A NEW SYNTHESIS OF PHENOLIC 1-HYDROXY-1-PHENYL-2, 3, 4, 5-TETRAHYDRO-1H-3-BENZAZEPINES

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Abstract – 7,8-Dihydroxy-1-phenyl- and 1-(3- and 4-hydroxyphenyl)-1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine derivatives (2a,b) and (3a-c) were synthesized by intramolecular Barbier reaction of N-(2-iodophenethyl)-phenacylamines (5a,b) and (12a-c) with n-C₄H₉Li as a key reaction step.

INTRODUCTION

3-Benzazepine compounds have attracted considerable interest in the past two decades because of their therapeutic potential of dopamine D₁ antagonists as antipsychotics.¹ The discovery of SCH 23390,² the first high-affinity and selective D₁/D₅ antagonist along with the partial agonist SKF 38393³ represented a major breakthrough in the pharmacology of dopamine receptors.⁴ In addition, fenoldopam is a selective peripheral D₁ agonist and has been developed as a parenteral treatment for emergencies⁵ (Figure 1).

We have reported that 4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (1a: PI-OH)⁶ and its phenolic derivatives (1b,c)⁷ having an ethanolamine moiety showed the strong norepinephrine (NE) potentiating activity due to the NE reuptake inhibiting effect. From these facts, phenolic 1-hydroxy-1-phenyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine derivatives (2) and (3) bearing the ethanolamine moiety are interesting compounds in the pharmacological and synthetic points of view. We now report a new synthetic method for the preparation of phenolic 1-hydroxy-1-phenyl-3-benzazepines (2) and (3).

RESULTS AND DISCUSSION

In our previous papers, we reported the convenient synthesis of PI-OH (1a) and the related compounds,⁸ and 3-hydroxy-3-phenylindole (4)⁹ by intramolecular Barbier reaction of corresponding N-benzyl- and N-phenylphenacylamines with n-C₄H₉Li in good yields. Thus, we carried out the synthesis of 7, 8-dihydr-
oxy-1-phenyl-3-benzazepines (2a,b) by intramolecular Barbier reaction of N-methyl- and N-benzyl-N-(2-iodophenethyl)phenacylamines (5a,b), of which the phenolic hydroxy groups were protected with a t-butyldimethylsilyl (TBDMS) group (Scheme 1). The key intermediates (5a,b) were prepared by the
condensation of phenacyl bromide (10) with phenolic N-alkyl-2-iodophenethylamines (9c,d) protected with silyl groups, which were obtained by acylation of the silylated phenethylamine (7b) derived from 3,4-dihydroxyphenethylamine (7a), followed by iodination of the products (8a,b) and reduction of the acyl compounds (9a,b) with diborane.

The cyclization of 5a,b with n-C4H9Li gave the protected 1-phenyl-3-benzazepines (6a,b) in 16.9 and 31.8% yields, along with deiodinated by-products (11a,b) of the starting material (5a,b) in the yields of 24.7 and 31.3%, respectively. Finally the deprotection of the silyl groups in 6a,b with tetrabutylammonium fluoride (TBAF) gave the target compounds (2a,b).

In the same way for the preparation of 2a,b as described above, the 3-benzazepines (3a-c) with a substituted 1-phenyl group were synthesized as shown in Scheme 2. The key intermediates (12a-c) were synthesized by condensation of phenacyl bromides (15a-c) with 2-ido-N-methylphenethylamine (14). Compound (14) was prepared by diborane reduction of 2-iodobenzyl cyanide (17) obtained from 2-iodobenzyl bromide (16) with sodium cyanide, followed by formylation of the produced phenethylamine (18) and then by reduction of the amide (19) in high over all yields from 16.
Intramolecular Barbier cyclization of 12a with n-C₄H₉Li gave 4-(4-methoxyphenyl)-3-benzazepine (3a) in 14.6% yield with a deiodinated by-product (20a) in 26.7% yield. The protected phenolic 3-benzazepines (13b,c) were obtained by the treatment of 12b,c with n-C₄H₉Li in 20.8 and 17.2% yields, respectively. Then the deprotection of 13b,c with TBAF gave the 3-benzazepines (3b,c) in 60.9 and 85.6% yields, respectively.

In conclusion, an intramolecular Barbier reaction of N-(2-iodophenethyl)phenacylamines with n-C₄H₉Li in this study provides an applicable method for the preparation of 1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine derivatives.

**EXPERIMENTAL**

General All melting points are given as uncorrected values. IR spectra were taken with a Perkin-Elmer 1720 infrared fourier transform spectrophotometer. High-resolution mass (HR-MS) spectra were recorded on a JEOL JMS-D 300 spectrometer. ¹H-NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer with TMS as a standard.

2-[3,4-Di(t-butyldimethylsilyloxy)phenethylamine (7b) A mixture of the hydrochloride (1.357 g, 7.16 mmol) of 7a, t-butyldimethylsilyl chloride (TBDMSCI) (3.236 g, 21.5 mmol) and imidazole (2.150 g, 35.8 mmol) in dry CH₂Cl₂ (30 mL) was stirred under N₂ at rt for 2 h. The precipitates formed were filtered. The filtrate was evaporated to give an oil (5.560 g). This was subjected to flash chromatography on SiO₂ with CH₂Cl₂-CH₃OH (5:1) to afford 7b as a pale yellow oil (2.617 g, 95.8 %). ¹H-NMR (CDCl₃) δ: 6.75 (1H, d, J=7.8 Hz), 6.67 (1H, d, J=2.2 Hz), 6.62 (1H,dd, J=7.8, 2.0 Hz), 2.90 (2H, t, J=6.6 Hz), 1.47 (2H, br s), 0.98 (18H, s), 0.19 (12H, s); IR (liquid film) cm⁻¹: 2930, 2859, 1295, 910. HR-MS m/z: Calcd for C₃₂H₃₀NO₃Si₂: 381.2519 (M⁺). Found: 381.2520.

2-[3,4-Di(t-butyldimethylsilyloxy)phenyl]-N-formylethylamine (8a) A mixture of 7b (2.353 g, 6.16 mmol), K₂CO₃ (8.518 g, 61.6 mmol), and 4A molecular sieves (8 g) in HCOOC₂H₅-C₂H₅OH (1:1) (100 mL) was refluxed under N₂ for 3 h. The mixture was filtered. The filtrate was evaporated and H₂O (50 mL) was added. The mixture was washed with CH₂Cl₂ (50 mL x 3). The extract was dried over MgSO₄, and evaporated to give a pale yellow oil (2.377 g). This was subjected to flash chromatography on SiO₂ with CH₂Cl₂-acetone (5:1) to give 8a as a pale yellow oil (2.110 g, 83.6 %). ¹H-NMR (CDCl₃) δ: 8.11 (1H, s), 6.76 (1H, d, J=7.6 Hz), 6.63 (2H, m), 5.60 (1H, br s), 3.55-3.42 (2H, m), 2.70 (2H, t, J=6.6 Hz), 0.98 (18H, s), 0.19 (12H, s). IR (liquid film) cm⁻¹: 3286, 3051, 1668, 1254. HR-MS m/z: Calcd for C₂₁H₂₉NO₃Si₂: 409.2468 (M⁺). Found: 409.2437.

2-[4,5-Di(t-butyldimethylsilyloxy)-2-iodophenyl]-N-formylethylamine (9a) A solution of iodine (1.187 g, 4.68 mmol) in CHCl₃ (80 mL) was added to a solution of 8a (1.192 g, 4.68 mmol) and silver trifluoroacetate (1.032 g, 4.68 mmol) in CHCl₃ (20 mL) under stirring at rt for 15 min. The mixture was
filtered and the filtrate was washed with a saturated solution of Na₂CO₃ in H₂O (50 mL). The CHCl₃ solution was dried over MgSO₄ and evaporated to give a pale yellow oil (2.370 g). This was subjected to flash chromatography on SiO₂ with CH₂Cl₂-acetone (10:1) to give 9a as a pale yellow oil (2.365 g, 94.4 %). ¹H-NMR (CDCl₃) δ: 8.16 (1H, s), 7.25 (1H, s), 6.69 (1H, s), 3.56-3.46 (2H, m), 2.84 (2H, t, J=6.8 Hz), 0.98 (18H, s), 0.19 (12H, s). IR (liquid film) cm⁻¹: 3261, 3076, 2931, 2852, 1632.

Found: 611.1775.

2-[4,5-Di(t-butyldimethylsilyloxy)-2-iiodophenyl]-N-methylethylamine (9c) To a solution of 9a (2.114 g, 3.95 mmol) in dry THF (10 mL) was added BH₃ (11.9 mL of 1M solution in THF, 11.9 mmol). The mixture was refluxed under N₂ for 1 h. C₂H₅OH (20 mL) was added and the mixture was evaporated to give a colorless oil (1.988 g). H₂O (50 ml) was added and the mixture was extracted with CH₂Cl₂. The extract was washed with a saturated solution of K₂CO₃ in H₂O (50 mL x 2), dried over MgSO₄, and evaporated to give a pale yellow oil (1.687 g). This was subjected to flash chromatography on SiO₂ with CH₂Cl₂-CH₃OH (5:1) to give 9c as a pale yellow oil (0.673 g, 32.7 %). ¹H-NMR (CDCl₃) δ: 7.23 (1H, s), 6.72 (1H, s), 2.80 (4H, s), 2.46 (3H, s), 1.74 (1H, br s), 0.98 (9H, s), 0.97 (9H, s), 0.19 (6H, s), 0.18 (6H, s). IR (liquid film) cm⁻¹: 2931, 2858, 1256, 910. HR-MS m/z: Calcd for C₇₃H₄₅NO₂Si₂: 535.1436 (M⁺). Found: 535.1435.

N-Benzoyl-2-[3,4-di(t-butyldimethylsilyloxy)phenyl]ethylamine (8b) A mixture of benzoyl chloride (0.813 g, 5.79 mmol) in benzene (15 mL) and 25% NaOH (14 mL, 131 mmol) were added to a solution of 7b (1.472 g, 3.86 mmol) in benzene (15 mL). The mixture was stirred at rt for 1 h. H₂O (100 mL) was added and the mixture was extracted with CH₂Cl₂ (100 mL x 3). The extract was dried over MgSO₄ and evaporated to give a colorless oil (1.641 g). This was subjected to flash chromatography on SiO₂ with CH₂Cl₂-acetone (20:1) to give 8b as a colorless oil (1.565 g, 83.5 %). ¹H-NMR (CDCl₃) δ: 7.67 (2H, dd, J=6.6, 1.7 Hz), 6.78 (1H, d, J=7.8 Hz), 6.69 (1H, s), 6.67 (1H, dd, J=7.8, 2.0 Hz), 6.12 (1H, br s), 3.66 (2H, t, J=6.8 Hz), 2.80 (2H, t, J=6.8 Hz), 0.98 (9H, s), 0.96 (9H, s), 0.19 (6H, s), 0.16 (6H, s). IR (liquid film) cm⁻¹: 3319, 3063, 2931, 2858, 1641. HR-MS m/z: Calcd for C₇₃H₄₅NO₂Si₂: 485.2780 (M⁺). Found: 485.2767.

N-Benzoyl-2-[4,5-di(t-butyldimethylsilyloxy)-2-iiodophenyl]ethylamine (9b) In the same way as 8a, compound (8b) (1.378 g, 2.84 mmol) was treated with silver trifluoroacetate (0.627 g, 2.84 mmol) and iodine (0.720 g, 2.84 mmol) in CHCl₃ (100 mL) to give 9b as colorless needles (from n-hexane) (1.209 g, 69.7 %), mp 131°C. ¹H-NMR (CDCl₃) δ: 7.73 (2H, d, J=7.3 Hz), 7.26 (1H, s), 6.72 (1H, s), 6.18 (1H, br s), 3.66 (2H, q-like, J=6.6 Hz), 2.94 (2H, t, J=6.8 Hz), 0.97 (9H, s), 0.92 (9H, s), 0.19 (6H, s), 0.12 (6H, s). IR (KBr) cm⁻¹: 3261, 3076, 2931, 2852, 1632. HR-MS m/z: Calcd for C₇₃H₄₅NO₂Si₂: 611.1749 (M⁺). Found: 611.1775. Anal. Calcd for C₇₃H₄₅NO₂Si₂ • 1/5H₂O: C, 52.70; H, 6.94; N, 2.28. Found: C, 52.59; H,
7.04; N, 1.95.

**N-Benzyl-2-[4,5-di(t-butyldimethylsilyloxy)-2-iodophenyl]ethylamine (9d)** In the same way as 9a, compound (9b) (1.064 g, 1.74 mmol) was treated with BH₃ (5.2 mL of 1M solution in THF, 5.2 mmol) in dry THF (5 mL) under N₂ for 6 h to give crude product (1.027 g). This was subjected to flash chromatography on SiO₂ with CH₂Cl₂-CH₃OH (10:1) to give 9d as a pale yellow oil (0.344 g, 33.1 %).

1H-NMR (CDCl₃) δ: 7.36-7.24 (5H, m), 7.22 (1H, s), 6.71 (1H, s), 3.83 (2H, s), 2.82 (4H, s), 1.85 (1H, br s), 0.98 (9H, s), 0.95 (9H, s), 0.18 (6H, s), 0.15 (6H, s). IR (liquid film) cm⁻¹: 2932, 2858, 1566.

HR-MS m/z: Calcd for C₃₇H₅⁰NO₂Si₂: 597.1950 (M⁺). Found: 597.1930.

**2-Iodobenzyl Cyanide (17)** A mixture of 2-iodobenzyl bromide (16) (15.998 g, 53.9 mmol), NaCN (10.037 g, 204.8 mmol) in EtOH (140 mL) was refluxed for 4 h. The mixture was evaporated in vacuo and H₂O (50 mL) was added to the residue. The mixture was extracted with ether (100 mL x 3). The extract was washed with a saturated solution of NaCl in H₂O, dried over MgSO₄, and evaporated to give a crude oil (12.625 g). This was distillated under reduced pressure to give 17 as colorless oil (12.110 g, 94.2 %), bp 110-112°C/3 mm Hg. 1H-NMR (CDCl₃) δ: 7.85 (1H, dd, J=7.8, 1.2 Hz), 7.51 (1H, dd, J=7.5, 1.2 Hz), 7.37 (1H, ddd, J=7.5, 7.5, 1.2 Hz), 7.03 (1H, ddd, J=7.8, 7.5, 1.2 Hz). IR (liquid film) cm⁻¹: 3059, 2973, 2252, 1566. HR-MS m/z: Calcd for C₃₇H₅₂NI: 243.9623 (M+1). Found: 243.9624. Anal. Calcd for C₃₇H₅₂NI: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.58; H, 2.58; N, 5.43.

**2-(2-Iodophenyl)ethylamine (18)** A solution of 17 (4.053 g, 16.7 mmol) in dry THF (15 mL) was added dropwise to a solution of BH₃ (40 mL of 1M solution in THF, 40 mmol). The mixture was refluxed for 1 h. C₂H₅OH (10 mL) was added to the mixture under ice-cooling and 1N HCl-CH₃OH (20 mL) was added. The mixture was evaporated to give crude crystals. These were recrystallized from CH₂OH-acetone to afford the hydrochloride of 18 as colorless cubes (3.459 g, 73.5 %), mp 226-237°C.

1H-NMR (free base; CDCl₃) δ: 7.82 (1H, d, J=7.8 Hz), 7.32-7.20 (2H, m), 6.90 (1H, ddd, J=7.8, 7.5, 1.2 Hz), 2.92 (4H, m). HR-MS (free base) m/z: Calcd for C₃₇H₅₄NI: 246.9858 (M⁺). Found: 246.9834. Anal. Calcd for C₃₇H₅₄NI·HCl: C, 33.88; H, 3.91; N, 4.97. Found: C, 34.15; H, 3.94; N, 4.83.

**N-Formyl-2-(2-iodophenyl)ethylamine (19)** In the same way as the formylation of 7a, 18 (4.877 g, 19.7 mmol) was reacted with HCOOC₂H₅-C₂H₅OH (1:1) (280 mL) in the presence of K₂CO₃ (21.2 g, 227.5 mmol) and 4A molecular sieves (22 g) to give crystals. These were subjected to flash chromatography on SiO₂ with CH₂Cl₂-acetone (1:1) to afford 19 as white crystals (4.875 g, 89.8 %), mp 58.0°C. 1H-NMR (CDCl₃) δ: 8.15 (1H, s), 7.83 (1H, dd, J=7.8, 1.0 Hz), 7.36-7.12 (2H, m), 6.93 (1H, m), 5.80 (1H, br s), 3.66-3.40 (2H, m), 2.97 (2H, m). HR-MS m/z: Calcd for C₃₇H₅₀NI: 274.9805 (M⁺). Found: 274.9823. Anal. Calcd for C₃₇H₅₀NI: C, 39.30; H, 3.66; N, 5.09. Found: C, 39.41; H, 3.69; N, 4.71.
2-(2-Iodophenyl)-N-methylethylamine (14)  In the same way as 9a, 19 (0.931 g, 3.38 mmol) was reacted with BH$_3$ (10 mL of 1M solution in THF, 10 mmol) in dry THF (10 mL) to give a white solid. This was recrystallized from CH$_3$OH-acetone to afford the hydrochloride of 14 as colorless plates (0.927 g, 92.0 %), mp 186-189°C. $^1$H-NMR (free base, CDCl$_3$) δ: 7.81 (1H, d, J=7.8 Hz), 7.24 (2H, m), 6.88 (1H, m), 2.91 (2H, m), 2.83 (2H, m), 2.48 (3H, s), 1.45 (1H, s). HR-MS m/z: Calcd for C$_9$H$_{12}$NI: 261.0015 (M$^+$). Found: 261.0015. Anal. Calcd for C$_9$H$_{12}$NI · HCl: C, 36.33; H, 4.40; N, 4.71. Found: C, 36.31; H, 4.33; N, 4.45.

N-{2-[4,5-Di(tert-butyldimethylsilyloxy)-2-iodophenyl]ethyl}-N-methylphenacylamine (5a) A solution of 9c (0.502 g, 0.96 mmol), phenacyl bromide (10) (0.191 g, 0.96 mmol), and propylene oxide (0.17 g, 2.9 mmol) in dioxane (5 mL) was heated at 105°C for 2 h. The mixture was evaporated to give an oil (0.681 g). This was subjected to flash chromatography on SiO$_2$ with CH$_3$Cl$_2$-ethyl acetate (15:1) to afford 5a as a pale yellow oil (0.525 g, 85.3 %). $^1$H-NMR (CDCl$_3$) δ: 7.99 (2H, dd, J=7.1, 1.7 Hz), 7.55 (1H, t, J=7.6 Hz), 7.43 (2H, t, J=7.8 Hz), 7.20 (1H, s), 6.71 (1H, s), 3.92 (2H, s), 2.82 (2H, m), 2.73 (2H, m), 2.48 (3H, s), 0.98 (9H, s), 0.96 (9H, s), 0.18 (6H, s), 0.17 (6H, s). IR (liquid film) cm$^{-1}$: 2931, 2858, 1683, 1255. HR-MS m/z: Calcd for C$_{29}$H$_{64}$NO$_3$Si$_2$: 638.1984 (M-1). Found: 638.1984.

Compounds (5b) and (12a-c) were prepared in the same way as 5a.

N-Benzyl-N-{2-[4,5-di(tert-butyldimethylsilyloxy)-2-iodophenyl]ethyl}phenacylamine (5b) Compound (9d) (0.272 g, 0.45 mmol) was reacted with 10 (0.090 g, 0.45 mmol) and propylene oxide (0.079 g, 1.35 mmol) in dioxane (3 mL) to give a crude oil (0.381 g). This was subjected to flash chromatography on SiO$_2$ with CH$_3$Cl$_2$-n-hexane (3:2) to afford 5b as a pale yellow oil (0.263 g, 80.8 %). $^1$H-NMR (CDCl$_3$) δ: 7.94 (2H, dd, J=6.8, 1.5 Hz), 7.58-7.25 (8H, m), 7.17 (1H, s), 6.60 (1H, s), 3.98 (2H, s), 3.87 (2H, s), 2.80 (4H, s), 0.96 (9H, s), 0.95 (9H, s), 0.17 (6H, s), 0.14 (6H, s). IR (liquid film) cm$^{-1}$: 3029, 2930, 2858, 1682, 1255, 911. HR-MS m/z: Calcd for C$_{36}$H$_{60}$NO$_3$Si$_2$: 714.2269 (M-1). Found: 714.2269.

4-Methoxy-N{2-(2-iodophenyl)ethyl}-N-methylphenacylamine (12a) Compound (14) (1.158 g, 4.43 mmol) was reacted with 15a (1.029 g, 4.43 mmol) and propylene oxide (0.800 g, 13.8 mmol) in dioxane (20 mL) to give a crude oil (2.557 g). This was subjected to flash chromatography on SiO$_2$ with CH$_3$Cl$_2$-ethyl acetate (8:1) to afford 12a as a pale brown oil (1.074 g, 60.2 %). $^1$H-NMR (CDCl$_3$) δ: 7.98 (2H, d, J=8.8 Hz), 7.79 (1H, d, J=7.8 Hz), 6.90 (2H, d, J=8.8 Hz), 3.86, 3.87 (5H, each s), 3.08-2.70 (4H, m), 2.48 (3H, s). HR-MS m/z: Calcd for C$_{18}$H$_{36}$NO$_3$I: 409.0540 (M$^+$). Found: 409.0580.

4-tert-Butyldimethylsilyloxy-N{2-(2-iodophenyl)ethyl}-N-methylphenacylamine (12b) Compound (14) (1.421 g, 5.44 mmol) was reacted with 15b$^7$ (1.752 g, 5.32 mmol) and propylene oxide (0.988 g, 17.0 mmol) in dioxane (20 mL) to give a crude oil (3.847 g). This was subjected to flash
chromatography on SiO\textsubscript{2} with CH\textsubscript{2}Cl\textsubscript{2} - ethyl acetate (5:1) to afford 12b as a pale yellow oil (2.282 g, 82.3 %). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 7.79 (1H, d, \( J=7.8 \) Hz), 7.02 (2H, m), 6.93 (1H, m), 3.96 (2H, s), 3.00 (2H, m), 2.80 (2H, m), 2.54 (3H, s), 0.99 (9H, s), 0.22 (6H, s). HR-MS \( m/z \): Calcd for \( C_{23}H_{32}NO_2Si \): 509.1248 (M\textsuperscript{+}). Found: 509.1246.

3-t-Butyldimethylsilyloxy-N-[2-(2-iodophenyl)ethyl]-N-methylphenacylammine (12c)

Compound (14) (1.290 g, 4.94 mmol) was reacted with \( 15c \)\textsuperscript{2} (1.627 g, 4.94 mmol) and propylene oxide (0.890 g, 15.3 mmol) in dioxane (20 mL) to give a crude oil (3.265 g). This was subjected to flash chromatography on SiO\textsubscript{2} with CH\textsubscript{2}Cl\textsubscript{2} - ethyl acetate (5:1) to afford 12c as a pale yellow oil (2.006 g, 79.7 %). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 7.78 (1H, d, \( J=7.6 \) Hz), 7.57 (1H, d, \( J=8.5 \) Hz), 7.48 (1H, s), 7.03 (1H, dd, \( J=7.8, 2.7 \) Hz), 6.86 (1H, m), 3.91 (2H, s), 2.96 (2H, m), 2.77 (2H, m), 2.50 (3H, s), 0.99 (9H,s), 0.27 (6H, s). HR-MS \( m/z \): Calcd for \( C_{23}H_{32}NO_2Si \): 509.1248 (M\textsuperscript{+}). Found: 509.1220.

7,8-Di(t-butyldimethylsilyloxy)-1-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (6a) 

\( N, N, N', N'\)-Tetramethylethlenediamine (0.068 mL, 0.49 mmol) and \( n-C_6H_5Li \) (0.28 mL of 1.6 M solution in \( n\)-hexane, 0.49 mmol) were added to a solution of 5a (0.181 g, 0.28 mmol) in \( n\)-hexane (2 mL) under N\textsubscript{2} at -78°C. The mixture was stirred for 10 min at -78°C. H\textsubscript{2}O (20 mL) was added and the mixture was extracted with ether (20 mL x 3). The extract was dried over MgSO\textsubscript{4} and evaporated to give a pale yellow oil (0.135 g). This was subjected to flash chromatography on SiO\textsubscript{2} with CH\textsubscript{2}Cl\textsubscript{2} - acetone (5:1). The first fraction gave 11a as a pale brown oil (0.036 g, 24.7 %). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 7.96 (2H, dd, \( J=6.8, 1.5 \) Hz), 7.55 (1H, t, \( J=7.3 \) Hz), 7.42 (2H, t, \( J=7.6 \) Hz), 6.72 (1H, d, \( J=7.8 \) Hz), 6.66 (1H, d, \( J=1.7 \) Hz), 6.61 (1H, dd, \( J=7.8, 1.7 \) Hz), 3.85 (2H, s), 2.73 (4H, s), 2.42 (3H, s), 0.99 (18H, s), 0.18 (6H, s), 0.17 (6H, s). IR (liquid film) cm\textsuperscript{-1}: 2930, 1683, 1254. HR-MS \( m/z \): Calcd for \( C_{29}H_{47}NO_2Si \): 514.3173 (M\textsuperscript{+}). Found: 514.3190.

The second fraction gave 6a as a pale yellow oil (0.025 g, 16.9 %). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 7.48-7.24 (5H, m), 6.53 (1H, s), 6.06 (1H, s), 3.31 (1H, ddd, \( J=15.0, 10.6, 2.6 \) Hz), 3.15 (1H, d, \( J=12.2 \) Hz), 3.02 (1H, ddd, \( J=15.0, 10.6, 2.6 \) Hz), 2.99 (1H, d, \( J=12.2 \) Hz), 2.67 (1H, ddd, \( J=14.8, 6.8, 2.5 \) Hz), 2.49 (3H, s), 2.48 (1H, m), 0.96 (9H, s), 0.79 (9H, s), 0.14 (6H, s), - 0.36 (3H, s), - 0.44 (3H, s). IR (liquid film) cm\textsuperscript{-1}: 3320, 2929, 2858, 1255. HR-MS \( m/z \): Calcd for \( C_{29}H_{47}NO_2Si \): 513.3094 (M\textsuperscript{+}). Found: 513.3085.

3-Benzazepines (6b), (3a), and (13b,c) were prepared in the same way as 6a.

3-Benzyl-7,8-di(t-butyldimethylsilyloxy)-1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (6b) 

Compound (5b) (8.192 g, 11.4 mmol) was reacted with \( n-C_6H_5Li \) (11.5 mL of 1.6 M solution in \( n\)-hexane, 18.3 mmol) in dry THF (200 mL). The crude product (7.108 g) was subjected to flash chromatography on SiO\textsubscript{2} with CHCl\textsubscript{3}. The first fraction gave 11b as a pale yellow oil (2.110 g, 31.3 %). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 7.90 (2H, dd, \( J=7.1, 1.7 \) Hz), 7.53-7.26 (8H, m), 6.69 (1H, d, \( J=8.1 \) Hz), 6.58 (1H,
s), 6.56 (1H, d, J=8.1 Hz), 3.91 (2H, s), 3.82 (2H, s), 2.96-2.84 (2H, m), 2.78-2.64 (2H, m), 0.97 (18H, s), 0.17 (6H, s), 0.15 (6H, s). IR (liquid film) cm⁻¹: 3029, 2932, 1682, 1255. HR-MS m/z: Calcd for C₁₃₅H₁₁₁NO₃Si₂: 589.3407 (M'). Found: 589.3419.

The second fraction gave 6b as a pale yellow oil (2.150 g, 31.8 %). ¹H-NMR (CDCl₃) δ: 7.45-7.27 (10H, m), 6.50 (1H, s), 6.07 (1H, s), 3.82 and 3.70 (each 1H, d, J=13.4 Hz), 3.28 and 3.16 (each 1H, d, J=12.2 Hz), 3.20-3.00 (2H, m), 2.80-2.36 (2H, m), 0.95 (12H, s), 0.97 (6H, s), - 0.34 (3H, s), - 0.46 (3H, s). IR (liquid film) cm⁻¹: 3356, 3029, 2932, 1682, 1255. HR-MS m/z: Calcd for C₁₃₅H₁₁₁NO₃Si₂: 589.3407 (M'). Found: 589.3388.

**1-Hydroxy-1-(4-methoxyphenyl)-3-methyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine (3a)**

Compound (12a) (0.546 g, 1.33 mmol) was reacted with n-C₄H₉Li (1.35 mL of 1.6 M solution in n-hexane, 1.68 mmol) in dry THF (5 mL). The crude product (0.356 g) was subjected to flash chromatography on SiO₂ with CH₂Cl₂- ethyl acetate (1:2). The first fraction gave 20a as a pale yellow oil (0.147 g, 26.7 %). ¹H-NMR (CDCl₃) δ: 7.96 (2H, d, J=9.0 Hz), 7.27-7.18 (5H, m), 6.88 (2H, d, J=9.0 Hz), 3.86 (3H, s), 3.81 (2H, s), 2.83 (4H, s), 2.43 (3H, s). HR-MS m/z: Calcd for C₁₈H₂₁NO₂: 282.1493 (M-1). Found: 282.1456.

The second fraction gave 3a as a pale yellow oil (0.056 g, 14.6 %). ¹H-NMR (CDCl₃) δ: 7.34 (2H, d, J=8.8 Hz), 6.90 (2H, d, J=8.8 Hz), 3.82 (3H, s), 3.22 (1H, d, J=12.7 Hz), 3.20 (1H, m), 2.92 (2H, m), 2.90 (1H, d, J=12.7 Hz), 2.50 (1H, m), 2.48 (3H, s). HR-MS m/z: Calcd for C₁₈H₂₁NO₂: 283.1572 (M'). Found: 283.1581.

**1-(4-t-Butyldimethylsilyloxyphenyl)-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (13b)**

Compound (12b) (1.943g, 3.81 mmol) was reacted with n-C₄H₉Li (3.45 mL of 1.6 M solution in n-hexane, 5.72 mmol) in dry THF (15 mL). The crude product (1.770 g) was subjected to flash chromatography on SiO₂ with CH₂Cl₂- ethyl acetate (1:4). The first fraction gave 20b as a pale brown oil (0.433 g, 29.6 %). ¹H-NMR (CDCl₃) δ: 7.65-7.20 (7H, m), 7.00(2H, m), 3.90 (3H, s), 3.02 (2H, m), 2.82 (2H, m), 2.50 (3H, s), 1.00 (9H, s), 0.21 (6H, s). HR-MS m/z: Calcd for C₂₃H₃₅NO₂Si: 383.2280 (M'). Found: 383.2296.

The second fraction gave 13b as a pale yellow oil (0.304 g, 20.8 %). ¹H-NMR (CDCl₃) δ: 7.30-6.90 (6H, m), 6.80 (2H, d, J=8.1 Hz), 3.82 (3H, s), 3.42-2.90 (3H, m), 3.18 (1H, d, J=12.7 Hz), 2.94 (1H, d, J=12.7 Hz), 2.78-2.40 (1H, m), 2.49 (3H, s), 0.97 (9H, s), 0.17 (6H, s). HR-MS m/z: Calcd for C₂₃H₃₅NO₂Si: 383.2280 (M'). Found: 383.2329.

**1-(3-t-Butyldimethylsilyloxyphenyl)-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (13c)**

Compound (12c) (1.869, 3.67 mmol) was treated with n-C₄H₉Li (2.75 mL of 1.6 M solution in n-hexane, 4.40 mmol) in dry THF (15 mL). The crude product (1.427 g) was subjected to flash chromatography on SiO₂ with CH₂Cl₂- ethyl acetate (1:4). The first fraction gave 20c as a pale brown oil (0.667 g, 34.8 %).
\[ \text{H-NMR (CDCl}_3 \delta: 7.54 (1H, dd, J=7.6, 1.0 Hz), 7.45 (1H, dd, J=1.2, 1.0 Hz), 7.31-7.18 (6H, m), 7.02 (1H, ddd, J=8.1, 1.2, 1.0 Hz), 3.84 (2H, s), 2.82 (4H, m), 2.45 (3H, s), 0.99 (9H, s), 0.21 (6H, s). HR-MS m/z: Calcd for C\text{_{25}H\text{_{33}}NO}_3: 383.2280 (M^+). Found: 383.2262.} \]

The second fraction gave 13c as a pale yellow oil (0.242 g, 17.2 %). 1\text{H}-NMR (CDCl\textsubscript{3}) \( \delta \): 7.24-6.95 (6H, m), 6.80 (2H, m), 3.30-3.20 (1H, m), 3.17 (1H, d, \( J=12.7 \) Hz), 3.05-2.71 (2H, m), 2.93 (1H, d, \( J=12.7 \) Hz), 2.50-2.40 (1H, m), 2.48 (3H, s), 0.97 (9H, s), 0.17 (6H, s). HR-MS m/z: Calcd for C\text{_{17}H\text{_{19}}NO}\textsubscript{2}: 267.1258 (M-H\textsubscript{2}O). Found: 267.1236.

3-Methyl-1-phenyl-1, 7, 8-trihydroxy-2, 3, 4, 5-tetrahydro-1\text{H}-3-benzazepine (2a) TBAF (1.65 mL of 1 M solution in THF, 1.65 mmol) was added to a solution of 6a (0.172 g, 0.33 mmol) in dry THF (10 mL) under ice-cooling. The mixture was stirred for 30 min. H\textsubscript{2}O (20 mL) was added and the mixture was extracted with ethyl acetate. The extract was washed with H\textsubscript{2}O, dried over MgSO\textsubscript{4}, and evaporated to give a pale brown oil (0.031 g, 31.5 %). 1\text{H}-NMR (acetone-d\textsubscript{6}) \( \delta \): 7.44-7.24 (5H, m), 6.56 (1H, s), 6.48 (1H, s), 3.58 (1H, d, \( J=13.0 \) Hz), 2.95 (1H, d, \( J=13.0 \) Hz), 3.08-2.80 (4H, m), 2.54 (3H, s). HR-MS m/z: Calcd for C\text{_{17}H\text{_{19}}NO}\textsubscript{2}: 267.1258 (M-H\textsubscript{2}O). Found: 267.1236.

3-Benzazepines (2b) and (3b, c) were prepared in the same way as 2a.

3-Benzyl-1-phenyl-1, 7, 8-trihydroxy-2, 3, 4, 5-tetrahydro-1\text{H}-3-benzazepine (2b) Compound (6b) (0.137 g, 0.23 mmol) was reacted with TBAF (0.70 mL of 1 M solution in THF, 0.70 mmol) in dry THF (3 mL) to give an oil (0.240 g). This was purified by preparative TLC on SiO\textsubscript{2} with CH\textsubscript{3}Cl\textsubscript{2} - acetone (2:1) to afford 2b as a pale brown oil (0.023 g, 27.7 %). 1\text{H}-NMR (CD\textsubscript{3}OD) \( \delta \): 7.40-7.12 (5H, m), 6.81 (1H, s), 6.52 (1H, s), 3.69 (1H, d, \( J=13.7 \) Hz), 3.61(1H, d, \( J=13.7 \) Hz), 3.47 (1H, d, \( J=12.9 \) Hz), 2.78 (1H, d, \( J=12.9 \) Hz), 2.84-2.46 (4H, m). HR-MS m/z: Calcd for C\text{_{25}H\text{_{33}}NO}_3Si: 383.1571 (M-H\textsubscript{2}O). Found: 343.1564.

1-\text{Hydroxy-1-(4-hydroxyphenyl)-3-methyl-2, 3, 4, 5-tetrahydro-1\text{H}-3-benzazepine (3b)} Compound (13b) (0.304 g, 0.79 mmol) was reacted with TBAF (1.60 mL of 1 M solution in THF, 1.60 mmol) in dry THF (10 mL) to give an oil (0.253 g). This was subjected to flash chromatography on SiO\textsubscript{2} with CH\textsubscript{3}Cl\textsubscript{2} - acetone (2:3) to give 3b as a pale yellow oil (0.130 g, 60.9 %). 1\text{H}-NMR (CDCl\textsubscript{3}) \( \delta \): 7.32-6.72 (8H, m), 3.36-2.40 (4H, m), 3.21 (1H, d, \( J=12.7 \) Hz), 2.94 (1H, d, \( J=12.7 \) Hz), 2.50 (3H, s). HR-MS m/z: Calcd for C\text{_{17}H\text{_{19}}NO}_2: 269.1398. Found: 269.1398.

1-Hydroxy-1-(3-hydroxyphenyl)-3-methyl-2, 3, 4, 5-tetrahydro-1\text{H}-3-benzazepine (3c) Compound (13c) (0.205 g, 0.535 mmol) was reacted with TBAF (1.10 mL of 1 M solution in THF, 1.10 mmol) in dry THF (10 mL) to give an oil (0.161 g). This was subjected to flash chromatography on SiO\textsubscript{2} with CH\textsubscript{3}Cl\textsubscript{2} - acetone (2:3) to give 3c as a pale yellow oil (0.123 g, 85.6 %). 1\text{H}-NMR (acetone-d\textsubscript{6}) \( \delta \): 8.20 (1H, br s), 7.30-7.21 (1H, m), 7.16-7.00 (4H, m), 6.90 (1H, m), 6.82 (1H, m), 6.71 (1H, ddd, \( J=8.1, 1.2, 1.0 \) Hz), 7.32 (2H, s), 2.82 (4H, m), 2.45 (3H, s), 0.99 (9H, s), 0.21 (6H, s). HR-MS m/z: Calcd for C\text{_{25}H\text{_{33}}NO}_3: 383.2280 (M^+). Found: 383.2262.
2.4, 1.0 Hz), 3.34 (1H, d, J=12.7 Hz), 2.96-2.86 (1H, m), 2.89 (1H, d, J=12.7 Hz), 2.76-2.50 (3H, m), 2.41 (3H, s). HR-MS m/z: Calcd for C_{17}H_{19}NO_2: 269.1415 (M^+). Found: 269.1376.

REFERENCES