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Microwave-promoted and Lewis acid catalysed synthesis of steroidal A- and D-ring fused 4,6-diarylpyridines

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ABSTRACT

The preparation of novel steroidal heterocycles containing 4,6-diaryl substituted pyridine moiety fused to the 2,3- and 16,17-positions of the steroid nucleus is described. The Michael reaction of steroidal ketones (**1a**, **1b** and **1c**) with in situ generated chalcones provided the intermediates 3,5-diaryl-1,5-dicarbonyl steroidal derivatives (**4a–s**). Subsequently, the intermediates **4a–s** were converted to the pyridine derivatives (**5a–s**) by solid phase reaction with urea in presence of $BF_3.OEt_2$ as the catalyst under microwave irradiation. All the synthesized heterosteroids are new compounds and are currently being evaluated for their biological activities.

1. Introduction

The pyridine substructure is one of the most prevalent heterocycle due to its widespread distribution in natural products, pharmaceuticals and synthetic biologically active compounds [1]. Consequently, the development of methods for the preparation of substituted pyridine derivatives is of importance to medicinal chemistry and represents a worthwhile goal of organic synthesis [2]. During the last decades, steroids bearing heterocycles fused to the A- or D-ring of the steroid skeleton continue to attract much pharmaceutical interest as many of these heterosteroids possess widespread biological activities [3–7]. Due to the remarkable importance from the pharmacological and synthetic viewpoints, great efforts are being made to annelate steroidal moiety with pyrazole, isoxazole, pyridine, pyran, pyrrole or pyrimidine rings using various synthetic strategies [8–10]. Some of the biologically active heterosteroids are shown in Fig. 1.

Among these annelated heterosteroids, the synthesis of A-and D-ring fused pyridines draw particular interest because of the inherent biological activities of these heterosteroids [7–8,10–11]. Over the last decade, microwave assisted organic synthesis (MAOS) has emerged as a new field in organic synthesis, which is recognized as a "green" technology has been applied as a very efficient way to accelerate the course of many organic reactions, producing.

high yields, higher selectivity, and lower quantities of side products [12]. In view of the therapeutic importance of heterosteroids and in continuation of our interest towards development of newer strategy for A- and D-ring annelated heterosteroids [13], herein we describe a microwave-promoted and Lewis acid catalysed synthesis of new steroidal 4,6-diarylpyridines from steroidal 1,5-dicarbonyl compounds. The intermediate, steroidal 1,5-dicarbonyl compounds were synthesized via a base catalyzed multicomponent reaction of ketosteroids, aromatic aldehydes and aryl ketones at room temperature.

2. Experimental

2.1. General remarks

Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR-2000 spectrometer using KBr pellets or on a thin film using chloroform. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (60–120 mesh, Merck Chemicals). All MW reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor.

2.2. Chemical synthesis

2.2.1. General procedure for synthesis of steroidal 1,5-dicarbonyl compounds

To a stirring solution of steroidal ketone (1.0 mmol), aromatic aldehyde (1.0 mmol) and aryl ketone (1.0 mmol) in toluene

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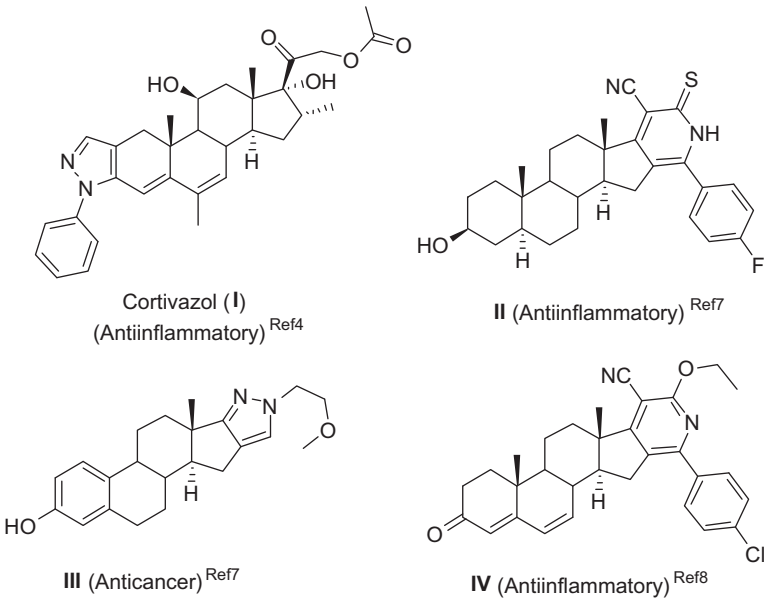


Fig. 1. Examples of biologically active heterosteroids (I-IV).

(5.0 mL), KOH (2.0 mmol) was added at room temperature. The reaction mixture was stirred for 6 h and after completion of the reaction, as indicated by TLC, solvent was removed under vacuum. The residue obtained was washed with water, extracted with DCM and dried over Na_2SO_4. The crude product obtained after removal of the solvent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to get pure steroidal 1,5-dicarbonyl compounds.

All the crude hydroxy 1,5-dicarbonyl compounds **4k**, **4m** and **4o** were treated with acetic anhydride (1.0 mL) and pyridine (1.0 mL) at room temperature for 6 hours. The crude product obtained after removal of the solvent and unreacted reagent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to get pure acetate derivatives **4l**, **4n** and **4p**.

*2.2.1.1. 2-(1′,3′-Diphenyl-propyl-3′-one)-5α-cholestan-3-one (**4a**).* White solid; m.p. 194–196 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88-7.03 (m, 10H), 3.58-3.50 (m, 2H), 3.18-3.02 (m, 1H), 2.80-2.70 (m, 1H), 2.36-0.52 (m, 44H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.7, 199.1, 142.2, 137.1, 132.8, 128.5, 128.4, 128.3, 128.2, 126.5, 56.2, 56.1, 53.7, 51.0, 49.3, 42.5, 41.4, 39.5, 36.5, 36.1, 35.8, 35.2, 28.2, 28.0, 24.2, 23.8, 22.83, 22.6, 21.3, 18.6, 12.6, 12.0; IR ($CHCl_3$, cm^{-1}) 2931, 2867, 1708, 1686, 1448, 1236, 756; MS (EI, *m/z*) 594 $[M]^+$. Anal. calcd. for $C_{42}H_{58}O_2$: C, 84.79; H, 9.83; Found: C, 84.98; H, 9.63.

*2.2.1.2. 2-[1′-(p-Methylphenyl)-3′-phenyl-propyl-3′-one]-5α-cholestan-3-one (**4b**).* White solid; m.p. 160-162 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (*d*, *J* = 9 Hz, 2H), 7.47-6.80 (m, 7H), 3.56-3.50 (m, 2H), 3.14-3.09 (m, 1H), 2.85-2.68 (m, 1H), 2.35-0.53 (m, 47H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.8, 199.3, 138.9, 137.1, 135.8, 132.7, 129.1, 128.4, 128.3, 128.2, 56.2, 56.1, 53.8, 51.1, 49.3, 42.6, 41.0, 39.5, 36.5, 36.1, 35.8, 35.2, 31.7, 28.2, 28.0, 23.8, 22.8, 22.6, 21.1, 18.6, 12.7, 12.0; IR ($CHCl_3$, cm^{-1}) 2933, 2867, 1709, 1687, 1447, 1235, 757; MS (EI, *m/z*) 608 $[M]^+$, 489 $[M^+$-$PhCOCH_2]$. Anal. calcd. for $C_{43}H_{60}O_2$: C, 84.81; H, 9.93; Found: C, 84.93; H, 9.74.

*2.2.1.3. 2-[1′-(p-Methoxyphenyl)-3′-phenyl-propyl-3′-one]-5α-cholestan-3-one (**4c**).* White solid; m.p. 162–163 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (*d*, *J* = 8.8 Hz, 2H), 7.50-6.81 (m, 7H), 3.82 (s, 3H), 3.69-3.56 (m, 2H), 3.28-3.17 (m, 1H), 2.79-2.69 (m, 1H), 2.41-0.62 (m, 44H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.5, 196.9, 140.8, 136.4, 134.7, 132.3, 129.9, 128.8, 117.3, 56.3, 55.9, 53.7, 51.01, 49.2, 42.5, 40.6, 39.5, 36.4, 36.1, 35.7, 35.2, 31.0, 28.2, 27.9, 24.2, 23.8, 22.8, 22.6, 18.4, 12.6, 12.2; IR ($CHCl_3$, cm^{-1}) 2933, 2868, 1707, 1688, 1448, 1224, 771; MS (EI, *m/z*) 624.4$[M]^+$, 505.4$[M^+$-$PhCOCH_2]$. Anal. calcd. for $C_{43}H_{60}O_3$: C, 82.64; H, 9.68; Found: C, 82.69; H, 9.86.

*2.2.1.4. 2-[1′-(p-Flurophenyl)-3′-phenyl-propyl-3′-one]-5α-cholestan-3-one (**4d**).* White solid; m.p. 180-183 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.94-6.89 (m, 9H), 3.64-3.59 (m, 2H), 3.22-3.17 (m, 1H), 2.82-2.68 (m, 1H), 2.42-0.66 (m, 44H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.4, 198.9, 162.9, 137.9, 136.9, 132.9, 130.4, 129.7, 128.7, 115.3, 56.2, 56.1, 53.7, 51.0, 49.2, 42.5, 40.6, 39.5, 36.5, 36.1, 35.7, 35.2, 30.9, 28.2, 28.0, 24.1, 23.8, 22.8, 22.6, 18.6, 12.6, 12.0; IR ($CHCl_3$, cm^{-1}) 2932, 2867, 1707, 1687, 1448, 1224, 759; MS (EI, *m/z*) 612.4 $[M]^+$. Anal. calcd. for $C_{42}H_{57}FO_2$: C, 82.31; H, 9.37; Found: C, 82.63; H, 9.56.

*2.2.1.5. 2-[3′-(p-Chlorophenyl)-1′-phenyl-propyl-3′-one]-5α-cholestan-3-one (**4e**).* White solid; m.p. 185-187 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.86-6.71 (m, 9H), 3.66-3.56 (m, 2H), 3.22-3.19 (m, 1H), 2.89-2.69 (m, 1H), 2.41-0.59 (m, 44H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.5, 196.9, 143.7, 138.4, 134.6, 129.4, 128.3, 126.6, 56.2, 56.0, 53.7, 51.0, 49.2, 42.6, 41.1, 39.5, 36.4, 36.0, 35.7, 35.1, 29.7, 28.2, 27.9, 23.2, 23.0, 22.5, 22.1, 18.4, 12.6, 12.0; IR ($CHCl_3$, cm^{-1}) 2932, 2868, 1706, 1687, 1447, 1221, 761; MS (EI, *m/z*) 628.4 $[M]^+$, 630.4 $[M^+$+2]. Anal. calcd. for $C_{42}H_{57}ClO_2$: C, 80.15; H, 9.13; Found: C, 80.26; H, 9.40.

*2.2.1.6. 2-[3′-(p-Chlorophenyl)-1′-(p-methylphenyl)-propyl-3′-one]-5α-cholestan-3-one (**4f**).* White solid; m.p. 172-175 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.89-6.78 (m, 8H), 3.64-3.56 (m, 2H), 3.18-3.17 (m, 1H), 2.76-2.66 (m, 1H), 2.44-0.60 (m, 47H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.3, 198.5, 138.4, 137.7, 134.6, 130.0, 129.4, 128.5, 127.1, 126.6, 56.2, 56.0, 53.7, 51.0, 49.2, 42.6, 40.6, 39.5, 36.4, 36.1, 35.7, 35.2, 28.6, 28.2, 28.0, 23.9, 23.0, 22.6, 21.7, 18.6, 12.7, 12.0; IR ($CHCl_3$, cm^{-1}) 2938, 2867.4, 1709, 1682, 1444, 1221, 772; MS (EI, m/z) 642.4 $[M]^+$, 644.4 $[M^+$+2]. Anal. calcd. for $C_{43}H_{59}ClO_2$: C, 80.27; H, 9.24; Found: C, 80.35; H, 9.45.

2.2.1.7. 2-[3′-(p-Chlorophenyl)-1′-(p-flurophenyl)-propyl-3′-one]-5α-cholestan-3-one (4g). White solid; m.p. 182-184 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.91-7.06 (m, 8H), 3.72-3.56 (m, 2H), 3.20-3.14 (m, 1H), 2.78-2.66 (m, 1H), 2.42-0.61 (m, 44H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.6, 197.6, 160.7, 137.1, 136.9, 134.1, 131.5, 129.2, 128.0, 115.3, 55.9, 55.0, 53.3, 51.2, 49.4, 42.5, 40.6, 38.2, 36.4, 36.1, 35.4, 34.9, 29.2, 28.1, 27.1, 24.2, 23.5, 22.8, 21.3, 19.0, 12.4, 12.0; IR ($CHCl_3$, cm^{-1}) 2932, 2867, 1709, 1682, 1446, 1220, 771; MS (EI, *m/z*) 646.2 $[M]^+$. Anal. calcd. for $C_{42}H_{56}ClFO_2$: C, 77.93; H, 8.72; Found: C, 77.76; H, 8.75.

*2.2.1.8. 2-[3′-(p-Methylphenyl)-1′-phenyl-propyl-3′-one)-5α-cholestan-3-one (**4h**).* White solid; m.p. 165-167 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (*d*, *J* = 8.8 Hz, 2H), 7.76-6.74 (m, 7H), 3.64-3.56 (m, 2H), 3.20-3.18 (m, 1H), 2.86-2.72 (m, 1H), 2.42-0.60 (m, 47H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.6, 198.8, 143.4, 142.3, 134.7, 129.2, 128.4, 128.3, 126.4, 56.2, 56.1, 53.8, 51.0, 49.3, 42.6, 41.4, 39.5, 36.6, 36.1, 35.6, 35.2, 28.2, 27.9, 23.8, 22.8, 22.6, 21.6, 21.3, 18.6, 12.6, 12.0; IR ($CHCl_3$, cm^{-1}) 2931.9, 2867.5, 1709.2, 1681.4, 1445.0, 1224.5, 758.4; MS (EI, m/z) 608.4$[M]^+$. Anal. calcd. for $C_{43}H_{60}O_2$: C, 84.81; H, 9.93; Found: C, 84.70; H, 9.78.

*2.2.1.9. 2-[1′,3′-bis(p-Methylphenyl)-propyl-3′-one]-5α-cholestan-3-one (**4i**).* White solid; m.p. 169-172 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.45-6.79 (m, 8H), 3.66-3.54 (m, 2H), 3.20-3.16 (m, 1H), 2.79-2.68 (m, 1H), 2.44-0.60 (m, 50H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.3, 198.7, 142.4, 139.1, 134.6, 132.1, 128.5, 128.4, 56.3, 56.1, 53.2, 51.4, 48.3, 42.5, 40.6, 38.5, 36.5, 36.1, 35.7, 35.1, 28.7, 28.1, 27.8, 23.9, 23.2, 22.6, 21.9, 18.6, 12.7, 11.9; IR ($CHCl_3$, cm^{-1}) 2932, 2868, 1709, 1681, 1445, 1225, 758; MS (EI, *m/z*) 622.5 $[M]^+$. Anal. calcd. for $C_{44}H_{62}O_2$: C, 84.83; H, 10.03; Found: C, 84.77; H, 9.98.

*2.2.1.10. 2-[1′-(p-Flurophenyl)-3′-(p-methylphenyl)-propyl-3′-one]-5α-cholestan-3-one (**4j**).* White solid; m.p. 175 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.97-6.88 (m, 8H), 3.64-3.55 (m, 2H), 3.17-3.15 (m, 1H), 2.85-2.68 (m, 1H), 2.42-0.61 (m, 47H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.5, 198.6, 163.0, 143.6, 137.9, 134.5, 129.8, 129.2, 128.3, 115.3, 56.2, 56.1, 53.8, 51.1, 49.2, 42.6, 40.7, 39.5, 36.5, 36.1, 35.8, 35.2, 28.7, 28.2, 28.0, 23.8, 22.8, 22.6, 21.6, 18.6, 12.6, 12.0; IR ($CHCl_3$, cm^{-1}) 2932, 2867, 1709, 1682, 1446, 1219, 771; MS (EI, m/z) 626.4$[M]^+$. Anal. calcd. for $C_{43}H_{59}FO_2$: C, 82.38; H, 9.49; Found: C, 82.64; H, 9.50.

*2.2.1.11. 3β-Hydroxy-16-(1′,3′-diphenyl-propyl-3′-one)-5-en-androst-17-one (**4k**).* Gum, 1H NMR ($CDCl_3$, 300 MHz) δ 7.87-7.17 (m, 10H), 5.41-5.36 (m, 1H), 3.60-3.48 (m, 1H), 1.08 (s, 3H), 0.96 (s, 3H), 2.88-0.89 (m, 21H); IR ($CHCl_3$, cm^{-1}) 3411, 2935, 1719, 1715, 1629, 1254, 1034; MS (EI, m/z) 478 $[M-18]^+$.

*2.2.1.12. 3β-Acetoxy-16-(1′,3′-diphenyl-propyl-3′-one)-5-en-androst-17-one (**4l**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.03 (m, 10H), 5.44-5.33 (m, 1H), 4.65-4.50 (m, 1H), 2.84-2.68 (m, 1H), 1.07 (s, 3H), 0.90 (s, 3H), 2.47-0.87 (m, 23H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 207.5, 170.2, 140.2, 139.5, 139.1, 134.0, 133.2, 132.4, 130.2, 129.5, 129.1, 128.5, 128.1, 121.7, 73.8, 50.4, 50.0, 49.7, 47.4, 38.0, 36.8, 36.6, 31.5, 31.3, 31.0, 30.9, 29.5, 27.6, 21.3, 20.3, 19.4, 14.3, 13.3; IR ($CHCl_3$, cm^{-1}) 2947, 1729, 1715, 1629, 1256, 1030; MS (EI, m/z) 478 $[M-60]^+$.

*2.2.1.13. 3β-Hydroxy-16-[1′-(p-methylphenyl)-3′-phenyl-propyl-3′-one]-5-en-androst-17-one (**4m**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.15 (m, 9H), 5.40-5.36 (m, 1H), 3.60-3.46 (m, 1H), 2.37 (s, 3H), 1.07 (s, 3H), 0.96 (s, 3H), 2.82-0.89 (m, 21H); IR ($CHCl_3$, cm^{-1}) 3428, 2946, 1729, 1713, 1628, 1255, 1032; MS (EI, m/z) 492 $[M-18]^+$.

*2.2.1.14. 3β-Acetoxy-16-[1′-(p-methylphenyl)-3′-phenyl-propyl-3′-one]-5-en-androst-17-one (**4n**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.64-7.00 (m, 9H), 5.42-5.34 (m, 1H), 4.60-4.51 (m, 1H), 2.85-2.68 (m, 1H), 2.44 (s, 3H), 2.04 (s, 3H), 1.09 (s, 3H), 0.89 (s, 3H), 2.45-0.88 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.8, 207.0, 170.5, 140.0, 139.9, 139.6, 134.9, 133.2, 132.8, 130.4, 129.5, 129.0, 128.6, 128.2, 121.8, 73.7, 50.2, 50.1, 49.8, 47.3, 38.1, 36.9, 36.8, 31.5, 31.46, 31.4, 31.1, 30.9, 29.4, 27.7, 21.5, 21.4, 20.4, 19.4, 14.3, 13.5; IR ($CHCl_3$, cm^{-1}) 2946, 1729, 1713, 1628, 1255, 1032, 755; MS (EI, m/z) 492 $[M-60]^+$.

*2.2.1.15. 3β-Hydroxy-16-[1′-(p-chlorophenyl)-3′-phenyl-propyl-3′-one]-5-en-androst-17-one (**4o**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.17 (m, 9H), 5.42-5.34 (m, 1H), 3.62-3.45 (m, 1H), 1.07 (s, 3H), 0.96 (s, 3H), 2.80-0.87 (m, 21H); IR ($CHCl_3$, cm^{-1}) 3432, 2948, 1726, 1715, 1626, 1259, 1036; MS (EI, m/z) 512 $[M-18]^+$.

*2.2.1.16. 3β-Acetoxy-16-[1′-(p-chlorophenyl)-3′-phenyl-propyl-3′-one]-5-en-androst-17-one (**4p**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.63-7.05 (m, 9H), 5.42-5.34 (m, 1H), 4.62-4.53 (m, 1H), 2.84-2.68 (m, 1H), 2.03 (s, 3H), 1.08 (s, 3H), 0.91 (s, 3H), 2.43-0.87 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.5, 207.2, 170.4, 140.1, 139.7, 139.6, 134.7, 133.1, 132.8, 130.4, 129.5, 129.0, 128.6, 128.2, 121.8, 73.5, 50.2, 50.1, 49.8, 47.2, 38.1, 36.9, 36.8, 31.5, 31.46, 31.4, 31.2, 30.9, 29.4, 27.5, 21.4, 20.4, 19.4, 14.4, 13.3; IR ($CHCl_3$, cm^{-1}) 2948, 1726, 1715, 1626, 1259, 1036; MS (EI, m/z) 512 $[M-60]^+$, 514 $[(M+2)-60]^+$.

*2.2.1.17. 2,16-Bis[1′-phenyl-3′-phenyl-propyl-3′-one]-5α-androst-3,17-dione (**4q**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.17 (m, 20H), 3.75-2.80 (m, 6H), 1.08 (s, 3H), 0.90 (s, 3H), 2.49-0.87 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.6, 212.2, 198.8, 198.6, 139.4, 139.2, 137.2, 133.1, 132.7, 132.9, 130.5, 129.5, 129.2, 128.9, 128.5, 128.4, 128.3, 128.1, 128.0, 125.5, 124.8, 53.0, 51.2, 47.8, 47.4, 44.1, 42.0, 40.9, 37.1, 36.6, 35.7, 35.2, 35.0, 31.6, 29.5, 26.3, 24.6, 22.6, 21.7, 21.4, 21.0, 13.9; IR ($CHCl_3$, cm^{-1}) 2924, 1709, 1686, 1448, 756; MS (ESI, m/z) 705.4 $[M+1]^+$.

*2.2.1.18. 2,16-Bis[1′-(p-methylphenyl)-3′-phenyl-propyl-3′-one]-5α-antrost-3,17-dione (**4r**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.17 (m, 18H), 3.75-2.80 (m, 6H), 2.18 (s, 6H), 1.07 (s, 3H), 0.91 (s, 3H), 2.46-0.87 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.9, 213.0, 199.1, 198.5, 139.6, 139.1, 137.0, 133.0, 132.9, 132.7, 130.9, 129.5, 129.0, 128.9, 128.5, 128.4, 128.3, 128.1, 128.0, 125.3, 53.8, 51.3, 47.8, 47.7, 44.1, 42.2, 40.9, 37.1, 36.9, 35.7, 35.1, 35.0, 31.6, 29.7, 26.3, 24.7, 22.6, 21.7, 21.5, 21.0, 13.8; IR ($CHCl_3$, cm^{-1}) 2948, 1727, 1715, 1625, 1260, 1036; MS (ESI, m/z) 733.4 $[M + 1]^+$, 755.9 $[M + 23]^+$.

*2.2.1.19. 2,16-Bis[1′-(p-chlorophenyl)-3′-phenyl-propyl-3′-one]-5α-antrost-3,17-dione (**4s**).* Gum; 1H NMR ($CDCl_3$, 300 MHz) δ 7.90-7.18 (m, 18H), 3.73-2.79 (m, 6H), 1.09 (s, 3H), 0.88 (s, 3H), 2.46-0.87 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.5, 213.1, 198.6, 198.2, 139.4, 139.0, 137.1, 132.7, 132.6, 132.6, 130.7, 129.3, 128.7, 128.5, 128.2, 128.1, 128.0, 127.8, 127.77, 127.5, 125.0, 53.8, 51.1, 47.8, 47.4, 44.1, 42.0, 40.9, 37.1, 36.9, 35.7, 35.0, 31.6, 29.8, 26.3, 24.7, 22.7, 21.7, 21.5, 21.1, 13.5; IR ($CHCl_3$, cm^{-1}) 2950, 1729, 1713, 1624, 1260, 1036; MS (ESI, m/z) 773.3 $[M + 1]^+$.

2.2.2. General procedure for synthesis of steroidal 4′,6′-diphenyl-pyridines

Steroidal 1,5-dicarbonyl compound (0.75 mmol) and ammonium acetate (1.5 mmol) were irradiated in a closed vessel in presence of 10 mol% of boron trifluoride etherate in a Synthos 3000 microwave reactor at 720 Watt (130 °C and 21 bar) for 6 min. The reaction mixture was treated with water (30 mL), extracted

with dichloromethane. The organic portion was washed with water, dried over anhydrous sodium sulfate and the solvent was removed to obtain a crude product which on silica gel column chromatographic purification using EtOAc/hexane as eluent afforded the pyridine derivative.

All the crude hydroxy pyridine derivatives **5k**, **5m** and **5o** were treated with acetic anhydride (1.0 mL) and pyridine (1.0 mL) at room temperature for 6 h. The crude product obtained after removal of the solvent and unreacted reagent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to get pure acetate derivative **5l**, **5n** and **5p**.

*2.2.2.1. 4′,6′-Diphenyl-5α-cholest[3,2-b]pyridine (**5a**).* White solid; m.p. 196 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (*d*, *J* = 7.1 Hz, 2H), 7.42-7.03 (m, 9H), 3.01-2.94 (m, 1H), 2.71-2.56 (m, 2H), 2.26 (*d*, *J* = 15 Hz, 1H), 2.01-0.82 (m, 34H), 0.72 (s, 3H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.8, 154.2, 150.8, 139.8, 139.7, 128.6, 128.56, 128.5, 128.3, 127.7, 127.4, 126.9, 119.3, 56.5, 56.4, 53.7, 42.5, 41.9, 39.9, 39.5, 36.2, 35.8, 35.6, 35.2, 31.7, 28.7, 28.3, 24.3, 23.9, 22.9, 22.6, 21.2, 18.7, 12.0, 11.7; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1588, 1541, 1445, 1218, 774; MS (EI, *m/z*) 573.4 $[M]^+$. Anal. calcd. for $C_{42}H_{55}N$: C, 87.90; H, 9.66; N, 2.44; Found: C, 87.82; H, 9.64; N, 2.27.

*2.2.2.2. 4′-(p-Methylphenyl)-6′-phenyl-5α-chloest[3,2-b]pyridine (**5b**).* White solid; m.p. 174-176 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (*d*, *J* = 7.1 Hz, 2H), 7.49-6.90 (m, 8H), 3.07-3.01 (m, 1H), 2.73-2.67 (m, 2H), 2.37 (s, 3H), 2.41-0.80 (m, 35H), 0.72 (s, 3H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 154.2, 150.7, 139.8, 137.5, 136.8, 129.1, 128.6, 128.5, 128.3, 127.5, 126.9, 119.4, 56.4, 56.3, 53.7, 42.4, 39.5, 36.2, 35.8, 35.6, 35.2, 31.0, 29.8, 28.3, 28.0, 24.3, 23.9, 22.9, 22.6, 21.3, 18.7, 12.0, 11.6; IR ($CHCl_3$, cm^{-1}) 2926, 2866, 1592, 1542, 1444, 1219, 773; MS (EI, *m/z*) 587.4 $[M]^+$. Anal. calcd. for $C_{43}H_{57}N$: C, 87.85; H, 9.77; N, 2.38; Found: C, 87.85; H, 9.79; N, 2.28.

*2.2.2.3. 4′-(p-Flurophenyl)-6′-phenyl-5α-chloest[3,2-b]pyridine (**5c**).* White solid; m.p. 185–186 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, *J* = 7.0 Hz, 2H), 7.52-7.10 (m, 8H), 3.02-2.96 (m, 1H), 2.60-2.52 (m, 2H), 2.30-0.73 (m, 35H), 0.71 (s, 3H), 0.63 (s, 3H),; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0, 153.3, 151.5, 139.0, 136.2, 132.2, 130.0, 128.6, 128.2, 127.6, 127.1, 126.8, 119.8, 56.4, 56.3, 53.8, 42.4, 41.9, 39.9, 39.6, 36.2, 35.9, 35.5, 35.2, 31.6, 28.3, 28.2, 24.2, 23.6, 22.9, 22.6, 18.7, 11.9, 11.6; IR ($CHCl_3$, cm^{-1}) 2927, 2866, 1597, 1540, 1444, 1219, 774; MS (EI, *m/z*) 591.4 $[M]^+$. Anal. calcd. for $C_{42}H_{54}FN$: C, 85.23; H, 9.20; N, 2.37; Found: C, 85.44; H, 9.10; N, 2.49.

*2.2.2.4. 4′-(p-Methoxyphenyl)-6′-phenyl-5α-chloest[3,2-b]pyridine (**5d**).* White solid; m.p. 183 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (*d*, *J* = 7.2 Hz, 2H), 7.50-7.03 (m, 8H), 3.84 (s, 3H), 3.01-2.94 (m, 1H), 2.63-2.56 (m, 2H), 2.24-0.74 (m, 35H), 0.70 (s, 3H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.1, 153.2, 151.6, 139.8, 134.7, 131.0, 129.2, 128.6, 128.0, 127.6, 127.4, 126.9, 119.6, 56.4, 56.2, 53.8, 42.4, 41.9, 39.9, 39.5, 36.2, 35.8, 35.6, 35.2, 31.7, 28.7, 28.3, 24.2, 23.9, 22.8, 22.6, 21.2, 18.7, 11.9, 11.7; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1589, 1543, 1445, 1218, 774; MS (EI, *m/z*) 603.4 $[M]^+$. Anal. calcd. for $C_{43}H_{57}NO$: C, 85.52; H, 9.51; N, 2.32; Found: C, 85.57; H, 9.48; N, 2.58.

*2.2.2.5. 6′-(p-Chlorophenyl)-4′-phenyl-5α-chloest[3,2-b]pyridine (**5e**).* White solid; m.p. 189 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (*d*, *J* = 7.1 Hz, 2H), 7.47-7.03 (m, 8H), 3.06-2.98 (m, 1H), 2.68-2.64 (m, 2H), 2.20-0.74 (m, 35H), 0.68 (s, 3H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0, 153.9, 151.1, 139.4, 136.9, 133.0, 129.3, 128.9, 128.7, 127.7, 127.1, 126.7, 119.1, 56.4, 56.2, 53.7, 42.5, 41.9, 40.0, 39.6, 36.3, 35.8, 35.6, 35.2, 28.3, 28.0, 23.0, 22.7, 22.2, 21.3, 21.3, 18.7, 11.9, 11.7; IR ($CHCl_3$, cm^{-1}) 2928, 2867, 1588, 1542, 1444, 1218, 775; MS (EI, *m/z*) 607.4 $[M]^+$. Anal. calcd. for $C_{42}H_{54}ClN$: C, 82.92; H, 8.95; N, 2.30; Found: C, 82.73; H, 8.94; N, 2.18.

*2.2.2.6. 6′-(p-Chlorophenyl)-4′-(p-methylphenyl)-5α-chloest[3,2-b]pyridine (**5f**).* White solid; m.p. 176-177 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.99-7.22 (m, 9H), 3.07-2.99 (m, 1H), 2.66-2.63 (m, 2H), 2.35 (s, 3H), 2.24-0.71 (m, 35H), 0.70 (s, 3H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.9, 153.7, 151.2, 139.4, 136.9, 133.0, 129.3, 129.0, 128.6, 127.6, 127.1, 126.7, 119.9, 56.5, 56.4, 53.8, 42.5, 41.9, 40.0, 39.7, 36.6, 35.7, 35.4, 35.2, 28.3, 28.1, 23.2, 22.7, 22.2, 21.3, 21.3, 18.6, 12.0, 11.7; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1589, 1542, 1444, 1223, 774; MS (EI, *m/z*) 621.4 $[M]^+$. Anal. calcd. for $C_{43}H_{56}ClN$: C, 82.98; H, 9.07; N, 2.25; Found: C, 82.74; H, 9.07; N, 2.21.

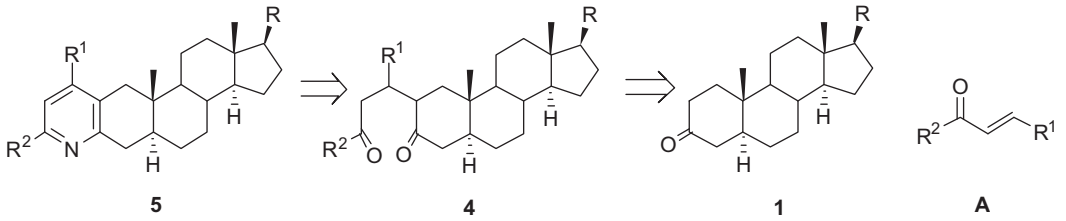
*2.2.2.7. 6′-(p-Chlorophenyl)-4′-(p-flurophenyl)-5α-chloest[3,2-b]pyridine (**5g**).* White solid; m.p. 185-186 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.94-7.26 (m, 9H), 3.04-2.87 (m, 1H), 2.67-2.60 (m, 2H), 2.20-0.70 (m, 35H), 0.72 (s, 3H), 0.62 (s, 3H),; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 156.8, 154.3, 150.1, 138.2, 135.0, 132.1, 130.0, 129.7, 128.3, 127.7, 127.1, 115.5, 56.4, 56.4, 53.8, 42.4, 41.9, 39.6, 36.2, 35.9, 35.5, 35.2, 28.7, 28.2, 27.1, 24.0, 23.8, 22.9, 22.6, 21.3, 18.7, 12.0, 11.7; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1600, 1542, 1443, 1223, 774; MS (EI, *m/z*) 625.4 $[M]^+$. Anal. calcd. for $C_{42}H_{53}ClFN$: C, 80.54; H, 8.53; N, 2.24; Found: C, 80.47; H, 8.81; N, 2.45.

*2.2.2.8. 6′-(p-Methylphenyl)-4′-phenyl-5α-chloest[3,2-b]pyridine (**5h**).* White solid; m.p. 169 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.22 (m, 10H), 3.06-2.99 (m, 1H), 2.69-2.63 (m, 2H), 2.38 (s, 3H), 2.21-0.71 (m, 35H), 0.70 (s, 3H), 0.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 154.2, 150.7, 139.9, 138.3, 136.9, 129.4, 128.6, 128.3, 127.7, 127.1, 126.7, 119.0, 56.4, 56.3, 53.7, 42.4, 41.9, 40.0, 39.5, 36.2, 35.8, 35.6, 35.2, 28.3, 28.1, 23.9, 22.9, 22.6, 21.3, 21.2, 18.7, 12.0, 11.7; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1588, 1542, 1445, 1218, 774; MS (EI, *m/z*) 587.5 $[M]^+$. Anal. calcd. for $C_{43}H_{57}N$: C, 87.85; H, 9.77; N, 2.38; Found: C, 87.48; H, 9.79; N, 2.16.

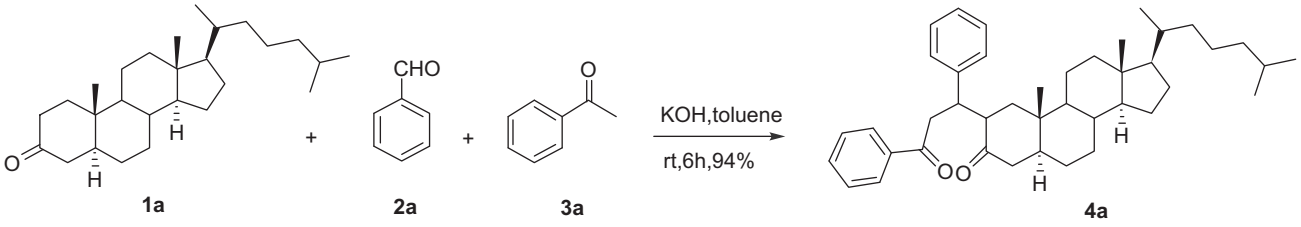
*2.2.2.9. 4′,6′-bis(p-Methylphenyl)-5α-chloest[3,2-b]pyridine (**5i**).* White solid; m.p. 189-192 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.97-7.25 (m, 9H), 3.08-2.99 (m, 1H), 2.71-2.65 (m, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.24-0.74 (m, 35H), 0.70 (s, 3H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0, 153.2, 150.9, 138.3, 136.4, 131.0, 129.4, 129.0, 128.4, 127.5, 127.2, 119.6, 56.5, 56.4, 54.0, 42.5, 41.9, 40.0, 39.7, 36.5, 35.3, 35.2, 35.1, 28.1, 28.0, 23.2, 22.9, 22.3, 21.5, 21.2, 18.3, 11.9, 11.1; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1590, 1542, 1444, 1223, 774; MS (EI, *m/z*) 601.5 $[M]^+$. Anal. calcd. for $C_{44}H_{59}N$: C, 87.79; H, 9.88; N, 2.33; Found: C, 87.86; H, 9.74; N, 2.45.

*2.2.2.10. 4′-(p-Flurophenyl)-6′-(p-methylphenyl)-5α-chloest[3,2-b]pyridine (**5j**).* White solid; m.p. 173-174 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.95-6.96 (m, 9H), 3.04-2.96 (m, 1H), 2.73-2.58 (m, 2H), 2.39 (s, 3H), 2.22-0.70 (m, 35H), 0.72 (s, 3H), 0.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 156.8, 154.2, 149.7, 138.4, 136.8, 130.3, 129.9, 128.8, 128.6, 127.1, 126.7, 115.2, 56.4, 56.3, 53.7, 42.4, 41.9, 39.5, 36.2, 35.8, 35.6, 35.2, 28.6, 28.3, 28.2, 24.3, 23.9, 22.9, 22.6, 21.3, 18.7, 11.9, 11.7; IR ($CHCl_3$, cm^{-1}) 2929, 2867, 1589, 1542, 1444, 1223, 775; MS (EI, *m/z*) 605.4 $[M]^+$. Anal. calcd. for $C_{43}H_{56}FN$: C, 85.24; H, 9.32; N, 2.31; Found: C, 85.36; H, 9.57; N, 2.40.

*2.2.2.11. 3β-Hydroxy-5-en-androst[17,16-b][4′-phenyl-6′-phenyl]pyridine (**5k**).* Gum; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00 (*d*, *J* = 6.4 Hz, 2H), 7.57-7.19 (m, 9H), 5.45-5.37 (m, 1H), 3.60-3.48 (m, 1H), 1.03

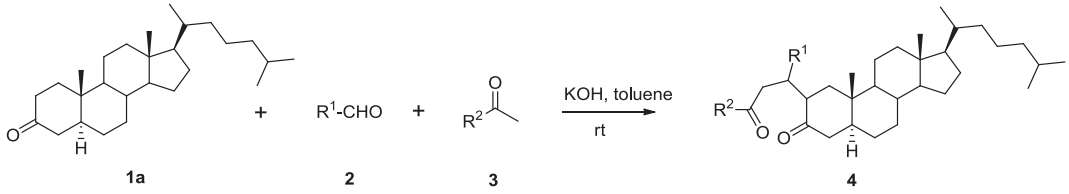


Scheme 1. Reterosynthetic analysis of steroidal pyridine derivatives.



Scheme 2. Synthesis of steroidal 1,5-dicarbonyl compound **4a**.

Table 1
Synthesis of steroidal 1, 5-dicarbonyl compounds **4a-o**.



Entry	R^1	R^2	Product[a]	Yield (%)[b]
1	C_6H_5	C_6H_5	**4a**	94
2	4-Me-C_6H_4	C_6H_5	**4b**	92
3	4-MeO-C_6H_4	C_6H_5	**4c**	93
4	4-F-C_6H_4	C_6H_5	**4d**	94
5	C_6H_5	4-Cl-C_6H_4	**4e**	88
6	4-Me-C_6H_4	4-Cl-C_6H_4	**4f**	89
7	4-F-C_6H_4	4-Cl-C_6H_4	**4g**	90
8	C_6H_5	4-Me-C_6H_4	**4h**	90
9	4-Me-C_6H_4	4-Me-C_6H_4	**4i**	92
10	4-F-C_6H_4	4-Me-C_6H_4	**4j**	90

[a] All the reactions were stirred at rt for 6 hours.
[b] Referring to the amount of product isolated by chromatography.

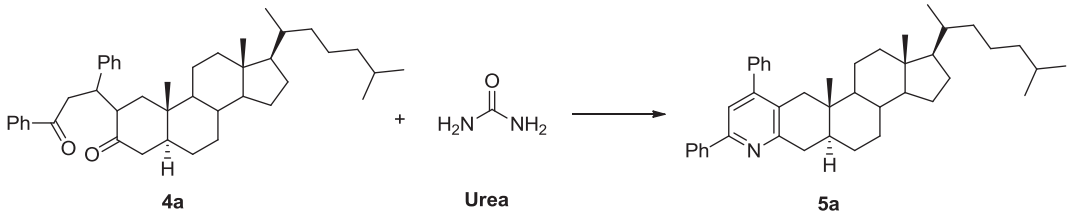
(s, 3H), 0.91 (s, 3H), 2.84-0.89 (m, 17H); IR ($CHCl_3$, cm^{-1}) 3414, 2933, 1255, 1031; MS (EI, m/z) 457 $[M-18]^+$.

*2.2.2.12. 3β-Acetoxy-5-en-androst[17,16-b][4′-phenyl-6′-phenyl]pyridine (**5l**).* White solid; m.p. 174 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 8.02 (*d*, *J* = 6.2 Hz, 2H), 7.56-7.19 (m, 9H), 5.42-5.35 (m, 1H), 4.63-4.49 (m, 1H), 2.04 (s, 3H), 1.06 (s, 3H), 0.93 (s, 3H), 2.84-0.89 (m, 17H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 154.8, 145.7, 140.2, 140.0, 138.0, 135.6, 132.1, 128.9, 128.1, 127.4, 127.1, 122.4, 117.3, 73.2, 56.7, 45.2, 38.1, 36.5, 33.8, 31.4, 30.6, 30.4, 27.6, 21.5, 21.3, 20.6, 19.2, 17.2; IR ($CHCl_3$, cm^{-1}) 2934, 1733, 1371, 1245; IR ($CHCl_3$, cm^{-1}) 2924, 1736, 1245, 772; MS (ESI, *m/z*) 518.3 $[M+1]^+$. Anal. calcd. for $C_{36}H_{39}NO_2$: C, 83.52; H, 7.59; N, 2.71; Found: C, 83.56; H, 7.47; N, 2.59.

*2.2.2.13. 3β-Hydroxy-5-en-androst[17,16-b][4′-(p-methylphenyl)-6′-phenyl]pyridine (**5m**).* Gum; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (*d*, *J* = 6.6 Hz, 2H), 7.59-7.16 (m, 8H), 5.44-5.34 (m, 1H), 3.62-3.48 (m, 1H), 2.42 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H), 2.82-0.91 (m, 17H); IR ($CHCl_3$, cm^{-1}) 3412, 2933, 1255, 1033; MS (EI, m/z) 471.3 $[M-18]^+$.

*2.2.2.14. 3β-Acetoxy-5-en-androst[17,16-b][4′-(p-methylphenyl)-6′-phenyl]pyridine (**5n**).* White solid; m.p. 177-179 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (*d*, *J* = 6.9 Hz, 2H), 7.57-7.21 (m, 8H), 5.42-5.37 (m, 1H), 4.63-4.50 (m, 1H), 2.84-2.69 (m, 1H), 2.43 (s, 3H), 2.04 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H), 2.44-0.87 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 155.9, 145.9, 140.3, 140.1, 138.2, 136.1, 132.2, 129.4, 128.6, 128.3, 128.2, 127.1, 122.1,

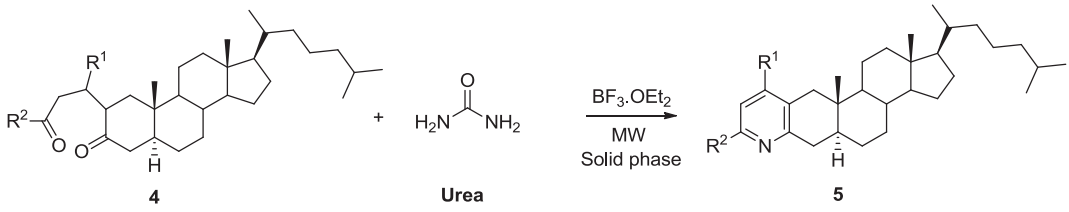
Table 2
Optimization of reaction condition for the synthesis of **5a**.



Entry	Solvent	Method[a]	Catalyst	Time	T (°C)	Yield (%)[b]
1	*i*-PrOH	TH	–	8 h	100	0
2	CH_3CN	TH	–	8 h	90	0
3	DMF	TH	–	8 h	155	21
4	Neat	TH	–	8 h	140	49
5	Neat	MW	–	8 min	140	62
6	Neat	MW	$AlCl_3$	8 min	140	66
7	Neat	MW	$TiCl_4$	8 min	140	53
8	Neat	MW	$BF_3.OEt_2$	8 min	140	90
9	Neat	MW	$ZnCl_2$	8 min	140	59
10	Neat	MW	$InCl_3$	8 min	140	64

[a] TH: thermal heating, MW: microwave irradiation.
[b] Yield of the isolated product.

Table 3
Synthesis of 4′,6′-diaryl-chloest[3,2-*b*]pyridine derivatives **5**.



Entry	R^1	R^2	Product[a]	Yield (%)[b]
1	C_6H_5	C_6H_5	**5a**	90
2	4-Me-C_6H_4	C_6H_5	**5b**	92
3	4-MeO-C_6H_4	C_6H_5	**5c**	93
4	4-F-C_6H_4	C_6H_5	**5d**	81
5	C_6H_5	4-Cl-C_6H_4	**5e**	86
6	4-Me-C_6H_4	4-Cl-C_6H_4	**5f**	84
7	4-F-C_6H_4	4-Cl-C_6H_4	**5g**	82
8	C_6H_5	4-Me-C_6H_4	**5h**	85
9	4-Me-C_6H_4	4-Me-C_6H_4	**5i**	82
10	4-F-C_6H_4	4-Me-C_6H_4	**5j**	88

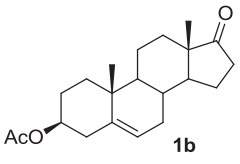
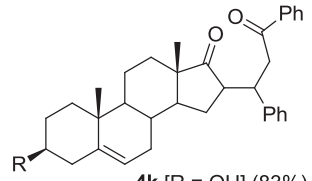
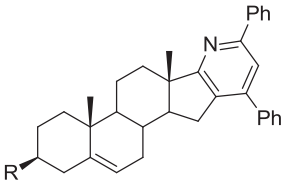
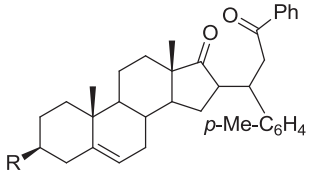
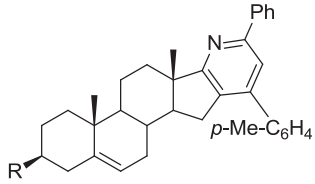
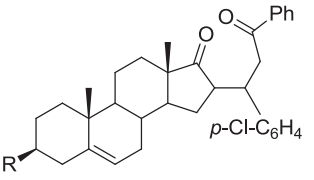
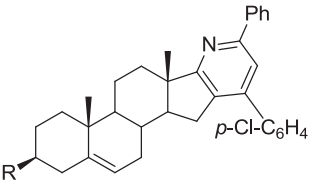
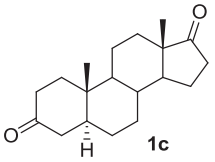
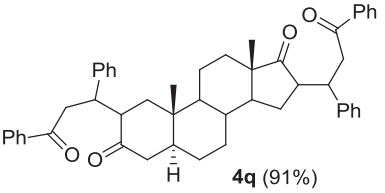
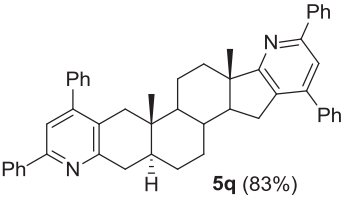
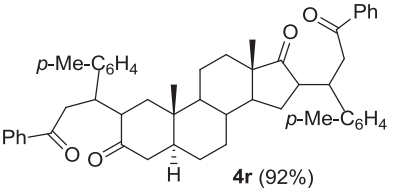
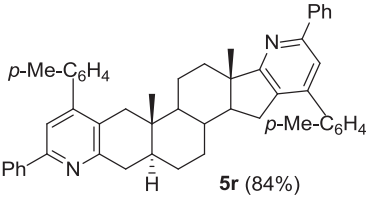
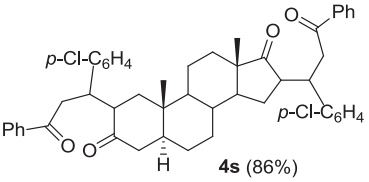
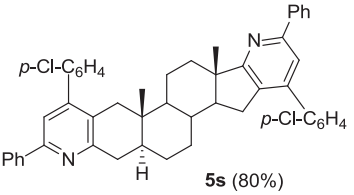
[a] Time taken 6 min.
[b] Referring to the amount of product isolated by chromatography.

117.8, 73.9, 56.2, 50.7, 45.8, 38.2, 36.9, 33.8, 31.4, 30.9, 30.4, 27.8, 21.5, 21.3, 20.6, 19.4, 17.4; IR ($CHCl_3$, cm^{-1}) 2934, 1733, 1371, 1245; MS (ESI, *m/z*) 532.7 $[M+1]^+$. Anal. calcd. for $C_{37}H_{41}NO_2$: C, 83.58; H, 7.77; N, 2.63; Found: C, 83.66; H, 7.64; N, 2.79.

*2.2.2.15. 3β-Hydroxy-5-en-androst[17,16-b][4′-(p-chlorophenyl)-6′-phenyl]pyridine (**5o**).* Gum; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (*d*, *J* = 6.6 Hz, 2H), 7.56-7.16 (m, 8H), 5.42-5.34 (m, 1H), 3.61-3.46 (m, 1H), 1.03 (s, 3H), 0.90 (s, 3H), 2.80-0.90 (m, 17H); IR ($CHCl_3$, cm^{-1}) 3409, 2936, 1254, 1033; MS (EI, m/z) 491.2 $[M-18]^+$.

2.2.2.16. 3β-Acetoxy-5-en-androst[17,16-b][4′-(p-chlorophenyl)-6′-phenyl]pyridine (5p). White solid; m.p. 185 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, *J* = 7.5 Hz, 2H), 7.57-7.11 (m, 8H), 5.41-5.37 (m, 1H), 4.60-4.50 (m, 1H), 2.80-2.65 (m, 1H), 2.04 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 2.34-0.86 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 156.5, 146.3, 140.8, 140.4, 138.6, 136.4, 132.4, 129.1, 128.7, 128.4, 128.3, 127.6, 122.2, 118.5, 73.7, 56.3, 50.9, 45.8, 38.2, 36.8, 33.8, 31.2, 30.9, 30.4, 27.9, 21.8, 21.3, 20.6, 19.8, 17.6; IR ($CHCl_3$, cm^{-1}) 2930, 1733, 1246, 772; MS (ESI, *m/z*) 552.3 $[M+1]^+$. Anal. calcd. for $C_{36}H_{38}ClNO_2$: C, 78.31; H, 6.94; N, 2.54; Found: C, 78.60; H, 6.68; N, 2.62.

Table 4
Synthesis of steroid fused pyridine derivatives **5k–s**.

Entry	Ketone (**1b–c**), R^1CHO & R^2COCH_3	1,5-Diketones (Yield)[a,b]	Pyridine derivatives (Yield)[a,c]
1	 **1b** PhCHO & $PhCOCH_3$	 Ac_2O, py → **4k** [R = OH] (83%); **4l** [R = OAc] (96%)	 Ac_2O, py → **5k** [R = OH] (86%); **5l** [R = OAc] (96%)
2	**1b**, *p*-Me-PhCHO & $PhCOCH_3$	 Ac_2O, py → **4m** [R = OH] (85%); **4n** [R = OAc] (93%)	 Ac_2O, py → **5m** [R = OH] (88%); **5n** [R = OAc] (95%)
3	**1b**, *p*-Cl-PhCHO & $PhCOCH_3$	 Ac_2O, py → **4o** [R = OH] (90%); **4p** [R = OAc] (93%)	 Ac_2O, py → **5o** [R = OH] (86%); **5p** [R = OAc] (94%)
4	 **1c** PhCHO & $PhCOCH_3$	 **4q** (91%)	 **5q** (83%)
5	**1c**, *p*-Me-PhCHO & $PhCOCH_3$	 **4r** (92%)	 **5r** (84%)
6	**1c**, *p*-Cl-PhCHO & $PhCOCH_3$	 **4s** (86%)	 **5s** (80%)

[a] Yield of the isolated product.
[b] Time taken = 12 h.
[c] Time taken = 6 min.

*2.2.2.17. 5α-Androst[3,2-b][17,16-b][bis-(4′-phenyl-6′-phenyl)]pyridine (**5q**).* Gum; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08-7.19 (m, 22H), 3.00-2.67 (m, 6H), 2.39-0.80 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 155.7, 146.2, 141.0, 140.2, 140.1, 138.6, 137.4, 135.4, 132.3, 129.8, 128.7, 128.5, 128.2, 127.4, 126.7, 122.6, 117.7, 74.0, 56.4, 51.7, 46.4, 39.3, 36.6, 33.8, 31.4, 30.7, 30.4, 27.4, 21.3, 21.2, 21.1, 20.7, 19.3, 17.2, 13.3; IR ($CHCl_3$, cm^{-1}) 2924, 1598, 1546, 775; MS (ESI, *m/z*) 662.4 $[M + 1]^+$.

*2.2.2.18. 5α-Androst[3,2-b][17,16-b][bis-{4′-(p-methylphenyl)-6′-phenyl}]pyridine (**5r**).* White solid; m.p. 187-188 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.99-7.17 (m, 20H), 3.02-2.65 (m, 6H), 2.38 (s, 3H), 2.37 (s, 3H), 2.36-0.81 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.6, 156.9, 145.4, 140.6, 140.1, 140.0, 138.8, 137.6, 135.4, 132.3, 129.8, 128.9, 128.8, 128.5, 127.6, 126.6, 122.4, 117.4, 73.8, 56.4, 51.7, 46.6, 39.5, 36.7, 33.8, 31.4, 30.5, 30.4, 27.4, 21.3, 21.1, 20.7, 19.2, 17.2, 13.5; IR ($CHCl_3$, cm^{-1}) 2924,

1597, 1547, 775; MS (ESI, *m/z*) 691.3 $[M+1]^+$. Anal. calcd. for $C_{51}H_{50}N_2$: C, 88.65; H, 7.29; N, 4.05; Found: C, 88.57; H, 7.35; N, 4.21.

*2.2.2.19. 5α-Androst[3,2-b][17,16-b][bis–{4′-(p-chlorophenyl)-6′-phenyl}]pyridine (**5s**).* Gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04-7.15 (m, 20H), 3.02-2.69 (m, 6H), 2.35-0.82 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 156.6, 146.8, 141.3, 140.8, 140.5, 138.9, 137.8, 135.5, 132.3, 129.7, 128.6, 128.5, 128.2, 127.4, 126.8, 122.6, 117.7, 74.2, 56.4, 51.7, 46.6, 39.3, 36.6, 33.9, 31.4, 31.1, 30.6, 27.4, 21.3, 21.1, 20.9, 19.4, 17.2, 13.4; IR ($CHCl_3$, cm^{-1}) 2926, 1598, 1547, 775; MS (ESI, *m/z*) 731.3 $[M+1]^+$.

3. Results and discussion

The first synthesis of steroidal heterocycles containing a pyridine ring was described by Miller T. C. using high temperature and multistep reaction strategy [14]. Chelucci and co-workers reported the synthesis of linear cholestanopyridine through a three-step pyridoannelation of its *N,N*-dimethylhydrazones with bromoethyl-1,3-dioxolane [15]. Another method to synthesize steroidal pyridines from corresponding carbonyl compounds was reported by Abbiati and co-workers using Gold (III) salts as a catalyst [11]. In a recent report, Yan and co-workers developed a method for the synthesis of steroidal [3,4] b pyridines from 3-keto steroids and propargylamine using Cu (II) salt as the catalyst with very low yield (6–51%) and limited substrate scope [10]. We also reported synthesis of steroidal A ring fused chloropyridines by refluxing a mixture of steroidal enamides with Vilsmeier reagent in DMF [16]. To the best of our knowledge, there is no report focusing on the synthesis of steroidal 4,6-diarylpyridines in the literature.

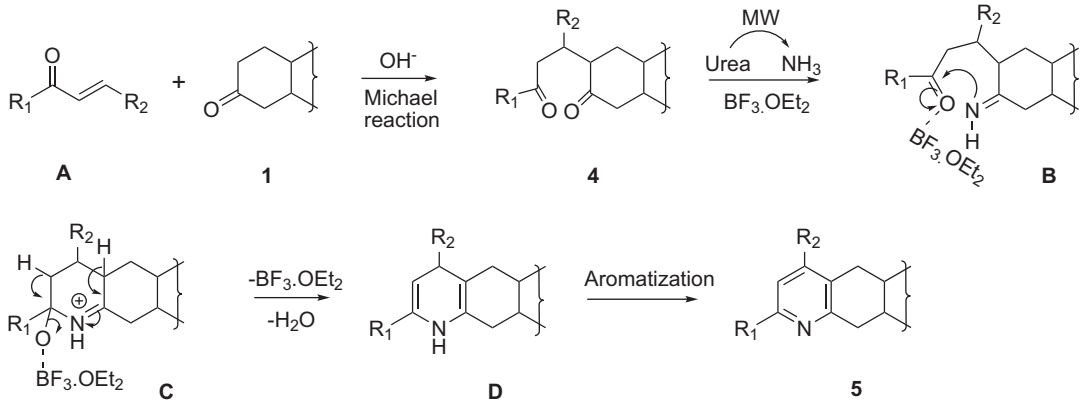
Scheme 1 illustrates our retrosynthetic analysis of steroidal pyridine derivatives **5**. The synthetic strategy was centered on cyclization of diketo compound **4**, to produce target pyridine derivative **5**, which contains not only the pyridine framework but also different substituents in the pyridine ring. A Michael reaction of chalcone with steroidal ketone would furnish diketo compound **4**. We envisioned that synthesis of compound **4** would be much more advantageous if the ketosteroid **1** could be reacted with an in-situ generated chalcone (from a suitable ketone and an aldehyde) instead of reacting it directly with chalcone, which requires another synthetic step.

Our initial effort was directed towards developing a suitable method for the synthesis of steroidal 1,5-dicarbonyl compound **4**. We began our study by investigating the reaction of equimolar amounts of 5α-cholestan-3-one (**1a**), benzaldehyde (**2a**) and acetophenone (**3a**) in presence of two equivalent of potassium hydroxide as base (Scheme 2) using acetonitrile as the solvent at room temperature, which afforded compound **4a** in only 24% yield. It was found that outcome of the reaction was dependent on the nature of the solvent used. The reaction was unsuccessful in most of the protic solvents such as methanol, ethanol, water and with some aprotic organic solvents such as DMF, 1,4-dioxane it gave very less yield of the products (19–21%) even after 12 h of heating. Surprisingly, when the reactants were stirred in toluene at room temperature for six hours, compound **4a** was obtained as the only product in 94% yield.

The scope of the reaction was then investigated by the reaction of steroidal ketones **1a, 1b, 1c** with a variety of aromatic aldehydes (**2**) and arylketones (**3**) including both electron-deficient and electron-rich groups (Tables 1–4). Gratifyingly, the 1,5-dicarbonyl compounds were obtained in excellent yield in all cases and no undesired side reactions were observed. For the steroidal ketones **1b** and **1c** the reaction took longer time for completion of the reaction. The products obtained were characterized by various spectroscopic means such as NMR, IR and mass spectrometric analysis.

In the next step, reaction of the 1,5-dicarbonyl compound **4a** with urea was explored. An extensive reaction optimization of the cyclization reaction was performed in order to find out the best condition to synthesize the pyridine fused steroid **5a** (Table 2). Initially, the synthesis of **5a** was evaluated using two different methodologies: conventional thermal heating (TH) and microwave irradiation (MW). When the reaction of **4a** with urea was carried in isopropanol and acetonitrile under thermal condition, the reaction could not afford product **5a** after 8 hours of refluxing (entry 1–2, Table 2). However, we observed that the use of DMF as the solvent, afforded 21% yield of **5a** (entry 3, Table 2). Performing the reaction in solid phase under TH and MW conditions increased the yield of the product **5a** up to 49% and 62% respectively (entry 4-5, Table 2). To further improve the product yield in the solid phase reaction, we screened several Lewis acids as the catalyst, employing microwave as a source of energy (entry 6–10, Table 2). The best result was obtained by conducting the reaction under MW irradiation and using $BF_3.OEt_2$ as the catalyst (entry 8, Table 2). With the optimized reaction conditions in hand, we then applied the protocol for the cyclization reaction of different steroidal diketones (**4b–s**), to afford steroidal pyridines (**5b–s**) in excellent yields (Table 3 and 4). All the new compounds were characterized by ^{1}H, ^{13}C NMR and mass spectra.

A proposed mechanism for the formation of pyridine ring fused to steroid backbone is shown in Scheme 3. Under the influence of base, steroidal ketone **1** undergoes Michael addition reaction to



Scheme 3. Proposed mechanism for the formation of steroidal pyrinine **5**.

in situ generated chalcone **A** to afford the steroidal 1,5-dicarbonyl intermediate **4**. It is believed that ammonia released by urea under microwave condition forms an imine intermediate **B** with the non conjugated carbonyl group of steroidal 1,5-dicarbonyl compound **4**. Activation of conjugated carbonyl group in intermediate **B** by $BF_3.OEt_2$ followed by the nucleophilic attack of the NH-group of imine on the activated carbonyl functionality facilitated the aza cyclization reaction with consequent loss of a water molecule to afford intermediate **D**. The oxidation of 1,4-dihydropyrinine intermediate **D** under aerial condition led to stable product **5** due to aromatization [17].

In summary, we have developed a solvent less one pot reaction of steroidal 1,5-diketo compound with urea by employing $BF_3.OEt_2$ as the catalyst, for the synthesis of steroidal A- and D-ring fused 4,6-diarylpyridines under microwave irradiation. The intermediate steroidal 1,5-diketo compounds were synthesized by Michael addition reaction of steroidal ketones with in situ generated chalcones from aromatic ketones and aldehydes.

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