A Steroidal Cyclic Dimer with Ethylene Glycol Bridges

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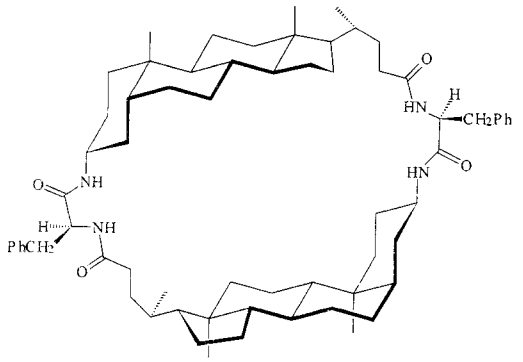
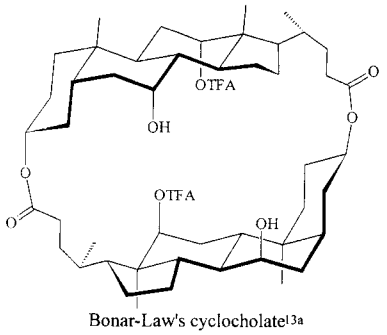
The steroid nucleus is one of the largest rigid and chiral units ubiquitous in nature. Since dimeric steroids were first observed as synthetic byproducts,[1,2] a large number of dimeric and oligomeric steroids from synthetic efforts and of natural origins have been reported and discoveries in this area up to late 1990's were the subject of a recent documentation.[3] Dimeric steroids exhibit such unique characteristics as detergent,[4] micellular,[5] medicinal,[6] catalytic,[7] and liquid crystal properties[8] that may lead to important applications. More recently, there has been a growing interest in constructing synthetic architectures in biomimetic and molecular recognition chemistry utilizing the dimeric and oligomeric structures of the steroid skeleton.[9-11] Examples of synthetic cyclic steroidal dimers elaborated so far for a molecular receptor or enzyme model can be divided into two types: the 'cyclocholamide'[12] and the 'cyclocholate'[13] in which two bile acid units are incorporated by the amide bonds and the ester linkages respectively.

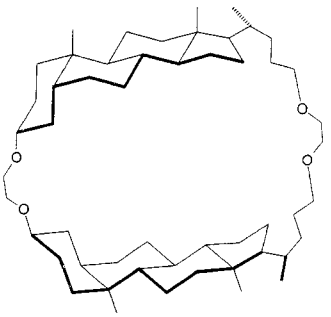


Feigel's Cyclocholamide[12c]



Bonar-Law's cyclocholate[13a]

We needed to develop synthetic hosts system which can surround organic molecules under severe reaction conditions such as the dissolving metal reduction and a high basic condition where an amide or ester bond may be easily cleaved. Herein we report the first synthesis of a steroidal cyclic dimer **1** where two molecules of the lithocholic acid are combined by two ethylene glycol units.



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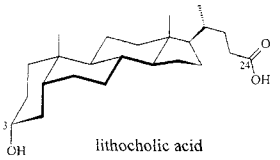


lithocholic acid

The steroidal cyclic dimer has a C_2 symmetry where two lithocholic acid units are combined in a head-to-head fashion. Molecular modeling study on **1** using HYPERCHEM parameters showed an extended conformation of the lowest energy shown in Figure 1. The dimension of the cavity for this conformation is about 11×9 Å, quite large enough to encapsulate small organic substrates.

Our synthetic method for the synthesis of **1** is exemplified in Scheme 1. The diol **2** was obtained by reduction of lithocholic acid with lithium aluminum hydride (90%). The first ethylene glycol unit was introduced selectively at the 24-position in the steroid structure by coupling of the diol **2** with ethylene glycol mono p-tosylate THP ether[14] to give a THP ether **3** (33%). Conversion of the THP ether compound **3** into the tosylate **5** was carried out in two steps (80%): deprotection with tosic acid and tosylation (TsCl, triethylamine). The 3-α-hydroxy function of **5** was then protected (TBDMSOTf, pyridine) to give **6** (99%). Reaction of the tosylate with the diol **2** in the presence of sodium hydride

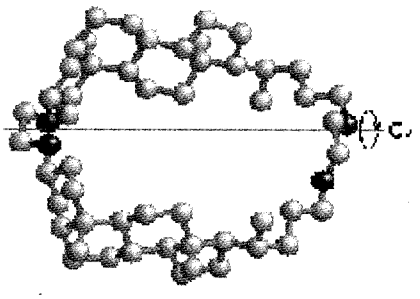


Figure 1. Energy minimized structure of **1**.

gave a linear steroidal dimer **7** (33%). The second elaboration at the 3-α-hydroxy function in the steroid skeleton of **7** with the ethylene glycol unit produced the corresponding silyl THP ether **8** (52%). Both TBDMS and THP groups of **8** were cleaved by tosic acid in methanol to yield the diol with two ethylene glycol units **9** (99%). Selective tosylation (TsCl, triethylamine) at the primary hydroxy function of the diol **9** gave **10** (45%). Finally, ring closure of **10** with sodium hydride gave the desired cyclic dimer **1** (47%) which showed 26 resonance signals in the ^{13}C NMR spectrum, reflecting its C_2 symmetry.

Experimental Section

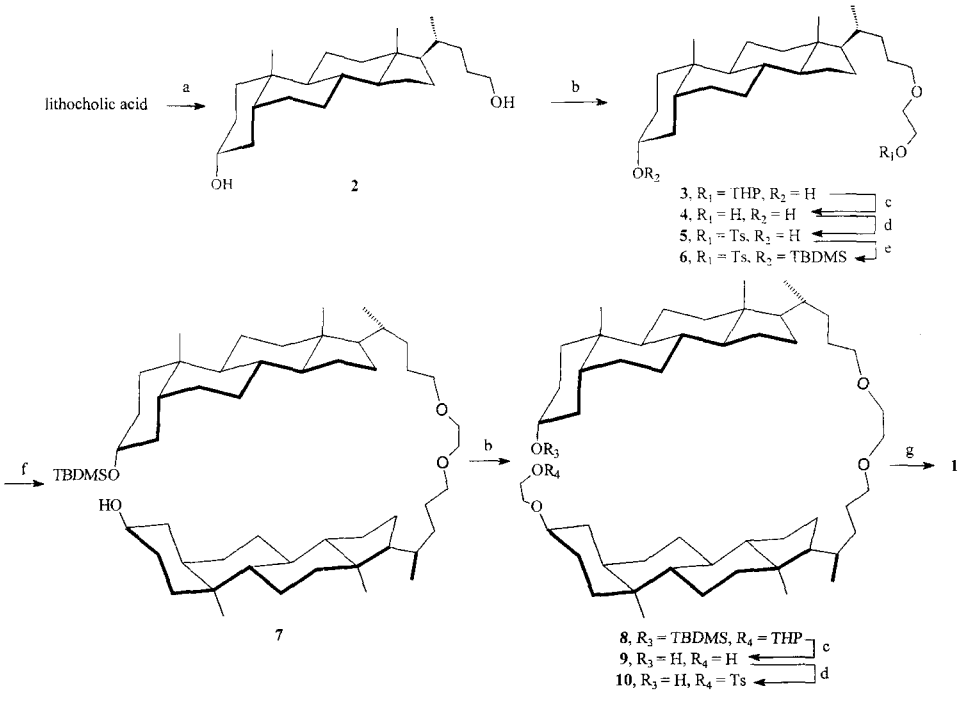
3-Hydroxy-5-cholastan-24-ol (2). To a cold (0 °C) solution of lithocholic acid (300 mg, 0.796 mmol) in anhydrous tetrahydrofuran (10 mL) was added lithium aluminum hydride (90 mg, 2.39 mmol). The mixture was magnetically stirred for 20 min at room temperature and then heated at reflux for 2 h. The cold (0 °C) reaction mixture was quenched by dropwise addition of a 10% hydrochloric acid solution (10 mL). The product was extracted into ether (3×30 mL) and the ethereal solution was dried and concentrated to give the desired diol (260 mg, 90%). The resulting white powder was submitted to the next reaction without further purification.

3-Hydroxy-5-cholastan-24-ol ethylene glycol mono THP ether (3). A mixture of 3-hydroxy-5-cholastan-24-ol (49.6 mg, 0.137 mmol), sodium hydride (60% oil) (23 mg, 0.477 mmol), and ethylene glycol mono p-tosylate THP ether (82.8 mg, 0.276 mmol) was heated at 78 °C (bath temperature). After 24 h, water was added to the reaction and the product was extracted into ether. The dried concentrated was subjected to flash chromatography (silica gel, elution with 20% ethyl acetate in *n*-hexane) to give 38 mg of **3** (56%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (t, J = 3.45 Hz, 1H), 3.88-3.55 (series of m, 9H), 2.15-1.01 (series of m, 32H), 0.10-0.86 (m, 9H), 0.61 (s, 3H).

3-Hydroxy-5-cholastan-24-ol ethylene glycol (4). A solution of **3** (175 mg, 0.356 mmol) and p-TsOH (6.8 mg, 0.036 mmol) in methanol (20 mL) was stirred at room temperature for 5 h. The customary workup furnished 143 mg of **4** (98.6%) as a white powder: ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (br, 2H), 3.64 (m, 1H), 3.50 (t, J = 2.11 Hz, 2H), 3.42 (m, 2H), 2.15-1.03 (series of m, 27H), 0.89 (m, 9H), 0.62 (s, 3H).

Tosylation of 3-hydroxy-5-cholastan-24-ol ethylene glycol. A cold (0 °C), magnetically stirred solution of **4** (20 mg, 0.05 mmol) and triethylamine (15.2 mg, 0.15 mmol) in dry dichloromethane (10 mL) was treated with toluenesulfonyl chloride (12.4 mg, 0.065 mmol), warmed to room temperature, and stirred for 5 h. Water was added and the product was taken up in dichloromethane (50 mL), and the organic phase was washed with saturated sodium bicarbonate solution (5 mL) and brine prior to drying. The concentrate was subjected to flash chromatography (silica gel, elution with 20% ethyl acetate in *n*-hexane) to give 23 mg of **5** (81%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.36 Hz, 2H), 7.32 (d, J = 7.95 Hz, 2H), 4.13 (t, J = 4.81 Hz, 2H), 3.59 (br, 1H), 3.58 (t, J = 4.83 Hz, 2H), 3.32 (t, J = 6.62 Hz, 2H), 2.43 (s, 3H), 1.96-0.90 (series of m, 34H), 0.86 (s, 3H), 0.61 (s, 3H).

3-*tert*-Buthyldimethylsiloxy-5-cholan-24-ol ethylene glycol tosylate (6). A cold (0 °C) solution of **5** (55 mg, 0.098 mmol), pyridine (15.5 mg, 0.20 mmol), and *t*-butyldimethylsilyltrifluoromethanesulfonate (39 mg, 0.147 mmol) in di-



Scheme 1. (a) $LiAlH_4$, Et_2O, 0 °C. (b) ethylene glycol mono p-tosylate THP ether, NaH (60%), THF, 65 °C, 3d. (c) TsOH, MeOH. (d) TsCl, Et_3N, CH_2Cl_2. (e) TBDMSOTf, pyridine, CH_2Cl_2. (f) **2**, NaH (60%), THF, 65 °C, 3d. (g) NaH (60%), THF, 65 °C, 3d.

chloromethane (5 mL) was magnetically stirred for 30 min. Water was added to the reaction and the product was taken up in ether (20 mL), and the organic phase was washed with brine prior to drying. The resulting yellow oil (65 mg, 99%) was submitted to the next reaction without further purification.

Linear head-to-head dimer (7). A mixture of **2** (130 mg, 0.36 mmol), sodium hydride (60% oil) (80 mg, 1.67 mmol), and **6** (243 mg, 0.36 mmol) was heated at 78 °C (bath temperature). After 66 h, water was added to the reaction and the product was extracted into ether. The dried concentrated was subjected to flash chromatography (silica gel, elution with 10% ethyl acetate in *n*-hexane) to give 103 mg of **7** (33%) as a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (br, 1H), 3.55 (s, 6H), 3.41 (t, J = 6.45 Hz, 4H), 2.15-0.95 (series of m, 62H), 0.87 (s, 9H), 0.86 (series of m, 6H), 0.62 (s, 3H), 0.61 (s, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.83, 72.03, 71.82, 56.48, 56.38, 56.19, 56.16, 42.65, 42.28, 42.09, 40.41, 40.17, 36.90, 36.45, 35.83, 35.57, 35.34, 34.57, 34.55, 32.03, 30.99, 30.54, 28.26, 27.30, 27.19, 26.41, 26.18, 25.96, 24.22, 23.37, 20.79, 18.59, 18.32, 12.01, 11.99, -4.61.

Ethylene glycol mono THP ether of the linear head-to-head dimer (8). A mixture of **7** (149 mg, 0.172 mmol), sodium hydride (60% oil) (43 mg, 1.07 mmol), and ethylene glycol mono p-tosylate THP ether (65 mg, 0.215 mmol) was heated at 78 °C (bath temperature). Purification of the oily residue from a customary workup by flash chromatography on silica gel (elution with 5% ethyl acetate in *n*-hexane) gave 89mg of **8** (52%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (t, J = 3.48 Hz, 1H), 3.89-3.78 (m, 2H), 3.64-3.45 (series of m, 10H), 3.40 (t, J = 6.67Hz, 4H), 1.93-0.92 (series of m, 63H), 0.60 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 98.93, 79.61, 72.84, 72.05, 70.08, 68.12, 67.25, 67.01, 62.23, 56.46, 56.40, 56.20, 56.17, 42.66, 42.30, 42.16, 40.28, 40.20, 40.17, 38.71, 36.92, 35.86, 35.84, 35.60, 35.40, 34.86, 34.58, 33.20, 32.03, 31.57, 31.01, 30.58, 30.34, 29.68, 28.90, 28.28, 27.34, 27.17, 26.40, 26.22, 25.97, 25.45, 24.23, 23.72, 23.39, 22.96, 22.63, 20.79, 19.51, 18.59, 18.32, 14.10, 14.03, 12.01, 10.94, -4.61.

Deprotection of 8. A solution of **8** (72 mg, 0.072 mmol) and p-TsOH (1.4 mg, 0.007 mmol) in methanol (20 mL) was stirred at room temperature for 5 h. The customary workup furnished the desired diol **9** (57 mg, 99%) as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72-3.52 (series of m, 10H), 3.43 (t, J = 6.65 Hz, 4H), 3.30 (m, 1H), 2.08-0.96 (series of m, 63H), 0.90 (s, 6H), 0.64 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 79.65, 71.99, 71.92, 71.87, 71.75, 71.68, 70.34, 70.04, 68.96, 67.30, 62.05, 61.78, 60.35, 56.44, 56.41, 56.10, 42.62, 42.05, 42.02, 40.37, 40.30, 40.21, 40.12, 36.38, 35.78, 35.54, 35.40, 35.23, 34.81, 34.51, 33.14, 31.99, 30.47, 28.24, 27.25, 27.17, 27.06, 26.39, 26.34, 26.11, 24.19, 23.34, 22.93, 22.64, 21.00, 20.76, 19.12, 18.56, 11.98.

Selective tosylation of 9. A cold (0 °C), magnetically stirred solution of **9** (56 mg, 0.070 mmol) and triethylamine (21 mg, 0.21 mmol) in dry dichloromethane (10 mL) was treated with toluenesulfonyl chloride (20 mg, 0.11 mmol), warmed to room temperature, and stirred for 5 h. Purification of the oily residue from a customary workup by flash chromatography on silica gel (elution with 20% ethyl acetate in *n*-hexane) gave 30 mg of **10** (45%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 7.94 Hz, 2H), 3.82 (br, 2H), 3.64-3.41 (series of m, 8H), 2.46 (s, 3H), 1.96-0.88 (series of m, 67H), 0.86 (s, 6H), 0.64 (s, 6H).

Cyclic head-to-head dimer (1). A mixture of **10** (48 mg, 0.05 mmol) and sodium hydride (60% oil) (4 mg, 0.10 mmol) was heated at reflux for 72 h. Purification of the oily residue obtained from a customary workup by preparative thin layer chromatography (Harrison Research, Model 7924T) on silica gel (elution with 6% ethyl acetate in *n*-hexane) gave 18.5 mg of **1** (47%) as a white solid: mp 155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64-3.56 (series of m, 6H), 3.53-3.48 (series of m, 2H), 3.34 (t, J = 7.94 Hz, 4H), 3.19 (m, 2H), 1.94-0.93 (series of m, 52H), 0.90-0.86 (series of m, 16H), 0.59 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 80.17, 72.93, 70.47, 68.96, 56.80, 53.66, 42.43, 42.18, 40.24, 40.05, 35.65, 35.51, 34.67, 34.55, 32.93, 30.84, 28.25, 27.18, 26.94, 26.14, 24.07, 23.45, 23.11, 20.80, 18.66, 11.83.

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