HETEROCYCLES, Vol. 68, No. 11, 2006, pp. 2319 - 2326. © The Japan Institute of Heterocyclic Chemistry
Received, 1st August, 2006, Accepted, 19th September, 2006, Published online, 22nd September, 2006. COM-06-10853

SYNTHESIS OF NEW 1, 2-DIPHENYL-4, 5-DIHYDRO-3*H*-3-BENZAZEPINES

Chiaki Kaito, Kumiko Sakamoto, Mitsushi Sakamoto, Aiko Yamauchi, and Masaru Kihara*

Faculty of Pharmaceutical Sciences, The University of Tokushima, 1-78, Sho-machi, Tokushima 770-8505, Japan; e-mail: mkihara@ph.tokushima-u.ac.jp

Abstract – 1,2-Diphenyl-4,5-dihydro-3*H*-3-benzazepine derivatives (**2a-d**) were synthesized *via* cyclization reaction of *N*-[2-(2-iodophenyl)ethyl]-α-phenylphenacylamines (**5a**-**c**) and (**5e**) with *n*-C_4H_9Li, followed by dehydration of the cyclization products, 1,2-diphenyl-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (**4a**-**d**) with trifluoromethanesulfonic acid.

INTRODUCTION

Tamoxifen is a well established estrogen antagonist and one of the most used anti-breast cancer drug.[1,2] This triarylethylene compound is today the drug of choice for palliative therapy of advanced breast cancer.[3] However, side effects including endometrial carcinoma are also sometimes observed as a major adverse consequence of drug treatment.[4]

In order to overcome these defects, in recent years, much attention has been paid to the design of novel alternate scaffolds for estrogen antagonists such as 4,5-diphenyl-2,3-dihydro-1-benzoxepins,[5] 3,4-diphenyl-quinolines and isoquinolines,[6] 1,2-diphenyl-1,2,3,4-tetrahydroisoquinolines,[7] 2-phenyl-1-phenyloxynaphthalenes,[8] and 2,3-diphenylindenes.[9]

We have reported the synthesis and biological evaluation of 3,4-diphenyl-2-methyl-1,2-dihydroisoquinoline (**1a**)[10] and the 7-phenolic compound (**1b**).[11] Compounds (**1a**,**b**) were found to have nearly equipotent anti-proliferative activities to that of tamoxifen against human mammary carcinoma MCF-7 cell line.

On the basis of these facts, 1,2-diphenyl-4,5-dihydro-3*H*-3-benzazepine (**2a**) having a novel structure is an interesting compound in the biological and synthetic points of view (Figure 1). We now report a convenient synthesis of **2a** and the substituted compounds (**2b**-**d**) on the 1-phenyl group.

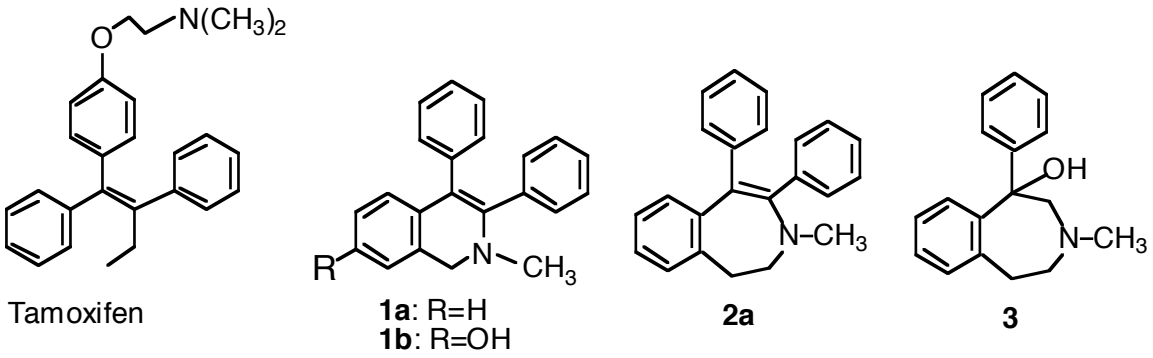
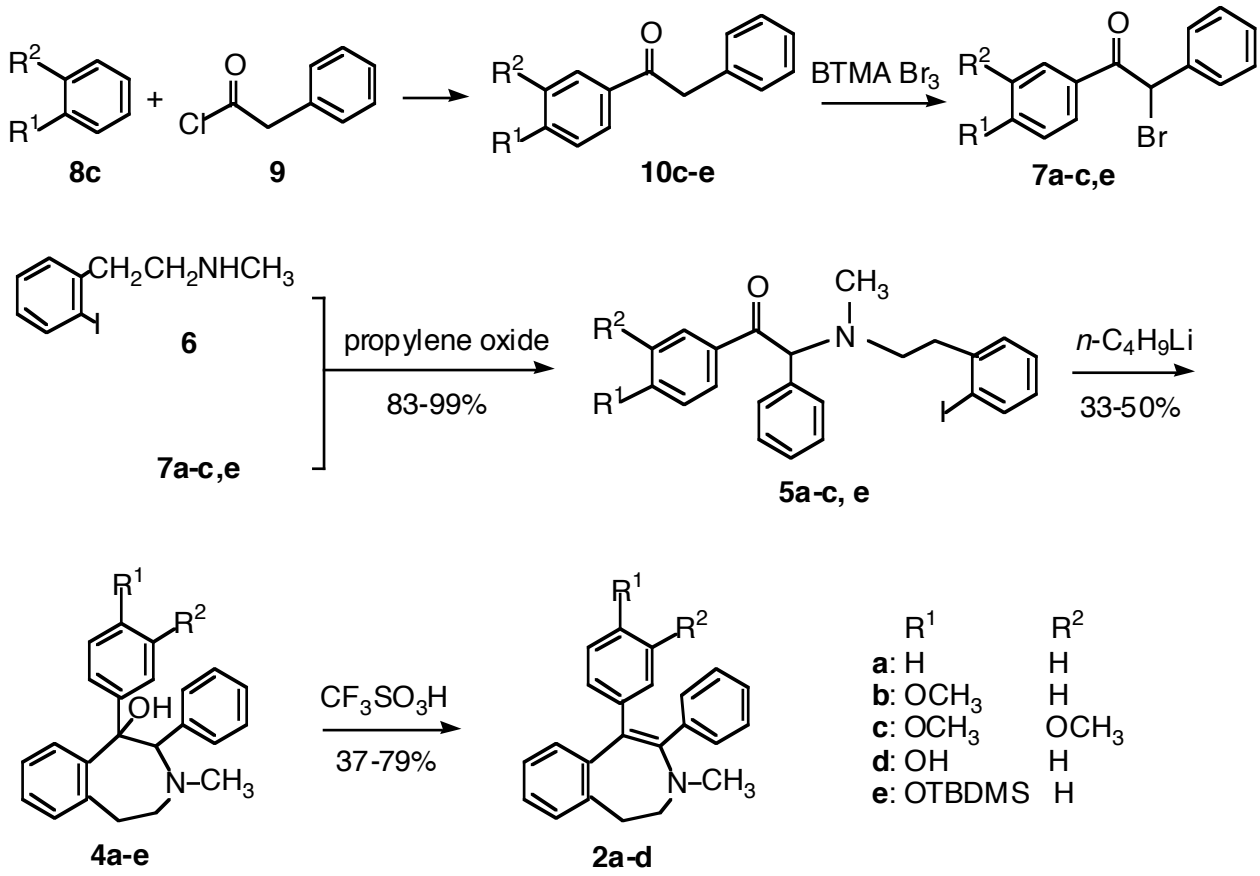


Figure 1



Scheme 1

RESULTS AND DISCUSSION

In our previous papers, we reported the synthesis of 3,4-diphenyl-1,2-dihydroisoquinolines (**1a**,**b**)[10,11] by acidic dehydration of the corresponding 3,4-diphenyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines, which were prepared by intramolecular Barbier reaction of *N*-(2-iodobenzyl)phenacylamines with *n*-butyllithium (*n*-C_4H_9Li). Recently, we reported[12] the synthesis of the phenolic derivatives of 1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**3**) by cyclization of *N*-[2-(2-iodophenyl)-

ethyl]phenacylamines with *n*-C_4H_9Li. Thus, we carried out the synthesis of 4,5-dihydro-1,2-diphenyl-3-methyl-3*H*-3-benzazepines (**2a**-**d**) by dehydration of 1,2-diphenyl-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (**4a**-**d**) with trifluoromethanesulfonic acid (CF_3SO_3H) as shown in Scheme 1. The compounds **4a**-**c** were synthesized by intramolecular Barbier reaction of the key intermediates, *N*-[2-(2-iodophenyl)ethyl]-α-phenylphenacylamines (**5a**-**c**) with *n*-C_4H_9Li in 33-43 % yields. The singlet signal (δ 4.65) of C2-H in the ^{1}H-NMR spectrum of **4a** showed a single diastereomer, which may be formed due to the steric hindrance between an α-phenyl group and a phenyl group of the phenacylamine in **5a**. Compounds (**5a-c**) were prepared by condensation of *N*-methyl-2-(2-iodophenyl)ethylamine (**6**) with α-phenylphenacyl bromides (**7a**-**c**) in the presence of propylene oxide in high yields. The bromides (**7a**),[13] (**7b**),[10] and (**7c**) were obtained by bromination of benzyl phenyl ketones (**10a**-**c**) with benzyltrimethyl- ammonium tribromide (BTMA Br_3) according to the method reported by us.[10] The ketone (**10c**) was prepared by Friedel-Crafts reaction of veratrole (**8c**) with phenylacetyl chloride (**9**).

The phenolic 1-hydroxy-1,2-diphenyl-3-benzazepine (**4d**) was obtained by deprotection of the *t*-butyldimethylsilyl (TBDMS) group of compound (**4e**) with tetrabutylammonium fluoride (TBAF). Compound (**4e**) was prepared in the same way as **4a**-**c** as follows. Protection of the phenolic group of benzyl phenyl ketone (**10d**) with *t*-butyldimethylsilyl chloride (TBDMSCl) and then bromination of the product (**10e**) with BTMA Br_3 gave an α-phenylphenacyl bromide (**7e**). The condensation of **7e** with **6** afforded a key intermediate (**5e**), which was treated with *n*-C_4H_9Li to give **4e** in 50% yield.

It is interesting to note that the yields (33-50%) of 1,2-diphenyl-1-hydroxy-3-benzazepines (**4**) in the cyclization reaction of *N*-[2-(2-iodophenyl)ethyl]-α-phenylphenacylamines (**5**) with *n*-C_4H_9Li in this study are higher than those (15-32%) of the phenolic derivatives protected with TBDMS of 1-hydroxy-1-phenyl-3-benzazepine (**3**) in cyclization of *N*-[2-(2-iodophenyl)ethyl]phenacylamines reported in our previous paper.[12] The higher yields of **4** may be attributed to the restriction of conformational freedom by the α-phenyl group in **5**.

In conclusion, a cyclization reaction of *N*-[2-(2-iodophenyl)ethyl]-α-phenylphenacylamines (**5**) with *n*-C_4H_9Li, followed by dehydration reaction of the products (**4**) in this study provides an applicable method for the preparation of 1,2-diphenyl-4,5-dihydro-3*H*-3-benzazepine derivatives (**2**).

EXPERIMENTAL

General All melting points are given as uncorrected values. 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.

Benzyl 3,4-Dimethoxyphenyl Ketone (10c) $AlCl_3$ (3.00 g, 22.5 mmol) was added to a mixture

of veratrole (**8c**) (6.31 mL, 49.5 mmol) and phenylacetyl chloride (**9**) (1.98 mL, 15 mmol) for 10 min and the mixture was stirred for 30 min at rt. The mixture was poured into a solution of 36 % HCl (5 mL) and ice-cold H_2O (50mL) and the mixture was extracted with $CHCl_3$ (100 mL x 3). The extract was washed with brine (50 mL), dried over $MgSO_4$, and evaporated to give a pale brawn oil. This was subjected to column chromatography on SiO_2 with *n*-hexane-AcOEt (5 : 1) to afford **10c** as colorless needles (from *n*-hexane) (3.57 g, 92.9 %), mp 76-78℃. ^{1}H-NMR ($CDCl_3$) δ: 7.66 (1H, d, *J*=8.4 Hz), 7.55 (1H, s), 7.29 (5H, m), 6.88 (1H, d, *J*=8.4 Hz), 4.24 (2H, s), 3.93 (3H, s), 3.90 (3H, s). HR-MS *m/z*: Calcd for $C_{16}H_{16}O_3$: 256.1100 (M^+). Found: 256.1077. *Anal*. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.02; H, 6.39.

Benzyl 4-(*t*-Butyldimethylsilyloxy)phenyl Ketone (10e) A mixture of **10d** (0.76 g. 3.59 mmol), TBDMSCl (0.82 g, 5.38 mmol), and imidazole (0.54 g, 8.97 mmol) in dry CH_2Cl_2 (20 mL) was stirred for 2 h at rt. The mixture was washed with brine (50 mL x 3), dried over $MgSO_4$, and evaporated to give **10e** as colorless plates (from EtOH) (1.13 g, 96.4 %), mp 97.5-99℃. ^{1}H-NMR ($CDCl_3$) δ: 7.93 (2H, d, *J*=8.7 Hz), 7.27 (5H, m), 6.86 (2H, d, *J*=8.7 Hz), 4.22 (2H, s), 0.98 (9H, s), 0.23 (6H, s). HR-MS *m/z*: Calcd for $C_{20}H_{26}O_2Si$: 326.1702 (M^+). Found: 326.1703. *Anal*. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.27; H, 7.99.

3,4-Dimethoxy-α-phenylphenacyl Bromide (7c) BTMA Br_3[10] (3.04 g, 7.80 mmol) was added to a solution of **10c** (2.00 g, 7.80 mmol) in CH_2Cl_2-CH_3OH (5:2) (35 mL). The mixture was refluxed for 5 h and evaporated *in vacuo*. H_2O (80 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (70 mL x 3). The extract was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give a pale brown oil. This was purified by column chromatography on SiO_2 with $CHCl_3$ to afford **7c** as pale yellow plates (from *n*-hexane) (1.24 g, 47.3%), mp 117-118℃. ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, d, *J*=8.4 Hz), 7.55 (1H, s), 7.53 (2H, d, *J*=7.5 Hz), 7.35 (3H, m), 6.85 (1H, d, *J*=8.4 Hz), 6.38 (1H, s), 3.93 (3H, s), 3.90 (3H, s). HR-MS *m/z*: Calcd for $C_{16}H_{15}O_3Br$: 334.0205 (M^+). Found: 334.0216. *Anal*. Calcd for $C_{16}H_{15}O_3Br$: C, 57.33; H, 4.51. Found: C, 57.20; H, 4.61.

4-(*t*-Butyldimethylsilyloxy)-α-phenylphenacyl Bromide (7e) In the same way as **10c**, compound (**10e**) (1.00 g, 3.06 mmol) was treated with BTMA Br_3 (1.43 g, 3.68 mmol) to give **7e** as a pale yellow oil (0.54 g, 43.3 %). ^{1}H-NMR ($CDCl_3$) δ: 7.91 (2H, d, *J*=9.0 Hz), 7.53 (2H, d, *J*=7.5 Hz), 7.35 (3H, m), 6.85 (1H, d, *J*=9.0 Hz), 6.34 (1H, s), 0.97 (9H, s), 0.22 (6H, s). HR-MS *m/z*: Calcd for $C_{20}H_{25}O_2BrSi$: 404.0807 (M^+). Found: 404.0766.

***N*-[2-(2-Iodophenyl)ethyl]-*N*-methyl-α-phenylphenacylamine (5a)** A solution of **6** (1.622 g, 6.19 mmol), α-phenylphenacyl bromide (**7a**) (1.42 g, 5.15 mmol), and propylene oxide (3 mL) in dioxane (40 mL) was heated at 110℃ for 1.5 h. The mixture was evaporated and H_2O (50 mL) was added to the residue. The mixture was basified with 25 % NaOH and extracted with $CHCl_3$ (50 mL x 3). The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a pale brown oil. This was subjected to column chromatography on SiO_2 with $CHCl_3$-acetone (100:1) to afford **5a** as a pale yellow oil (2.04 g, 87.0 %). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (2H, d, *J*=7.2 Hz), 7.74 (1H, d *J*=7.8 Hz), 7.47-7.36 (5H, m), 7.28 (3H,

m), 7.20 (1H, t-like, *J*=7.5 Hz), 7.09 (1H, d, *J*=7.5 Hz), 6.84 (1H, m), 5.19 (1H, s), 2.90 (4H, m), 2.49 (3H, s). HR-MS *m/z*: Calcd for $C_{23}H_{22}NOI$: 455.0747 (M^+). Found: 455.0709.

Compounds (**5b**,**c** and **5e**) were prepared in the same way as **5a**.

***N*-[2-(2-Iodophenyl)ethyl]-4-methoxy-*N*-methyl-α-phenylphenacylamine (5b)** Reaction of **6** (1.32 g, 5.03 mmol) with **7b** (1.28 g, 4.19 mmol) and propylene oxide (2.57 mL) in dioxane (20 mL) gave **5b** as a pale yellow oil (2.10 g, 98.0 %). ^{1}H-NMR ($CDCl_3$) δ: 8.01 (2H, d, *J*=8.7 Hz), 7.73 (1H, d *J*=7.7 Hz), 7.38-7.25 (5H, m), 7.20 (1H, t-like, *J*=7.5 Hz), 7.09 (1H, d, *J*=7.5 Hz), 6.84 (2H, d, *J*=8.7 Hz), 5.13 (1H, s), 3.81 (3H, s), 2.93-2.61 (4H, m), 2.48 (3H, s). HR-FABMS *m/z*: Calcd for $C_{24}H_{25}NO_2I$: 486.0931 (M+H). Found: 486.0923.

3,4-Dimethoxy-*N*-[2-(2-iodophenyl)ethyl]-*N*-methyl-α-phenylphenacylamine (5c) Reaction of **6** (1.03 g, 3.93 mmol) with **6c** (0.80 g, 2.93 mmol) and propylene oxide (2.01 mL) in dioxane (28 mL) gave **5c** as an amorphous (1.18 g, 99.4 %). ^{1}H-NMR ($CDCl_3$) δ: 7.73 (1H, d, *J*=8.4 Hz), 7.70 (1H, d *J*=8.6 Hz), 7.57 (1H, d, *J*=1.8 Hz), 7.40-7.23 (5H, m), 7.20 (1H, dd, *J*=7.5 and 7.7 Hz), 7.09 (1H, d, *J*=7.7 Hz), 6.84 (2H, t-like, *J*=7.5 Hz), 6.79 (1H, d, *J*=8.4 Hz), 5.15 (1H, s), 3.90 (3H. s), 3.88 (3H, s), 2.97-2.61 (4H, m), 2.49 (3H, s). HR-FABMS *m/z*: Calcd for $C_{25}H_{27}NO_3I$: 516.1031 (M+H). Found: 516.1026.

4-*t*-Butyldimethylsilyloxy-*N*-[2-(2-iodophenyl)ethyl]-*N*-methyl-α-phenylphenacylamine (5e) Reaction of **6** (0.426 g, 1.63 mmol) with **7e** (0.52 g, 1.29 mmol) and propylene oxide (0.85 mL) in dioxane (6 mL) gave **5e** as a pale yellow oil (0.628 g, 83.3 %). ^{1}H-NMR ($CDCl_3$) δ: 7.94 (2H, d, *J*=8.7 Hz), 7.73 (1H, d *J*=7.8 Hz), 7.38 (5H, m), 7.20 (1H, t-like, *J*=7.5 Hz), 7.08 (1H, d, *J*=7.8 Hz), 6.84 (2H, t-like, *J*=7.5 Hz), 6.77 (2H, d, *J*=8.7 Hz), 5.12 (1H, s), 2.96-2.62 (4H, m), 2.47 (3H, s), 0.96 (9H, s), 0.20 (6H, s). HR-MS *m/z*: Calcd for $C_{29}H_{36}NO_2ISi$: 585.1560. Found: 585.1537.

1-Hydroxy-3-methyl-1,2-diphenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4a) *n*-C_4H_9Li (3.13 mL of 1.53 M solution in *n*-hexane, 4.79 mmol) were added to a solution of **5a** (1.452 g, 3.19 mmol) in dry THF (30 mL) under argon atmosphere at -78℃. The mixture was stirred for 30 min at rt. H_2O (30 mL) was added and the mixture was extracted with ether (50 mL x 3). The extract was dried over $MgSO_4$ and evaporated to give a pale brawn oil. This was subjected to column chromatography on SiO_2 with *n*-hexane-AcOEt (10:1) to afford **4a** as a pale yellow oil (0.450 g, 42.8 %). ^{1}H-NMR ($CDCl_3$) δ: 7.48 (1H, d, *J*=7.5 Hz), 7.40 (2H, d, *J*=7.2 Hz), 7.30-7.09 (9H, m), 6.78 (2H, d, *J*=7.7 Hz), 4.65(1H, s), 3.01-2.61 (4H, m), 2.18 (3H, s). HR-MS *m/z*: Calcd for $C_{23}H_{23}NO$: 329.1780 (M^+). Found: 329.1770.

1-Hydroxy-3-benzazepines (**4b**,**c**) and (**4e**) were prepared in the same way as **4a**.

1-Hydroxy-1-(4-methoxyphenyl)-3-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4b) Compound (**5b**) (0.50 g, 1.03 mmol) was reacted with *n*-C_4H_9Li (1.04 mL of 1.53 M solution in *n*-hexane, 1.58 mmol) in dry THF (8 mL). The crude product was purified by column chromatography on SiO_2 with *n*-hexane-AcOEt (5:1) to give **4b** as a pale yellow oil (0.123 g, 33.2 %). ^{1}H-NMR ($CDCl_3$) δ: 7.52 (1H, d,

J=7.5 Hz), 7.33 (2H, d, *J*=8.7 Hz), 7.21-7.10 (6H, m), 6.83 (2H, d, *J*=8.7 Hz), 6.75 (2H, d, *J*=7.2 Hz), 4.62 (1H, s), 3.78 (3H, s), 3.01-2.59 (4H, m), 2.18 (3H, s). HR-MS *m/z*: Calcd for $C_{24}H_{25}NO_2$: 359.1886 (M^+). Found: 359.1888.

1-(3,4-Dimethoxyphenyl)-1-hydroxy-3-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4c) Compound (**5c**) (0.41 g, 0.80 mmol) was reacted with *n*-C_4H_9Li (0.78 mL of 1.53 M solution in *n*-hexane, 1.20 mmol) in dry THF (2.5 mL). The crude product was purified by column chromatography on SiO_2 with $CHCl_3$-acetone (20:1) to give **4c** as a pale brown amorphous (0.108 g, 34.9 %). ^{1}H-NMR ($CDCl_3$) δ: 7.47 (1H, d, *J*=7.3 Hz), 7.20-7.10 (6H, m), 6.99 (1H, d, *J*=2.0 Hz), 6.91 (1H, dd, *J*=8.5 and 2.0 Hz), 6.79 (2H, d, *J*=7.2 Hz), 6.78 (1H, d, *J*=8.5 Hz), 4.58 (1H, s), 3.84 (3H, s), 3.78 (3H, s), 3.10-2.63 (4H, m), 2.19 (3H, s). HR-MS *m/z*: Calcd for $C_{25}H_{27}NO_3$: 389.1991 (M^+). Found: 389.2004.

1-[4-(*t*-Butyldimethylsilyloxy)phenyl]-1-hydroxy-3-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4e) Compound (**5e**) (0.48 g, 0.83 mmol) was reacted with *n*-C_4H_9Li (0.76 mL of 1.53 M solution in *n*-hexane, 1.16 mmol) in dry THF (2.5 mL). The crude product was purified by column chromatography on SiO_2 with *n*-hexane-AcOEt (15:1) to give **4e** as a pale yellow oil (0.19 g, 50.0 %). ^{1}H-NMR ($CDCl_3$) δ: 7.49 (1H, d, *J*=7.5 Hz), 7.40-7.09 (10H, m), 6.74 (2H, d, *J*=8.8 Hz), 4.59 (1H, s), 3.00-2.83 (2H, m), 2.71-2.60 (2H, m), 2.17 (3H, s), 0.90 (9H, s), 0.17 (6H, s). HR-MS *m/z*: Calcd for $C_{29}H_{37}NO_2Si$: 459.2593 (M^+). Found: 459.2579.

1-Hydroxy-1-(4-hydroxyphenyl)-3-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4d) A solution of TBAF (1.20 mL of 1.0 M solution in THF, 1.20 mmol) in dry THF (1.2 mL) was added to a solution of **4e** (0.184 g, 0.40 mmol) in dry THF (3 mL) under ice-cooling. The mixture was stirred for 30 min. H_2O (70 mL) was added and the mixture was extracted with $CHCl_3$ (100 mL x 3). The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a pale brown oil. This was purified by column chromatography on SiO_2 with $CHCl_3$-acetone (10:1) to give **4d** as a pale yellow amorphous (0.081 g, 58.5 %). ^{1}H-NMR ($CDCl_3$) δ: 7.48 (1H, d, *J*=7.5 Hz), 7.32-7.10 (8H, m), 6.75 (2H, d, *J*=7.5 Hz), 6.63 (2H, d, *J*=8.3 Hz), 4.62 (1H, s), 3.12-2.63 (4H, m), 2.16 (3H, s). HR-MS *m/z*: Calcd for $C_{23}H_{23}NO_2$: 345.1729 (M^+). Found: 345.1729.

3-Methyl-1,2-diphenyl-4,5-dihydro-3*H*-3-benzazepine (2a) CF_3SO_3H (0.162 ml, 1.82 mmol) was added to a solution of **4a** (0.120 g, 0.37 mmol) in dry benzene (5 mL) and the mixture was refluxed for 30 min at 100℃. The reaction mixture was made basic with 5 % NaOH and extracted with $CHCl_3$ (70 mL x 3). The extract was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give **2a** as a pale yellow solid (0.089 g, 78.5 %). ^{1}H-NMR ($CDCl_3$) δ: 7.17 (1H, m), 7.00 (12H, m), 6.85 (1H, m), 3.49 (2H, m), 3.11 (2H, m), 2.42 (3H, s). HR-MS *m/z*: Calcd for $C_{23}H_{21}N$: 311.1674 (M^+). Found: 311.1646.

1, 2-Diphenyl-3-benzazepines (**2b**-**d**) were prepared in the same way as **2a**.

1-(4-Methoxyphenyl)-3-methyl-2-phenyl-4,5-dihydro-3*H*-3-benzazepine (2b) Compound **4b**

(0.093 g, 0.26 mmol) was reacted with CF_3SO_3H (0.114 mL, 1.29 mmol) in benzene (5 mL) for 30 min at 100℃. The crude product was purified by column chromatography on SiO_2 with *n*-hexane-AcOEt (5:1) to give **2b** as a pale yellow solid (0.033 g, 36.9 %). ^{1}H-NMR ($CDCl_3$) δ: 7.18 (1H, m), 7.09 (4H, m), 7.05-7.00 (3H, m), 6.91 (2H, d, *J*=8.5 Hz), 6.88 (1H, m), 6.59 (2H, d, *J*=8.5 Hz), 3.70 (3H, s), 3.49 (2H, m), 3.10 (2H, m), 2.41 (3H, s). HR-MS *m*/*z*: Calcd for $C_{24}H_{23}NO$: 341.1779 (M^+). Found: 341.1809.

1-(3,4-Dimethoxyphenyl)-3-methyl-2-phenyl-4,5-dihydro-3*H*-3-benzazepine (2c) Compound (**4c**) (0.041 g, 0.11 mmol) was reacted with CF_3SO_3H (0.082 mL, 0.55 mmol) in benzene (3.5 mL) for 30 min at 90℃. The crude product was purified by column chromatography on SiO_2 with *n*-hexane-AcOEt (10:1) to give **2c** as a pale yellow solid (0.0153 g, 37.7 %). ^{1}H-NMR ($CDCl_3$) δ: 7.18 (1H, m), 7.10-7.01 (7H, m), 6.92 (1H, m), 6.58-6.52 (3H, m), 3.77 (3H, s), 3.65 (3H, s), 3.46 (2H, m), 3.08 (2H, m), 2.43 (3H, s). HR-MS *m*/*z*: Calcd for $C_{25}H_{25}NO_2$: 371.1886 (M^+). Found: 371.1858.

1-(4-Hydroxyphenyl)-3-methyl-2-phenyl-4,5-dihydro-3*H*-3-benzazepine (2d) Compound (**4d**) (0.017 g, 0.048 mmol) was reacted with CF_3SO_3H (0.021 mL, 0.24 mmol) in benzene (1.0 mL) for 30 min at 90℃. The crude product was purified by column chromatography on SiO_2 with *n*-hexane-AcOEt (5:1) to give **2d** as a pale yellow oil (0.0083 g, 52.9 %). ^{1}H-NMR ($CDCl_3$) δ: 7.18 (1H, m), 7.10-6.70 (7H, m), 6.88 (1H, m), 6.85 (2H, d, *J*=8.5 Hz), 6.51 (2H, d, *J*=8.5 Hz), 3.48 (2H, m), 3.09 (2H, m), 2.40 (3H, s). HR-MS *m*/*z*: Calcd for $C_{23}H_{21}NO$: 327.1623 (M^+). Found: 327.1592.

ACKNOWLEDGEMENTS

The authors are grateful to Mr. Kazunori Yamaguchi for technical assistance.

REFERENCES

1. V. C. Jordan, N. F. Fritz, and M. M. Gottardis, *J. Steroid Biochem.*, 1987, **27**, 493.
2. J. L. Mansi and I. E. Smith, *Cancer Topics*, 1989, **7**, 57.
3. M. Fornier, P. Munster, and A. D. Seidman, *Oncology (USA),* 1999, **13**, 647.
4. M. L. Carcangiu, *Anat. Pathol.,* 1997, **2**, 53.
5. D. G. Lloyd, R. B. Hughes, D. M. Zisterer, D. C. Williams, C. Fattorusso, B. Catalanotti, G. Campiani, and M. J. Meegan, *J. Med. Chem.*, 2004, **47**, 5612.
6. M. Croisy-Delcey, A. Croisy, D. Carrez, C. Huel, A. Chiaron, P. Ducrot, E. Bisagni, L. Jin, and G. Leclercq, *Bioorg. Med. Chem.*, 2000, **8**, 2629.
7. J. Renaud, S. F. Bischoff, T. Buhl, P. Floersheim, B. Fournier, C. Halleux, J. Kallen, H. Keller, J.-H. Schlaeppi, and W. Stark, *J. Med. Chem.*, 2003, **46**, 2945.
8. C. W. Hummel, A. G. Geiser, H. U. Bryant, I. R. Cohen, R. D. Dally, K. C. Fong, S. A. Frank, R. Hinklin, S. A. Jones, G. Lewis, D. J. McCann, D. G. Rudmann, T. A. Shepherd, H. Tian, O. B.

Wallace, M. Wang, Y. Wang, and J. A. Dodge, *J. Med. Chem.*, 2005, **48**, 6772.

9. N. J. Clegg, S. Paruthiyil, D. C. Leitman, and T. S. Scanlan, *J. Med. Chem.*, 2005, **48**, 5989.
10. M. Kihara, M. Ikeuchi, and Y. Nagao, *Drug Des. Discov.*, 1995, **12**, 259.
11. M. Kihara, M. Ikeuchi, A. Yamauchi, M. Nukatsuka, H. Matsumoto, and T. Toko, *Chem. Pharm. Bull.*, 1997, **45**, 939.
12. M. Ikeuchi, M. Ikeuchi, K. Inoue, S. Yamamoto, A. Yamauchi, and M. Kihara, *Heterocycles*, 2005, **65**, 2925.
13. M. Kihara, M. Ikeuchi, K. Jinno, M. Kashimoto, Y. Kobayashi, and Y. Nagao, *Tetrahedron*, 1993, **49**, 1017.