Lithiation and Electrophilic Substitution of 8-Chlorodibenz[*b,f*][1,4]-oxazepine-10-*tert*-butylcarbamate: The Preparation of Novel Fused Heterocyclic Derivatives of 8-Chlorodibenzoxazepine

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Lithiation of 8-chlorodibenz[*b,f*][1,4]oxazepine-10-*tert*-butylcarbamate (**1**) is described. Electrophilic substitution of the resulting *N*-Boc dibenzoxazepine α- lithioamine **2** with ketones, aldehydes, nitriles, isocyanates and imines, followed by an *in-situ* cyclization, gave fused carbamates **5-26**, fused 2*H*-imidazol-2-ones **27-29**, fused hydantoins **30-32**, and fused ureas **33-35**, respectively, in 11-66% yield.

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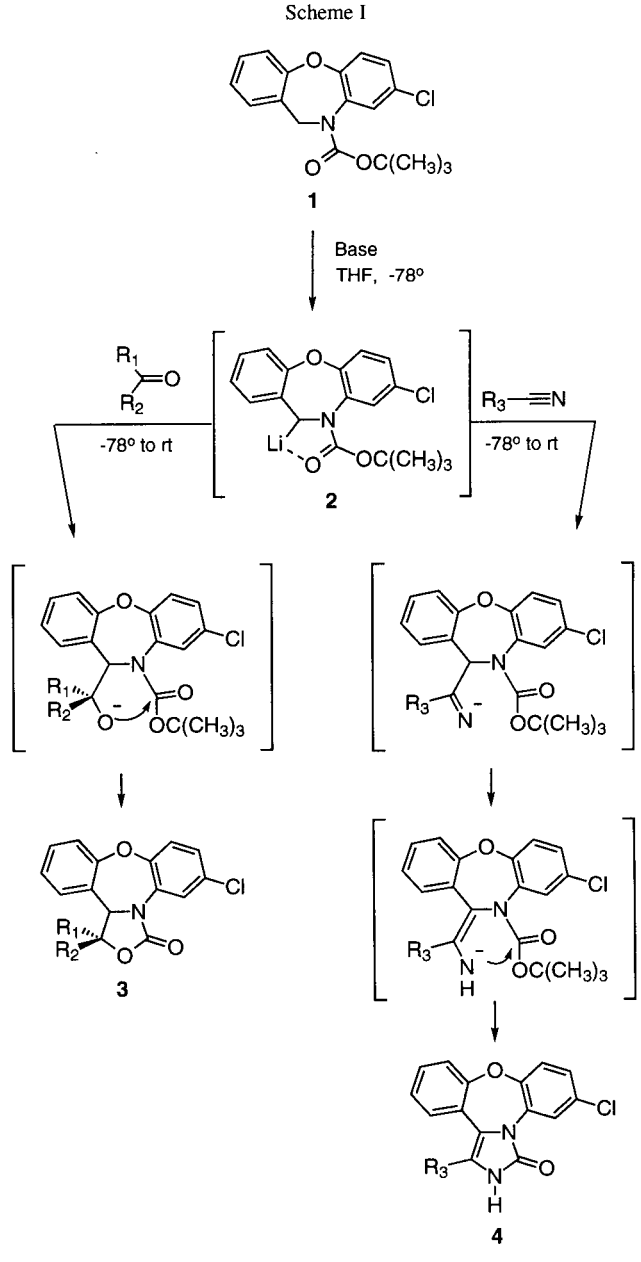
Introduction.

The preparation and elaboration of amines *via* α-lithioamine synthetic equivalents have been developed into very useful synthetic methods [3] and one of the more widely used activating groups employed in this methodology is the *tert*-butoxylcarbonyl (Boc) group [4-9]. Beak and coworkers have used the Boc group in the metalation of secondary amines [4] and primary allylamine [5]; one notable example is their enantioselective lithiation of Boc-pyrrolidine [4c]. In addition, lithiation of Boc-glycine for the preparation of (D,L)-amino acids has been reported by Nicola, Einhorn and Luche [6]. More recently, Greene and coworkers have prepared the Taxotere side chain by using Boc-benzylamine [7].

As part of our continuing efforts in the area of analgesic prostaglandin E_2 antagonists [10], we became interested in preparing dibenzoxazepine analogs with a "tetracyclic core" moiety (*e. g.*, **3** and **4** in Scheme I) for our structure-activity relationship studies. An efficient method of preparing such analogs involves lithiation of 8-chlorodibenz[*b,f*][1,4]oxazepine-10-*tert*-butylcarbamate (**1**) followed by electrophilic substitution and *in-situ* cyclization of the lithium alkoxide or lithium amide with the *tert*-butoxylcarbonyl group, as demonstrated in the general sequence shown in Scheme I.

Recently Hagen and coworkers have published the synthesis of 11-substituted *N*-Boc dibenzoxazepines [10b]. We now wish to report the preparation of novel fused carbamate, fused 2*H*-imidazol-2-one, fused hydantoin and fused urea derivatives of 8-chlorodibenzoxazepine *via* directed lithiation of *N*-Boc dibenzoxazepine **1**.

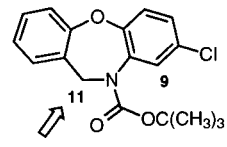
Scheme I



Results and Discussion.

As reported earlier [10b] when *n*-butyllithium was used as the base, a *ca.* 25% of the lithiation occurred at the 9-position of *N*-Boc dibenzoxazepine **1**, while lithium diisopropylamide metalated predominantly at the 11-position. We found that lithiation proceeded regioselectively (90%) at the 11-position by using methyllithium as well based

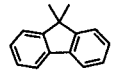
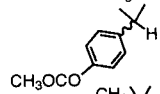
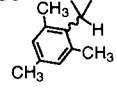
on the proton integration (^{1}H nmr) of the trimethylsilyl (TMS) group in a trimethylsilyl chloride trapping reaction. While *n*-butyllithium was employed in a few initial experiments, a milder base such as lithium diisopropylamide or methyllithium was generally used for achieving the better selectivity for 11-position in the first metalation step. It was desirable to lithiate at the 11-position of **1** in order to obtain the fused heterocyclic derivatives of 8-chlorodibenzoxazepine of our interests, *e. g.*, **3** and **4** as shown in Scheme I.



The *N*-Boc dibenzoxazepine **1** was prepared according to a modification of the literature procedure in 83% yield [10b,11]. Lithiation of **1** was carried out at -78° for 30 minutes with lithium diisopropylamide, methyllithium or *n*-butyllithium as the base. The resulting lithium anion **2** was allowed to react with a variety of electrophiles at -78° followed by warming to ambient temperature overnight. Subsequent cyclization of the lithium alkoxide or lithium amide with the *tert*-butoxylcarbonyl group occurred *in situ* to give the desired 8-chlorodibenzoxazepine derivatives **5-35** in 11-66% yield as summarized in the following tables. All yields reported herein are actual isolated pure compounds which were characterized by ^{1}H nmr, mass spectra and elemental analyses.

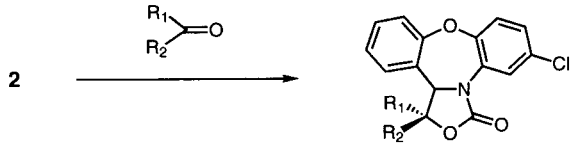
Preparation of Fused Carbamates.

Table I
Reaction of the 11-Lithio-Boc-dibenzoxazepine **2** with Ketones and Aldehydes

Ketone or Aldehyde	Product		R_1 & R_2	Yield (%)
Cyclobutanone	**5**			36
Cyclopentanone	**6**			43
Cyclohexanone	**7**			39
9-Fluorenone	**8**			18
2-Indanone	**9**			11
1-Indanone	**10 & 11**	[a]		7 & 31
α-Tetralone	**12 & 13**	[a]		26 & 8
Benzaldehyde	**14 & 15**	[a]		31 & 35
4-Pyridinecarboxaldehyde	**16 & 17**	[a]		7 & 26
3-Pyridinecarboxaldehyde	**18**	[b]		22
2-Pyridinecarboxaldehyde	**19 & 20**	[a]		30 & 9
3-Thiophenecarboxaldehyde	**21**	[b]		19
2-Furaldehyde	**22**	[b]		15
1-Methylpyrrol-2-carboxaldehyde	**23**	[b]		12
Methyl 4-formyl benzoate	**24 & 25**	[a]		13 & 50
Mesitaldehyde	**26**	[c]		25

[a] Two diastereoisomers were readily separable. [b] Only one diastereoisomer was purified. [c] An inseparable mixture arising from lithiation at the 11- and 9-positions of **1**.

Reaction of the anion **2** with a variety of ketones and aldehydes, followed by an *in-situ* cyclization, gave fused carbamates **5-26** in 11-66% yield after purification by chromatography as shown in Table I. The lower yields observed for **8** and **9** may be due to the steric hindrance of the carbonyl group of 9-fluorenone and the readily enolizable protons of 2-indanone.



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Preparation of Fused 2*H*-Imidazol-2-ones.

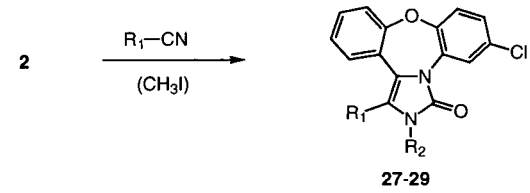
Table II shows the reaction of anion **2** with benzonitrile and hydrocinnamonitrile to give the fused 2*H*-imidazol-2-ones **27** and **29** in 42 and 21% yield, respectively, after purification by chromatography. The addition of iodomethane to the reaction mixture subsequent to the addition of benzonitrile gave *N*-methylated 2*H*-imidazol-2-one **28** in a one-pot reaction sequence in 32% overall yield. Reaction of the anion **2** with phenylacetonitrile, however, failed to provide the desired product, presumably due to rapid proton transfer from relatively acidic benzylic position.

Preparation of Fused Hydantoins.

Similarly, reaction of the anion **2** with several isocyanates gave the corresponding fused hydantoins **30-32** in 44-54% yield after purification by chromatography, as shown in Table III. In contrast to the previous observation with phenylacetonitrile, benzylic protons in benzyl isocyanate appears to have little effect on the overall reaction yield.

Table II

Reaction of the 11-Lithio-Boc-dibenzoxazepine **2** with Nitriles



27-29

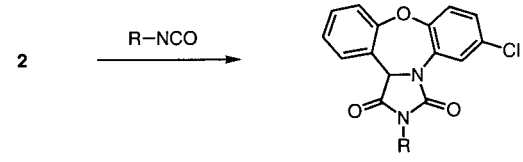
Product	R_1	R_2	Yield (%)
27	Ph	H	42
28	Ph	CH_3	32
29	$PhCH_2CH_2$	H	21

Preparation of Fused Ureas.

The addition of the anion **2** to *N*-bezylidine methylamine or to the 1-position of isoquinoline, followed by cyclization on the *tert*-butoxylcarbonyl group, gave the fused ureas **33** and **34** in 32 and 43% yield, respectively. On the basis of ^1H nmr and thin-layer chromatography, only one diastereoisomer was detected in both reactions. Subsequent hydrogenation of **34** provided the saturated analog **35** in 72% yield.

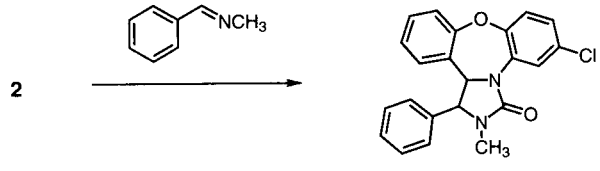
Table III

Reaction of the 11-Lithio-Boc-dibenzoxazepine **2** with Isocyanates

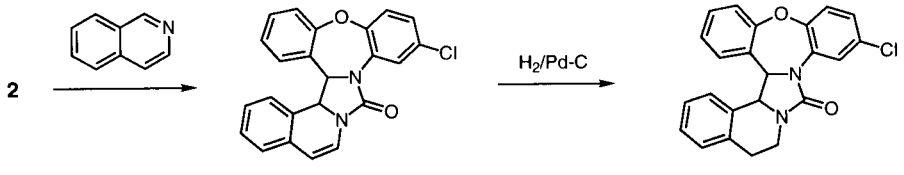


30-32

Product	R	Yield (%)
30	Ph	46
31	$PhCH_2$	44
32	$PhCH_2CH_2$	54



33 (32%)



34 (43%) **35** (72%)

Conclusion.

Lithiation of *N*-Boc dibenzoxazepine **1** can be achieved regioselectively at the 11-position in THF at -78° when lithium diisopropylamide or methyllithium is employed as the base. Electrophilic substitution proceeds with a variety of electrophiles such as ketones, aldehydes, nitriles, isocyanates and imines. The subsequent *in-situ* cyclization of the lithium alkoxide or lithium amide intermediates, generated in the initial electrophilic substitution reaction, with the *tert*-butoxylcarbonyl group of the *N*-Boc dibenzoxazepine to give five-membered cyclic analogs appears to be general and very useful in the preparation of a variety of novel fused heterocyclic derivatives of 8-chlorodibenzoxazepine.

EXPERIMENTAL

General.

Proton nuclear magnetic resonance spectra (^{1}H nmr, 300 MHz) were obtained on a Varian Unity 300, a VXR-300 or a XL-300 MHz NMR spectrometer, chemical shifts (δ) are reported in parts per million down field from an internal tetramethylsilane or chloroform (7.24 ppm) reference. Deuteriochloroform (99.8% D) was used as the solvent except where otherwise specified. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened; dt, doublet of triplet; dd, doublet of doublet; AB, AB quartet. Fast Atom Bombardment (FAB) mass spectra were obtained on a VG40-250 mass spectrometer. Electron impact (EI) mass spectra were obtained on a Finnigan 4500 mass spectrometer. High-resolution mass spectra (hrms) were obtained on a Finnigan MAT 90 mass spectrometer with (FAB) or EI ionization. High performance liquid chromatography (hplc) separations were performed on a Waters Associates LC 2000 or Prep 500A System with silica gel columns. Melting points were determined on a Thomas-Hoover melting point apparatus, and are uncorrected. Differential Scanning Calorimetry (DSC) measurements were determined on a DuPont 910 DSC instrument. When involving air-sensitive reagents, all glassware was oven dried prior to use and all reactions were done under a nitrogen atmosphere. Elemental analyses were performed by Galbraith Laboratories, Inc.

Materials.

Tetrahydrofuran (THF) was distilled from sodium and benzophenone under a nitrogen atmosphere. Lithium diisopropylamide (monotetrahydrofuran complex, 1.5 *M* in cyclohexane), methyllithium (1.4 *M* in diethyl ether) and *n*-butyllithium (1.6 *M* in hexanes) were purchased from Aldrich Chemical Company. All other reagents and solvents were obtained from commercial sources and used without further purification.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10-*tert*-butylcarbamate (**1**).

Under nitrogen, a solution of 50 g (216 mmoles) of 8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepine [11] and 57 g (261 mmoles) of Boc-anhydride in 1400 ml of anhydrous THF was treated with a catalytic amount of dimethylaminopyridine, and stirred at reflux for 18 hours. The THF was removed *in vacuo*, and the residue was dissolved in dichloromethane/hexane, which was washed with 0.25 *N* hydrochloric acid and dried over magnesium sulfate. Purification on silica gel with 5% ethyl acetate/hexane as the eluent, and subsequent recrystallization from dichloromethane/hexane gave 59.8 g (83 %) of **1** as a colorless solid, mp 107.0-107.4°; ^{1}H nmr: δ 7.19-7.35 (m, 2H, ArH), 7.08-7.17 (m, 4H, ArH), 7.02 (dt, J = 8, 1.5 Hz, 1H, ArH), 4.78 (s, 2H, $ArCH_2$), 1.42 (s, 9H, $C(CH_3)_3$), ms: (FAB) m/z 388 (M+Li); hrms Calcd. for $C_{18}H_{18}NO_3Cl$ (M^+); 331.0975. Found: 331.0988.

Anal. Calcd. for $C_{18}H_{18}NO_3Cl$: C, 65.16; H, 5.47; N, 4.22; Cl, 10.69. Found: C, 65.16; H, 5.56; N, 4.22; Cl, 10.98.

General Procedure A. Lithiation of **1** and Subsequent Reaction with Various Electrophiles.

Under nitrogen, a solution of 1.0 g (3.0 mmoles) of **1** in 20 ml of anhydrous THF at -78° was treated with 1.2 equivalents of lithium diisopropylamide, methyllithium or *n*-butyllithium, and stirred for 30 minutes prior to the addition of *ca.* 2 equivalents of the appropriate electrophile at -78°. The solution was allowed to stir at -78° for 3 hours followed by ambient temperature overnight prior to the addition of saturated ammonium chloride. The mixture was diluted with ethyl acetate or diethyl ether, washed with brine and dried with magnesium sulfate or sodium sulfate. Purification by mplc or hplc on silica gel gave the desired product.

6-Chloro-1,13b-dihydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*]-[1,4]oxazepin-1,1'-cyclobutan]-3-one (**5**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 7% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 355 mg (36%) of **5**; ^{1}H nmr: δ 7.62 (s, 1H, ArH), 7.16-7.40 (m, 6H, ArH), 5.19 (s, 1H, ArCH), 2.75-2.84 (m, 1H, cyclobutyl), 2.45-2.60 (m, 1H, cyclobutyl), 2.28-2.42 (m, 1H, cyclobutyl), 2.12-2.26 (m, 1H, cyclobutyl), 1.82-2.00 (m, 1H, cyclobutyl), 1.30-1.45 (m, 1H, cyclobutyl). ms: (FAB) m/z 334 (M+Li); hrms Calcd. for $C_{18}H_{14}NO_3LiCl$ (M+Li): 334.0822. Found: 334.0867.

Anal. Calcd. for $C_{18}H_{14}NO_3Cl$: C, 65.96; H, 4.31; N, 4.27; Cl, 10.82. Found: C, 65.86; H, 4.31; N, 4.31; Cl, 10.46.

6-Chloro-1,13b-dihydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*]-[1,4]oxazepine-1,1'-cyclopentan]-3-one (**6**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 5% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 443 mg (43%) of **6**; ^{1}H nmr: δ 7.62 (s, 1H, ArH), 7.31 (d, J = 4 Hz, 2H, ArH), 7.06-7.20 (m, 4H, ArH), 5.21 (s, 1H, ArCH), 2.26-2.38 (m, 1H, cyclopentyl), 1.98-2.14 (m, 1H, cyclopentyl), 1.72-1.95 (m, 3H, cyclopentyl), 1.60-1.72 (m, 1H, cyclopentyl), 1.39-1.55 (m, 1H, cyclopentyl), 1.25-1.38 (m, 1H, cyclopentyl); ms: (FAB) m/z 348 (M+Li); hrms Calcd. for $C_{19}H_{16}NO_3LiCl$ (M+Li): 348.0979. Found: 348.0997.

Anal. Calcd. for $C_{19}H_{16}NO_3Cl$: C, 66.77; H, 4.72; N, 4.10; Cl, 10.37. Found: C, 66.54; H, 4.82; N, 4.05; Cl, 10.12.

6-Chloro-1,13b-dihydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*]-[1,4]oxazepine-1,1'-cyclohexan]-3-one (**7**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 10% ethyl

acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 419 mg (39%) of **7**; ^{1}H nmr: δ 7.60 (s, 1H, ArH), 7.31 (s, 2H, ArH), 7.02-7.21 (m, 4H, ArH), 4.90 (s, 1H, ArCH), 2.10-2.18 (m, 1H, cyclohexyl), 1.94-2.05 (m, 1H, cyclohexyl), 1.60-1.93 (m, 5H, cyclohexyl), 1.42-1.57 (m, 1H, cyclohexyl), 1.00-1.18 (m, 1H, cyclohexyl), 0.72-0.86 (m, 1H, cyclohexyl); ms: (FAB) m/z 362 (M+Li); hrms Calcd. for $C_{20}H_{18}NO_3LiCl$ (M+Li): 362.1135. Found: 362.1143.

Anal. Calcd. for $C_{20}H_{18}NO_3Cl$: C, 67.51; H, 5.10; N, 3.94; Cl, 9.96. Found: C, 67.52; H, 5.19; N, 3.89; Cl, 9.57.

6-Chloro-1,13b-dihydro-3*H*,9'*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*]-[1,4]oxazepine-1,9'-fluoren]-3-one (**8**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 5% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 231 mg (18%) of **8**; ^{1}H nmr: δ 7.73-7.77 (m, 2H, ArH), 7.66 (d, J = 7 Hz, 1H, ArH), 7.56 (d, J = 7 Hz, 1H, ArH), 7.35-7.49 (m, 4H, ArH), 7.12-7.25 (m, 2H, ArCH), 6.99-7.04 (m, 2H, ArH), 6.92 (t, J = 7 Hz, 1H, ArH), 6.51 (d, J = 8 Hz, 1H, ArH), 6.04 (d, J = 7 Hz, 1H, ArH), 5.71 (s, 1H, ArH); ms: (FAB) m/z 438 (M+H); hrms Calcd. for $C_{27}H_{16}NO_3LiCl$ (M+Li): 444.0979. Found: 444.1004.

Anal. Calcd. for $C_{27}H_{16}NO_3Cl$: C, 74.06; H, 3.68; N, 3.20; Cl, 8.10. Found: C, 73.82; H, 3.75; N, 3.28; Cl, 8.16.

6-Chloro-1,13b-dihydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*]-[1,4]oxazepine-1,2'-indan]-3-one (**9**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 10% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 133 mg (11%) of **9**; ^{1}H nmr: δ 7.58 (s, 1H, ArH), 7.00-7.29 (m, 7H, ArH), 6.80-6.95 (m, 3H, ArH), 5.28 (s, 1H, ArCH), 3.53 (AB, J_{AB} = 18 Hz, ΔV = 38 Hz, 2H, $ArCH_2$), 3.00 (AB, J_{AB} = 18 Hz, ΔV = 57 Hz, 2H, $ArCH_2$); ms: (FAB) m/z 396 (M+Li); hrms Calcd. for $C_{23}H_{16}NO_3LiCl$ (M+Li): 396.0979. Found: 396.1015.

Anal. Calcd. for $C_{23}H_{16}NO_3Cl$: C, 70.86; H, 4.14; N, 3.59; Cl, 9.09. Found: C, 70.76; H, 4.13; N, 3.67; Cl, 9.50.

6-Chloro-1,13b-dihydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*]-[1,4]oxazepine-1,1'-indan]-3-one (**10**) and 6-Chloro-1,13b-dihydro-3*H*-spiro[dibenz[*b,f*]oxazolo-[3,4-*d*][1,4]oxazepin-1,1'-indan]-3-one (**11**).

General Procedure A, lithium diisopropylamide as the base, and purification by silica gel chromatography with 10% ethyl acetate/hexane as the eluent gave two diasterioisomers **10** and **11** which were both lyophilized from acetonitrile/water to give 85 mg (7%) of higher Rf isomer and 365 mg (31%) of lower Rf isomer.

The isomer with the higher Rf had ^{1}H nmr: δ 7.67 (s, 1H, ArH), 7.58-7.61 (m, 1H, ArH), 7.32-7.38 (m, 2H, ArH), 7.13-7.26 (m, 5H, ArH), 6.76 (t, J = 7 Hz, 1H, ArH), 6.15 (t, J = 7 Hz, 1H, ArH), 5.31 (s, 1H, ArCH), 2.72-2.81 (m, 1H), 2.41-2.50 (m, 1H), 2.15-2.23 (m, 1H), 1.87-1.98 (m, 1H); ms: (FAB) m/z 396 (M+Li); hrms Calcd. for $C_{23}H_{16}NO_3LiCl$ (M+Li): 396.0979. Found: 396.0933.

Anal. Calcd. for $C_{23}H_{16}NO_3Cl$: C, 70.86; H, 4.14; N, 3.59; Cl, 9.09. Found: C, 70.83; H, 4.28; N, 3.52; Cl, 9.29.

The isomer with the lower Rf had ^{1}H nmr: δ 7.62 (s, 1H, ArH), 7.41 (d, J = 8 Hz, 1H, ArH), 6.92-7.18 (m, 7H, ArH), 6.77-6.79 (m, 2H, ArH), 5.43 (s, 1H, ArCH), 3.03-3.13 (m, 1H), 2.63-2.90 (m, 3H); ms: (FAB) m/z 396 (M+Li); hrms Calcd. for $C_{23}H_{16}NO_3LiCl$ (M+Li): 396.0979. Found: 396.1025.

Anal. Calcd. for $C_{23}H_{16}NO_3Cl$: C, 70.86; H, 4.14; N, 3.59; Cl, 9.09. Found: C, 70.51; H, 4.29; N, 3.49; Cl, 9.36.

6-Chloro-1,1',2',3',4'-13b-hexahydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-d][1,4] oxazepine-1,1'-naphthalen]-3-one (**12**) and 6-Chloro-1,1',2',3',4'-13b-hexahydro-3*H*-spiro[dibenz[*b,f*]oxazolo[3,4-*d*][1,4] oxazepine-1,1'-naphthalen]-3-one (**13**).

General procedure A, lithium diisopropylamide as the base, and purification by silica gel chromatography with 10% ethyl acetate/hexane as the eluent gave two disastereoisomers **12** and **13** which were both lyophilized from acetonitrile/water to give 311 mg (26%) of higher Rf isomer and 94 mg (8%) of lower Rf isomer.

The isomer with the higher Rf; had ^{1}H nmr: δ 7.69-7.73 (m, 2H, ArH), 7.07-7.34 (m, 6H, ArH), 6.18 (t, J = 7 Hz, 1H, ArH), 6.29 (t, J = 8 Hz, 1H, ArH), 5.59 (s, 1H, ArCH), 2.62-2.71 (m, 1H), 2.39-2.49 (m, 1H), 1.91-2.12 (m, 2H), 1.61-1.69 (m, 1H), 1.02-1.14 (m, 1H); ms: (FAB) m/z 410 (M+Li); hrms Calcd. for $C_{24}H_{18}NO_3LiCl$ (M+Li): 410.1135. Found: 410.1111.

Anal. Calcd. for $C_{24}H_{18}NO_3Cl$: C, 71.38; H, 4.49; N, 3.47; Cl, 8.78. Found: C, 71.47; H, 4.56; N, 3.56; Cl, 8.92.

The isomer with the lower Rf had ^{1}H nmr: δ 7.59 (s, 1H, ArH), 7.18-7.28 (m, 3H, ArH), 7.15 (d, J = 6 Hz, 1H, ArH), 6.94-7.06 (m, 3H, ArH), 6.84 (t, J = 7 Hz, 1H, ArH), 6.68 (t, J = 7 Hz, 1H, ArH), 6.56 (t, J = 6 Hz, 1H, ArH), 5.26 (s, 1H, ArCH), 2.68-2.96 (m, 2H), 2.46-2.58 (m, 2H), 2.00-2.20 (m, 2H); ms: (FAB) m/z 410 (M+Li); hrms Calcd. for $C_{24}H_{18}NO_3LiCl$ (M+Li): 410.1135. Found: 410.1136.

Anal. Calcd. for $C_{24}H_{18}NO_3Cl$ (0.31CH_3CN): C, 70.98; H, 4.58; N, 4.41; Cl, 8.51. Found: C, 71.13; H, 4.65; N, 4.51; Cl, 8.67.

6-Chloro-1,13b-dihydro-1-phenyl-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**14**) and 6-Chloro-1,13b-dihydro-1-phenyl-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**15**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 10% ethyl acetate/hexane to 100% ethyl acetate as the eluent gave 365 mg (31%) of **14** and 390 mg (35%) of **15**.

The isomer with the higher Rf had DSC 116.4°; ^{1}H nmr: δ 7.93-7.91 (m, 1H), 7.55-7.40 (m, 5H), 7.37-7.08 (m, 5H), 6.98-6.95 (m, 1H), 5.67 (d, J = 9 Hz, 1H), 5.52 (d, J = 9 Hz, 1H).

Anal. Calcd. for $C_{21}H_{14}NO_3Cl$ (0.25H_2O): C, 68.48; H, 3.97; N, 3.80; Cl, 9.63. Found: C, 68.31; H, 4.23; N, 3.95; Cl, 9.81.

The isomer with the lower Rf had DSC 213.07°; ^{1}H nmr: δ 7.69 (d, J = 2.5, 1H), 7.23-7.14 (m, 7H), 7.07-7.00 (m, 2H), 6.93-6.89 (m, 1H), 6.85-6.83 (m, 1H), 5.81 (d, J = 8 Hz, 1H), 5.65 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{21}H_{14}NO_3Cl$ (0.25H_2O): C, 68.48; H, 3.97; N, 3.80; Cl, 9.63. Found: C, 68.46; H, 3.90; N, 3.76; Cl, 9.57.

trans-6-Chloro-1,13b-dihydro-1-(4-pyridyl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**16**) and *cis*-6-Chloro-1,13b-dihydro-1-(4-pyridyl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**17**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 5% methanol/chloroform as the eluent gave 78 mg (7%) of **16** and 288 mg (26%) of **17**. The stereochemistry is assigned by X-ray crystal structure analysis.

The *trans*-isomer **16** had DSC 178.98°; ^{1}H nmr: δ 8.75 (br s, 2H), 7.80 (d, J = 2.5 Hz, 1H), 7.40-7.01 (m, 8H), 5.20 (d, J = 7.5 Hz, 1H), 4.81 (d, J = 7.5 Hz, 1H).

Anal. Calcd. for $C_{20}H_{13}N_2O_3Cl$: C, 65.85; H, 3.59; N, 7.68; Cl, 9.72. Found: C, 65.69; H, 3.74; N, 7.46; Cl, 9.78.

The *cis*-isomer **17** had DSC 216.87°; ^{1}H nmr: δ 8.41 (d, J = 4 Hz, 2H), 7.67 (d, J = 2.5 Hz, 1H), 7.30-6.95 (m, 8H), 5.77 (d, J = 8 Hz, 1H), 5.74 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{20}H_{13}N_2O_3Cl$: C, 65.85; H, 3.59; N, 7.68; Cl, 9.72. Found: C, 65.55; H, 3.67; N, 7.58; Cl, 9.89.

6-Chloro-1,13b-dihydro-1-(3-pyridyl)-3*H*-dibenz[*b,f*]oxazolo-[3,4-*d*][1,4]oxazepin-3-one (**18**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 5:40:55 methanol:ethyl acetate:hexane as the eluent gave 246 mg (22%) of **18**; ^{1}H nmr: δ 8.45-8.47 (m, 1H), 8.29 (br s, 1H), 7.69 (d, J = 2.5 Hz, 1H), 7.65-7.61 (m, 1H), 7.26-6.89 (m, 7H), 5.86 (d, J = 8 Hz, 1H), 5.73 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{20}H_{13}N_2O_3Cl$: C, 65.85; H, 3.59; N, 7.68; Cl, 9.72. Found: C, 65.43; H, 3.69; N, 7.61; Cl, 9.92.

6-Chloro-1,13b-dihydro-1-(2-pyridyl)-3*H*-dibenz[*b,f*]oxazolo-[3,4-*d*][1,4]oxazepin-3-one (**19**) and 6-Chloro-1,13b-dihydro-1-(2-pyridyl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**20**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 5% methanol/chloroform as the eluent gave 336 mg (30%) of **19** and 94 mg (9%) of **20**.

The isomer with the higher Rf had DSC 151.42°; ^{1}H nmr: δ 8.69-8.67 (m, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.83-7.81 (m, 1H), 7.65 (d, J = 8 Hz, 1H), 7.38-7.11 (m, 7H), 6.01 (d, J = 5.4 Hz, 1H), 5.84 (d, J = 5.4 Hz, 1H).

Anal. Calcd. for $C_{20}H_{13}N_2O_3Cl$: C, 65.85; H, 3.59; N, 7.68; Cl, 9.72. Found: C, 65.87; H, 3.61; N, 7.59; Cl, 9.68.

The isomer with the lower Rf had DSC 220.87°; ^{1}H nmr: δ 8.35-8.33 (m, 1H), 7.68 (d, J = 2.5 Hz, 1H), 7.55-7.51 (m, 1H), 7.35-7.33 (m, 1H), 7.24-6.89 (m, 7H), 6.00 (d, J = 9 Hz, 1H), 5.78 (d, J = 9 Hz, 1H).

Anal. Calcd. for $C_{20}H_{13}N_2O_3Cl$: C, 65.85; H, 3.59; N, 7.68; Cl, 9.72. Found: C, 65.61; H, 3.48; N, 7.52; Cl, 9.96.

6-Chloro-1,13b-dihydro-1-(3-thienyl)-3*H*-dibenz[*b,f*]oxazolo-[3,4-*d*][1,4]oxazepin-3-one (**21**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 10% ethyl acetate/hexane as the eluent gave 215 mg (19%) of **21**; DSC 182.5°; ^{1}H nmr: δ 7.70 (d, J = 2.2 Hz, 1H), 7.23-7.07 (m, 6H), 6.99-6.96 (m, 1H), 6.92-6.90 (m, 1H), 6.87-6.85 (m, 1H), 5.92 (d, J = 8 Hz, 1H), 5.63 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{19}H_{12}NO_3SCl$ (0.1H_2O): C, 61.41; H, 3.31; N, 3.77; S, 8.63; Cl, 9.54. Found: C, 61.25; H, 3.30; N, 3.66; S, 8.69; Cl, 9.71.

6-Chloro-1,13b-dihydro-1-(2-furyl)-3*H*-dibenz[*b,f*]oxazolo-[3,4-*d*][1,4]oxazepin-3-one (**22**).

General Procedure A, *n*-butyllithium as the base, purification by mplc with 20% ethyl acetate/hexane as the eluent gave 155 mg (15%) of **22** as a solid, mp 170.5-173.5°; ^{1}H nmr: δ 7.87 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 1 Hz, 1H), 7.34-7.08 (m, 5H), 6.87-6.85 (m, 1H), 6.65 (d, J = 3 Hz, 1H), 6.49-6.48 (m, 1H), 5.77 (d, J = 8 Hz, 1H), 5.58 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{19}H_{12}NO_3Cl$ (1.1H_2O): C, 63.82; H, 4.00, N, 3.92; Cl, 9.91. Found: C, 63.79; H, 3.62; N, 3.79; Cl, 9.85.

6-Chloro-1,13b-dihydro-1-(*N*-methylpyryl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**23**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 20% ethyl acetate/hexane as the eluent gave 140 mg (12%) of **23** as a solid, mp 149-152°; ^{1}H nmr: δ 7.83 (d, J = 2.4 Hz, 1H), 7.40-7.04 (m, 6H), 6.78-6.77 (m, 1H), 6.43-6.42 (m, 1H), 6.20-6.19 (m, 1H), 5.76 (d, J = 9 Hz, 1H), 5.65 (d, J = 9 Hz, 1H), 3.73 (s, 3H).

Anal. Calcd. for $C_{20}H_{15}N_2O_3Cl$ (0.23 hexane and 0.41 H_2O): C, 65.18; H, 4.88; N, 7.11; Cl, 8.99. Found: C, 65.18; H, 4.95; N, 7.05; Cl, 9.12.

6-Chloro-1,13b-dihydro-1-(4-carboxymethylphenyl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**24**) and 6-Chloro-1,13b-dihydro-1-(4-carboxymethylphenyl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**25**).

General procedure A, *n*-butyllithium as the base, and purification by mplc with 25% ethyl acetate/hexane as the eluent gave 160 mg (13%) of **24** and 630 mg (50%) of **25**.

The isomer with the higher Rf had DSC had 217.88°; ^{1}H nmr: δ 8.15-8.14 (m, 2H), 7.91 (d, J = 2.5 Hz, 1H), 7.58-7.56 (m, 2H), 7.38-7.11 (m, 5H), 6.96-6.94 (m, 1H), 5.70 (d, J = 8 Hz, 1H), 5.51 (d, J = 8 Hz, 1H), 3.9 (s, 3H).

Anal. Calcd. for $C_{23}H_{16}NO_5Cl$ (0.25H_2O): C, 64.79; H, 3.90; N, 3.29; Cl, 8.32. Found: C, 64.85; H, 3.65; N, 3.30; Cl, 8.41.

The isomer with the lower Rf had DSC 233.9°; ^{1}H nmr: δ 7.84-7.81 (m, 2H), 7.65 (d, J = 2.5 Hz, 1H), 7.30-6.85 (m, 8H), 5.87 (d, J = 8 Hz, 1H), 5.72 (d, J = 8 Hz, 1H), 3.87 (s, 3H).

Anal. Calcd. for $C_{23}H_{16}NO_5Cl$: C, 65.45; H, 3.82; N, 3.32; Cl, 8.40. Found: C, 65.10; H, 3.72; N, 3.28; Cl, 8.39.

6-Chloro-1,13b-dihydro-1-(trimethylphenyl)-3*H*-dibenz[*b,f*]oxazolo[3,4-*d*][1,4]oxazepin-3-one (**26**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 25% ethyl acetate/hexane as the eluent gave 495 mg (41%) of an inseparable product mixture arising from lithiation at 11- and 9-position of **1**; ^{1}H nmr analysis indicated *ca.* 60% of the mixture was the desired product **26**; ^{1}H nmr: δ 7.73-7.72 (m, 1H), 7.36-6.91 (m, 6H), 6.71 (s, 1H), 6.62-6.59 (m, 1H), 5.86 (d, J = 10 Hz, 1H), 5.40 (d, J = 10 Hz, 1H), 2.32 and 2.31 (two s, 9H).

Anal. Calcd. for $C_{24}H_{20}NO_3Cl$: C, 71.02; H, 4.97; N, 3.45; Cl, 8.73. Found: C, 71.34; H, 5.19; N, 3.40; Cl, 9.12.

6-Chloro-1-phenyl-2*H*-dibenz[*b,f*] imidazo[1,5-*d*][1,4]oxazepin-3-one (**27**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 20% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 467 mg (42%) of **27**; ^{1}H nmr (mixed deuteriochloroform and DMSO-d_6): δ 10.50 (s, 1H, NH), 7.26-7.28 (m, 1H, ArH), 6.61-6.68 (m, 2H, ArH), 6.46-6.60 (m, 6H, ArH), 6.43 (dd, J = 9, 3 Hz, 1H, ArH), 6.36 (d, J = 8 Hz, 1H, ArH), 6.22 (t, J = 8 Hz, 1H, ArH); ms: (EI) (70 ev) m/z (relative intensity) 360 (M^+, 100), 229 (12), 104 (35), 77 (13); hrms Calcd. for $C_{21}H_{13}N_2O_2Cl$ (M^+): 360.0666. Found: 360.0689.

Anal. Calcd. for $C_{21}H_{13}N_2O_2Cl$: C, 69.91; H, 3.63; N, 7.76; Cl, 9.83. Found: C, 69.62; H, 3.82; N, 7.34; Cl, 9.53.

6-Chloro-2-methyl-1-phenyl-2*H*-dibenz[*b,f*]imidazo[1,5-*d*]-[1,4]oxazepin-3-one (**28**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 10-20% ethyl acetate/hexane as the eluent and subsequent recrystallization from dichloromethane/hexane gave 360 mg (32%) of **28** as a solid, mp 220-221.5°; ^{1}H nmr: δ 8.11 (s, 1H, ArH), 7.40-7.45 (m, 3H, ArH), 7.33-7.40 (m, 2H, ArH), 7.21-7.27 (m, 2H, ArH), 7.18 (dt, J = 8, 2 Hz, 2H, ArH), 6.76-6.87 (m, 2H, ArH), 3.27 (s, 3H, NCH_3); ms: (FAB) m/z 375 (M+H); hrms Calcd. for $C_{22}H_{15}N_2O_2LiCl$ (M+Li): 381.0982. Found: 381.1050.

Anal. Calcd. for $C_{22}H_{15}N_2O_2Cl$ (0.12CH_2Cl_2): C, 69.06; H, 3.99; N, 7.28; Cl, 11.35. Found: C, 69.28; H, 4.12; N, 7.23; Cl, 11.51.

6-Chloro-1-(2-phenylethyl)-2*H*-dibenz[*b,f*]imidazo[1,5-*d*]-[1,4]oxazepin-3-one (**29**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 0-50% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 250 mg (21%) of **29**; ^{1}H nmr: δ 10.00 (s, 1H, NH), 8.06 (s, 1H, ArH), 7.20-7.36 (m, 7H, ArH), 7.07-7.17 (m, 4H, ArH), 2.95-3.07 (m, 4H, $PhCH_2CH_2$); ms: (EI) (70 ev) m/z (relative intensity) 388 (22), 299 (33), 297 (100), 255 (14), 254 (13), 91 (30); hrms Calcd. for $C_{23}H_{17}N_2O_2Cl$ (M^+): 388.0979. Found: 388.0993.

Anal. Calcd. for $C_{23}H_{17}N_2O_2Cl$: C, 71.04; H, 4.41; N, 7.20; Cl, 9.12. Found: C, 71.17; H, 4.43; N, 7.15; Cl, 9.36.

6-Chloro-2-phenyl-2,13b*H*-dibenz[*b,f*]imidazo[1,5-*d*]-[1,4]oxazepine-1,3-dione (**30**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 2-10% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 520 mg (46%) of **30**; ^{1}H nmr: δ 8.41 (d, J = 3 Hz, 1H, ArH), 7.37-7.58 (m, 8H, ArH), 7.22-7.32 (m, 2H, ArH), 7.14 (dd, J = 8, 3 Hz, 1H, ArH), 6.14 (s, 1H, ArCH); ms: (FAB) m/z 377 (M+H); hrms Calcd. for $C_{21}H_{13}N_2O_3LiCl$ (M+Li): 383.0775. Found: 383.0806.

Anal. Calcd. for $C_{21}H_{13}N_2O_3Cl$: C, 66.94; H, 3.48; N, 7.43; Cl, 9.41. Found: C, 67.00; H, 3.51; N, 7.32; Cl, 9.71.

6-Chloro-2-(phenylmethyl)-2*H*,13b*H*-dibenz[*b,f*]imidazo[1,5-*d*]-[1,4]oxazepine-1,3-dione (**31**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 2-10% ethyl acetate/hexane as the eluent and subsequent recrystallization from diethyl ether/hexane gave 515 mg (44%) of **31** as a solid, mp 82-84°; ^{1}H nmr: δ 8.44 (d, J = 3 Hz, 1H, ArH), 7.42-7.52 (m, 2H, ArH), 7.28-7.40 (m, 5H, ArH), 7.15-7.25 (m, 3H, ArH), 7.07 (dd, J = 9, 3 Hz, 1H, ArH), 6.00 (s, 1H, ArCH), 4.84 (s, 2H, $PhCH_2$); ms: (FAB) m/z 391 (M+H); hrms Calcd. for $C_{22}H_{15}N_2O_3LiCl$ (M+Li): 397.0931. Found: 397.0958.

Anal. Calcd. for $C_{22}H_{15}N_2O_3Cl$: C, 67.61; H, 3.87; N, 7.17; Cl, 9.07. Found: C, 67.71; H, 4.04; N, 7.25; Cl, 9.16.

6-Chloro-2-(2-phenylethyl)-2*H*,13b*H*-dibenz[*b,f*]imidazo[1,5-*d*]-[1,4]oxazepine-1,3-dione (**32**).

General Procedure A, lithium diisopropylamide as the base, purification by silica gel chromatography with 2-10% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 660 mg (54%) of **32**; ^{1}H nmr: δ 8.44 (d, J = 3 Hz, 1H, ArH), 7.10-7.40 (m, 10H, ArH), 7.00 (d, J = 3 Hz, 1H, ArH), 5.92 (s, 1H, ArCH), 4.00-4.10 (m, 1H, NCH), 3.86-3.95 (m, 1H, NCH), 3.06 (t, J = 8 Hz, 2H, $PhCH_2$); ms: (FAB) m/z 411 (M+Li); hrms Calcd. for $C_{23}H_{17}N_2O_3LiCl$ (M+Li): 411.1088. Found: 411.1088.

Anal. Calcd for $C_{23}H_{17}N_2O_3Cl$: C, 68.24; H, 4.23; N, 6.92; Cl, 8.76. Found: C, 68.30; H, 4.43; N, 6.79; Cl, 9.15.

6-Chloro-1,13b-dihydro-1-(phenyl)-3-(methyl)dibenz-[*b,f*]imidazolo[3,4-*d*][1,4]oxazepin-3-one (**33**).

General Procedure A, *n*-butyllithium as the base, and purification by mplc with 50% ethyl acetate/hexane as the eluent gave 363 mg (32%) of **32**; DSC 102.45°; ^{1}H nmr: δ 7.69-7.68 (m, 1H), 7.12-7.09 (m, 7H), 7.00-6.85 (m, 4H), 5.45 (d, J = 8 Hz, 1H), 4.85 (d, J = 8 Hz, 1H), 2.80 (s, 3H).

Anal. Calcd. for $C_{22}H_{17}N_2O_2Cl$ (0.31 $CHCl_3$ and 0.27 H_2O): C, 63.69; H, 4.29; N, 6.68; Cl, 16.43. Found: C, 63.95; H, 4.30; N, 6.46; Cl, 16.43.

12-Chloro-15*H*-benz[*b*]isoquino[2',1':3,4]imidazo[1,5-*d*]-[1,4]benzoxazepin-15-one (**34**).

General procedure A, methyllithium as the base, purification by silica gel chromatography with 5% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 550 mg (43%) of **34**. ^{1}H nmr: δ 8.33 (s, 1H, ArH), 7.40-7.45 (m, 1H, ArH), 7.10-7.33 (m, 8H, ArH), 7.07 (d, J = 7 Hz, 1H, ArCH), 6.97 (d, J = 8 Hz, 1H, ArH), 6.86 (d, J = 8 Hz, 1H, ArH), 6.22 (d, J = 11 Hz, 1H, CH=), 6.07 (d, J = 7 Hz, 1H, ArCH), 5.35 (d, J = 11 Hz, 1H, CH=); ms: (FAB) m/z 393 (M+Li). hrms Calcd. for $C_{23}H_{15}N_2O_2LiCl$ (M+Li) 393.0982. Found: 393.0967.

Anal. Calcd. for $C_{23}H_{15}N_2O_2Cl$ (0.03 CH_2Cl_2): C, 71.00; H, 3.90; N, 7.19; Cl, 9.70. Found: C, 71.19; H, 4.04; N, 7.18; Cl, 9.84.

12-Chloro-17,18-dihydro-15*H*-benz[*b*]isoquino[2',1':3,4]imidazo[1,5-*d*][1,4] benzoxazepin-15-one (**35**).

A solution of 400 mg (1.03 mmoles) of **34** and 50 mg of Pd-C (10%) in 10 ml of ethanol was shaken for 2 hours under 30 psi of hydrogen in a PARR Apparatus. The catalyst was removed by filtration. Purification by silica gel chromatography with 0-10% ethyl acetate/hexane as the eluent and subsequent lyophilization from acetonitrile/water gave 290 mg (72%) of **35**; ^{1}H nmr: δ 8.22 (s, 1H, ArH), 7.52 (d, J = 7 Hz, 1H, ArH), 7.36-7.42 (m, 1H, ArH), 7.10-7.35 (m, 7H, ArH), 6.91 (d, J = 6 Hz, 1H, ArH), 5.86 (d, J = 4 Hz, 1H, ArCH), 5.30 (s, 1H, ArCH), 4.19-4.28 (m, 1H), 3.16-3.40 (m, 2H), 2.78 (d, J = 17 Hz, 1H); ms: (FAB) m/z 395 (M+Li); hrms Calcd. for $C_{23}H_{17}N_2O_2LiCl$ (M+Li): 395.1139. Found: 395.1136.

Anal. Calcd. for $C_{23}H_{17}N_2O_2Cl$: C, 71.04; H, 4.41; N, 7.20; Cl, 9.12. Found: C, 71.06; H, 4.62; N, 7.14; Cl, 8.98.

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REFERENCES AND NOTES

[1] Department of Chemistry, Searle Research & Development, Skokie, IL 60077.

[2] Present address: Department of Biochemistry, Upjohn Laboratories, The Upjohn Company, Kalamazoo, MI 49011.

[3] P. Beak, W. J. Zajdel and D. B. Reitz, *Chem. Rev.*, **84**, 471 (1984).

[4a] P. Beak and W-K. Lee, *J. Org. Chem.*, **55**, 2578 (1990); [b] P. Beak and W-K. Lee, *Tetrahedron Letters*, **30**, 1197 (1989); [c] S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, **113**, 9708 (1991); [d] P. Beak and E. K. Yum, *J. Org. Chem.*, **58**, 823 (1993).

[5] J. E. Resek and P. Beak, *Tetrahedron Letters*, **34**, 3043 (1993).

[6] A. D. Nicola, J. Einhorn and J-L. Luche, *Tetrahedron Letters*, **33**, 6461 (1992).

[7] A. M. Kanazawa, A. Correa, J-N. Denis, M-J. Luche and A. E. Greene, *J. Org. Chem.*, **58**, 255 (1993).

[8a] J. M. Muchowski and M. C. Venuti, *J. Org. Chem.*, **45**, 4798 (1980); [b] P. Stanetty, H. Koller and M. Mihovilovic, *J. Org. Chem.*, **57**, 6833 (1992).

[9] R. D. Clark and Jahangir, *Heterocycles*, **32**, 1699 (1991).

[10a] E. A. Hallinan, T. J. Hagen, R. K. Husa, S. Tsymbalov, S. N. Rao, J-P. vanHoeck, M. F. Rafferty, A. Stapelfeld, M. A. Savage and M. Reichman, *J. Med. Chem.*, **36**, 3293 (1993); [b] T. J. Hagen, M. F. Rafferty, J. T. Collins, D. J. Garland, J. J. Li, M. B. Norton, D. B. Reitz, S. Tsymbalov, B. S. Pitzele and E. A. Hallinan, *Heterocycles*, **38**, 601 (1994).

[11] W. E. Coyne and J. W. Cusic, *J. Med. Chem.*, **11**, 1158 (1968).