A Facile Synthesis of Cyclopenta[*d*][1,2]oxazines through [6+4] Cycloaddition Reaction

Sung Yun Cho,* Seung Kyu Kang, Jin Hee Ahn, Jae Du Ha, Gyu Hwan Yon, and Joong-Kwon Choi

Bio-Medicinal Science Division, Korea Research Institute of Chemical Technology, Yuseong-gu, Daejeon 305-600, Korea
**E-mail: sycho@krict.re.kr*
Received May 15, 2006

Key Words : Cyclopenta[*d*][1,2]oxazine, Cycloaddition

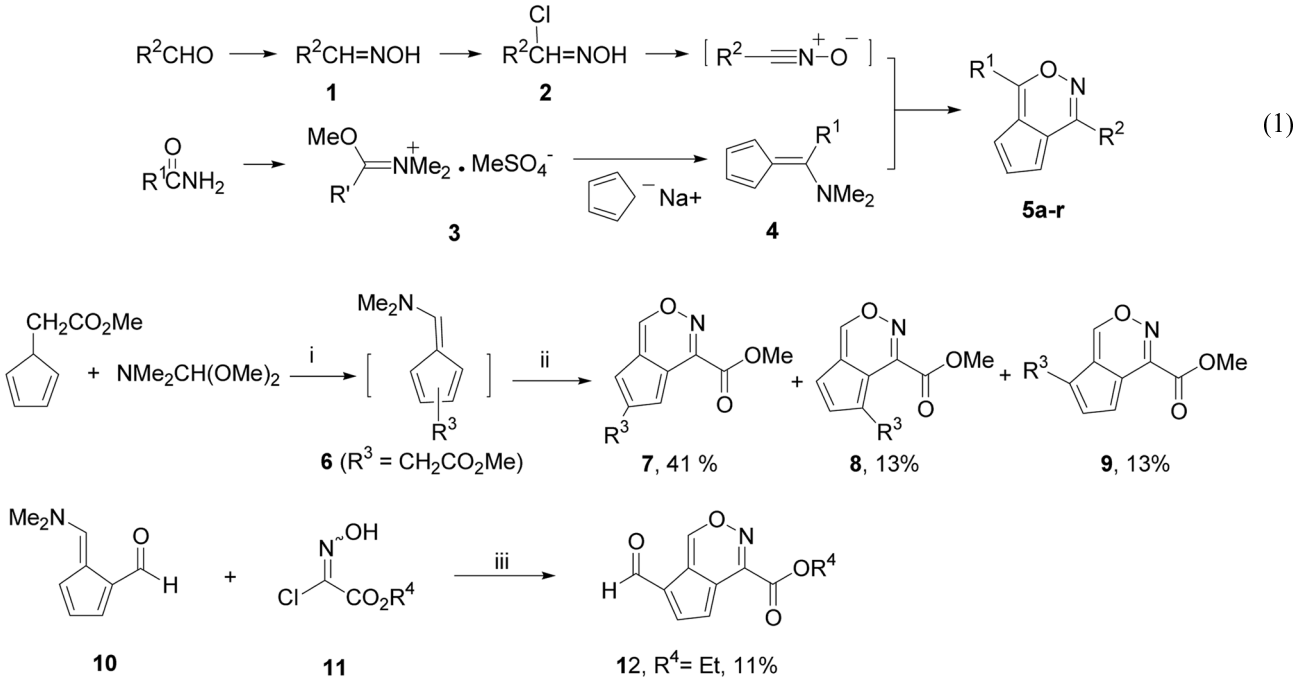
Functionalized 1,2-oxzines[1] are known to exhibit various pharmacological properties, such as antibacterial activity,[2] acetylcholinesterase inhibitory activity,[3] protein tyrosine phosphatase inhibitory activity.[4] They also occur as a key structural subunit in biologically active natural products.[5]

However, there have been only limited methods for the synthesis of cyclopenta[*d*][1,2]oxazines and their derivatives. Linn and Sharkey[6] reported the first practical synthesis of cyclopenta[*d*][1,2]oxazine by use of benzoylated cyclopentadiene. Lloyd and co-workers[7] also reported the synthesis of cyclopenta[*d*][1,2]oxazine by reaction of diaroylcyclopentadienes with hydroxylamine. The reaction of benzonitrile oxide with fulvene was known to yield both 1 : 1 and 2 : 1 adducts.[8]

Herein, we report the first example of a facile and convenient synthesis of various cyclopenta[*d*][1,2]oxazines starting from chlorooxime and fulvene through [6+4] cycloaddition. In an effort to pursue of PTP1B inhibitors,[9] a convenient synthesis of functionalized cyclopenta[*d*][1,2]-oxazine derivatives was required. Fulvenes were obtained from the reaction of dimethyl sulfate salt of dimethylamides **3** and cyclopentadienyl sodium as cited.[10]

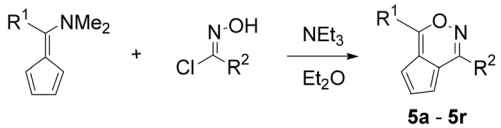
Howe and co-workers[11] reported a convenient synthesis of chlorooximes by the use of *N*-chlorosuccinimide in DMF in place of chlorine, avoiding the use of hazardous chlorine and ring chlorination as side reactions with benzaldoximes that contain electron-donating substituents. Based on this efficient synthetic methodology for chlorooximes **2**, we could achieve a facile synthesis of various cyclopenta[*d*][1,2]-oxazines **5** by the cyclocondensation of **2** with fulvene **4** in the presence of triethylamine (eq. 1). The introduction of alkyl or aromatic substituents at 1-position could be accomplished by the use of substituted fulvenes or chlorooximes as given in Table 1. Diethyl ether was the solvent of choice over dichloromethane (41% yield, **5a**) for cycloaddition and all of the reaction afforded the corresponding cyclopenta[*d*]-[1,2]oxazines in moderate yields. The relatively low yields for **5c**, **5i**, and **5l** were presumably due to the deprotection of protective group, *t*-butyl or acetyl group. Cycloadditions of chlorooxime with fulvene are affected by the steric factor of the substituents (**5o-5r**), as the introduction of substituent (R^1) lowered the reaction yield.

This method was then applied to substituted fulvenes **6**,[12] *in situ* generated from the corresponding cyclopentadiene, and **10**[13] as shown in Scheme 1. As can be seen, carbometh-

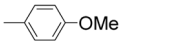
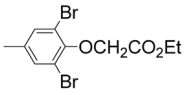
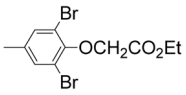
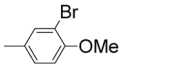
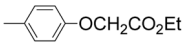
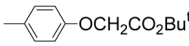
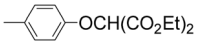
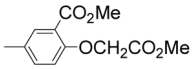
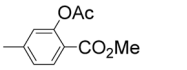
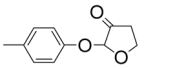
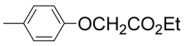
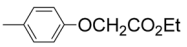
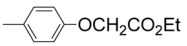
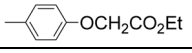


Scheme 1. *Reagents and conditions*: i) 60 °C; ii) **2** (R = CO_2Me), NEt_3; iii) **11** (R^4 = Me) NEt_3/ether.

Table 1. Cycloaddition of chlorooximes and fulvenes



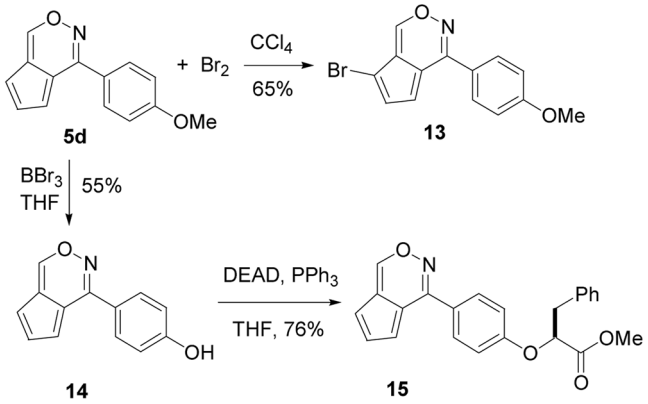
5a - 5r

No	R^1	R^2	Yield (%)
5a	H	$-CO_2Me$	65
5b	H	$-CO_2Et$	80
5c	H	$-CO_2Bu^t$	42
5d	H		58
5e	H		58
5f	Me		77
5g	Me		74
5h	H		67
5i	H		45
5j	H		52
5k	H		57
5l	H		51
5m	H		62
5n	Me		52
5o	4-MeOPh		42
5p	4-EtOPh		45
5q	4-PhOPh		48
5r	Ph		47

oxy group is readily introduced, although with low regioselectivity, to cyclopenta[*d*][1,2]oxazine skeleton **7**. The other possible isomers were also isolated and identified (**8**, 13%; **9**, 13%). Compound **12** was also prepared from the corresponding substrate **10** in low yield.

Regioselective introduction of bromine to parent cyclopenta[*d*][1,2]oxazines was easily accomplished by the treatment of **5d** with bromine in carbon tetrachloride to afford 7-bromocyclopenta[*d*][1,2]oxazine **13** in moderate yield (Scheme 2).

For the derivatization of the parent cyclopenta[*d*][1,2]-oxazines, Mitsunobu reaction was applied to **14**, the demethylated product of **5d**, to afford the alkylated product **15** in moderate yield. The successful utilization of cyclo-



Scheme 2

addition of chlorooximes and *N,N*-dimethylaminofulvene to construct various cyclopenta[*d*][1,2]oxazines in this reaction provides a convenient approach to the useful structural derivatives of cyclopenta[*d*][1,2]oxazine. Ongoing studies are being directed toward the further elaboration of cyclopenta[*d*][1,2]-oxazine derivatives, extending the scope of parent compound to improve the corresponding biological activities.

Experimental Section

Cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (5a). To a stirred solution of cyclopenta-2,4-dienylidenmethyl dimethylamine (6.7 g, 55 mmol) and chlorohydroxyiminoyl acetic acid methyl ester (6 g, 55 mmol) in ether was added dropwise triethylamine (7.6 mL, 55 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, and poured into water. The resulting mixture was extracted with ethyl acetate and organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **5a** as yellow solid (6.3 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 1.2 Hz, 1H), 7.42 (m, 2H), 7.10 (dd, J = 3.6, 1.8 Hz, 1H), 4.15 (s, 3H); MS m/e (relative intensity) 177 (100, M^+), 132 (28), 104 (50).

Likewise the following compounds were prepared.

Cyclopenta[*d*][1,2]oxazine-4-carboxylic acid ethyl ester (5b). IR (KBr) 1727, 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.00 (d, J = 1.2 Hz, 1H), 7.45 (m, 2H), 7.12 (dd, J = 4.1, 1.2 Hz, 1H), 4.56 (q, J = 7.3 Hz, 2H), 1.50 (t, J = 7.3 Hz, 3H); MS *m/e* (relative intensity) 191 (M^+, 100), 119 (52), 118 (60).

Cyclopenta[*d*][1,2]oxazine-4-carboxylic acid *tert*-butyl ester (5c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 1.2 Hz, 1H), 7.39 (m, 2H), 7.09 (dd, J = 3.4, 1.2 Hz, 1H), 1.75 (s, 9H); MS *m/e* (relative intensity) 219 (M^+, 1), 176 (0.3), 118 (2.9), 57 (100).

4-(4-Methoxyphenyl)cyclopenta[*d*][1,2]oxazine (5d). ^{1}H NMR ($CDCl_3$) δ9.01 (d, J = 1.2 Hz, 1H), 7.44-7.25 (m, 4H), 7.15 (m, 2H), 7.07 (dd, J = 4.4, 1.2 Hz, 1H), 4.84 (s, 3H); MS *m/e* (relative intensity) 225 (50, M^+), 182 (24), 154 (15).

(2,6-Dibromo-4-cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy)-

acetic acid ethyl ester (5e). IR (KBr) 1713, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ9.1 (d, J = 1.2 Hz , 1H), 8.25 (s, 2H), 7.39 (m, 1H), 6.98 (m, 1H), 4.64 (s, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

[2,6-Dibromo-4-(1-methyl cyclopenta[*d*][1,2]oxazin-4-yl)phenoxy]acetic acid ethyl ester (5f). ^1H NMR (300 MHz, $CDCl_3$) δ8.06 (s, 2H), 7.31 (m, 1H), 7.13 (dd, J = 4.4, 1.2 Hz, 1H), 6.90 (dd, J = 3.0, 1.2 Hz, 1H), 4.69 (s, 2H), 4.35 (q, J = 7.1 Hz, 2H), 2.85 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); MS *m/e* (relative intensity) 471 (M^+, 57), 454 (50), 382 (100), 288 (15), 117 (37).

4-(3-Bromo-4-methoxyphenyl)-1-methylcyclopenta[*d*]-[1,2]oxazine (5g). ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.81 (m, 2H), 7.08 (m, 2H), 6.90 (dd, J = 2.8, 1.0 Hz, 1H), 3.98 (s, 3H), 2.84 (s, 3H); MS *m/e* (relative intensity) 320 (M^+, 14), 302 (100), 208 (16), 152 (17), 63 (49).

(4-Cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy) acetic acid ethyl ester (5h). IR (KBr) 1752, 1621, 1607, 1513, 1409 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 1.2 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.37 (dd, J = 4.5, 2.7 Hz, 2H), 7.12 (m, 3H), 6.99 (m, 1H), 4.75 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); MS *m/e* (relative intensity) 297 (60, M^+), 210 (100).

(4-Cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy)acetic acid *tert*-butyl ester (5i). IR (KBr) 1732, 1621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.25 (dd, J = 4.8, 3.0 Hz, 1H), 7.07 (m, 3H), 6.95 (d, J = 1.2 Hz, 1H), 5.20 (s, 2H), 1.42 (s, 9H); MS *m/e* (relative intensity) 269 (M^+-57, 13), 210 (17), 166 (16).

2-(4-Cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy)malonic acid diethyl ester (5j). ^1H NMR (300 MHz, $CDCl_3$) δ9.00 (s, 1H), 7.33 (m, 7H), 5.30 (s, 1H), 4.35 (m, 4H), 1.33 (m, 6H); MS *m/e* (relative intensity) 370 (M^+, 21), 224 (15), 210 (100), 182 (12).

(2-Cyclopenta[*d*][1,2]oxazin-4-yl-5-methoxycarbonyl-methoxyphenoxy)acetic acid methyl ester (5k). ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.57 (s, 1H), 7.32 (m, 2H), 7.04 (m, 1H), 6.78 (m, 1H), 6.58 (m, 1H), 4.78 (s, 2H), 4.58 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H).

2-Acetoxy-5-cyclopenta[*d*][1,2]oxazin-4-ylbenzoic acid methyl ester (5l). ^1H NMR (300 MHz, $CdCl_3$) δ9.03 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 2.3 Hz, 1H), 8.12 (dd, J = 8.5, 2.4 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.14 (dd, J = 4.4, 1.2 Hz, 1H), 6.99 (dd, J = 2.4, 1.2 Hz, 1H), 3.91 (s, 3H), 2.41 (s, 3H).

3-(4-Cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy)dihydro-furan-2-one (5m). ^1H NMR (300 MHz, $CDCl_3$) δ9.00 (d, J = 1.2 Hz, 1H), 7.82 (m, 2H), 7.33 (m, 1H), 7.21 (m, 2H), 7.17 (m, 1H), 6.96 (m, 1H), 5.06 (t, J = 7.7 Hz, 1H), 4.49 (m, 2H), 2.66 (m, 2H); MS *m/e* (relative intensity) 296 (M^+, 13), 210 (59), 154 (43), 63 (41), 41 (100).

[4-(1-Methylcyclopenta[*d*][1,2]oxazin-4-yl)phenoxy]acetic acid ethyl ester (5n). IR (KBr) 3077, 3014, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.83 (m, 2H), 7.25 (m, 2H), 7.09 (m, 2H), 6.88 (m, 1H), 4.69 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 2.81 (s, 3H), 1.35 (t, J = 7 Hz, 3H); MS m/z (relative intensity) 373 (M^+, 46), 296 (100), 268 (45), 209 (36).

4-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]-1-(4-methoxy-benzyl)cyclopenta[*d*][1,2] oxazine (5o). ^1H NMR (300 MHz, $CDCl_3$) δ7.76 (d, J = 8.6 Hz, 2H), 7.32 (m, 3H), 7.01 (m, 7H), 4.37 (s, 2H), 3.78 (s, 3H), 1.03 (s, 9H), 0.29 (s, 6H); MS m/z (relative intensity) 445 (M^+, 23), 325 (22), 252 (7), 135 (13), 121 (22), 73 (25).

{4-[1-(4-Ethoxybenzyl)cyclopenta[*d*][1,2]oxazin-4-yl]-phenoxy}acetic acid ethyl ester (5p). IR (KBr) 2976, 1736, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.81 (d, J = 8.6 Hz, 2H), 7.32 (m, 4H), 7.10 (m, 2H), 6.911 (m, 3H), 4.88 (s, 2H), 4.37 (m, 6H), 1.31 (m, 4H); MS m/z (relative intensity) 373 (M^+, 17), 296 (100), 268 (27), 107 (28).

{4-[1-(4-Benzyloxyphenyl)cyclopenta[*d*][1,2]oxazin-4-yl]phenoxy} acetic acid ethyl ester (5q). ^1H NMR (300 MHz, $CDCl_3$) δ8.12 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 7.2 Hz, 2H), 7.31 (m, 12H), 5.18 (s, 2H), 4.69 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 1.26 (t, 3H); MS m/z (relative intensity) 465 (M^+, 98), 388 (59), 360 (27), 207 (15), 91 (100).

[4-(1-Phenylcyclopenta[*d*][1,2]oxazin-4-yl)phenoxy]acetic acid ethyl ester (5r). ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (m, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.59 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.72 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); MS m/z (relative intensity) 373 (M^+, 100), 286 (77), 258 (18), 207 (220, 139 (250, 77 (30).

6-Methoxycarbonylmethylcyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (7). To a stirred solution of methyl 2,4-cyclopentadienyl-1-acetate (3.4 g, 10 mmol), *N*,*N*-dimethylformamide dimethyl acetal (1.19 g, 10 mmol) was stirred at 60 °C for 1 hr. To a reaction mixture was added dichloromethane (50 mL) and methyl chlorooximido acetate (1.38 g, 19 mmol). The resulting mixture was stirred at room temperature for 1 h, and poured into water (30 mL), and extracted with ethyl acetate (70 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **7** (1.04 g, 41%): mp 93-94 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.33 (s, 1H), 6.95 (s, 1H), 4.05 (s, 3H), 3.82 (s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ170.9, 162.3, 154.3, 146.5, 144.1, 122.5, 119.6, 114.2, 111.9, 53.0, 52.0, 35.9; IR (KBr, cm^{-1}) 3391, 1721, 1196, 1175, 1145, 1090; MS m/z (relative intensity) 249 (M^+, 66), 248 (2), 191 (41), 190 (25), 147 (23), 146 (99), 59 (100).

8 (0.32 g, 13% in yield): ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.23 (d, J = 4.6 Hz, 1H), 7.03 (d, J = 4.6 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 2H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 163.1, 154.6, 149.1, 138.9, 124.1, 123.6, 115.6, 107.1, 53.4, 52.0, 34.4.

9 (0.32 g, 13% in yield); mp. 90-92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ9.02 (s, 1H), 7.26 (d, J = 2.5 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H), 4.02 (s, 3H), 3.80 (s, 2H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0, 162.2, 155.0, 146.8, 136.2, 122.3, 121.4, 117.9, 111.5, 52.9, 52.0, 33.2.

7-Formylcyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (12). To a stirred solution of 1-formyl-6-dimethylaminofulvene (3.4 g, 0.028 mmol) in dichloromethane (50 mL) was added methyl chlorooximido acetate (3.85 g, 0.028 mmol) and triethylamine (2.8 g, 0.028 mmol). The reaction mixture was stirred at room temperature for 13

h. The resulting mixture was poured into ice water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **12** (0.63 g, 11%): mp. 139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 9.73 (d, J = 1.2 Hz, 1H), 8.02 (d, J = 3.3 Hz, 1H), 7.43 (dd, J = 3.3, 1.2 Hz, 2H), 4.58 (q, J = 7.4 Hz, 2H), 1.50 (t, J = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 186.1, 161.3, 159.8, 148.7, 145.3, 127.9, 119.8, 118.3, 117.3, 63.1, 14.1; MS m/z (relative intensity) 219 (M^+, 49), 146 (33), 119 (55), 118 (100), 91 (21), 90 (79).

7-Bromo-4-(4-methoxyphenyl)cyclopenta[*d*][1,2]oxazine (13). To a solution of 4-(4-methoxyphenyl)cyclopenta[*d*]-[1,2]oxazine **5d** (100 mg, 0.35 mmol) in carbon tetrachloride (3 mL) was added bromine (62 mg, 0.39 mmol) at room temperature. The reaction mixture was stirred for 1 h at the same temperature. The resulting mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **13** (102 mg, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.82 (m, 2H), 7.28 (m, 1H), 7.15 (m, 2H), 6.82 (m, 1H), 1.26 (q, J = 7.1 Hz, 3H); MS m/e (relative intensity) 305 (M^+, 61), 303 (59), 290 (34), 288 (28), 196 (25).

4-Cyclopenta[*d*][1,2]oxazin-4-ylphenol (14). To a stirred solution of 4-(4-methoxyphenyl)cyclopenta[*d*][1,2]oxazine **5d** (2.2 g, 9.79 mmol) in dichlomethane (5 mL) was added boron tribromide in dichloromethane (14 mL of 1 M solution, 14 mmol) dropwise at −78 °C and stirred for 13 h at room temperature. The resulting mixture was poured into water, and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **14** (1.7 g, 55%): ^{1}H NMR (300 MHz, $CdCl_3$) δ 9.01 (s, 1H), 7.36-7.25 (m, 3H), 7.10 (dd, J = 4.6, 1.2 Hz, 1H), 6.97-6.86 (m, 2H), 6.68-6.64 (m, 1H), 6.19 (brs, 1H); MS m/e (relative intensity) 211 (M^+, 10), 182 (26), 154 (8), 127 (5).

(s)-2-(4-Cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy)-3-phenyl propionic acid methyl ester (15). To a stirred solution of 4-cyclopenta[*d*][1,2]oxazin-4-yl-phenol **13** (300 mg, 1.38 mmol), (*R*)-2-hydroxy-3-phenyl propionic acid methyl ester (298 mg, 1.68 mmol), triphenylphosphine (726 mg 2.76 mmol) in tetrahydrofuran (5 mL) was added dropwise diisopropylazodicarboxylate (492 mg, 2.76 mmol) at 0 °C and stirred for 12 h at room temperature. The resulting mixture was poured into water, and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **15** (246 mg, 76%): ^{1}H NMR (300 MHz, $CdCl_3$) δ 9.02 (d, J = 1.4 Hz, 1H), 7.41-7.22 (m, 9H), 7.09-7.06 (m, 2H), 6.58-6.56 (m, 1H), 4.81 (t, J = 6.4 Hz, 1H), 3.70 (s, 3H), 3.25 (d, J = 6.6 Hz, 2H).

Acknowledgement. The authors appreciate the financial support of Ministry of Science and Technology of Korea and Bioneer Corporation.

References

1. (a) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 915. (b) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149.
2. (a) D'Andrea, S.; Zheng, Z. B.; DenBleyker, K.; Fung-Tomc, J. C.; Yang, H. K.; Clark, J.; Taylor, D.; Bronson, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*(11), 2834. (b) Lin, Y.; Shao, Z.; Jiang, G.; Zhou, S.; Cai, J.; Vrijmoed, L. L. P.; Jones, E. B. *Tetrahedron* **2000**, *56*, 9607.
3. Yu, Q.-S.; Zhu, X.; Holloway, H. W.; Whittaker, N. F.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2002**, *45*, 3684.
4. (a) Cho, S. Y.; Baek, J. Y.; Han, S. S.; Kang, S. K.; Ha, J. D.; Ahn, J. H.; Lee, J. D.; Kim, K. R.; Cheon, H. G.; Rhee, S. D.; Yang, S. D.; Yon, G. H.; Pak, C. S.; Choi, J.-K. *Bioorg. Med. Chem. Lett.* **2006**, *163*, 499. (b) Cho, S. Y.; Kang, S. K.; Ahn, J. H.; Ha, J. D.; Choi, J.-K. *Tet. Lett.* **2006**, *47*, 5237.
5. (a) Lin, Y.; Shao, Z.; Jiang, G.; Zhou, S.; Cai, J.; Vrijmoed, L. L. P.; Jones, E. B. *Tetrahedron* **2000**, *56*, 9607.
6. Linn, W. J.; Sharkey, W. H. *J. Am. Chem. Soc.* **1957**, *79*, 4970.
7. Lloyd, D.; Preston, N. W. *J. Chem. Soc. (C)* **1970**, 610.
8. (a) Quilico, A.; Grunanger, P.; Mazzini, R. *Gazz. Chim. Ital.* **1952**, *82*, 349. (b) Carmella, P.; Fattini, P.; Grunanger, P. *Tet. Lett.* **1971**, *41*, 3817.
9. (a) Shrestha, S; Hwang, S. Y.; Lee, K.-H.; Cho, H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1138. (b) Shrestha, S.; Lee, K.-H.; Cho, H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1303. (c) Ahn, J. H.; Cho, S. Y.; Ha, J. D.; Kang, S. K.; Jung, S. H.; Kim, H. M.; Kim, S. S.; Kim, K. R.; Cheon, H. G.; Yang, S. D.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1505. (d) Cho, S. Y.; Ahn, J. H.; Ha, J. D.; Kang, S. K.; Baek, J. Y.; Han, S. S.; Shin, E. Y.; Kim, S. S.; Kim, K. R.; Cheon, H. G.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1455. (e) Ahn, J. H.; Cho, S. Y.; Ha, J. D.; Chu, S. Y.; Jung, S. H.; Jung, Y. S.; Baek, J. Y.; Choi, I. K.; Shin, E. Y.; Kang, S. K.; Kim, S. S.; Cheon, H. G.; Yang, S. D.; Choi, J.-K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1941.
10. Hafner, K. H.; Vopel, G. P.; Konig, C. *Org. Synth.* **1973**, *Coll. Vol. 5*, 431.
11. (a) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916. (b) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366.
12. Fujisawa, T; Sakai, K. *Tet. Lett.* **1976**, *17*, 3331.
13. Hafner, K. *Ann.* **1963**, *52*, 661.