Synthesis of 3-Aryl-2,5-dihydro-1-benzoxepines from Phenol *via* Ring-closing Metathesis

Jui-Chi Tsai[a] (蔡瑞琪), Sie-Rong Li[a] (李協融), Liang-Yeu Chen[a] (陳亮宇), Po-Yuan Chen[b] (陳伯淵), Jia-Ying Joung[b] (鍾佳穎), Chung-Jung Shu[b] (徐崇榮), Yu-Fuan Lo[b] (羅怡芳), Chun-Nan Lin[a] (林忠男) and Eng-Chi Wang[b]* (王英基)

[a]*Faculty of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan, R.O.C.*

[b]*Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan, R.O.C.*

In this paper, the synthesis of 3-aryl-2,5-dihydro-1-benzoxepines is described. While the reaction was started from phenol and based on the sequential reactions such as Claisen rearrangement, *O*-alkylation, Wittig reaction, and ring-closing metathesis (RCM), a series of new 3-aryl-1-benzoxepines were prepared in good overall yields.

Keywords: 3-Aryl-2,5-dihydro-1-benzoxepine; Ring-closing metathesis.

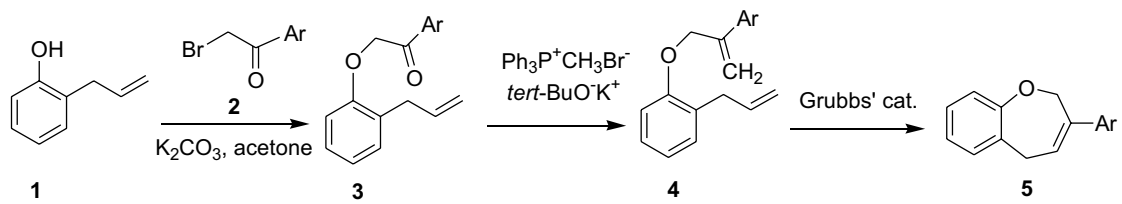
INTRODUCTION

1-Benzoxepine moiety, which plays an important role as the core structure for certain biological active compounds, is attractive to chemists. The major bioactivities reported include hypotensive activity,[1] anti-fungal activity,[2] anti-implantation,[3] anti-HIV-1 activity,[4] etc. Therefore, new preparation of various 1-benzoxepines is requisite and significant. Up to the present, major synthetic methods reported for 1-benzoxepines include intramolecular Mitsunobu cyclization of biofunctional phenolic and alcoholic molecule,[5] ring-closure of isoprenyl terminal epoxides,[6] and sulfur ylide annulation of 2-(*o*-hydroxyphenyl) alkyl ketones and dimethyloxosulfonium methylide. Since the discovery of Grubbs' catalyst for RCM,[8] its application has become a powerful tool for preparing benzoheterocyclic compounds which were tedious to be prepared by other methods. Recently, some relative benzoxepines which prepared using RCM have been published.[9] Although various synthetic methods have been reported, the synthesis of 3-aryl-1-benzoxepine is still lacking in current researches. In continuing our studies on benzoheterocyclic compounds,[10] herein we would like to disclose a new strategy for the synthesis of 3-aryl-1-benzoxepines (Scheme I).

RESULTS AND DISCUSSION

As depicted in Scheme I, 2-allylphenol (**1**) prepared from allyloxybenzene *via* the Claisen rearrangement was reacted with α-bromoacetophenones (**2a-d**) in the presence of dry potassium carbonate in refluxing acetone to undergo *O*-alkylation and give 2-(2-allylphenoxy)-1-phenylethanone (**3a-d**) in 91-94% yield. The singlet signal of 2 protons at δ 5.15-5.17 in the ^{1}H-NMR spectra of **3a-d** indicates the formation of PhO-CH_2-COAr. The results showed the

Scheme I



a. Ar = C_6H_5; b. Ar = 4-ClC_6H_5 ; c. Ar = 4-BrC_6H_5; d. Ar = 4-MeOC_6H_5

* Corresponding author. E-mail: enchwa@kmu.edu.tw

success of the simple *O*-alkylation. Subsequently, the Wittig reactions of **3a-d** and methylenetriphenylphosphorane *in situ* generated from the reaction of methyltriphenylphosphonium bromide (MTPPB) and potassium *tert*-butoxide at 0 °C afforded 3-(2-allylphenoxy)-2-(4-substituted phenyl)-prop-1-ene (**4a-d**), respectively, in yields of 90-92%. The disappearance of carbonyl group in IR spectra and the appearance 2 doublet signals of 1 proton of **4a-d** at 5.56-5.72 and 5.67-5.82 with coupling constant J = 0.8-1.2 Hz in ^{1}H-NMR spectra indicate the formation of the methylene group. Moreover, the spectral data ^{13}C-NMR, MS, and HRMS are all consistent with the structures of **4a-d**. Finally, **4a-d** was subjected to RCM by the utilization of Grubbs catalyst (2nd generation) in dichloromethane to give the desired 3-aryl-1-benzoxepines (**5a-d**) in the yields of 50-55%, respectively. The structures of **5a-d** are supported by their spectroscopic data including ^{1}H-NMR, ^{13}C-NMR, MS, and HRMS. In addition, in the ^{1}H-NMR spectra, protons of H-2 coupling with H-4 and H-5 exhibited doublet triplet signals with coupling constant J 2.0-2.2, 2.0-2.2 Hz; proton of H-4 coupling with H-5 and H-2 exhibited triplet triplet signals with coupling constant J 5.6-5.8, 2.2-2.0 Hz; protons of H-5 exhibited doublet triplet signals with coupling constant J 5.6-5.8, 2.2-2.0 Hz are all found and consistent with structures **5a-d**, respectively. The selected signals of 3-aryl-2,5-dihydro-1-benzoxepines (**5a-d**) in ^{1}H-NMR are depictedin Table 1.

Thus, we have established a new and concise route for the synthesis of 3-aryl-1-benzoxepines which are all new compounds.

EXPERIMENTAL SECTION

General Procedures

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Gemini-200 or Varian Unity plus 400 Spectrometer. Chemical shifts are indicated in parts per million with respect to TMS. Mass spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model, Gas-Liquid Chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230-400 mesh) for column chromatography and precoated silica gel plates (60 F-254) for TLC was purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

As the general procedure, 2-allylphenol (**1**) was prepared, by heating allyloxybenzene in decaline for 3 hr, in 75% yield.

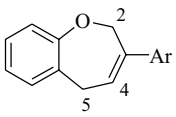
General procedure for the preparation of 2-(2-allylphenoxy)-1-arylethanone (3a-d)

Under the protection of nitrogen, the solution of 2-allylphenol (3.35 g, 25 mmol) dissolved in dry acetone (150 mL) was added K_2CO_3 (4.85 g, 35 mmol) and 2-bromoacetophenones (**2a-d**) (25 mmol) in sequence. The obtained reaction mixture was heated to the reflux for 3-4 hr which was monitored by TLC. After cooling to room temperature, the resulting reaction mixture was filtered to remove the solid. The filtrate which was obtained was concentrated *in vacuo* to remove the solvent. The resulting residue was purified by column chromatography (ethyl acetate: *n*-hexane = 1: 10) to provide pure **3a-d**, respectively.

2-(2-Allylphenoxy)-1-phenylethanone (3a)

(5.9 g, 94%) was obtained as colorless crystal, mp 66~65 °C, R_f = 0.42 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.37 (d, J = 6.6 Hz, 2H, ArC$\underline{H}_2$CH=CH_2), 4.91-5.00 (m, 2H, ArCH_2CH=C$\underline{H}_2$), 5.15 (s, 2H, ArOCH_2CO), 5.81-6.02 (m, 1H, ArCH_2C$\underline{H}$=CH_2),

Table 1. The typical and selected signals of 3-aryl-2,5-dihydro-1-benzoxepines (**5a-d**) in ^{1}H-NMR spectra



5

a. Ar = C_6H_5;
b. Ar = 4-ClC_6H_5;
c. Ar = 4-BrC_6H_5;
d. Ar = 4-MeOC_6H_5

Compound	H-2	H-4	H-5
5a	5.01 (dt, J = 2.2, 2.2 Hz)	6.20 (tt, J = 5.6, 2.2 Hz)	3.72 (dt, J = 5.6, 2.2 Hz)
5b	4.88 (dt, J = 2.2, 2.2 Hz)	6.10 (tt, J = 5.8, 2.2 Hz)	3.63 (dt, J = 5.8, 2.2 Hz)
5c	4.90 (dt, J = 2.2, 2.2 Hz)	6.13 (tt, J = 5.6, 2.2 Hz)	3.63 (dt, J = 5.6, 2.2 Hz)
5d	4.90 (dt, J = 2.0, 2.0 Hz)	6.04 (tt, J = 5.6, 2.0 Hz)	3.62 (dt, J = 5.6, 2.0 Hz)

6.68 (d, J = 8.0 Hz, 1H, ArH), 6.84 (t, J = 8.0 Hz, 1H, ArH), 7.01-7.14 (m, 2H, ArH), 7.33-7.55 (m, 3H, ArH), 7.90 (dd, J = 8.8, 1.4 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 34.22, 71.17, 111.61, 115.44, 121.49, 127.19, 128.14, 128.64, 129.12, 130.11, 133.63, 134.64, 136.76, 155.67, 194.73; EI-MS (70 eV) *m/z* (rel. intesity, %): 252 (M^+, 2), 234 (6), 145 (13), 134 (9), 133 (100), 106 (9), 105 (56), 91 (12), 77 (23); HRMS (ESI), Calcd for $C_{17}H_{16}O_2Na$: 275.1048. Found: 275.1049.

2-(2-Allylphenoxy)-1-(4-chlorophenyl)ethanone (3b)

(6.6 g, 93%) was obtained as pale yellow liquid, R_f = 0.49 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.43 (d, J = 6.4 Hz, 2H, ArC$\underline{H}_2$CH=CH_2), 5.00-5.05 (m, 2H, ArCH$_2$CH=C$\underline{H}_2$), 5.17 (s, 2H, ArOCH$_2$CO), 5.93-6.03 (m, 1H, ArCH$_2$C$\underline{H}$=CH_2), 6.75 (d, J = 7.8 Hz, 1H, ArH), 6.92 (td, J = 7.8, 0.8 Hz, 1H, ArH), 7.11-7.17 (m, 2H, ArH), 7.43 (d, J = 8.4 Hz, 2H, ArH), 7.93 (d, J = 8.4 Hz, 2H, ArH), ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 34.16, 71.13, 111.42, 115.56, 121.60, 127.26, 128.98, 129.71, 130.21, 132.86, 136.67, 140.14, 155.48, 193.89, EI-MS (70 eV) *m/z* (rel. intesity, %) 288 ([M+2]$^+$, 0.5), 286 (M^+, 1.5), 141 (44), 140 (21), 139 (100), 134 (91), 133 (44), 132 (70), 130 (25); HRMS (ESI), Calcd for $C_{17}H_{15}ClO_2Na$: 309.0658. Found: 309.0657.

2-(2-Allylphenoxy)-1-(4-bromophenyl)ethanone (3c)

(7.6 g, 92%) was obtained as colorless crystal, mp 85~86 °C, R_f = 0.46 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.43 (d, J = 6.4 Hz, 2H, ArC$\underline{H}_2$CH=CH_2), 5.00-5.05 (m, 2H, ArCH$_2$CH=C$\underline{H}_2$), 5.17 (s, 2H, ArOCH$_2$CO), 5.30-6.30 (m, 1H, ArCH$_2$C$\underline{H}$=CH_2), 6.75 (d, J = 8.4 Hz, 1H, ArH), 6.93 (td, J = 7.2, 0.8 Hz, 1H, ArH), 7.12-7.17 (m, 2H, ArH), 7.61 (d, J = 8.8 Hz, 2H, ArH), 7.86 (d, J = 8.8 Hz, 2H, ArH), ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 34.19, 71.19, 111.47, 115.58, 121.66, 127.30, 128.96, 129.02, 129.83, 130.25, 132.01, 133.32, 136.70, 155.52, 194.15, EI-MS (70 eV) *m/z* (rel. intesity, %) 332 ([M+2]$^+$, 0.5), 330 (M^+, 0.5), 185 (17), 183 (18), 134 (17), 133 (100), 131 (11), 105 (18), 91 (15); HRMS (ESI), Calcd for $C_{17}H_{15}BrO_2Na$: 353.0153. Found: 353.0155.

2-(2-Allylphenoxy)-1-(4-methoxyphenyl)ethanone (3d)

(6.5 g, 92%) was obtained as pale yellow liquid, R_f = 0.27 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.45 (d, J = 6.6 Hz, 2H, ArC$\underline{H}_2$CH=CH_2), 3.81 (s, 3H, ArOCH$_3$), 5.00-5.05 (m, 2H, ArCH$_2$CH=C$\underline{H}_2$), 5.16 (s, 2H, ArOC$\underline{H}_2$CO), 5.91-6.11 (m, 1H, ArOCH$_2$C$\underline{H}$=CH_2), 6.75 (d, J = 8.2 Hz, 1H, ArH), 6.86-6.90 (m, 1H, ArH), 6.91 (d, J = 8.8 Hz, 2H, ArH), 7.05-7.16 (m, 2H, ArH), 7.96 (d, J = 8.8 Hz, 2H, ArH), ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 34.15, 55.30, 70.93, 111.51, 113.75, 113.86, 115.35, 121.24, 127.10, 128.89, 129.91, 130.40, 136.72, 155.66, 163.78, 193.06; EI-MS (70 eV) *m/z* (rel. intesity, %) 282 (M^+, 0.5), 150 (28), 136 (9), 135 (100), 133 (14), 121 (6), 107 (6), 77 (16); HRMS (ESI), Calcd for $C_{18}H_{18}O_3Na$: 305.1154. Found: 305.1153.

General procedure for the preparation of 1-aryloxy-2-phenyl-1-propenes (4a-d)

Under the protection of N_2, the suspension of MTPPB (9.0 g, 25.2 mmol) in THF (100 mL) was cooled in ice-bath and was added *t*-BuOK (3.03 g, 27.0 mmol) in portions. Then, the reaction mixture was stirred at 0 °C for 30 min. To this cooled solution, **3a-e** (20.0 mmol) in THF (40 mL) was added in drops and stirred for 4 hr. Then, the resulting mixture was quenched with water and extracted with CH_2Cl_2 (50 mL × 5). The organic layer was combined and washed with brine (50 mL × 2), and then was concentrated *in vacuo* to give crude **4a-d** which was further purified from silica gel column chromatography (ethyl acetate: *n*-hexane = 1: 10) to give pure **4a-d**.

1-Allyl-2-(2-phenylallyloxy)benzene (4a)

(4.51 g, 90%) was obtained as pale yellow liquid, R_f = 0.68 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.62 (d, J = 6.6 Hz, 2H, ArC$\underline{H}_2$CH=CH_2), 5.10 (s, 2H, ArOCH$_2$), 5.20-5.30 (m, 2H, ArCH$_2$CH=C$\underline{H}_2$), 5.72 (d, J = 1.2 Hz, 1H, ArOCH$_2$C=C$\underline{H}_a$H$_b$), 5.82 (d, J = 1.2 Hz, 1H, ArOCH$_2$C=CH$_a$$\underline{H}_b$), 6.09-6.29 (m, 1H, ArCH$_2$C$\underline{H}$=CH_2), 7.11-7.19 (m, 2H, ArH), 7.38-7.41 (m, 2H, ArH), 7.53-7.61 (m, 3H, ArH), 7.67-7.72 (m, 2H, ArH), ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 34.39, 69.72, 111.64, 114.21, 115.29, 120.80, 126.03, 127.19, 127.87, 128.37, 129.03, 129.85, 136.89, 138.47, 143.31, 156.11; EI-MS (70 eV) *m/z* (rel. intesity, %) 250 (M^+, 11), 209 (25), 133 (24), 132 (71), 131 (55), 117 (44), 115 (100), 91 (41); HRMS (EI), Calcd for $C_{18}H_{18}O$: 250.1358. Found: 250.1361.

1-Allyl-2-[(2-(4-chlorophenyl)allyloxy)]benzene (4b)

(4.65 g, 91%) was obtained as pale yellow liquid, R_f = 0.66 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.45 (d, J = 6.6 Hz, 2H, ArC$\underline{H}_2$CH=CH_2), 4.95 (s, 2H, ArOCH$_2$), 5.06-5.13 (m, 2H, ArCH$_2$CH=C$\underline{H}_2$) 5.59 (d, J = 1.0 Hz, 1H, ArOCHC=C$\underline{H}_a$CH$_b$), 5.68 (d, J = 1.0 Hz, 1H, ArOCHC=CH$_a$C$\underline{H}_b$), 5.92-6.13 (m, 1H, ArCH$_2$C$\underline{H}$=CH_2), 6.98-7.07 (m, 2H, ArH), 7.25-7.36 (m, 2H, ArH), 7.38-7.52 (m, 4H, ArH), ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 34.32, 69.53, 111.52, 114.98, 115.36, 120.93, 126.45, 127.21, 127.35, 128.49, 128.94, 129.93, 133.72, 136.77, 142.25,

155.98, EI-MS (70 eV) *m/z* (rel. intesity, %) 284 (M^+, 7), 243 (17), 133 (18), 132 (73), 131 (55), 125 (17), 116 (94), 115 (100); HRMS (EI), Calcd for $C_{18}H_{17}ClO$: 284.0968. Found: 284.0967.

1-Allyl-2-[(2-(4-bromophenyl)allyloxy)]benzene (4c)

(5.90 g, 90%) was obtained as pale yellow liquid, R_f = 0.67 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.48 (d, *J* = 5.4 Hz, 2H, $ArC\underline{H}_2CH=CH_2$), 4.97 (s, 2H, $ArOCH_2$), 5.13 (m, 2H, $ArCH_2CH=C\underline{H}_2$) 5.63 (d, *J* = 0.8 Hz, 1H, $ArOCHC=C\underline{H}_aCH_b$), 5.71 (d, *J* = 0.8 Hz, 1H, $ArOCHC=CH_aC\underline{H}_b$), 5.95-6.15 (m, 1H, $ArCH_2C\underline{H}=CH_2$), 7.00-7.09 (m, 2H, ArH), 7.28-7.33 (m, 2H, ArH), 7.42-7.47 (m, 2H, ArH), 7.56-7.62 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 34.30, 69.74, 111.52, 115.07, 115.36, 120.91, 121.89, 127.21, 127.67, 128.94, 129.93, 131.45, 136.76, 137.24, 142.29, 155.95; EI-MS (70 eV) *m/z* (rel. intesity, %) 330 ($[M+2]^+$, 51), 328 (53), 234 (44), 208 (43), 132 (74), 131 (51), 116 (100), 115 (61); HRMS (EI), Calcd for $C_{18}H_{17}BrO$: 328.0463. Found: 328.0460.

1-Allyl-2-[(2-(4-methoxyphenyl)allyloxy)]benzene (4d)

(5.15 g, 92%) was obtained as pale yellow liquid, R_f = 0.51 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.54 (d, *J* = 6.6 Hz, 2H, $ArC\underline{H}_2CH=CH_2$), 3.93 (s, 3H, $ArOCH_3$), 5.01 (s, 2H, $ArOCH_2$), 5.14-5.23 (m, 2H, $ArCH_2CH=C\underline{H}_2$), 5.56 (d, *J* = 0.8 Hz, 1H, $ArOCHC=C\underline{H}_aCH_b$), 5.67 (d, *J* = 0.8 Hz, 1H, $ArOCH_2C=CH_aC\underline{H}_b$), 6.02-6.22 (m, 1H, $ArOCH_2C\underline{H}=CH_2$), 7.00-7.11 (m, 2H, ArH), 7.03 (d, *J* = 8.8 Hz, 1H, ArH), 7.32 (d, *J* = 7.6 Hz, 1H, ArH), 7.37-7.38 (m, 1H, ArH), 7.57 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 34.35, 55.10, 69.81, 111.63, 112.56, 113.70, 115.25, 120.72, 127.10, 127.15, 128.96, 129.77, 130.84, 136.87, 142.55, 156.13, 159.37; EI-MS (70 eV) *m/z* (rel. intesity, %) 280 (M^+, 14), 239 (19), 149 (60), 148 (100), 133 (19), 131 (21), 115 (27), 91 (50); HRMS (EI), Calcd for $C_{19}H_{20}O_2$: 280.1463. Found: 280.1462.

General procedure for the preparation of 4-aryl-2,5-dihydro-1-benzoxepines (5a-d)

The solution of **4** (**a-d**) (3.0 mmol) which was dissolved in CH_2Cl_2 (80 mL) was added Grubbs' catalyst (II) (0.08 g, 0.097 mol). The reaction mixture was stirred at room temperature for 24 h. Afterward, the resulting mixture was passed through a short silica gel column to remove the catalyst and then concentrated *in vacuo* to remove the solvent. The obtained residue was purified from silica gel column chromatography (ethyl acetate: *n*-hexane = 1: 15) to give pure **5a-d**.

3-Phenyl-2,5-dihydro-1-benzoxepine (5a)

(0.37 g, 55%) was obtained as colorless liquid, R_f = 0.63 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.72 (dt, *J* = 5.6, 2.2 Hz, 2H, H-5), 5.01 (dt, *J* = 2.2, 2.2 Hz, 2H, H-2), 6.20 (tt, *J* = 5.6, 2.2 Hz, 1H, H-4), 7.08-7.21 (m, 4H, ArH), 7.24-7.42 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 31.54, 72.59, 121.00, 123.87, 124.65, 126.03, 127.29, 127.93, 128.34, 128.80, 134.63, 138.46, 140.17, 158.54; EI-MS (70 eV) *m/z* (rel. intesity, %) 222 (M^+, 77), 221 (49), 207 (65), 194 (53), 178 (39), 165 (18), 152 (12), 145 (36), 131 (100), 115 (40), 107 (24), 91 (56), 131 (100), 115 (39), 91 (56), 77 (28), 63 (11), 51 (20); HRMS (EI), Calcd for $C_{16}H_{14}O$: 222.1045. Found: 222.1045.

3-(4-Chlorophenyl)-2,5-dihydro-1-benzoxepine (5b)

(0.38 g, 50%) was obtained as colorless liquid, R_f = 0.61 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.63 (dt, *J* = 5.8, 2.2 Hz, 2H, H-5), 4.88 (dt, *J* = 2.2, 2.2, 2H, H-2), 6.10 (tt, *J* = 5.8, 2.2, 1H, H-4), 7.01-7.05 (m, 2H, ArH), 7.06-7.15 (m, 2H, ArH), 7.18-7.29 (m, 4H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 31.54, 72.39, 121.04, 121.27, 124.02, 125.35, 127.36, 128.06, 128.54, 128.86, 134.44, 137.47, 139.00, 158.42; EI-MS (70 eV) *m/z* (rel. intesity, %) 258 ($[M+2]^+$, 17), 256 (M^+, 50), 241 (44), 221 (47), 220 (32), 178 (30), 145 (30), 131 (100), 91 (33); HRMS (EI), Calcd for $C_{16}H_{13}ClO$: 256.0655. Found: 256.0657.

3-(4-Bromophenyl)-2,5-dihydro-1-benzoxepine (5c)

(0.47 g, 52%) was obtained as colorless liquid, R_f = 0.62 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.63 (dt, *J* = 5.6, 2.2 Hz, 2H, H-5), 4.90 (dt, *J* = 2.2, 2.2 Hz, 2H, H-2), 6.13 (tt, *J* = 5.6, 2.2 Hz, 1H, H-4), 7.03-7.29 (m, 4H, ArH), 7.13 (d, *J* = 8.8 Hz, 2H, ArH), 7.44 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 31.54, 77.00, 121.03, 124.04, 125.38, 127.68, 128.06, 128.84, 131.48, 134.41, 137.48, 139.05, 158.42, 179.59; EI-MS (70 eV) *m/z* (rel. intesity, %) 302 ($[M+2]^+$, 15), 300 (M^+, 15), 221 (53), 220 (45), 204 (28), 145 (34), 132 (30), 131 (100); HRMS (EI), Calcd for $C_{16}H_{13}BrO$: 300.0150. Found: 300.0147.

3-(4-Methoxyphenyl)-2,5-dihydro-1-benzoxepine (5d)

(0.41 g, 54%) was obtained as colorless liquid, R_f = 0.46 (ethyl acetate: *n*-hexane = 1: 10), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.62 (dt, *J* = 5.6, 2.0 Hz, 2H, H-5), 3.79 (s, 3H, $ArOCH_3$), 4.90 (dt, *J* = 2.0, 2.0 Hz, 2H, H-2), 6.04 (tt, *J* = 5.6, 2.0 Hz, 1H, H-4), 6.83 (d, *J* = 9.2 Hz, 2H, ArH), 7.04 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H,

ArH), 7.13 (dd, J = 7.6, 1.6 Hz, 1H, ArH), 7.21 (td, J = 7.6, 1.6 Hz, 1H, ArH), ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 31.44, 55.24, 72.72, 113.74, 113.98, 121.03, 123.40, 123.94, 127.16, 127.84, 127.93, 128.78, 137.82, 158.52, 158.93, EI-MS (70 eV) *m/z* (rel. intesity, %) 252 (M^+, 67), 251 (31), 237 (77), 144 (38), 132 (31), 131 (100), 121 (77), 108 (47); HRMS (EI), Calcd for $C_{17}H_{16}O_2$: 252.1150. Found: 252.1153.

ACKNOWLEDGEMENT

Financial support (Grant No.: NSC-97-2113-M-037-001) from NSC, Taiwan is gratefully acknowledged.

Received June 25, 2008.

REFERENCES

1. TenBrink, R. E.; McCall, J. M.; Pals, D. T.; McCall, R. B.; Orley, J.; Humphrey, S. J.; Wendling, M. G. *J. Med. Chem.* **1981**, *24*, 64-67.
2. Engler, M.; Anke, T.; Sterner, O.; Brandt, U. *J. Antibiot.* **1997**, *50*, 325-329.
3. Vishnu, K. T.; Sanjay, R. *Lett. Drug Des. Discov.* **2005**, *2*, 36-39.
4. Shiraishi, M.; Aramaki, Y.; Seto, M.; Imoto, H.; Nishikawa, Y.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Nishimura, O.; Baba, M.; Fujino, M. *J. Med. Chem.* **2000**, *43*, 2049-2063.
5. Yamaguchi, S.; Furihata, K.; Miyazawa, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett*. **2000**, *41*, 4787-4790.
6. Baird, K. J.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, *8*, 1820-1825.
7. (a) Bravo, P.; Ticozzi, C.; Fronza, G.; Bernardi, R.; Maggi, D. *Gazz. Chim. Ital.* **1979**, *109*, 137-143. (b) Bravo, P.; Ticozzi, C.; Maggi, D. *J. Chem. Soc*., *Chem. Commun*. **1976**, *19*, 789-790.
8. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041.
9. (a) Clavier, H.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 8029-8036. (b) Han, S.-H.; Hirakawa, T.; Fukuba, T.; Hayase, S.; Kawatsura, M.; Itoh, T. *Tetrahedron*: *Asymmetry* **2007**, *18*, 2484-2490. (c) Roy, A.; Biswas, B.; Sen, P. K.; Venkateswaran, R. V. *Tetrahedron Lett*. **2007**, *48*, 6933-6936. (d) Chattopadhyay, S. K.; Biswas, T.; Maity, S. *Synlett* **2006**, *14*, 2211-2214.
10. (a) Wang, E. C.; Hsu, M. K.; Lin, Y. L.; Huang, K. S. *Hetreocycles* **2002**, *57*, 1997-2010. (b) Wang, E. C.; Wang, C. C.; Hsu, M. K.; Huang, K. S. *Hetreocycles* **2002**, *57*, 2021-2034. (c) Tsai, T. W.; Wang, E. C.; Huang, K. S.; Li, S. R.; Wang, Y. F.; Lin, Y. L.; Chen, Y. H. *Heterocycles* **2004**, *63*, 1771-1781. (d) Tsai, T. W.; Wang, E. C.; Li, S. R.; Chen, Y. H.; Lin, Y. L.; Wang, Y. F.; Huang, K. S. *J. Chin. Chem. Soc.* **2004**, *51*, 1307-1318. (e) Huang, K. S.; Li, S. R.; Wang, Y. F.; Lin, Y. L.; Chen, Y. H.; Tsai, T. W.; Yang, C. H.; Wang, E. C. *J. Chin. Chem. Soc.* **2005**, *52*, 159-167. (f) Wang, E. C.; Lin, Y. L.; Chen, H. M.; Li, S. R.; Tsai, J. C.; Kabuto, C.; Takeuchi, Y. *Heterocycles* **2006**, *68*, 125-136. (g) Li, S. R.; Chen, L. Y.; Tsai, J. C.; Tzeng, J. Y.; Tsai, I. L.; Wang, E. C. *Tetrahedron Lett.* **2007**, *48*, 2139-2141. (h) Li, S. R.; Chen, H. M.; Chen, L. Y.; Tsai, J. C.; Chen, P. Y.; Hsu, S. C. N.; Wang, E. C. *ARKIVOC*, **2008**, *2*, 172-182. (i) Tsai, J. C.; Li, S. R.; Chen, L. Y.; Chen, P. Y.; Hsu, S. C. N.; Lin, C. N.; Wang, E. C. *ARKIVOC*, **2008**, *12*, 205-217.