m/z 258 (M^+, 5), 111 (100), 185 (90), 55 (85), 15 (82), 83 (77), 173 (64), 216 (41); ^1H NMR δ 4.1 (H-6), 2.55 (H-5), 2.7 (H-3), 4.30 (CH_2CH_3), 1.30 (CH_2CH_3), 145 (CH_3) ($J_{5,6}$ = 5.8 Hz, J_{CH_2,CH_3} = 7.1 Hz, $J_{6\text{-}CH_3}$ = 7.0); ^{13}C NMR δ 62.5 (C-6), 33.9 (C-5), 196.9 (C-4), 27.5 (C-3), 80.0 (C-6), 62.2 (CH_2CH_3), 14.1 (CH_2CH_3), 15.3 (CH_3), 166.4 (COO).

Ethyl 3-methyl-2,4,5,6-tetrahydro-5-pyrone-2,2-dicarboxylate (24): bp 165 °C (0.2 mmHg); yield 40%; ^1H NMR δ 3.9 (H-6), 2.65 (H-4), 3.00 (H-3), 4.30 (CH_2CH_3), 1.30 (CH_2CH_3), 1.20 (CH_3) ($J_{3,4}$ = 4.5 Hz, $J_{3\text{-}CH_3}$ = 6.8 Hz, J_{CH_2,CH_3} = 7.10 Hz); ^{13}C NMR δ 48.1 (C-6), 200.8 (C-5), 37.6 (C-4), 27.5 (C-3), 85.8 (C-6), 62.4 (CH_2CH_3), 14.1 (CH_2CH_3), 12.3 (CH_3).

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Registry No. 1, 59414-23-2; 2, 6651-43-0; 3, 38053-91-7; 4, 54781-39-4; 5, 54781-19-0; 6, 82508-82-5; 8, 82456-87-9; 9, 82456-88-0; 10, 82456-89-1; 11, 82456-90-4; 12, 82456-91-5; 13, 82456-92-6; 14, 82456-93-7; 15, 59414-33-4; 16, 82456-94-8; 18, 19185-89-8; 20a, 82456-95-9; 20b, 34339-49-6; 23, 82456-96-0; 24, 82456-97-1; acetaldehyde, 75-07-0; ethyl mesoxalate, 609-09-6.

Synthetic Approaches to 9-Chloro-7-(*o*-fluorophenyl)-5*H*-dibenz[*c*,*e*]azepine

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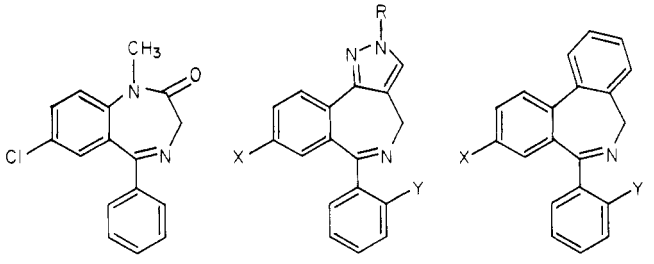
A retrosynthetic analysis of the title compound 1, a potential new anxiolytic agent, is presented. The regiospecific formation of an aryl–aryl bond is considered as the key step. Two synthetic approaches are described which are based on the nucleophilic aromatic substitution of 2-(methoxyaryl)oxazolines. The nature of the organometallic nucleophile, particularly with respect to its need for coordinating ligands, is of crucial importance for the success of these reactions. In the second synthesis, the vinyl lactam **22** is used as the immediate precursor to 1. The vinyl lactam functionality and the quaternary oxazoline **7** are found to be the only derivatives of the carboxyl group with sufficient reactivity toward the labile (*o*-fluorophenyl)lithium. The two syntheses of 1 proceed in ten and eight steps, respectively, with an overall yield of 22–23%.

Extensive structure–activity studies[1,2] on the anxiolytic properties of benzodiazepines reveal that the amide group represents one of the more promising functionalities for molecular modifications. Specifically, it was the transgression from an N-substituted amide to a five-membered heterocycle, such as a triazole, which produced agents with high potency and selectivity, thus leading to a whole new array of additional structural variations.

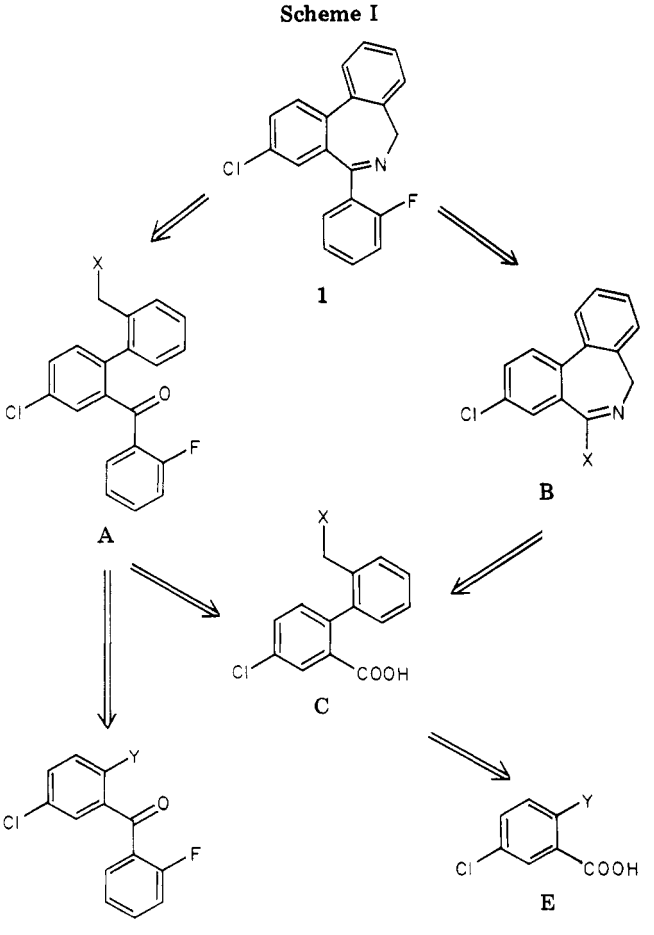
Our own interest in this field was based on the hypothesis that the desired pharmacological profile should be maintained in a benzazepine system, that is by replacing the amide functionality in diazepam by two sp^2-hybridized



diazepam I II

carbon atoms. This hypothesis proved to be correct, as we have shown with several pyrazolobenzazepine (I) systems.[3] More recent studies were designed to explore the pharmacological potential of dibenzazepines of type II, that is of molecules in which the five-membered heterocycle of triazolobenzodiazepines, for example, or of the pyrazolobenzazepines of type I has been replaced by a carbocyclic aromatic ring. This and the following paper report on

Scheme I



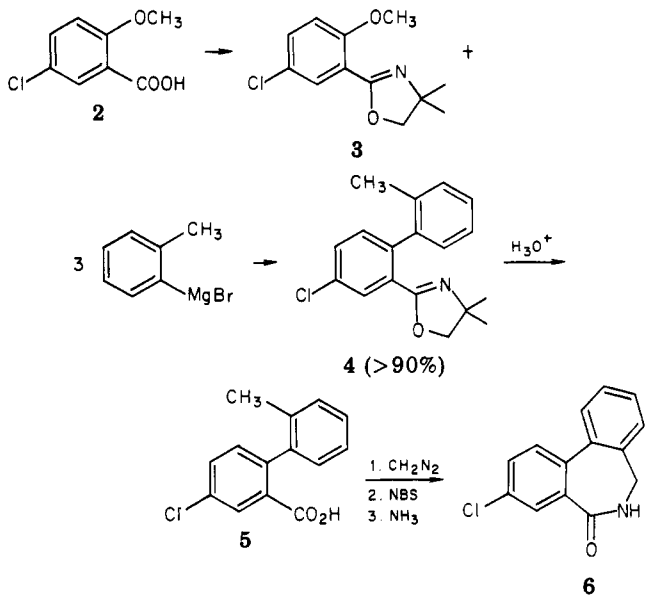
three different syntheses of these compounds.

Retrosynthetic Analysis. The chlorofluoro derivative 1 was chosen as a synthetic target on the basis of the

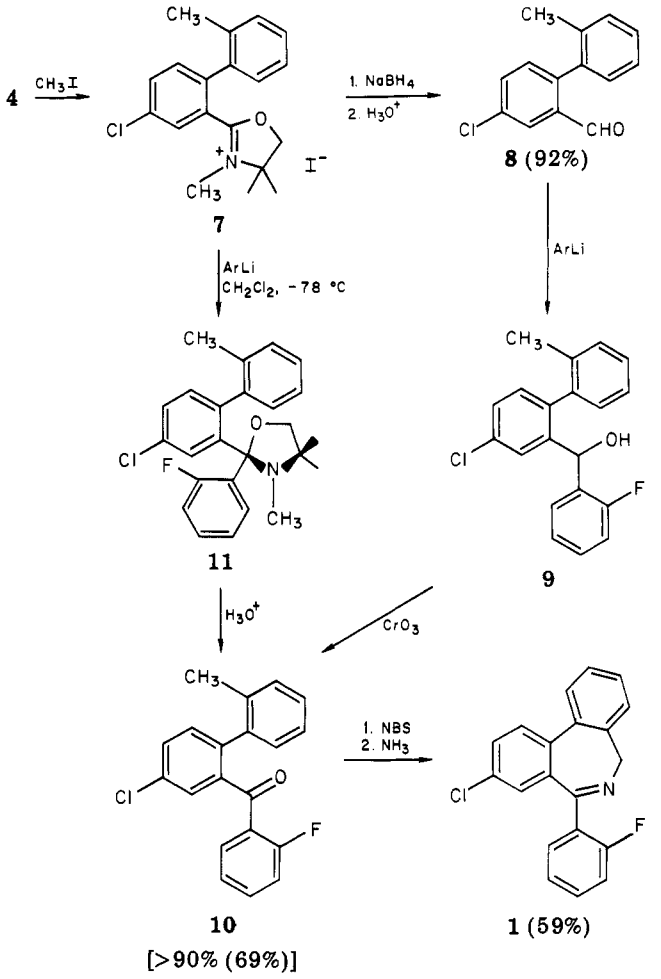
(1) Gschwend, H. W. "Anxiolytics"; Fielding, S., Lal, H. Ed.; Futura Publishing Co.: Mt. Kisco, NY, 1979; p 1.
(2) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
(3) U.S. Patent 3 947 585, 1976. U.S. Patent 4 022 801, 1976. U.S. Patent 4 028 381, 1977.

0022-3263/82/1947-3652$01.25/0

Scheme II



Scheme III[a]



[a] Ar = 2-FC_6H_4.

premise that both halogen substituents in the indicated positions would elicit optimal pharmacological activity. While synthetic access to a nonhalogenated version of 1 would appear to be rather straightforward, the lack of symmetry in 1 poses some challenging problems. Two suitable precursors to 1 are the benzophenone A and the tricyclic lactam derivative B in which X represents a leaving group (Scheme I). In A the leaving group will serve to introduce the nitrogen function, while in B, X would be displaced by the fluorophenyl substituent. An analysis of the synthetic access, not only to A and B specifically but also to 1 quite generally, leads to the conclusion that any approach to either compound would have to contend with the problems of forming the strategic aryl–aryl bond in a regioselective or better regiospecific manner. Precursor A could be arrived at either from a biphenic acid C, or from a benzophenone, D, in which a suitable leaving group Y would have to be replaced by an appropriately substitued aryl moiety. Methodology for such a transformation would clearly have to be developed. The tricyclic lactam B or a reactive derivative thereof could be prepared from the same central biphenic acid C in a routine manner. For the synthesis of C, however, either of two crucial problems would have to be dealt with, namely, the regiospecific introduction of a carboxyl function in an appropriately substituted biphenyl or the formation of an aryl–aryl bond by starting from a benzoic acid derivative E.

This paper describes two synthetic approaches to 1, both of which are based on a derivative of C as a key intermediate. The first sequence to 1 proceeds via A and the second via B.

Synthesis A. The synthesis of C is outlined in Scheme II and is based on the very useful and efficient method developed by Meyers and co-workers.[4] When the aryloxazoline 3, prepared from the acid 2, was reacted with 3 molar equiv of freshly prepared o-tolylmagnesium bromide in a mixture of tetrahydrofuran/ether at 25 °C, the diaryloxazoline 4 was obtained in better than 90% yield. As alluded to in the original paper by Meyers, this nucleophilic aromatic substitution is presumed to proceed via a precoordination of the organometallic with the substrate 3, itself a bidentate ligand, followed by an addition/elimination reaction. Aqueous acidic hydrolysis of 4 produced the acid 5 which, after esterification with diazomethane, was functionalized with N-bromosuccinimide. The crude benzylic bromide was then treated with methanolic ammonia, thus producing the high-melting tricyclic lactam 6 in an overall yield of 66%. The direct introduction of the o-fluorophenyl moiety into 6, specifically the reaction of (o-fluorophenyl)lithium with either the imino ether or the imino chloride of 6, failed, most likely because of an unfavorable reactivity balance between the electrophilic and nucleophilic components. It is well-known that (o-fluorophenyl)lithium undergoes elimination of LiF above −50 °C with formation of benzyne.[5] For similar reasons the biphenic acid 5 did not react with (o-fluorophenyl)-lithium at suitable temperatures.

Accordingly, the reactivity of the carbonyl carbon had to be increased substantially. This was achieved by converting the oxazoline 4 to the aldehyde 8 as outlined in Scheme III.

The aldehyde 8 reacted with (o-fluorophenyl)lithium at −70 °C, producing an approximately 50:50 mixture of the two diastereomeric alcohols 9. The o-tolyl residue in 9 is apparently sufficiently bulky to lead to rotational isomerism. The mixture of alcohols was then oxidized to the desired benzophenone 10 in an overall yield of over 90% based on 8. Benzylic bromination proceeded in moderate

(4) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

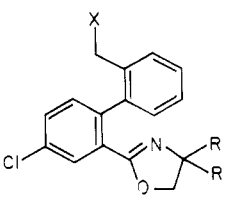
(5) Gilman, H.; Soddy, T. S. *J. Org. Chem. Soc.* **1957**, *22*, 1715.
(6) Köbrich, G.; Werner, W. *Tetrahedron Lett.* **1969**, 2181 and references cited therein.

to good yield. The crude bromination product, containing both starting ketone **10** as well as the dibromide, was treated with a saturated ethanolic solution of ammonia, leading via the primary benzylic amine directly to the desired tricyclic compound **1** in an overall yield of 59%. The crystalline dibenzazepine **1** exhibits a C=N absorption at 1610 cm^{-1} (IR), whereas its UV spectrum is characterized by major absorptions at 226 and 241 nm with a longer wavelength absorption at 312 nm. The characteristic feature in the NMR spectrum is the absorption of the benzylic hydrogens at δ 3.95 and 5.00 with a coupling constant of 11 Hz. The considerable chemical shift difference of the two protons is indicative of the cup-shaped topology of the tricyclic ring system. In Me_2SO solvent these signals start to broaden at 80 °C and eventually coalesce to a broad singlet at 120 °C suggestive of a substantial ring-inversion barrier.

The adjustment of oxidation states from **4** to **8** to **10**, although at first for expediency's sake practical, was clearly undesirable and lacked elegance. The idea of a direct use of the quaternary oxazoline **7** as a more electrophilic partner in the reaction with (*o*-fluorophenyl)lithium was attractive but suffered from the practical problems of solubility: **7** was insoluble in ether, tetrahydrofuran, and glyme. The fact that methylene chloride is deprotonated by alkyl lithiums at low temperature appears to have created a strong bias against the use of this solvent in reactions with organometallic reagents.[6] However, its tremendous solubilizing properties for many quaternary salts, **7** included, were reason enough to ignore the potential problem of deprotonation of the solvent itself. Accordingly, a solution of **7** in methylene chloride was added dropwise to an ethereal solution of (*o*-fluorophenyl)lithium, prepared from *o*-bromofluorobenzene and *n*-butyllithium at −78 °C. The expected adduct **11**, a diastereoisomeric mixture of oxazolidines, was formed in respectable yield as judged by the NMR spectrum of the crude reaction product. Hydrolysis with hydrochloric acid produced a 69% overall yield of the benzophenone **10**, identical with that obtained via the previous route. The synthetic scheme starting from **2** to **1** thus involves ten steps and proceeds in an overall yield of 22%.

Synthesis B. Despite the rather respectable overall yield attained for the synthesis of **1**, the sequence does involve at least two operations which would prove somewhat problematic with reaction scale-ups. One of these is the low-temperature reaction necessary to generate (*o*-fluorophenyl)lithium and the other is the benzylic halogenation of **10** proceeding in only moderate and often varying yields. Scheme B was designed to address the second problem.

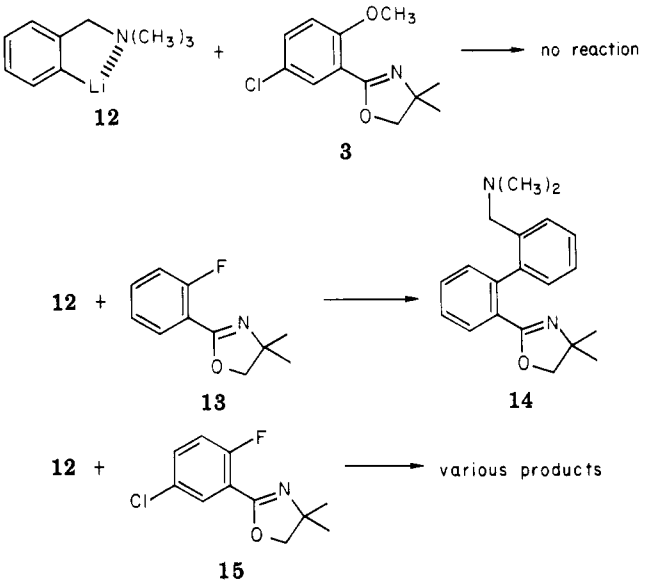
The key to such an improved scheme is an intermediate F in which X should not only be a functionality compatible



F

with subsequent transformations, but most importantly it should be amenable to a convenient and practical replacement by a primary nitrogen function. A second and somewhat more ambitious goal was the desire to utilize the oxazoline nitrogen in F as the source of the nitrogen in the final product **1**. For this purpose it seemed necessary to change from the *gem*-dimethyl substitution pattern to an unsubstituted oxazoline (R = H).

Our previous experience with the ortho metalation of various substituted *N,N*-dimethylbenzylamines made the choice of X = $N(CH_3)_2$ an obvious and very attractive one. To our dismay, however, the attempted reaction of the lithiated benzylamine **12** with the oxazoline **3** under a

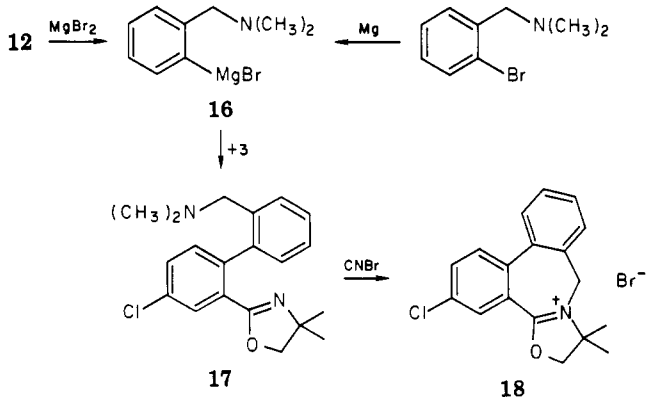


variety of conditions resulted in the exclusive recovery of starting material. Conversely, the (*o*-fluorophenyl)oxazoline **13**, which is also known to undergo a smooth nucleophilic substitution,[7] reacted readily with **12** to give the diphenyl derivative **14** in better than 80% yield. The desired oxazoline **15** was prepared from the corresponding acid, which in turn was obtained by ortho lithiation of *p*-chlorofluorobenzene followed by carboxylation. When **15** was reacted with **12** under conditions where **14** was formed cleanly, however, a multitude of products resulted. A reason for the failure of this reaction may be the high acidity of the proton between oxazoline and chlorine in **15** and thus a transmetalation between **12** and **15**.

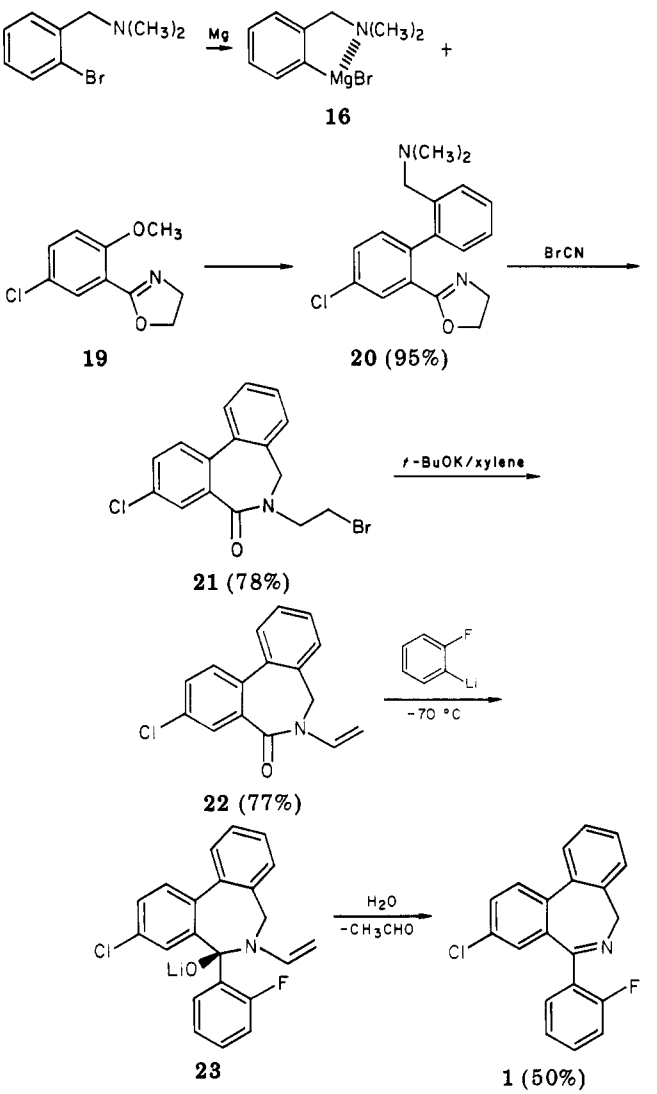
With the failure of the fluoro precursor **15** to serve as a suitable starting material, our attention returned to the reaction between **12** and **3**, in particular to the reasons for its failure. As our own study of the mechanism of this nucleophilic aromatic substitution has shown, a prerequisite for a successful reaction is a precoordination between the metal of the nucleophile with one or more ligands of the electrophilic substrate. Clearly, the Lewis-acid character of **12**, or the demand of the lithium for an external ligand, is very much reduced due to the internal coordination. Accordingly, it was postulated that the prerequisite precoordination condition could be met by choosing a metal with a greater need for external ligands in addition to the intramolecular coordination to the benzylic nitrogen atom. This strategy proved to be correct. When the Grignard reagent **16** (2 equiv), prepared either by transmetalation of **12** with anhydrous $MgBr_2$ or by direct Grignard formation from *N,N*-dimethyl-*o*-bromobenzylamine, was reacted with the oxazoline **3**, the desired product **17** was formed in nearly quantitative yield (Scheme IV). This intermediate, however, proved to be of little use, as selective quaternization of the oxazoline nitrogen appeared impossible, whereas treatment with cyanogen bromide, leading to cleavage of the benzylic amine and internal quaternization, resulted in the for-

(7) Meyers, A. I.; Williams, B. E. *Tetrahedron Lett.* **1978**, 223.

Scheme IV



Scheme V



mation of the high-melting product **18**.

The nucleophilic aromatic substitution reaction was thus repeated on the oxazoline **19** (Scheme V) lacking the *gem*-dimethyl substitution pattern. As outlined in Scheme V, addition of 1.3 equiv of the Grignard reagent **16** to the oxazoline **19** produced an almost quantitative yield of the desired and crystalline diphenyl derivative **20**. Activation of the benzylic carbon was achieved by treatment of **20** with cyanogen bromide, resulting in the intermediate formation of the benzylic bromide, internal quaternization, and finally a nucleophilic attack by the bromide ion at the oxazoline carbon and thus formation of the *N*-bromoethyl lactam **21**. Dehydrobromination was achieved by refluxing the bromide **21** with potassium *tert*-butoxide in xylene. The overall transformation of the oxazoline **20** to the *N*-vinyl lactam **22** not only brought about an increased electrophilicity of the lactam carbonyl, with the vinyl group as a suitable protecting group, but it also achieved the goal of utilizing the oxazoline nitrogen for the formation of the dibenzazepine system. The vinyl lactam **22** proved to be sufficiently reactive toward (*o*-fluorophenyl)lithium at −70 °C to lead to the initial adduct **23**. Upon aqueous workup, the enamine **23** was hydrolyzed with the loss of acetaldehyde, thus leading to the original target **1** identical in all respects with the one prepared via the previous route (synthesis A). This second synthesis then consists of eight steps (including three for the formation of **19**) and proceeds in an overall yield of 23%.

The pharmacological activity of **1** and its various derivatives will be reported elsewhere.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); IR spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 with Me_4Si as an internal standard. The following abbreviations are used: br, broad; w, weak; ex, exchangeable with D_2O; s, singlet; t, triplet; q, quartet; m, multiplet.

2-(5-Chloro-2-methoxyphenyl)-4,4-dimethyloxazoline (3). A suspension of 85 g (0.454 mol) of 5-chloro-2-methoxybenzoic acid in 170 mL of thionyl chloride was stirred at ambient temperature for 30 min. Excess thionyl chloride was then evaporated under water aspirator vacuum to give a solid residue (mp 59–60 °C) of the acid chloride. The crude acid chloride was then dissolved in 450 mL of methylene chloride and added to a stirred solution of 81 g (0.91 mol) of 2-amino-2methyl-1-propanol in 450 mL of methylene chloride. After the mixture was stirred at 25 °C for 3 h, the organic layer was washed with ice-cold aqueous sodium carbonate, dried, and evaporated. The residue was crystallized from hexane to give the amide: mp 103–105 °C; 92.5 g. The solid amide was then treated with 92 mL of thionyl chloride for 1 h at ambient temperature. Subsequently, 500 mL of dry ether was added with stirring. The ether was decanted, and the residue was taken up in methylene chloride and washed with ice-cold sodium hydroxide and then with basic brine. After the mixture was dried and the solvent evaporated, the residue was crystallized from hexane to give **3**: mp 48–50 °C; 73.2 g (67.2% from the acid); IR (Nujol) 1622 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (s, 6 H), 3.85 (s, 3 H), 4.08 (s, 2 H), 6.83 (d, J = 10 Hz, 1 H), 7.33 (dd, J = 10, 3 Hz), 7.72 (d, J = 3 Hz, 1 H). Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.11; H, 5.88; N, 5.87. Found: C, 59.93; H, 5.82; N, 5.74.

2-(2-*o*-Tolyl-5-chlorophenyl)-4,4-dimethyloxazoline (4). The Grignard reagent prepared from 3.6 g (0.15 mol) of magnesium and 25.65 g (0.15 mol) of *o*-bromotoluene in 250 mL of ether was added dropwise to an ice-cold, stirred solution of 12 g (50 mmol) of the oxazoline **3** in 100 mL of tetrahydrofuran. After the addition, the reaction mixture was stirred for 2 h at ambient temperature, cooled again, and washed with an ice-cold solution of ammonium chloride. The organic extract was subsequently washed with brine, dried over sodium sulfate, and evaporated to yield 16.5 g of a thick viscous oil consisting of essentially pure diaryloxazoline **4**. It was used without further purification in the following steps: NMR ($CDCl_3$) δ 1.15 (s, 6 H), 2.03 (s, 3 H), 3.6 (s, 2 H), 7.0–7.4 (m, 7 H).

2-*o*-Tolyl-5-chlorobenzoic Acid (5). A solution of 17 g of crude oxazoline **4** in 150 mL of dioxane and 160 mL of 5 N hydrochloric acid was refluxed for 3 days. The dioxane was then evaporated and the aqueous phase basified with concentrated sodium hydroxide. The basic layer was washed twice with a portion of ether, acidified, and extracted with methylene chloride. After evaporation, the acid **5** was crystallized from hexane to give a total of 10.1 g (72%) of purified product: mp 135–137 °C; IR (Nujol) 1682 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3 H), 7.0–7.3 (m, 5 H),

7.6 (dd, J = 10, 3 Hz, 1 H), 8.03 (d, J = 3 Hz, 1 H), 10.65 (s, 1 H). Anal. Calcd for $C_{14}H_{11}ClO_2$: C, 68.29; H, 4.47. Found: C, 68.29; H, 4.65.

3-Chloro-6,7-dihydrodibenz[*c*,*e*]azepin-5-one (6). A solution of 15.6 g (63.1 mmol) of the acid **5** in 200 mL of methylene chloride was treated with an excess of diazomethane. The solvent and excess reagent were evaporated, and the residue was taken up in hexane and filtered through HyFlo. A solution of 11.7 g (44.8 mmol) of this crude ester in 500 mL of carbon tetrachloride was brominated with 8.8 g (49.3 mmol) of *N*-bromosuccinimide and 250 mg of benzoyl peroxide. After the completion of the bromination (5 h), the solvent was evaporated, giving the crude bromide **6** contaminated with starting material. This crude bromide was then stirred at room temperature in a methanolic solution of ammonia for 3 days. A first crop of 5.6 g of the lactam **6** could be filtered directly from the reaction mixture. An additional 1.4 g was obtained after evaporaton of the mother liquor and aqueous workup of the residue: total yield 7.2 g (66%); mp 226–228 °C; IR (Nujol) 3280, 3175, 1651 cm^{-1}; NMR ($CDCl_3$) δ 4.04 (d, J = 5 Hz, 1 H), 4.15 (d, J = 4 Hz, 1 H), 7.2–7.8 (m, 6 H), 8.0 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{14}H_{10}ClNO \cdot 0.25H_2O$: C, 68.02; H, 4.25; N, 5.66. Found: C, 67.99; H, 4.24; N, 5.29.

Quaternary Oxazoline 7. A solution of 46 g (0.15 mol) of crude oxazoline **4** in 300 mL of acetone was refluxed with 150 mL of methyl iodide for 16 h. After the mixture cooled, the crystalline methiodide **7** could be collected: 53.8 g (81.1%); mp 190–192 °C; IR (Nujol) 1652 cm^{-1}; NMR (Me_2SO-d_6) δ 1.3 (s, 6 H), 2.2 (s, 3 H), 2.96 (s, 3 H), 4.78 (d, J = 3 Hz, 2 H), 7.1–8.1 (m, 6 H), 8.3 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{19}H_{21}ClINO$: C, 51.70; H, 4.76; N, 3.17. Found: C, 51.47; H, 4.71; N, 3.03.

2-*o*-Tolyl-5-chlorobenzaldehyde (8). To an ice-cooled solution of 13.3 g (30 mmol) of **7** in 380 mL of ethanol was added 1.28 g (30 mmol) of sodium borohydride. The solution was stirred in an ice bath for 1 h and was then acidified with 2 N hydrochloric acid. After the mixture was stirred for 1 h at ambient temperature, the ethanol was evaporated *in vacuo*. The residue was partitioned between ice water and ether, and the organic layer was washed with brine, dried, and evaporated. The residue of 5.9 g was crystallized from ether/hexane to give 5.7 g (82.6%) of aldehyde **8**: mp 63–64 °C; IR (Nujol) 1688 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3 H), 7.1–7.7 (m, 6 H), 8.0 (d, J = 2 Hz, 1 H), 9.65 (s, 1 H). Anal. Calcd for $C_{14}H_{11}ClO$: C, 73.04, H, 4.78. Found: C, 72.98; H, 4.96.

Carbinol 9. A solution of 6.87 mL of *n*-butyllithium (1.6 M in hexane, 11 mmol) in 20 mL of ether was cooled to −70 °C. A solution of 1.92 g (11 mmol) of *o*-bromofluorobenzene in 20 mL of ether was then added over a period of 6 min. After the mixture was stirred an additional 10 min at −70 °C, a solution of 2.3 g (10 mmol) of aldehyde **8** in 20 mL of ether was added at once. The reaction mixture was then stirred for 40 min at ambient temperature and quenched with ice-water. After the solvent was dried and evaporated, a residue of 3.5 g was obtained, consisting of a mixture of diastereomeric alcohols **9**: NMR ($CDCl_3$) δ 1.66 and 2.05 (s, 1.4 and 1.6 H), 2.45 (br s, ex, 1 H), 5.8 (m, 1 H), 6.7–7.7 (m, 11 H).

5-Chloro-2′-fluoro-2-*o*-tolylbenzophenone (10). The crude carbinol **9** (3.5 g) was dissolved in 200 mL of ether and oxidized with 13 mL of a 2 N chromic acid solution at ice-bath temperature for 3 h. Excess oxidizing reagent was then destroyed with an aqueous solution of sodium thiosulfate. After separation and a wash with brine, the ethereal layer was dried and evaporated. The residue was filtered through a short column of silica gel with ether/hexane (1:9) as the eluent, yielding 3.0 g (86%) of essentially pure benzophenone **10**. Crystallization from hexane gave an analytical sample: mp 69–71 °C; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 6.6–7.7 (m, 11 H).

9-Chloro-7-(*o*-fluorophenyl)-5*H*-dibenz[*c*,*e*]azepine (1). A solution of 3.0 g (9.23 mmol) of benzophenone **10** in 100 mL of carbon tetrachloride was brominated with 1.8 g (10 mmol) of *N*-bromosuccinimide and 150 mg of benzoyl peroxide as an initiator. After the consumption of all of the brominating agent, the reaction mixture was cooled in an ice bath and filtered. The residue of 3.8 g of the crude benzylic bromide was subsequently dissolved in 150 mL of ethanolic ammonia. After a reaction time of 6 days (25 °C), the solvent was evaporated, and the residue was taken up in methylene chloride and washed with aqueous sodium carbonate. The solvent was dried and evaporated and the residue chromatographed on 25 g of silica gel with benzene as the solvent. The first four fractions contained largely unreacted benzophenone **10**, whereas fractions 5–9 yielded a total of 2.1 g of product **1**. Crystallization from ether/hexane gave analytically pure benzazepine **1**: mp 107–109 °C; 1.7 g (58.6%); IR (Nujol) 1610, 1590 cm^{-1}; UV (CH_3OH) λ_{max} 226 nm (ϵ 33 580), 241 (32 210), 312 (2120); NMR ($CDCl_3$) δ 3.95 (d, J = 11 Hz, 1 H), 5.00 (d, J = 11 Hz, 1 H), 6.8–7.8 (m, 11 H); MS, m/e 321, 302, 286, 165. Anal. Calcd for $C_{20}H_{13}ClFN$: C, 74.66; H, 4.07; N, 4.35. Found: C, 74.67; H, 4.11; N, 4.40.

5-Chloro-2′-fluoro-2-*o*-tolylbenzophenone (10) via Oxazolidine 11. To a solution of 56 mL of *n*-butyllithium (2.2 M in hexane, 125 mmol) in 250 mL of ether was added dropwise at −70 °C a solution of 22 g (125 mmol) of *o*-bromofluorobenzene over a period of 35 min. After the mixture was stirred an additional 10 min at −70 °C, a solution of 44.2 g (100 mmol) of the quaternary iodide **7** in 250 mL of methylene chloride was added at such a rate that the inside temperature did not exceed −65 °C. After the addition, the reaction mixture was stirred at ambient temperature for 16 h. A worked up sample of the reaction mixture indicated the presence of a diastereomeric mixture of the oxazolidines **11** (NMR). The reaction mixture was evaporated, taken up in a mixture of 600 mL of dioxane and 300 mL of 1 N hydrochloric acid, and refluxed for 2 h. After cooling, the mixture was diluted with ether/hexane and the aqueous layer separated. After the organic layer was dried and evaporated, the residue was chromatographed on silica gel with hexane as the solvent. A total of 22.5 g (69.2%) of the ketone **10** was obtained; mp 69–71 °C. It was identical in all respects with that obtained via oxidation of the carbinol **9**.

2-[2-[*o*-[(Dimethylamino)methyl]phenyl]phenyl]-4,4-dimethyloxazoline (14). To a solution of 1.35 g (10 mmol) of *N*,*N*-dimethylbenzylamine in 25 mL of ether was added 5 mL of *n*-butyllithium (2.2 M in hexane, 11 mmol) at 0 °C. Subsequently, the mixture was stirred for 22 h at ambient temperature. The resulting solution of *N*,*N*-dimethyl-*o*-lithiobenzylamine was then cooled to −70 °C, and a solution of 1.9 g (10 mmol) of 2-(2-fluorophenyl)-4,4-dimethyloxazoline (**13**) in 5 mL of tetrahydrofuran was added. The reaction mixture was allowed to warm to 20 °C and was subsequently kept at 0 °C for 16 h. The product was partitioned between ether and aqueous sodium carbonate, followed by a wash with brine. After the ethereal layer was dried over sodium sulfate and the solvent evaporated, 2.5 g of a thick, oily residue was obtained, consisting of essentially pure product **14** contaminated with less than 10% of starting material **13**: NMR ($CDCl_3$) δ 1.16 (s, 6 H), 2.1 (s, 6 H), 3.2 (s, 2 H), 3.6 (s, 2 H), 7.1–7.9 (m, 8 H); MS, m/e 308, 293, 264, 250, 165.

2-(5-Chloro-2-fluorophenyl)-4,4-dimethyloxazoline (15). A solution of 65.5 g (0.5 mol) of *p*-chlorofluorobenzene in 500 mL of tetrahydrofuran was cooled to −70 °C. Then a solution of 181.8 mL of *n*-butyllithium (2.72 M in hexane, 0.5 mol) was added dropwise. After 4 h at −70 °C a slow stream of dry carbon dioxide was slowly passed through the reaction mixture. After an excess of carbon dioxide had been added, the reaction mixture was stirred at ambient tmeperature for 16 h. The acid was then extracted into dilute sodium hydroxide, the aqueous layer acidified, and the product extracted into ether. The solid residue (mp 143–146 °C) of 71.3 g (82%) obtained after the solvent was dried and evaporated was essentially pure 5-chloro-2-fluorobenzoic acid. Anal. Calcd for $C_7H_4ClFO_2$: C, 48.27; H, 2.29. Found: C, 48.21; H, 2.40.

The conversion of this acid via the acid chloride and amide into the oxazoline **15** was carried out essentially as described for the preparation of **3**. The oxazoline **15** was obtained as a viscous oil: NMR ($CDCl_3$) δ 1.4 (s, 6 H), 4.1 (s, 2 H), 7.16 (dd, J = 9.5, 18.5 Hz, 1 H), 7.4 (ddd, J = 2.5, 5, 9.5 Hz, 1 H), 7.91 (dd, J = 2.5, 6 Hz, 1 H); MS, m/e 227, 212, 197, 194, 184, 156.

Methanesulfonate of 9-Chloro-7-(*o*-fluorophenyl)-5*H*-dibenz[*c*,*e*]azepine (1). A solution of 19 g of *o*-bromofluorobenzene in 220 mL of ether was added very slowly at −70 °C to a stirred solution of 43 mL of 2.56 M *n*-butyllithium in hexane and 220 mL of ether under a nitrogen atmosphere. The mixture was stirred for 10 min after the addition. Then a solution of 20 g of 3-chloro-6,7-dihydro-6-vinyldibenz[*c*,*e*]azepin-5-one (**22**) in 200 mL of tetrahydrofuran was added at −70 °C. Thereafter the mixture was stirred at room temperature for 16 h and washed

with cold water, and the organic phase was dried and evaporated under reduced pressure. The residue was then dissolved in toluene and filtered through a pad of 100 g of silica gel. The sovent was evaporated under reduced pressure, and the residue was dissolved in acetone and neutralized with methanesulfonic acid to yield 14 g of the methanesulfonate of 9-chloro-7-(o-fluorophenyl)-5H-dibenz[c,e]azepine (1) melting at 184–186 °C. This methanesulfonate salt was identical with a sample prepared from 1 synthesized by the previous route. Anal. Calcd for $C_{20}H_{13}ClFN \cdot CH_3SO_3H$: C, 60.31; H, 4.10; N, 3.35. Found: C, 60.21; H, 4.19; N, 3.34.

2-(5-Chloro-2-methoxyphenyl)oxazoline (19). A mixture of 75 g (0.4 mol) of 5-chloro-2-methoxybenzoic acid and 50 mL of thionyl chloride was stirred at room temperature for 1 h. Then the excess thionyl chloride was evaporated under reduced pressure and the residue dissolved in 400 mL of methylene chloride. Thereafter this solution was added slowly to a cold, stirred mixture of 27 g of 2-aminoethanol in 170 mL of methylene chloride and 320 mL of saturated aqueous sodium carbonate. After 4 h the organic layer was separated, dried, and evaporated under reduced pressure to yield 93 g of 5-chloro-N-(hydroxyethyl)-2-methoxybenzamide, mp 99–101 °C. The mixture of 93 g thereof and 100 mL of thionyl chloride was stirred at room temperature for 80 min and the excess thionyl chloride evaporated under reduced pressure. The residue was then stirred in a mixture of 400 mL of methylene chloride, 120 mL of 50% aqueous sodium hydroxide, and 1 g of tetrabutylammonium hydrogen sulfate for 2 h at room temperature. Thereafter, the organic layer was separated, dried, and evaporated under reduced pressure. The residue was crystallized from ether to yield 71 g (83.9%) of 2-(5-chloro-2-methoxyphenyl)oxazoline (19): mp 100–101 °C; IR (Nujol) 1637, 1624 cm^{-1}; NMR ($CDCl_3$) δ 3.9 (s, 3 H), 4.2 (m, 4 H), 6.9 (d, J = 9 Hz, 1 H), 7.35 (dd, J = 9, 3 Hz, 1 H), 7.8 (d, J = 3 Hz, 1 H). Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.87; H, 4.73; N, 6.63. Found: C, 56.73; H, 5.00; N, 6.23.

2-[5-Chloro-2-[o-[(dimethylamino)methyl]phenyl]-phenyl]oxazoline (20). A solution of [o-[(dimethylamino)-methyl]phenyl]magnesium bromide (16) in 660 mL of ether [prepared from 8.0 g of magnesium (0.33 mol) and 71.3 g (0.333 mol) of N,N-dimethyl-o-bromobenzylamine] was added with mechanical stirring to an ice-cooled solution of 52.75 g (0.25 mol) of oxazoline 19 in 300 mL of tetrahydrofuran. After the addition a pale yellow, gummy precipitate started to form. The reaction mixture was stirred at ambient temperature for 16 h. The mixture was cooled and quenched with 200 mL of a saturated solution of ammonium chloride. The organic layer was separated, dried, and evaporated under reduced pressure to give the crude crystalline oxazoline 20: 80 g (95%); mp 74–76 °C; IR (Nujol) 1652, 1640 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 6 H), 3.15 (s, 2 H), 3.9 (m, 4 H), 6.9–7.7 (m, 6 H), 7.9 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.78; H, 6.05; N, 8.91. Found: C, 68.57; H, 6.27; N, 8.72.

6-(Bromoethyl)-3-chloro-6,7-dihydrodibenz[c,e]azepin-5-one (21). To an ice-cooled solution of 22.5 g (71.6 mmol) of oxazoline 20 in 290 mL of methylene chloride was added a solution of 84 mL of cyanogen bromide (79 mmol) in methylene chloride. The mixture was stirred at ambient temperature for 16 h and evaporated to dryness. The residue was taken up in a small amount of methlylene chloride and ether and filtered through a layer of filter-cel and silica gel, and the filtrate was evaporated. The residue of 24.1 g was crystallized from toluene/hexane to give 18.9 g (75%) of bromide 21: mp 94–97 °C; IR (Nujol) 1627, 1588 cm^{-1}; NMR ($CDCl_3$) δ 3.3–4.6 (m, 6 H), 7.1–8.1 (m, 7 H); MS, m/e 349, 270, 256, 243. Anal. Calcd for $C_{16}H_{13}BrClNO$: C, 54.85; H, 3.71; N, 4.00. Found: C, 55.18; H, 3.85; N, 3.81.

3-Chloro-6,7-dihydro-6-vinyldibenz[c,e]azepin-5-one (22). A solution of 43.8 g (0.125 mol) of bromide 21 in 1 L of xylene was refluxed for 1.5 h with 15.4 g (0.137 mol) of potassium *tert*-butoxide under an atmosphere of nitrogen. After cooling, some activated charcoal was added and the mixture filtered through Hy-Flo. The filtrate was evaporated to give 30.6 g of solid vinyl lactam 22. The crude product was crystallized from hot toluene to give a total of 24.2 g (72%; several crops) of vinyl lactam: mp 169–172 °C; IR (Nujol) 1640, 1620 cm^{-1}; NMR ($CDCl_3$) δ 4.21 (d, J = 15 Hz, 1 H), 4.62 (d, J = 15 Hz, 1 H), 4.5–5.1 (m, 2 H), 7.1–7.7 (m, 8 H), 8.05 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.37; H, 4.46; N, 5.20. Found: C, 71.18; H, 4.47; N, 4.89.

3-Chloro-6,7-dihydrodibenz[c,e]azepine-5-one (6, from 22). A solution of 270 mg of 22 in 10 mL of ethanol and 1 mL of 1 N hydrochloric acid was stirred at ambient temperature for 18 h. The solvent was removed at reduced pressure, and the residue was taken up in toluene, dried, and evaporated. The crystalline residue of 220 mg melted at 224–226 °C and was identical with 6 prepared from the acid 5.

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