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Synthesis of steroidal dimers: Selective amine catalysed steroidal dimerization

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Abstract. Some new dimeric steroids namely cholest-5-en-3-spiro-[6′α,5′-oxa]-5′α-cholest-3′-one (**2**), cholest-5-en-7-spiro-[4′α,5′-oxa]-5′α-cholest-7′-one (**4a**) and 3β-substitutedcholest-5-en-7-spiro-[4′α,5′-oxa]-3′β-substituted-5′α-cholestan-7′-ones (**4b, c**) are synthesized starting from cholest-5-en-3-one (**1**), cholest-5-en-7-one (**3a**) and 3β-substituted-cholest-5-en-7-ones (**3b, c**) respectively by using DMAP and xylene. All the synthesized compounds were characterized by using IR, MS and ^{1}H, ^{13}C NMR spectral and elemental analysis.

Keywords. Unsaturated steroidal ketones; DMAP; amine catalysed dimerization; xylene; steroidal dimers.

1. Introduction

The steroid nucleus is one of the largest rigid units readily available with multiple chiral centres. The biological importance of this structural entity is also well-documented.[1,2] Dimeric steroids were first observed as synthetic by-products and then discovered in nature.[3,4] With the discovery of a second dimeric steroid class,[5] it may be conjectured that eventually other naturally occurring dimeric steroids may be identified. This belief is further reinforced by the reported steroid dimers in which carbon atoms comprise a benzene nucleus.[6] A standard colour test for the presence of cholesterol is the formation of a green colour in concentrated sulphuric acid, and this was shown to be due to a polyenyl steroidal dimer carbocation.[7–9] Many dimeric and oligomeric steroids exhibit interesting micellular, detergent and liquid crystal behaviour.[10,11] Most of the steroidal dimmers are also well-known for their pharmacological activity.[12–17] It might be expected that polymers of steroidal ketones (or ketone derivatives) would readily be formed in reaction media of amine catalysed dimerization.[18] Here we are presenting new dimeric steroids namely cholest-5-en-3-*spiro*-[6′α,5′-oxa]-5′α-cholest-3′-one (**2**), cholest-5-en-7-*spiro*-[4′α,5′-oxa]-5′α-cholest-7′-one (**4a**) and 3β-substituted-cholest-5-en-7-*spiro*-[4′α,5′-oxa]-3′β-substituted-5′α-cholestan-7′-ones (**4b, c**) which were prepared from cholest-5-en-3-one (**1**), cholest-5-en-7-one (**3a**) and 3β-substituted-cholest-5-en-7-ones (**3b, c**), respectively by amine catalysed dimerization[18] using DMAP and xylene.

2. Experimental

Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on spectrolab Interspec 2020 FT-IR spectrometer as KBr pellets (values are given in cm^{-1}). ^{1}H NMR spectra were measured on a 300 MHz instrument and ^{13}C NMR spectra on a Bruker Avance II 400 spectrometer at 100 MHz, using TMS as internal standard and $CDCl_3$ as solvent. Chemical shift (δ) were expressed in ppm downfield from internal standard. Mass spectra were obtained on a Jeol spectrometer SX-102 (FAB). Column chromatography was performed over silica gel (60–120 mesh) column. Thin layer chromatography was carried out on commercially available Merck silica gel plates. The homogeneity of the compounds was determined on the TLC plates. The spots were developed in the iodine chamber. All compounds gave satisfactory elemental analysis.

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2.1 *Preparation of steroidal dimers (***2, 4a–c***)*

General Procedure: To a stirred solution of steroidal ketones (**1, 3a–c**) (1.3 mmol) in xylene (50 mL), 4-(dimethylamino)-pyidine (1.3 mmol) was added, and the resulting solution was heated under reflux for 1–2 h. Completion of reaction was monitored by TLC. After cooling to room temperature, excess of solvent was distilled out under reduced pressure to give the oily residue. It was dissolved in diethyl ether and washed successively with water, 5% $NaHCO_3$ solution and again with water. The organic layer was dried over anhyd. sodium sulphate and evaporation of solvent gave the crude product, which was purified by column chromatography on silica gel with hexane-diethyl ether (5:1) as eluant, to give the corresponding steroidal dimers (**2, 4a–c**), recrystallized from methanol.

2.2 *Cholest-5-en-3-spiro-[6′α,5′-oxa]-5′ α-cholest-3′-one (***2***)*

Yield: (52%); m.p.: 230–233°C; ^{1}H NMR (300 MHz, $CDCl_3$) δppm: 5.59 (dd, 1H, J = 7.6, 5.2 Hz, C_6-H, olefinic proton), 2.31 (dd, 1H, J = 6.3, 4.8 Hz, C_6'-H, methine proton), 2.47 (s, 2H, $C_{4'}$-H_2), 2.16 (s, 2H, C_4-H_2), 1.18 (s, 3H, C_{10}-CH_3), 0.77 (s, 3H, C_{13}-CH_3), 1.14 (s, 3H, $C_{10'}$-CH_3), 0.73 (s, 3H, $C_{13'}$-CH_3), 0.92, 0.90, 0.84, 0.80 (other steroidal side-chain methyl protons). ^{13}C NMR (100 MHz, $CDCl_3$,) δppm: 204.75 (*C*O), 133.51 ($C_{5'}$), 95.63 (C_3), 155.56 (C_5), 131.09 (C_6), 31.50 (C_1), 38.62 (C_2), 49.07 (C_4), 31.29 (C_7), 29.16 (C_8), 44.35 (C_9), 40.72 (C_{10}), 20.96 (C_{11}), 32.83 (C_{12}), 38.46 (C_{13}), 47.90 (C_{14}), 21.86 (C_{15}), 21.06 (C_{16}), 46.89 (C_{17}), 20.38 (C_{18}), 20.48 (C_{19}), 31.01 (C_{20}), 19.93 (C_{21}), 37.08 (C_{22}), 26.25 (C_{23}), 38.78 (C_{24}), 29.90 (C_{25}), 22.49 (C_{26}), 22.74 (C_{27}), 27.03 ($C_{1'}$), 48.53 ($C_{2'}$), 48.75 ($C_{4'}$), 53.02 ($C_{6'}$), 21.96 ($C_{7'}$), 28.50 ($C_{8'}$), 37.11 ($C_{9'}$), 43.26 ($C_{10'}$), 21.19 ($C_{11'}$), 32.07 ($C_{12'}$), 40.63 ($C_{13'}$), 49.35 ($C_{14'}$), 21.98 ($C_{15'}$), 21.05 ($C_{16'}$), 48.60 ($C_{17'}$), 18.09 ($C_{18'}$), 19.06 ($C_{19'}$), 29.06 ($C_{20'}$), 19.88 ($C_{21'}$), 38.90 ($C_{22'}$), 26.01 ($C_{23'}$), 41.05 ($C_{24'}$), 29.48 ($C_{25'}$), 22.36 ($C_{26'}$), 22.87 ($C_{27'}$). IR data (cm^{-1}) KBr pellet: 1730 (C=O), 1628 (C=C), 1048 (C−O). MS (*m*/*z*) 768 [M]; Anal. Calcd. for $C_{54}H_{88}O_2$: C, 84.37; H, 11.45. Found: C, 84.34; H, 11.48%.

2.3 *Cholest-5-en-7-spiro-[4′α,5′-oxa]-5′ α-cholestan-7′-one (***4a***)*

Yield: (57%); m.p.: 224–226°C. ^{1}H NMR (300 MHz, $CDCl_3$) δppm: 5.31 (s, 1H, C_6-H, olefinic proton), 2.74 (s, 2H, $C_{6'}$-H_2), 2.19 (dd, 2H, J = 6.1, 4.8 Hz, C_4 − H_2), 2.41 (dd, 1H, J = 5.7, 4.2 Hz, $C_{4'}$-H), 1.19 (s, 3H, C_{10}-CH_3), 0.76 (s, 3H, C_{13}-CH_3), 1.15 (s, 3H, $C_{10'}$-CH_3), 0.74 (s, 3H, $C_{13'}$-CH_3), 0.96, 0.92, 0.85, 0.80 (other steroidal side-chain methyl protons). ^{13}C NMR (100 MHz, $CDCl_3$,) δppm: 206.53 (*C*O), 95.32 (C_7), 152.91 (C_5), 129.11 (C_6), 58.13 ($C_{4'}$), 97.36 ($C_{5'}$), 37.91 (C_1), 29.53 (C_2), 31.16 (C_3), 35.83 (C_4), 40.01 (C_8), 35.04 (C_9), 42.58 (C_{10}), 21.62 (C_{11}), 32.03 (C_{12}), 44.09 (C_{13}), 49.17 (C_{14}), 21.38 (C_{15}), 22.99 (C_{16}), 39.16 (C_{17}), 20.27 (C_{18}), 20.68 (C_{19}), 30.37 (C_{20}), 19.65 (C_{21}), 34.07 (C_{22}), 27.42 (C_{23}), 40.71 (C_{24}), 28.81 (C_{25}), 22.41 (C_{26}), 22.85 (C_{27}), 31.05 ($C_{1'}$), 25.67 (**C**$_{2'}$), 23.18 ($C_{3'}$), 49.39 ($C_{6'}$), 45.19 ($C_{8'}$), 30.66 ($C_{9'}$), 42.38 ($C_{10'}$), 21.88 ($C_{11'}$), 33.16 ($C_{12'}$), 40.28 ($C_{13'}$), 48.11 ($C_{14'}$), 20.96 ($C_{15'}$), 21.01 ($C_{16'}$), 39.90 ($C_{17'}$), 19.10 ($C_{18'}$), 19.93 ($C_{19'}$), 28.12 ($C_{20'}$), 18.81 ($C_{21'}$), 35.43 ($C_{22'}$), 26.14 ($C_{23'}$), 40.18 ($C_{24'}$), 29.92 ($C_{25'}$), 22.28 ($C_{26'}$), 22.95 ($C_{27'}$). IR data (cm^{-1}) KBr pellet: 1719 (C=O), 1625 (C=C), 1042 (C−O). MS (*m*/*z*) 768 [M]; Anal. Calcd. for $C_{54}H_{88}O_2$: C, 84.31; H, 11.53. Found: C, 84.27; H, 11.56%.

2.4 *3β-Chlorocholest-5-en-7-spiro-[4′α,5′-oxa]-3′ β-chloro-5′α-cholestan-7′-one (***4b***)*

Yield: (62%); m.p. 240–242°C. ^{1}H NMR (300 MHz, $CDCl_3$) δppm: 5.49 (s, 1H, C_6-H, olefinic proton), 2.42 (s, 2H, $C_{6'}$-H_2), 3.86 (br m, 1H, $W^1/_2$, 17.3 Hz, $C_3\alpha$-H), 3.59 (br m, 1H, $W^1/_2$, 16.6 Hz, $C_{3'}\alpha$-H), 2.13 (d, 2H, J = 6.1 Hz, C_4-H_2), 2.86 (d, 1H, J = 5.8 Hz, C_4'-H), 1.16 (s, 3H, C_{10}-CH_3), 0.75 (s, 3H, C_{13}-CH_3), 1.12 (s, 3H, $C_{10'}$-CH_3), 0.70 (s, 3H, $C_{13'}$-CH_3), 0.96, 0.94, 0.87, 0.81 (other steroidal side-chain methyl protons). ^{13}C NMR (100 MHz, $CDCl_3$) δppm**:** 205.31 (*C*O), 90.55 (C_7), 56.93 (C_3), 161.02 (C_5), 125.42 (C_6), 48.18 ($C_{3'}$), 57.63 ($C_{4'}$), 93.07 ($C_{5'}$), 34.19 (C_1), 37.68 (C_2), 45.02 (C_4), 38.35 (C_8), 35.25 (C_9), 42.53 (C_{10}), 21.15 (C_{11}), 32.18 (C_{12}), 43.10 (C_{13}), 48.07 (C_{14}), 21.28 (C_{15}), 22.01 (C_{16}), 39.22 (C_{17}), 20.13 (C_{18}), 20.38 (C_{19}), 30.15 (C_{20}), 18.98 (C_{21}), 36.43 (C_{22}), 26.61 (C_{23}), 39.66 (C_{24}), 29.89 (C_{25}), 22.48 (C_{26}), 22.96 (C_{27}), 25.32 ($C_{1'}$), 29.78 ($C_{2'}$), 46.14 ($C_{6'}$), 43.94 ($C_{8'}$), 31.57 ($C_{9'}$), 43.66 ($C_{10'}$), 21.18 ($C_{11'}$), 32.43 ($C_{12'}$), 40.91 ($C_{13'}$), 48.06 ($C_{14'}$), 21.07 ($C_{15'}$), 21.49 ($C_{16'}$), 39.01 ($C_{17'}$), 20.01 ($C_{18'}$), 20.65 ($C_{19'}$), 29.83 ($C_{20'}$), 19.11 ($C_{21'}$), 36.23 ($C_{22'}$), 27.19 ($C_{23'}$), 40.31 ($C_{24'}$), 29.40 ($C_{25'}$), 22.15 ($C_{26'}$), 22.70 ($C_{27'}$). IR data (cm^{-1}) KBr pellets: 1717 (C=O), 1622 (C=C), 1052 (C−O), 728, 736 (C−Cl). MS (*m*/*z*) 836 [M]: Anal. Calcd. for

$C_{54}H_{86}Cl_2O_2$: C, 77.38; H, 10.34. Found: C, 77.36; H, 10.37%.

2.5 *3β-Acetoxycholest-5-en-7-spiro-[4′α,5′-oxa]-3′β-acetoxy-5′α-cholestan-7′-one (**4c**)*

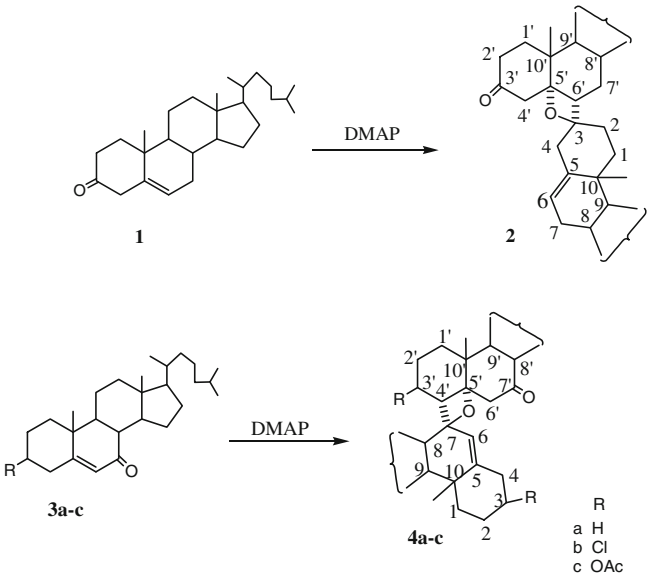
Yield: (58%); m.p. 219–221°C. ^{1}H NMR (300 MHz, $CDCl_3$) δppm: 5.63 (s, 1H, C_6-*H*, olefinic proton), 2.38 (s, 2H, $C_{6'}$-H_2), 4.63 (br m, 1H, $W^1/_2$, 17.6 Hz, $C_3\alpha$-*H*), 4.46 (br m, 1H, $W^1/_2$, 16.8 Hz, $C_{3'}\alpha$-*H*), 2.51 (d, 2H, J = 6.6 Hz, C_4'-H_2), 3.12 (d, 1H, J = 5.9 Hz, C_4'-*H*), 2.04 (s, 3H, of acetate -CH_3), 2.01 (s, 3H, of acetate -C$H_{3'}$), 1.18 (s, 3H, C_{10}-CH_3), 0.70 (s, 3H, C_{13}-CH_3), 1.16 (s, 3H, $C_{10'}$-CH_3), 0.74 (s, 3H, $C_{13'}$-CH_3), 0.94, 0.90, 0.83, 0.81 (other steroidal side-chain methyl protons). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 208.13 (*C*O), 88.03 (C_7), 82.35 (C_3), 158.27 (C_5), 129.76 (C_6), 70.83 ($C_{3'}$), 61.38 ($C_{4'}$), 96.08 ($C_{5'}$), 33.25 (C_1), 33.86 (C_2), 41.93 (C_4), 39.04 (C_8), 35.32 (C_9), 35.98 (C_{10}), 21.54 (C_{11}), 32.01 (C_{12}), 42.06 (C_{13}), 49.21 (C_{14}), 21.28 (C_{15}), 21.86 (C_{16}), 38.83 (C_{17}), 20.39 (C_{18}), 20.81 (C_{19}), 30.18 (C_{20}), 19.63 (C_{21}), 35.99 (C_{22}), 26.15 (C_{23}), 41.55 (C_{24}), 28.87 (C_{25}), 22.35 (C_{26}), 22.80 (C_{27}), 173.03 and 18.6 for carbonyl carbon and methyl carbon of acetate (C_3), 24.11 ($C_{1'}$), 26.81 ($C_{2'}$), 45.97 ($C_{6'}$), 44.90 ($C_{8'}$), 30.55 ($C_{9'}$), 43.82 ($C_{10'}$), 20.68 ($C_{11'}$), 31.95 ($C_{12'}$), 41.52 ($C_{13'}$), 48.11 ($C_{14'}$), 21.16 ($C_{15'}$), 21.35 ($C_{16'}$), 40.71 (**C**$_{17'}$), 19.58 ($C_{18'}$), 20.09 ($C_{19'}$), 29.84 ($C_{20'}$), 19.16 ($C_{21'}$), 37.02 ($C_{22'}$), 24.13 ($C_{23'}$), 39.61 ($C_{24'}$), 23.45 ($C_{25'}$), 22.21 ($C_{26'}$), 22.62 ($C_{27'}$), 170.45 and 19.3 for carbonyl carbon and methyl carbon of acetate ($C_{3'}$). IR data (cm^{-1}) KBr pellets: 1714 (C=O), 1739, 1732 (OAc), 1621 (C=C), 1063 (C−C). MS (*m*/*z*) 884 [M]; Anal. Calcd. for $C_{58}H_{92}O_6$: C, 78.68; H, 10.47. Found: C, 78.76; H, 11.50%.

3. Results and discussion

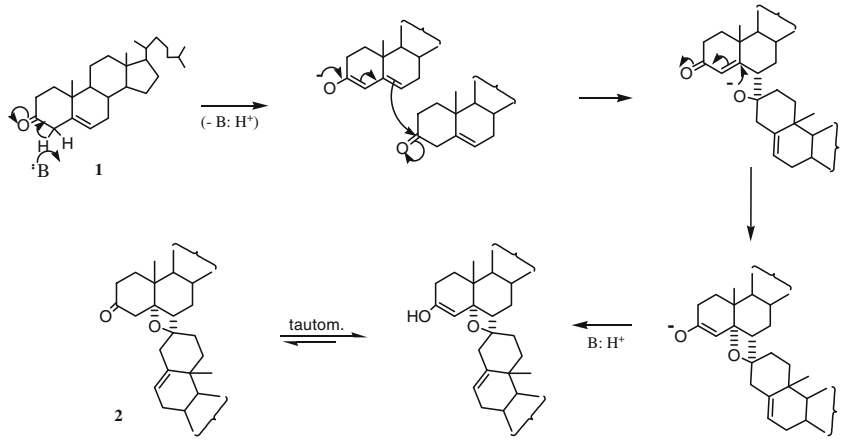
The cholest-5-en-3-one (**1**), cholest-5-en-7-one (**3a**) and its 3β-substituted derivatives (**3b, c**) on reaction with DMAP in xylene undergo amine catalysed dimerization to give steroidal dimers cholest-5-en-3-*spiro*-[6′α,5′-oxa]-5′α-cholestan-3′-one (**2**), cholest-5-en-7-*spiro*-[4′α,5′-oxa]-5′α-cholestan-7′-one (**4a**) and 3β-substituted-cholest-5-en-7-*spiro*-[4′α,5′-oxa]-3′β-substituted-5′α-cholestan-7′-one (**4b, c**) (scheme 1).

The obtained compound **2** was correctly analysed for $C_{54}H_{88}O_2$ [$M^{+\cdot}$ 768]. The appearance of molecular ion at m/z 768 clearly suggested the formation of a dimer. Its IR spectrum exhibited characteristic absorption bands at 1730 (C=O), 1628 (C=C) and 1048 cm^{-1} (C–O–C). The ^{1}H NMR spectrum of compound **2** displayed two double doublets integrating for one proton each at δ 5.59 (J = 7.6, 5.2 Hz) and 2.31 (J = 6.3, 4.8 Hz) for C_6-olefinic proton and $C_{6'}$-methine proton, respectively. The absence of another signal for olefinic proton in the ^{1}H NMR spectrum of **2** also suggested the formation of a dimer.

Two singlets for two protons each at 2.47 and 2.16 were assigned for $C_{4'}$-H_2 and C_4-H_2 respectively. Its ^{13}C NMR spectrum showed characteristic peaks at 95.63



Scheme 1. The formation of steroidal dimers from ketones.



Scheme 2. Mechanism for the formation of steroidal dimer.

(C_3) and 204.75 for carbonyl carbon ($C_{3'}$). Other important peaks were at δ 155.56 (C_5), 131.09 (C_6), 103.51 ($C_{5'}$) and 53.02 ($C_{6'}$).[19,20] Remaining carbon atoms of steroidal skeleton were appeared at expected regions. The IR spectra of compounds **4a–c** exhibited characteristic absorption bands at 1719 – 1714 (C=O), 1625 – 1621 for C=C and 1063–1042 cm^{-1} (C–O–C). The ^1H NMR spectra of compounds **4a–c** displayed two singlets integrating for one and two protons at δ 5.63 – 5.31 and 2.74 – 2.38 for C_6-olefinic proton and $C_{6'}-H_2$, respectively. $C_{4'}$-Proton of **4a** appeared as a double doublet at 2.41 (J = 5.7, 4.2 Hz) while in **4b** and **4c** it appeared as a doublet at 2.86 (J = 5.8 Hz) and 3.12 (J = 5.9 Hz) respectively (scheme 2).

Compounds **4b** and **4c** in their ^1H NMR spectra showed two doublets integrating for two protons at δ 2.13 (J = 6.1 Hz) and δ 2.51 (J = 6.6 Hz), respectively for C_4-H_2. Two broad multiplets integrating for one proton each appeared at δ 4.63 – 3.86 ($W1/2$ = 17.6–17.3 Hz) and 4.46 – 3.59 ($W1/2$ = 16.8–16.6 Hz) for $C_3\alpha$-H and $C_{3'}\alpha$-H, respectively.

In the ^{13}C NMR spectra of compounds **4a–c** characteristic signals were observed at δ 206.53 – 205.31 for carbonyl carbon ($C_{7'}$) and 95.32 – 88.03 for C_7 *spiro* carbon atom. Other important peaks at δ 161.02 – 152.91, 129.76 – 125.42, 61.38 – 57.63 and 97.36 – 93.07 were attributed for C_5, C_6, $C_{4'}$ and $C_{5'}$ respectively. Remaining carbon atoms of two steroidal skeletons appeared in the expected region. Compound **4b** showed positive Beilstein test for chlorine.

4. Conclusion

The present procedure provides a good method for the selective dimerization of steroidal ketones.

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