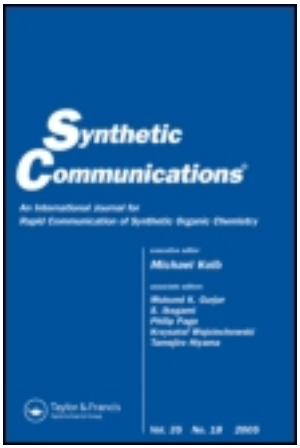

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Simple and Efficient Synthesis of Steroidal Hybrids of Estrogen and Vitamin D_3

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Abstract: A simple and efficient synthesis of steroidal hybrids of estrogen and vitamin D_3 through modification of estrone (**5**) at position 16 of the steroid nucleus is described.

Estrogens, mainly estradiol (**1**) and vitamin-D_3 (**2**), are the hormones involved in the maintenance of bones (Fig. 1).[1] In the body, both of these hormones are synthesized from the same starting material, cholesterol (**3**), in a multistep synthesis. Structurally, estradiol (**1**) has a tetracyclic rigid system with two hydroxyl groups placed at definite distance, required for its biological activity, whereas vitamin D_3 (**2**) has a highly flexible triene system (9,10-*seco*-steroid or b-ring *seco*-steroid).[2] In addition to this, vitamin D_3 has a flexible side chain with 1,25α-hydroxy groups required for its calcemic and antiproliferative activity.[3–7] In our search for bone-selective, antiproliferative agents for treatment of osteoporosis and breast cancer, we designed and synthesized steroidal hybrids of estrogen and vitamin D_3 of type **4** (Fig. 1). The target compounds (see structure **4**, $R = CH_3$ or $R = CH_2CH_3$) were made through modifications of estrone (**5**) at position 16 to which a side chain

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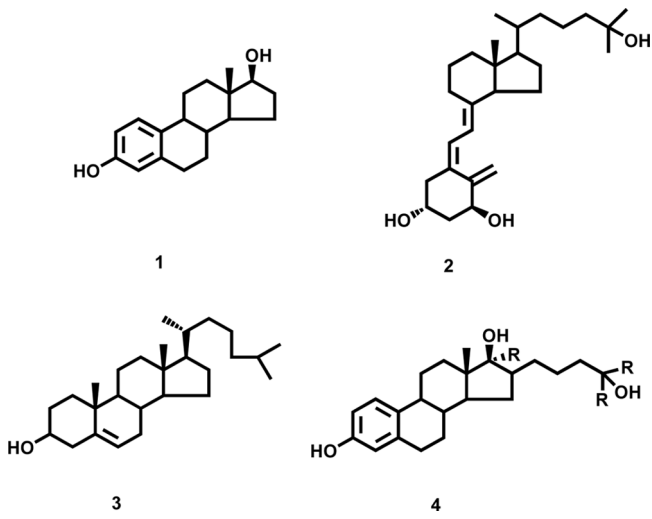
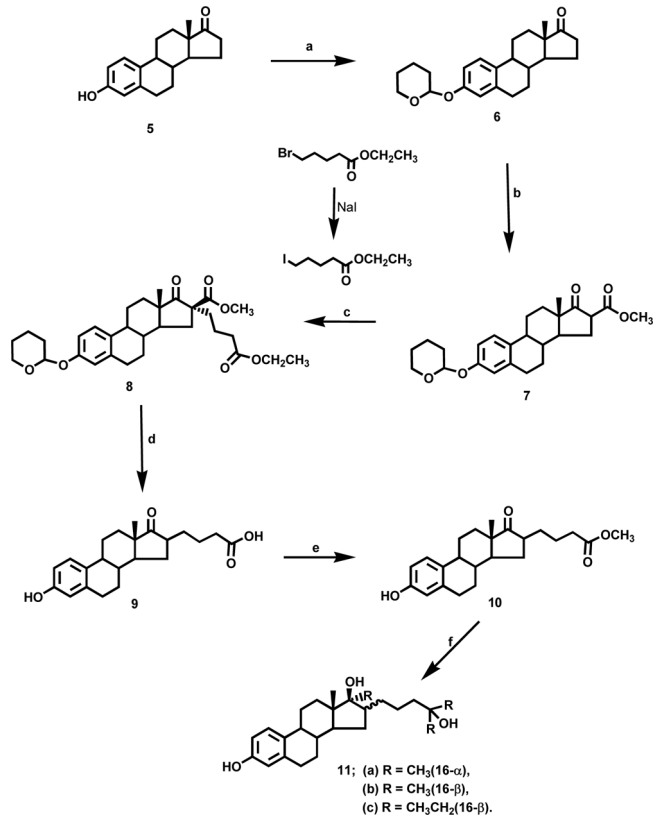


Figure 1. Biologically active steroidal molecules.

was incorporated as present in the vitamin D_3 (**2**) and its synthetic analogs as well as the tetracyclic core of estradiol (**1**) itself.

This communication presents a simple and efficient synthesis of steroidal hybrids of estrogen and vitamin-D_3 (**4**). The synthesis of the final compound (**4**) started from estrone (**5**) (Scheme 1). Estrone (**5**) was protected using dihydropyran in dichloromethane at room temperature (Rt), yielding 3-tetrahydropyranyloxy estrone (**6**) in 100% yield. Compound **6** was activated at position 16 through formation of β-ketoester (**7**). Compound **7** was obtained by reaction of **6** with dimethyl carbonate in the presence of potassium hydride (KH) in dry THF at reflux temperature in 90% yield. Alkylation of compound **7** with ethyl 4-iodobutyrate, prepared from ethyl 4-bromobutyrate, in biphasic medium using 10% aqueous solution of sodium hydroxide and dichloromethane and in the presence of benzyltriethylammonium chloride [$Bn(Et)_3N^+Cl^-$, phase-transfer catalyst (PTC)] gave compound **8** in 64% yield. It is noteworthy that the alkylation of compound **7** with ethyl 4-bromobutyrate to produce **8** under PTC reaction conditions was inefficient, so the corresponding ethyl 4-iodobutyrate ester was used instead. Decarboalkoxylation of compound **8** with lithium chloride in *N,N*-dimethylformamide at reflux temperature for 22 h gave compound **9** in 75% yield. Esterification of compound **9** with thionyl chloride in methanol at reflux temperature gave **10** in 95% yield. Grignard reaction was done on compound **10** using methyl and ethyl magnesium bromide in a dry diethyl ether–THF



Scheme 1. (a) Dihydropyran, pyridinium *p*-toluenesulphonate, DCM, 22 °C; (b) dimethyl carbonate, KH, dry THF, reflux; (c) ethyl 4-iodobutyrate, $Bn(Et)_3N^+Cl^-$, 10% NaOH, DCM, reflux; (d) LiCl, DMF, reflux; (e) thionyl chloride, CH_3OH, reflux; (f) CH_3MgBr or CH_3CH_2MgBr, dry Et_2O-THF, 22 °C.

mixture, which gave the target compounds **11a–c** in 48–70% yields. The Grignard reaction with methyl magnesium bromide on compound **10** gave a separable mixture of 16-α and β-alkyl substituted compounds (**11a** and **11b**) with β-orientation of the 17-hydroxy group. On a thin-layer chromatogram, the retention factors for 16-α and 16-β isomer in 30% acetone–hexane solvent system are 0.16 and 0.11 respectively. The 16-β isomer (compound **11b**) was the major product in this case, whereas the Grignard reaction with ethyl magnesium bromide yielded mainly the 16-β isomer (compound **11c**), which was the sole isolated product and has a 0.19 retention factor in 30% acetone–hexane solvent system. In ^1H NMR spectra, the 16-α (**11a**) and 16-β isomers (**11b**) showed singlets at

0.94 ppm and 0.84 ppm respectively for the 18-CH_3 group, whereas in ^{13}C NMR, these isomers showed signals at 13.8 ppm and 14.9 ppm for 18-CH_3 in 16-α and 16-β isomers, respectively. It is reported in the literature that 16α-alkyl substituted estradiol derivatives showed signals for 18-CH_3 group at higher ppm values in ^1H NMR spectra and at lowers ppm values in ^{13}C NMR spectra as compared to the corresponding 16-β isomer.[11] We assigned the stereochemistry of these novel compounds on the basis of observed similarities between our results and the reported data.

EXPERIMENTAL

Anhydrous reactions were performed under an inert atmosphere, with the setup assembled and cooled under dry nitrogen. Unless otherwise noted, starting material, reactant, and solvents were obtained commercially and were used as such or purified and dried by standard means.[8] Organic solutions were dried over magnesium sulfate ($MgSO_4$) and evaporated on a rotatory evaporator under reduced pressure. All reactions were monitored by UV fluorescence or stained with iodine. Commercial thin-layer chromatography (TLC) plates were Sigma T 6145 (polyester silica gel 60 Å, 0.25 mm). Flash chromatography was performed according to the method of Still and coworkers on Merck grade 60 silica gel, 230–400 mesh.[9] All solvents used in chromatography had been distilled. Melting points (MP) were recorded in open capillaries on an Electrothermal apparatus and are uncorrected. The infrared spectra (IR) were taken on a Nicolet model 205 FT-IR spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained in a $CDCl_3$ solution (unless otherwise noted), on a Varian 200-MHz instrument: chemical shifts were measured relative to the internal standard, tetramethylsilane (TMS, δ 0 ppm), for ^1H NMR. Chemical shifts (δ) are expressed in parts per million (ppm); the coupling constants (J) are expressed in hertz (Hz). Multiplicities are described by the following abbreviations: s for singlet, d for doublet, dd for double of doublet, t for triplet, q for quartet, m for multiplet, #m for several multiplets, and bs for broad singlet.

Synthesis of 3-Tetrahydropyranyloxy-1,3,5(10)-estratrien-17-one (6)[10]

To a solution of estrone **5** (5.00 g, 18.62 mmol) in dichloromethane (50 mL), dihydropyran (5.1 mL, 55.85 mmol) and pyridinium *p*-toluenesulfonate (100 mg) were added. The reaction mixture was stirred at 23 °C for 18 h. Afterward, sodium bicarbonate ($NaHCO_3$, 500 mg) and

$MgSO_4$ (5.0 g) were added to the reaction mixture and stirred 15 min before being filtered on a short pad of Celite® silica gel (1 cm/4 cm) using dichloromethane (DCM) as the eluent. The filtrate was evaporated to a viscous oil (100% yield), which was used without further purification in the next step.

IR (KBr, ν_{max}, cm^{-1}): 1742. ^1H NMR (200 MHz, $CDCl_3$, δ ppm): 7.19 (d, $J = 8.50$ Hz, 1H, ArH), 6.90–6.76 (2H, m, ArH), 5.39 (t, $J = 3.50$ Hz, 1H, CH_2), 3.90–3.58 (m, 2H, CH), 2.88 (m, 2H, CH_2), 2.60–1.30 (#m, 19H, $3 \times CH$ and $8 \times CH_2$), 0.90 (3H, s, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 220.9, 155.3, 137.9, 133.2, 126.4, 116.8, 114.4, 96.6, 62.2, 50.7 48.2, 44.3, 38.6, 36.1, 31.8, 30.7, 29.8, 26.8, 26.1, 25.5, 21.8, 19.0, 14.1.

Synthesis of 3-Tetrahydropyranyloxy-16α,β-methoxycarbonyl-1,3,5(10)-estratrien-17-one (7)[10]

A solution of 3-tetrahydropyranyloxy-1,3,5(10)-estratrien-17-one (**6**) (6.58 g, 18.20 mmol) in dry THF (50 mL) was added over a period of 20 min to a solution of dimethylcarbonate (3.98 mL, 47.2 mmol) and potassium hydride [2.27 g (3.6 g, 70% in oil), 56.68 mmol] in dry THF (40 mL). The mixture was heated to reflux for a period of 3 h. Most of the solvent was then evaporated, and the residue was diluted with ethyl acetate (100 mL) and treated with a saturated ammonium chloride solution (50 mL). The organic phase was washed with water (6×40 mL), dried, and evaporated to give a yellowish solid. Trituration of the residue with a mixture of acetone–hexanes (1:1) yielded the title compound in 90% yield as a white solid.

IR (NaCl, ν_{max}, cm^{-1}): 1755, 1728; ^1H NMR (200 MHz, $CDCl_3$, δ ppm): 7.19 (d, $J = 8.5$ Hz, 1H, ArH), 6.90–6.76 (m, 2H, ArH), 5.39 (t, $J = 3.50$ Hz, 1H, CH), 3.90–3.58 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 3.21 (t, $J = 8.6$ Hz, 1H, CH), 2.88 (m, 2H, CH_2), 2.50–1.20 (#m, 19H, $3 \times CH$ and $8 \times CH_2$), 0.98 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 212.4, 170.1, 155.3, 137.8, 132.9, 126.5, 116.7, 114.3, 96.5, 62.2, 54.3, 52.8, 49.2, 48.1, 44.3, 38.1, 32.2, 30.6, 29.8, 26.8, 26.6, 26.0, 25.5, 19.0, 14.6.

Synthesis of Ethyl 4-Iodobutyrate

Sodium iodide (0.58 g, 3.85 mmol) was added to a solution of ethyl 4-bromobutanoate (0.50 g, 2.56 mmol) in dry acetone (7 mL). The reaction mixture was stirred at an ambient temperature of 22 °C for 19 h in an inert atmosphere of nitrogen. Then, acetone was evaporated, and

the residue was taken in the diethyl ether (50 mL) and washed with a solution of thiosulfate (5% w/v, 2×20 mL) and 3×20 mL of water. The organic phase was separated dried over anhydrous $MgSO_4$ and concentrated to give desired compound as brown oil (0.60 g) in 100% yield. The product has been used without any purification in the next step.

IR (ν_{max}, cm^{-1}): 1731, 1200, 1164; ^{1}NMR (200 MHz, $CDCl_3$, δ ppm): 4.15 (q, $J = 7.20$ Hz, 2H, CH_2), 3.20 (t, $J = 6.60$ Hz, 2H, CH_2), 2.40 (t, $J = 7.00$ Hz, 2H, CH_2), 2.08 (q, $J = 7.10$ Hz, 2H, CH_2), 1.19 (t, $J = 7.20$ Hz, Hz, 3H, CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 172.4, 60.7, 35.0, 28.7, 14.4, 5.80.

Synthesis of 3-Tetrahydropyranyloxy-16β-(methoxycarbonyl)-16α-(4-ethoxycarbonylbutyl)-1,3,5(10)-estratrien-17-one (8)

A solution containing compound **7** (0.28 g, 0.67 mmol), the 4-ethyl iodobutyrate (0.65 g, 1.67 mmol), benzyltriethylammonium chloride (100 mg) and sodium hydroxide to 10% w/v (4 mL), 6 mL of dichloromethane was stirred vigorously and heated at reflux for 20 h. The reaction mixture was diluted with ether (10 mL) and extracted with a saturated solution of ammonium chloride (2×20 mL), and with water (4×10 mL). The organic phase was filtered, evaporated, and dried. The crude was purified by flash column chromatography with a mixture of hexane–acetone (8.5:1.5) to give the desired product **8** in 64% yield.

IR (ν_{max}, cm^{-1}): 1727, 1717, 1600, 1031; ^{1}H NMR (200 Hz, $CDCl_3$, δ ppm): 7.16 (d, $J = 8.60$ Hz, 1H, ArH), 6.86–6.78 (m, 2H, ArH), 5.39–5.37 (bs, 1H, CH), 4.14 (q, 2H, CH_2), 3.96–3.84 (m, 1H, CH), 3.71 (s, 3H, OCH_3), 3.65–3.52 (m, 1H, CH), 2.89–2.85 (m, 2H, CH_2), 2.33–2.6 (m, 4H, CH_2), 2.08–1.79 (#m, 9H, 3CH and $3CH_2$), 1.79–1.36 (#m, 13H, CH and numbers of CH_2), 0.92 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 213.9, 173.2, 171.7, 155.3, 137.8, 132.9, 126.4, 116.7, 114.3, 96.5, 62.1, 60.6, 60.2, 52.9, 49.7, 46.3, 44.3, 38.1, 34.9, 34.4, 32.3, 30.7, 30.6, 29.8, 26.7, 25.9, 25.5, 21.1, 19.0, 14.5.

Synthesis of 3-Hydroxy-16α,β-(4-carboxylbutyl)-1,3,5(10)-estratrien-17-one (9)

Estrone derivative **8** (0.20 g, 0.33 mmol), lithium chloride (0.31 g, 7.37 mmol), and water (0.4 mL) were dissolved in *N,N*-dimethylformamide (2 mL) and refluxed for 22 h. On the completion of reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with a solution of hydrochloric

acid 10% v/v and water. After filtration, the organic phase was dried and evaporated. The resulting product was purified by flash chromatography with a mixture of hexane solvents–acetone (85: 15), which gave compound **9** in 75% yield.

Mp 206–08 °C; IR (NaCl, ν_{max}, cm^{-1}): 3200–3600, 1711, 1604, 1231, 1021; ^{1}H NMR (200 Hz, $CDCl_3$, δ ppm): 11.20 (s, 1H, OH). 7.20 (d, $J = 8.70$ Hz, 1H, ArH), 6.89 (dd, $J = 2.60$ Hz and $J = 8.70$ Hz, 1H, ArH), 6.69 (d, $J = 2.00$ Hz, 1H, ArH), 5.20 (s, 1H, OH), 2.88–2.83 (m, 2H, CH_2), 2.40–1.20 (#m, 23H, $1 \times CH_3$, $4 \times CH$ and $8 \times CH_2$), 0.98 (s, 3H, 18-CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$ and DMSO-d_6, δ ppm): 222.8, 222.3, 176.3, 176.2, 155.0, 137.9, 131.0, 126.4, 115.6, 113.3, 49.3, 49.1, 48.8, 48.6, 48.4, 44.9, 44.3, 44.1, 38.5, 38.2, 34.2, 32.1, 30.6, 29.7, 28.7, 27.5, 26.9, 26.7, 26.0, 23.7, 14.8, 14.2.

Synthesis of 3-Hydroxy-16α,β-(4-methyloxycarbonylbutyl)-1,3,5(10)-estratrien-17-one (10)

Thionyl chloride (0.23 mL) was added drop by drop to a solution of acid **9** (0.20 g 0.56 mmol) in dry methanol at 0 °C. The ice bath was removed after complete addition, and the mixture was refluxed for 4 h. The solvent was evaporated, and residue was taken in the ether (15 mL) and washed with water (3×5 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated. The crude was purified by flash chromatography using a mixture of hexane–acetone (95:5), yielding compound **10** in 95% yield.

MP 144–46 °C; IR (NaCl, ν_{max}, cm^{-1}): 3200–3600, 1711, 1604, 1231, 1021; ^{1}H NMR (200 Hz, $CDCl_3$, δ ppm): 7.18 (d, $J = 8.70$ Hz, 1H, ArH), 6.91 (dd, $J = 2.60$ Hz and $J = 8.70$ Hz, 1H, ArH), 6.69 (d, $J = 2.00$ Hz, 1H, ArH), 5.10 (s, 1H, OH), 3.67 (s, 3H, CH_3), 2.88–2.83 (m, 2H, CH_2), 2.40–1.20 (#m, 23H, $4 \times CH$ and $8 \times CH_2$), 0.98 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 223.5, 222.9, 174.6, 174.5, 154.3, 138.1, 131.8, 126.5, 115.6, 113.2, 52.0, 49.4, 49.1, 50.0, 48.8, 48.5, 44.9, 44.3, 44.1, 38.5, 38.2, 34.2, 34.1, 32.1, 31.9, 31.2, 30.7, 29.7, 28.7, 27.5, 26.9, 26.7, 26.1, 23.7, 14.9, 14.2.

Synthesis of 16α-(4-Hydroxy-4-methylpentyl)-17α-methyl-1,3,5(10)-estratrien-3,17β-diol (11a) and 16β-(4-Hydroxy-4-methylpentyl)-17α-methyl-1,3,5(10)-estratrien-3,17β-diol (11b)

To a solution of methyl magnesium bromide (3.00 molar solution in Et_2O, 5.61 mL, 15.14 mmol), a solution of methyl ester (**10**) (0.18 g,

0.50 mmol) dissolved in anhydrous THF was added drop by drop at room temperature (Rt). The reaction mixture was stirred for 3 h. On the completion of reaction, the mixture was quenched with a saturated solution of ammonium chloride and extracted with ethyl acetate. The organic phase was dried and concentrated to crude product. The purification of the crude product was carried out on a silica-gel column using a mixture of hexane–acetone (75:25) as the eluent, which gave pure compound **11a** (22% yield) and **11b** (48% yield) as white solids.

Spectral data for **11a**: MP 122–24 °C; IR (ν_{max}, cm^{-1}): 3350, 1507, 1456, 1240, 1157, 1089, 758; ^{1}H NMR (200 Hz, acetone, δ ppm): 7.93 (bs, 1H, OH), 7.08 (d, $J = 8.00$ Hz, 1H, ArH), 6.61–6.51 (m, 2H, ArH), 3.12 (bs, 1H, OH), 2.90 (bs, 1H, OH), 2.74 (bs, 2H, CH_2), 2.31–2.23 (m, 1H, CH), 2.07–2.02 (m, 2H, CH_2), 1.90–1.81 (m, 1H, CH), 1.61–1.21 (m, 12H, CH and CH_2), 1.15 (s, 6H, $2 \times CH_3$), 0.94 (s, 3H, CH_3); ^{13}C NMR (50 MHz, acetone, δ ppm): 155.3, 137.8, 131.6, 126.3, 115.3, 112.9, 81.9, 69.5, 48.2, 47.3, 46.8, 44.6, 44.3, 40.1, 32.2, 31.9, 29.7, 29.0, 27.7, 26.6, 24.03, 18.9, 13.8.

Spectral data for **11b**: MP 149–151 °C; IR (ν_{max}, cm^{-1}): 3365, 1513, 1456, 1291, 1254, 1220, 1154, 755; ^{1}H NMR (200 Hz, acetone, δ ppm): 7.92 (bs, 1H, OH), 7.09 (d, $J = 8.20$ Hz, 1H, ArH), 6.61–6.51 (m, 2H, ArH), 3.15 (bs, 1H, OH), 2.92 (bs, 1H, OH), 2.76 (bs, 2H, CH_2), 2.31–1.80 (m, 4H, CH and CH_2), 1.73–1.23 (m, 14H, CH and CH_2), 1.20 (s, 3H, CH_3), 1.15 (s, 6H, $2 \times CH_3$), 0.84 (s, 3H, CH_3); ^{13}C NMR (50 MHz, acetone, δ ppm): 155.3, 137.8, 131.6, 126.3, 115.3, 112.9, 80.2, 69.6, 49.7, 48.5, 46.8, 44.6, 44.1, 39.6, 34.0, 33.1, 32.9, 29.8, 28.4, 28.0, 27.9, 26.6, 23.9, 14.9.

Synthesis of 16β-(4-Hydroxy-4-ethylhexyl)-17α-methyl-1,3,5(10)-estratrien-3,17β-diol (11c)

Compound **11c** was synthesized in 50% yield with the same experimental procedure used for the synthesis of compound **11a**, substituting methylmagnesium bromide by ethylmagnesium bromide.

Mp 91–93 °C; IR (ν_{max}, cm^{-1}): 3350, 1613, 1502, 1456, 1291, 1257, 1074, 755; ^{1}H NMR (200 Hz, acetone, δ ppm): 7.92 (bs, 1H, OH), 7.09 (d, $J = 10.00$ Hz, 1H, ArH), 6.61–6.51 (m, 2H, ArH), 3.76–3.69 (dd, 1H, CH), 3.53–3.49 (dd, 1H, CH), 3.47–3.39 (m, 1H, CH), 3.31 (d, $J = 6.00$ Hz, Hz, 1H, CH), 2.84–2.73 (m, 2H, CH_2), 2.31–1.61 (m, 2H, CH_2), 1.54–0.97 (m, 16H, $3 \times CH_3$ and #CH_2), 0.95 (t, $J = 7.40$ Hz, $2 \times CH_2$), 0.78 (s, 3H, CH_3); ^{13}C NMR (50 MHz, acetone, δ ppm): 155.3, 137.8, 131.5, 126.4, 115.3, 112.9, 81.7, 72.2, 48.9, 44.3, 40.8, 38.9, 38.1, 37.8, 32.8, 32.2, 30.4, 29.7, 27.7, 26.6, 25.2, 25.1, 12.5, 9.79.

CONCLUSIONS

In conclusion, this communication presents a simple and efficient synthesis of biologically important steroid based hybrids of estradiol and vitamin D_3 (**4**) through simple modifications of estrone **5** at position 16 of the steroid nucleus.

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