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A NEW SYNTHESIS OF PHENOLIC 1-HYDROXY-1-PHENYL-2, 3, 4, 5-TETRAHYDRO-1*H*-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-1*H*-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*-C_4H_9Li 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 D_1 antagonists as antipsychotics.[1] The discovery of SCH 23390,[2] the first high-affinity and selective D_1/D_5 antagonist along with the partial agonist SKF 38393[3] represented a major break-through in the pharmacology of dopamine receptors.[4] In addition, fenoldopam is a selective peripheral D_1 agonist and has been developed as a parenteral treatment for emergencies[5] (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-tetrahydo-1*H*-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*-C_4H_9Li in good yields. Thus, we carried out the synthesis of 7, 8-dihydr-

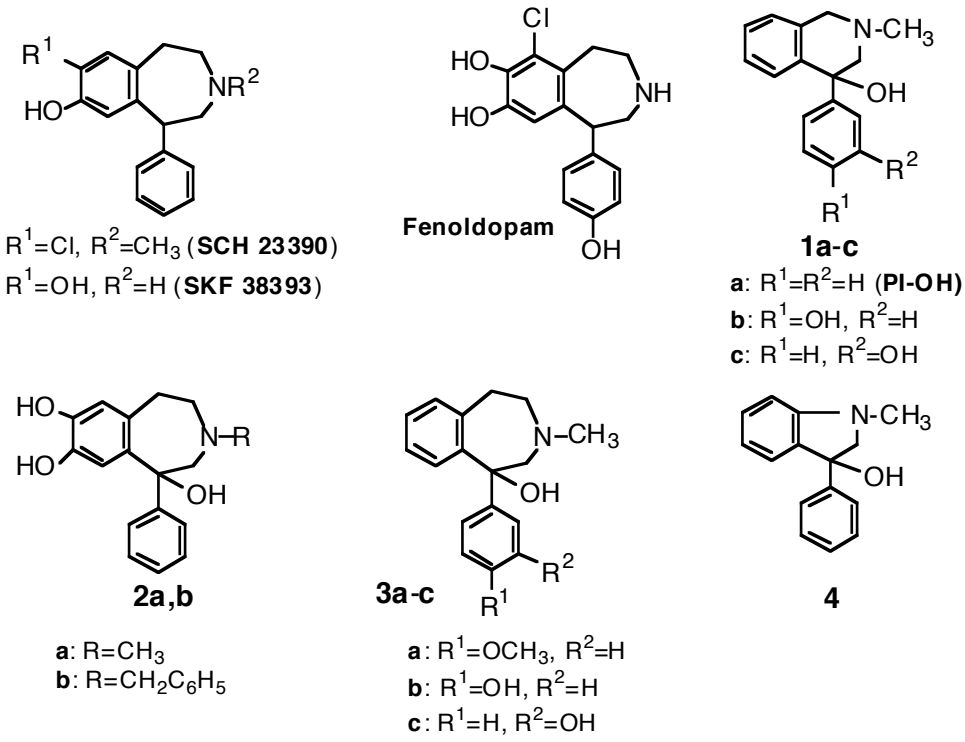
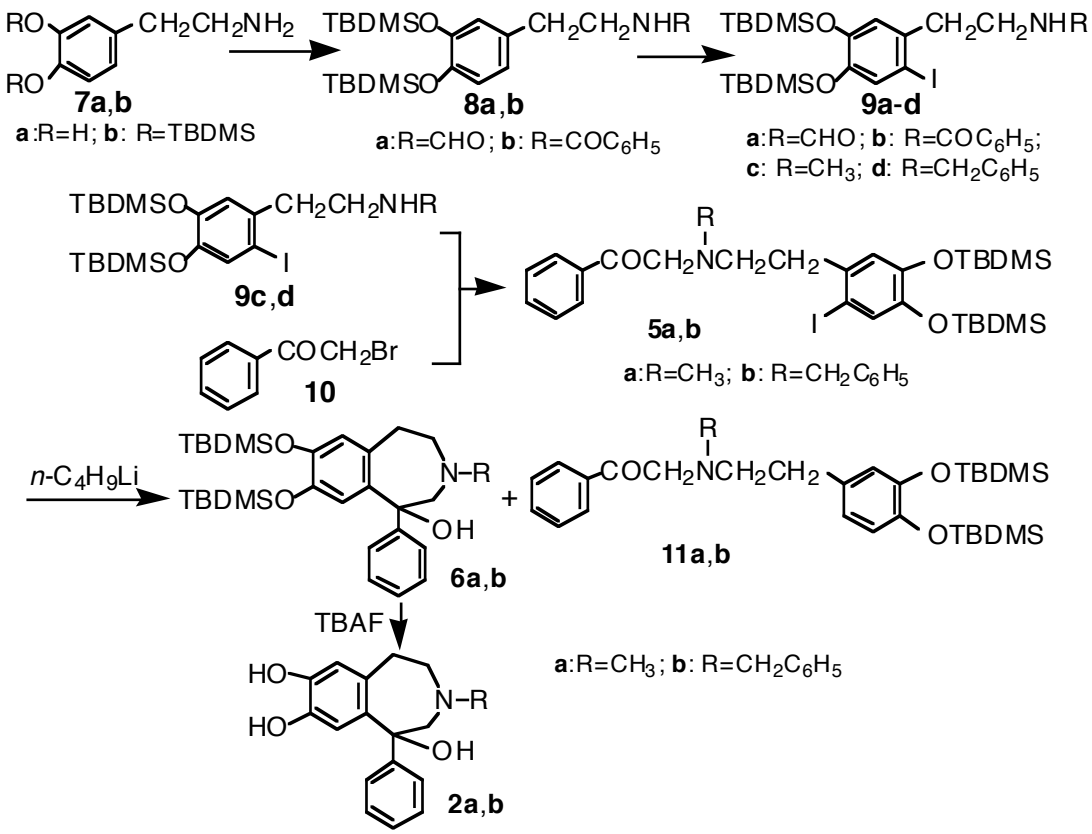


Figure 1



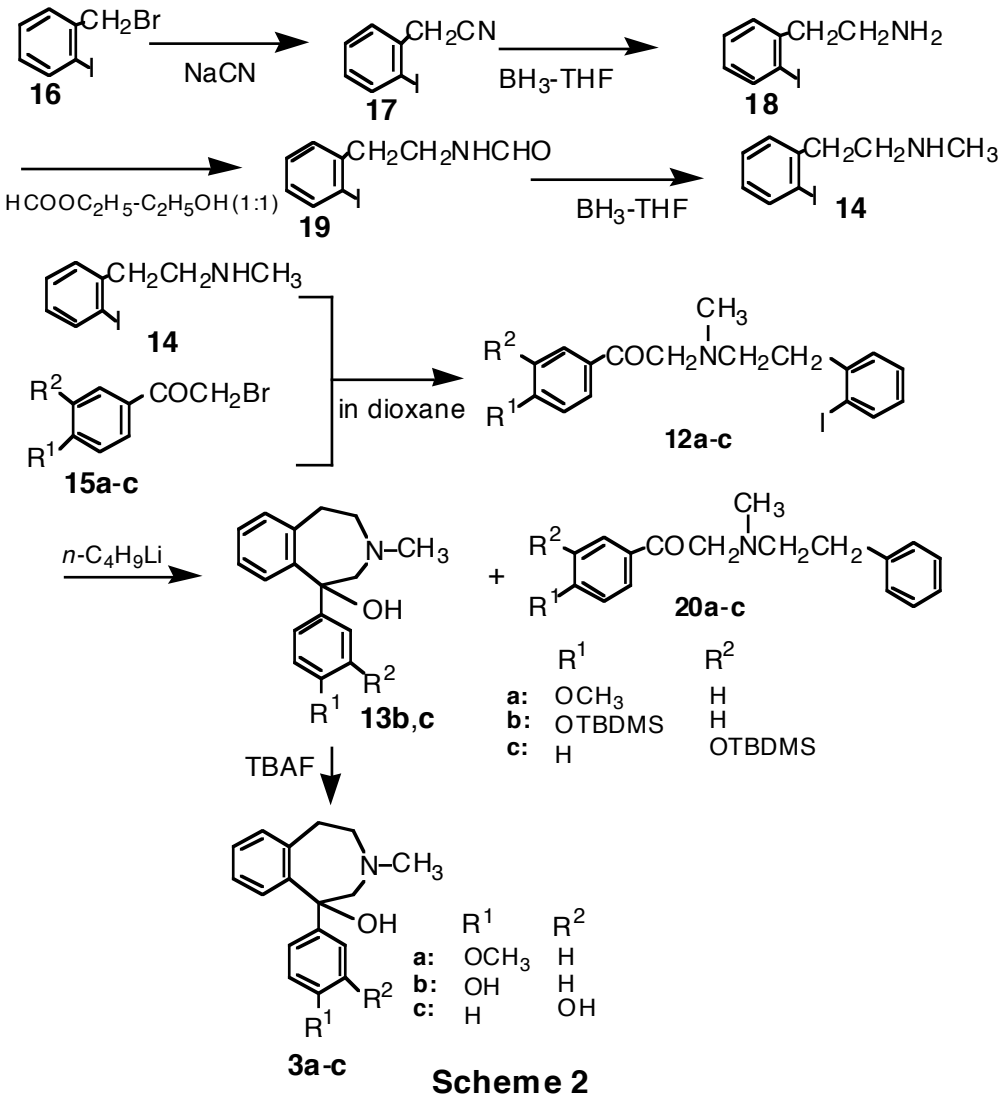
Scheme 1

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*-C_4H_9Li 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-iodo-*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**.



Scheme 2

Intramolecular Barbier cyclization of **12a** with *n*-C_4H_9Li 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*-C_4H_9Li 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*-C_4H_9Li in this study provides an applicable method for the preparation of 1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-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. ^{1}H-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 (TBDMSCl) (3.236 g, 21.5 mmol) and imidazole (2.150 g, 35.8 mmol) in dry CH_2Cl_2 (30 mL) was stirred under N_2 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 SiO_2 with CH_2Cl_2-CH_3OH (5:1) to afford **7b** as a pale yellow oil (2.617 g, 95.8 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{20}H_{39}NO_2Si_2$: 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), K_2CO_3 (8.518 g, 61.6 mmol), and 4A molecular sieves (8 g) in $HCOOC_2H_5$-C_2H_5OH (1:1) (100 mL) was refluxed under N_2 for 3 h. The mixture was filtered. The filtrate was evaporated and H_2O (50 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL x 3). The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a pale yellow oil (2.377 g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_2-acetone (5:1) to give **8a** as a pale yellow oil (2.110 g, 83.6 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{21}H_{39}NO_3Si_2$: 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 $CHCl_3$ (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 $CHCl_3$ (20 mL) under stirring at rt for 15 min. The mixture was

filtered and the filtrate was washed with a saturated solution of Na_2CO_3 in H_2O (50 mL). The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated to give a pale yellow oil (2.370 g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_2-acetone (10:1) to give **9a** as a pale yellow oil (2.365 g, 94.4 %). ^{1}H-NMR ($CDCl_3$) 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}: 3283, 2981, 2859, 1667, 1256. HR-MS *m/z*: Calcd for $C_{21}H_{38}NO_3ISi_2$: 535.1436 (M^+). Found: 535.1435.

2-[4,5-Di(*t*-butyldimethylsilyloxy)-2-iodophenyl]-*N*-methylethylamine (9c) To a solution of **9a** (2.114 g, 3.95 mmol) in dry THF (10 mL) was added BH_3 (11.9 mL of 1M solution in THF, 11.9 mmol). The mixture was refluxed under N_2 for 1 h. C_2H_5OH (20 mL) was added and the mixture was evaporated to give a colorless oil (1.988 g). H_2O (50 ml) was added and the mixture was extracted with CH_2Cl_2. The extract was washed with a saturated solution of K_2CO_3 in H_2O (50 mL x 2), dried over $MgSO_4$, and evaporated to give a pale yellow oil (1.687 g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_2-CH_3OH (5:1) to give **9c** as a pale yellow oil (0.673 g, 32.7 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{21}H_{40}NO_2ISi_2$: 522.1722 (M + 1). Found: 522.1715.

***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. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (100 mL x 3). The extract was dried over $MgSO_4$ and evaporated to give a pale yellow oil (1.641 g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_2 -acetone (20:1) to give **8b** as a colorless oil (1.565 g, 83.5 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{27}H_{43}NO_3Si_2$: 485.2780 (M^+). Found: 485.2767.

***N*-Benzoyl-2-[4,5-di(*t*-butyldimethylsilyloxy)-2-iodophenyl]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 $CHCl_3$ (100 mL) to give **9b** as colorless needles (from *n*-hexane) (1.209 g, 69.7 %), mp 131℃. ^{1}H-NMR ($CDCl_3$) 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 $C_{27}H_{42}NO_3ISi_2$: 611.1749 (M^+). Found: 611.1775. *Anal*. Calcd for $C_{27}H_{42}NO_3ISi_2 \cdot 1/5H_2O$: 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 BH_3 (5.2 mL of 1M solution in THF, 5.2 mmol) in dry THF (5 mL) under N_2 for 6 h to give crude product (1.027 g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_2-CH_3OH (10:1) to give **9d** as a pale yellow oil (0.344 g, 33.1 %). ^{1}H-NMR ($CDCl_3$) 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, 1255, 911. HR-MS *m/z*: Calcd for $C_{27}H_{44}NO_2ISi_2$: 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 H_2O (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 H_2O, dried over $MgSO_4$, 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℃/3 mm Hg. ^{1}H-NMR ($CDCl_3$) 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 C_8H_7NI: 243.9623 (M+1). Found: 243.9624. *Anal*. Calcd for C_8H_6NI: 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 BH_3 (40 mL of 1M solution in THF, 40 mmol). The mixture was refluxed for 1 h. C_2H_5OH (10 mL) was added to the mixture under ice-cooling and 1N HCl-CH_3OH (20 mL) was added. The mixture was evaporated to give crude crystals. These were recrystallized from CH_3OH-acetone to afford the hydrochloride of **18** as colorless cubes (3.459 g, 73.5 %), mp 226-237℃. ^{1}H-NMR (free base; $CDCl_3$) 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 $C_8H_{10}NI$: 246.9858 (M^+). Found: 246.9834. *Anal*. Calcd for $C_8H_{10}NI \cdot HCl$: 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 $HCOOC_2H_5$-C_2H_5OH (1:1) (280 mL) in the presence of K_2CO_3 (21.2 g, 227.5 mmol) and 4A molecular sieves (22 g) to give crystals. These were subjected to flash chromatography on SiO_2 with CH_2Cl_2-acetone (1:1) to afford **19** as white crystals (4.875 g, 89.8 %), mp 58.0℃. ^{1}H-NMR ($CDCl_3$) 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 $C_9H_{10}NOI$: 274.9805 (M^+). Found: 274.9823. *Anal*. Calcd for $C_9H_{10}NOI$: 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_3OH-acetone to afford the hydrochloride of **14** as colorless plates (0.927 g, 92.0 %), mp 186-189℃. ^{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 $C_9H_{12}NI$: 261.0015 (M^+). Found: 261.0015. *Anal*. Calcd for $C_9H_{12}NI \cdot HCl$: C, 36.33; H, 4.40; N, 4.71. Found: C, 36.31; H, 4.33; N, 4.45.

***N*-{2-[4,5-Di(*t*-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℃ 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_2Cl_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 $C_{29}H_{46}NO_3ISi_2$: 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(*t*-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_2Cl_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 $C_{35}H_{50}NO_3ISi_2$: 714.2296 (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 (2.557g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_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 $C_{18}H_{20}NO_2I$: 409.0540 (M^+). Found: 409.0580.

4-*t*-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_2 with CH_2Cl_2 - ethyl acetate (5:1) to afford **12b** as a pale yellow oil (2.282 g, 82.3 %). ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{23}H_{32}NO_2ISi$: 509.1248 (M^+). Found: 509.1246.

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

Compound (**14**) (1.290 g, 4.94 mmol) was reacted with **15c**[7] (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_2 with CH_2Cl_2 - ethyl acetate (5:1) to afford **12c** as a pale yellow oil (2.006 g, 79.7 %). ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{23}H_{32}NO_2ISi$: 509.1248 (M^+). Found: 509.1220.

7,8-Di(*t*-butyldimethylsilyloxy)-1-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-bezazepine (6a) *N*, *N*, *N'*, *N'*-Tetramethylethylenediamine (0.068 mL, 0.49 mmol) and *n*-C_4H_9Li (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_2 at -78℃. The mixture was stirred for 10 min at -78℃. H_2O (20 mL) was added and the mixture was extracted with ether (20 mL x 3). The extract was dried over $MgSO_4$ and evaporated to give a pale yellow oil (0.135 g). This was subjected to flash chromatography on SiO_2 with CH_2Cl_2 - acetone (5:1). The first fraction gave **11a** as a pale brown oil (0.036 g, 24.7 %). ^{1}H-NMR ($CDCl_3$) δ: 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^{-1}: 2930, 1683, 1254. HR-MS *m/z*: Calcd for $C_{29}H_{47}NO_3Si_2$: 514.3173 (M+1). Found: 514.3190.

The second fraction gave **6a** as a pale yellow oil (0.025 g, 16.9 %). ^{1}H-NMR ($CDCl_3$) δ: 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^{-1}: 3320, 2929, 2858, 1255. HR-MS *m/z*: Calcd for $C_{29}H_{47}NO_3Si_2$: 513.3094 (M^+). 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-1*H*-3-bezazepine (6b) Compound (**5b**) (8.192 g, 11.4 mmol) was reacted with *n*-C_4H_9Li (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_2 with $CHCl_3$. The first fraction gave **11b** as a pale yellow oil (2.110 g, 31.3 %). ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{35}H_{51}NO_3Si_2$: 589.3407 (M^+). Found: 589.3419.

The second fraction gave **6b** as a pale yellow oil (2.150 g, 31.8 %). ^{1}H-NMR ($CDCl_3$) 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), 0.13 (6H, s), - 0.34 (3H, s), - 0.46 (3H, s). IR (liquid film) cm^{-1}: 3356, 3029, 2931, 2858, 1568, 1255. HR-MS *m/z*: Calcd for $C_{35}H_{51}NO_3Si_2$: 589.3407 (M^+). Found: 589.3388.

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

Compound (**12a**) (0.546 g, 1.33 mmol) was reacted with *n*-C_4H_9Li (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 SiO_2 with CH_2Cl_2 - ethyl acetate (1:2). The first fraction gave **20a** as a pale yellow oil (0.147 g, 26.7 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{18}H_{21}NO_2$: 282.1493 (M-1). Found: 282.1456.

The second fraction gave **3a** as a pale yellow oil (0.056 g, 14.6 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{18}H_{21}NO_2$: 283.1572 (M^+). Found: 283.1581.

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

Compound (**12b**) (1.943g, 3.81 mmol) was reacted with *n*-C_4H_9Li (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 SiO_2 with CH_2Cl_2- ethyl acetate (1:4). The first fraction gave **20b** as a pale brown oil (0.433 g, 29.6 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{23}H_{33}NO_2Si$: 383.2280 (M^+). Found: 383.2296.

The second fraction gave **13b** as a pale yellow oil (0.304 g, 20.8 %). ^{1}H-NMR ($CDCl_3$) 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 $C_{23}H_{33}NO_2Si$: 383.2280 (M^+). Found: 383.2329.

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

Compound (**12c**) (1.869, 3.67 mmol) was treated with *n*-C_4H_9Li (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 SiO_2 with CH_2Cl_2 - ethyl acetate (1:4). The first fraction gave **20c** as a pale brown oil (0.667 g, 34.8 %).

^{1}H-NMR ($CDCl_3$) δ: 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 $C_{23}H_{33}NO_2Si$: 383.2280 (M^+). Found: 383.2262.

The second fraction gave **13c** as a pale yellow oil (0.242 g, 17.2 %). ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{23}H_{33}NO_2Si$: 383.2280 (M^+). Found: 383.2279.

3-Methyl-1-phenyl-1, 7, 8-trihydroxy-2, 3, 4, 5-tetrahydro-1*H*-3-bezazepine (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_2O (20 mL) was added and the mixture was extracted with ethyl acetate. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a pale brown oil (0.031 g, 31.5 %). ^{1}H-NMR (acetone-d_6) δ: 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 $C_{17}H_{17}NO_2$: 267.1258 (M-H_2O). 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*H*-3-bezazepine (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_2 with CH_2Cl_2 - acetone (2:1) to afford **2b** as a pale brown oil (0.023 g, 27.7 %). ^{1}H-NMR (CD_3OD) δ: 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 $C_{23}H_{21}NO_2$: 343.1571 (M-H_2O). Found: 343.1564.

1- Hydroxy-1-(4-hydroxyphenyl)-3-methyl-2, 3, 4, 5-tetrahydro-1*H*-3-bezazepine (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_2 with CH_2Cl_2 - acetone (2:3) to give **3b** as a pale yellow oil (0.130 g, 60.9 %). ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{17}H_{19}NO_2$: 269.1415 (M^+). Found: 269.1398.

1-Hydroxy-1-(3-hydroxyphenyl)-3-methyl-2, 3, 4, 5-tetrahydro-1*H*-3-bezazepine (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_2 with CH_2Cl_2 - acetone (2:3) to give **3c** as a pale yellow oil (0.123 g, 85.6 %). ^{1}H-NMR (acetone-d_6) δ: 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,

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.

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