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Regioselective synthesis of pyrimidine annelated heterocycles from 6-(cyclohex-2-enyl)-1,3-dimethyl-5-hydroxyuracil☆

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Abstract—6-(Cyclohex-2-enyl)-1,3-dimethyl-5-hydroxyuracil when treated with bromine in chloroform at 0–5°C for 6 h furnishes 6-bromo-1,3-dimethylhexahydrobenzofuro[3,2-*d*]pyrimidine-2,4-dione in 80% yield. The same heterocycle is also obtained in 90% yield on treatment of the same substrate with pyridine hydrobromide perbromide for 30 min or with hexamethylenetetramine hydrotribromide for 15 min in methylene chloride at 0–5°C. Cyclization of the same substrate with bis-benzonitrile palladium(II) chloride in benzene in the presence of sodium methoxide afforded 1,3-dimethyl-6,7,8,9-tetrahydrobenzofuro[3,2-*d*]pyrimidine-2,4-dione in 82% yield. The same substrate on treatment with cold conc. sulfuric acid at 0–5°C for 2 h gave 1,3-dimethyl-5-oxabicyclo[3.3.1]nonano[3,2-*d*]pyrimidine-2,4-dione in 94% yield.

5-Substituted uracils and their nucleosides are of immense biological significance because of their use in the chemotherapy of cancer[2] [e.g. FU (5-fluorouracil), FUDR (5-fluoro-2′-deoxy-uridine)] and viral diseases [F_3TdR (trifluorothymidine), BVDU {E-5-(2-bromovinyl-2′-deoxy-uridine)}, AZT (3′azido-3′-deoxythymidine)][3–6] and CEDU {5-(2-chloroethyl)-2′-deoxyuridine}.[7] Both BVDU and CEDU compounds effectively inhibit herpes simplex type 1 virus (HSV-1) and varicella zoster virus (VZU) replication in vitro[3,7–10] and AZT[11] is anti-AIDS. Also, many 5-substituted uracils have been developed as enzyme inhibitors[12] and have been used in the synthesis of modified nucleotides.[13] Recently, a 6-substituted uracil derivative 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT)[14–16] has attained considerable significance as a specific inhibitor of HIV-1, a causative agent of AIDS.[17] Functionalisation of uracils at C-5 and C-6 leads to biologically interesting molecules but is not a simple task, requiring rather sophisticated and tedious reaction conditions.[18–20] Here we report simple and regioselective synthesis of a number of hitherto unreported pyrimidine annelated heterocycles.

The starting material for this study 6-(cyclohex-2-enyl)-1,3-dimethyl-5-hydroxyuracil (**1**) was obtained in 90% yield by the reaction of 1,3-dimethyl-5-hydroxyuracil with 3-bromocyclohexene in refluxing acetone in the presence of anhydrous potassium carbonate.

Three approaches were considered for the cyclization of substrate **1**. Our first approach for the cyclization of compound **1** was to try brominating agents such as pyridine hydrobromide perbromide, hexamine hydrobromide perbromide and elemental bromine. Accordingly compound **1** was treated with pyridine hydrotribromide in chloroform at 0–5°C for 30 min to give the linearly fused bromo compound 6-bromo-1,3-dimethylhexahydrobenzofuro[3,2-*d*]pyrimidine-2,4-dione (**2**) in 90% yield. The same product **2** was also obtained in 92% yield when compound **1** was treated with hexamethylenetetramine hydrotribromide in methylene chloride at 0–5°C for 15 min. Substrate **1** on treatment with elemental bromine in chloroform at 0–5°C for 6 h also furnished the same product **2** in 80% yield (Scheme 1). It may be noted that similar cyclization of *o*-cyclohexenyl phenols with pyridine hydrobromide[21] or hexamethylene hydrotribromide[22] generated bicyclic heterocycles by a 6-*endo* cyclization.

Compound **2** on treatment with alcoholic potassium hydroxide at room temperature for 5 min furnished the dehydrobrominated product 1,3-dimethyl-7,8,9,9a-tetrahydrobenzofuro[3,2-*d*]pyrimidine-2,4-dione (**5**) in 85% yield. Compound **5** was further dehydrogenated by refluxing with palladised charcoal in diphenyl ether for 30 min to give the aromatised product 1,3-dimethylbenzofuro[3,2-*d*]pyrimidine-2,4-dione (**6**) in 40% yield (Scheme 2). Final confirmation for structure **2** came from its COSY-, HETCOR- and ^{13}C NMR spectral data. COSY spectrum of compound **2** shows that proton H-1 at δ 4.72 correlates with proton H-9 at δ 3.30–3.38 and proton H-2 at δ 4.78.

☆ See Ref. 1.

Keywords: pyrimidine annelated heterocycles; heterocyclization; palladium chloride bis-benzonitrile; pyridine hydrotribromide; 6-cyclohex-2-enyl-1,3-dimethyl-5-hydroxy pyrimidine-2,4-dione.

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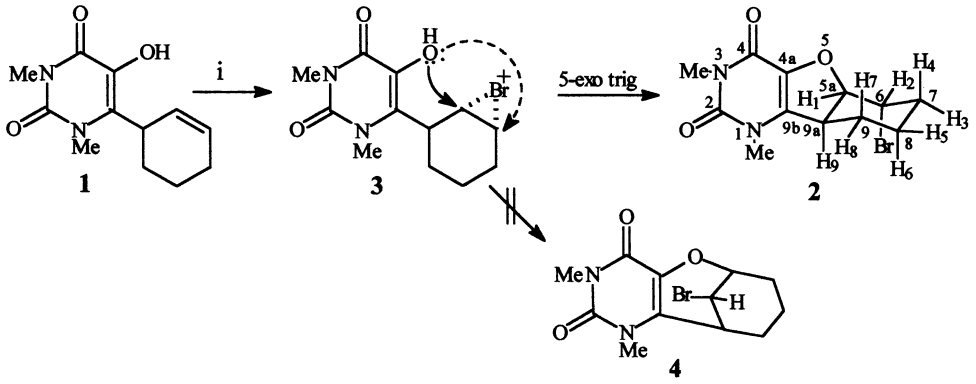
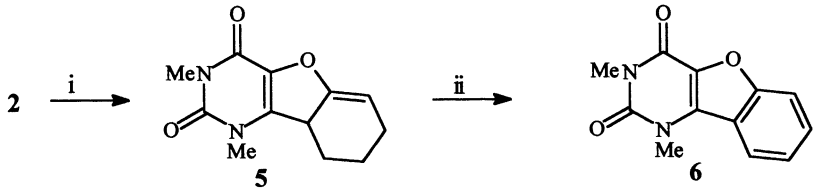


Scheme 1. *Reagents*: (i) Br_2, $CHCl_3$, 6 h (80%) or $PyHBr_3$, CH_2Cl_2, 0.5 h (90%) or $C_6H_{12}N_4HBr_3$, CH_2Cl_2, 15 min (92%).

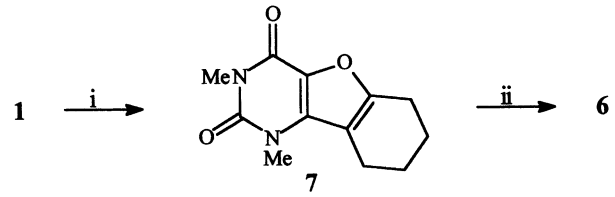


Scheme 2. *Reagents*: (i) KOH/EtOH, 5 min, rt (85%); (ii) Pd/C, Ph_2O, 30 min (40%).

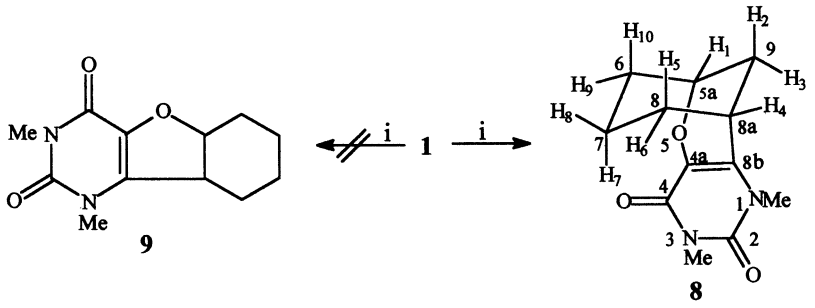
Proton H-2 at δ 4.78 correlates with proton H-3 at δ 2.1–2.18, H-4 at δ 2.08 and H-1 at δ 4.72. Proton H-9 at δ 3.30–3.38 correlates with proton H-1 at δ 4.72, H-7 at δ 1.30 and H-8 at δ 2.1–2.18. Proton H-5 at δ 1.8–1.9 correlates with H-7 at δ 1.30, H-4 at δ 2.08 and H-3 and H-8 at δ 2.1–2.18. Proton H-6 at δ 1.65 correlates with H-7 at δ 1.30, H-4 at δ 2.08 and H-3 and H-8 at δ 2.1–2.18. Proton H-6 at δ 1.65 correlates with H-7 at δ 1.30, H-4 at δ 2.08 and H-3 and H-8 at δ 2.1–2.8. The ^{13}C chemical shifts of compound 2 are assigned by DEPT and HETCOR experiments. Multiplicity was established by DEPT experiment. DEPT shows eight protonated carbons, two $-CH_3$, three $>CH-$, and three $-CH_2-$. Protonated carbon resonances are established by direct correlation with proton resonances by HETCOR experiment (normal one bond C–H coupling). Methyl proton resonance at δ 3.40 is related with protonated carbon resonance at δ 29.26 and another methyl proton at δ 3.42 is related with protonated carbon resonance at δ 33.88. Methine protons resonance at δ 4.70–4.80 (H-1 and H-2) are related with carbon resonances at δ 83.93 (C-5a) and 47.74 (C-6) and at δ 3.30–3.38 (H-9) is related with carbon resonance at δ 39.27 (C-9a). Methylene protons resonances at δ 1.65 (H-6) and 1.8–1.9 (H-5) are related with carbon resonance at δ 17.71 (C-8), δ 2.08 (H-4) is related with carbon resonance at δ 30.03 (C-7), δ 2.10–2.18 (H-3 and H-8) are related with carbon resonance at δ 30.03 (C-7) and 28.49 (C-9), respectively and at δ 1.3 (H-7) is related with carbon resonance at δ 28.49 (C-9). Therefore, the alternative structure **4** for the product was ruled out on the basis of chemical and spectroscopic evidences.

Our second approach for the cyclization of substrate **1** was to try the palladium mediated reaction. Therefore, substrate **1** was refluxed with bis-benzonitrile palladium(II) chloride in benzene in the presence of sodium methoxide for 3 h and a linearly cyclized new product 1,3-dimethyl-6,7,8,9-tetrahydrobenzofuro-[3,2-*d*]pyrimidine-2,4-dione (**7**) was obtained in 82% yield. It was characterised from its elemental analysis and spectral data. This was subjected to dehydrogenation by refluxing with palladised charcoal in diphenyl ether for 1 h to give the aromatised product **6** (Scheme 3).

Acid catalysed cyclization of the substrate **1** was also attempted. The substrate **1** was treated with cold conc. sulfuric acid at 0–5°C for 2 h to give a single product,1,3-dimethyl-5-oxabicyclo[3.3.1]nonano[3,2-*d*]pyrimi-dine-2,4-dione (**8**) in 94% yield. Compound **8** resisted dehydrogenation when refluxed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in xylene or with palladised charcoal in diphenyl ether (Scheme 4). This was characterised from its elemental analysis and spectral data. The alternative structure **9** for this cyclization product was ruled out from COSY-, HETCOR- and ^{13}C NMR spectral data. COSY spectrum of compound **8** shows that proton H-1 at δ 4.60–4.70 correlates with proton H-9 at δ 2.08–2.20, H-2 and H-3 at δ 1.88–1.96 and H-10 at δ 1.48–1.55. Proton H-4 at δ 3.00–3.06 correlates with proton H-2 and H-3 at δ 1.88–1.96 and H-5 and H-6 at δ 1.76–1.83. Protons H-2 and H-3 correlate with H-1 at δ 4.60–4.70 and H-4 at δ 3.00–3.06. The ^{13}C chemical shifts of compound **8** are assigned by DEPT and HETCOR experiments. Multiplicity was established by DEPT experiment. DEPT shows eight protonated



Scheme 3. *Reagents*: (i) $PdCl_2(PhCN)_2$, C_6H_6, heat (82%); (ii) Pd/C, Ph_2O, heat (40%).



Scheme 4. *Reagents*: (i) Conc. H_2SO_4, 2 h (94%).

carbons, two $-CH_3$, two >CH– and four $-CH_2-$. Protonated carbon resonances are established by direct correlation with proton resonances by HETCOR experiment (normal one bond C–H coupling). Methyl proton resonance at δ 3.32 is related with protonated carbon resonance at δ 28.49 and another methyl proton at δ 3.34 is related with protonated carbon resonance at δ 30.03. Methine proton resonance at δ 3.00–3.06 (H-4) is related with carbon resonance at δ 27.72 (C-8a) and δ 4.60–4.70 (H-1) is related with carbon resonance at δ 70.02 (C-5a). Methylene protons resonance at δ 1.38–1.47 (H-7) is related with carbon resonance at δ 17.71 (C-7), δ 1.48–1.55 (H-10) is related with carbon resonance at δ 32.34 (C-6), δ 1.58–1.63 (H-8) is related with carbon resonance at δ 17.71 (C-7), δ 1.76–1.83 (H-5 and H-6) are related with carbon resonance at δ 29.26 (C-8), δ 1.88–1.96 (H-2 and H-3) are related with carbon resonance at δ 29.27 (C-9), δ 2.08–2.20 (H-9) is related with carbon resonance at δ 32.34 (C-6). Its resistance to dehydrogenation has also indicated its bicyclic nature.

In conclusion, 6-(cyclohex-2-enyl)-1,3-dimethyl-5-hydroxyuracil (**1**) has been successfully and regioselectively cyclized under simple and mild reaction conditions to give different pyrimidine-annelated heterocycles in excellent yields. The cyclization with elemental bromine is noteworthy. These heterocylic derivatives have the potential to be useful as drugs.

1. Experimental

1.1. General

Melting points are uncorrected. UV absorption spectra were recorded in EtOH. IR spectra were run on KBr discs. ^1H NMR spectra were determined for solution in $CDCl_3$ with TMS as an internal standard on Jeol FX-100 spectrometer at IICB, Calcutta and DRX-500 (500 MHz) at Nottingham, England. Elemental analysis and recording of mass spectra were carried out at RSIC (CDRI), Lucknow. Silica gel (60–120 mesh) was used for chromatographic separation. Petroleum ether refers to the fraction boiling between 60 and 80°C.

1.1.1. 6-(Cyclohex-2-enyl)-5-hydroxy-1,3-dimethyluracil (1). A mixture of 1,3-dimethyl-5-hydroxyuracil (1.56 g, 10.0 mmol), 3-bromocyclohexene (1.6 g, 10.0 mmol) and anhydrous potassium carbonate (3 g) in dry acetone (100 mL) was refluxed for 8 h. The reaction mixture was cooled, filtered and the solvent was removed. The residue was extracted with chloroform (3×20 mL), the organic layer was separated, washed with water (2×20 mL), dried (Na_2SO_4) and the solvent evaporated. Purification of crude product by column chromatography (benzene–ethyl acetate, 5:1) over silica gel gave the *title compound* **1** (2.12 g, 90%) as a white solid, mp 176°C; [Found: C 61.25, H 6.99, N 11.58. $C_{12}H_{16}N_20_3$ requires C 61.02, H 6.78, N 11.86%]; ν_{max}(KBr) 3300, 2960, 1700, 1620, 1300, 1100, 720 cm^{-1}; λ_{max} (log ϵ) 212 (3.03), 290 (3.04) nm; δ_H (500 MHz, $CDCl_3$) 1.60–1.70 (2H, m),1.78–1.88 (2H, m), 1.95–2.05 (2H, m), 3.32 (3H, s), 3.38 (3H, s), 3.90–4.00 (1H, m), 5.48–5.55 (2H, m), 5.74–5.82 (1H, m); *m/z* 236 (M^+).

1.1.2. 6-Bromo-1,3-dimethylhexahydrobenzofuro[3,2-*d*]pyrimidine-2,4-dione (2). Pyridine hydrotribromide (0.45 g, 1.5 mmol) was added to a stirred solution of compound **1** (0.35 g, 1.5 mmol) in dichloromethane (25 mL) at 0–5°C. Stirring was continued for 30 min. It was then extracted with water and dried (Na_2SO_4). The solvent was removed and the crude mass was purified by column chromatography over silica gel. Elution of the column with benzene–ethyl acetate (3:1) furnished the *title compound* **2** (0.42 g, 90%) as white solid, mp 146°C; [Found C 45.91, H 4.99, N 8.59. $C_{12}H_{15}BrN_2O_3$ requires C 45.71, H 4.76, N 8.89%]; ν_{max}(KBr) 3040, 1680, 1640, 1480, 1100, 750 cm^{-1}; λ_{max} (log ϵ) 213 (3.17), 296 (3.03) nm; δ_H (500 MHz, $CDCl_3$) 1.30 (8 lines, H-7, *J*=4.23, 13.6 Hz), 1.65 (dt, H-6, *J*=3.7, 13.7 Hz), 1.8–1.9 (m, H-5), 2.08 (dt, H-4, *J*=3.4, 15.12 Hz), 2.1–2.18 (2H, m, H-3 and H-8), 3.30–3.38 (m, H-9) 3.40 (3H, s), 3.42 (3H, s), 4.70–4.80 (2H, m, H-1 and H-2); δ_C (67.8 MHz, $CDCl_3$) 17.71 (C-8), 28.49 (C-9), 29.26 (N–CH_3), 30.03 (C-7), 33.88 (N–CH_3), 39.27 (C-9a), 47.74 (C-6), 83.93 (C-5a), 132.34 (C-9b), 143.12 (C-4a), 152.36 (C-4), 156.98 (C-2); *m/z* 314, 316 (M^+).

Similarly hexamethylenetetramine hydrotribromide (0.57 g, 1.5 mmol) was added to a solution of compound **1** (0.35 g, 1.5 mmol) in CH_2Cl_2 at 0–5°C and stirring was continued for 15 min. It was extracted with water and worked up as above. Yield 0.43 g, 92%, mp 146°C.

Similarly bromine (0.25 g, 1.5 mmol) in 20 mL chloroform was added slowly to a stirred solution of compound **1** (0.35 g, 1.5 mmol) in 5 mL chloroform at 0–5°C. Stirring was continued for 6 h. It was then extracted with water and worked up as above. Yield 0.38 g, 80%, mp 146°C.

1.1.3. 1,3-Dimethyl-7,8,9,9a-tetrahydrobenzofuro[3,2-*d*]pyrimidine-2,4-dione (5). A mixture of compound **2** (0.315 g, 1.0 mmol) and potassium hydroxide (0.056 g, 1.0 mmol) in rectified spirit (5 mL) was stirred for 5 min. Solvent was removed and the residue was extracted with chloroform. The chloroform extract was washed repeatedly with water and dried (Na_2SO_4). Removal of solvent gave the *title compound* **5**, which was recrystallised from chloroform–petroleum ether (60–80°C), (0.26 g, 85%) as a white solid, mp 138°C; [Found: C 61.34, H 6.25; N 11.77. $C_{12}H_{14}N_2O_3$ requires C 61.54, H 5.98, N 11.97%]; ν_{max}(KBr) 2960, 1680, 1650, 1100, 750 cm^{-1}; λ_{max} (log ϵ) 213 (3.06), 307 (2.84) nm; δ_H (500 MHz, $CDCl_3$) 1.12–1.20 (2H, m H-8), 1.80–1.84 (1H, m H-9), 2.01–2.08 (2H, m H-9 and H-7), 2.21–2.50 (1H, m H-7), 2.36–2.40 (1H, m H-9a), 3.35 (3H, s), 3.60 (3H, s), 4.56 (1H, brs H-6); *m/z* 234 (M^+).

1.1.4. 1,3-Dimethylbenzofuro[3,2-*d*]pyrimidine-2,4-dione (6). Compound **5** (0.06 g, 0.25 mmol) was refluxed with 10% palladium on charcoal (0.02 g) in diphenyl ether (2 mL) for 30 min. The mixture was chromatographed over silica gel. The column was eluted with petroleum ether (60–80°C) to remove diphenyl ether and the *title compound* **7** was obtained as a yellow solid by using benzene–ethyl acetate (3:1) as eluant (0.02 g, 40%), mp 264°C; [Found: C 62.81, H 4.45, N 12.07. $C_{12}H_{10}N_2O_3$ requires C 62.61, H 4.35, N 12.17%]; ν_{max}(KBr) 3040, 1680, 1640, 1460, 1200, 750 cm^{-1}; λ_{max} (log ϵ) 243 (3.26), 295 (2.81), 346 (2.72) nm; δ_H (100 MHz, $CDCl_3$) 3.52 (3H, s), 4.04 (3H, s), 7.08–7.40 (3H, m), 8.46 (1H, brs); *m/z* 230 (M^+).

1.1.5. 1,3-Dimethyl-6,7,8,9-tetrahydrobenzofuro-[3,2-*d*]pyrimidine-2,4-dione (7). Into the suspension of sodium salt prepared from compound **1** (0.118 g, 0.5 mmol) and sodium methoxide (0.027 g, 0.5 mmol) in benzene (5 mL) was added $PdCl_2(PhCN)_2$ (0.019 g, 0.5 mmol) at rt. After refluxing the solution for 3 h, the resulted palladium black was filtered off and filtrate was concentrated and the mixture was purified by column chromatography over silica gel. Elution of the column with benzene–ethyl acetate (3:1) gave the *title compound* **7** (0.10 g, 82%) as white solid, mp 140°C; [Found: C 61.75, H 6.23, N 11.74. $C_{12}H_{14}N_2O_3$ requires C 61.54, H 5.98, N 11.97%]; ν_{max}(KBr) 3040, 1680, 1640, 1478, 1100, 750 cm^{-1}; λ_{max} (log ϵ) 224 (2.8), 284 (2.9) nm; δ_H (100 MHz, $CDCl_3$)) 1.76–1.96 (4H, m), 2.56–2.92 (4H, m), 3.22 (3H, s), 3.60 (3H, s); *m/z* 234 (M^+).

1.1.6. Dehydrogenation of compound 7. Compound **7** (0.06 g, 0.25 mmol) was refluxed with 10% palladium on charcoal (0.02 g) in diphenyl ether (2 mL) for 1 h. The mixture was chromatographed over silica gel. The column was eluted by petroleum ether to remove diphenyl ether and the product was obtained by using benzene–ethyl acetate (3:1) as eluant, yield 0.02 g, 40%. Mixed mp and IR comparison showed this to be compound **6**.

1.1.7. 8-Oxabicyclo[3.3.1]nonano[3,2-*d*]pyrimidine-2,4-dione (8). Compound **1** (0.236 g, 1 mmol) was added to stirred conc. sulfuric acid (3 mL) at 0–5°C. Stirring was continued for 2 h. It was then poured into crushed ice, neutralised with $NaHCO_3$ and extracted with $CHCl_3$ (2×50 mL), washed with water and dried with sodium sulphate. The solvent was removed and the residual mass was chromatographed over a silica gel column. Elution of the column with benzene–ethyl acetate (3:1) gave the *title compound* **8** (0.22 g, 94%) as a white solid, mp 90°C; [Found; C 61.18, H 6.88, N 11.56. $C_{12}H_{16}N_2O_3$ requires C 61.02, H 6.78, N 11.86%]; ν_{max}(KBr) 2960, 1680, 1640, 1100, 750 cm^{-1}; λ_{max} (log ϵ) 211 (3.24), 292 (3.20) nm; δ_H (500 MHz, $CDCl_3$) 1.38–1.47 (1H, m, H-7), 1.48–1.55 (1H, m, H-10), 1.58–1.63 (1H, m, H-8), 1.76–1.83 (2H, m, H-5 and H-6), 1.88–1.96 (2H, m, H-2 and H-3), 2.08–2.20 (1H, m, H-9), 3.00–3.06 (1H, m, H-4), 3.32 (3H, s), 3.34 (3H, s), 4.60 (1H, brs, H-1); δ_C (67.8 MHz, $CDCl_3$) 17.71 (C-7), 27.72 (C-8a), 28.49 (N–CH_3), 29.26 (C-8), 29.27 (C-9), 30.03 (N–CH_3), 32.34 (C-6), 70.02 (C-5a), 130.80 (C-8b), 131.57 (C-4a), 150.77 (C-4), 158.47 (C-2); *m/z* 236 (M^+).

1.1.8. Attempted dehydrogenation of compound 8. Compound **8** (0.236 g, 1 mmol) was refluxed with DDQ (0.2 g) in dry xylene (5 mL) for 2 h. No change was observed as evidenced from TLC of the reaction mixture. Co-TLC with the starting material **8**, superimposable IR spectra and mmp also indicated the recovery of the starting material.

Similarly compound **8** (0.118 g, 0.05 mmol) was refluxed with 10% palladium on charcoal (0.02 g) in diphenyl ether (4 mL) for 2 h. No change was observed as evidenced from the TLC of the reaction mixture, co-TLC with the starting material **8** and also from superimposable IR spectra.

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