(S)-Pinanediol [(1R,2R)-2-(Benzyloxy)-3-hydroxypropyl]boronate-1-d (5Dc). A solution of 0.6 g (1.3 mmol) of **5Db** in 10 mL of dichloromethane was stirred with 2.5 mL of water, and 0.36 g (1.56 mmol) of 2,3-dichloro-5,6-dicyanoquinone was added. After being stirred for 2.5 h at 20–25 °C, the mixture was filtered through a celite pad with the aid of more dichloromethane. The dichloromethane phase was stirred with an equal volume of water for 0.5 h, then washed with water and saturated sodium chloride, and then concentrated. The residue was chromatographed on silica with 2:1 diethyl ether/light petroleum ether to yield 0.493 g (90%) of **5Dc**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl C*H*), 1.26 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.82–2.33 (m, 6, pinyl C*H* + C*H*DB), 3.58–3.83 (m, 3, HOCH_2C*H*(OBn)CHD), 4.27 (dd, 1, J = 1.9 Hz, J = 8.0 Hz, pinyl C*H*OB), 4.64 (s, 2, PhCH_2), 7.23–7.35 (m, 5, C_6H_5). Anal. Calcd for $C_{20}H_{28}DBO_4$: C, 69.58; H, 8.50; B, 3.13. Found: C, 69.34; H, 8.72; B, 2.78.

(S)-Pinanediol [(1R,2R)-2-(Benzyloxy)-3-oxopropyl]boronate-1-d (10D). A 190-mg (0.55-mmol) sample of **5Dc** was oxidized under Swern conditions (oxalyl chloride, triethylamine, dimethyl sulfoxide).[23] Flash chromatography on silica with 1:1 diethyl ether/light petroleum ether yielded 170 mg (91%) of **10D**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl C*H*), 1.26 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.82–2.33 (m, 6, pinyl C*H* + C*H*DB), 4.05 (dd, 1, J = 1.7 Hz, J = 7.4 Hz, C*H*(OBn)), 4.29 (dd, 1, J = 1.8 Hz, J = 8.6 Hz, pinyl C*H*OB), 4.64 (s, 2, PhCH_2), 7.23–7.35 (m, 5, C_6H_5), 9.67 (d, 1, J = 1.7 Hz, C*H*O). Anal. Calcd for $C_{20}H_{26}DBO_4$: C, 69.98; H, 7.96; B, 3.15. Found: C, 69.63; H, 8.50; B, 2.70.

Detritylation of (1S,2R)-1,2-Bis(benzyloxy)-3-(triphenylmethoxy)-propane-1-d (8Dd). A solution of 120 mg (0.2 mmol) of **8Dd** in 15 mL of methanol, 5 mL of ether, and 0.5 mL of water was stirred with 0.5 g of Amberlyst 15 sulfonic acid resin overnight at 35–40 °C.[31] Flash chromatography on silica with 1:1 ether/light petroleum ether yielded 50 mg (92%) of **8Dc**, confirmed by ^{1}H NMR. An alternative detritylation of **8Ld** was discovered accidentally. A solution of **8Ld** ($[\alpha]^{21}_{546}$ +10.72° (*c* 0.554, $CHCl_3$ + 0.6% EtOH)) was kept 1 week at ~20 °C. The rotation changed to α^{21}_{546} −0.059°, α^{21}_{577} −0.048°, calculated $[\alpha]^{21}_{546}$ −20.1°, $[\alpha]^{21}_{577}$ −16.3° if the **8Ld** is assumed completely detritylated to **8Lc** [lit.[19] $[\alpha]^{25}_{D}$ −17.2° (*c* 1, $CHCl_3$)]. This material had the same TLC retention time as **8Lc**, plus a mobile component assumed to be unchanged **8Ld**.

Acknowledgment. We thank the National Institutes of Health for Grant No. GM33801, the National Science Foundation for Grant No. CHE-8618762, and the Boeing Corp. for partial support of the departmental purchase of the 200-MHz NMR instrument.

Registry No. 1a, 87190-25-8; **1b**, 125783-40-6; **2a**, 110744-89-3; **2b**, 125783-41-7; **3Da**, 110744-92-8; **3Db**, 125783-42-8; **3La**, 110848-81-2; **4Da**, 110744-93-9; **4Db**, 125783-43-9; **4La**, 125783-58-6; **4Lb**, 125783-49-5; **4Lb** (chloro analogue), 125783-62-2; **5Da**, 125783-56-4; **5Db**, 125783-44-0; **5Dc**, 125783-60-0; **5La**, 125873-85-0; **5Lb**, 125873-84-9; **6Da**, 125783-57-5; **6Db**, 125783-45-1; **6La**, 125783-59-7; **6Lb**, 125783-50-8; **7D**, 125257-42-3; **7L**, 125257-50-3; **8Db**, 125783-46-2; **8Dc**, 125783-47-3; **8Dd**, 125783-54-2; **8Lb**, 125783-51-9; **8Lc**, 125783-52-0; **8Ld**, 125783-55-3; **9D**, 125783-48-4; **9L**, 125783-53-1; **10D**, 125783-61-1; *p*-MeO$C_6H_4CH_2OH$, 105-13-5; KDB(OCHMe_2)$_3$, 125783-63-3; (*S*)-pinanediol (chloromethyl)boronate, 110744-85-9.

(31) Malanga, C. *Chem. Ind. (London)* **1987**, 856–857.

Atropisomers of 1,4-Benzodiazepines. Synthesis and Resolution of a Diazepam-Related 1,4-Benzodiazepine

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Abstract: The resolution of 7-chloro-1,3-dihydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7**), the N^1-*tert*-butyl analogue of diazepam, is described. Compound **7** does not contain an asymmetric center but exists as a mixture of conformational isomers. The resolution of **7** was effected by resolving the 4,5-dihydro form of **7**, compound **8**, which now contains two elements of asymmetry. The resulting enantiomers **9** and **10** were then oxidized to reintroduce the 4,5 double bond, which removed the center of asymmetry and led to the enantiomers of **7**, compounds **11** and **12**. The absolute configurations of compounds **10** and **12** were determined by single-crystal X-ray analysis. The interaction of the two enantiomers **11** and **12** with the benzodiazepine receptor in a binding assay showed that the active conformer has the *R* (3-methylene group exo) configuration. Attempts to resolve the 2′-chloro and 2′-fluoro analogues of **7** were not successful. On the basis of molecular mechanics calculations, the barrier to inversion of **22** (the 2′-chloro analogue) was determined to be less than that found for compound **7**. Compounds **11** and **12** represent the first examples of optically active 1,4-benzodiazepines whose asymmetry is due only to conformational elements.

Since the introduction of the first 1,4-benzodiazepine, chlordiazepoxide (**1**), in 1960, the 1,4-benzodiazepines[1] have become the drugs of choice for the treatment of anxiety, sleep disorders, status epilepticus, and other convulsive disorders. In addition, they are also used as muscle relaxants, for alleviation of panic attacks, and as induction agents in anesthesiology. The discovery[2,3] 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 that interact with the receptor. Many of these compounds are non-benzodiazepines[4] and in vivo manifest pharmacological effects similar to those of the benzodiazepines.

Many reports[5] have appeared that attempt to correlate structure with binding affinity at the benzodiazepine receptor from both

(1) Reviews: (a) *Anxiolytics*; Fielding, S., Lal, H., Eds.; Futurea: New York, 1979. (b) Haefely, W. In *Discoveries in Pharmacology*; Parnham, M. J., Bruinvals, J., Eds.; Elsevier: Amsterdam, 1983; Vol. 1, pp 239–306.

(2) Möhler, H.; Okada, T. *Science (Washington, D.C.)* **1977**, *198*, 849–851.

(3) Braestrup, C.; Squires, R. F. *Nature (London)* **1977**, *266*, 732–734.

(4) (a) Williams, M. *J. Med. Chem.* **1983**, *26*, 619–628. (b) Braestrup, C.; Honore, T.; Nielsen, M.; Petersen, E. N.; Jensen, L. H. *Biochem. Pharmacol.* **1984**, *33*, 859–862.

(5) (a) Sternbach, L. H. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser: Basel, 1978; Vol. 22, pp 229–266. (b) Seiler, P.; Zimmerman, I. *Drug Research* **1983**, *33*, 1519–1522. (c) Borea, P. A.; Gilli, G.; Bertolasi, V.; Ferretti, V. *Mol. Pharmacol.* **1987**, *31*, 334–344. (d) Crippen, G. M. *Mol. Pharmacol.* **1982**, *22*, 11–19. (e) Fryer, R. I. In *Benzodiazepines. From Molecular Biology to Clinical Practice*; Costa, E., Ed.; Raven Press: New York, 1983; pp 7–20. (f) Fryer, R. I.; Cook, C.; Gilman, N. W.; Walser, A. *Life Sci.* **1986**, *39*, 1947–1957. (g) Codding, P. W.; Muir, A. S. *Mol. Pharmacol.* **1985**, *28*, 178–184. (h) Tebib, S.; Bourguignon, J.-J.; Wermuth, C.-G. *J. Comput.-Aided Mol. Des.* **1987**, *1*, 153–170. (i) Snyder, S. H. *Isr. J. Med. Sci.* **1987**, *23*, 145–152.

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Chart I

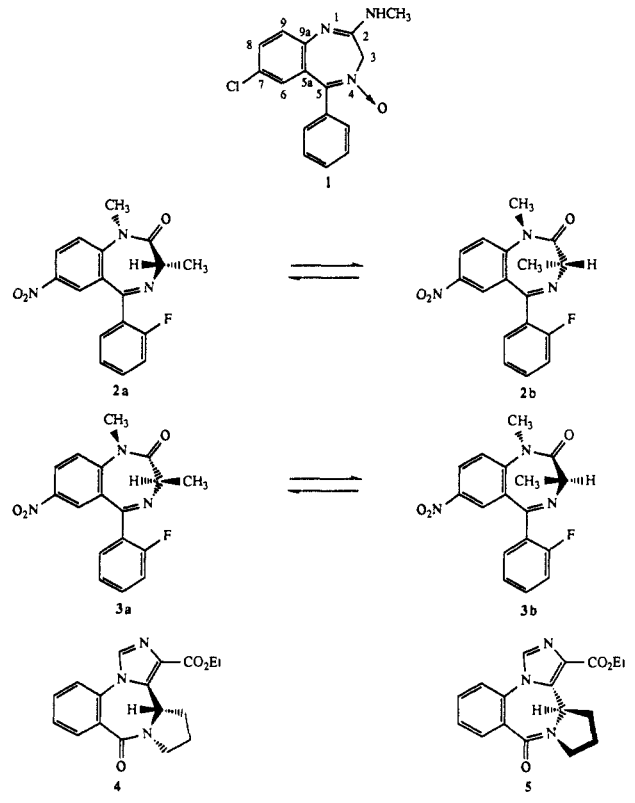
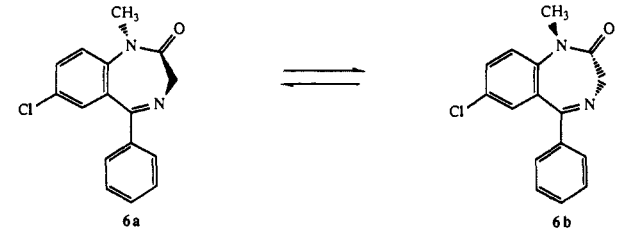


Chart II



empirical and stereochemical approaches. Ring inversion between **6a** and **6b** (Chart II) (which amounts to racemization since **6a** and **6b** are enantiomers) is too rapid to allow for the separation of the enantiomers at room temperature, in agreement with a calculated inversion barrier of 17.6 kcal/mol,[6] although **6** shows a distinct AB pattern for the C-3 methylene protons indicating a slow interconversion on the NMR time scale. For comparison, the inversion barrier for N^1-desmethyldiazepam has been found to be 12.3 kcal/mol, and the C-3 methylene protons appear as a singlet, indicating a rapid interconversion.[6,7] To impart conformational stability to the benzodiazepine nucleus, the chiral 3-methyl derivatives **2** and **3** and the tetracyclic compounds **4** and **5** were prepared. On the basis of X-ray crystallography, compounds **2** and **3** may best be represented by structures **2a** and **3a** in which the methyl group is in the equatorial position. It is proposed that these compounds show the same conformational stability in solution in view of an NMR study on the structurally similar 7-chloro-5-(phenyl-d_5)-3(*S*)-methyldihydro-1,4-benzodiazepin-2-one. From this study, Šunjic et al. concluded that the 3-methyl group was equatorially disposed.[8] On the basis of the much larger binding affinities of the chiral benzodiazepines **2a** and the structurally rigid compound **4** as compared to **3a** and **5**, respectively (Chart I), the receptor-binding conformation of **6** is identified as **6a**[9] (Chart II).

(6) Lehn J. M.; Linscheid, P. *Bull. Soc. Chim. Fr.* **1967**, 992–997.
(7) Šeděe, W. *Arch. Pharm (Weinheim)* **1969**, *302*, 769–774.
(8) Šunjič, V.; Lisini, A.; Sega, A.; Kovač, T.; Kajfez, F.; Ruščič, B. *J. Heterocycl. Chem.* **1979**, *16*, 757–761.
(9) Blount, J. F.; Fryer, R. I.; Gilman, N. W.; Todaro, L. J. *Mol. Pharmacol.* **1983**, *24*, 425–428.

To further probe the conformational features of diazepam required for binding at the benzodiazepine receptor, the synthesis and resolution of a conformationally stable 1,4-benzodiazepine (**7**), closely related to diazepam, were undertaken. This compound is asymmetric due to the presence of conformational enantiomers that arise due to the spatial relationship of the C-3 methylene group that can be either above (exo) or below (endo) the plane defined by the atoms 5, 5a, 9a, and 1 (see structure **1** for numbering), in contrast to the 3-methyl compounds **2** and **3**, as well as **4** and **5**, that contain chiral centers. Since the 3-dimensional structure of the benzodiazepine receptor is not known, probes of the ligand–receptor interaction are based on ligand structures. Although many hundreds of benzodiazepines have been prepared, to date, the resolution of diazepam-related compounds based strictly on conformational grounds has not been reported. This report describes methodology for accomplishing the resolution of **7**.

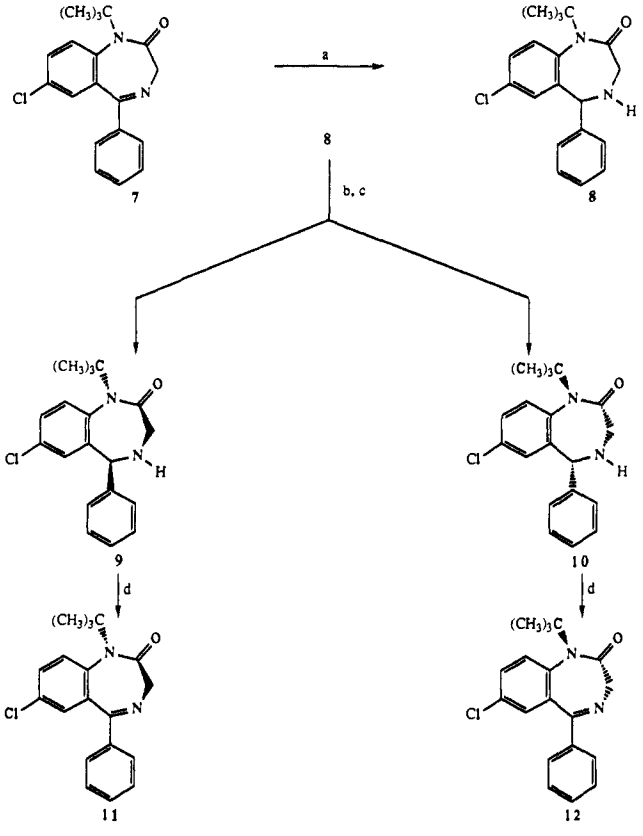
Results and Discussion

***N*^{1}-*tert*-Butyldiazepam.** Since diazepams **6a** and **6b** cannot be resolved, we sought to increase the barrier of inversion by replacing the N^1-methyl group with a N^1-*tert*-butyl group (compound **7**). The selection of **7** was based on the following: (1) the substitution of the *tert*-butyl group for the methyl group at the N^1 position should give a compound with the same overall 3-dimensional spatial volumes as **6** except for the extra bulk of the *tert*-butyl group; (2) the electronic nature of **6** and **7** should be the same; (3) the use of the *tert*-butyl group in the N^1 position will increase the steric hindrance between positions 1 and 9 and may allow the enantiomers to be separated (atropisomers of the biphenyl type). On the basis of the effect of the N^1-methyl group on the interconversion of **6** as compared to N^1-desmethyldiazepam (addition of approximately 5 kcal/mol to the inversion barrier) and on the basis of Dreiding models and molecular modeling with the SYBYL program,[10] it was anticipated that a *tert*-butyl group in the 1-position may impart sufficient steric bulk to block the interconversion of the enantiomers **11** and **12**. Since compound **7** shows an AB pattern for the C-3 methylene protons similar to that of diazepam, NMR studies measuring the temperature effect on the degree of coalescence of the AB pattern were used to evaluate the energy required for the interconversion of **11** and **12**.

The synthesis of compound **7** in racemic form has been described previously.[11] The NMR spectrum of this compound showed an AB pattern for the C-3 methylene protons at 3.87 and 4.58 ppm, which did not collapse at 200 °C in tetramethylsulfolane. In contrast, diazepam **6** showed an AB quartet at 50 °C, which deteriorated to two very broad peaks at 100 °C and collapsed to a sharp singlet at 200 °C. The results obtained for **7** are indicative of an energy barrier of greater than 24 kcal/mol for the interconversion of the enantiomers **11** and **12**, so that a successful separation of **11** and **12** at room temperature could be anticipated, on the basis of the reported value of at least 20 kcal/mol that is needed for the resolution of rotational isomers in the biphenyl series.[12] The direct resolution of **7** with a number of optically active acids was not successful, although salt formation was observed in some instances. Thus, an alternate method was designed that involved the reduction of the imine double bond, resolution of the resulting secondary amines (which now contain an asymmetric center), and finally, oxidation back to the imine. As shown in Scheme I, reduction of **7** with sodium cyanoborohydride gave the dihydro compound **8**. Resolution of **8** with camphor-d_{10}-sulfonic acid gave the intermediate salts (not shown) that were converted to the enantiomeric amines **9** and **10**. Oxidation of **9** and **10** with a mixture of lead tetraacetate and iodine

(10) SYBYL: Tripos Associates, 1699 S. Hanley Road, St. Louis, Missouri 63144.
(11) Gilman, N. W.; Sternbach, L. H. *J. Heterocycl. Chem.* **1971**, *8*, 297–300.
(12) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 177. For acetanilides, barriers to rotation around the aryl nitrogen bond as high as 25.4 kcal/mol have been found: Siddall, T. H., III; Stewart, W. E. *J. Phys. Chem.* **1969**, *73*, 40.

Scheme I[a]



[a](a) $NaCNBH_3$, AcOH, MeOH; (b) camphor-d_{10}-sulfonic acid, *i*-PrOH; (c) NH_4OH; (d) $Pb(OAc)_4$, I_2, CH_2Cl_2.

then gave the enantiomers **11** and **12**, respectively.

The NMR spectrum of the reduction product **8** indicated the presence of two *tert*-butyl resonances at 1.57 (major) and 0.89 (minor) ppm. Although Dreiding models showed that two conformations were possible for compound **8**, namely **8a** and **8b** (Figure 1 shows the conformations of **8a** and **8b** in two different perspective views), the appearance of two peaks for the *tert*-butyl group was not expected, since, a priori, **8b** was not given consideration as a low-energy conformation on the basis of the interaction of the *tert*-butyl group and the phenyl group. Compound **8b** cannot be formed from the direct reduction of **7** since a corresponding conformation of **7** does not exist. (For racemic compounds, only one enantiomer is shown in the figures and schemes for clarity reasons). The atom numberings in Figures 1–5 and 7 correspond to the X-ray numbering schemes obtained by X-ray analysis and are consistent with the data contained in the supplementary material. However, MM2 calculations with the MODEL program[13] showed that the difference in energy between **8a** and **8b** is only on the order of 1 kcal/mol. In the minor conformer **8b**, the *tert*-butyl group is interacting with the phenyl group in a face-on orientation, as can be seen in the structure shown at the bottom right of Figure 1, and is reflected in the higher field signal of the *tert*-butyl group in the NMR spectrum. Further evidence supporting the presence of two conformations for **8** was provided by observing the difference in ratios between **8a** and **8b** (integration of the two *tert*-butyl resonances in the NMR spectra) in different solvents.[14] Thus, in deuteriochloroform the ratio of **8a** to **8b** was 29:1 (1.57 and 0.89 ppm) and in dimethyl-d_6 sulfoxide the ratio was 7:1 (1.52 and 0.79 ppm), corresponding to energy differences of 1.99 and 1.15 kcal/mol, respectively.

Compound **8** contains two elements of chirality, namely the asymmetric center at the 5-position and the conformational isomers

Table I. Selected X-ray Data for Compounds **10**, **12**, and **28**

	10	**12**	**28**
formula	$C_{19}H_{21}ClN_2O \cdot 1/2H_2O$	$C_{19}H_{19}ClN_2O$	$C_{19}H_{20}Cl_2N_2O$
fw	337.85	326.83	363.29
cryst syst	monoclinic	orthorhombic	monoclinic
space group	*A*2	$P2_12_12_1$	$P2_1$
a (Å)	14.013 (3)	9.467 (1)	11.652 (3)
b (Å)	10.033 (2)	12.357 (3)	17.267 (4)
c (Å)	12.983 (3)	15.049 (1)	9.2771 (2)
β (deg)	98.32 (2)		92.56 (2)
Z	4	4	4
d_{calcd} (g cm^{-1})	1.242	1.23	1.295
μ (Cu Kα)	19.5	19.69	32.0
cryst size (mm)	0.08 × 0.35 × 0.45	0.13 × 0.35 × 0.60	0.08 × 0.35 × 0.45
max θ	57	60	57°
no. of reflcns	1269	1513	2614
no. of obsd, reflcns	1125	1379	2353
final *R*	0.034	0.038	0.031
final R_w	0.036	0.049	0.033
final diff map, largest (e Å^{-3})	<±0.3	<0.1	>±0.1

defined by the C-3 methylene group. Interconverting structures **8a** and **8b** does not change the chirality sense of the asymmetric center but changes the conformational asymmetry from *R* to *S*, on the basis of IUPAC rules.[15] The presence of **8b** might have caused difficulties in obtaining compounds **11** and **12** in optically pure form since **8a** would eventually lead to compound **12** (after resolution and oxidation) while **8b** would yield compound **11**, which is enantiomeric to **12**. This, however, did not prove to be the case. Possibly, any contamination from this minor isomer was removed during the purification process or the rate of oxidation of the minor isomer is much less than that of the major isomer, although this point was not investigated. The resolution of **8** was carried out by treatment with camphor-d_{10}-sulfonic acid in 2-propanol. The salt was collected by filtration and recrystallized from methanol and ether to give the salt with a rotation of +47.9°. Cleavage of the salt with ammonium hydroxide then gave compound **9**, which had a rotation of +106.9°. The enantiomer **10** was isolated from the filtrates obtained after isolation of **9** by concentrating and recrystallizing the solid from 2-propanol and ether and finally from methanol and ether. The camphor-d_{10}-sulfonic acid salt of **10** had a rotation of −7.2°. Treatment of the salt with ammonium hydroxide then gave **10**, which had a rotation of −97.4°. The optical purity was determined by the use of europium shift reagents. Addition of europium to the racemic compound **8** showed a splitting of the *tert*-butyl peak at 1.57 ppm into two identical peaks with a shift to downfield to 3.40 and 3.51 ppm. The NMR spectrum of **9** and **10** in the presence of the europium shift reagent showed only one *tert*-butyl peak, indicating the compounds were optically pure within the limits of detection for the enantiomer (5% or less). In the presence of the europium shift reagent, the *tert*-butyl peak of the minor conformer (similar to **8b**) is masked and was not observed. Both compounds **9** and **10**, in the absence of the europium reagent, showed two *tert*-butyl groups, as was the case for **8**, indicating the presence of two conformations. The absolute configuration of compound **10** was determined by single-crystal X-ray analysis and shown to be as depicted in formula **10** (cf. Figure 2). Selected X-ray data for compound **10** are shown in Table I. The absolute configuration of compound **9** was then assigned accordingly. The conversion of **9** to **11** (and **10** to **12**) was best accomplished with the use of a combination of lead tetraacetate and iodine in a 1:1 ratio and in excess. Optical purities were again determined with europium shift reagents, which showed that **11** and **12** were obtained with optical purities of greater than 95%. The racemic compound **7**, in the presence of the europium shift reagent, shows two equal

(13) MODEL: Serena Software, P.O. Box 3076, Bloomington, IN 47402.
(14) 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.

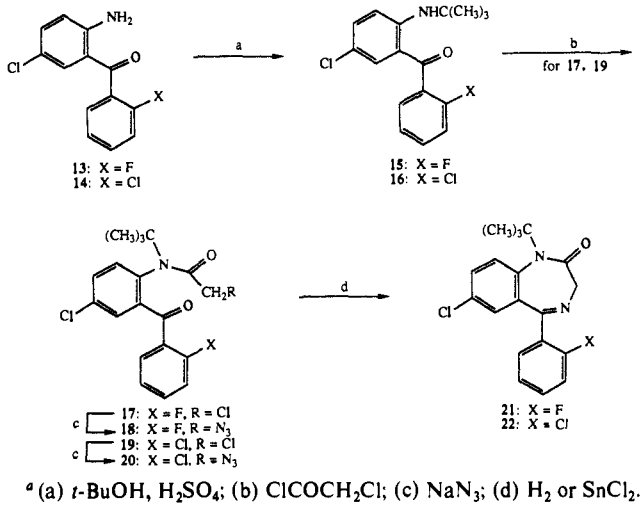
(15) IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry. *J. Org. Chem.* **1970**, *35*, 2849–2867.

Table II. Biological Data for Compounds 6, 7, 11, 12, 21, and 22

compd	IC_{50},[a] nM [^{3}H]diazepam binding	ED_{50},[b] mg/kg antipentylenetetrazole
6	5	1
7	>1000	inactive
11	420	inactive
12	>1000	inactive
21	78	185
22	26	58

[a] The method described in ref 2 was used for this assay. [b] A modification of the Everett and Richards[24] method was used for this assay. Results are reported as 95% fiducial limits.

Scheme II[a]



[a] (a) *t*-BuOH, H_2SO_4; (b) $ClCOCH_2Cl$; (c) NaN_3; (d) H_2 or $SnCl_2$.

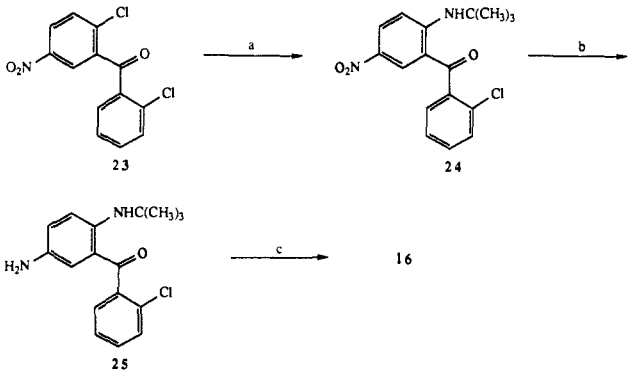
peaks for the *tert*-butyl group, similar to compound **8**. The absolute configuration of compound **12** was determined by X-ray analysis (see Table I and Figure 3). Because of the locked type of conformation found in compounds **9** and **10**, oxidation proceeds to give an imine derivative in which the relative positions of the 3-methylene group and the *tert*-butyl group are maintained. Thus, the absolute configuration of **12** corresponds to compound **10** in that the 3-methylene group is "down" relative to the plane of the fused benzene ring and the *tert*-butyl group is in front of this plane. The antipodes **11** and **12**, which are conformational isomers, were thus obtained from compounds **9** and **10**, respectively, which have two elements of asymmetry. Although both **11** and **12** maintained their optical integrity in the solid state, they slowly racemized in solution. In a qualitative experiment with europium shift reagents to follow the racemization, compound **11** was completely racemized after storage for 3 days in deuteriochloroform. The exact barriers to rotation for inversion of **11** and **12** were not determined, but must be greater than 24 kcal/mol as discussed previously.

To determine the affinity of compounds **7**, **11**, and **12** for the benzodiazepine receptor, a binding assay was done with tritiated diazepam as the radioligand.[2,16] The results are shown in Table II. Although the affinity of compound **11** is rather weak (compare with the IC_{50} for diazepam which is 5 nM), the lack of affinity of compound **12** clearly indicates that the benzodiazepine receptor is recognizing the conformation in which the 3-methylene group is above the plane of the benzene ring as depicted in Scheme I, i.e., compound **11**. This conformation (**11**), which is recognized by the benzodiazepine receptor, is in agreement with the proposed active conformation of diazepam, i.e., **6a**.[9]

2′-Chloro- and 2′-Fluoro-N^1-*tert*-butyldiazepam. Since it was known from early work on structure–activity relationships with the benzodiazepines that the presence of a 2′-halo substituent in the 5-phenyl ring enhanced activity,[17] attention was turned to the

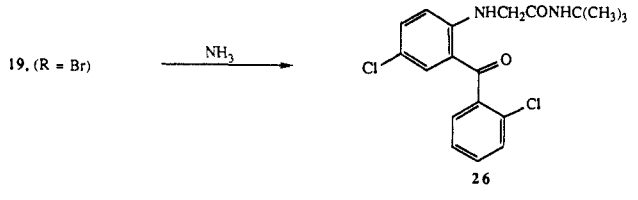
(16) All IC_{50} values for compounds evaluated in the diazepam binding assay were determined by members of the Department of Pharmacology, Hoffmann-LaRoche, Inc., Nutley, NJ, or of the Pharmaceutical Research Department, Hoffmann-LaRoche & Co., Ltd., Basel, Switzerland. The assays were performed as previously described.[2]

Scheme III[a]



[a] (a) *t*-$BuNH_2$; (b) $SnCl_2$; (c) $NaNO_2$, CuCl.

Scheme IV



synthesis and resolution of compounds **21** and **22**, which have a 2′-fluoro and 2′-chloro substituents, respectively. It was expected that the binding affinities of these compounds for the benzodiazepine receptor would be much greater than that of **11**, which was only 420 nM. The syntheses of **21** and **22** are shown in Scheme II. Compound **15** was prepared from **13** by treatment with *tert*-butyl alcohol in the presence of ethanolic hydrogen chloride in a bomb at 150–155 °C. Although the yield was quite low (23%), the simplicity of the reaction and the recovery of starting material made this intermediate readily available. Two methods were employed for the synthesis of **16**: (1) treatment of **14** with *tert*-butyl alcohol similar to the preparation of **15** and (2) displacement of the activated chlorine in compound **23** with *tert*-butylamine to give **24**, followed by reduction of the nitro group to the amine **25** and finally a Sandmeyer reaction to give **16**, as shown in Scheme III. Compounds **15** and **16** were chloroacetylated with chloroacetyl chloride to give **17** and **19**, respectively. Azides **18** and **20** were prepared by treatment of **17** and **19** with sodium azide in the presence of sodium iodide. Reduction of the azides either by catalytic hydrogenation or by treatment with stannous chloride then gave the benzodiazepines **21** and **22** directly. Presumably, the intermediate primary amines cyclized under the reaction conditions. Bromoacetyl bromide could be substituted for chloroacetyl chloride to prepare **17** and **19** (R = Br), but in many cases some loss of the *tert*-butyl group occurred. Attempts to react **19** (R = Br) directly with ammonia to give **22** gave none of the benzodiazepine but led instead to the Smiles rearrangement product **26**[18,19] (Scheme IV).

High-temperature (200 °C) NMR studies with both **21** and **22** showed an unexpected collapse of the AB pattern for the methylene protons, indicating that the barrier for inversion is less than that of **7**. On the basis of this result, attempts to isolate the enantiomers of **21** and **22** would be expected to give only racemic products due to rapid interconversion. The resolution of **22** was nevertheless undertaken following the procedure described for the resolution of **7**. (See Scheme V.) Thus, reduction of **22** with sodium cyanoborohydride gave the dihydro compound **27**, which was resolved with camphor-d_{10}-sulfonic acid to give enantiomers **28** and **29**.

(17) Sternbach, L. H. In *The Benzodiazepines*; Garattini, E., Mussini, E., Randall, L. O., Eds.; Raven Press: New York, 1973; pp 1–26.
(18) Gilman, N. W.; Levitan, P.; Sternbach, L. H. *Tetrahedron Lett.* **1970**, 4121.
(19) Gilman, N. W.; Levitan, P.; Sternbach, L. H. *J. Org. Chem.* **1973**, *38*, 373.

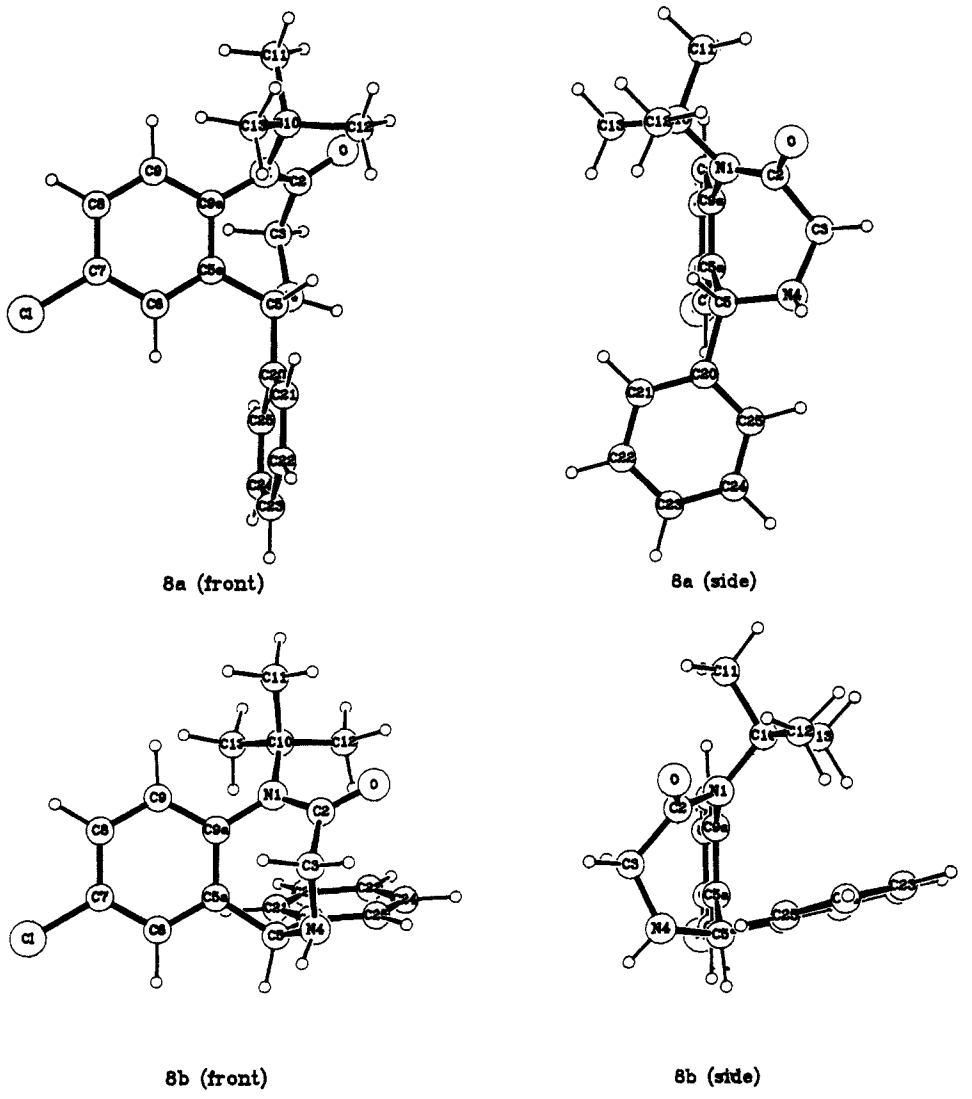


Figure 1. ORTEP drawings of **8a** (top) and **8b** (bottom).

The NMR spectrum of **27** showed only 1 *tert*-butyl peak at 1.59 ppm in contrast with that of **8** (see discussion above). The absence of conformers in **27** may be due to the added extra steric component from the chlorine atom in the 2'-position. The NMR spectra of **28** and **29** in the presence of a europium shift reagent showed that the compounds were pure enantiomers within the limits of detection (less than 5% of the opposite enantiomer). The absolute configuration of compound **28** was determined by single-crystal X-ray analysis. The unit cell contains 2 independent molecules, that is, two molecules not related by crystallographic symmetry. The conformations of the two independent molecules are similar and differ mainly by the degree of rotation of the phenyl ring. (Figure 4 shows the structure for one of the independent molecules.) The selected X-ray data for **28** are shown in Table I. As predicted, the oxidation of **28** and **29** with lead tetraacetate/iodine as described above for the preparation of **11** and **12** led only to the isolation of the racemic compound **22**.

Since the reasons for the difference of stability of **7** to racemization relative to **22** are not readily apparent, molecular mechanics calculations were carried out for the pathway to invert the seven-membered ring for compounds **7** and **22**. All calculations were performed with the program MODEL, which employs a generalized MM2 force field potential. The following representations are based on model calculations and are not meant to imply exact transition-state geometries or energies. In addition, the model calculations compare the *relative* inversion energies for **7** and **22**, which have very similar geometries with the same, albeit approximate, force fields. In fact, the difference between the structures is larger in the ground state than in the putative transition state. The calculated ground-state geometry for **12** with the MODEL program agrees excellently with the X-ray structure. The only difference between the two structures is a slight variation in the angle of twist of the 5-phenyl ring.

Points along the pathway were determined by varying the C5a–C9a–N1–C2 and N1–C2–C3–N4 angles (see Figure 4 for numbering) in small increments starting from one of the minimum energy structures and minimizing the remaining internal coordinates. As a check, the pathway was determined in reverse as well, starting from the inverted structure.

The pathway for inversion in terms of these two angles for compounds **7** and **22** is shown in Figure 5. The corresponding steric energy as a function of the fractional distance along each path is shown in Figure 6. Although we chose to vary (decrease) the C5a–C9a–N1–C2 angle first, we could have chosen to vary N1–C2–C3–N4. This would have led to an alternate path that, for X = H, is equivalent to the path shown by symmetry.

The potential surface for compound **7** has 2-fold symmetry. The structures corresponding to the starting and final points on the path are enantiomers. For compound **22**, the symmetry is only approximate: the final geometry along the inversion path is 0.8 kcal/mol lower than the starting point. This geometry requires a rotation of the 2'-chlorophenyl group to complete the racemization pathway. The barrier for this rotation is calculated to be significantly smaller than the barrier to inversion (5.1 vs 16.5 kcal/mol). As an additional check on the calculated barriers, the potential energy surface was scanned as a function of the N1–C2–C3–N4 angle from 110° to −110° while the C5a–C9a–N1–C2 angle was kept fixed at 0°. The lowest point along this axis was

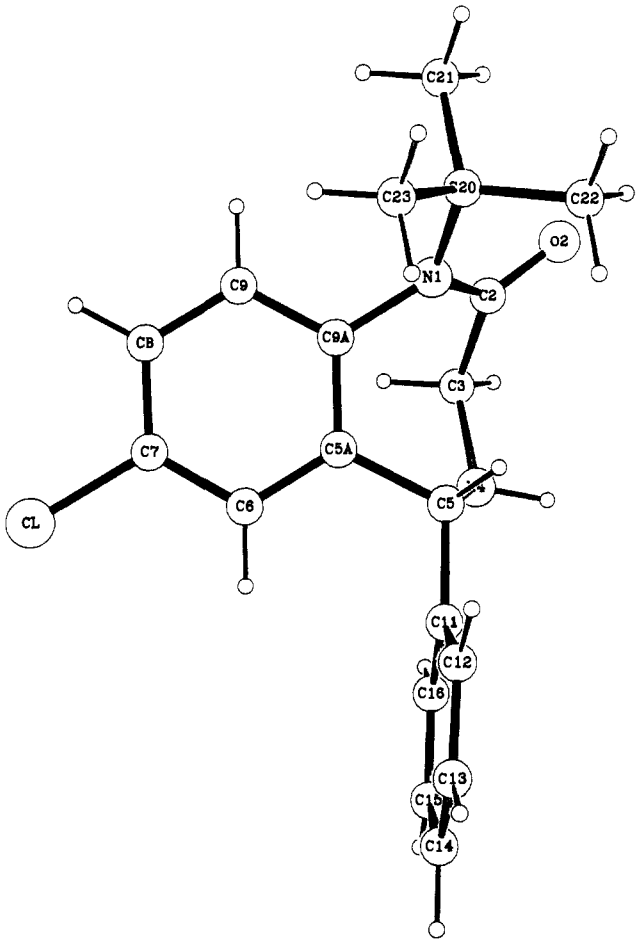


Figure 2. Perspective drawing of the X-ray structure of **10**.

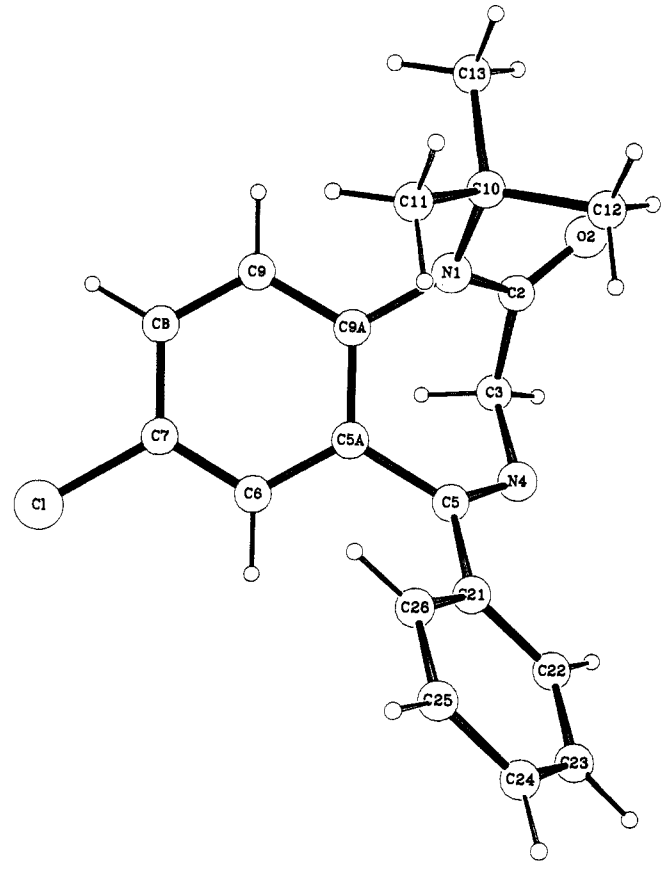
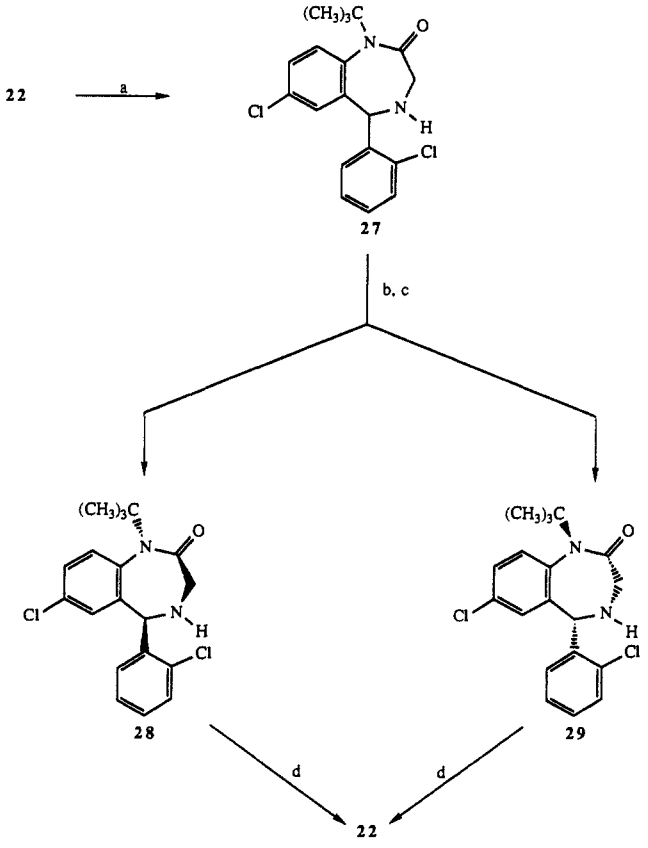


Figure 3. Perspective drawing of the X-ray structure of **12**.

Scheme V[a]



[a](a) $NaCNBH_3$, AcOH, MeOH; (b) camphor-d_{10}-sulfonic acid, *i*-PrOH; (c) NH_4OH; (d) $Pb(OAc)_4$, I_2, CH_2Cl_2.

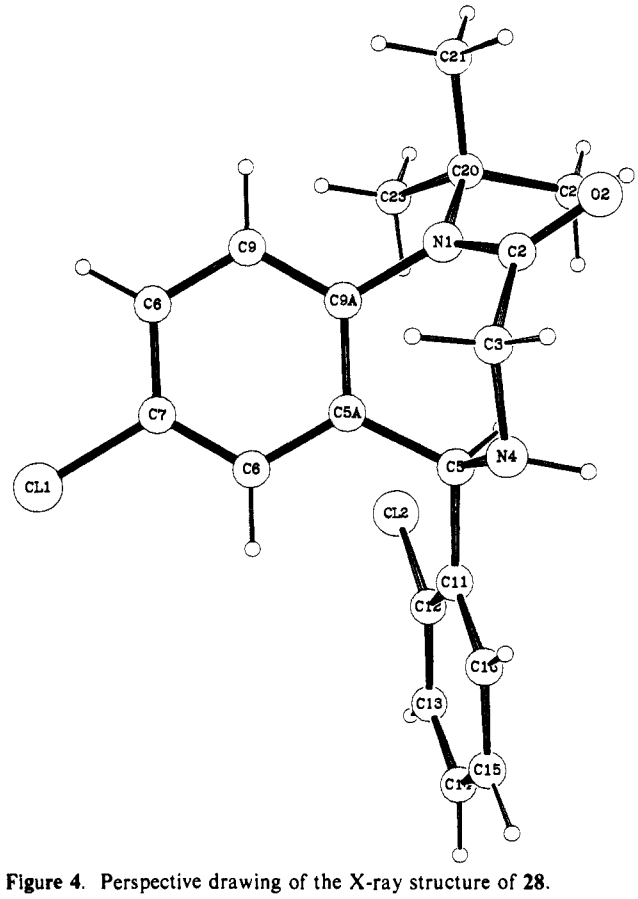


Figure 4. Perspective drawing of the X-ray structure of **28**.

on the previously determined pathway at 97° (**22**, 47.0 kcal/mol; **7**, 43.2 kcal/mol), and the highest point was at 20° (**22**, 57.8 kcal/mol). There is an additional pathway that has a saddle point near the origin having energies of 56.9 kcal/mol for **22** and 54.0

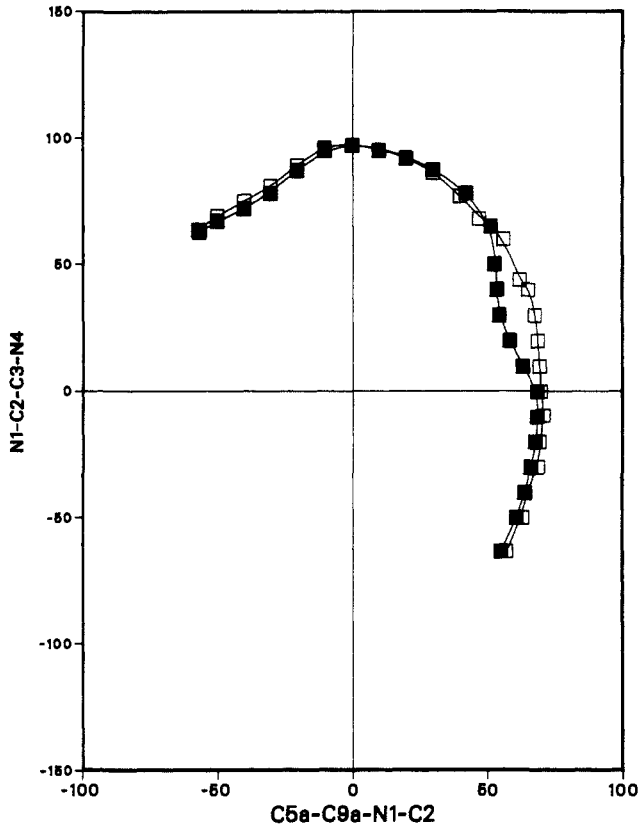


Figure 5. Pathway for inversion of the C5a–C9a–N1–C2 and N1–C2–C3–N4 angles for inversion of compounds **7** and **22**. Each data point corresponds to the steps shown in Figure 6. See Figure 6 for legend.

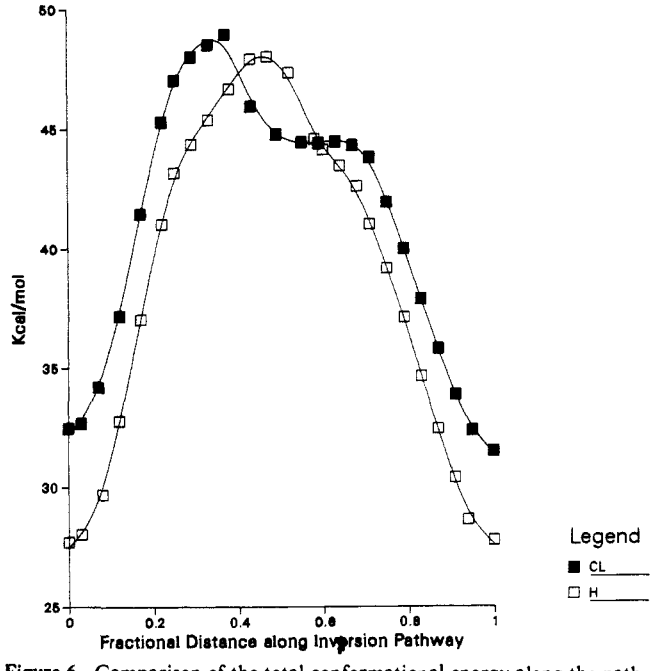


Figure 6. Comparison of the total conformational energy along the path for interconversion of the enantiomers of compounds **7** and **22**.

kcal/mol for **7** and is thus a higher energy barrier than the one previously described.

The difference in the barrier to inversion between compounds **7** and **22** is 2.8 kcal/mol in favor of compound **22**. This result is consistent with the experimental results: compound **7** could be resolved, and the NMR spectrum showed no collapse of the AB pattern at 200 °C; compound **22** (X = Cl) could not be resolved, and the AB pattern collapsed below 200 °C. A comparison of the structures and energy terms of the ground states and transition states suggests that the lowering barrier for inversion

Table III. Selected Parameters for the Ground and Transition States for Compounds **7** and **22**

		22, H21 → Cl		**22**, H22 → Cl	
	7	unrelaxed	relaxed	unrelaxed	relaxed
		Ground State			
C5a–C5–C20–C21(22),[a] deg	−156.0	−156.0	−126.6	24.2	48.6
energy, total	27.73	34.69	32.26	35.66	31.52
stretch	1.73	1.73	1.81	1.73	1.95
stretch–bend	0.12	0.13	0.12	0.13	0.16
angle	2.42	2.45	0.52	2.45	3.42
torsion	18.23	19.27	21.36	19.27	19.53
van der Waals	11.87	15.13	11.24	18.21	12.13
dipole	−6.62	−4.03	−4.78	−6.14	−5.67
H21→N4 dist, Å	2.6	2.7	3.1	4.3	4.2
H22→*t*-Bu dist, Å	2.9	5.5	6.3	2.5	3.0
		Transition State			
C5a–C5–C20–C21(22), deg	−116.0	−116.0	−97.0	64.8	78.8
energy, total	48.16	51.07	48.97	50.70	48.76
stretch	1.96	1.97	2.60	1.97	2.60
stretch–bend	0.22	0.23	0.27	0.23	0.27
angle	7.10	7.13	7.20	7.13	7.18
torsion	34.88	35.94	32.43	35.94	32.24
van der Waals	10.87	11.27	11.96	11.36	11.89
dipole	−6.87	−5.46	−5.49	−5.92	−5.42
H21→N4 dist, Å	3.0	3.2	3.5	3.7	3.6
H22→*t*-Bu dist, Å	5.7	5.5	5.8	6.9	6.8

[a] Numbering of carbons corresponds to structures shown in Figure 7. All energy terms are in kilocalories per mol.

of compound **22** is due to ground-state destabilization relative to compound **7**.

This ground-state destabilization can be most clearly visualized by considering the structures derived from the ground and transition states of **7** in which the 2′- (or 6′-) hydrogen is replaced by a chlorine without relaxing the geometry. The results of this analysis are given in Table III. In the ground state, replacing the 2′-hydrogen results in a 6.3 kcal/mol increase in the van der Waals energy while replacing the 6′-hydrogen increase both the van der Waals (3.3 kcal) and dipole (2.6 kcal) energy terms. The latter results from an interaction between the chlorine and imine nitrogen. Subsequent minimization removes the bad contacts at the cost of additional strain in the seven-membered ring. In the transition state, replacing the 2′-hydrogen leads to an increase in total energy of only 2.5 kcal/mol of which only 0.5 kcal/mol is the result of van der Waals repulsion. The distances between the chlorine (or hydrogen) and the imine nitrogen as well as the most proximate *tert*-butyl hydrogen are also given in Table III (cf. Figure 7).

Although compounds **21** and **22** could not be obtained *in* optically active form, the introduction of the 2′-halo substituent had the desired effect in that both compounds showed increased potency both in vitro and in vivo. The biological testing results for **21** and **22** in comparison to compound **7** and diazepam (**6**) are shown in Table II.

Conclusion

A novel method for the resolution of an asymmetric diazepam-type compound **7** has been demonstrated. A *tert*-butyl group was utilized to "lock" the conformation of the seven-membered ring system of the benzodiazepine molecule and to prevent inversion of the C-3 methylene group. Resolution was effected by a sequence that involved reduction of the imine double bond in **7** to yield the asymmetric dihydro derivative **8**, subsequent resolution of **8**, and finally oxidation of **9** and **10** to give the optically pure compounds **11** and **12**. As a consequence of the oxidation, the center of asymmetry is lost while the conformational asymmetry is retained. On the basis of the affinities found for compounds **11** and **12** for the benzodiazepine receptor, the active conformer clearly resides in compound **11** in which the 3-methylene group lies above the plane of the benzene ring. This is in agreement with the proposed active conformer of diazepam.

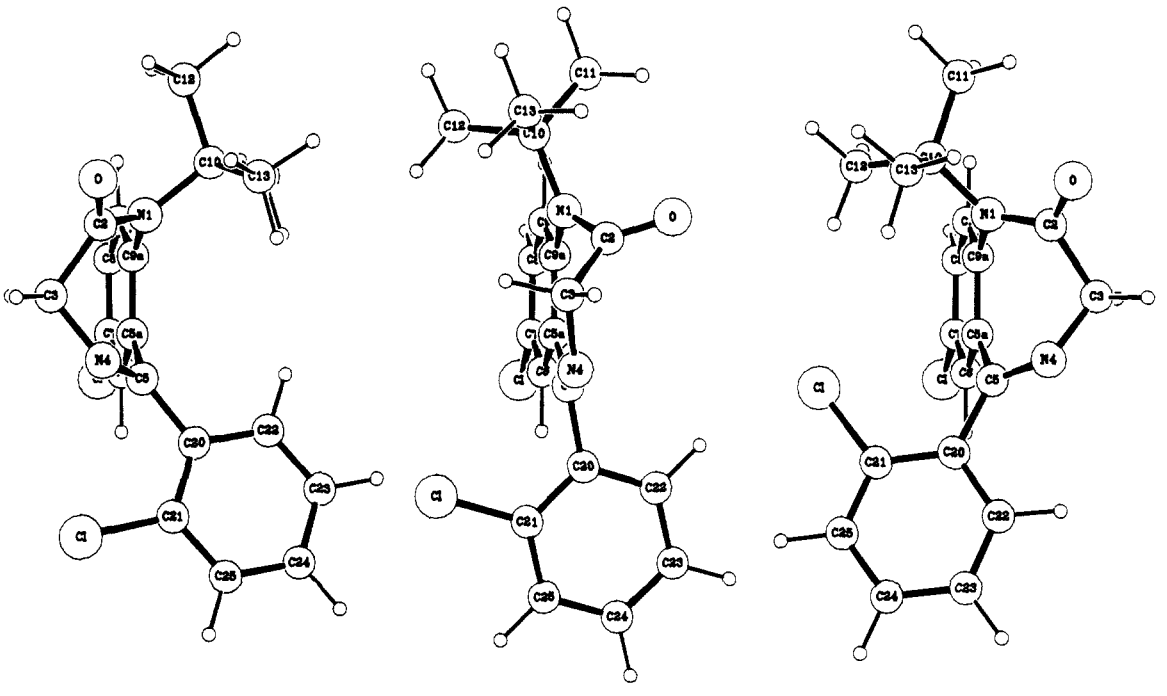


Figure 7. ORTEP drawings of compound **22** undergoing inversion of the seven-membered ring system. Panel **22a** represents the starting point, **22b** is the transition state for inversion, and **22c** is the final geometry. Note that **22c** is not the mirror image of **22a** (the 2'-chlorophenyl ring needs to be rotated to obtain the mirror image).

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 with tetramethylsilane as an internal reference. Optical purities were determined by NMR analysis with 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 with silica gel 60, 70–230 mesh, E. Merck. Organic solutions were dried with either anhydrous sodium sulfate or magnesium sulfate before being concentrated at water aspirator pressure (20–25 mm).

X-ray Analysis. (1) Compound 10. 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. For the observed reflections, $I > 2.5\sigma(I)$. The structure was solved by a multiple-solution procedure[20] and was refined by full-matrix least squares. In the final refinement, 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 absolute configuration of **10** is based on the anomalous scattering of the chlorine atom and was established by refining both enantiomers. The final weighted R values were 0.0364 for the configuration shown in structure **10** and 0.0415 for the antipode **9**. Thus, the absolute configuration is as shown by Hamilton's test (cf. Figure 2).[21]

(2) Compound 12. The intensity data were measured on an Enraf-Nonius diffractometer (graphite-monochromated Cu Kα radiation, ω–2θ scans). For the observed reflections $I > 3.0\sigma(I)$. The structure was solved by a multiple-solution procedure[22] and was refined by full-matrix least squares. Eleven reflections that were strongly affected by extinctions were excluded from the final refinement. In the final refinement, 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 absolute configuration of **12** is based on the anomalous scattering of the chlorine atom and was established by refining both enantiomers. The final weighted R values were 0.0493 for the configuration shown for **12** and 0.0680 for the antipode **11**. Thus, by Hamilton's test,[21] the configuration shown corresponds to the absolute configuration (cf. Figure 3).

(3) Compound 28. The unit cell of this compound contains 2 independent molecules, that is, 2 molecules not related by crystallographic symmetry. The conformations of the independent molecules are very similar, and they differ only in the rotation angle of the 5-phenyl group. The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). For the observed reflections $I > 2.5\sigma(I)$. The structure was solved by a multiple-solution procedure[20] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for 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 absolute configuration of **28** is based on the anomalous scattering of the chlorine atoms and was established by refining both enantiomers. The final weighted R values were 0.0327 for the configuration shown for **28** and 0.0386 for the antipode **29**. Thus, by Hamilton's test,[21] the configuration shown for **28** corresponds to the absolute configuration (cf. Figure 4).

7-Chloro-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8). To a solution of 1.9 g (5.81 mmol) of **7**[11] in 10 mL of glacial acetic acid and 55 mL of methanol was added 0.7 g (11.1 mmol) of sodium cyanoborohydride. The reaction was carried out in an ice bath and stirred for 30 min. The ice bath was removed, and stirring continued for 2 h. After the addition of cold water, the product was extracted with CH_2Cl_2, which was washed with dilute NH_4OH, dried, and concentrated. The residue was filtered through silica gel with a mixture of CH_2Cl_2 and methanol (5:1) as the eluent. Removal of the solvents and recrystallization of the residue from CH_2Cl_2/petroleum ether gave 1.5 g (79%) of **8** as colorless prisms: mp 160–163 °C; IR ($CHCl_3$) 3327 (NH), 1657 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 9 H, $C(CH_3)_3$), ~4% of $C(CH_3)_3$ at 0.89, 3.05 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N), 3.26 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-NH) 5.40 (s, 1 H, CH-N); MS, m/e 328 (M^+). Anal. Calcd for $C_{19}H_{21}ClN_2O$: C, 69.40; H, 6.44; N, 8.52. Found: C, 69.75; H, 6.47; N, 8.61.

7-Chloro-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8)–7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic Acid (1:1) Salt (+). To a hot solution of 3.4 g (0.103 mol) of **8** in 80 mL of 2-propanol was added a solution of 2.6 g (0.103 mol) of camphor-d_{10}-sulfonic acid in 20 mL of 2-propanol. The solution was stored at −10 °C for several hours. The solid that formed was collected by filtration and washed with ether to give 2.6 g (87% based on theoretical yield of 50%) of the salt. A small portion was recrystallized from methanol/ether to give the salt as colorless needles: mp

(20) Germain, G.; Woolfson, M. M. *Acta Crystallogr., Sect. A: Found Crystallogr.* **1971**, *27*, 368–376.
(21) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502–510.
(22) Main, P.; Fiske, S.; Hull, L.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN 11/82; Universities of York and Louvain: York, England and Louvain, Belgium, 1982.

252–255 °C; $[\alpha]^D_{25}$ +47.9 (c = 1.0, CH_2Cl_2); IR (KBr) 1745, 1687 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.74, 1.03 (2s, 6 H, $C(CH_3)_2$), 1.53 (s, 9 H, $C(CH_3)_3$), 2.36 (d, 1 H, J_{AB} = 14 Hz, CH_AH_B–SO_3H), 2.87 (d, 1 H, J_{AB} = 14 Hz, CH_AH_B–SO_3H), 5.53 (s, 1 H, CH–N). Anal. Calcd for $C_{19}H_{21}ClN_2O{\cdot}C_{10}H_{16}O_4S$: C, 62.07; H, 6.65; N, 4.99. Found: C, 61.53; H, 7.23; N, 4.67.

(*S*)-7-Chloro-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (9). The salt from the above experiment was partitioned with dilute NH_4OH and ether. The organic fraction was dried and concentrated. The residue was crystallized from ether/petroleum ether to give 1.4 g (82% based on **8**) of **9** as colorless rods: mp 100–107 °C; $[\alpha]^D_{25}$ +106.9 (c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.56 (s, 9 H, $C(CH_3)_3$), [trace of $C(CH_3)_3$ at 0.89], 3.02 (d, 1 H, J_{AB} = 14 Hz, CO–CH_AH_B–N), 3.22 (d, 1 H, J_{AB} = 14 Hz, CO–CH_AH_B–N), 5.41 (s, 1 H, CH–N). Anal. Calcd for $C_{19}H_{21}ClN_2O$: C, 69.40; H, 6.44; N, 8.52. Found: C, 69.10; H, 6.53; N, 8.36.

7-Chloro-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8)–7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic Acid (1:1) Salt (−). To a hot solution of 3.4 g (0.103 mol) of **8** in 80 mL of 2-propanol was added a solution of 2.6 g (0.103 mol) of camphor-d_{10}-sulfonic acid in 20 mL of 2-propanol. The solution was stored at −10 °C overnight and the solid collected by filtration. The filtrates were concentrated, and the residue was crystallized from methanol/ether to give 2.4 g (80% based on theoretical yield of 50%) of the salt of **10** as colorless rods: mp 240–250 °C; $[\alpha]^D_{25}$ −7.2° (c = 1.0, CH_2Cl_2); IR (KBr) 3575, 3510 (salt bands), 1745, 1676 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.74, 1.04 (2 s, 6 H, $C(CH_3)_2$, 1.54 (s, 9 H, $C(CH_3)_3$), 2.35 (d, 1 H, J_{AB} = 14 Hz, $CH_AH_BSO_3H$), 2.85 (d, 1 H, J_{AB} = 14 Hz, $CH_AH_BSO_3H$), 5.53 (s, 1 H, CH–N). Anal. Calcd for $C_{19}H_{21}ClN_2O{\cdot}C_{10}H_{16}O_4S$: C, 62.07; H, 6.65; N, 4.99. Found: C, 61.22; H, 6.48; N, 4.96.

(*R*)-7-Chloro-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (10). The salt from the above experiment was partitioned with dilute NH_4OH and ether. The ether extracts were dried and concentrated. The residue was crystallized from ether/petroleum ether to give 1.3 g (76% based on **8**) of **10** as colorless prisms: mp 82–88 °C; $[\alpha]^D_{25}$ −97.4 (c = 1.0, CH_2Cl_2): IR ($CHCl_3$) 3420 (NH), 1665 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 9 H, $C(CH_3)_3$), [~5% of $C(CH_3)_3$ at 0.90], 3.04 (d, 1 H, J_{AB} = 14 Hz, CO–CH_ACH_B–NH), 3.25 (d, 1 H, J_{AB} = 14 Hz, CO–CH_ACH_B–NH); m/e 328 (M^+). Anal. Calcd for $C_{19}H_{21}ClN_2O$: C, 69.40; H, 6.44; N, 8.52. Found: C, 69.75; H, 6.47; N, 8.61.

(*R*)-7-Chloro-1,3-dihydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (11). To a cold solution of 0.6 g (1.82 mmol) of **9** in 35 mL of CH_2Cl_2 was added a solution of 1.2 g (2.73 mmol) of lead tetraacetate and 0.74 g (2.91 mmol) of iodine in 35 mL of CH_2Cl_2. After the solution was stirred for 90 min, dilute sodium bicarbonate and sodium thiosulfate were added followed by dilute potassium carbonate. The mixture was extracted with CH_2Cl_2, and the organics were combined, dried, and concentrated. The residue was filtered through a small amount of silica gel with ether/petroleum ether as the eluent. The fractions containing the product were combined and concentrated, and the oily residue was dissolved in ether/petroleum ether and allowed to stand at −10 °C overnight. The solid was collected and recrystallized from the same solvent mixture to give 0.3 g (50%) of **11** as colorless prisms: mp 100–110 °C; $[\alpha]^D_{25}$ −23.9 (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 1677 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H, $C(CH_3)_3$), 3.70 (d, 1 H, J_{AB} = 12 Hz, CO–CH_ACH_B–N), 4.61 (d, 1 H, J_{AB} = 12 Hz, CO–CH_ACH_B–N). Anal. Calcd for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; N, 8.57. Found: C, 70.11; H, 5.85; N, 8.52.

(*S*)-7-Chloro-1,3-dihydro-1-(1,1-dimethylethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (12). To a cold solution of 0.6 g (1.82 mmol) of **10** in 35 mL of CH_2Cl_2 was added a solution of 1.2 g (2.73 mmol) of lead tetraacetate and 0.74 g (2.91 mmol) of iodine in 35 mL of CH_2Cl_2 over 20 min. After the solution was stirred for 90 min, dilute sodium bicarbonate and sodium thiosulfate were added followed by dilute potassium carbonate to make the solution basic. The product was extracted with CH_2Cl_2, which was dried and concentrated. The residue was crystallized from ether/petroleum ether to give 0.3 g (50%) of **12** as colorless prisms: mp 98–108 °C; $[\alpha]^D_{25}$ + 25.2 (c = 1.0, CH_2Cl_2); IR ($CHCl_3$) 1660 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.41 (s, 9 H, $C(CH_3)_3$), 3.66 (d, 1 H, J_{AB} = 12 Hz, CO–CH_ACH_B–NH), 4.57 (d, 1 H, J_{AB} = 12 Hz, CO–CH_ACH_B–NH). Anal. Calcd for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.83; H, 5.95; N, 8.60.

[5-Chloro-2-[(1,1-dimethylethyl)amino]phenyl](2-fluorophenyl)-methanone (15). A mixture of 10.0 g (0.040 mol) of **13**,[23] 100 mL of *tert*-butyl alcohol, and 5 mL of 10 N ethanolic hydrogen chloride was heated in a steel bomb for 11 h. The contents of the bomb were partitioned between ether and dilute NH_4OH. The organics were dried and concentrated, and the residue was crystallized from petroleum ether to give 6.5 g of recovered starting material. The filtrates from the crystallization were concentrated, and the residue was chromatographed on alumina with petroleum ether/ether (20:1) as the eluent. Removal of the solvents and crystallization of the residue from petroleum ether gave 2.3 g (23%) of **15** as yellow prisms: mp 79–81 °C; IR ($CHCl_3$) 3300 (NH), 1624 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 9 H, $C(CH_3)_3$), 9.24 (s, 1 H, NH); MS, m/e 305 (M^+). Anal. Calcd for $C_{17}H_{17}ClFNO$: C, 66.78; H, 5.60; N, 4.58. Found: C, 66.63; H, 5.72; N, 4.42.

[5-Chloro-2-[(1,1-dimethylethyl)amino]phenyl](2-chlorophenyl)-methanone (16). This compound was prepared with the same procedure described for the synthesis of **15**, starting with compound **14**.[24] The product was obtained as a pale yellow oil: IR ($CHCl_3$) 3290 (NH), 1620 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.51 (s, 9 H, $C(CH_3)_3$), 9.32 (s, 1 H, NH); MS, m/e 321 (M^+). Anal. Calcd for $C_{17}H_{17}Cl_2NO$: C, 63.37; H, 5.32; N, 4.35. Found: C, 63.07; H, 5.25; N, 4.22.

2-Chloro-*N*-[4-chloro-2-(2-fluorobenzoyl)phenyl]-*N*-(1,1-dimethylethyl)acetamide (17). A solution of 0.2 g (0.65 mol) of **15**, 0.22 g (2.0 mol) of chloroacetyl chloride, and 30 mL of toluene was stirred and refluxed for 7 h. The solution was washed with dilute $NaHCO_3$ and then dried and concentrated. The residue was crystallized from ether/petroleum ether to give 0.1 g (40%) of **17** as colorless prisms: mp 135–137 °C; IR ($CHCl_3$) 1672 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 9 H, $C(CH_3)_3$), 3.70 (d, 1 H, J_{AB} = 7 Hz, CO–CH_ACH_B–Cl), 3.97 (d, 1 H, J_{AB} = 7 Hz, CO–CH_ACH_B–Cl); MS, m/e 381 (M^+). Anal. Calcd for $C_{19}H_{18}Cl_2FNO_2$: C, 59.70; H, 4.75; N, 3.66. Found: C, 59.70; H, 4.78; N, 3.64.

2-Azido-*N*-[4-chloro-2-(2-fluorobenzoyl)phenyl]-*N*-(1,1-dimethylethyl)acetamide (18). A mixture of 2.0 g (5.24 mmol) of **17**, 0.8 g (5.24 mmol) of sodium iodide, 0.5 g (7.86 mmol) of sodium azide, and 25 mL of dimethylformamide was stirred at room temperature for 24 h and then allowed to stand for 3 days. The mixture was poured into ice water and the solid collected by filtration. The solid was partitioned between CH_2Cl_2 and water. The organics were dried and concentrated. The residue was crystallized from CH_2Cl_2/petroleum ether to give 1.8 g (89%) of **18** as colorless prisms: mp 98–102 °C; IR ($CHCl_3$) 2110 (N_3), 1671 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.32 (s, 1 H, $C(CH_3)_3$), 3.27 (d, 1 H, J_{AB} = 15 Hz, CO–CH_ACH_B–N_3), 3.74 (d, 1 H, J_{AB} = 15 Hz, CO–CH_ACH_B–N_3); MS, m/e 388 (M^+). Anal. Calcd for $C_{19}H_{18}ClFN_4O_2$: C, 58.69; H, 4.67; N, 14.41. Found: C, 58.59; H, 4.76; N, 14.16.

2-Chloro-*N*-[2-(2-chlorobenzoyl)-4-chlorophenyl]-*N*-(1,1-dimethylethyl)acetamide (19). A mixture of 3.0 g (9.31 mmol) of **16**, 2.1 mL (26 mmol) of chloroacetyl chloride, and 130 mL of toluene was stirred and refluxed for 6 h. The reaction mixture was cooled and partitioned between dilute $NaHCO_3$ and ethyl acetate. The organics were dried and concentrated. The residue was filtered through silica gel with methylene chloride, and the fractions containing the product were combined and concentrated. The residue was crystallized from CH_2Cl_2/ether to give 2.9 g (78%) of **19** as pale yellow prisms: mp 169–173 °C; IR ($CHCl_3$) 1677 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 9 H, $C(CH_3)_3$), 3.63 (d, 1 H, J_{AB} = 13 Hz, CO–CH_ACH_B–Cl), 3.87 (d, 1 H, J_{AB} = 13 Hz, CO–CH_ACH_B–Cl); MS, m/e 397 (M^+). Anal. Calcd for $C_{19}H_{18}Cl_3NO_2$: C, 57.24; H, 4.55; N, 3.51. Found: C, 56.94; H, 4.59; N, 3.38.

2-Bromo-*N*-[2-(2-chlorobenzoyl)-4-chlorophenyl]-*N*-(1,1-dimethylethyl)acetamide (19, R = Br). A mixture of 0.7 g (2.17 mmol) of **16**, 0.5 mL (5.43 mmol) of bromoacetyl bromide, and 20 mL of CH_2Cl_2 was stirred and refluxed for 4 h. After it was washed with dilute $NaHCO_3$, the organic phase was dried and concentrated. The residue was recrystallized from CH_2Cl_2/petroleum ether to give 0.2 g (21%) of **19** (R = Br) as colorless prisms: mp 148–152 °C; IR ($CHCl_3$) 1672 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 9 H, $C(CH_3)_3$), 3.42 (d, 1 H, J_{AB} = 11 Hz, CO–CH_ACH_B–Br), 3.73 (d, 1 H, J_{AB} = 11 Hz, CO–CH_ACH_B–Br); MS, m/e 441 (M^+). Anal. Calcd for $C_{19}H_{18}BrCl_2NO_2$: C, 51.50; H, 4.09; N, 3.16. Found: C, 51.16; H, 4.14; N, 3.26.

2-Azido-*N*-[4-chloro-2-(chlorobenzoyl)phenyl]-*N*-(1,1-dimethylethyl)acetamide (20). A mixture of 2.5 g (6.3 mmol) of **19**, 0.41 g (6.3 mmol) of sodium azide, 0.15 g (1.0 mmol) of sodium iodide, and 50 mL of *N*,*N*-dimethylformamide was stirred at room temperature for 7 days and then poured into ice water. The solid was collected by filtration and partitioned between CH_2Cl_2 and water. The organic layer was dried and concentrated. The residue was crystallized from CH_2Cl_2/ether to give 1.6 g (63%) of **20** as off-white prisms: mp 153–156 °C; IR ($CHCl_3$) 2110 (N_3), 1675 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 9 H, $C(CH_3)_3$),

(23) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Sach, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3781–3788.

(24) Sternbach, L. H.; Reeder, E.; Keller, O.; Metlesics, W. *J. Org. Chem.* **1961**, *26*, 4488–4497.

3.25 (d, 1 H, J_{AB} = 15 Hz, CO-CH_ACH_B-N_3), 3.65 (d, 1 H, J_{AB} = 15 Hz, CO-CH_ACH_B-N_3); MS, *m/e* 404 (M^+). Anal. Calcd for $C_{19}H_{18}Cl_2N_4O_2$: C, 56.31; H, 4.48; N, 13.82. Found: C, 56.01; H, 4.40; N, 13.81.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(1,1-dimethylethyl)-2*H*-1,4-benzodiazepin-2-one (21). To a solution of 1.0 g (2.57 mmol) of **18** in 20 mL of acetic acid was added in portions 2.9 g (12.9 mmol) of stannous chloride dihydrate. After the mixture was stirred for 5 h, it was poured over ice and partitioned with 10 N NaOH and ether. The organics were dried and concentrated. The residue was refluxed in ethanol for 3 h, and the solvents were concentrated. The residue was chromatographed on silica gel with CH_2Cl_2/ether (20:1) as the eluent. Removal of the solvents and crystallization of the solid from ether/petroleum ether gave 0.4 g (45%) of **21** as off-white rods: mp 126–129 °C; IR ($CHCl_3$) 1680 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s, 9 H, $C(CH_3)_3$), 3.69 (d, 1 H, J_{AB} = 11 Hz, CO-CH_ACH_B-N), 4.61 (d, 1 H, J_{AB} = 11 Hz, CO-CH_ACH_B-N); MS, *m/e* 344 (M^+). Anal. Calcd for $C_{19}H_{18}ClFN_2O$: C, 66.18; H, 5.26; N, 8.12. Found: C, 66.26; H, 5.27; N, 8.11.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-1-(1,1-dimethylethyl)-2*H*-1,4-benzodiazepin-2-one (22). A mixture of 0.3 g (0.78 mmol) of **20**, 7 mL of tetrahydrofuran, 20 mL of ethanol, and one spatula of Raney nickel was hydrogenated at atmospheric pressure for 3 h. The catalyst was removed by filtration, and the filtrate was refluxed for 12 h to ensure that any ring-opened primary amine cyclized to the benzodiazepine. The solvents were concentrated, and the residue was purified by thick-layer chromatography with CH_2Cl_2/ether (5:1) as the developing solvent mixture. The band containing the product was removed and the product crystallized from ether/petroleum ether to give 50 mg (18%) of **22** as off-white rods: mp 127–132 °C; IR ($CHCl_3$) 1677 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.52 (s, 9 H, $C(CH_3)_3$), 3.71 (d, 1 H, J_{AB} = 11 Hz, CO-CH_ACH_B-N), 4.67 (d, 1 H, J_{AB} = Hz, CO-CH_ACH_B-N); MS, *m/e* 360 (M^+). Anal. Calcd for $C_{19}H_{18}Cl_2N_2O$: C, 63.17; H, 5.02; N, 7.75. Found: C, 63.44; H, 5.01; N, 7.83.

[5-Nitro-2-[(1,1-dimethylethyl)amino]phenyl](2-chlorophenyl)-methanone (24). A mixture of 5.0 g (17 mmol) of **23**[25] and 7.2 g (99 mol) of *tert*-butylamine was heated in a sealed steel bomb at 200 °C for 20 h. The bomb was cooled in an ice bath, and the contents were partitioned between a saturated solution of $NaHCO_3$ and CH_2Cl_2. The organic phase was dried and concentrated to give a dark oil. Crystallization of this oil from ethanol gave 3.3 g of **24** as a yellow solid. The filtrates were chromatographed on silica gel to give an additional 1.0 g of product (total yield 76%). An analytical sample was prepared by recrystallization from ethanol to give **24** as yellow needles: mp 127–129 °C; IR ($CHCl_3$) 1634 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; N, 8.42. Found: C, 61.32; H, 4.97; N, 8.46.

[5-Amino-2-[(1,1-dimethylethyl)amino]phenyl](2-chlorophenyl)-methanone (25). To a solution of 6.32 g (20 mmol) of **24** in 75 mL of warm acetic acid was added a solution of 13.6 g (60 mmol) of stannous chloride dihydrate in a mixture of 15 mL of 6 N hydrochloric acid and 80 mL of acetic acid. After the mixture was stirred at room temperature overnight, an additional 2 g of stannous chloride dihydrate in 2 mL of 6 N hydrochloric acid and 5 mL of acetic acid was added. After the mixture was stirred for an additional 24 h, the reaction mixture was poured over ice, made basic with 40% NaOH, and extracted with CH_2Cl_2. The organics were washed with brine, dried, and concentrated to give 6.5 g (100%) of amine **25** as a red oil. The amine was air sensitive and was used in the next step without further purification. For the purposes of characterization, the amine was converted to the picrate salt and also to the 5-acetamido derivatives as follows. A small sample of the amine was dissolved in ethanol and treated with an excess of picric acid in ethanol. The addition of water caused the precipitation of the salt, which was collected and recrystallized from ethanol/water to give the picrate as yellow needles: mp 213–215 °C; IR (KBr) 1653 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClN_2O \cdot C_6H_3N_3O_7$: C, 51.99; H, 4.17; N, 13.17. Found: C, 51.80; H, 4.01; N, 13.27.

For the preparation of the amide, a small amount of the amine was treated with acetic anhydride and allowed to stand for 15 min. The mixture was partitioned with 3 N NaOH and CH_2Cl_2. The CH_2Cl_2 was washed with water, dried, and concentrated. The solid residue was crystallized from ethanol/water to give the amide as yellow needles: mp 218–220 °C; IR (KBr) 1654, 1633 (C=O) cm^{-1}; NMR (DMSO-d_6) δ 1.50 (s 9 H, $C(CH_3)_3$), 1.88 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{19}H_{21}ClN_2O_2$: C, 66.18; H, 6.14; N, 8.12. Found: C, 66.03; H, 5.83; N, 8.21.

2-[[4-Chloro-2-(2-chlorobenzoyl)phenyl]amino]-*N*-(1,1-dimethylethyl)acetamide (26). A mixture of 0.2 g (0.45 mmol) of **19** (R = Br), 8 mL of ether, and 8 mL of saturated methanolic ammonia was allowed to stand for 3 days. The solution was saturated with ammonia and allowed to stand for 24 h. After being partitioned between CH_2Cl_2 and water, the organics were combined, dried, and concentrated. The residue was filtered through a small amount of silica gel with ether. The solvent was removed and the solid residue crystallized from CH_2Cl_2/ether/petroleum ether to give 0.1 g (59%) of **26** as yellow needles: mp 199–203 °C; IR (KBr) 3323, 3080 (NH), 1654, 1628 (C=O) cm^{-1}; NMR (DMSO-d_6) δ 1.29 (s, 9 H, $C(CH_3)_3$), 3.88 (d, 2 H, CH_2), 7.74 (s, 1 H, NH), 9.19 (s, 1 H, NH); MS, *m/e* 378 (M^+). Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 60.17; H, 5.32; N, 7.39. Found: C, 59.94; H, 5.27; N, 7.18.

7-Chloro-5-(2-chlorophenyl)-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-2*H*-1,4-benzodiazepin-2-one (27). To a solution of 0.5 g (1.4 mmol) of **22** in 5 mL of acetic acid and 2.5 mL of methanol (stirred in an ice bath) was added 0.17 g (2.8 mmol) of sodium cyanoborohydride. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. After the mixture was partitioned with CH_2Cl_2 and water, the organic layer was washed with dilute NH_4OH, dried, and concentrated. The residue was crystallized from CH_2Cl_2 and methanol to give 0.4 g (79%) of **27** as off-white prisms: mp 236–240 °C; IR (KBr) 3304 (NH), 1656 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.59 (s, 9 H, $C(CH_3)_3$), 2.30 (b, 1 H, NH), 3.03 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N), 3.20 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N), 5.70 (s, 1 H, CH); MS, *m/e* 362 (M^+). Anal. Calcd for $C_{19}H_{20}Cl_2N_2O$: C, 62.82; H, 5.55; N, 7.71. Found: C, 63.05; H, 5.67; N, 7.77.

(*R*)-7-Chloro-5-(2-chlorophenyl)-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-2*H*-1,4-benzodiazepin-2-one (28). To a suspension of 3.9 g (0.11 mol) of **27** in 100 mL of 2-propanol was added a small amount of CH_2Cl_2 to give a clear solution, followed by a solution of 2.7 g (0.11 mol) of camphor-d_{10}-sulfonic acid in 40 mL of 2-propanol. The solution was concentrated to approximately 75% of the original volume and then stored at −10 °C for 16 h. The solid was collected by filtration to give 1.8 g of the salt of **28**. The filtrates were concentrated to 50 mL, and 40 mL of ether was added. The solution was cooled and the precipitate collected by filtration to give an additional 1.2 g of salt. The two crops of salt were combined and dissolved in a small amount of methanol followed by the addition of 2-propanol. The methanol was removed in vacuo, and ether was added to precipitate the salt that was collected by filtration to give 2.5 g (76% based on theoretical yield of 50%). The salt was partitioned between CH_2Cl_2 and dilute NH_4OH, and the organic layer was dried and concentrated. The residue was crystallized from ether/petroleum ether to give 1.5 g (77% based on theoretical yield of 50%) of **28** as off-white prisms: mp 134–137 °C; $[\alpha]^D_{25}$ + 117.5° (*c* = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3334 (NH), 1665 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 9 H, $C(CH_3)_3$), 3.04 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N), 3.27 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N). Anal. Calcd for $C_{19}H_{20}Cl_2N_2O$: C, 62.82; H, 5.55; N, 7.71. Found: C, 62.86; H, 5.82; N, 7.66.

(*S*)-7-Chloro-5-(2-chlorophenyl)-1,3,4,5-tetrahydro-1-(1,1-dimethylethyl)-2*H*-1,4-benzodiazepin-2-one (29). The filtrates from the isolation of the salt in the previous experiment were concentrated to a small volume, and ether was then added. The solid was collected by filtration to give 2.3 g (70% based on theoretical yield 50%) of the salt. The salt was partitioned with dilute NH_4OH and CH_2Cl_2, and the organic phase was dried and concentrated. The residue was crystallized from ether/petroleum ether to give 1.2 g (62% based on theoretical yield of 50%) of **29** as off-white prisms: mp 135–137 °C; $[\alpha]^D_{25}$ −120.1° (*c* = 1.0, CH_2Cl_2); IR ($CHCl_3$) 3324 (NH), 1662 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.59 (s, 9 H, $C(CH_3)_3$), 3.06 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N), 3.29 (d, 1 H, J_{AB} = 14 Hz, CO-CH_ACH_B-N), 5.69 (s, 1 H, CH). Anal. Calcd for $C_{19}H_{20}Cl_2N_2O$: C, 62.82; H, 5.55; N, 7.71. Found: C, 63.15; H, 5.68; N, 7.63.

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Supplementary Material Available: Tables of final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compounds **10**, **12**, and **28** (15 pages). Ordering information is given on any current masthead page.

(25) Field, G. F.; Fryer, R. I.; Trybulski, E. J.; Walser, A. U.S. Patent 4,379,765, 1983.

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