A new example of a steroid–amino acid hybrid: construction of constrained nine membered D-ring steroids†‡

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Received 6th November 2006, Accepted 10th November 2006
First published as an Advance Article on the web 4th December 2006
DOI: 10.1039/b616155c

A new archetype of steroid–amino acid hybrids containing a nine membered D-ring with hetero atoms has been synthesized for the first time from estrone and amino acids by using Yamaguchi coupling reactions.

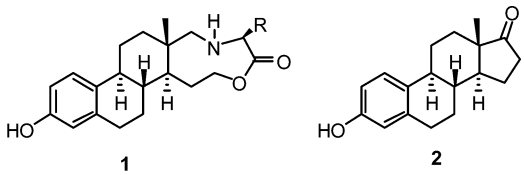
Introduction

Nature remains the unending source for biologically important natural products of molecular diversity and complexity. These naturally occurring molecules, which are essentially derived from particular or combined biosynthetic pathways, possess novel physical, chemical and biological properties.[1] The human quest to acquire novel molecules with interesting properties has generated an idea of architecting an inexhaustible reservoir of novel synthetic endeavours by rationally combining two or more different classes of natural products.[2] During the past two decades, the design and synthesis of such molecular structures have received much attention and these have been referred to as 'hybrid molecules'.

Hybrids or conjugates between hydrophobic steroids and hydrophilic amino acids or peptides, *i.e.* peptidyl steroids, have been reported to play important roles to enhance oral antiarrhythmic activity, to promote delivering prodrugs to specific target tissues and to achieve 'permissive action'.[3–5] Several peptidyl steroids such as polymastiamide A, a tyrosine conjugated steroid analog isolated from the Norwegian marine sponge *Polymastia boletiformis* exhibiting antimicrobial activity and bufetoxin, a 3-arginyl derived steroid product isolated from the Chinese hoptoad have been reported.[6] Moreover, cholyl glycine or cholyl taurine which exists in the bile of animals and contains a glycyl or a taurinyl group at the 17-position of the steroid, has led to the development of several steroid–amino acid conjugates for estrogen dependent biological activity,[7] ^{14}C-cholyl-glycine breath test,[8] and as antidepressant agents.[9] To date, it is mainly peptidyl steroids of the androstane and estrone series comprising amino acids or peptides attached with the unchanged nucleus of steroids through an amide or ester bond, that have been synthesized and examined. There is no reported example of a chiral amino acid incorporated D-ring modified peptidyl steroid.

Results and discussion

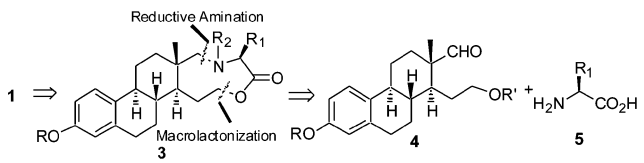
Here we describe the design and synthesis of a new archetype of 'steroid–amino acid hybrid' **1** with amino acids incorporated onto the D-ring of steroid **2** (Fig. 1). The projected molecule **1**, having a constrained nine membered D-ring with hetero atoms on the steroidal framework, provides a highly efficient access to novel molecular hybrids. To the best of our knowledge, only one example of a nine membered D-ring on a steroid using Heck coupling is reported.[10] Intramolecular macrolactonization on a steroidal framework to furnish a nine membered D-ring has not been reported so far.



1 **2**

Fig. 1 Structures of projected molecule **1** and estrone **2**.

Retrosynthetic analysis revealed that projected molecule **1** could be accessed from **3** which could be obtained from building blocks *seco*-estrone aldehyde **4** and amino acid **5** through utilization of reductive amination and macrolactonization (Scheme 1).



1 **3** **4** **5**

Scheme 1 Retrosynthetic analysis of target molecule.

The synthesis of *seco*-estrone aldehyde **4** was accomplished from readily available estrone **2** (Scheme 2). Alkylation of estrone **2** with benzyl bromide–K_2CO_3 followed by base and an iodine mediated haloform reaction gave marrianolic acid benzyl ether **6** (75%).[11] LAH reduction of **6** led to diol **7** (35%). The overall yield of **7** from **2** was very poor (26%). It was therefore decided to develop an alternative strategy for large scale access to **7**. Towards this objective, estriol **8** was initially synthesized from **2** following literature procedures.[12] The phenolic hydroxy of **8** was benzylated to give **9** (95%). The vicinal hydroxyl groups of estriol 3-benzyl ether **9** were subjected to periodate cleavage ($NaIO_4$) to deliver the dialdehyde **10** which was subjected to LAH reduction to furnish **7** with 62% overall yield. Further, the C_{16} hydroxyl group of diol **7** was selectively protected as TBDMS derivative **11** (67%) by treatment of alcohol **7** with 1 : 1 equivalents of TBDMSCl

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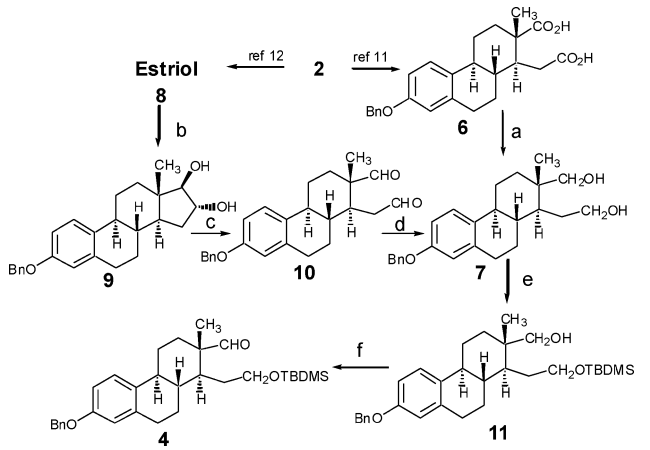
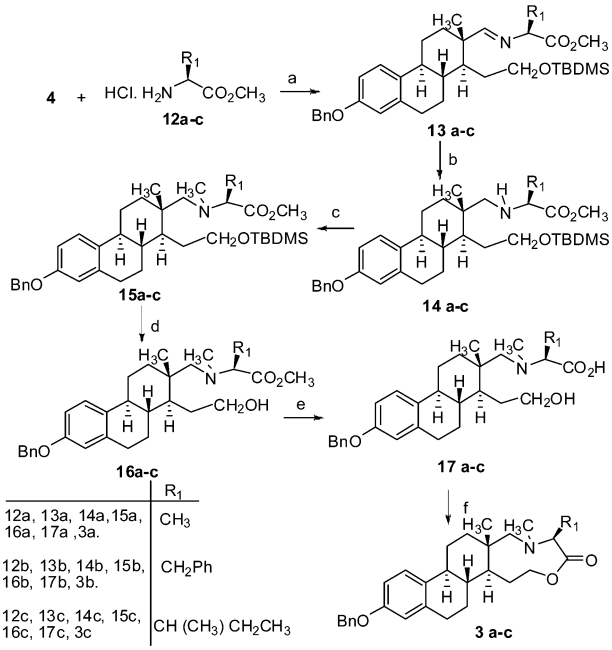
† CDRI Communication number 6739.

‡ Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **3–17** and ^{1}H-^{1}H COSY, HSQC and HMBC spectra of **3b**. See DOI: 10.1039/b616155c



Scheme 2 Synthesis of key intermediate D-*seco* estrone aldehyde **4**. *Reagents and conditions:* a) LAH, THF, 0–5 °C, 1 h, 35%; b) benzyl bromide, K_2CO_3, acetone, reflux, 8 h, 95%; c) $NaIO_4$, methanol–H_2O (4 : 1), 0 °C, 24 h; d) LAH, THF, 0–5 °C, 1 h, 81% (two steps); e) TBDMSCl, imidazole, DCM, 0 °C–rt, 6 h, 67%; f) TPAP, NMO, MS 4 Å, DCM, rt, 1 h, 82%.



Scheme 3 Synthesis of **3a–c**. *Reagents and conditions:* a) TEA, methanol–THF (4 : 1), reflux–rt, 12 h; b) $NaBH_4$, methanol, 0–5 °C, 1 h, **14a** = 80%, **14b** = 78% and **14c** = 73% for two steps; c) MeI, K_2CO_3, acetone, rt, 24 h, **15a** = 97%, **15b** = 95% and **15c** = 93%; d) AcOH–H_2O–THF (3 : 1 : 1), 60 °C, 2 h, **16a** = 66%, **16b** = 63% and **16c** = 70%; e) 1 N NaOH, dioxane, 60 °C, 1 h, **17a** = 70%, **17b** = 67% and **17c** = 72%; f) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt, then DMAP, PhMe, reflux, **3a** = 53%, **3b** = 63% and **3c** = 42%.

and imidazole. TPAP mediated oxidation of the primary hydroxyl group in **11** led to the key aldehyde **4** in 82% yield. The aldehyde **4** was prepared on a large scale for the execution of reductive amination with chiral amino acid ester.

Reductive amination of **4** with amino acid methyl ester hydrochloride[13] **12a–c** in the presence of $NaBH_3CN$ and acetic acid was performed to afford amine **14a** (30%), **14b** (34%) and **14c** (31%). Yield of the amine **14a–c** was improved (80%, 78% and 73% respectively) by performing the reaction in two steps through initial formation of imine **13a–c** followed by reduction with $NaBH_4$. It was decided to convert the secondary amine to a tertiary one to avoid unnecessary reactions in the next steps. Treatment of amine **14a–c** with MeI–K_2CO_3 in acetone furnished the fully protected product **15a** (97%), **15b** (95%) and **15c** (93%). Upon exposure to AcOH–H_2O–THF (3 : 1 : 1) at 50–60 °C, deprotection of TBDMS ether occurred to afford the alcohol **16a** (66%), **16b** (63%) and **16c** (70%).

Finally the methyl ester of **16a–c** was hydrolyzed in the presence of 1 N NaOH–dioxane to furnish the hydroxy acid **17a** (70%), **17b** (67%) and **17c** (72%). The hydroxy acid was then subjected to macrolactonization using the Yamaguchi method[14] to furnish the corresponding lactone **3a** (53%), **3b** (63%) and **3c** (42%) which can afford the target molecule **1** on deprotection of a benzyl group, Scheme 3. The structure of steroid–amino acid hybrid **3a–c** was secured from incisive analysis of ^1H, ^{13}C NMR, ^1H-^1H COSY, HSQC and HMBC spectra.

In conclusion, we have demonstrated a new prototype of steroid–amino acid hybrid **1** from easily available estrone **2** and amino acids *i.e.* alanine, phenyl alanine and isoleucine through a series of simple and efficient steps involving $NaIO_4$ cleavage of estriol, reductive amination and Yamaguchi coupling reactions. A simple and convenient approach to access chiral amino acid incorporated D-ring modified steroid–amino acid hybrids (peptidyl steroids) is described. In the process, we have synthesized several important molecules such as diol, D-*seco* estrone aldehyde and and D-*seco* estrone amino acid conjugates which can be used as advanced intermediates for accessing new steroid derivatives. Additionally, the acid functionality of **17a–c** can be further coupled with other amino acids to elaborate macrocyclic steroid–amino acid hybrids for interesting biological functions. Efforts in this direction are in progress.

Experimental

General

All the reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulfate (2% $CeSO_4$ in 2 N H_2SO_4) sprayed plates on a hot plate or in an oven at about 100 °C. Silica gel 60–120 mesh was used for column chromatography. Melting points were recorded on an electrically heated apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 or FT IR 820/PC instrument and values are expressed in cm^{-1}. Electron impact mass spectra were recorded on a JEOL (Japan)/D-300 instrument and FAM mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using Argon/Xenon (6 KV, 10 MA) as the FAB gas. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 200 MHz instrument using TMS as an internal reference. Chemical shift values are expressed in δ ppm. Specific rotation was determined with a Rudolph Autopol III[rd] polarimeter at 28 °C. Elementary analysis was carried out on a Carlo ERBA-1108 analyzer. Commercially available grades of organic solvents of adequate purity were used in many reactions. Acetone was refluxed with $KMnO_4$ for 4 h, after that it was distilled and stored in a bottle containing dried K_2CO_3. Benzene was refluxed with freshly

cut and dried sodium metal pieces pressed in 3 Å sieves for 4–6 h. It was distilled and stored in a dry bottle. Tetrahydrofuran was dried initially over calcium sulfate and then refluxed over lithium aluminium hydride. Peroxide was removed by passage through a column of alumina and distilled and stored over molecular sieves 3 Å.

Experimental procedure

Diol 7. To a stirred solution of estriol 3-benzyl ether **9** (2.62 g, 6.93 mmol) in methanol (40 ml) at 0 °C was added a solution of $NaIO_4$ (2.22 g, 10.40 mmol) in water (10 ml). After stirring at 0 °C for 24 h, the methanol was evaporated *in vacuo* at low temperature. The aqueous solution was extracted with CH_2Cl_2 twice. The combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum to yield dialdehyde **10** (3.0 g) as a yellow viscous oil which was used as such for the next step.

Dialdehyde **10** (3.0 g) in THF (5 ml) was added dropwise to a stirred solution of LAH (0.45 g, 11.97 mmol) in 40 ml of THF at 0 °C. The resulting solution was stirred at rt for 1 h. After completion (monitored by TLC), the reaction was quenched with ethyl acetate followed by water at 0 °C. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was chromatographed over silica gel and elution with 40% ethyl acetate in hexane ($R_f = 0.5$) furnished diol **7** (2.12 g, 81%) as white solid, mp 135 °C. IR (KBr): 3336, 2920, 1606, 1255, 1035, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.44–7.20 (m, 6H, –O–CH_2–C_6H_5 and C-1-*H*), 6.78 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.4$, C-2-*H*), 6.70 (d, 1H, $J = 2.4$, C-4-*H*), 5.02 (s, 2H, –O–CH_2–C_6H_5), 4.00–3.85 (m, 1H, C-16-*H*), 3.67 (d, 1H, $J = 11.7$, C-17-*H*), 3.61–3.46 (m, 1H, C-16-*H*), 3.09 (d, 1H, $J = 11.7$, C-17-*H*), 2.85–2.83 (m, 2H, C-6-H_2), 2.33–2.26 (m, 2H), 2.01–1.95 (m, 2H), 1.75–1.28 (m, 7H), 0.69 (s, 3H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.1 (C-3), 138.2 (C-5), 137.7, 133.4 (C-10), 128.9, 128.2, 127.9, 127.0 (C-1), 114.8 (C-4), 112.9 (C-2), 70.5 (C-17), 70.4 (–O–CH_2–C_6H_5), 64.3 (C-16), 43.9, 42.2, 41.2, 38.9 (C-13), 35.7, 31.0, 30.3 (C-6), 27.8 (C-12), 27.0 (C-11), 16.4 (C-18). MASS (FAB): *m/z* (%): 380 (100, [M^+]), 363 (40, [M^+–OH)]). Anal. Calcd for ($C_{25}H_{32}O_3$): C, 78.91; H, 8.48%. Found: C, 79.17; H, 8.60%.

TBDMS derivative 11. To a solution of diol **7** (2 g, 5.26 mmol) in CH_2Cl_2 (20 ml) at 0 °C was added imidazole (0.36 g, 5.26 mmol) followed by TBDMSCl (0.79 g, 5.26 mmol). The mixture was stirred at rt overnight. The reaction was quenched with H_2O and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was chromatographed over silica gel and elution with 10% ethyl acetate in hexane (R_f = 0.5) furnished **11** (1.75 g, 67%) as a white solid, mp 77 °C with recovery of starting material **7** (0.592 g, 30%). IR (KBr): 3473, 2927, 1500, 1463, 1253, 1046, 836 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.28–7.22 (m, 5H, –O–CH_2–C_6H_5), 7.12 (d, 1H, J = 8.6, C-1-*H*), 6.69 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.4$, C-2-*H*), 6.59 (d, 1H, $J = 2.4$, C-4-*H*), 4.97 (s, 2H, –O–CH_2–C_6H_5), 3.85–3.69 (m, 1H, C-16-*H*), 3.55 (d, 1H, $J = 12$, C-17-*H*), 3.43–3.32 (m, 1H, C-16-*H*), 2.95 (d, 1H, $J = 12$, C-17-*H*), 2.73–2.72 (m, 2H, C-6-H_2), 2.32–2.09 (m, 2H), 1.95–1.91 (m, 9H), 0.81 {s, 9H, –C(CH_3)$_3$}, 0.56 (s, 3H, C-18-H_3), 0.04 {s, 6H, –Si(CH_3)$_2$–}. ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.1 (C-3), 138.1 (C-5), 137.7, 133.4 (C-10), 128.9, 128.2, 127.8, 127.1 (C-1), 114.9 (C-4), 112.9 (C-2), 70.9 (C-17), 70.3 (–O–CH_2–C_6H_5), 65.8 (C-16), 44.0, 42.3, 41.0, 38.9 (C-13), 35.8, 31.0, 30.8 (C-6), 27.8 (C-12), 27.1(C-11), 26.5 {–C(CH_3)$_3$}, 19.1{–*C*(CH_3)$_3$}, 16.3 (C-18), −4.9 {Si(CH_3)$_2$–}. MASS (FAB): *m/z* (%): 495 (40, [M^+ + H]), 363 (70, [M^+–OH,-TBDMS]). Anal. Calcd for ($C_{31}H_{46}O_3Si$): C, 75.25; H, 9.37%. Found: C, 75.42; H, 9.64%.

Aldehyde 4. To a solution of **11** (1 g, 2.02 mmol) in CH_2Cl_2 (25 ml) were added molecular sieves (4 Å) followed by NMMO (0.41 g, 3.04 mmol). After stirring the mixture for 10 min, TPAP (0.07 g, 0.20 mmol) was added and it was stirred at rt for 2 h. After completion (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 and was washed with sodium sulfite, brine, saturated $CuSO_4$ solution, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was chromatographed over silica gel and elution with 10% ethyl acetate in hexane ($R_f = 0.6$) furnished **4** (0.82 g, 82%) as white solid, mp 80 °C. IR (KBr): 3417, 2945, 1724, 1598, 1359, 1093, 837, 771 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 9.37 (s, 1H, C-17-*H*), 7.36–7.29 (m, 5H, –O–CH_2–C_6H_5), 7.16 (d, 1H, $J = 8.6$, C-1-*H*), 6.71 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.4$, C-2-*H*), 6.67 (d, 1H, $J = 2.4$, C-4-*H*), 4.98 (s, 2H, –O–CH_2–C_6H_5), 3.61–3.39 (m, 2H, C-16-H_2), 2.72–2.88 (m, 2H, C-6-H_2), 2.35–2.22 (m, 2H), 2.15–2.02 (m, 1H), 1.71–1.15 (m, 8H), 1.00 (s, 3H, C-18-H_3), 0.85 {s, 9H, –C(CH_3)$_3$}, 0.00 {s, 6H, –Si(CH_3)$_2$–}. ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.0 (C-17), 157.3 (C-3), 138.2 (C-5), 137.6, 132.5 (C-10), 128.9, 128.3, 127.8, 126.8 (C-1), 114.9 (C-4), 113.0 (C-2), 70.3 (–O–CH_2–C_6H_5), 63.4 (C-16), 51.1 (C-13), 43.6, 41.0, 40.6, 34.1, 33.0, 30.7 (C-6), 27.4 (C-12), 26.4 {–C(CH_3)$_3$}, 25.8 (C-11), 18.7{–*C*(CH_3)$_3$}, 13.4 (C-18), −4.8 {Si(CH_3)$_2$–}. MASS (FAB): *m/z* (%): 492 (60, [M^+]), 491 (80, [M^+–H]). Anal. Calcd for ($C_{31}H_{44}O_3Si$): C, 75.56; H, 9.00%. Found: C, 75.76; H, 9.29%.

Amine 14a. To a solution of alanine methyl ester hydrochloride **12a** (0.16 g, 1.13 mmol) in methanol (12 ml) was added triethyl amine (0.21 ml, 1.50 mmol). After stirring the mixture for 5 min, a solution of aldehyde **4** (0.37 g, 0.75 mmol) in THF (3 ml) was added and the reaction mixture was refluxed for 2 h. After stirring at rt overnight, the solvent was removed and the residue was dissolved in ethyl acetate. The undissolved material was filtered off and the filtrate was concentrated to afford the crude imine **13a** (0.4 g).

To a solution of crude imine **13a** (0.4 g) in methanol (15 ml), $NaBH_4$ (0.04 gm, 1.04 mmol) was added in a small portion at 0 °C. After 15 min, the solvent was removed under vacuum and the residue was passed through silica gel and elution with 10% ethyl acetate in hexane ($R_f = 0.4$) furnished **14a** (0.35 g, 80%) as a white solid, mp 72 °C, $[a]_D^{20}$ +17 (*c* 2, MeOH). IR (KBr): 3570, 2935, 1737, 1598, 1463, 1251, 1093, 840, 775 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.39–7.02 (m, 6H, –O–CH_2–C_6H_5 and C-1-*H*), 6.61 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.4$, C-2-*H*), 6.58 (d, 1H, $J = 2.4$, C-4-*H*), 4.94 (s, 2H, –O–CH_2–C_6H_5), 3.65 (s, 3H, –CO_2CH_3), 3.63–3.39 (m, 2H, C-16-H_2), 3.26–3.06 (m, 1H, –C*H*–CH_3), 2.80–2.62 (m, 2H, C-6-H_2), 2.29 (s, 2H, C-17-H_2), 2.28–2.01 (m, 3H), 1.65–1.47 (m, 4H), 1.40–1.09 (m, 4H), 1.22 (d, 3H, $J = 7$, –CH–CH_3), 0.84 {s, 9H, –C(CH_3)$_3$}, 0.72 (s, 3H, C-18-H_3), 0.00 {s, 6H, –Si(CH_3)$_2$–}. ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.1 (–CO_2CH_3), 157.1 (C-3), 138.4 (C-5), 137.9, 133.5 (C-10), 128.9, 128.2, 127.8, 126.9 (C-

1), 114.8 (C-4), 112.8 (C-2), 70.3 (–O–*C*H$_2$–C$_6$H$_5$), 64.8 (C-16), 58.4 (C-17), 57.8 (–*C*H–CH$_3$), 52.0 (–CO$_2$*C*H$_3$), 43.9, 42.4, 42.1, 37.9 (C-13), 36.9, 32.8, 31.0 (C-6), 28.0 (C-12), 26.9 (C-11), 26.5 {–C(*C*H$_3$)$_3$}, 19.4 {–*C*(CH$_3$)$_3$}, 18.9 (–CH–*C*H$_3$), 18.1 (C-18), −4.7 {Si(*C*H$_3$)$_2$–}. MASS (FAB): *m/z* (%): 580 (100, M$^+$). Anal. Calcd for (C$_{35}$H$_{53}$NO$_4$Si): C, 72.49; H, 9.21; N, 2.42%. Found: C, 72.71; H, 9.39; N, 2.51%.

Amine 14b. As described for **14a**, phenylalanine methyl ester hydrochloride **12b** (0.20 g, 0.91 mmol) in methanol (15 ml), triethyl amine (0.17 ml, 1.22 mmol), aldehyde **4** (0.3 g, 0.61 mmol) in THF (3 ml) furnished imine **13b** (0.33 g).

13b (0.33 g, 0.505 mmol) in methanol (15 ml), NaBH$_4$ (0.03 g, 0.76 mmol) furnished **14b** (0.31 g, 78%) as a viscous oil, R_f = 0.45 (10% ethyl acetate in hexane), $[\alpha]_D^{20}$ +27 (*c* 2, MeOH). IR (Neat): 3427, 2931, 1737, 1598, 1355, 1091, 839, 773 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.33–7.11 (m, 11H, –O–CH$_2$–C$_6$*H*$_5$, –CH–CH$_2$–C$_6$*H*$_5$ and C-1-*H*), 6.58 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-*H*), 6.65 (d, 1H, J = 2.4, C-4-*H*), 4.94 (s, 2H, –O–C*H*$_2$–C$_6$H$_5$), 3.56 (s, 3H, –CO$_2$C*H*$_3$), 3.46–3.34 (m, 3H, C-16-*H*$_2$ and –C*H*–CH$_2$–C$_6$H$_5$), 2.85 (d, 2H, J = 6.8, –CH–C*H*$_2$–C$_6$H$_5$), 2.83–2.77 (m, 2H, C-6-*H*$_2$), 2.44–2.34 (m, 2H, C-17-*H*$_2$), 2.26–2.09 (m, 3H), 2.02 (bs, 1H, –N*H*–), 1.59–1.19 (m, 8H), 0.84 {s, 9H, –C–(C*H*$_3$)$_3$}, 0.68 (s, 3H, C-18-*H*$_3$), 0.00 {s, 6H, –Si(C*H*$_3$)$_2$–}. ^{13}C NMR (50 MHz, CDCl$_3$): δ 175.8 (–*C*O$_2$CH$_3$), 157.1 (C-3), 138.4 (C-5), 138.0, 137.7, 133.5 (C-10), 129.7, 128.9, 128.7, 128.2, 127.8, 127.0 (C-1), 114.8 (C-4), 112.8 (C-2), 70.3 (–O–*C*H$_2$–C$_6$H$_5$), 64.7 (C-16), 64.5 (–*C*H–CH$_2$–C$_6$H$_5$), 58.5 (C-17), 51.9 (–CO$_2$*C*H$_3$), 44.0, 42.4, 42.2, 40.4 (–CH–*C*H$_2$–C$_6$H$_5$), 38.2 (C-13), 36.8, 32.9, 31.0 (C-6), 28.0 (C-12), 26.9 (C-11), 26.4 {–C(*C*H$_3$)$_3$}, 18.8 {–*C*(CH$_3$)$_3$}, 18.1 (C-18), −4.6 {Si(*C*H$_3$)$_2$–}. MASS (FAB): *m/z* (%): 656 (100, M$^+$ + H). Anal. Calcd for (C$_{41}$H$_{57}$NO$_4$Si): C, 75.07; H, 8.76; N, 2.14%. Found: C, 75.18; H, 8.88; N, 2.05%.

Amine 14c. As described for **14a**, isoleucine methyl ester hydrochloride **12c** (0.17 g, 0.91 mmol) in methanol (15 ml), triethyl amine (0.17 ml, 1.22 mmol), aldehyde **4** (0.3 g, 0.61 mmol) in THF (3 ml) furnished imine **13c** (0.35 g).

13c (0.35 g, 0.57 mmol) in methanol (15 ml), NaBH$_4$ (0.03 g, 0.85 mmol) furnished **14c** (0.28 g, 73%) as a viscous oil, R_f = 0.5 (10% ethyl acetate in hexane), $[\alpha]_D^{20}$ +19.5 (*c* 2, MeOH). IR (Neat): 3447, 2930, 1733, 1609, 1500, 1463, 1382, 1252, 1091, 837, 759 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.36–7.21 (m, 5H, –O–CH$_2$–C$_6$*H*$_5$), 7.19–7.03 (d, 1H, J = 8.6, C-1-*H*), 6.65 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-*H*), 6.62 (d, 1H, J = 2.4, C-4-*H*), 4.92 (s, 2H, –O–C*H*$_2$–C$_6$H$_5$), 3.63 (s, 3H, –CO$_2$C*H*$_3$), 3.52–3.35 (m, 2H, C-16-*H*$_2$), 3.52–3.35 {m, 1H, –C*H*–CH–(CH$_3$)–CH$_2$–CH$_3$}, 2.80–2.68 (m, 2H, C-6-*H*$_2$), 2.35–1.89 (m, 5H), 1.62–1.14 (m, 15H), 0.83 {bs, 12H, –C(C*H*$_3$)$_3$}, 0.69 (s, 3H, C-18-*H*$_3$), 0.00 {s, 6H, –Si(C*H*$_3$)$_2$–}. ^{13}C NMR (50 MHz, CDCl$_3$): δ 176.5 (–*C*O$_2$CH$_3$), 157.1 (C-3), 139.2 (C-5), 138.4, 133.6 (C-10), 128.9, 128.2, 127.8, 126.9 (C-1), 114.9 (C-4), 112.8 (C-2), 70.3 (–O–*C*H$_2$–C$_6$H$_5$), 67.9 {–*C*H–CH–(CH$_3$)–CH$_2$–CH$_3$}, 64.8 (C-16), 59.0 (C-17), 51.6 (–CO$_2$*C*H$_3$), 44.0, 42.4, 42.2, 39.0 {–CH–*C*H–(CH$_3$)–CH$_2$–CH$_3$}, 38.2 (C-13), 37.0, 33.0, 31.1 (C-6), 28.1 (C-12), 26.9 (C-11), 26.5 {–C(*C*H$_3$)$_3$}, 26.2 {–CH–CH–(CH$_3$)–*C*H$_2$–CH$_3$}, 18.8 {–*C*(CH$_3$)$_3$}, 18.3 (C-18), 16.2 {–CH–CH–(*C*H$_3$)–CH$_2$–CH$_3$}, 12.0 {–CH–CH–(CH$_3$)–CH$_2$–*C*H$_3$}, −4.6 {Si(*C*H$_3$)$_2$–}. MASS (FAB): *m/z* (%): 621 (100, M$^+$). Anal. Calcd for (C$_{38}$H$_{59}$NO$_4$Si): C, 73.38; H, 9.56; N, 2.25%. Found: C, 73.45; H, 9.25; N, 2.12%.

***N*-Methyl amine derivative 15a.** A mixture of **14a** (0.2 g, 0.35 mmol), anhydrous K$_2$CO$_3$ (0.24 g, 1.72 mmol), methyl iodide (0.04 ml, 0.69 mmol) and dry acetone (15 ml) was stirred at room temperature for 24 h. K$_2$CO$_3$ was filtered off and the acetone was removed *in vacuo*. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was chromatographed over silica gel and elution with 5% ethyl acetate in hexane (R_f = 0.45) furnished **15a** (0.20 g, 97%) as a white semi solid, $[\alpha]_D^{20}$ +39.5 (*c* 2, MeOH). IR (KBr): 3460, 2932, 1735, 1609, 1500, 1461, 1248, 1091, 772 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.30–7.17 (m, 5H, –O–CH$_2$–C$_6$*H*$_5$), 7.05 (d, 1H, J = 8.6, C-1-*H*), 6.69 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-*H*), 6.57 (d, 1H, J = 2.4, C-4-*H*), 4.93 (s, 2H, –O–C*H*$_2$–C$_6$H$_5$), 3.60 (s, 3H, –CO$_2$C*H*$_3$), 3.59–3.18 (m, 3H, C-16-*H*$_2$ and –C*H*–CH$_3$), 2.81–2.67 (m, 2H, C-6-*H*$_2$), 2.55 (d, 1H, J = 11.8, C-17-*H*), 2.31 (s, 3H, –N–C*H*$_3$), 2.29 (d, 1H, J = 11.8, C-17-*H*), 2.29–1.99 (m, 3H), 1.81–1.26 (m, 8H), 1.21 (d, 3H, J = 7.1, –CH–C*H*$_3$), 0.84 {s, 9H, –C(C*H*$_3$)$_3$}, 0.77 (s, 3H, C-18-*H*$_3$), 0.01 {s, 6H, –Si(C*H*$_3$)$_2$–}. ^{13}C NMR (50 MHz, CDCl$_3$): δ 174.7 (–*C*O$_2$CH$_3$), 157.1 (C-3), 138.3 (C-5), 137.7, 133.5 (C-10), 128.9, 128.2, 127.8, 127.0 (C-1), 114.8 (C-4), 112.8 (C-2), 70.3 (–O–*C*H$_2$–C$_6$H$_5$), 67.8 (C-17), 64.8 (C-16), 64.0 (–*C*H–CH$_3$), 51.4 (–CO$_2$*C*H$_3$), 44.6, 44.1, 42.2, 40.7 (–N–*C*H$_3$), 40.2 (C-13), 37.9, 33.2, 31.0 (C-6), 28.0 (C-12), 26.9 (C-11), 26.5 {–C(*C*H$_3$)$_3$}, 18.9 {–*C*(CH$_3$)$_3$}, 16.7 (–CH–*C*H$_3$), 16.0 (C-18), −4.6 {Si(*C*H$_3$)$_2$–}. MASS (FAB): *m/z* (%): 594 (100, M$^+$). Anal. Calcd for (C$_{36}$H$_{55}$NO$_4$Si): C, 72.80; H, 9.33; N, 2.36%. Found: C, 72.96; H, 9.49; N, 2.45%.

***N*-Methyl amine derivative 15b.** As described for **15a**, amine **14b** (0.22 g, 0.34 mmol), K$_2$CO$_3$ (0.23 g, 1.68 mmol), methyl iodide (0.04 ml, 0.67 mmol) in acetone (15 ml) furnished **15b** (0.21 g, 95%) as a white semi-solid, R_f = 0.5 (5% ethyl acetate in hexane), $[\alpha]_D^{20}$ +12.5 (*c* 2, MeOH). IR (KBr): 3375, 2935, 1738, 1598, 1352, 1245, 1089, 771 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.32–7.08 (m, 11H, –O–CH$_2$–C$_6$*H*$_5$, –CH–CH$_2$–C$_6$*H*$_5$ and C-1-*H*), 6.68 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-*H*), 6.61 (d, 1H, J = 2.4, C-4-*H*), 4.93 (s, 2H, –O–C*H*$_2$–C$_6$H$_5$), 3.58 (s, 3H, –CO$_2$C*H*$_3$), 3.48–3.23 (m, 3H, C-16-*H*$_2$ and –C*H*–CH$_2$–C$_6$H$_5$), 2.97–2.71 (m, 2H, –CH–C*H*$_2$–C$_6$H$_5$), 2.69–2.52 (m, 2H, C-6-*H*$_2$), 2.38–2.24 (m, 5H, C-17-*H*$_2$ and –N–C*H*$_3$), 2.09–1.14 (m, 11H), 0.83 {s, 9H, –C–(C*H*$_3$)$_3$}, 0.63 (s, 3H, C-18-*H*$_3$), 0.00 {s, 6H, –Si(C*H*$_3$)$_2$–}. ^{13}C NMR (50 MHz, CDCl$_3$): δ 173.3 (–*C*O$_2$CH$_3$), 157.1 (C-3), 139.3 (C-5), 138.3, 137.8, 133.6 (C-10), 129.9, 128.9, 128.6, 128.2, 127.8, 127.0 (C-1), 126.7, 114.7 (C-4), 112.8 (C-2), 71.0 (–*C*H–CH$_2$–C$_6$H$_5$), 70.3 (–O–*C*H$_2$–C$_6$H$_5$), 68.2 (C-17), 64.7 (C-16), 51.4 (–CO$_2$*C*H$_3$), 43.7, 43.5, 42.3, 40.5 (–N–*C*H$_3$), 40.4 (C-13), 37.4, 36.5 (–CH–*C*H$_2$–C$_6$H$_5$), 33.2, 31.0 (C-6), 27.9 (C-12), 26.9 (C-11), 26.5 {–C(*C*H$_3$)$_3$}, 18.9 {–*C*(CH$_3$)$_3$}, 17.0 (C-18), −4.6 {Si(*C*H$_3$)$_2$–}. MASS (FAB): *m/z* (%): 670 (100, M$^+$ + H). Anal. Calcd for (C$_{42}$H$_{59}$NO$_4$Si): C, 75.29; H, 8.88; N, 2.09%. Found: C, 75.45; H, 9.15; N, 2.19%.

***N*-Methyl amine derivative 15c.** As described for **15a**, amine **14c** (0.2 g, 0.32 mmol), K$_2$CO$_3$ (0.22 g, 1.61 mmol), methyl iodide (0.04 ml, 0.64 mmol) in acetone (15 ml) furnished **15c** (0.19 g, 93%) as a viscous oil, R_f = 0.55 (5% ethyl acetate in hexane), $[\alpha]_D^{20}$ +12 (*c* 2, MeOH). IR (Neat): 3438, 2931, 2361, 1731, 1461, 1378, 1249, 1093, 772 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36–7.23 (m, 5H, –O–CH$_2$–C$_6$*H*$_5$), 7.13 (d, 1H, J = 8.7, C-1-*H*), 6.70 (dd, 1H, J_1 = 8.7, J_2 = 2.5, C-2-*H*), 6.62 (d, 1H, J = 2.4, C-4-*H*), 4.95

(s, 2H, –O–CH_2–C_6H_5), 3.62 (s, 3H, –CO_2CH_3), 3.55–3.42 (m, 2H, C-16-H_2), 2.81–2.75 {m, 3H, –CH–CH–(CH_3)–CH_2–CH_3 and C-6-H_2}, 2.36–2.34 (m, 2H, C-17-H_2), 2.27 (s, 3H, –N–CH_3), 2.26–2.14 (m, 2H), 1.97–1.10 (m, 3H), 1.84–1.60 (m, 3H), 1.34–1.22 (m, 4H), 0.97–0.90 (m, 1H), 0.84 (bs, 12H, –C(CH_3)$_3$), 0.77–0.73 (m, 6H, C-18-H_3), 0.72–0.66 (m, 1H), 0.00 {s, 6H, –Si(CH_3)$_2$–}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (–CO_2CH_3), 156.7 (C-3), 137.9 (C-5), 137.6, 133.1 (C-10), 128.5, 127.8, 127.4, 126.5 (C-1), 114.4 (C-4), 112.8 (C-2), 74.0 {–CH–CH–(CH_3)–CH_2–CH_3}, 69.9 (–O–CH$_2$–C_6H_5), 67.4 (C-17), 64.4 (C-16), 50.5 (–CO_2CH_3), 44.1, 43.6, 41.8, 40.2 40.2 (C-13), 39.0 (–N–CH_3), 37.7, 34.5 {–CH–CH–(CH_3)–CH_2–CH_3}, 32.8, 30.6 (C-6), 29.6, 27.6 (C-12), 26.5 (C-11), 26.0 {–C(CH_3)$_3$}, 25.1 {–CH–CH–(CH_3)–CH_2–CH_3}, 18.4 {–C(CH_3)$_3$}, 16.4 {–CH–CH–(CH_3)–CH_2–CH_3}, 16.1 (C-18), 11.3 {–CH–CH–(CH_3)–CH_2–CH_3}, −5.1 {Si(CH_3)$_2$–}. MASS (FAB): m/z (%): 636 (100, M$^+$ + H). Anal. Calcd for ($C_{39}H_{61}NO_4Si$): C, 73.65; H, 9.67; N, 2.20%. Found: C, 73.99; H, 9.79; N, 2.30%.

Alcohol 16a. Compound **15a** (0.15 g, 0.25 mmol) was heated at 60 °C in acetic acid (3 ml), water (1 ml), THF (1 ml) (3 : 1 : 1) for 2 h. The solvent was removed under vacuum. The residue was chromatographed over silica gel and elution with 30% ethyl acetate in hexane (R_f = 0.45) furnished **16a** (0.08 g, 66%) as a white semi-solid, $[\alpha]_D^{20}$ +36.5 (*c* 2, MeOH). IR (KBr): 3400, 2927, 1732, 1598, 1353, 1236, 1037, 744 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.26 (m, 5H, –O–CH_2–C_6H_5), 7.14 (d, 1H, J = 8.6, C-1-H), 6.72 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-H), 6.64 (d, 1H, J = 2.4, C-4-H), 5.00 (s, 2H, –O–CH_2–C_6H_5), 3.70 (s, 3H, –CO_2CH_3), 3.69–3.35 (m, 3H, C-16-H_2 and –CH–CH_3), 2.90–2.71 (m, 2H, C-6-H_2), 2.31 (s, 3H, –N–CH_3), 2.30–2.11 (m, 2H, C-17-H_2), 2.07–2.03 (m, 2H), 1.75–1.62 (m, 4H), 1.49–1.21 (m, 5H), 1.21 (d, 3H, J = 7.1, –CH–CH_3), 0.82 (s, 3H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.3 (–CO_2CH_3), 157.1 (C-3), 138.2 (C-5), 137.7, 133.2 (C-10), 128.9, 128.2, 127.8, 127.0 (C-1), 114.7 (C-4), 112.9 (C-2), 70.3 (–O–CH$_2$–C_6H_5), 67.3 (C-17), 64.1 (C-16), 63.7 (–CH–CH_3), 51.6 (–CO_2CH_3), 43.9, 43.5, 42.7, 39.7 (–N–CH_3), 39.3 (C-13), 38.3, 33.0, 31.0 (C-6), 27.8 (C-12), 27.4 (C-11), 18.3 (–CH–CH_3), 15.4 (C-18). MASS (FAB): m/z (%): 480 (100, M$^+$). Anal. Calcd for ($C_{30}H_{41}NO_4$): C, 75.12; H, 8.62; N, 2.92%. Found: C, 75.38; H, 8.76; N, 3.15%.

Alcohol 16b. As described for **16a**, **15b** (0.17 g, 0.25 mmol) in AcOH–H_2O–THF (3 : 1 : 1) furnished **16b** (0.09 g, 63%) as a white semi-solid, R_f = 0.5 (30% ethyl acetate in hexane), $[\alpha]_D^{20}$ +16.5 (*c* 2, MeOH). IR (KBr): 3980, 2925, 1730, 1606, 1498, 1454, 1222, 1029, 763 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44–7.14 (m, 11H, –O–CH_2–C_6H_5, –CH–CH_2–C_6H_5 and C-1-H), 6.78 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-H), 6.64 (d, 1H, J = 2.4, C-4-H), 5.01 (s, 2H, –O–CH_2–C_6H_5), 3.65 (s, 3H, –CO_2CH_3), 3.57–3.44 (m, 3H, C-16-H_2 and –CH–CH_2–C_6H_5), 3.05–2.85 (m, 2H, –CH–CH_2–C_6H_5), 2.81–2.65 (m, 2H, C-6-H_2), 2.55–2.25 (m, 5H, C-17-H_2 and –N–CH_3), 2.19–1.12 (m, 11H), 0.72 (s, 3H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.2 (–CO_2CH_3), 157.1 (C-3), 139.0 (C-5), 138.2, 137.7, 133.4 (C-10), 129.9, 128.9, 128.6, 128.2, 127.8, 127.0 (C-1), 126.7, 114.7 (C-4), 112.9 (C-2), 70.9 (–CH–CH_2–C_6H_5), 70.3 (–O–CH$_2$–C_6H_5), 67.9 (C-17), 64.1 (C-16), 51.5 (–CO_2CH_3), 43.6, 43.2, 42.5, 40.2 (–N–CH_3), 40.0 (C-13), 37.6, 36.4 (–CH–CH$_2$–C_6H_5), 33.1, 31.0 (C-6), 27.8 (C-12), 27.1 (C-11), 17.9 (C-18). MASS (FAB): m/z (%): 556 (100, M$^+$ + H). Anal. Calcd for ($C_{36}H_{45}NO_4$): C, 77.80; H, 8.16; N, 2.52%. Found: C, 77.99; H, 8.37; N, 2.77%.

Alcohol 16c. As described for **16a**, **15c** (0.15 g, 0.24 mmol) in AcOH–H_2O–THF (3 : 1 : 1) furnished **16c** (0.1 g, 70%) as a transparent viscous liquid, R_f = 0.55 (30% ethyl acetate in hexane), $[\alpha]_D^{20}$ +35 (*c* 0.8, MeOH). IR (Neat): 3989, 2927, 1734, 1611, 1490, 1459, 1228, 1021, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.19 (m, 6H, –O–CH_2–C_6H_5 and C-1-H), 6.79 (dd, 1H, J_1 = 8.7, J_2 = 2.5, C-2-H), 6.71 (d, 1H, J = 2.5, C-4-H), 5.03 (s, 2H, –O–CH_2–C_6H_5), 3.70 (s, 3H, –CO_2CH_3), 3.45–3.39 (m, 2H, C-16-H_2), 2.91–2.83 {m, 3H, {–CH–CH–(CH_3)–CH_2–CH_3 and C-6-H_2}, 2.48–2.39 (m, 2H, C-17-H_2), 2.35 (s, 3H, –N–CH_3), 2.71–2.27 (m, 2H), 2.03–1.67 (m, 9H), 1.45–1.32 (m, 2H), 0.95–0.8 (m, 11H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7 (–CO_2CH_3), 156.2 (C-3), 138.1 (C-5), 137.2, 133.5 (C-10), 128.4, 127.6, 127.5, 126.4 (C-1), 114.7 (C-4), 112.2 (C-2), 74.2 {–CH–CH–(CH_3)–CH_2–CH_3}, 70.0 (–O–CH$_2$–C_6H_5), 67.0 (C-17), 64.2 (C-16), 50.2 (–CO_2CH_3), 44.5, 43.2, 41.7, 40.5 (C-13), 39.5 (–N–CH_3), 37.5, 34.5 {–CH–CH–(CH_3)–CH_2–CH_3}, 32.2, 30.5 (C-6), 27.5 (C-12), 26.2 (C-11), 25.5 {–CH–CH–(CH_3)–CH_2–CH_3}, 16.5 {–CH–CH–(CH_3)–CH_2CH_3}, 16.2 (C-18), 11.2 {–CH–CH–(CH_3)–CH_2–CH_3}. MASS (FAB): m/z (%): 507 (100, M$^+$).

Hydroxy acid 17a. To a solution of **16a** (0.1 g, 0.21 mmol) in dioxane (5 ml) was added 1 N NaOH (0.1 ml) and the resulting solution was heated at 70 °C for 2 h. The reaction mixture was cooled and acidified with 1 N HCl. The resulting solution was extracted with ethyl acetate and dried over Na_2SO_4 and concentrated *in vacuo.* The residue was chromatographed over silica gel and elution with 10% methanol in chloroform (R_f = 0.5) furnished **17a** (0.07 g, 70%) as a light yellow foam, $[\alpha]_D^{20}$ +52 (*c* 2, MeOH). IR (KBr): 3442, 2925, 1707, 1596, 1500, 1352, 1028, 800, 582 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.29 (m, 5H, –O–CH_2–C_6H_5), 7.13 (d, 1H, J = 8.6, C-1-H), 6.75 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-H), 6.67 (d, 1H, J = 2.4, C-4-H), 4.99 (s, 2H, –O–CH_2–C_6H_5), 3.91–3.84 (m, 2H, C-16-H_2), 3.63–3.53 (m, 1H, –CH–CH_3), 3.03–2.95 (m, 2H, C-6-H_2), 2.86 (s, 3H, –N–CH_3), 2.82–2.69 (m, 2H, C-17-H_2), 2.30–2.25 (m, 2H), 2.04–1.73 (m, 4H), 1.49 (d, 3H, J = 7, –CH–CH_3), 1.48–1.25 (m, 5H), 0.94 (s, 3H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5 (–CO_2H), 157.2 (C-3), 138.0 (C-5), 137.6, 132.3 (C-10), 128.9, 128.2, 127.8, 126.9 (C-1), 114.8 (C-4), 113.0 (C-2), 70.3 (–O–CH$_2$–C_6H_5), 66.5 (C-17), 65.3 (C-16), 62.9 (–CH–CH_3), 43.3, 42.9, 41.1 (–N–CH_3), 38.6 (C-13), 37.8, 32.5, 30.8 (C-6), 27.5 (C-12), 27.0 (C-11), 18.8 (–CH–CH_3), 12.1 (C-18). MASS (FAB): m/z (%): 466 (100, M$^+$). Anal. Calcd for ($C_{29}H_{39}NO_4$): C, 74.81; H, 8.44; N, 3.01%. Found: C, 74.99; H, 8.72; N, 3.11%.

Hydroxy acid 17b. As described for **17a**, **16b** (0.10 g, 0.18 mmol) in dioxane (5 ml), 1 N NaOH (0.1 ml) furnished **17b** (0.07 g, 67%) as a light yellow foam, R_f = 0.55 (10% methanol in chloroform), $[\alpha]_D^{20}$ +49 (*c* 2, MeOH). IR (KBr): 3445, 2923, 1709, 1593, 1506, 1354, 1026, 801, 584 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41–7.12 (m, 10H, –O–CH_2–C_6H_5, –CH–CH_2–C_6H_5) 7.03 (d, 1H, J = 8.6, C-1-H), 6.67 (dd, 1H, J_1 = 8.6, J_2 = 2.4, C-2-H), 6.57 (d, 1H, J = 2.4, C-4-H), 5.01 (s, 2H, –O–CH_2–C_6H_5), 3.95–3.42 (m, 1H, –CH–CH_2–C_6H_5), 3.75–3.61 (m, 2H, C-16-H_2), 3.43–2.29 (m, 2H, –CH–CH_2–C_6H_5), 2.98–3.18 (m, 2H, C-6-H_2), 2.91 (s, 3H, –N–CH_3), 2.74–2.67 (m, 2H, C-17-H_2), 2.18–1.13 (m,

11H), 0.75 (s, 3H, C-18-H_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (–CO_2H), 156.8 (C-3), 137.9 (C-5), 137.6, 137.0, 132.2 (C-10), 129.5, 128.7, 128.5, 127.8, 127.4, 126.8 (C-1), 126.5, 114.4 (C-4), 112.6 (C-2), 71.9 (–CH–CH_2–C_6H_5), 69.9 (–O–CH_2–C_6H_5), 66.2 (C-17), 62.7 (C-16), 42.9, 42.7, 42.3, 41.3 (N–CH_3), 38.8 (C-13), 37.4, 33.6 (–CH–CH_2–C_6H_5), 32.1, 30.4 (C-6), 27.1 (C-12), 26.5 (C-11), 17.8 (C-18). MASS (FAB): m/z (%): 542 (100, M^+ + H). Anal. Calcd for ($C_{35}H_{43}NO_4$): C, 77.60; H, 8.00; N, 2.59%. Found: C, 77.86; H, 8.26; N, 2.78%.

Hydroxy acid 17c. As described for **17a**, **16c** (0.1 g, 0.19 mmol) in dioxane (5 ml), 1 N NaOH (0.1 ml) furnished **17c** (0.07 g, 72%) as a light yellow viscous oil, $R_f = 0.6$ (10% methanol in chloroform), $[\alpha]_D^{20}$ +28 (c 2, MeOH). IR (Neat): 3438, 2929, 1708, 1587, 1509, 1358, 1029, 805, 589 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.11 (m, 6H, –O–CH_2–C_6H_5, and C-1-H), 6.77–6.69 (m, 2H, C-2-H and C-4-H), 4.99 (s, 2H, –O–CH_2–C_6H_5), 3.77–3.73 (m, 2H, C-16-H_2), 2.80–2.73 {m, 3H, –CH–CH–(CH_3)–CH_2–CH_3 and C-6-H_2}, 2.38–2.26 (m, 2H, C-17-H_2), 2.23 (s, 3H, –N–CH_3), 2.16–1.39 (m, 13H), 1.00–0.89 (m, 8H), 0.59 (s, 3H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5 (–CO_2H), 157.2 (C-3), 138.1 (C-5), 137.9, 132.5 (C-10), 128.9, 128.2, 127.8, 126.9 (C-1), 114.9 (C-4), 112.9 (C-2), 73.5 {–CH–CH–(CH_3)–CH_2–CH_3}, 70.2 (–O–CH_2–C_6H_5), 66.9 (C-17), 62.4 (C-16), 44.6, 43.3, 42.4, 42.0 (C-13), 38.4 (–N–CH_3), 36.4, 34.9 {–CH–CH–(CH_3)–CH_2–CH_3}, 32.6, 30.7 (C-6), 27.5 (C-12), 26.6 (C-11), 25.9 {–CH–CH–(CH_3)–CH_2–CH_3}, 16.9 {–CH–CH–(CH_3)–CH_2–CH_3}, 14.6 (C-18), 12.4 {–CH–CH–(CH_3)–CH_2–CH_3}. MASS (FAB): m/z (%): 507 (100, M^+).

Lactone 3a. A stirred solution of hydroxy acid **17a** (20 mg, 0.04 mmol) in THF (1 ml) at RT under N_2 was treated with triethyl amine (0.06 ml, 0.43 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.04 ml, 0.26 mmol) and it was stirred overnight. The solution was diluted with toluene (5 ml) and added dropwise over 4 h to a refluxing solution of DMAP (60 mg, 0.51 mmol) in toluene (30 ml) under N_2. The reaction was further stirred for 2 h at reflux, and allowed to cool to room temperature. It was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$. The layers were separated and the water layer was extracted with ethyl acetate. The combined organic extracts were washed with 0.1 M aq. HCl, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was chromatographed over silica gel and elution with 10% ethyl acetate in hexane ($R_f = 0.4$) furnished **3a** (10 mg, 53%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.31 (m, 5H, –O–CH_2–C_6H_5), 7.21 (d, 1H, $J = 8.6$, C-1-H), 6.78 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.4$, C-2-H), 6.71 (d, 1H, $J = 2.4$, C-4-H), 5.03 (s, 2H, –O–CH_2–C_6H_5), 4.79–4.71 (m, 1H, C-16-H), 3.98–3.81 (m, 1H, C-16-H), 3.62–3.60 (m, 1H, –CH–CH_3), 2.88–2.78 (m, 2H, C-6-H_2), 2.55 (s, 3H, –N–CH_3), 2.48–2.20 (m, 2H, C-17-H_2), 2.00–1.97 (m, 2H), 1.84–1.73 (m, 3H), 1.43–1.30 (m, 3H), 1.16 (d, 3H, $J = 6.6$, –CH–CH_3), 0.88–0.81 (m, 3H), 0.61 (s, 3H, C-18-H_3). MASS (FAB): m/z (%): 448 (100, M^+ + H). Exact Mass (ESI-MS) calculated for $C_{29}H_{37}NO_3$ $[M]^+$: 447.27735, found: 447.27740.

Lactone 3b. As described for **3a**, **17b** (20 mg, 0.04 mmol) in THF (1 ml), triethyl amine (0.05 ml, 0.37 mmol), 2,4,6-trichlorobenzoyl chloride (0.03 ml, 0.22 mmol), DMAP (50 mg, 0.44 mmol) in toluene (30 ml) furnished **3b** (12 mg, 63%) as a light yellow oil, $R_f = 0.5$ (10% ethyl acetate in hexane), $[\alpha]_D^{20}$ +15.5 (c 2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (m, 11H, –O–CH_2–C_6H_5, –CH–CH_2–C_6H_5 and C-1-H), 6.79 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.4$, C-2-H), 6.72 (d, 1H, $J = 2.4$, C-4-H), 5.04 (s, 2H, –O–CH_2–C_6H_5), 4.53–4.50 (m, 1H, C-16-H), 4.19–4.05 (m, 1H, C-16-H), 3.66–3.64 (m, 1H, –CH–CH_2–C_6H_5), 3.07–2.91 (m, 2H, –CH–CH_2–C_6H_5), 2.87–2.86 (m, 2H, C-6-H_2), 2.66 (s, 3H, –N–CH_3), 2.39–2.27 (m, 2H, C-17-H_2), 2.05–1.81 (m, 4H), 1.68–1.27 (m, 7H), 0.68 (s, 3H, C-18-H_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.9 (–CO–), 156.8 (C-3), 138.9 (C-5), 137.9, 137.3, 133.2 (C-10), 129.3, 128.5, 128.4, 127.8, 127.4, 126.2(C-1), 126.1, 114.4 (C-4), 112.4 (C-2), 71.8(–CH–CH_2–C_6H_5), 69.9 (–O–CH_2–C_6H_5), 67.1 (C-16), 61.1 (C-17), 46.2 (–N–CH_3), 43.1, 42.4, 41.1, 40.4 (C-13), 37.3, 30.4 (C-6), 29.7, 28.6 (–CH–CH_2–C_6H_5), 27.6 (C-12), 26.0 (C-11), 17.9 (C-18). MASS (FAB): m/z (%): 524 (100, M^+ + H). Anal. Calcd for ($C_{35}H_{41}NO_3$): C, 80.27; H, 7.89; N, 2.67%. Found: C, 80.48; H, 7.99; N, 2.86%.

Lactone 3c. As described for **3a**, **17c** (20 mg, 0.04 mmol) in THF (1 ml), triethyl amine (0.05 ml, 0.39 mmol), 2,4,6-trichlorobenzoyl chloride (0.04 ml, 0.24 mmol), DMAP (60 mg, 0.47 mmol) in toluene (30 ml) furnished **3c** (8 mg, 42%) as a light yellow oil, $R_f = 0.45$ (10% ethyl acetate in hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.30 (m, 5H, –O–CH_2–C_6H_5), 7.19 (d, 1H, $J = 8.7$, C-1-H), 6.77 (dd, 1H, $J_1 = 8.7$, $J_2 = 2.7$, C-2-H), 6.71 (d, 1H, $J = 2.7$, C-4-H), 5.02 (s, 2H, –O–CH_2–C_6H_5), 4.40–4.21 (m, 1H, C-16-H), 4.21–4.16 (m, 1H, C-16-H), 3.15–3.19 (m, 1H, –CH–CH–(CH_3)–CH_2–CH_3}, 2.86–2.85 (m, 2H, C-6-H_2), 2.80–2.75 (m, 1H), 2.31–2.23 (m, 4H, –N–CH_3), 1.95–1.75 (m, 5H), 1.73–1.07 (m, 7H), 0.94–0.68 (m, 8H), 0.68 (s, 3H, C-18-H_3). MASS (FAB): m/z (%): 490 (100, M^+ + H).

Acknowledgements

Financial support of this work by DST (SR/FTP/CSA-05/2002) and MOH, New Delhi and a fellowship to Shagufta by CSIR are gratefully acknowledged. Dr Raja Roy is sincerely thanked for recording ^{1}H-^{1}H COSY, HSQC and HMBC spectra.

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