Atropisomers of 1,4-Benzodiazepines. 2. Synthesis and Resolution of Imidazo[1,5-*a*][1,4]Benzodiazepines

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The resolution of the 1-*tert*-butylimidazo[1,5-*a*][1,4]benzodiazepines **12**, **25**, and **31** is described. These compounds do not contain a center of asymmetry but exist as conformational isomers due to the presence of a chiral plane. The resolution was carried out by the following sequence of reactions: (1) reduction of the 5,6-imine bond in **12**, **25**, and **31** to give the dihydro derivatives **13**, **27**, and **33**, respectively, which contain two elements of asymmetry, (2) resolution of **13**, **27**, and **33** employing optically active acids, and (3) oxidation of the enantiomers of **13** (**13a**, **13b**), **27** (**27a**, **27b**), and **33** (**33a**, **33b**) to reintroduce the 5,6-imine bond to give the enantiomers of **12** (**12a**, **12b**), **25** (25a, **25b**), and **31** (**31a**, **31b**), respectively. As a consequence of the oxidation, the center of asymmetry is lost while the conformational integrity is maintained. The absolute configurations of **12b**, **25b**, and **31a** were determined by single crystal X-ray analysis. Based on the biological activity of enantiomeric pairs, the [*R*] configuration is required for recognition at the benzodiazepine receptor complex.

Introduction

Since the introduction of the first 1,4-benzodiazepine, chlordiazepoxide (**1**), in 1960, followed in 1963 with the introduction of diazepam (**2**), the benzodiazepines have become one of the most frequently prescribed drugs for the treatment of anxiety, sleep disorders, seizure disorders, and alcohol withdrawal. In addition, they are used as preoperative agents and induction agents in anesthesia, especially midazolam (**3**).[1,2] The discovery[3,4] in 1977 of specific, high-affinity receptors in mammalian brain tissue for 1,4-benzodiazepines has led to a useful screening procedure for identifying compounds which interact with the receptor. This assay has formed the basis for many structure–activity relationships for both 1,4-benzodiazepines and also non-benzodiazepines which have been found to interact with the receptor.[5]

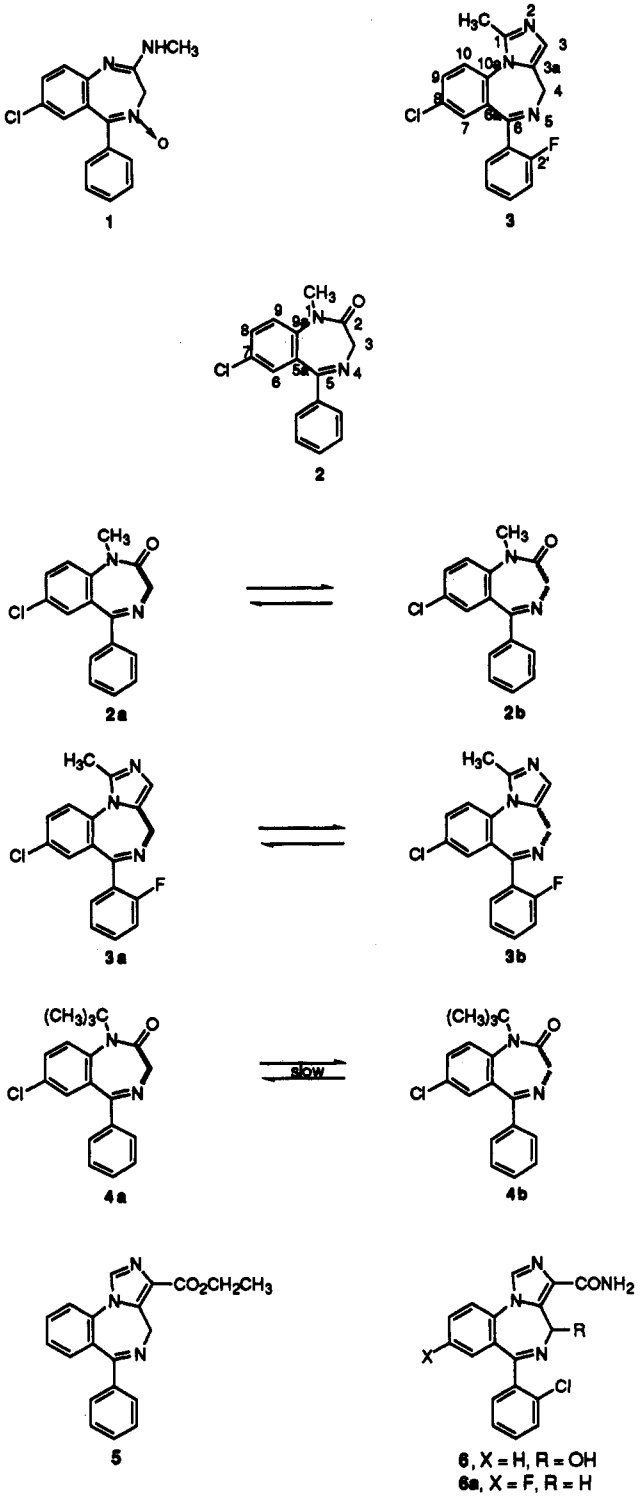
As we recently described,[6] and based on previous work discussed therein, the conformation of diazepam (and by inference related 1,4-benzodiazepines) which recognizes the receptor was shown to be as depicted in structure **2a**. The inversion of the 3-methylene group **2a** ⇌ **2b** (which amounts to racemization since **2a** and **2b** are enantiomers) in diazepam is too rapid at room temperature to allow for the separation of the enantiomers. With the introduction of a *tert*-butyl group at the N^1 position of diazepam, we have previously shown[6] that conformational racemization could be effectively inhibited thus making possible the synthesis of the two enantiomers **4a** and **4b**. As expected, only **4a**, which has the 3-methylene group above the plane of the fused benzene ring, had affinity for the benzodiazepine receptor. Compounds **4a** and **4b** represent the first examples of asymmetric 1,4-benzodiazepines which contain a chiral plane but no center of asymmetry (see Chart I).

Currently, there are three different types of ligands known for the benzodiazepine receptor: agonists, inverse agonists, and antagonists.[7] Agonists have positive intrinsic efficacy, inverse agonists have negative intrinsic efficacy, and antagonists have zero intrinsic efficacy but can reverse the activity of both agonists and inverse agonists.[7] There are also varying degrees of activity across this spectrum, such that partial agonists and partial inverse agonists have also been identified.[7] The partial agonists can also be described as mixed agonists/antagonists since their overall pharmacology gives a spectrum of activity in which some parameters are characteristic of agonists and others of antagonists. The "classical benzodiazepines" such as diazepam (**2**) are full agonists, whereas the imidazo[1,5-*a*][1,4]benzodiazepines have shown a range of activities from full agonists, e.g. midazolam (**3**) to full antagonists,[8] e.g. **5**, to mixed agonists/antagonists, e.g. **6**[9] and **6a**. Thus, structural changes can shift the profile of activity for these benzodiazepines. What is not clear, however, is whether the diversity of activities found in this series of compounds is due solely to chemical modifications or whether the conformational requirements of these imidazobenzodiazepines are different from those of diazepam. On the basis of the similarities and differences in the profile of activity of the classical benzodiazepines as compared with the imidazobenzodiazepines, it became of interest to determine the effect of conformational chirality on rec-

(1) Greenblatt, D. J.; Shader, R. I.; Abernathy, D. R. *New Engl. J. Med.* **1983**, *309*, 410.
(2) Greenblatt, D. J.; Shader, R. I.; Abernathy, D. R. *New Engl. J. Med.* **1983**, *309*, 354.
(3) Mohler, H.; Okada, T. *Science (Washington, D.C.)* **1977**, *198*, 849.
(4) Braestrup, C.; Squires, R. F. *Nature (London)* **1977**, *266*, 732.
(5) (a) Sternbach, L. H. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser: Basel, 1978; Vol. 22, p 229. (b) Seiler, P.; Zimmerman, I. *Drug Research*, **1983**, *33*, 1505. (c) Borea, P. A.; Gilli, G.; Bertolasi, V.; Ferretti, V. *Mol. Pharmacol.* **1987**, *31*, 334. (d) Crippen, G. M. *Mol. Pharmacol.* **1982**, *22*, 11. (e) Fryer, R. I. In *Benzodiazepines. From Molecular Biology to Clinical Practice*; Costa, E., Ed.; Raven Press: New York, 1983; p 7. (f) Fryer, R. I.; Cook, C.; Gilman, N. W.; Walser, A. *Life Sci.* **1986**, *39*, 1947. (g) Codding, P. W.; Muir, A. S. *Mol. Pharmacol.* **1985**, *28*, 178. (h) Tebib, S.; Bourguignon, J.-J.; Wermuth, C.-G. *J. Comput.-Aided Mol. Des.* **1987**, *1*, 153. (i) Snyder, S. H. *Isr. J. Med. Sci.* **1987**, 145.
(6) Gilman, N. W.; Rosen, P.; Earley, J. V.; Cook, C.; Todaro, L. J. *J. Am. Chem. Soc.* **1990**, *112*, 3969.
(7) Kyburz, E. *Il Farmaco*, **1989**, *4*, 345.
(8) Fryer, R. I.; Cook, C.; Gilman, N. W.; Walser, A. *Life Sci.* **1986**, *39*, 1947.
(9) Sepinwall, J.; Sullivan, J. W.; Glinka, S.; Gold, L.; Boff, E.; Gamzu, E.; Keim, K.; Pietrusiak, N.; Smart, T. *Abstracts of Papers*, 16th Annual Meeting of the Society for Neuroscience, Washington, D.C., 1986; Abstracts 181.9.

0022-3263/93/1958-3285$04.00/0

Chart I



ognition by the benzodiazepine receptor in the imidazobenzodiazepine series of compounds.

This report describes the synthesis and separation of the diastereomeric imidazo[1,5-*a*][1,4]benzodiazepines **10** and **11**, and also, the synthesis of the enantiomers of the imidazo[1,5-*a*][1,4]benzodiazepines **12**, **25**, and **31**, all of which are structurally related to midazolam (**3**) or the mixed agonists/antagonists **6** and **6a**. The biological testing data for these compounds (Table I) indicated that **12** and **31** are agonists, while **25** is a mixed agonist/antagonist. To date, no reports have appeared describing the separation of enantiomers of imidazo[1,5-*a*][1,4]-benzodiazpines whose asymmetry is due only to a chiral plane. The interaction of these compounds with the benzodiazepine receptor will be discussed.

Table I. Biological Data for Imidazo[1,5-*a*][1,4]benzodiazepines

compd	[^{3}H]diazepam binding: IC_{50}[a] nM	antipentylenetetrazole: ED_{50}[b] mg/kg
2	5	1
3	4	0.1
10	88	inactive
11	>1000	inactive
12	24	5
12a	19.5	1.9
12b	250	131
18	>1000	inactive
19	>1000	8.5
19a	>1000	inactive
19b	>1000	1.5
25	13	3.4
25a	7	0.18
25b	220	5.5
30	>1000	21
31	54	138
31a	26.5	55
31b	540	78

[a] The method described in ref 3 was used for this assay. [b] A modification of the Everett and Richards[21] method was used for this assay. Results are reported as 95% fiducial limits.

Results and Discussion

Synthesis and Separation of the Diastereomeric Benzodiazepines 10 and 11. Midazolam (**3**) exists as the racemate **3a**, **3b**, and cannot be resolved at room temperature due to the rapid interconversion **3a** ⇌ **3b** (Chart I). A high temperature NMR study (200 °C) of **3** showed a collapse of the AB pattern for the 4-methylene protons, indicating a barrier to interconversion of **3a** and **3b** of less than 24 kcal/mol. We had previously shown[6] that substitution of a *tert*-butyl group for the methyl group in diazepam (**2**) to give **4** was sufficient to allow for the separation of the enantiomers **4a** and **4b**. In this case there was no collapse of the 3-methylene protons in the NMR spectrum at 200 °C, indicating a barrier of inversion of >24 kcal/mol.[10] From an examination of the structure of midazolam (**3**), it was evident that the fused benzene and imidazo rings form a biphenyl type system in which the introduction of a bulky substituent (such as *tert*-butyl) at the 1-position might provide enough steric hindrance between the 1 and 10 positions during the interconversion process (see structure **3** for numbering) to allow for the separation of the atropisomers.[11] Molecular mechanics calculations have now been performed to investigate the structural and energetic aspects of the ring inversion for compound **4** as well as compounds **2**, **3**, and **31**. The calculations were carried out using the standard Tripos force field in the SYBYL program.[12a] The pathways for ring inversion were determined by computing the potential energy surface as a function of the C2–C3, C9a–N1, and C5–C5a torsional angles for compounds **2** and **4** and as a function of the C3a–C4, C10a–N, and C6–C6a torsional angles for **3** and **31** (see structures **2** and **3** for numbering). For **4**, the potential energy surface shows a saddle point

(10) Shanan-Atidi, H. Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961. We carried out the calculations by assuming that an equal population of the two enantiomers were present.

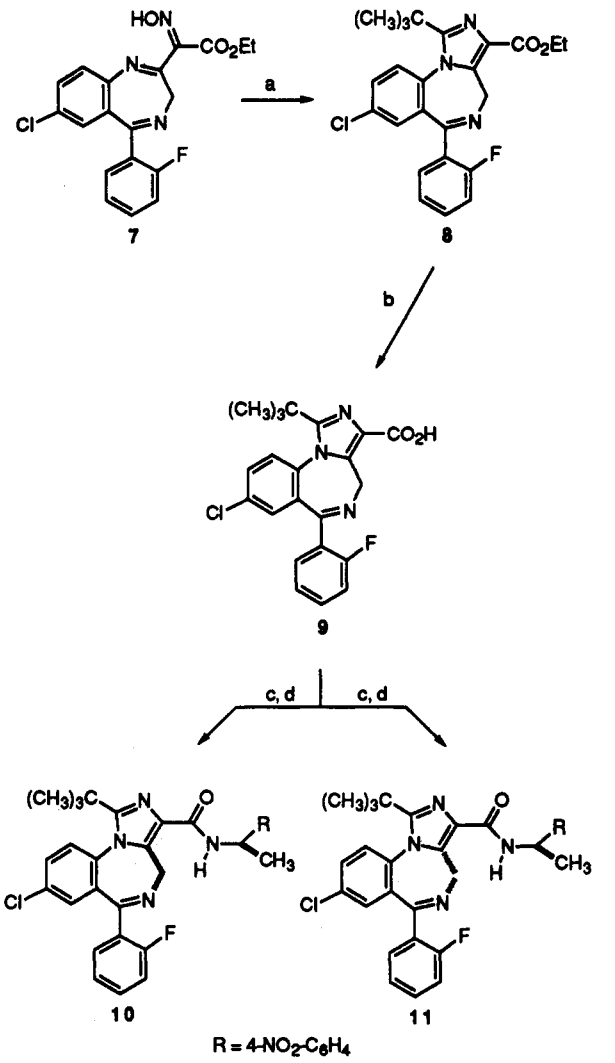
(11) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962, p 177.

(12) SYBYL, Version 5.41; Tripos Associates, 1699 Henley Road, St. Louis, MO 63144.

at torsional angles of C9a–N1 = 60° and C5–C5a = –30° at an energy of approximately 24.1 kcal/mol over the unconstrained (ground-state) minimum. The completely symmetrical, planar transition state (in which both the C9a–N1 and C5–C5a torsional angles = 0°) is predicted to lie 13.1 kcal/mol above this saddle point. For **31**, the lowest energy pathway is similar with a saddlepoint energy of 24.2 kcal/mol. The methyl analogues of **4** and **31** (compounds **2** and **3**), as expected, show much smaller barriers at 13.5 and 18.3 kcal/mol, respectively. Because the molecular mechanics method of calculation does not allow for rehybridization and changes in π bonding, the energy and structures of the transition states may not be correct in detail but they are representative of the types of changes expected upon substitution of a *tert*-butyl group for a methyl group. As discussed in the following section, the high-temperature NMR spectrum of such a substituted ring system, e.g. **12** indicated that the separation of the enantiomers would indeed be possible. The antipodes of the carboxylic acid **9** appeared to be attractive intermediates for the direct preparation of the enantiomers of both **12** and **31** by simple manipulation of the carboxylic acid function (i.e., conversion to an amide and decarboxylation, respectively). Since all attempts to resolve **9** by salt formation on treatment with optically active amines were unsuccessful, the preparation of the diasteromeric compounds **10** and **11** was undertaken (Scheme I). The oxime ester[13] **7** was hydrogenated in the presence of trimethylacetaldehyde to give the imidazobenzodiazepine **8**. This one-pot procedure is preferable to the two-step procedure (hydrogenation followed by treatment of the enediamine with acetaldehyde) previously described[14] for the synthesis of the 6-(2-chlorophenyl) analog of **3**, since the isolation of the unstable intermediate enediamine is avoided. Basic hydrolysis of **8** then gave the acid **9**. The diastereomeric amides **10** and **11** were prepared by treatment of **9** with phosphorus pentachloride followed by *d*-(+)-α-methyl-4-nitrobenzylamine. The amides were separated by thick-layer chromatography or HPLC and purified by recrystallization. Although the hydrolysis of the amide bond in **10** and **11** might have led to the isolation of the two enantiomers of **9**, only racemic **9** was obtained under the experimental conditions. This result was not unexpected since complete equilibration of the amides **10** and **11** was observed after refluxing for 30 min in methanol (approximately 10% equilibration was observed after 24 h at room temperature). The absolute configuration of **10** and **11** were determined by single crystal X-ray analysis and are as shown in Figures 1 and 2. Additional details for all X-ray determinations are given in the Experimental Section. In the in vitro benzodiazepine binding assay[3] compound **10** was active with an IC_{50} of 88 nM (diazepam 5 nM) whereas compound **11** was inactive (IC_{50} > 1000 nM; Table I lists the IC_{50}'s for many of the compounds discussed in this paper). The benzodiazepine receptor appears, therefore, to selectively only recognize **10**.

Synthesis and Resolution of the 1-*tert*-Butyl-3-carboxamide Benzodiazepine 12. Since the acid **9** could not be obtained in optically active form, the resolution of **12** was undertaken. The choice of the 3-amide substituent was based on observations that this substituent greatly increased the potency of the imidazo class of benzodiazepines[9,15] and also was present in compounds with mixed agonist/antagonist properties (i.e., **6** and **6a**). Compound **12** was prepared by treatment of the ester **8** with ammonia or alternatively, by treatment of the acid **9** with thionyl

Scheme I[a]



a (a) H_2, $(CH_3)_3CCHO$; (b) KOH; (c) PCl_5; (d) *d*-(+)-α-methyl-4-nitrobenzylamine.

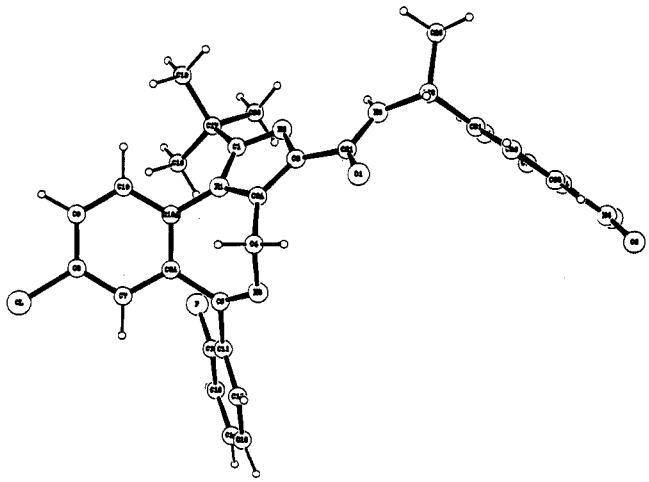


Figure 1. Perspective drawing of the X-ray structure of **10**.

(13) Walser, A.; Flynn, T.; Mason, C.; Fryer, R. I. *J. Heterocycl. Chem.* **1986**, *23*, 1303.
(14) Walser, A.; Flynn, T.; Fryer, R. I. *J. Heterocycl. Chem.* **1978**, *15*, 577.
(15) Unpublished observations from Hoffmann-LaRoche, Inc., Nutley, NJ.

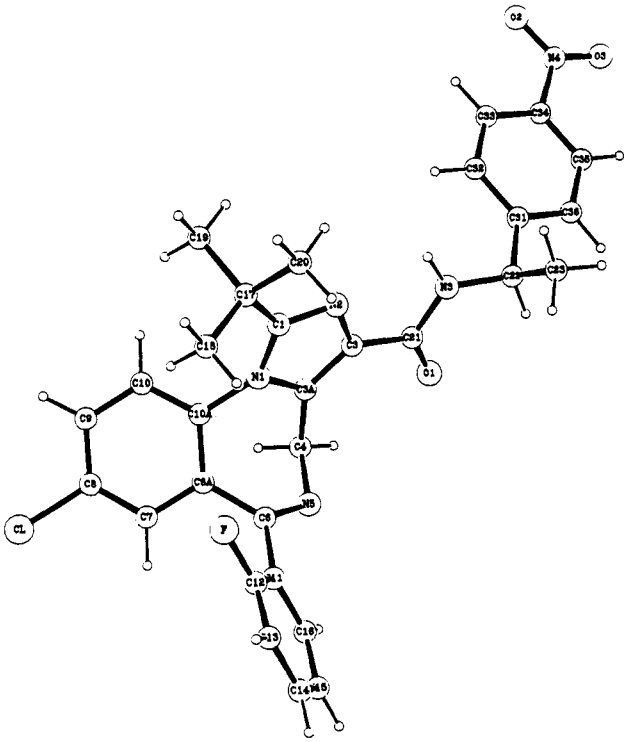
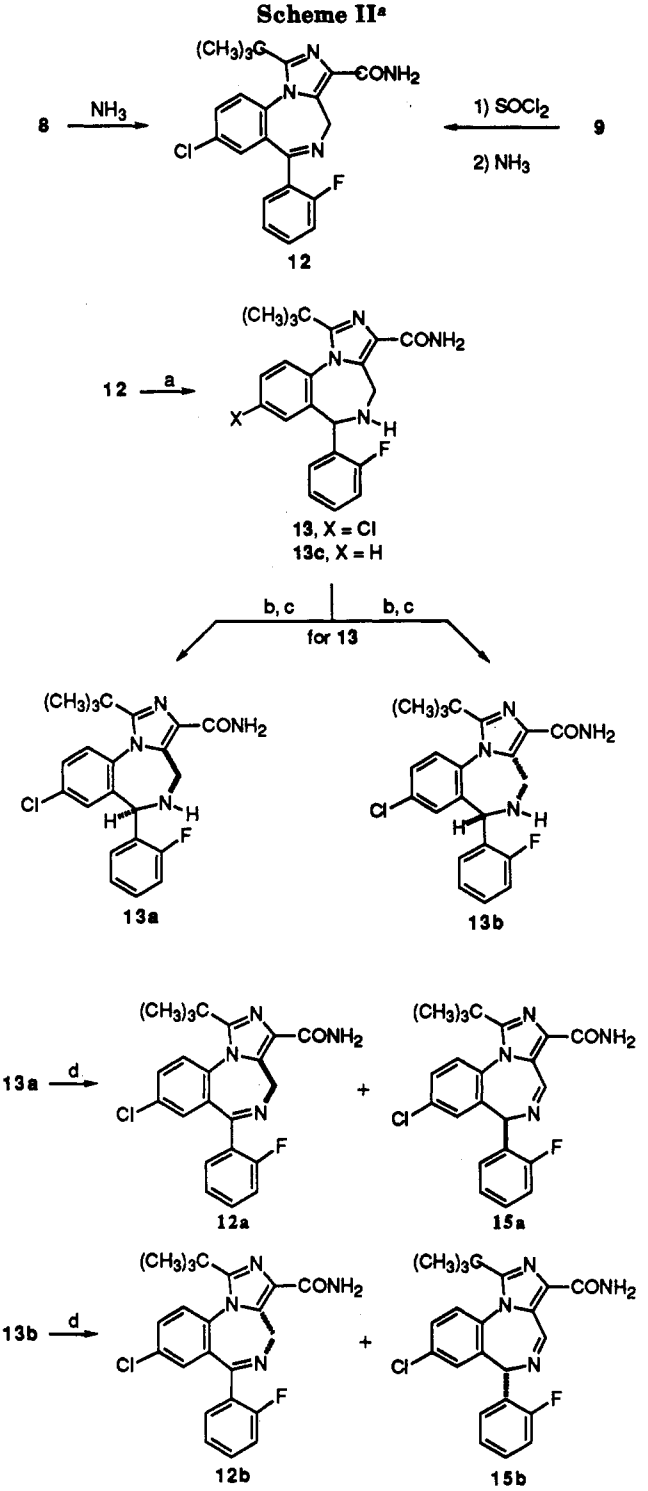


Figure 2. Perspective drawing of the X-ray structure of 11.

chloride followed by ammonia (Scheme II). The NMR spectrum of **12** at 200 °C showed no collapse of the AB pattern for the C-4 methylene protons, indicating that the rate of interconversion of **12a** and **12b** is slow enough to allow for the separation of the two enantiomers. Attempts to directly resolve **12** with optically active acids were not successful. Therefore, the resolution of **12** was accomplished by the following sequence: (1) reduction of the imine bond in **12** with sodium cyanoborohydride or with zinc in acetic acid gave the dihydro compound **13** (attempts to reduce the imine double bond in **12** by hydrogenation with platinum oxide as catalyst led to **13** along with the deschloro analog **13c**); (2) treatment of **13** with (1*S*)-(+)-10-camphorsulfonic acid furnished the salts **14a** and **14b**; (3) cleavage of the salts with ammonia gave the two enantiomers **13a** and **13b**; and (4) oxidation of **13a** and **13b** with lead tetraacetate/iodine afforded **12a** and **12b**, respectively, along with minor amounts (<10%) of the 4,5-double bond isomers **15a** and **15b**, (see Scheme II; for ease of representation, the salts **14a** and **14b** are not shown). The NMR spectrum (DMSO-d_6) of **13** was interesting in that two signals for the *tert*-butyl moiety were observed at 1.41 and 0.98 ppm, in the ratio of 7:1, respectively; this ratio changed to 16:1 in $CDCl_3$ indicating the presence of two conformers[16] that were postulated to have the structures **16** and **17** (Figure 3). The minor isomer was assigned to structure **17** based on the higher field signal of the *tert*-butyl group in the NMR spectrum. In this "closed" conformation the *tert*-butyl group is interacting with the phenyl group, in a face-on orientation which results in the higher field NMR signal. Although two compounds could be detected by thin-layer chromatography, all attempts at isolation proved fruitless, in that the same two spots reappeared after separation, standing

(16) For similar solvent effects on conformation: Whitesides, G. M.; Grocki, J. J.; Holtz, D.; Steinberg, H.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 1058.

Scheme II[a]



[a] (a) $NaCNBH_3$; (b) (1*S*)-(+)-10-camphorsulfonic acid; (c) NH_3; (d) $Pb(OAc)_4$, I_2.

for a short time, and rechromatography. The same results were obtained by HPLC, in which case the two peaks were collected, but upon reinjection the original ratio was obtained for the two compounds. Upon slow crystallization from methanol, two crystal forms were obtained, namely rods and prisms. These were separated manually and the prisms developed rapidly by tlc which gave a single spot, corresponding to the major product **16**. The rods showed two spots in the ratio of 1:1. The two crystal forms were dissolved in dichloromethane and after standing for a short time the TLC's were found to be identical showing the original two spots. Molecular mechanics calculations with

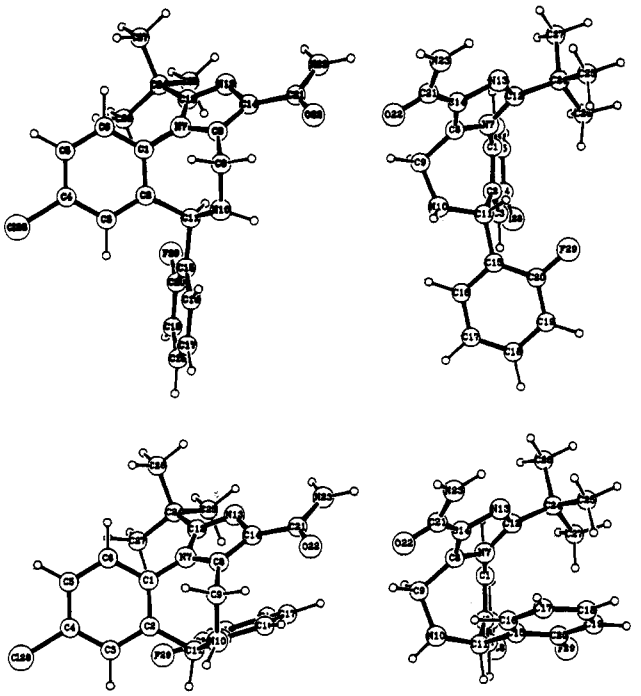
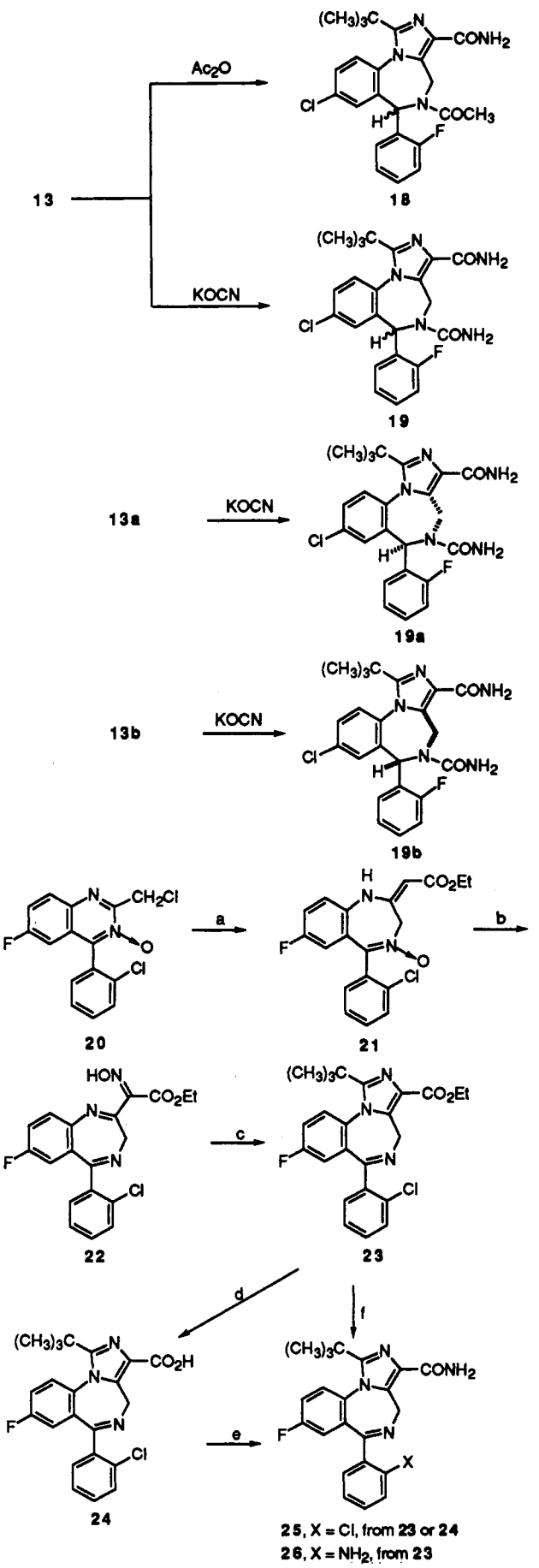


Figure 3. ORTEP drawings of the conformers **16** (top) and **17** (bottom), postulated for compound **13**. The views on the left have the fused benzene ring in the plane of the paper; this ring has been rotated approximately 90° for the views on the right. For clarity, only one enantiomer is shown.

electrostatic terms including using MAXIMIN2 within the SYBYL[12] modeling program gave a minimized energy of 34.7 kcal/mol for conformer **16** (the "open" form) and 31.2 kcal/mol for conformer **17** (the "closed" form). The X-ray structure of **13a** was used as the starting point for calculating the energy of **16**. The conformation of **17** which was chosen for minimization was obtained by inverting the chirality at the asymmetric center of the X-ray structure of **13b**. Based on these calculations conformer **17** is favored which is contrary to the NMR observations. However, these are gas-phase based calculations and do not include the effects of nonpolar, aprotic solvents such as deuterochloroform (used for the NMR experiments), which should preferentially stabilize the open form. In water, the closed form might be preferred due to the "hydrophobic collapse" effect. There is a significant van der Waals interaction between the *tert*-butyl group and the pendant phenyl ring in the closed form which accounts for 3.0 kcal/mol of the 3.5 kcal/mol difference in the calculated energies. Interestingly, when the amine **13** was acetylated to give **18** or treated with potassium cyanate to give the urea **19**, only one *tert*-butyl peak corresponding to the high field peak in **13** (the closed form) was observed. In addition to preparing racemic **19** the enantiomers **13a** and **13b** were also converted to the optically active ureas **19a** and **19b** (see Scheme III). Using europium shift reagents, both **19a** and **19b** were shown to be optically pure. Single crystal X-ray analyses were carried out for both **18** (racemic) and **19b** (optically active). Energy minimization using MAXIMIN2 for the closed form **18** (the X-ray structure) showed this to be the preferred conformer with a minimum energy of 29.5 kcal/mol. The open form of **18** gave a minimum energy of 35.2 kcal/mol. Similarly, energy calculations for **19a** gave a value of 26.3 kcal/mol for the closed form and an energy of 31.6 kcal/mol for the open form. Although the calculations predict

Scheme III[a]



[a] (a) EtOAc, *n*-BuLi, LDA; (b) (1) PCl_3, (2) $NaNO_2$; (c) H_2, Raney Ni, $(CH_3)_3CCHO$; (d) KOH; (e) PCl_5, NH_3; (f) NH_3.

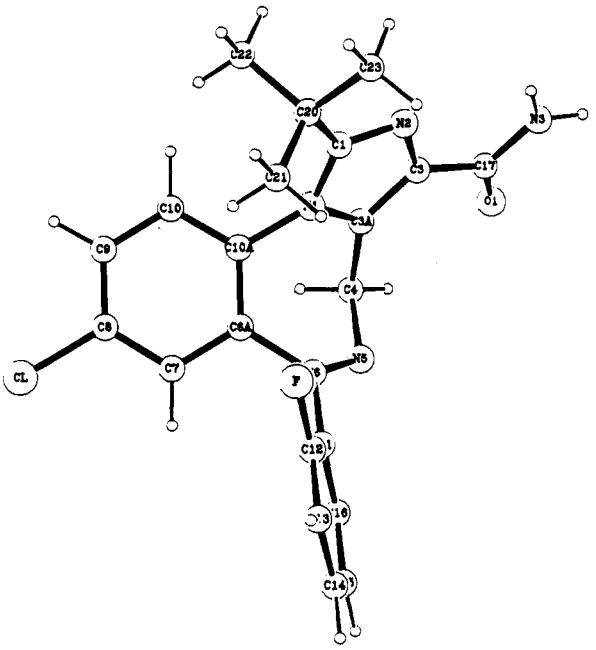


Figure 4. Perspective drawing of the X-ray structure of **12b**.

that the closed form is favored in all three cases, the difference in energy is smallest for the unsubstituted amine **13**.

The absolute configurations of **13a** and **13b** were determined by single crystal X-ray analyses. The structures correspond to conformer **16**, the major component. In the presence of the europium shift reagent, racemic **13** showed two identical *tert*-butyl peaks shifted downfield (1.56 and 1.60 ppm). Both **13a** and **13b** showed only one *tert*-butyl peak indicating at least 95% enantiomeric purity. Apparently binding of the shift reagent either conceals or eliminates the previously observed *tert*-butyl group of the minor conformer **17**.

Although many different oxidizing agents (DDQ, MnO_2, diphenylselenic anhydride, CrO_3, etc.) were explored to effect the conversion of **13a** (and **13b**) to **12a** (and **12b**), respectively, lead tetraacetate/iodine proved to be the most advantageous. Diphenylselenic anhydride and DDQ gave only the racemic compound **12**, as well as varying amounts of the 4,5-double bond isomer. MnO_2 gave partially racemized product along with approximately 50% of the 4,5-double bond isomer, while nickel peroxide gave almost exclusively the 4,5-double bond isomer. (An authentic sample of racemic **15** which was used for comparison studies was prepared by oxidizing compound **13** with MnO_2). The mechanism of the oxidation by which **13a** and **13b** lead to racemized products is not understood. When lead tetraacetate/iodine was used as the oxidizing agent, compounds **12a** and **12b** were obtained optically pure[17] as determined with europium shift reagents. The amount of **15a** and **15b** formed under these oxidizing conditions was less than 10%. The absolute configuration of **12b** was determined by single-crystal X-ray analysis and the structure is shown in Figure 4. The absolute configuration of **12a** was then assigned accordingly. It should be noted that compounds **13a** and **13b** contain both a center of asymmetry and a chiral plane which sets the chirality due to conformational differences. Compound **13a** was assigned the absolute configuration [*R*]-(6*R*) and **13b** the [*S*]-(6*S*) absolute configuration where [*R*] and [*S*] indicates the conformational chirality associated with the plane passing through the chlorine atom, the fused benzene ring, the nitrogen at the 1-position, and the carbon at the 6-position. The [*R*] or [*S*] assignments were based on the IUPAS rules.[18] Other structures in this report containing conformational chirality were assigned the [*R*] or [*S*] nomenclature based on the same criteria. Because of the introduction of the double bond to give **12a** and **12b**, the center of asymmetry is lost but the chiral plane is maintained, thus leading to optically active compounds due to the conformational chirality.

From a stereochemical aspect, the preparation of compounds **19a** and **19b** is of interest. When compound **13a** is converted to the urea **19a**, the configuration changes from [*R*]-(6*R*) to [*S*]-(6*R*) with the 4-methylene group being inverted to the down position (see Scheme III). In a similar manner **13b** is converted to the urea **19b**. These inversions of the conformational chirality are also consistent with the pharmacological data (see Table I). Thus, **12a** (formed by oxidation of **13a**) which has the [*R*] configuration is more active both in vitro and in vivo than **12b** ([*S*] configuration). The ureas **19a** and **19b** which do not recognize the receptor (IC_{50}'s for both >1000 nM) are probably metabolized in vivo to **12b** and **12a**, respectively.[19] The urea **19a** (which gives **12b**) is inactive in vivo while the urea **19b** (which gives **12a**) is equiactive with **12a**. Thus, for **12**, which was shown to be an agonist,[20] the [*R*] conformational chirality is required for recognition by the benzodiazepine receptor. This is the same conformational chirality as that of diazepam,[6] which is also an agonist.

Synthesis and Resolution of the 1-*tert*-Butyl-3-carboxamide Benzodiazepine 25. The resolution of a similar imidazobenzodiazepine (**25**) in which the halogens have been reversed was undertaken since many of these 8-fluoro-2′-chloroimidazobenzodiazepines have a pharmacological profile indicating mixed agonist–antagonist properties.[15] Thus, compound **12** is a pure agonist whereas compound **25** is a mixed agonist-antagonist. Compound **25** had the profile of an agonist in some pharmacological tests but was inactive in other tests unless diazepam (a full agonist) was present, in which case the agonist effects of diazepam were blocked by **25**.[20]

Due to some synthetic difficulties in trying to synthesize **24** following the chemistry shown in Scheme I, an alternate sequence was used (Scheme III). Thus, the (chloromethyl)quinazoline **20** was treated with the anion of ethyl acetate to give the ring-expanded product **21**. Compound **21** was converted to the oxime **22** and then cyclized to the imidazo compound **23** by reaction with hydrogen in the presence of trimethylacetaldehyde. Compound **23** was

(17) Although in principle, the presence of the minor conformer **17** could lead to some racemization in the preparation of **12a** and **12b** since the asymmetry due to the presence of the chiral plane is inverted, this did not prove to be the case. Either the rates of the oxidation of the conformers are different or any minor amount of the antipode was removed during the purification process.

(18) IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry. *J. Org. Chem.* **1970**, *35*, 2849–2867.

(19) The corresponding urea of diazepams has been shown to be converted in vivo (rat) to diazepam and its metabolites: Tegyey, Z.; Vereczkey, L.; Tamas, J.; Rohricht, J.; Kisfaludy, L.; Otvos, L. *Chem. Abstr.* **1985**, *103*, 153198r.

(20) Data not shown. Experiments to classify compounds as agonists, antagonists, or mixed agonists/antagonists discussed in this paper were carried out by the Departments of Pharmacology and/or Toxicology, Hoffmann-LaRoche, Inc., Nutley, NJ.

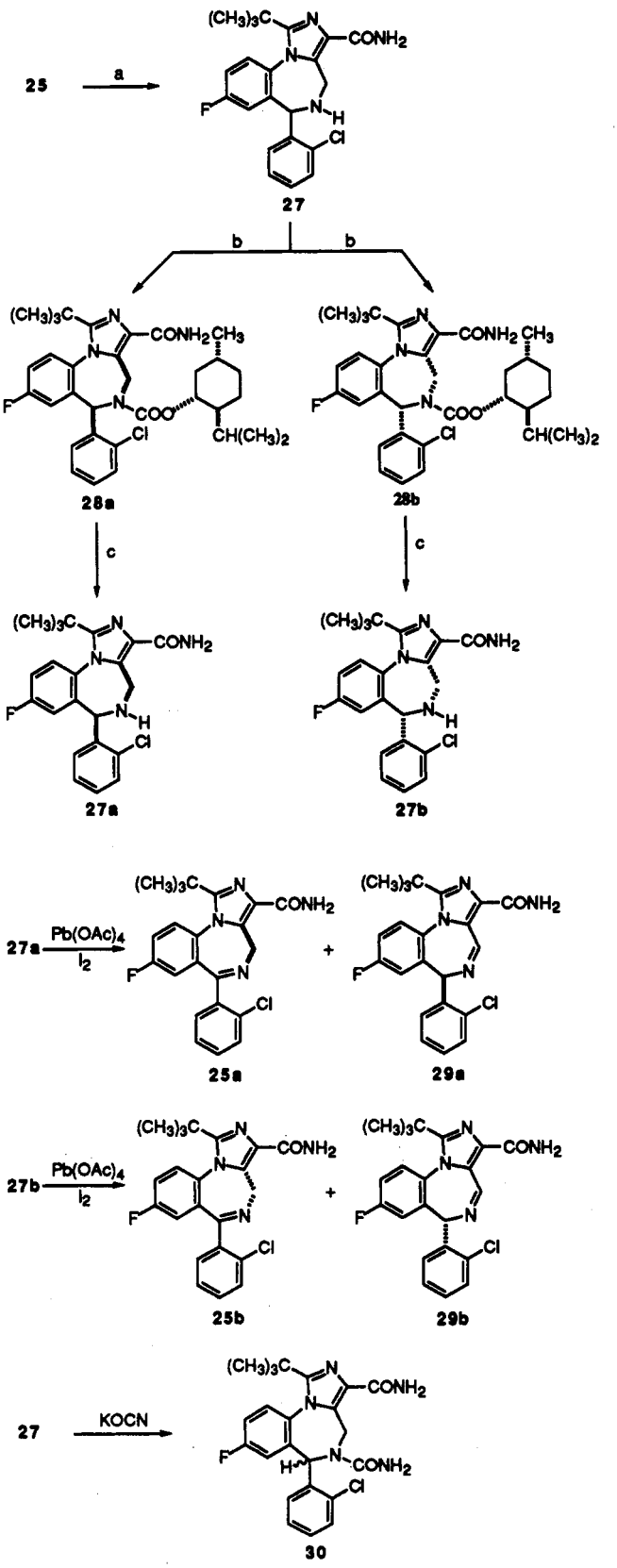
(21) Everett, G. M.; Richards, R. K. *J. Pharmacol. Exp. Ther.* **1944**, *81*, 402–407.

hydrolyzed to the acid **24** which was converted to the amide **25** by treatment with PCl_5 followed by ammonia. Attempts to go directly from the ester **23** to the amide were only partially successful in that there were always varying amounts of the 2'-amino compound **26** present in the reaction mixture. Compound **25** was reduced to the dihydro derivative **27** with sodium cyanoborohydride. Attempts to resolve **27** following the procedure described for the resolution of **13** were not successful and an alternate method was used which involved the preparation of the diastereomeric urethanes **28a** and **28b**. Thus, treatment of **27** with (−)-menthyl chloroformate gave **28a** and **28b** which were separated by column chromatography. Hydrolysis of the urethane group with HBr in HOAc yielded **27a** and **27b** (Scheme IV), which were shown to be optically pure by the appearance of only one *tert*-butyl peak in the presence of a europium chemical shift reagent (the racemic compound **27** showed two *tert*-butyl peaks in the ratio of 1:1). Oxidation of **27a** with lead tetraacetate and iodine gave optically active **25a** along with optically active **29a**, the 4,5-double bond isomer of **25a**. Similar treatment of **27b** gave **25b** and the double bond isomer **29b**. Compounds **25a** and **25b** were obtained with an optical purity of at least 95% as determined by europium shift reagents. The absolute configuration of **25b**, which is [*S*], was determined by X-ray analysis, and the configurations of the other compounds were then assigned accordingly. The X-ray structure of **25b** is shown in Figure 5. Compound **27** was also converted to the urea **30**, analogous to the preparation of the urea **19** (see Scheme IV).

The pharmacological data in Table I for compounds **25a** and **25b** again indicate the preference for the 3-methylene group to be in the up position ([*R*] conformational chirality) for maximum activity. Although the pharmacological data for compound **25a** showed the profile of a mixed agonist–antagonist,[20] the [*R*] conformational chirality was still required in order for binding to take place at the benzodiazepine receptor. The urea **30** does not recognize the benzodiazepine receptor (IC_{50} > 1000 nM) but is active in vivo, probably due to metabolism to compound **25**.[19] These results are analogous to those found for the urea **19**.

Synthesis and Resolution of the 1-*tert*-Butylbenzodiazepine 31. To complete our study on the resolution and the pharmacological activity of imidazobenzodiazepines we synthesized compound **31**. When the 3-carboxylic acid **9** was decarboxylated by refluxing in 1,2,4-trichlorobenzene, the benzodiazepine **31** was formed in addition to the isomer **32**. Compound **31** was reduced with sodium cyanoborohydride to give the dihydro compound **33**. The resolution of **33** was accomplished with the use of (1*R*)-(−)-10-camphorsulfonic acid to give the enantiomer **33a** (via the salt **34a**) and with (1*S*)-(+)-10-camphorsulfonic acid to give the other enantiomer **33b** (via the salt **34b**; Scheme V). The absolute configurations of both **33a** and **33b** were determined by single crystal X-ray analysis. Oxidation of **33a** with lead tetraacetate and iodine gave optically active **31a** and the 4,5-double bond isomer **32a**. In a similar manner **33b** led to **31b** and the double bond isomer **32b** (Scheme V). The absolute configuration of **31a** was determined by X-ray analysis and a perspective drawing is shown in Figure 6. Again the **31a** which has the [*R*] chirality is the more active enantiomer (Table I), although much weaker in potency that midazolam.

Scheme IV[a]



[a] (a) $NaCNBH_3$; (b) (−)-menthyl chloroformate; (c) (1) HBr, (2) NH_4OH.

Conclusions

A novel method for the resolution of imidazo[1,5-*a*]-[1,4]benzodiazepine type compounds has been demonstrated. A *tert*-butyl group at the 1-position of the imidazo ring was utilized to "lock" the conformation of the seven-

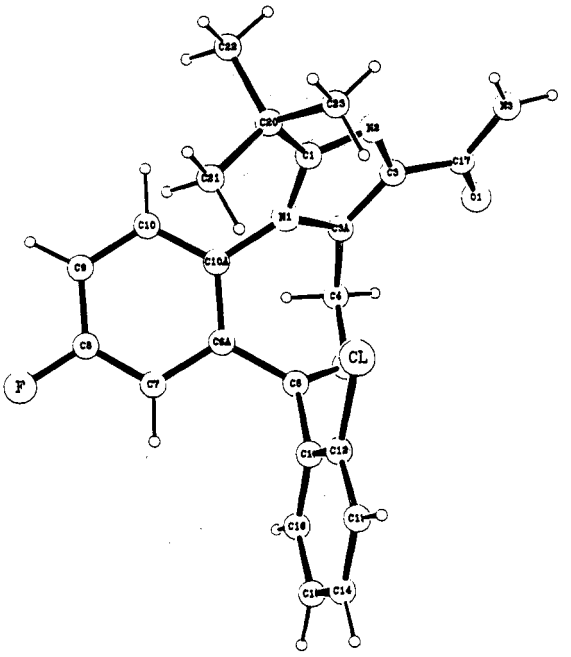


Figure 5. Perspective drawing of the X-ray structure of **25b**.

membered ring of the benzodiazepines to prevent inversion of the 4-methylene group (and thus racemization). Resolution was accomplished by the following sequence: (1) reduction of the 5,6-imine double bond to give the asymmetric dihydro compounds; (2) resolution of the dihydro derivatives; and (3) oxidation back to the optically active imines. As a consequence of the oxidation, the center of asymmetry is lost while the conformational asymmetry is retained. For all compounds prepared and tested, the [*R*] enantiomer, with the 4-methylene group in the up position relative to the fused benzene ring for optimum recognition at the receptor complex, is more active.

Experimental Section

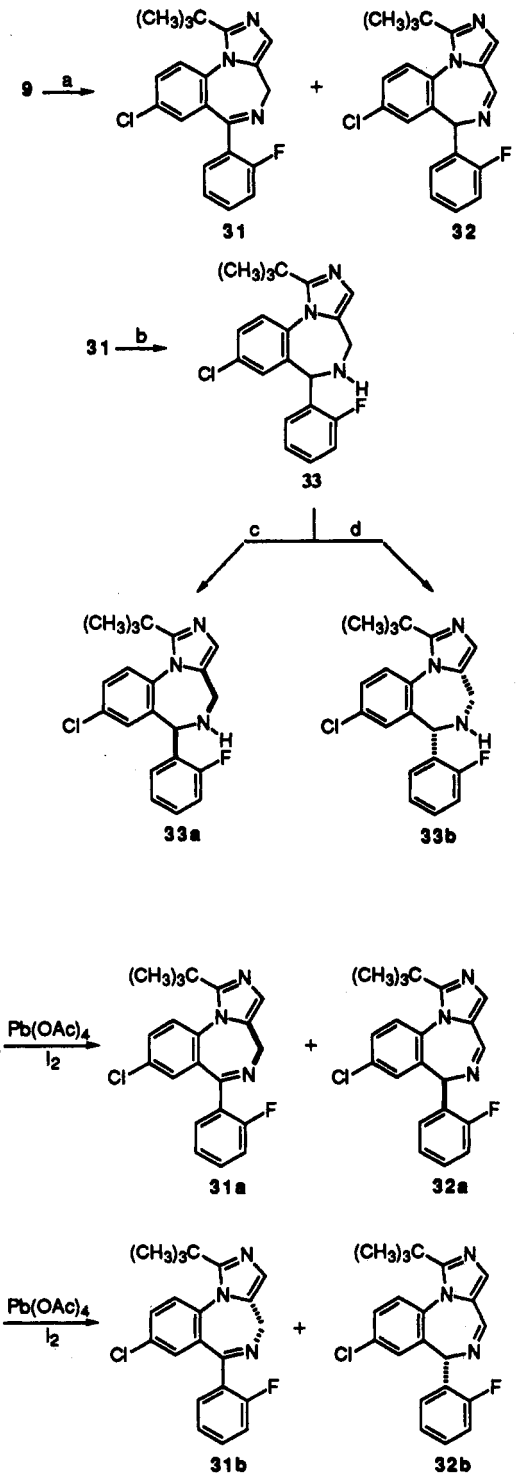
Melting points were determined either on a Thomas-Hoover capillary apparatus or on a hot stage apparatus and are uncorrected. NMR spectra were measured with a Varian XL-400 instrument using tetramethylsilane as an internal reference. Optical purities were determined by NMR analysis using the chiral shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III), Eu(hfc)$_3$, Fluka Chemicals. Mass spectra were determined on a Varian MAT CH5, VG ZAB-1F, or VG 7070E-HF instrument. Infrared spectra were determined with a Digilab FTS15E instrument. All chromatography was done using silica gel 60, 70–230 mesh, E. Merck. Organic solutions were dried with either anhydrous sodium sulfate or magnesium sulfate, before concentrating at water aspirator pressure (20–25 mm).

X-ray Analysis. Compounds 10, 11, 12b, 13a, 13b, 18, 19b, 25b, 31a, 33a, and 33b.[22] The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The data were corrected for absorption and for the observed reflections, $I > 2.5\sigma(I)$. In the final refinements, anisotropic thermal parameters were used for the non-hydrogen atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The structure of **10** was solved by a multiple-solution procedure[23] and was refined by block-diagonal least squares in which the matrix was partitioned into four blocks. The structure of **19b** was solved by a multiple-solution procedure[23] and was refined by block-diagonal least squares in which the matrix was partitioned into two blocks. All of the other structures were solved by a multiple-solution procedure[23] and were refined by full-matrix least squares. The unit cell of **10** contained two independent molecules, that is, two molecules not related by crystallographic symmetry. The conformations of the independent molecules are very similar and only differ in the rotation

(22) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(23) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* 1971, *27*, 368–376.

Scheme V[a]



[a] (a) 1,2,4-Trichlorobenzene, heat; (b) $NaCNBH_3$; (c) (1*R*)-(−)-10-camphorsulfonic acid; (d) (1*S*)-(+)-10-camphorsulfonic acid.

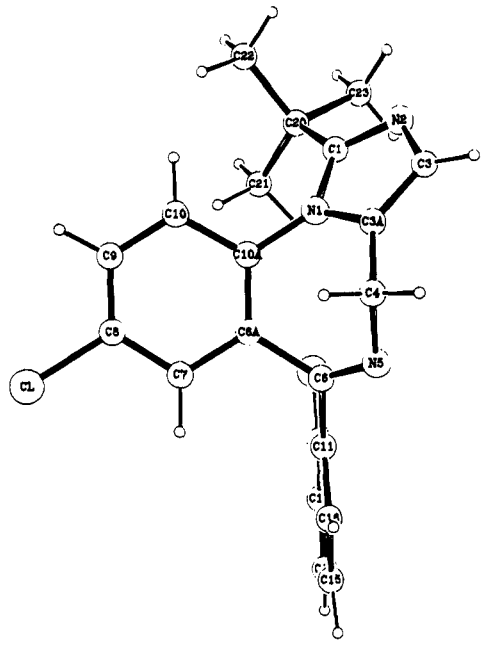


Figure 6. Perspective drawing of the X-ray structure of **31a**.

Table II

compound	final R_w	R_w final wR (antipode)
10	0.0434	0.0448
11	0.0384	0.0462
12b	0.0538	0.0594
13a	0.0481	0.0593
13b	0.0555	0.0668
19b	0.0377	0.0412
25b	0.0389	0.0561
31a	0.0602	0.0653
33a	0.0378	0.0669
33b	0.0367	0.0638

angle of the side-chain phenyl group. For clarity, only one of the independent molecules is shown in Figure 1. Compound **12b** cocrystallized with methanol and methylene chloride, and the crystal used for data collection was first measured and then coated with epoxy cement to prevent solvent evaporation. Compounds **13a** and **13b** cocrystallized with methanol and methylene chloride and since the solvents were disordered in the crystal, the hydrogen atoms of the solvents were considered insignificant and were excluded from the final refinement. Compound **13a** had two reflections and **13b** had one reflection which were strongly affected by extinction and were excluded from the final refinement. For compound **18**, six reflections were excluded from the final refinement, and for **33b**, five reflections were excluded. The unit cell of **19b** contained two independent molecules, that is, two molecules not related by crystallographic symmetry. The conformations of the independent molecules are very similar and only differ in the rotation angle of the 5-phenyl group. The absolute configurations of **10**, **11**, **12b**, **13a**, **13b**, **19b**, **25b**, **31a**, **33a**, and **33b** were based on the anomalous scattering of the chlorine atom and were established by refining both enantiomers of each compound. The final weighted R values for the above compounds and their antipodes are shown below. Thus, by Hamilton's test,[23] the configurations shown in the Figures 1, 2, and 4–6 correspond to the absolute configurations. The atomic coordinates of **13b** were obtained by inverting those of compounds **13a** and those of **33a** were obtained by inverting the coordinates of **33b**.

Specific experimental details for the compounds in Table II follow.

X-ray analysis of 10: $C_{30}H_{27}ClFN_5O_3$, FW = 560.03; space group = $P2_1$; a = 18.547(3), b = 8.417(2), c = 18.138(3) Å; β = 94.17(1)°; Z = 4; ρ_{calcd} = 1.317 g cm^{-1}; μ (Cu Kα) = 16.0 cm^{-1}; crystal size = 0.06 × 0.10 × 0.65 mm; maximum θ = 70°; number of reflections = 5637; number of observed reflections = 3883; final R = 0.048; final R_w = 0.043; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 11: $C_{30}H_{27}ClFN_5O_3$, FW = 560.03; space group = $P2_12_12_1$; a = 10.691(4), b = 13.787(5), c = 18.906(5) Å; Z = 4; ρ_{calcd} = 1.335 g cm^{-1}; μ (Cu Kα) = 16.3 cm^{-1}; crystal size = 0.08 × 0.08 × 0.55 mm; maximum θ = 57°; number of reflections = 2149; number of observed reflections = 1513; final R = 0.043; final R_w = 0.038; final difference map, largest peak = <±0.2 e Å^{-3}.

X-ray analysis of 18: $C_{24}H_{24}ClFN_4O_2$, FW = 454.93; space group = $P2_1/a$; a = 11.901(3), b = 21.634(4), c = 9.028(2) Å; β = 101.86(1)°; Z = 4; ρ_{calcd} = 1.328 g cm^{-1}; μ (Cu Kα) = 18.1 cm^{-1}; crystal size = 0.14 × 0.40 × 0.45 mm; maximum θ = 48°; number of reflections = 2136; number of observed reflections = 1940; final R = 0.038; final R_w = 0.047; final difference map, largest peak = <±0.2 e Å^{-3}.

X-ray analysis of 19b: $C_{23}H_{23}ClFN_5O_2 \cdot H_2O$, FW = 473.93; space group = $A2$; a = 28.036(5), b = 10.058(2), c = 16.701(2) Å; β = 106.23 (1)°; Z = 8; ρ_{calcd} = 1.392 g cm^{-1}; μ (Cu Kα) = 18.9 cm^{-1}; crystal size = 0.12 × 0.14 × 0.55 mm; maximum θ = 57°; number of reflections = 3240; number of observed reflections = 2553; final R = 0.038, final R_w = 0.038; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 13a: $C_{22}H_{22}ClFN_4O$, FW = 471.38; space group = $C222_1$; a = 25.946(4), b = 9.526(2), c = 19.052(3) Å; Z = 8; ρ_{calcd} = 1.330 g cm^{-1}; μ (Cu Kα) = 27.7 cm^{-1}; crystal size = 0.15 × 0.25 × 0.40 mm; maximum θ = 57°; number of reflections = 1798; number of observed reflections = 1598; final R = 0.042; final R_w = 0.0481; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 13b: $C_{22}H_{22}ClFN_4O$, FW = 471.38; space group = $C222_1$; a = 25.960(5), b = 9.529(2), c = 19.060(5) Å; Z = 8; ρ_{calcd} = 1.328 g cm^{-1}; μ (Cu Kα) = 27.6 cm^{-1}; crystal size = 0.20 × 0.30 × 0.65 mm; maximum θ = 57°; number of reflections = 1801; number of observed reflections = 1644; final R = 0.047; final R_w = 0.0555; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 12b: $C_{22}H_{20}ClFN_4O \cdot 0.5CH_2Cl_2 \cdot 0.5CH_3OH$, FW = 469.37; space group = $B22_12$; a = 9.615(1), b = 19.164(3), c = 25.866(3) Å; Z = 8; ρ_{calcd} = 1.308 g cm^{-1}; μ (Cu Kα) = 27.3 cm^{-1}; crystal size = 0.12 × 0.20 × 0.40 mm; maximum θ = 57°; number of reflections = 1825; number of observed reflections = 1361; final R = 0.055; final R_w = 0.054; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 25b: $C_{22}H_{20}ClFN_4O$, FW = 410.88; space group = $P2_12_12_1$; a = 9.205(2), b = 9.589(2), c = 22.711(5) Å; Z = 4; ρ_{calcd} = 1.361 g cm^{-1}; μ (Cu Kα) = 19.5 cm^{-1}; crystal size = 0.20 × 0.40 × 0.70 mm; maximum θ = 57°; number of reflections = 1583; number of observed reflections = 1500; final R = 0.033; final R_w = 0.039; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 33a: $C_{21}H_{21}ClFN_3$, FW = 369.87; space group = $P2_12_12_1$; a = 10.156(2), b = 11.691(2), c = 15.839(4) Å; Z = 4; ρ_{calcd} = 1.306 g cm^{-1}; μ (Cu Cα) = 19.6 cm^{-1}; crystal size = 0.45 × 0.55 × 0.75 mm; maximum θ = 57°; number of reflections = 1470; number of observed reflections = 1458; final R = 0.029; final R_w = 0.0378; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 33b: $C_{21}H_{21}ClFN_3$, FW = 369.87; space group = $P2_12_12_1$; a = 10.158(1), b = 11.688(1), c = 15.842(2) Å; Z = 4; ρ_{calcd} = 1.306 g cm^{-1}; μ (Cu Kα) = 19.6 cm^{-1}; crystal size = 0.25 × 0.45 × 0.80 mm; maximum θ = 57°; number of reflections = 1473; number of observed reflections = 1455; final R = 0.028; final R_w = 0.0367; final difference map, largest peak = <±0.3 e Å^{-3}.

X-ray analysis of 31a: $C_{21}H_{19}ClFN_3$, FW = 367.85; space group = $P2_12_12_1$; a = 9.166(2), b = 13.106(3), c = 15.627(3) Å; Z = 4; ρ_{calcd} = 1.301 g cm^{-1}; μ (Cu Kα) = 19.7 cm^{-1}; crystal size = 0.04 × 0.25 × 0.30 mm; maximum θ = 57°; number of reflections = 1472; number of observed reflections = 937; final R = 0.068; final R_w = 0.060; final difference map, largest peak = <±0.4 e Å^{-3}.

8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid, Ethyl Ester (8). To a solution of 30 g (77.3 mmol) of **7**[13] and 13.3 g (155 mmol) of trimethylacetaldehyde in 300 mL of THF and 300 mL of EtOH was added 2 teaspoons of Raney nickel. The mixture

(24) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 506–510.

was hydrogenated at atmospheric pressure for 5 h and then filtered through a filter aid. The filtrates were concentrated and the residue crystallized from CH_2Cl_2/ether to give 21.9 g (64%) of **8** as white rods: mp 157–160 °C; IR ($CHCl_3$) 1723 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.39 (t, 3 H, CH_3), 1.39 (s, 9 H, $C(CH_3)_3$), 3.82, (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BN$), 5.95 (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BNH$), 4.40 (m, 2 H, CH_2CH_3), 6.94–7.42 (m, 7 H, arom). Anal. Calcd for $C_{24}H_{23}ClFN_3O_2$: C, 65.53; H, 5.27; N, 9.55. Found: C, 65.55; H, 5.25; N, 9.48.

8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid (9). A mixture of 25 g (56.8 mmol) of **8**, 6.4 g (114 mmol) of KOH, 375 mL of CH_3OH, and 75 mL of water was stirred and refluxed for 6 h. The CH_3OH was removed by distillation and the residue partitioned between 600 mL of ether and 500 mL of water. The organics were washed with water and the combined aqueous fractions were acidified with HOAc, cooled, and filtered to give 22.8 g (97%) of **9**. The analytical sample was prepared by crystallization from CH_3OH and obtained as white prisms: mp 230–235 °C; IR (KBr) 1722 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 1.31 (s, 9 H, $C(CH_3)_3$), 3.84 (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BN$) 5.74 (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BNH$), 7.15–7.92 (m, 7 H, arom). Anal. Calcd for $C_{22}H_{19}ClFN_3O_2$: C, 64.16; H, 4.65; N, 10.20. Found: C, 64.04; H, 4.86; N, 10.22.

[*R*]-(−)-(*R*)-8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-*N*-(4-nitro-1-phenylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (10). A solution of 2 g (4.87 mmol) of **9** and 1.2 g (5.84 mmol) of phosphorus pentachloride in 30 mL of CH_2Cl_2 was stirred for 1 h and then 1.1 g (5.84 mmol) of *d*-(+)-α-methyl-4-nitrobenzylamine hydrochloride was added followed by 8 mL of triethylamine. After stirring for 2 h the mixture was partitioned between CH_2Cl_2 and diluted potassium carbonate. The organic phase was dried and concentrated, and the residue was filtered through florisil using ether as the eluent. The ether was removed under reduced pressure and the oily residue purified by thick-layer chromatography on silica gel plates using ether/pentane (1:1) as the developing solvent. Two main bands at R_f 0.5 and 0.6 were observed. The band at R_f was removed and the product purified by crystallization from CH_2Cl_2/CH_3OH to give 0.5 g (36% based on a theoretical yield of 50%) of **10** as white rods: mp 229–231 °C; $[\alpha]^{25}_D$ −207.9° (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) 3400 (NH), 1662 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H, $C(CH_3)_3$), 1.62 (d, 3 H, CH_3), 3.77 (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BN$), 6.07 (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BNH$), 5.33 (m, 1 H, CH), 6.88–8.22 (m, 12 H, NH and arom); MS *m/e* 559 (M^+). Anal. Calcd for $C_{30}H_{27}ClFN_5O_5$: C, 64.34; H, 4.86; N, 12.51. Found: C, 64.16; H, 4.93; N, 12.51.

[*S*]-(+)-(*R*)-8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-*N*-(4-nitro-1-phenylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (11). The band at R_f 0.6 from the above experiment was removed and the product purified by crystallization from CH_2Cl_2/CH_3OH to give 0.5 g (36% based on a theoretical yield of 50%) of **11** as white rods: mp 197–200 °C; $[\alpha]^{25}_D$ +238.7° (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) 3400 (NH), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, $C(CH_3)_3$), 1.59 (d, 3 H, CH_3), 3.77 (d, 1 H, J_{AB} = 13 Hz, $COCH_AH_BN$), 6.07 (d, 1 H, J_{AB} = Hz, $COCH_AH_BNH$), 5.33 (m, 1 H, CH), 6.88–8.22 (m, 12 H, NH and arom); MS *m/e* 559 (M^+). Anal. Calcd for $C_{30}H_{27}ClFN_5O_5$: C, 64.34; H, 4.86; N, 12.51. Found: C, 64.38; H, 4.92; N, 12.52.

8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (12). A mixture of 8 g (18.2 mmol) of **8**, 8 g (150 mmol) of ammonium chloride, and 110 mL of a saturated solution of methanolic ammonia was heated for 18 h at 125–130 °C in a stainless steel bomb. The bomb was emptied and washed with 400 mL of water and 200 mL of CH_2Cl_2. The organics were separated and the aqueous layer was extracted with 200 mL of CH_2Cl_2. The organics were combined, dried, filtered with charcoal, and concentrated. The residue was crystallized from MeOH/EtOAc to give 5.3 g (71%) of **12** as white prisms: mp 277–279 °C; IR (KBr) 3455, 3310, 3260, 3190 (NH_2), 1662 cm^{-1} (CO); ^1H NMR (DMSO-d_6) δ 1.33 (s, 9 H, $C(CH_3)_3$), 3.80, (d, 1 H, J_{AB} = 12 Hz, $COCH_AH_BN$), 5.88 (d, 1 H, J_{AB} = 12 Hz, $COCH_AH_BNH$), 7.10–7.90 (m, 9 H, arom and NH_2); MS *m/e* 410 (M^+). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.91; N, 13.64. Found: C, 64.52; H, 4.90; N, 13.72.

Compound 12. From 9. A solution of 5.0 g (12.2 mmol) of **9** in 200 mL of CH_2Cl_2, in an ice bath, was treated with 2.8 g (13.4 mmol) of PCl_5 and allowed to stir for 30 min. The solution was then saturated with ammonia, allowed to warm to room temperature and stirred overnight. Water (250 mL) was added and the CH_2Cl_2 was removed under reduced pressure. The residue was cooled and the solid collected by filtration. Crystallization from EtOH gave 1.1 g (22%) of **12**, identical to the product obtained above.

[*R*]-(−)-8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxamide (12a), and (6*R*)-(−)-8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (15a). A solution of 8.5 g (19.3 mmol) of lead tetraacetate and 5.5 g (21.6 mmol) of iodine in 300 mL of CH_2Cl_2 was added with stirring over 30 min to 7 g (15.4 mmol) of **13a** in 350 mL of CH_2Cl_2, in an ice bath. After 2.5 h, 1 g (2.26 mmol) of lead tetraacetate and 0.5 g (1.95 mmol) of iodine were added. Stirring was continued for 1 h and the mixture was quenched with an aqueous solution of $NaHCO_3$ followed by the addition of 7.5 g (30.2 mmol) of sodium thiosulfate. Dilute potassium carbonate was added with stirring until the mixture was colorless. After filtering through Celite, the layers were separated and the aqueous fraction was extracted with 250 mL of CH_2Cl_2. The organics were combined, dried, and concentrated. The residue was chromatographed on 150 g of silica gel using ether/pentane (5/1) as the eluent. The solvents were concentrated and the residue crystallized from CH_3OH/ether/pentane to give 0.4 g (6.3%) of **15a** as white prisms: mp 238–242 °C; $[\alpha]^{25}_D$ −392.54° (*c* = 1.0, DMSO); IR (KBr) 3460, 3350, 3276, 3175 (NH_2), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H, $C(CH_3)_3$), 5.60 (s, 1 H, CH), 9.03 (d, 1 H, N=CH); MS *m/e* 410 (M^+). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.92; N, 13.64. Found: C, 64.06; H, 4.94; N, 13.64.

After the removal of **15a**, the solvent for elution was changed to ether. The fractions containing the product were combined and concentrated in vacuo. The residue was crystallized from methanol/ether/pentane to give 4.4 g (70%) of **12a** as white rods: mp 284–291 °C; $[\alpha]^{25}_D$ −270.4° (*c* 1.0, DMSO); IR (KBr) 3520, 3478, 3397, 3302 (NH_2), 1687, 1672 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.35 (s, 9 H, $C(CH_3)_3$), 3.80 (d, 1 H, J_{AB} = 12 Hz, $COCH_AH_BN$), 6.11 (d, 1 H, J_{AB} = 12 Hz, $COCH_AH_BNH$), 5.40 (bs, 1 H, CONH), 6.92–7.88 (m, 8 H, arom and CONH); MS *m/e* 410 (M^+). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.92; N, 13.64. Found: C, 64.29; H, 4.88; N, 13.65.

[*S*]-(+)-8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxamide (12b) and (6*S*)-(+)-8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (15b) The same procedure described for the preparation of compound **12a** was used to prepare **12b**. The first product isolated from the column was **15b** (6% yield) which was obtained as white rods: mp 236–240 °C; $[\alpha]^{25}_D$ +378.31° (*c* = 1.0, DMSO); IR (KBr) 3488, 3352, 3295, 3195 (NH_2), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H, $C(CH_3)_3$), 5.60 (s, 1 H, CH), 9.04 (d, 1 H, N=CH); MS *m/e* 410 (M^+). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.92; N, 13.64. Found: C, 64.17; H, 4.92; N, 13.40.

Further elution from the column using ether as the solvent gave **12b** in 79% yield which was obtained as white prisms: mp 288–292 °C; $[\alpha]^{25}_D$ +252.7° (*c* 1.0, DMSO); ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H, $C(CH_3)_3$), 3.81 (d, 1 H, J_{AB} = 12 Hz, $COCH_AH_BN$), 6.13 (d, 1 H, J_{AB} = 12 Hz, $COCH_AH_BNH$), 5.40 (bs, 1 H, CONH), 6.90–7.85 (m, 8 H, arom and CONH); MS *m/e* 410 (M^+). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.92; N, 13.64. Found: C, 64.57; H, 4.87; N, 13.62.

8-Chloro-1-(1,1-dimethylethyl)-5,6-dihydro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (13). A solution of 20.4 g (49.6 mmol) of **12** in 120 mL of CH_3OH and 245 mL of acetic acid was cooled to 10 °C and 6.2 (99.3 mmol) of sodium cyanoborohydride was added with stirring. After 1 h at 10 °C, the mixture was warmed to room temperature and stirred for 30 min and then 750 mL of water was added. Following extraction with CH_2Cl_2 (3 × 250 mL), the organics were washed with dilute NH_4OH and concentrated to a small volume. The residue was treated with ether and pentane and the resulting solid was collected by filtration to give 19.9 g (99%)

of **13**. The analytical sample was prepared by crystallization from CH_2Cl_2/ether to give colorless rods: mp 257–259 °C; IR (KBr) 3453, 3324, 3275, 3180 (NH, NH_2), 1662 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 0.98, 1.41 (s, 9 H, $C(CH_3)_3$), 3.16 (d, 1 H, J_{AB} = 15 Hz, $COCH_AH_BN$), 5.00 (d, 1 H, J_{AB} = 15 Hz, $COCH_AH_BNH$), 5.35 (b, 1 H, NH), 6.74 (d, 1 H, CH), 6.90–7.96 (m, 7 H, arom); MS *m/e* 412 (M^+). Anal. Calcd for $C_{22}H_{22}ClFN_4O$: C, 64.00; H, 5.37; N, 13.57. Found: C, 63.77; H, 5.37; N, 13.31.

6-(2-Fluorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (13c). To a solution of 0.5 g (1.22 mmol) of **12** in 15 mL of acetic acid and 3 mL of H_2O was added 50 mg of platinum oxide. The mixture was hydrogenated at atmospheric pressure for 8 h and the catalyst was removed by filtration. The filtrate was concentrated and the residue partitioned between EtOAc and dilute NH_4OH. The organic fraction was dried and concentrated. The product was isolated by thick-layer chromatography using EtOAc as the developing solvent. The product was crystallized from CH_2Cl_2/ether/pentane to give 60 mg (13%) of **13c** as white prisms: mp 220–225 °C; IR (KBr) 3452, 3320, 3270, 3212 (NH_2, NH), 1642 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 0.81, 1.33 (s, 9 H, $C(CH_3)_3$), 2.94 (d, 1 H, J_{AB} = 15 Hz, $COCH_AH_BN$), 4.85 (d, 1 H, J_{AB} = 15 Hz, $COCH_AH_BNH$), 6.61 (d, 1 H, CH); MS *m/e* 378 (M^+). Anal. Calcd for $C_{22}H_{23}FN_4O$: C, 69.81; H, 6.12; N, 14.81. Found: C, 69.57; H, 6.34; N, 14.67.

8-Chloro-1-(1,1-dimethylethyl)-5,6-dihydro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide, Salt with (−)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic Acid (14a). A solution of 37.8 g (91.5 mmol) of **13** and 22.9 g (91.5 mmol) of (1*S*)-(+)-10-camphorsulfonic acid in 1.2 L of EtOH was concentrated to 750 mL and allowed to cool. The solid was collected by filtration and recrystallized from EtOH/ether to give 24 g (81% based on theoretical yield of 50%). The analytical sample was prepared by recrystallization from EtOH and obtained as white needles: mp (sealed tube) 270–271 °C; $[\alpha]^{25}_D$ −19.8 (*c* 1.0, DMSO); IR (KBr) 3480, 3358 (NH, NH_2), 1748, 1738, 1678, 1672 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 0.73, 1.02 (2s, 6 H, $C(CH_3)_2$), 1.36 (s, 9 H, $C(CH_3)_3$), 3.72 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 5.20 (s, 1 H, NCH), 5.41 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$). Anal. Calcd for $C_{22}H_{22}ClFN_4O{\cdot}C_{10}H_{164}S$: C, 59.57; H, 5.96; N, 8.50. Found: C, 59.38; H, 6.40; N, 8.50.

[*R*]-(6*R*)-(−)-8-Chloro-6-(2-fluorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide·0.5CH_2Cl_2 (13a). The salt (24 g) obtained from the previous reaction was partitioned between dilute NH_4OH and CH_2Cl_2. The aqueous fraction was extracted with CH_2Cl_2 and all the organics were combined and concentrated to approximately one-half of the original volume. An excess of methanol was added and the mixture further concentrated to remove most of the CH_2Cl_2. The methanol fraction was cooled and the resulting precipitate collected by filtration. Recrystallization from CH_2Cl_2/CH_3OH gave 15.1 g (73%) of **13a** as white prisms: mp 186–193 °C; $[\alpha]^{25}_D$ −62.89° (*c* = 1.0, DMSO); ^1H NMR ($CDCl_3$) δ 0.85, 1.38 (2s, 9 H, $C(CH_3)_3$, 17/1 ratio), 3.18 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 4.96 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 4.977 (s, 1 H, NCH), 5.60 (b, 1 H, NH). Anal. Calcd for $C_{22}H_{22}ClFN_4O{\cdot}0.5CH_2Cl_2$: C, 59.34; H, 5.09; N, 12.31. Found: C, 59.06; H, 5.27; N, 12.27.

[*S*]-(6*S*)-(+)-8-Chloro-6-(2-fluorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide·0.5 CH_2Cl_2 (13b). The first filtrates from the preparation of the salt of **13a** were concentrated and the residue crystallized from 2-propanol/ether to give an additional 2 g of **13a**. The filtrates contained the enriched salt of **13b** which was not isolated. The filtrates were concentrated and the residue partitioned with CH_2Cl_2 and dilute NH_4OH. The aqueous phase was extracted with CH_2Cl_2 and all of the organics were combined, dried, and concentrated to approximately one-third of the original volume. Methanol was added and the mixture was further concentrated to remove most of the CH_2Cl_2. The methanol solution was cooled and the precipitate collected by filtration. The solid was recrystallized two times from CH_2Cl_2/CH_3OH to give 14.5 g (70%) of **13b** as white prisms: mp 178–191 °C; $[\alpha]^{25}_D$ +62.79° (*c* = 1.0, DMSO); ^1H NMR ($CDCl_3$) δ 0.85, 1.37 (2s, 9 H, $C(CH_3)_3$, 20/1 ratio), 3.18 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 4.96 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 4.97 (s, 1 H, NCH), 5.50 (b, 1 H, NH). Anal. Calcd for $C_{22}H_{22}ClFN_4O{\cdot}0.5\ CH_2Cl_2$: C, 59.34; H, 5.09; N, 12.31. Found: C, 58.96; H, 5.29; N, 12.29.

Oxidation of 13a with Diphenylselenic Anhydride. A solution of 0.2 g (0.44 mmol) of **13a** in 10 mL of CH_2Cl_2 was treated with 0.17 g (0.46 mmol) of diphenylselenic anhydride and the mixture stirred for 7 h. Following the addition of H_2O, the layers were separated and the organics were dried and concentrated. The residue was crystallized from ether/pentane and then from CH_2Cl_2/CH_3OH to give 0.1 g (50%) of **12** as white prisms, mp 285–290 °C. The optical rotation was 0°. With europium shift reagents, the NMR spectrum showed two *tert*-butyl peaks in the ratio of 1:1.

8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (15). A mixture of 2.0 g (4.84 mmol) of **13**, 10 g of activated MnO_2, and 100 mL of CH_2Cl_2 was refluxed for 20 h and then filtered. The solids were washed with CH_2Cl_2 and the filtrates concentrated. The residue was triturated with petroleum ether and the solids collected by filtration. Recrystallization from CH_2Cl_2/CH_3OH gave 0.7 g (33%) of **15** as white rods: mp 280–283 °C. The spectra were identical to those described for the enantiomers **15a** and **15b**. Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.92; N, 13.64. Found: C, 64.22; H, 5.06; N, 13.86.

5-Acetyl-8-chloro-6-(2-fluorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (18). A solution of 1 g (2.42 mmol) of **13** and 50 mL of acetic anhydride was heated at 90 °C for 90 min, cooled, and filtered. The filtrates were concentrated, and the residue was crystallized from ether. The solid from the first filtration were combined with these solids and recrystallized from CH_2Cl_2/CH_3OH/ether to give 0.8 g (73%) of **18** as white prisms: mp 304–306 °C; IR (KBr) 3490, 3373 (NH_2), 1675 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 0.84 (s, 9 H, $C(CH_3)_3$), 2.35 (s, 3 H, CH_3), 3.73 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 6.04 (d, 1 H, J_{AB} = 14 Hz, $NCH_AH_BC{=}C$), 6.62 (s, 1 H, CH); MS, *m/e* 454 (M^+). Anal. Calcd for $C_{24}H_{24}ClFN_4O_2$: C, 63.36; H, 5.32; N, 12.32. Found: C, 64.07; H, 5.12; N, 12.24.

8-Chloro-6-(2-fluorophenyl)-4,6-dihydro-1-(1,1-dimethylethyl)-5*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3,5-dicarboxamide (19). To a solution of 5 g (12.1 mmol) of **13** in 50 mL of acetic acid was added 25 mL of H_2O and 2 g (24.7 mmol) of potassium cyanate. After stirring for 2 h, ice and NH_4OH were added. The solids were collected by filtration and crystallized from CH_2Cl_2/CH_3OH to give 4.9 g (89%) of **19**. Recrystallization from CH_2Cl_2/CH_3OH/ether gave the analytical sample as white prisms: mp 267–269 °C; IR (KBr) 1664, 1652 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 3.68 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.81 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 6.60 (s, 1 H, CH); MS *m/e* 455 (M^+). Anal. Calcd for $C_{23}H_{23}ClFN_5O_2$: C, 60.59; H, 5.07; N, 15.36. Found: C, 59.95; H, 4.97; N, 15.14.

[*S*]-(6*S*)-(−)-8-Chloro-6-(2-fluorophenyl)-4,6-dihydro-1-(1,1-dimethylethyl)-5*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3,5-dicarboxamide (19a). This compound was prepared following the procedure given for compound **19** using 5 g of **13a** as the starting material. The product was recrystallized from EtOAc/ether/pentane to give 4.7 g (85%) of **19a** as white prisms: mp 218–222 °C; $[\alpha]^{25}_D$ −277.22° (*c* = 1.0, DMSO); IR (KBr) 1655 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 3.68 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.82 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 6.60 (s, 1 H, CH). Anal. Calcd for $C_{23}H_{23}ClFN_5O_2$: C, 60.59; H, 5.07; N, 15.36. Found: C, 60.47; H, 5.05; N, 15.32.

[*R*]-(6*S*)-(+)-8-Chloro-6-(2-fluorophenyl)-4,6-dihydro-1-(1,1-dimethylethyl)-5*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3,5-dicarboxamide (19b). This compound was prepared following the procedure given for compound **19** using 4.9 g of **13b** as the starting material. The product was recrystallized from EtOAc/ether/pentane to give 4.4 g (81%) of the product **19b** as white crystals: mp 222–232 °C; $[\alpha]^{25}_D$ +280.96°; IR (KBr) 1664, 1651 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.91 (s, 9 H, $C(CH_3)_3$), 3.68 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.79 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 6.60 (s, 1 H, CH). Anal. Calcd for $C_{23}H_{23}ClFN_5O_2$: C, 60.59; H, 5.07; N, 15.36. Found: C, 60.32; H, 5.12; N, 15.34.

5-(2-Chlorophenyl)-7-fluoro-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylideneacetic Acid Ethyl Ester 4-Oxide (21). To 400 mL (800 mmol) of a 2 M solution of diisopropylamine in THF at −50 to −60 °C was added 258 mL (413 mmol) of 1.6M *n*-butyllithium in hexane over a 15-min period. After stirring for 5 min, 78 mL (800 mmol) of EtOAc was added over a 10-min period. After stirring for 10 min, a solution of 62 g (200 mmol) of **20** in 900 mL of THF was added rapidly. After 2.5 h, 80 mL of HOAc was added followed by 500 mL of H_2O. The layers were separated and the organics were washed with water, dried, and concentrated. The residue was triturated with 750 mL of hot ether, cooled, and filtered to give 58.4 g of **21**. A second crop gave 2.6 g for a total of 61 g (81%). The analytical sample was prepared by recrystallization from ether/petroleum ether and obtained as pale yellow rods: mp 185–187 °C; IR ($CHCl_3$) 1664 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, CH_3), 4.22 (q, 2 H, OCH_2), 4.55 (s, 2 H, NCH_2), 5.04 (s, 1 H, =CH), 10.65 (s, 1 H, NH); MS *m/e* 374 (M^+). Anal. Calcd for $C_{19}H_{16}ClFN_2O_3$: C, 60.89; H, 4.30; N, 7.47. Found: C, 60.91; H, 4.15; N, 7.48.

5-(2-Chlorophenyl)-7-fluoro-α-(hydroxyimino)-3*H*-1,4-benzodiazepine-2-acetic Acid Ethyl Ester (22). To a solution of 58.4 g (156 mmol) of **21** in 935 mL of CH_2Cl_2 at 0 °C was added 16.3 mL (187 mmol) of PCl_3. The mixture was stored at 5 °C overnight and then concentrated to dryness at a bath temperature of 25 °C. The residue was dissolved in 1.5 L of CH_2Cl_2 and washed with 350 mL of Na_2CO_3/H_2O and 350 mL of H_2O, dried, and concentrated. The resulting oil was dissolved in 470 mL of HOAc, and 12.9 g (187 mmol) of $NaNO_2$ was added over 15 min. After stirring for 20 min, 1.4 L of H_2O was added and the solid was collected by filtration and washed with H_2O. The solid was triturated with 600 mL of CH_2Cl_2 and ether for 1 h and then filtered to give 54 g (90%) of **22**. The analytical sample was prepared by recrystallization from CH_2Cl_2/ether and obtained as off-white prisms: mp 217–219 °C dec; IR (KBr) 1737 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H, CH_3), 4.20–4.60 (m, 4 H, 2 CH_2), 12.51 (s, 1 H, =NOH); MS *m/e* 387 (M^+). Anal. Calcd for $C_{19}H_{15}ClFN_3O_3$: C, 58.85; H, 3.90; N, 10.84. Found: C, 58.66; H, 3.97; N, 10.71.

6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid, Ethyl Ester (23). To a solution of 37 g (95.4 mmol) of **22** and 20.7 mL (191 mmol) of trimethylacetaldehyde in 370 mL of THF were added 2 teaspoons of Raney nickel and 370 mL of EtOH. The mixture was hydrogenated at atmospheric pressure for 5.5 h at which time the uptake of H_2 was 5.2 L (theory 4.7 L). The catalyst was removed by filtration and washed with CH_2Cl_2. The filtrates were concentrated, and the residue was treated with 1.1 L of ether which was concentrated to a small volume, cooled, and filtered to give 20.2 g (48%) of **23**. The analytical sample was prepared by recrystallization from CH_2Cl_2/ether and obtained as off-white prisms: mp 213–215 °C; IR ($CHCl_3$) 1713 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, CH_3), 1.41 (s, 9 H, $C(CH_3)_3$), 3.78 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.98 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 4.37 (m, 2 H, OCH_2); MS *m/e* 439 (M^+). Anal. Calcd for $C_{24}H_{23}ClFN_3O_2$: C, 65.53; H, 5.27; N, 9.55. Found: C, 65.44; H, 5.54; N, 9.45.

6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid (24). A mixture of 20.2 g (45.9 mmol) of **23**, 5.1 g (91.8 mmol) of KOH, 300 mL of CH_3OH, and 60 mL of H_2O was refluxed for 6 h and the CH_3OH removed in vacuo. The residue was partitioned between 500 mL of a 1:1 mixture of H_2O and ether. The aqueous layer was made acidic with HOAc, cooled, and filtered to give 17.4 g (92%) of **24**. Recrystallization of a small sample from CH_3OH gave off-white needles: mp 300–302 °C; IR (KBr) 1700, 1655 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 1.33, 1.39 (s, 9 H, $C(CH_3)_3$), ratio 4/1, 3.76 (d, 1 H, J_{AB} = 7 Hz, $NCH_AH_BC{=}C$), 5.90 (d, 1 H, J_{AB} = 7 Hz, $NCH_AH_BC{=}C$); MS *m/e* 411 (M^+). Anal. Calcd for $C_{22}H_{19}ClFN_3O_2$: C, 64.16; H, 4.65; N, 10.20. Found: C, 64.28; H, 4.67; N, 10.04.

6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (25). To a mixture of 25 g (60.7 mmol) of **24** and 750 mL of CH_2Cl_2 was added 15.2 g (72.8 mmol) of PCl_5. The mixture was stirred for 1 h and then cooled to 0 °C. Ammonia was bubbled into the mixture until the pH was >10 and the mixture then stirred for 15 min followed by the addition of 500 mL of H_2O. The organic layer was separated, washed with brine, dried, and concentrated. Crystallization of the residue from CH_3OH/ether gave 15 g of **25**. The filtrates were filtered with charcoal and allowed to cool to give an additional 6.5 g for a total yield of 21.5 g (86%) of **25**. Recrystallization of a sample from CH_2Cl_2/CH_3OH gave white prisms: mp 292–295 °C.

6-(2-Aminophenyl)-8-fluoro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (26). A mixture of 8 g (18.2 mmol) of **23**, 8 g (150 mmol) of NH_4Cl, and 110 mL of saturated methanolic ammonia was heated in a stainless steel bomb for 20 h at 120 °C. The solvents were removed in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2 and the organics were combined, dried, and concentrated. The residue was crystallized from CH_3OH/EtOAc/ether to give 4.7 g (63%) of **25**. The filtrates were concentrated, and the residue was crystallized from ether to give 1.8 g of crude **26**. The pure product was isolated by column chromatography using CH_2Cl_2/ether (1:1) as the eluent. After crystallization from CH_2Cl_2/ether, 0.5 g (7%) of **26** was obtained as off-white needles: mp 252–254 °C, IR ($CHCl_3$) 3503, 3470, 3390, 3262 (2 NH_2), 1661 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.24 (s, 9 H, $C(CH_3)_3$), 3.70 (d, 1 H, J_{AB} = 12 Hz, $NCH_AH_BC{=}C$), 5.86 (d, 1 H, J_{AB} = 12 Hz, $NCH_AH_BC{=}C$); MS *m/e* 391 (M^+). Anal. Calcd for $C_{22}H_{22}FN_5O$: C, 67.50; H, 5.67; N, 17.90. Found: C, 67.55; H, 5.65; N, 18.08.

6-(2-Chlorophenyl)-8-fluoro-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (27). A solution of 29 g (70.6 mmol) of **25** in 350 mL of HOAc and 175 mL of CH_3OH was cooled in an icebath and 8.9 g (141 mmol) of sodium cyanoborohydride was added. After stirring for 4 h, 1 L of water was added and the mixture was extracted with 3 × 300 mL of CH_2Cl_2. The organics were washed with 700 mL of dilute NH_4OH, dried, and concentrated to a small volume. A mixture of ether and petroleum ether was added and the mixture cooled and filtered to give 26 g in two crops (89%) of **27**. A small sample was recrystallized from CH_2Cl_2/CH_3OH to give white prisms: mp 260–265 °C; IR (KBr) 3490, 3355, 3296 (NH_2, NH), 1668 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H, $C(CH_3)_3$), 3.15 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 4.94 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.06 (s, 1 H, CH), 5.43 (bs, 1 H, NH). Anal. Calcd for $C_{22}H_{22Cl}FN_4O$: C, 64.00; H, 5.37; N, 13.57. Found: C, 64.15; H, 5.53; N, 13.82.

[6*S*-[5-(1*S*,2*R*,5*S*]]-8-Fluoro-6-(2-chlorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[4,3-*a*][1,4]benzodiazepine-5-carboxylic Acid 5-Methyl-2-(1-methylethyl)-cyclohexyl Ester (28a) and [6*R*-[5-(1*S*,2*R*,5*S*]]-8-Fluoro-6-(2-chlorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[4,3-*a*][1,4]benzodiazepine-5-carboxylic Acid 5-Methyl-2-(1-methylethyl)cyclohexyl Ester (28b). To a solution of 18 g (43.6 mmol) of **27** in 150 mL of CH_2Cl_2 was added 52.3 mL (52.3 mmol) of (−)-menthyl chloroformate and 8 mL of pyridine. The mixture was stirred for 2 h and then washed with 100 mL of dilute Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried and concentrated. The residue was dissolved in a small amount of CH_2Cl_2 and chromatographed over silica gel using EtOAc/petroleum ether (1:2) as the eluent. The solvents were removed in vacuo and the residue triturated with a small amount of ether and filtered. The filtrates were concentrated and the solid crystallized from ether/petroleum ether to give 9.5 g (73%) of **28a** as white rods: mp 160–166 °C; $[\alpha]^{25}_D$ −94.54° (*c* = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3510, 3390 (NH_2), 1673 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 3.38, 3.53 (d, 1 H, $NCH_2C{=}C$), 5.45 (bs, 1 H, $NCH_2C{=}C$), 4.65 (bs, 1 H, CHOCO). Anal. Calcd for $C_{33}H_{40}ClFN_4O_3$: C, 66.60; H, 6.77; N, 9.41. Found: C, 67.69; H, 7.58; N, 8.78.

Further elution of the above column followed by concentration of the solvents gave a solid residue which was triturated with ether and filtered. The filtrates were concentrated and the residue was crystallized from ether/petroleum ether to give 9.9 g (76%) of **28b** of white prisms: mp 130–133 °C; $[\alpha]^{25}_D$ +162.44° (*c* = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3525, 3402 (NH_2), 1676 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 3.38, 3.53 (d, 1 H, $NCH_2C{=}C$), 5.53 (bs, 1 H, $NCH_2C{=}C$), 4.50 (bs, 1 H, CHOCO); MS *m/e* 594 (M^+). Anal. Calcd for $C_{33}H_{40}ClFN_4O_3$: C, 66.60; H, 6.77; N, 9.41. Found: C, 66.60; H, 6.92; N, 9.25.

(6*S*)-6-(2-Chlorophenyl)-8-fluoro-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (27a). A solution of 8.6 g (14.5 mmol) of **28a** in 65 mL of 30–32% HBr in HOAc was heated at 55–60 °C for 6 h. Ice was added followed by dilute NH_4OH and the mixture extracted with CH_2Cl_2. The organics were dried and concentrated and the resulting oil was crystallized from ether/petroleum ether to give the crude product which was dissolved in CH_2Cl_2 and chromatographed through a small amount of silica gel with CH_2Cl_2 followed by EtOAC. The EtOAc fractions were concentrated and the residue was crystallized from ether/petroleum ether to give 4.3 g (72%) of **27a** as white prisms: mp 182–185 °C; $[\alpha]^{25}_D$ −126.54° (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3508, 3396 (NH, NH_2), 1663 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H, $C(CH_3)_3$), 3.16 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 4.94 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.06 (s, 1 H, CH), 5.45 (bs, 1 H, NH); MS m/e 412 (M^+). Anal. Calcd for $C_{22}H_{22}ClFN_4O$: C, 64.00; H, 5.37; N, 13.57. Found: C, 63.63; H, 5.74; N, 13.20.

(6*R*)-6-(2-Chlorophenyl)-8-fluoro-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (27b). A mixture of 8.8 g (14.8 mmol) of **28b** and 65 mL of 30–32% HBr in HOAc was heated at 55–60 °C for 7 h and then quenched with ice. The mixture was made basic with NH_4OH and extracted with CH_2Cl_2. The organics were dried and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2, then EtOAC, and finally EtOAc/CH_3OH (10:1) to elute the product. After removing the solvents, the residue was crystallized from ether/petroleum ether to give 4.9 g (80%) of **27b** as white prisms: mp 181–183 °C; $[\alpha]^{25}_D$ +123.35° (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3510, 3395, 3320 (NH, NH_2), 1663 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $C(CH_3)_3$), 3.15 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 4.96 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.10 (s, 1 H, CH), 5.42 (bs, 1 H, NH). Anal. Calcd for $C_{22}H_{22}ClFN_4O$: C, 64.00; H, 5.37; N, 13.57. Found: C, 63.49; H, 5.73; N, 12.94.

(6*S*)-(−)-6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-6*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxamide (29a) and [*R*]-(−)-6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-4*H*-imidazo[1,5-*a*][1,5-*a*][1,4]benzodiazepine-3-carboxamide (25a). To 8.2 g (20 mmol) of **27a** in 375 mL of CH_2Cl_2, cooled in an ice bath, was added a mixture of 13.3 g (30 mmol) of lead tetraacetate and 8.1 g (32 mmol) of iodine in 350 mL of CH_2Cl_2 over 1 h. After 3 h an additional 4.1 g of lead tetraacetate and 6.7 g of iodine were added in portions over 1 h. After 2 h the mixture was quenched with Na_2CO_3 followed by 15 g of sodium thiosulfate in H_2O. The products were extracted with CH_2Cl_2 which was dried and concentrated. The residue was chromatographed on silica gel using ether/petroleum ether (5:1) as the eluent. The first fractions from the column were combined and concentrated. The residue was crystallized from CH_2Cl_2/ether/petroleum ether to give 2.3 g (28%) of **29a** as white prisms: mp 223–230 °C; $[\alpha]^{25}_D$ −433.56° (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3513, 3402 (NH_2), 1677 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, $C(CH_3)_3$), 5.59 (s, 1 H, CH), 8.97 (d, 1 H, N=CH). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.91; N, 13.64. Found: C, 64.57; H, 4.96; N, 13.52.

Continued elution of the above column led to the isolation of **25a** which was recrystallized from CH_2Cl_2/ether/petroleum ether to give 4.4 g (54%) of **25a** as white prisms: mp 292–296 °C; $[\alpha]^{25}_D$ −317.66° (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3515, 3504 (NH_2), 1674 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, $C(CH_3)_3$), 3.77 (d, 1 H, J_{AB} = 13 Hz, $NCH_AH_BC{=}C$), 6.14 (d, 1 H, J_{AB} = 13 Hz, $NCH_AH_BC{=}C$). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.91; N, 13.64. Found: C, 64.38; H, 4.98; N, 13.41.

(6*R*)-(−)-6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-6*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxamide (29b) and [*S*]-(−)-6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (25b). The same procedure as described for the synthesis of **29a** and **25a** was used to prepare these compounds. The crude reaction mixture was purified by column chromatography with **29b** eluted first followed by **25b**. Compound **29b**, 28% yield, was obtained as white prisms: mp 221–230 °C; $[\alpha]^{25}_D$ +422.36° (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3525, 3400 (NH_2), 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H, $C(CH_3)_3$), 5.60 (s, 1 H, CH), 8.97 (d, 1 H, N=CH). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.91; N, 13.64. Found: C, 64.03; H, 5.17; N, 13.46.

Compound **25b** was obtained in 49% yield and obtained as colorless rods: mp 296–300 °C; $[\alpha]^{25}_D$ +326.29° (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3540, 3408 (NH_2) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H, $C(CH_3)_3$), 3.78 (d, 1 H, J_{AB} = 13 Hz, $NCH_AH_BC{=}C$), 6.15 (d, 1 H, J_{AB} = 13 Hz, $NCH_AH_BC{=}C$). Anal. Calcd for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.91; N, 13.64. Found: C, 64.26; H, 5.14; N, 13.51.

6-(2-Chlorophenyl)-1-(1,1-dimethylethyl)-8-fluoro-4,6-dihydro-5*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3,5-dicarboxamide (30). A solution of 2.0 g (4.85 mmol) of **27** in 20 mL of HOAc was treated with 10 mL of H_2O followed by 786 mg (9.7 mmol) of potassium cyanate. After stirring for 2 h the mixture was poured over ice and made basic with NH_4OH. The precipitate was collected by filtration, washed with H_2O, and air-dried. The product was filtered through a small amount of florisil using EtOAc/CH_3OH (10:1) as the eluent. Removal of the solvents and crystallization of the residue from CH_2Cl_2/CH_3OH gave 0.7 g (29%) of **30** (containing 1 mol of CH_3OH as a solvate) as off-white plates: mp 245–257 °C; IR (KBr) 3488, 3300, 3200 (NH_2), 1740, 1782 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 3.60 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.81 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 6.59 (s, 1 H, CH); MS m/e 455 (M^+). Anal. Calcd for $C_{23}H_{23}ClFN_4O_2{\cdot}CH_3OH$: C, 59.07; H, 5.58; N, 14.35. Found: C, 59.07; H, 5.47; N, 14.33.

8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethylethyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine (32). A mixture of 10.9 g (26.5 mmol) of **9** and 165 mL of 1,2,4-trichlorobenzene was refluxed for 3 h and allowed to cool to room temperature. The product was extracted with 3 N HCl (2 × 150 mL). The aqueous phase was made basic with cold NH_4OH and extracted with CH_2Cl_2 (3 × 100 mL) which was dried and concentrated to a volume of 50 mL. This solution was chromatographed on 300 g of florisil using increasing amounts of EtOAc in CH_2Cl_2 for elution. The first fractions were concentrated and the residue crystallized from EtOH and then recrystallized from ether/petroleum ether to give 0.6 g (6.2%) of **32** as white prisms: mp 174–176 °C; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, $C(CH_3)_3$), 5.67 (s, 1 H, CH), 6.77 (s, 1 H, N=CH); MS m/e 367 (M^+). Anal. Calcd for $C_{21}H_{19}ClFN_3$: C, 68.57; H, 5.21; N, 11.42. Found: C, 68.45; H, 5.30; N, 11.42.

8-Chloro-6-(2-fluorophenyl)-1-(1,1-dimethyethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (31). The later fractions from the column chromatography described above were concentrated and the residue crystallized from CH_2Cl_2/CH_3OH to give 5.1 g (53%) of **31** as white prisms: mp 227–229 °C; ^1H NMR (DMSO-d_6) δ 1.34 (s, 9 H, $C(CH_3)_3$), 3.87 (d, 1 H, J_{AB} = 7 Hz, $NCH_AH_BC{=}C$), 5.04 (d, 1 H, J_{AB} = 7 Hz, $NCH_AH_BC{=}C$), 7.02 (s, 1 H, C=CH); MS m/s 367 (M^+). Anal. Calcd for $C_{21}H_{19}ClFN_3$: C, 68.57; H, 5.21; N, 11.42. Found: C, 68.31; H, 5.40; N, 11.44.

8-Chloro-6-(2-fluorophenyl)-5,6-dihydro-1-(1,1-dimethylethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (33). To a solution of 10.7 g (29.2 mmol) of **31** in 130 mL of HOAc was added 65 mL of CH_3OH. The mixture was cooled in an ice bath and 3.7 g (58.3 mmol) of sodium cyanoborohydride was added. After stirring at room temperature for 90 min, 400 mL of H_2O was added and the mixture extracted with CH_2Cl_2 (2 × 350 mL). The organics were combined and washed with 300 mL of dilute NH_4OH, dried, and concentrated to a small volume. The residue was triturated with a mixture of ether and pentane and the solids collected by filtration to give 10.2 g (95%) of **33**. The analytical sample was prepared by recrystallization from CH_2Cl_2/CH_3OH and obtained as white prisms: mp 236–241 °C; IR (KBr) 3263 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 0.85, 1.49 (s, 9 H, $C(CH_3)_3$, ratio 1:10), 3.27 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 3.94 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.06 (s, 1 H, CH); MS m/e 369 (M^+). Anal. Calcd for $C_{21}H_{21}ClFN_3$: C, 68.19; H, 5.72; N, 11.36. Found: C, 68.04; H, 5.78; N, 11.27.

(6*S*)-[*S*]-8-Chloro-1-(1,1-dimethylethyl)-5,6-dihydro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine, Salt with (−)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic Acid (34b). A solution of 25.5 g (68.9 mmol) of **33** and 34.5 g (138 mmol) of *d*-camphor-10-sulfonic acid in 400 mL of EtOH was concentrated to 150 mL and 200 mL of *i*-PrOH was added. The solution was cooled and the precipitate collected by

filtration. The filtrates were used to prepare the (6*R*) enantiomer, see experimental for **34a**. The product was crystallized from EtOH/*i*-PrOH to give 20 g (67%) of **34b** as white rods: mp 178–190 °C; $[\alpha]^{25}_D$ +50.05° (*c* = 1.0, DMSO); IR (KBr) 1745 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 0.74 (s, 6 H, 2 × CH_3), 1.02 (s, 6 H, 2 × CH_3) 1.32 (s, 9 H, $C(CH_3)_3$, 3.72 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 4.78 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.78 (s, 1 H, CH). Anal. Calcd for $C_{21}H_{21}ClFN_3{\cdot}2C_{10}H_{16}O_4S$: C, 59.01; H, 6.40; N, 5.04. Found: C, 58.52; H, 6.75; N, 4.71.

(6*S*)-[*S*]-8-Chloro-1-(1,1-dimethylethyl)-5,6-dihydro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (33b). The salt from the preceding experiment was partitioned between NH_4OH and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the organics were combined, dried, and concentrated. The residue was crystallized from CH_2Cl_2/pentane to give 1.2 g of **33** (racemic). The filtrates were concentrated, and the residue was crystallized from CH_2Cl_2/ether/pentane to give 6.2 g (49%) of **33b** as white rods: mp 186–196 °C; $[\alpha]^{25}_D$ −21.64° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.86, 1.40 (s, 9 H, $C(CH_3)_3$, ratio 1:10), 3.32 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 3.98 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.06 (s, 1 H, CH). Anal. Calcd for $C_{21}H_{21}ClFN_3$: C, 68.19; H, 5.72; N, 11.36. Found: C, 68.00; H, 5.74; N, 11.33.

(6*R*)-[*R*]-8-Chloro-1-(1,1-dimethylethyl)-5,6-dihydro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine, Salt with (+)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic acid (34a). The filtrates obtained from the preparation of **34b** were concentrated, and the residue was partitioned between dilute NH_4OH and CH_2Cl_2. The organics were dried and concentrated. Pentane was added to the residue and the solid removed by filtration. The solid was identified as racemic **33**. The pentane was removed to leave 10 g of a mixture of **33** and **33a**. The mixture was dissolved in EtOH and treated with 12.5 g of *l*-camphor-10-sulfonic acid. The EtOH was removed in vacuo and the residue recrystallized several times from EtOH/*i*-PrOH/ether to give **34a** as white rods: mp 195–200 °C; $[\alpha]^{25}_D$ −49.94° (*c* = 1.0, DMSO); IR (KBr) 1737 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 0.74 (s, 6 H, 2 × CH_3), 1.02 (s, 6 H, 2 × CH_3) 1.46 (s, 9 H, $C(CH_3)_3$, 3.78 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 4.85 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.78 (s, 1 H, CH). Anal. Calcd for $C_{21}H_{21}ClFN_3{\cdot}2C_{10}H_{16}O_4S$: C, 59.01; H, 6.40; N, 5.04. Found: C, 58.48; H, 6.78; N, 4.93.

(6*R*)-[*R*]-8-Chloro-1-(1,1-dimethylethyl)-5,6-dihydro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (33a). The salt from the preceding experiment was treated with dilute NH_4OH and extracted with CH_2Cl_2. The organics were dried and concentrated, and the residue was recrystallized several times from ether/pentane to give 7.4 g (58%) of **33a** as white rods: mp 187–200 °C; $[\alpha]^{25}_D$ +21.78° (*c* = 1.0, CH_2Cl_2); IR ($CHCl_3$) 2970 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.87, 1.40 (s, 9 H, $C(CH_3)_3$, ratio 1:11), 3.30 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 3.96 (d, 1 H, J_{AB} = 15 Hz, $NCH_AH_BC{=}C$), 5.06 (s, 1 H, CH). Anal. Calcd for $C_{21}H_{21}ClFN_3$: C, 68.19; H, 5.72; N, 11.36. Found: C, 67.92; H, 5.72; N, 11.12.

(6*R*)-[*R*]-8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-6*H*-imidazo-[1,5-*a*][1,4]benzodiazepine (32a). To a solution of 7.3 g (19.7 mmol) of **33a** in 200 mL of CH_2Cl_2, cooled in an ice bath, was added with stirring over 10 min a solution of 10.5 g (23.6 mmol) of lead tetraacetate and 6.4 g (25.0 mmol) of iodine in 300 mL of CH_2Cl_2. After 2.5 h the reaction mixture was neutralized by the addition of dilute Na_2CO_3 followed by 8.5 g (34.3 mmol) of sodium thiosulfate. Solid K_2CO_3 was added until the pH was 8.5 and the mixture allowed to stir until the iodine color had disappeared. The mixture was filtered through filter aid, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the organics were combined, dried, and concentrated to a small volume. The residue was chromatographed on silica gel using ether/pentane (3:2) as the eluent. The first fractions were concentrated and the residue crystallized from ether/pentane to give 0.5 g (7%) of **32a** as white prisms: mp 161–165 °C; $[\alpha]^{25}_D$ −363.96° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 5.70 (s, 1 H, CH), 6.80 (s, 1 H, N=CH); Anal. Calcd for $C_{21}H_{19}ClFN_3$: C, 68.57; H, 5.21; N, 11.42. Found: C, 68.40; H, 5.18; N, 11.31.

[*R*]-8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (31a). Following the isolation of **32a** described above, the later fractions from the column led to the isolation of **31a**. The product was recrystallized from CH_3OH/ether/pentane to give 5.8 g (79%) of **31a** as white prisms: mp 227–230 °C; $[\alpha]^{25}_D$ −35.94° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $C(CH_3)_3$), 3.86 (d, 1 H, J_{AB} = 12 Hz, $NCH_AH_BC{=}C$), 5.04 (d, 1 H, J_{AB} = 12 Hz, $NCH_AH_BC{=}C$). Anal. Calcd for $C_{21}H_{19}ClFN_3$: C, 68.57; H, 5.21; N, 11.42. Found: C, 68.32; H, 5.21; N, 11.73.

(6*R*)-[*S*]-8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-6*H*-imidazo-[1,5-*a*][1,4]benzodiazepine (32b). To a solution of 6.5 g (17.6 mmol) of **33b** in 180 mL of CH_2Cl_2, cooled in an ice bath, was added with stirring over 10 min a solution of 9.3 g (21.1 mmol) of lead tetraacetate and 5.6 g (22.0 mmol) of iodine in 240 mL of CH_2Cl_2. After 2.5 h the reaction mixture was neutralized by the addition of dilute Na_2CO_3 followed by 7 g (28.2 mmol) of sodium thiosulfate. Solid K_2CO_3 was added until the pH was 8.5 and the mixture allowed to stir until the iodine color had disappeared. The mixture was filtered through filter aid, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the organics were combined, dried, and concentrated to a small volume. The residue was chromatographed on silica gel using ether/pentane (3:2) as the eluent. The first fractions were concentrated, and the residue crystallized from ether/pentane to give 0.4 g (6%) of **32b** as white prisms: mp 167–169 °C; $[\alpha]^{25}_D$ +369.76° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.49 (s, 9 H, $C(CH_3)_3$), 5.66 (s, 1 H, CH), 6.77 (s, 1 H, N=CH); Anal. Calcd for $C_{21}H_{19}ClFN_3$: C, 68.57; H, 5.21; N, 11.42. Found: C, 68.41; H, 5.23; N, 11.46.

[*S*]-8-Chloro-1-(1,1-dimethylethyl)-6-(2-fluorophenyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine (31b). Following the isolation of **32b** described above, the later fractions from the column led to the isolation of **31b**. The product was recrystallized from CH_3OH/ether/pentane to give 5 g (77%) of **31b** as white prisms: mp 227–229 °C; $[\alpha]^{25}_D$ +34.22° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H, $C(CH_3)_3$), 3.87 (d, 1 H, J_{AB} = 12 Hz, $NCH_AH_BC{=}C$), 5.02 (d, 1 H, J_{AB} = 12 Hz, $NCH_AH_BC{=}C$), 7.02 (s, 1 H, C=CH); MS *m/e* 367 (M^+). Anal. Calcd for $C_{21}H_{19}ClFN_3$: C, 68.57; H, 5.21; N, 11.42. Found: C, 68.88; H, 5.20; N, 11.41.

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