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Synthetic studies towards steroid-amino acid hybrids

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New prototype of natural steroid amino acid hybrid containing nine membered D-ring in the steroid skeleton has been synthesized from commercially available estrone using standard synthetic organic transformations. $NaIO_4$ cleavage of the D-ring of the benzylated estriol furnishes the D-*seco* diol **8**, which after a series of organic reactions (protection of the hydroxyl group, oxidation, reductive amination, deprotection and the Yamaguchi cross coupling) gives the coveted steroid-amino acid hybrids. The methodology can be extended for combinatorial synthesis of new and interesting steroid amino acid hybrids.

Keywords: Steroid, amino acids, hybrid, Yamaguchi coupling, macrolactonization

Naturally occurring molecules possess novel physical, chemical and biological properties[1]. But the research and development of novel therapeutic agents are often handicapped by the availability in small quantities from natural sources. To mimic the nature and to have a diverse range of natural product like molecules, efforts are made to combine the structural features of one or two natural products from Nature's structural diversity into a hybrid molecule that could have more useful properties. Much attention has been paid in the last two decades[2a-g] and such hybrids have been synthesized either by classical organic methods or by rationally combining two or more active pharmacophores of different classes of natural products into a hybrid one. From application point of view, this approach appears to be quite useful.

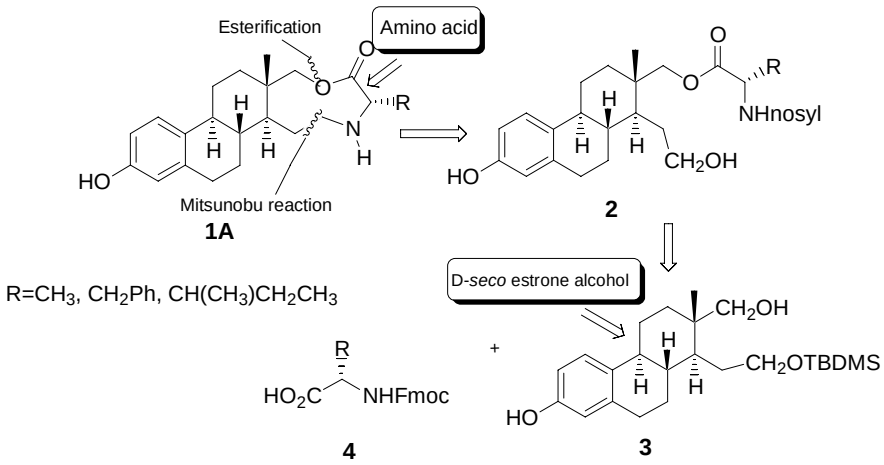
Various hybrid molecules derived from steroids[3], C_{60}-fullerene[4], taxoids[5], β-lactams[6], duocarmycin[7] and carbohydrates[8] are being widely explored for creating new molecular entities of biological importance. For example, hybrids originated from steroids and amino acids or peptides, *i.e.* peptidyl steroids, have been reported recently[9-12]. In this article, details of our synthetic efforts towards accessing steroid amino acid hybrids by incorporation of amino acids into the D-ring of steroids are reported.

Results and Discussion

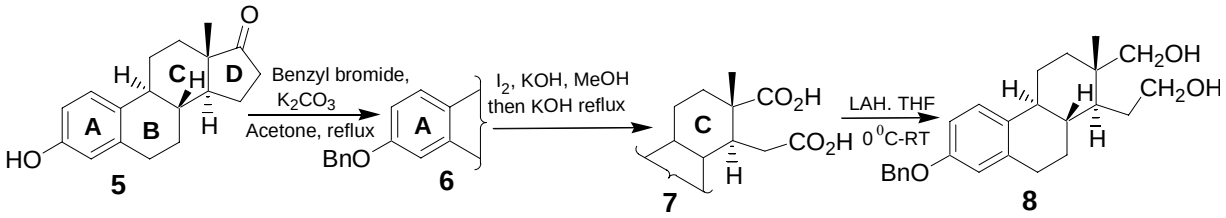
The targeted molecule **1A**, having constrained 9 membered D-ring with heteroatoms on steroidal framework which provides a highly efficient access to novel molecular hybrids on retrosynthetic analysis bifurcates into two residues *i.e.* D-*seco* estrone alcohol **3** and amino acid **4**, which are joined together by carbon (C) – nitrogen (N) and ester bonds. [Esterification reaction between D-*seco* estrone alcohol **3** and N-Fmoc protected amino acid **4** may give the intermediate **2**, which under Mitsunobu reaction conditions would furnish the target molecule **1A**] (**Scheme I**).

It is evident that the D-*seco* estrone alcohol **3** is the intermediate for accessing **1A** and it is readily synthesized from readily available estrone **5**. Estrone **5** was converted to its benzylated derivative **6**. Compound **6** on haloform reaction provided the benzyl-*O*-marrianolic acid **7**. They were identified by comparing their FABMS and ^{1}H NMR spectra with the reported ones[13]. The diacid **7** was then converted to diol **8** through lithium aluminium hydride (LAH) treatment at 0°C in tetrahydrofuran (THF) (**Scheme II**) but the overall yield was very low (26%). Therefore, an alternating strategy for large-scale synthesis of diol **8** was developed.

To realise this objective, estriol **9** was synthesised from benzylated estrone **6** and then transformed it to diol **8**. Accordingly, benzylated estrone **6** was converted into enol acetate **10** by reaction with isopropenyl acetate in presence catalytic amount of H_2SO_4 (Ref 14). Treatment of enol acetate **10** with *m*-chloroperbenzoic acid (*m*CPBA) gave the epoxide **11**,



Scheme I — Retrosynthetic anaysis of target **1A**



Scheme II — Synthesis of diol **8**

which on reduction with lithium aluminium hydride (LAH) afforded benzylated estriol **9** with an overall yield of 60% (**Scheme III**)[14].

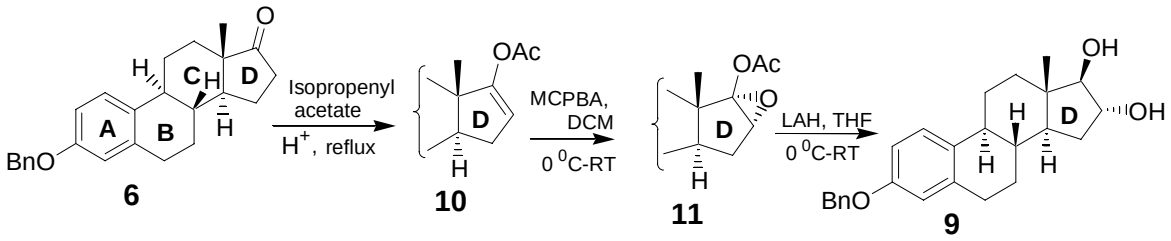
Treatment of **9** with sodium meta periodate ($NaIO_4$) in methanol afforded the unstable dialdehyde **12**. It is unstable at RT but is stable at -4°C for 5-10 days. LAH reduction of **12** at 0°C afforded the diol **8** in 81% yield. The overall yield of diol **8** from estrone **5** through this route is 42%, which is better than the yield (26%) obtained by previous procedure (**Scheme II**).

The next objective of obtaining the key intermediate mono protected D-*seco* estrone alcohol **3** from **8** was accomplished in protecting **8** with 1:1 equivalent of *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DCM at 0°C in 67% yield (**Scheme IV**).

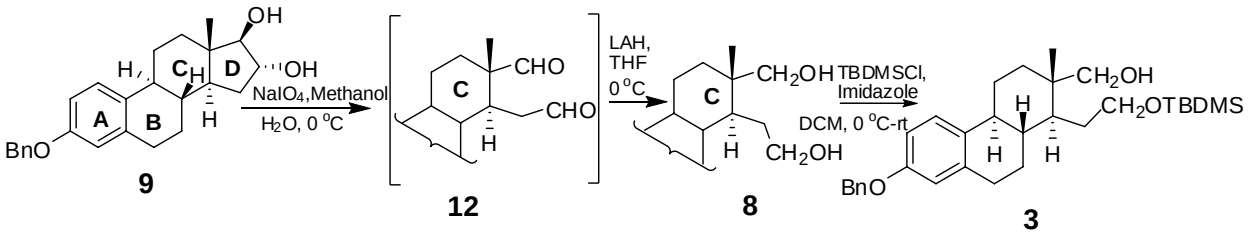
To synthesize target molecule **1A**, D-*seco* estrone alcohol **3** was esterified with 9-fluorenylmethoxy carbonyl (Fmoc) protected amino acid **4** (R=$CH_2C_6H_5$) in the presence of N, N′-diisopropylarbodiimide (DIC), 4-dimethyl aminopyridine (DMAP) and dichloromethane (DCM) to afford the ester **13** in 62% yield. The amino group in **13** was deprotected from the Fmoc group to obtain the free amine **14**. It was activated for Mitsunobu reaction by reprotecting it with *o*-nitro benzene sulphonyl chloride to afford the N-nosyl derivative **15** (86%). The TBDMS group in **15** was then eliminated by treatment with AcOH: H_2O: THF (3:1:1) at 50-60°C to afford the alcohol **16** in 69% yield. The intermediate **16** was then subjected to intramolecular Mitsunobu reaction in presence of triphenylphosphine (PPh_3), diethylazodicarboxylate (DEAD) and THF to afford the derivative of **1A** (**Scheme V**). But this cyclization did not yield the desired products even after several attempts.

At this point, instead of **1A**, its steroid amino acid hybrid **1B** has been made the synthetic target. Retrosynthetic analysis **1B** illustrates that it could be obtained through intermediate **18** by initial formation of C-N bond by Mitsunobu reaction between D-*seco* estrone alcohol **3** and N-nosyl amino acid methyl ester **19** followed by macrolactonization reaction (**Scheme VI**).

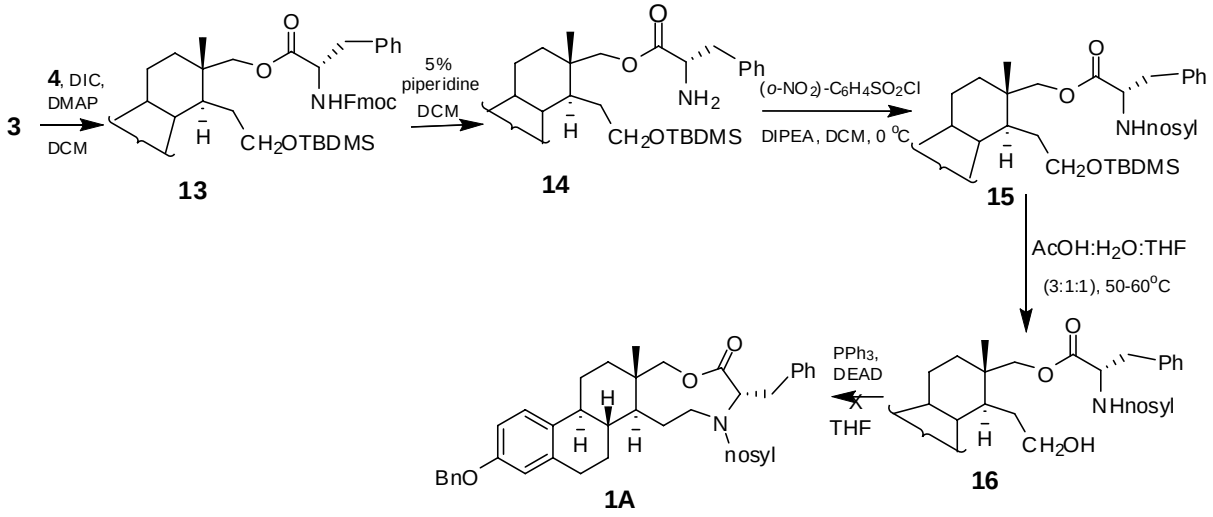
The approach adopted for the synthesis of **1B** is that D-estrone alcohol **3** was converted into the corresponding aldehyde **20** and the C-N bond was built on it by reductive amination. Thus **21** was synthesized from D-*seco* estrone alcohol **3** in 82% yield by using N-methyl morpholine N-oxide



Scheme III — Synthesis of benzylated **9**



Scheme IV — Synthesis of key intermediate mono protected D-*seco* estrone alcohol **3**



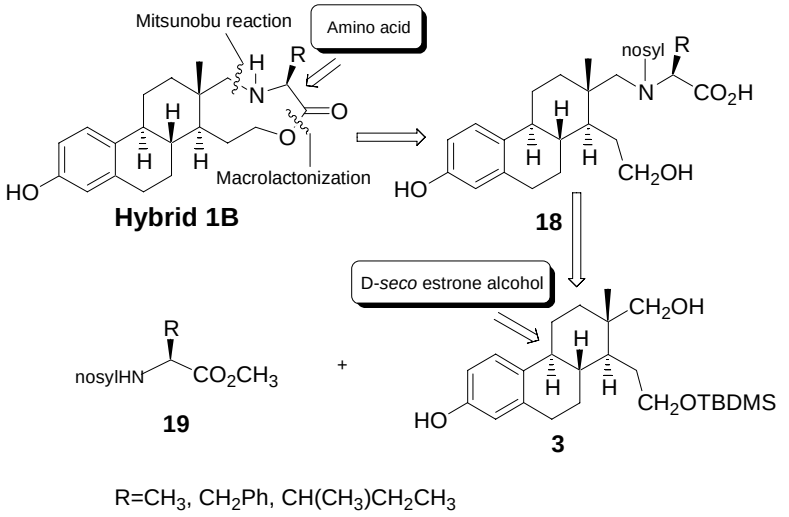
Scheme V — Unsuccessful synthesis of **1A**

(NMMO) and tetra-*n*-propyl ammonium per ruthenate (TPAP) in DCM.

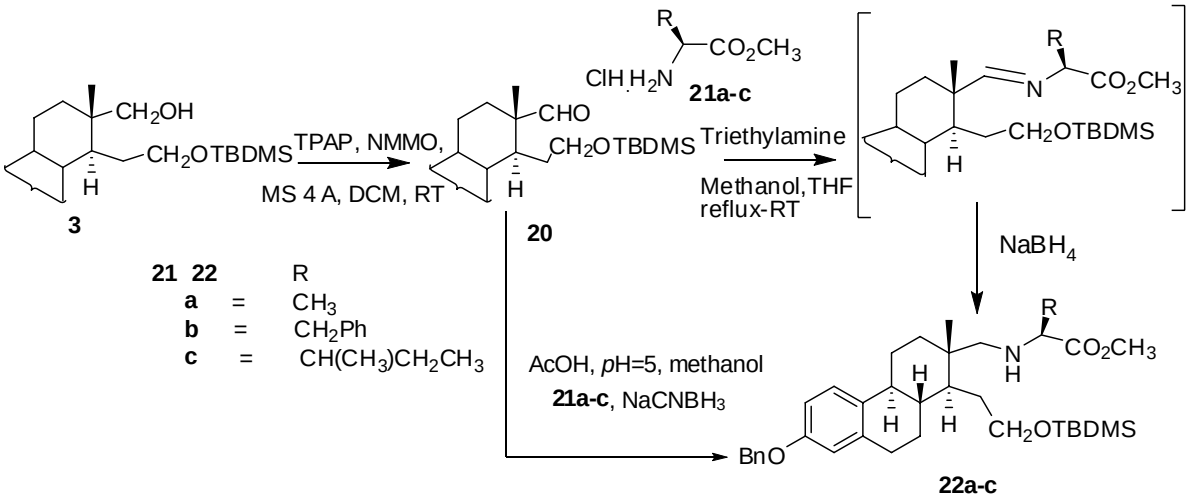
Reaction of **20** with three amino acid methyl ester hydrochlorides[16] **21a-c** in the presence of sodium cyano borohydride ($NaCNBH_3$) and acetic acid under mild acidic *p*H (=5) afforded the amino acid esters **22a-c** in 30, 34 and 31% yield respectively (**Scheme VII**). Yields of **22a-c** were improved (80%, 78% and 73% respectively) by performing the reaction in two steps through initial formation of imines followed by reduction with $NaBH_4$.

Further, to avoid the side reactions in the next steps, the secondary amine function in **22a-c** was converted to tertiary amine **23a-c** in 97, 95 and 93% respectively by methylation. Subsequent deprotection of alcohol group in **23a-c** from TBDMS furnished **24a-c** which were further converted to hydroxyl acids **25a-c** on hydrolysis.

Macrolactonization of the hydroxy acids **25a-c** by using 2,4,6-trichlorobenzoyl chloride, triethyl amine and DMAP in toluene afforded[17] the corresponding lactones **28a** (53%) **28b** (63%) and **28c** (42%) which



Scheme VI — Retrosynthetic anaysis of target **1B**

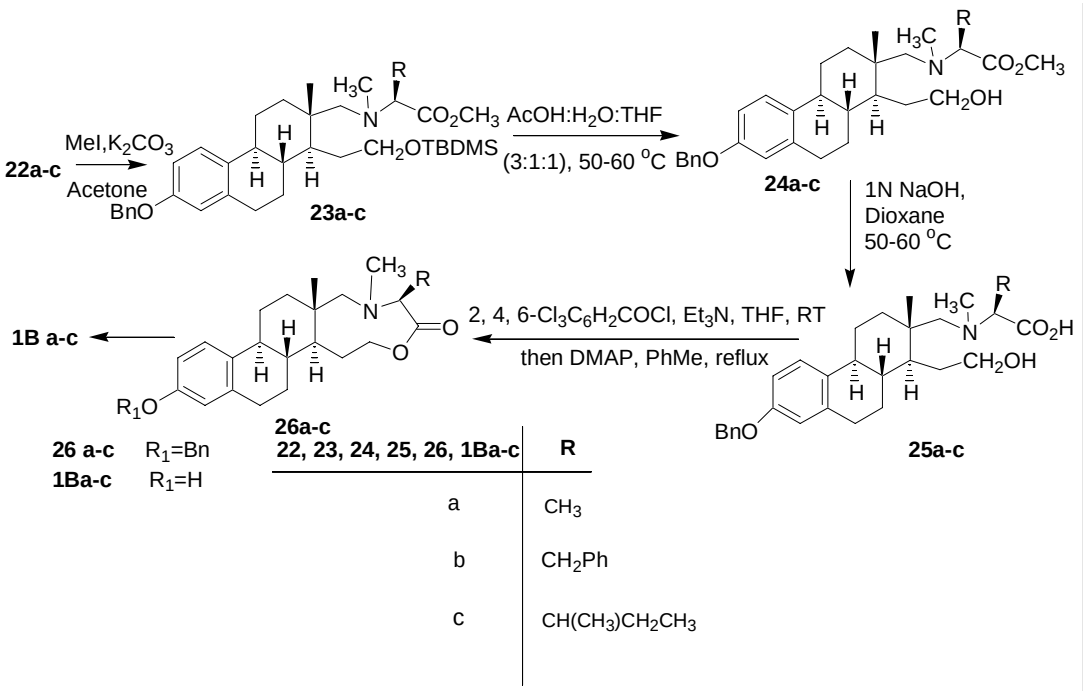


Scheme VII — Synthesis of amines **22a-c**

can afford the target molecules **1Ba, 1Bb** and **1Bc** on deprotection of benzyl group (**Scheme VIII**). The structures of lactones **26a-c** were confirmed by analysis of FABMS and NMR spectra. FABMS spectra of **26a-c** showed M^++H peak at *m/z* 448, 524 and 490 respectively. In ^{1}H NMR spectrum of **26a**, the protons at C-16 appeared as two sets of multiplets at δ 4.79-4.71 and δ 3.98-3.81. The -C*H*-CH_3 and C-17 protons appeared as multiplets at δ 3.62-3.60 and δ 2.43-2.27 respectively. A doublet for three methyl protons (-CH-CH_3) appeared at δ 1.16 (J = 6.6 Hz). The ^{1}H NMR of **26b** displayed two characteristic multiplets at δ 4.53-4.50 and δ 4.19-4.05 for C-16 protons, a one proton multiplet at δ 3.66-3.64 for -C*H*-CH_2-C_6H_5, a two proton multiplets at δ 3.07-2.91 for -CH-CH_2-C_6H_5 and two proton multiplet at δ 2.39-2.27 for C-17. ^{13}C NMR, ^{1}H-^{1}H COSY, HMQC and HSQC spectra further confirmed the identity of **26b**.

The ^{1}H NMR of **26c** also showed two characteristic multiplets at δ 4.40 - 4.21 and δ 4.21- 4.16 for C-16 protons, one proton multiplet at δ 3.15-3.19 for -C*H*-CH-(CH_3)-CH_2-CH_3 and two multiplet at δ 1.95-1.75 and δ 1.73-1.70 for -CH-C*H*-(CH_3)-CH_2-CH_3 protons.

In conclusion, we have accomplished synthesis of a new prototype of steroid-amino acid hybrids **1B** from easily available estrone **5** and amino acids through a series of simple and efficient steps involving $NaIO_4$ cleavage of estriol, reductive amination and macrol-



Scheme VIII — Synthesis of benzylated target molecule **1B**

actonization reactions. In the process, several molecules such as diol **8**, D-*seco* estrone alcohol **3**, D-*seco* estrone aldehyde **20** and D-*seco* estrone amino acid conjugates **22a-c**, **23a-c**, **24a-c** and **25a-c** which can be used as advanced intermediates for accessing novel steroid derivatives have also been synthesized. In addition a simple and convenient approach for the preparation of novel 9 membered D-ring heteroteroids by incorporation of amino acids into the D-ring of steroid has been developed. This approach may enable access to combinatorial type solution phase library synthesis of steroid-amino acid hybrids and pave the way for finding new leads for drug development.

Experimental Section

All the reactions were monitored by thin layer chromatography using silica gel coated TLC plates. The spots on TLC were visualized by spraying 2% $CeSO_4$ in 2N H_2SO_4 on the plates and warming on a hot plate or in an oven at about 100°C. Silica gel 60-120 mesh was used for column chromatography. Melting point was recorded on an electrically heated REMI MP-1 apparatus and is uncorrected. IR spectra were recorded on Perkin Elmer 881 or FT IR 820/PC instrument and values are expressed in cm^{-1}. Electron impact mass spectra were recorded on JEOL/D-300 instrument. FAB mass spectra were recorded on JEOL SX 102/DA-6000 mass using Argon /Xenon (6 KV, 10 MA) as the FAB gas. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 200 MHz using TMS as internal reference in $CDCl_3$. Chemical shift value is expressed in δ ppm. Elemental analysis was carried out on Carlo ERBA-1108 analyzer. Commercially available grades of organic solvents of adequate purity were used. Acetone after heating at reflux with $KMnO_4$ for 4 hr, was distilled and stored in a bottle over dry K_2CO_3. Tetrahydrofuran was dried over calcium sulphate and then refluxed over lithium aluminium hydride and passed through a column of alumina to remove peroxides. It was distilled and stored over molecular sieves 3Å.

3-Benzyloxy-estran-16α, 17β-diol, 9

To a stirred solution of LAH (0.54 g, 14.35 mmole) in THF (30 mL) at 0°C was added a solution of epoxide **11** (4 g, 9.57 mmole) in THF (5 mL). The resulting solution was stirred at RT for 1 hr. After completion (monitored by TLC), the reaction was quenched with ethyl acetate followed by water at 0°C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was charged over silica gel and eluted

with 50% ethyl acetate in hexane (R_f = 0.3) to furnish the diol **9** (3.12 g, 86%) as white solid, m.p. 83°C.

IR (KBr): 3423, 2931, 1608, 1499, 1219, 1023, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.31(m, 5H, -O-CH_2-C_6H_5), 7.19 (d, 1H, *J* = 8.6 Hz, C-1-*H*), 6.78 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.4 Hz, C-2-*H*), 6.72 (d, 1H, *J* = 2.4 Hz, C-4-*H*), 5.03 (s, 2H, -O-CH_2-C_6H_5), 4.20-4.16 (m, 1H, C-16-*H*), 3.59 (d, 1H, *J* = 5.7 Hz, C-17-*H*), 2.92-2.73 (m, 2H, C-6-H_2), 2.54 (bs, 2H, C-16-O*H* and C-17-O*H*), 2.40-2.22 (m, 2H), 1.93-1.83 (m, 3H), 1.68-1.29 (m, 6H), 0.80 (s, 3H, C-18-H_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.1 (C-3), 138.3 (C-5), 137.7, 133.1 (C-10), 128.9, 128.2, 127.8, 126.6 (C-1), 115.2 (C-4), 112.7 (C-2), 90.1 (C-17), 78.8 (C-16), 70.3 (-O-*C*H_2-C_6H_5), 48.2, 44.3, 38.6, 37.0, 33.9, 30.1 (C-6), 27.6 (C-12), 26.2(C-11), 12.7 (C-18); MS (FAB): *m/z* (%) 378 (70, [M^+]), 289 (50, [M^+-CH_2-C_6H_5)]). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.67; H, 8.31%.

3-Benzyloxy-16, 17-secoestra-1, 3, 5(10)-triene-16-(*tert*-butyl-dimethyl-silanyloxymethyl)-17-{2*S*-(9*H*-Fluoren-9-ylmethoxycarbonylamino)(3-phenyl-proionic acid), 13

To a solution of D-*seco* estrone alcohol **3** (0.46 g, 0.93 mmole), fmoc phenyl alanine **4** (0.54 g, 1.39 mmole) and DMAP (0.17 g, 1.39 mmole) in DCM (10 mL) at 0°C was added DIC (0.22 mL, 1.39 mmole). The reaction mixture was stirred at RT overnight. The reaction was quenched with H_2O and diluted with DCM. The organic layer was separated and the aqueous layer was extracted with DCM twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was charged over silica gel and eluted with 15% ethyl acetate in hexane (R_f = 0.5) to furnish **13** (0.5 g, 62.4%) as yellow viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 2H, *J* = 7.5 Hz, Ar*H*), 7.59-7.56 (m, 2H, Ar*H*), 7.46-7.29 (m, 12H, Ar*H),* 7.21-7.15 (m, 2H, Ar*H*), 6.82 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.4 Hz, C-2-*H*), 6.75 (d, 1H, *J* = 2.4 Hz, C-4-*H*), 5.32 (d, 1H, *J* = 8.1 Hz, -N*H*-), 5.05 (s, 2H, -O-CH_2-C_6H_5), 4.75-4.72 (m, 1H, -C*H*-CH_2-C_6H_5), 4.49-4.43 (m, 1H, -CO-O-CH_2-CH-), 4.35-4.30 (m, 1H, -CO-O-CH_2-CH-), 4.24-4.13 (m, 2H, C-17-H_2), 3.83 (d, 1H, *J* = 10.8 Hz, -CO-O-CH_2-C*H*-), 3.65-3.63 (m, 1H, C-16-*H*), 3.52-3.49 (m, 1H, C-16-*H*), 3.20-3.13 (m, 2H, -CH-CH_2-C_6H_5), 2.87-2.85 (m, 2H, C-6-H_2), 2.24-2.21 (m, 2H), 2.09-2.06 (m, 1H), 1.41-1.28 (m, 8H), 0.92 {s, 9H, -C(CH_3)$_3$}, 0.85 (s, 3H, C-18-H_3), 0.04 {s, 6H, -Si(CH_3)$_2$-}; MS (FAB): *m/z* (%) 864 (100, [M^++H]). Anal. Calcd for $C_{55}H_{65}NO_6Si$: C,76.44; H, 7.58; N, 1.62. Found: C, 76.64; H, 7.99; N, 1.87%.

3-Benzyloxy-16, 17-secoestra-1,3, 5(10)-triene-16-(*tert*-butyl-dimethyl-silanyloxymethyl)-17-(2*S*-amino-3-phenyl-propionic acid), 14

Compound **13** (0.4 g, 0.46 mmole) was treated with 5 mL of 5% piperidine in DCM and kept for 2-3 hr. The reaction mixture was diluted with DCM and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was charged over silica gel and eluted with 25% ethyl acetate in hexane (R_f = 0.5) to furnish **14** (0.23 g, 77%) as light yellow viscous oil.

^1H NMR (200 MHz, $CDCl_3$): δ 7.42-7.20 (m, 11H, -O-CH_2-C_6H_5, -CH-CH_2-C_6H_5 and C-1-*H*), 6.79 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.4 Hz, C-2-*H*), 6.66 (d, 1H, *J* = 2.4 Hz, C-4-*H*), 5.01 (s, 2H, -O-CH_2-C_6H_5), 4.24-4.21 (m, 2H, C-17-H_2), 3.87-3.85 (m, 1H, -C*H*-CH_2-C_6H_5), 3.65-3.51 (m, 2H, C-16-H_2), 3.21-3.17 (m, 2H, -CH-CH_2-C_6H_5), 2.87-2.85 (m, 2H, C-6-H_2), 2.32-2.29 (m, 2H), 2.27 (s, 1H, -NH_2), 2.25-2.20 (m, 1H), 1.47-1.21 (m, 8H), 0.95 {s, 9H, -C(CH_3)$_3$}, 0.87 (s, 3H, C-18-H_3), 0.08 {s, 6H, -Si(CH_3)$_2$-}; MS (FAB): *m/z* (%) 642 (100, [M^++H]). Anal. Calcd for $C_{40}H_{55}NO_4Si$: C, 74.84; H, 8.64; N, 2.18. Found: C, 75.35; H, 8.97; N, 2.55%.

3-Benzyloxy-16, 17-secoestra-1, 3, 5(10)-triene-16-(*tert*-butyl-dimethyl-silanyloxymethyl)-17-2*S*-(2-nitrobenzenesulfonylamino)(3-phenylpropionic acid), 15

To a solution of amine **14** (0.2 g, 0.31 mmole) in DCM (5 mL) at 0°C was added triethyl amine (0.07 mL, 0.47 mmole). After stirring the mixture for 5 min, *o*-nitro benzene sulphonyl chloride (0.07 g, 0.31 mmole) was added and the reaction mixture was kept at -4°C for 24 hr. After completion (monitored by TLC), the reaction mixture was diluted with DCM and washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was charged over silica gel and eluted with 20% ethyl acetate in hexane (R_f = 0.3) to obtain **15** (0.22 g, 86%) as yellow viscous oil. ^1H NMR (200 MHz, $CDCl_3$): δ 8.08-8.02 (m, 1H, Ar*H*), 7.94-7.89 (m, 1H, Ar*H*), 7.75-7.72 (m, 2H, Ar*H*), 7.46-7.18 (m, 11H, -O-CH_2-C_6H_5, -CH-CH_2-C_6H_5 and C-1-*H*), 6.81 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.4 Hz, C-2-*H*), 6.68 (d, 1H, *J* = 2.4 Hz, C-4-*H*), 6.12 (d, 1H, *J* = 8.3 Hz, -N*H*-), 5.02 (s, 2H, -

O-C*H*$_2$-C$_6$H$_5$), 4.26-4.20 (m, 2H, C-17-*H*$_2$), 4.18-4.10 (m, 1H, -C*H*-CH$_2$-C$_6$H$_5$), 3.67-3.54 (m, 2H, C-16-*H*$_2$), 3.25-3.19 (m, 2H, -CH-C*H*$_2$-C$_6$H$_5$), 2.88-2.86 (m, 2H, C-6-*H*$_2$), 2.33-2.29 (m, 2H), 2.25-2.22 (m, 1H), 1.46-1.20 (m, 8H), 0.92 {s, 9H, -C(C*H*$_3$)$_3$}, 0.84 (s, 3H, C-18-*H*$_3$), 0.06 {s, 6H, -Si(C*H*$_3$)$_2$-}; MS (FAB): *m/z* (%) 827 (100, [M$^+$+H]). Anal. Calcd for $C_{46}H_{58}N_2O_8SSi$: C, 66.80; H, 7.07; N, 3.39. Found: C, 66.97; H, 7.51; N, 3.55%.

3-Benzyloxy-16,17-secoestra-1,3,5(10)-triene-16-(hydroxymethyl)-17-2*S*-(2-nitrobenzenesulfonylamino)(3-phenylpropionic acid), 16

Compound **15** (0.2 g, 0.24 mmole) was heated at 60°C in acetic acid (3 mL), water (1 mL), THF (1 mL), for 2 hr. The solvent was removed under vacuum. The residue was charged over silica gel and eluted with 30% ethyl acetate in hexane (R_f = 0.5) to get **16** (0.118 g, 69%) as white viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06-8.18 (m, 1H, Ar*H*), 7.91-7.85 (m, 1H, Ar*H*), 7.71-7.65 (m, 2H, Ar*H*), 7.45-7.15 (m, 11H, -O-CH$_2$-C$_6$*H*$_5$, -CH-CH$_2$-C$_6$*H*$_5$ and C-1-*H*), 6.78 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.4 Hz, C-2-*H*), 6.62 (d, 1H, *J* = 2.4 Hz, C-4-*H*), 6.16 (d, 1H, *J* = 8.3 Hz, -N*H*-), 5.02 (s, 2H, -O-C*H*$_2$-C$_6$H$_5$), 4.26-4.21 (m, 2H, C-17-*H*$_2$), 4.20-4.15 (m, 1H, -C*H*-CH$_2$-C$_6$H$_5$), 3.65-3.57 (m, 2H, C-16-*H*$_2$), 3.22-3.17 (m, 2H, -CH-C*H*$_2$-C$_6$H$_5$), 2.86-2.84 (m, 2H, C-6-*H*$_2$), 2.35-2.29 (m, 2H), 2.26-2.21 (m, 1H), 1.45-1.25 (m, 8H), 0.82 (s, 3H, C-18-*H*$_3$); MS (FAB): *m/z* (%): 713 (100, [M$^+$+H]). Anal. Calcd for $C_{40}H_{44}N_2O_8S$: C, 67.40; H, 6.22; N, 3.93. Found: C, 67.68; H, 6.49; N, 4.25%.

Acknowledgements

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