 40.65, 13; 40.65, 3; 40.43, 12; 39.42, 4; 36.04, 20; 35.62, 8; 35.24, 10; 34.32, 1; 32.45, 2; 31.30, 22 + 23; 31.25, 6; 28.45, 16; 27.45, 7; 24.43, 15; 24.11, 19; 21.12, 11; 18.52, 21; 12.29, 18.

2.2.2.2. Condensation with pyrrole with TFA. Trifluoroacetic acid (8 μl) was added to the mixture of methyl ester of 3-oxo-5-β-cholan-24-oic acid (194 mg, 0.5 mmol) and pyrrole (2 ml, 3.01 g, 44 mmol) under argon and the mixture was stirred for 3 h at room temperature. Then, the mixture was evaporated and co-evaporated with toluene (3 × 1 ml). The residue was dissolved in dichloromethane (20 ml), filtered through silica gel (10 g), and washed with dichloromethane (50 ml). The filtrate was evaporated and the residue chromatographed on a column of silica gel (27 g) by cyclohexane: ether 9:1, yielding **3** (185 mg; 73%), as above.

2.2.3. Condensation of methyl-3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3** with carbonyl compounds

2.2.3.1. General procedure. All reactions were performed under inert atmosphere of argon using the vacuum line. Trifluoroacetic acid was added under stirring to a mixture of methyl-3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3** (0.5 mmol) and 10 equivalents of the respective carbonyl compound in a suitable solvent were also added. The reaction mixture was monitored by TLC and was stirred until acceptable conversion. Then, dry Na_2CO_3 was added and, after filtration, the filtrate was evaporated to dryness. The rough product was purified by column chromatography on silica gel.

2.2.3.2. Condensation with pentafluorobenzaldehyde. The reaction was set using 913 mg (5 mmol) of pentafluorobenzaldehyde, 253 mg (0.5 mmol) steroidal dipyrrylmethane **3** in dry dichloromethane (5 ml) and 154 μl TFA. After 3 h, DDQ (116 mg) in dry dichloromethane (5 ml) was added and the mixture was kept at room temperature overnight. For purification, 120 g of silica gel were used in cyclohexane: diethyl ether (24:1 mixture). It yielded 6.1 mg (2%) of product **5** as a brown colored amorphous powder. ^{1}H NMR ($CDCl_3$; 400 MHz): 0.64–2.46 m, steroid skeleton; 3.67 s, 3 H, (24-$COOCH_3$); 5.40–5.60 m (pyrrole); 5.95–6.20 m, (pyrrole); 7.55 m, 1 H (NH-pyrrole); 7.70 m, 1 H (NH-pyrrole). For $C_{80}H_{90}F_{10}N_4O_4$ (1361.579) monoisotopic mass 1360.680; found MS: *m*/*z*: 1360 ($M^{+\cdot}$), 1359 ($M^{+}-H$), 167 ($-C_6F_5$).

2.2.3.3. Condensation with acetone. Steroidal dipyrromethane **3** (252 mg, 0.5 mmol) was mixed with 50 ml of dry acetone and 8 μl TFA for 1 h. Chromatography with C_6H_{12}:CH_2Cl_2 1:1 yielded 11 mg (3%) of **10**, as in Section 2.2.3.4.

2.2.3.4. MacDonald [2 + 2] condensation with 2,2′-propane-2,2-diylbis(1H-pyrrole) and acetone. Steroidal dipyrromethane **3** (249 mg, 0.5 mmol) and 2,2′-propane-2,2-diylbis(1*H*-pyrrole) [21] (176.5 mg, 1.0 mmol) in 50 ml of dry acetone and 8 μl TFA were stirred for 1.5 h. Chromatography on 100 g silica gel in cyclohexane: dichloromethane 2:1 yielded 183 mg of **10** (24%) as a brownish amorphous powder. ^{1}H NMR (299.97 MHz; pyridine-d5, see Fig. 1 for atom numbering): 0.88 s, 3 H (18-CH_3); 1.08 s, 3 H (19-CH_3); 1.21 d, $^{2}J_{H\text{-}H}$ = 6.0, 3 H (21-CH_3); 1.98 bs, 18 H (6 CH_3-calix[4]pyrrole); 1.05–2.9 m steroid skeleton; 3.96 s, 3 H (24-$COOCH_3$); 6.14–6.36 m, 8 H); 8.67 bs, NH, 8.84 bs, NH, 9.79 pseudo-d (2 NH). 1H NMR (300 MHz; MeOD): 0.66 s 3 H (18-CH_3); 0.90–0.96 bs, 3 H (19-CH_3); 0.96–0.98 m, 3 H (21-CH_3); 2.11–2.29 m, 2 H (6 CH_3-calix[4]pyrrole); 1.0–2.4 m (steroid skeleton); 3.63 s, 5 H (24-$COOCH_3$); 5.49–6.22 m, 8 H (calix[4]pyrrole); 7.21 (dt, J = 8.50, 2.56 Hz, 1 H) 7.66 (ddd, J = 32.31, 5.64, 3.59 Hz, 1 H); 7.84 (d, J = 51.29 Hz, 1 H); 8.46 (d, J = 16.41 Hz, 1 H). ^{13}C NMR (75.48 MHz, MeOD): 12.53, 18; 18.79, 21; 22.03, 11; 25.31, 19; 27.68, 2; –, 15; –, 16; 29.27, 7; 30.27, 23′; 30.93, 22′; 31.35, 21′; 31.77, 20′; 30.08, 24′; 29.99, 25′; 31.88, 22; 31.88, 23; 32.26, 6; 34.08, 1; 36.73, 10; 35.96,

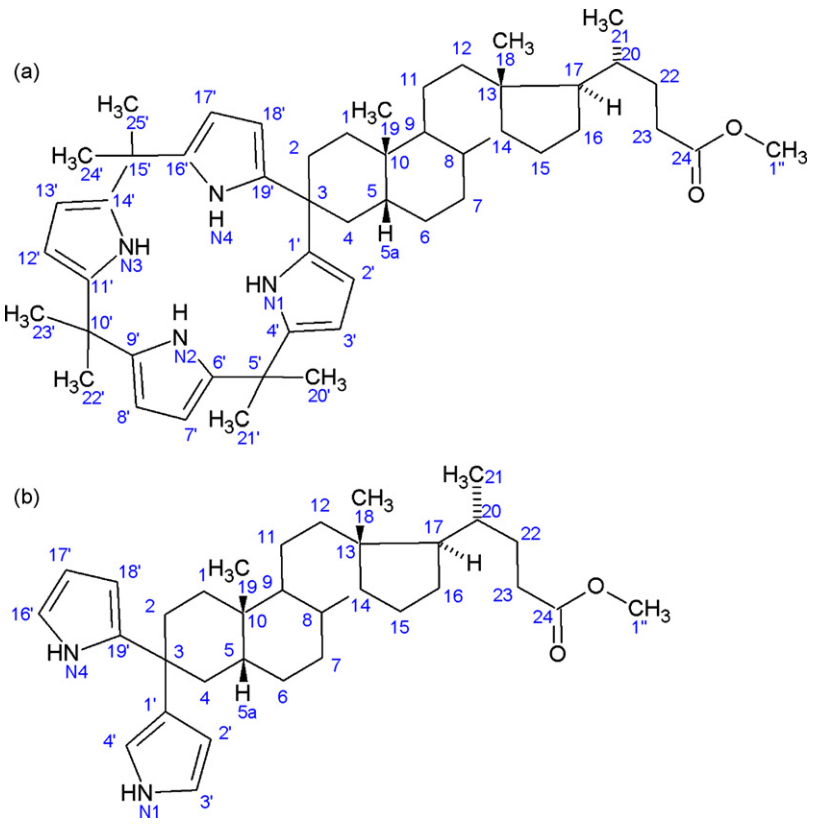


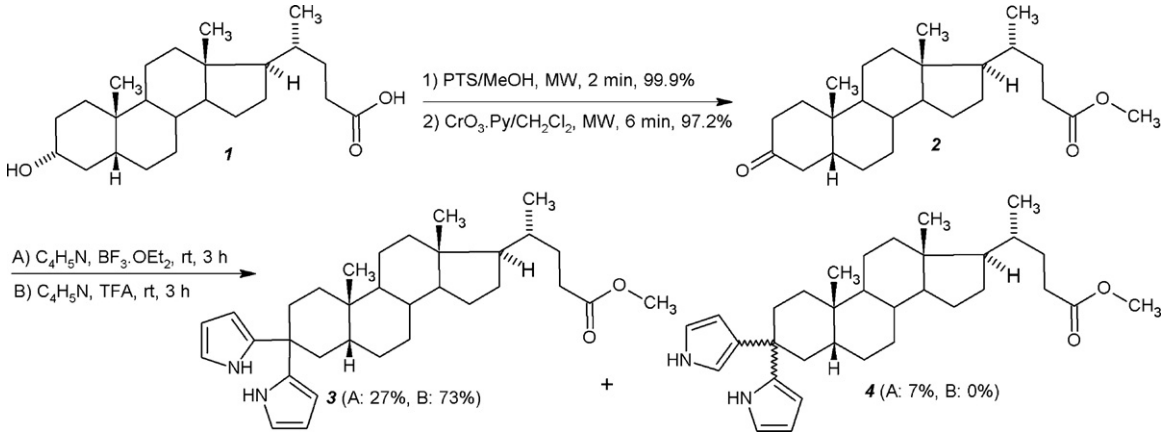
Fig. 1. (a) Atom numbering in **10** for description of ^{13}C NMR spectrum; (b) atom numbering in **4** for description of ^{13}C NMR spectrum.

20; 36.45, 8; 36.73, 5′; 36.73, 15′; 37.27, 10′; 32.26, 12; 38.36, 4; 40.62, 13; 41.36, 5; 41.81, 3; 43.96, 9; 52.05, 1″; 57.34, 17; 57.92, 14; 101.59, 18′; 101.59, 2′; 103.81, 12′; 104.07, 13′; 103.28, 8′; 102.78, 7′; 106.21, 3′; 106.21, 17′; 129.90, 1′; 132.39, 19′; 139.17, 16′; 136.35, 4′; 140.04, 9′; 142.34, 11′; 139.89, 6′; 139.93, 14′; 176.51, 24. For $C_{50}H_{70}N_4O_2$ (759.116) monoisotopic mass 758.549; found 758 (M^+).

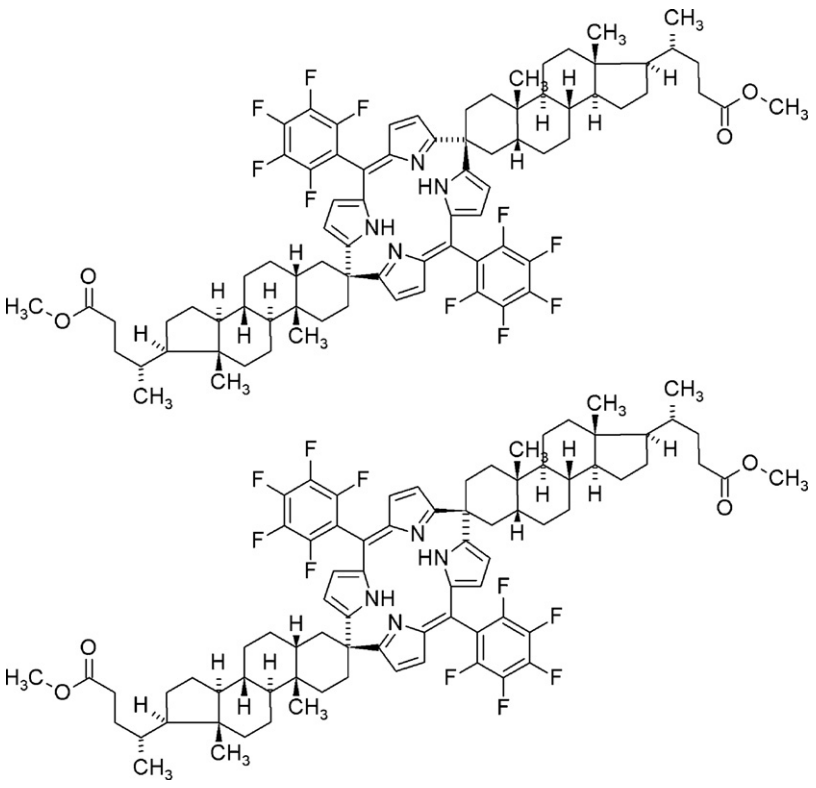
3. Results and discussion

The synthesis of the title compounds originated from lithocholic acid **1,** which was transformed into the carbonyl compound **2** in two steps: esterification, protecting the carboxylic acid, followed by the oxidation of a 3α-hydroxygroup. Both steps were performed in a microwave environment [11], allowing the shortening of the reaction times to 2 and 6 min with good yields—97% (see Scheme 1). Both intermediates, i.e. the methyl ester of the lithocholic acid and the subsequent methyl-3-oxo-5β-cholan-24-oate **2** were obtained very pure. In both cases, the intermediates crystallized immediately after the work-up of the reaction mixture.

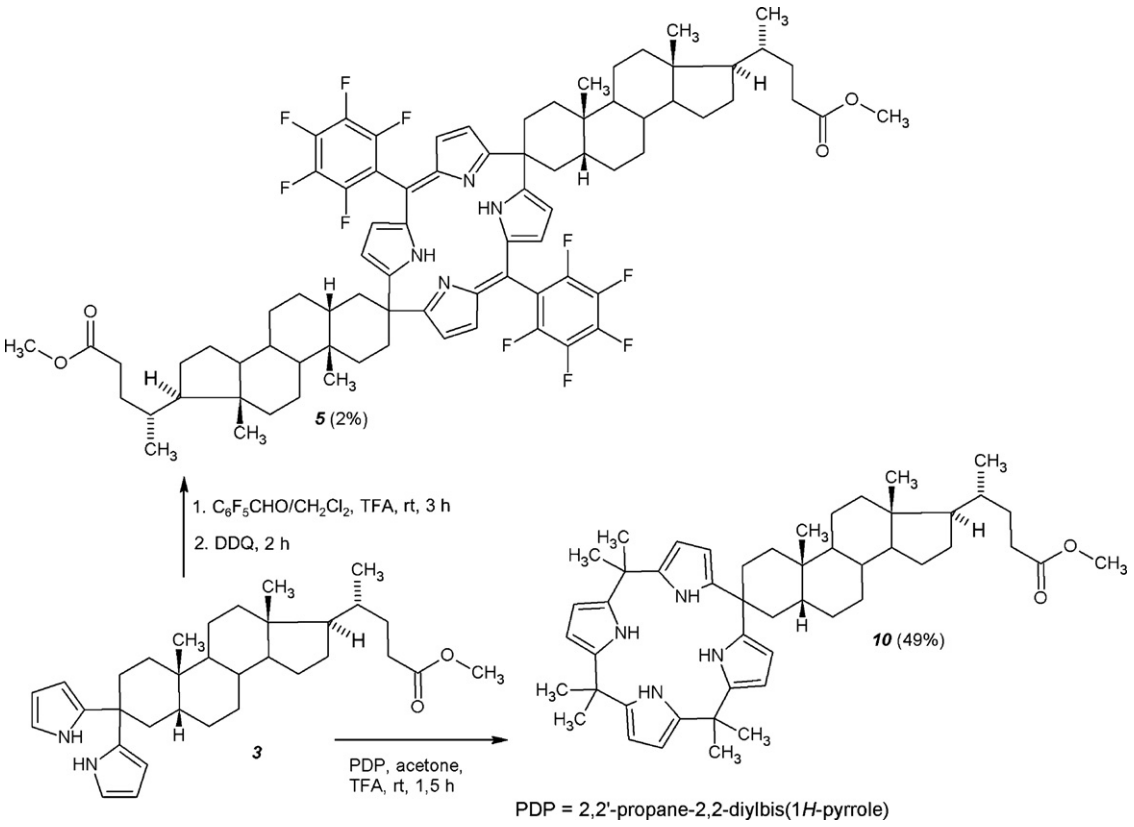
The reaction of methyl-3-oxo-5β-cholan-24-oate **2** with 20 equivalents of pyrrole, under the catalysis of $BF_3.OEt_2$ without any solvent, was performed in an inert atmosphere of argon at room temperature [12,13]. In addition to the expected product, the methyl 3,3-bis(1*H*-pyrrol-2-yl)-5β-cholan-24-oate **3** (27%), a mixture of the isomers of methyl 3ξ-(1*H*-pyrrol-2-yl)-3ξ-(1*H*-pyrrol-3-yl)-5β-cholan-24-oates **4** (7%) was also isolated. From the two broad N–H signals at 7.68 and 8.13 we assume that there are two kinds of pyrrole moieties in the molecule. This assumption is further supported by 5 different proton signals of pyrrole C–H at 6.03, 6.13 (2H),



Scheme 1. .



Scheme 2. Two diastereoisomers of **5**.



Scheme 3. .

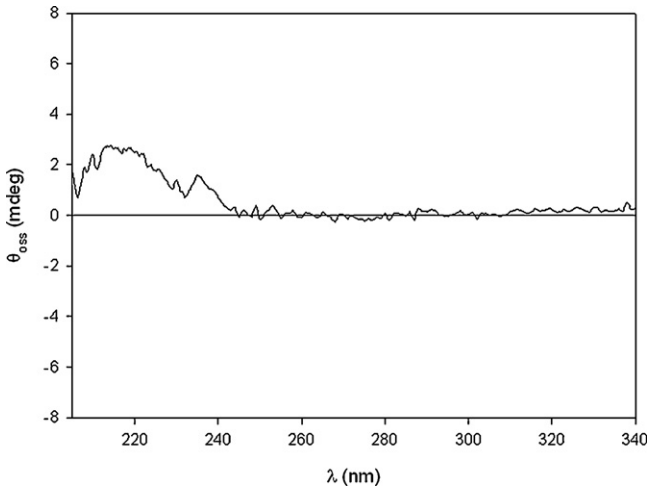


Fig. 2. UV spectrum of **10** in CH_3OH, conc. = 4.6×10^{-5} M.

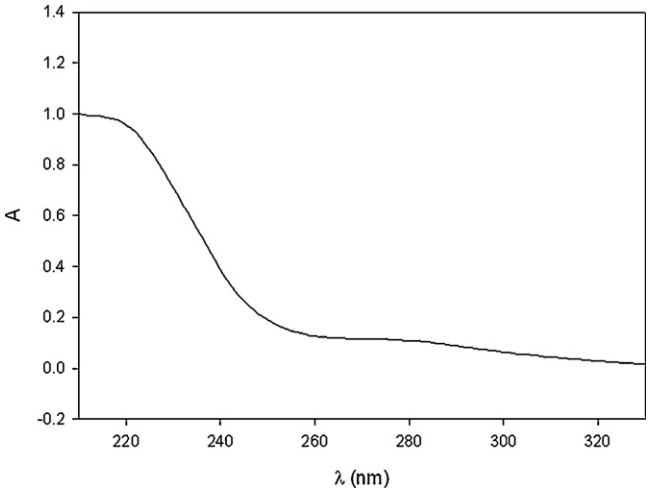


Fig. 3. CD spectrum of **10** in CH_3OH, conc. = 4.6×10^{-5} M.

6.50, 6.67, and 6.78, together with 6 protons. Similarly, the bis-2′-substituted pyrrole only has 3 proton signals here [20]. Both the 2′-pyrrolyl-3-alfa/3′-pyrrolyl-3-beta and the 2′-pyrrolyl-3-beta/3′-pyrrolyl-3-alfa are present in the mixture. This structure is further supported by all ^{13}C NMR lines obtained. We assume, based on stereochemical considerations, that the 2-substituted pyrrole and the 3-substituted pyrrole are present 1:1 in a mixture that we are not able to separate. Under catalysis of the trifluoracetic acid only product **3** was isolated in a good yield (73%) and there were even no traces of **4**. Isolation of **4** is the main focus of this report (Scheme 1).

The condensation products of methyl-3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3** with carbonyl compounds are formed with difficulty for several reasons. Steroidal dipyrromethane **3** is rather unstable in the reaction media used, being readily decomposed back to free pyrrole, which reacts with other components of the reaction mixture to give complex mixtures. Thus, the reaction with pentafluorobenzaldehyde, catalyzed by trifluoroacetic acid (TFA) in dry dichloromethane under Ar and at room temperature, with the subsequent oxidation by DDQ (dichlordicyanoquinone, 4,5-dichlor-3,6-dioxocyklohexa-1,4-dien-1,2-dicarbonitrile, gave the expected product **5**, with only a 2% yield (Scheme 2). The product is expected to be a mixture of two diastereoisomers, having two steroid units connected to the calix[4]pyrrole, with the same or the opposite absolute stereochemistry on the spiro-carbon. This interesting feature, which is supported by the broad lines of the ^1H NMR spectrum and t hexperience from the previous synthetic work [22], is being further investigated. Although we were able to isolate and characterize the compound, due to a very low yield we did not have the possibility to do any separation or stereochemical study so far.

The reaction of **3** with benzaldehyde under the catalysis of $BF_3{\cdot}Et_2O$ or TFA, as well as the condensation of steroid dipyrromethane **3** with trimethylorthoformate and the condensation with 5,5′-propane-2,2-diylbis(1*H*-pyrrole-2-carbaldehyde) [5,5-dimethyldipyrromethan-1,9-dicarbaldehyde in some publications] with TFA did not give even a trace of the expected product(s). This could be due to the insufficient electrophilicity of the carbonyl carbon. Hence, we tried stronger Lewis acids, such as $BF_3.Et_2O$ and $SnCl_4$, but also in this case we did not isolate any traces of product **8**. Condensation of **3** with acetone did not give the expected product **9** but the spiro-calixpyrrole **10** (3%). On the other hand, MacDonald [2 + 2] condensation of methyl 3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3** with 2,2′-propane-2,2-diylbis(1*H*-pyrrole) and acetone gave desired product **10** in 49% yield (Scheme 2).

Acid catalyzed condensations of methyl 3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate **3** with carbonyl compounds and with

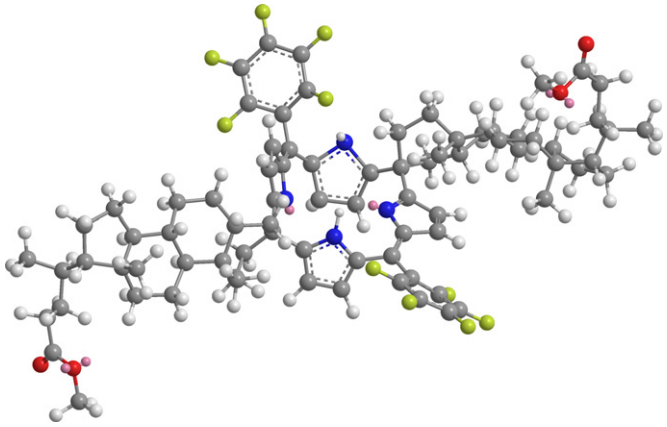


Fig. 4. Spatial representation of one diastereoisomer of **5** after molecular mechanics geometry optimization (Cambridge Software, Chem Office, ver. 2008).

2,2′-propane-2,2-diylbis(1*H*-pyrrole) have been studied to search for suitable preparation of new types of spiro-calix[4]pyrroles with bile acid (Scheme 3). Results of this study will serve to broaden the synthetic capacity of synthetic receptors containing highly organized chiral natural compounds. A systematic effort to improve the low yields of the target compounds has been undertaken. However, as it is well recognized, the cyclization of oligopyrrole macrocycles could give a 10% yield considered "very high for this reaction".

Spiro steroidal calix[4]pyrrole **10** was characterized by spectrometric measurements that, under the conditions used in the experiments, did not show any superassembly observed in relative steroidal derivatives [23]. Relatively simple UV spectrum in methanol (see Fig. 2) did not show any interesting changes with time (3 h, 1 d) or with concentration changes. Similarly, the CD spectrum in methanol (see Fig. 3) showed only a weak chiral effect, again, with no interesting changes with time (3 h, 1 d) or concentration. The reason could be, as discussed above, that it is a mixture of stereoisomers, which we were not able to separate so far (Fig. 4).

Acknowledgements

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