with 2 N HCl, and the mixture was extracted with ether/ethyl acetate (1:1, 3 × 10 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and evaporated. Purification by chromatography (silica gel, 40% ether in dichloromethane) gave lactone **33**: 220 mg, 40%; $[\alpha]_D$ +27.5° (*c* 3.5, $CHCl_3$); other spectral data, identical with that from **33** prepared by yeast reduction of dione **8**.

(2*S*,3*S*)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclopentanone Ethylene Acetal (40). Lactone **33** was converted to the corresponding ethylene acetal **41** by the procedure used for **38**. To a stirred solution of $LiAlH_4$ (36 mg, 0.94 mmol) in THF (2 mL) at 0 °C was added a solution of lactone **41** (0.1 g, 0.5 mmol) in THF (2 mL). The mixture was stirred for 3 h at 25 °C, after which saturated aqueous ether (5 mL) followed by methanol (1 mL) was added. After 4 h, the solids were filtered and washed with THF (3 × 10 mL). The filtrate was evaporated to provide the crude diol **42**, which was diacetylated by the same procedure as that used for **38**. Purification by chromatography (silica gel, 20% ether in CH_2Cl_2) gave **40**: 80 mg, 53%; $[\alpha]_D$ +17.1° (*c* 4, $CHCl_3$); other spectral data, identical with that for **40** prepared from **38**.

General Procedure for Ring Expansion. (2*S*,3*S*)- and (2*R*,3*S*)-3-[(+)-α-[(Trifluoromethyl)phenyl]acetoxy]-2-methyl-2-propylcycloheptanone (90a, 91a). To a stirred solution of a mixture of MTPA esters **9a** and **11a** (67:33; 0.4 g, 1 mmol) in ether (2 mL) at 0 °C was added a solution of CH_2N_2 (2.1 equiv of 0.5 M CH_2N_2 in ether) followed by anhydrous $AlCl_3$ (10 mg). The mixture was stirred for 1 h, after which solid $NaHCO_3$ (100 mg) was added; the mixture was filtered and evaporated. The crude product was analyzed by ^1H NMR and found to consist of mainly the seven-membered homologues **90a** and **91a**, which were used as correlation standards after purification by chromatography (silica gel, 30% ethyl acetate in hexane). **90a**: ^1H NMR ($CDCl_3$, 470 MHz) δ 0.78 (3 H, t, *J* = 7 Hz, CH_3), 1.08 (3 H, s, CH_3), 1.05–1.80 (9 H, m), 2.17 (1 H, m), 2.34 (1 H, m), 2.60 (1 H, m), 3.55 (3 H, br s, OCH_3), 5.13 (1 H, d, *J* = 8 Hz), 7.40 (3 H, m), 7.55 (2 H, m); MS, *m/e* M^+ 400. **91a**: ^1H NMR ($CDCl_3$, 470 MHz) δ 0.76 (3 H, t, *J* = 7 Hz, CH_3), 1.05 (3 H, s, CH_3), 1.05–1.80 (9 H, m), 2.17 (1 H, m), 2.34 (1 H, m), 2.60 (1 H, m), 3.58 (3 H, br s, OCH_3), 5.38 (1 H, dd, *J* = 9, 2 Hz), 7.40 (3 H, m), 7.55 (2 H, m); MS, *m/e* M^+ 400.

(2*S*,3*S*)- and (2*R*,3*S*)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclohexanone Ethylene Acetal (83, 84). The diacetates **83** and **84** were prepared from ketols **61** and **63** by a sequence of (1) acetylation, (2) ethylene acetal formation, (3) hydroboration–oxidation, (4) separation of the mixture of diastereomeric alcohols **81** and **82** by chromatography (silica gel, 20% ether in dichloromethane), and (5) acetylation, using similar procedures as described for the conversion of ketol **13** to diacetate **40**. **83**: $[\alpha]_D$ +18.5° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 0.92 (3 H, s, CH_3), 1.5–1.7 (10 H, m), 2.04 (6 H, s, 2 CH_3), 3.90 (4 H, m), 4.02 (2 H, t, *J* = 7 Hz), 4.91 (1 H, dd, *J* = 4, 4 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 16.2 (CH_3), 19.1 (CH_2), 21.1 (CH_3), 21.3 (CH_3), 23.8 (CH_2), 25.9 (CH_2), 27.2 (CH_2), 29.7 (CH_2), 45.5 (C), 64.6 (CH_2), 65.2 (CH_2), 65.7 (CH_2), 77.5 (CH), 112.6 (C), 170.5 (COO), 171.2 (COO); MS, *m/e* M^+ 314. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.16; H, 8.34. Found: C, 61.04; H, 8.47. **84**: $[\alpha]_D$ +27.9° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.05 (3 H, s, CH_3), 1.4–1.8 (10 H, m), 2.03 (6 H, s, 2 CH_3), 3.92 (6 H, m), 4.89 (1 H, dd, *J* = 3, 5 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.3 (CH_3), 19.0 (CH_2), 21.0 (CH_3), 21.3 (CH_3), 24.4 (CH_2), 26.3 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 45.0 (C), 64.3 (CH_2), 65.0 (CH_2), 66.7 (CH_2), 76.2 (CH), 113.1 (C), 170.5 (COO), 171.2 (COO); MS, *m/e* M^+ 314. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.16; H, 8.34. Found: C, 61.24; H, 8.12.

(2*S*,3*S*)-6-Methyl-2-oxabicyclo[4.4.0]decane-3,7-dione 3,7-Diethylene Acetal (85) and (2*R*,3*S*)-6-Methyl-2-oxabicyclo[4.4.0]decan-3-one Ethylene Acetal (86). To a solution of lactones **77** and **79** (35:65; 100 mg, 0.5 mmol) in benzene (50 mL) were added ethylene glycol (170 mg, 2.7 mmol) and *p*-toluenesulfonic acid (9 mg, 0.05 mmol). The solution was refluxed for 16 h with azeotropic removal of water. The mixture was cooled to 25 °C, solid $NaHCO_3$ was added, and the solvent was evaporated. The residue was purified by chromatography (silica gel, 10% dichloromethane in ether) to give two products, the ortho ester **85** (33 mg, 25%) and the lactone **86** (57 mg, 50%). **85**: ^1H NMR ($CDCl_3$, 470 MHz) δ 1.08 (3 H, s, CH_3), 1.47 (6 H, m), 1.74 (2 H, m), 2.02 (2 H, m), 3.9 (8 H, m), 4.15 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.4 (CH_3), 19.7 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.0 (CH_2), 30.0 (CH_2), 41.7 (C), 63.4 (CH_2), 64.6 (CH_2), 64.9 (CH_2), 65.3 (CH_2), 75.7 (CH), 112.3 (C), 119.2 (C); MS, *m/e* M^+ 270.

(2*R*,3*S*)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclohexanone Ethylene Acetal (84). Lactone **86** was converted to diacetate **84** by a similar procedure of $LiAlH_4$ reduction and acetylation as used for the conversion of **41** to **40**. The diacetate **84** prepared in this manner had $[\alpha]_D$ +27.7° (*c* 10, $CHCl_3$) and other spectral data, identical with that for **84** prepared from **63**.

Synthesis and Resolution of 3-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones

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Two efficient synthetic routes to the 3-amino-1,4-benzodiazepin-2-ones **2** and **3** were developed. The first sequence was carried out in 55–60% overall yield and involves a novel mercuric ion assisted ammonia displacement of the (alkylthio)glycinamide **14** to produce the key intermediate α-aminoglycinamide **15**. The second approach features a practical two-step amination of the parent 1,4-benzodiazepine ring system **24** to afford the title compound **3** in 49% overall yield from 2-aminobenzophenone. The 3-amino-1,4-benzodiazepine **3** was resolved via the separation of the corresponding diastereomeric phenylalanyl amides. The desired (−)-**3** enantiomer was then liberated by use of the Edman degradation.

The ubiquity of the benzodiazepines in the chemical literature is doubtless a consequence of the multifarious biological responses they elicit in animals. The use of this class of compounds as therapeutic agents is not merely confined to the management of anxiety and stress-related conditions as additional novel applications are continuously emerging.[1-3] The recent demonstration that the 5-phenyl-1,4-benzodiazepine ring system can serve as a useful template in the construction of ligands for peptide receptors has imparted further interest in these compounds

† Rahway, NJ.

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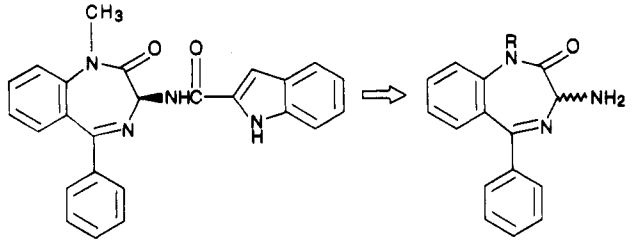
from yet another perspective.[4] In this context, we recently disclosed the design and synthesis[4] of a highly specific, nonpeptidal antagonist[5] of the gastrointestinal hormone cholecystokinin (CCK). This agent, (3*S*)-(−)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide (**1**) was prepared from the corresponding 3-amino-1,4-benzodiazepinone **3**, a key intermediate in these and related structure–function studies.[6]



1 **2**, R = H; **3**, R = CH_3

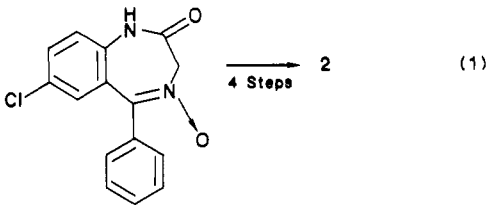
Critical to the success of the structure–function studies, culminating in the preparation of **1**, was the ready accessibility of the intermediates **2** and **3** in quantity and in high optical purity.

Although two synthetic approaches had been previously devised for the preparation of 3-amino-1,4-benzodiazepines, each is burdened with liabilities. The first method involves the preparation of the benzodiazepine *N*-oxide **4** in four steps and eventual transformation to the 3-amino derivatives **2** in less than 10% overall yield (eq 1).[7-9] The other approach employs a novel elimination–addition reaction on the 2-(*N*-acetoxyacetamido)-2′-benzoylacetanilide **5** enroute to **2**. The latter process, requiring only six synthetic operations, nevertheless, proceeded in less than 5% overall yield in our experience (eq 2).[10-13] The fact that a substituent cannot be introduced at the N-1 position without difficulty is an additional disadvantage with both processes.

With these precedents in mind, our synthetic plan for preparing 3-amino-1,4-benzodiazepines was tailored to meet the objectives alluded to above, thereby permitting the rapid evaluation of diverse structures. Accordingly, refinement of published procedures and the development of new methodology were required. In the discussion that follows we give a full account of two efficient processes which were designed for synthesizing and resolving 3-amino-1,4-benzodiazepin-2-ones like **2** and **3**.

Results and Discussions

(1) Attempted Preparation of 2. The ready availability of the crystalline 3-carbethoxy-1,4-benzodiazepinone **6** from 2-aminobenzophenone and diethyl aminomalonate[14]



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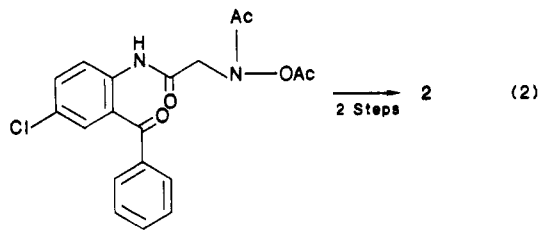

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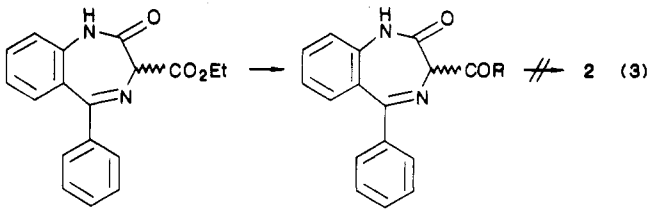
compensated for the modest yield (~30%) in which it was obtained. It was our expectation that conversion of **6** to the desired 3-amino-1,4-benzodiazepinone **2** via amide **7** could be achieved in a straightforward manner (eq 3).



6 **7**, R = NH_2; **8**, R = $NHNH_2$; **9**, R = N_3

However, despite numerous attempts, this plan could not be reduced to practice. Hofmann rearrangement on **7** under a variety of standard conditions,[15] including also the use of bis(trifluoracetoxy)phenyliodine,[16,17] failed to produce even traces of **2**. When **9** was subjected to Curtius rearrangement conditions,[18,19] similar results were obtained. In both reactions (i.e., Hofmann and Curtius), starting material was typically consumed, and complex reaction mixtures were formed from which the corresponding decarboxylated product was the only characterizable material which could be isolated in quantity.

The above scheme for the preparation of **2** was eventually abandoned in favor of an even more direct route via the intermediacy of the 2-benzoyldichloroacetanilide (**10**). This material can be prepared quantitatively from aminobenzophenone and dichloroacetyl chloride. A further attraction of this compound is its potential reaction with ammonia, or a derivative thereof, to give an intermediate which could cyclize to afford the target compound **2** in essentially two synthetic operations overall. Support of this proposal was gained from the documented reaction of morpholine with dichloroacetic acid to give the adduct **11**.[20] In practice, the reaction of **10** with ammonia took a different course (eq 4). The dichloroacetanilide **10** could not be induced to react with ammonia at the geminal dichlorocarbon atom under any of the conditions which

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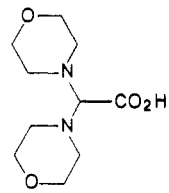

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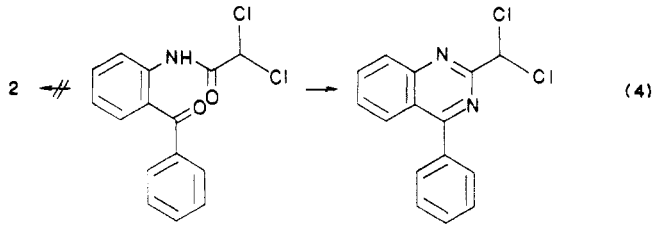
were examined. Modifications of the reaction conditions



(4)

10 12

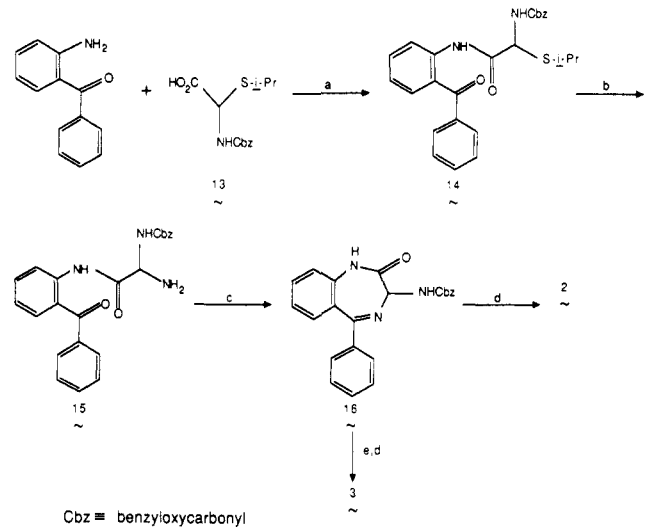
included variations in the pH of the reaction medium, solvents, temperature (23–250 °C), and pressure, as well as the use of the Lewis acid additives titanium tetrachloride[21] and trimethylaluminum.[22] Instead, in addition to uncharacterizable decomposition and/or polymerization products, there were isolated varying amounts of the 4-phenylquinazoline **12**.

(2) Cyclization of an Aminoglycine Derivative. The successful strategy we adopted derives from a retrosynthetic dissection of **2** which revealed it to be the cyclization product of α-aminoglycine and 2-aminobenzophenone.[23] Since the desired reaction of **10** and ammonia was in principle to have passed through a similar intermediate(s), we reasoned that a reactive synthetic equivalent of the unstable α-aminoglycine[24] was required which, when preformed could be coupled to aminobenzophenone and subsequently elaborated to the target compound. The execution of this plan is summarized in Scheme I.

According to the precedent established by Ben-Ishai,[25] the (isopropylthio)-N^{α}-(benzoyloxycarbonyl)glycine (**13**) was obtained in two steps from glyoxylic acid, benzylcarbamate, and 2-propanethiol in 70% overall yield. The protected α-aminoglycine synthon **13** thus formed was then converted to the corresponding mixed anhydride with isobutyl chloroformate in the presence of *N*-methylmorpholine and reacted in situ with 2-aminobenzophenone to give **14**, in excess of 90% yield, after extractive workup. In the critical step, the (alkylthio)glycinamide **14** was dissolved in dry tetrahydrofuran saturated with ammonia and treated with 1.1 equiv of mercuric chloride. The intermediate α-aminoglycinamide **15** was obtained in essentially quantitative yield and could be isolated and purified chromatographically. Nevertheless, in practice, crude **15** was most conveniently dissolved in glacial acetic acid containing ammonium acetate and stirred at room temperature overnight to effect the cyclization. In this way, **16** was obtained as a crystalline solid in 70–75% yield.

The reagents and conditions reported above which were developed to effect the condensation of **15** are optimized.

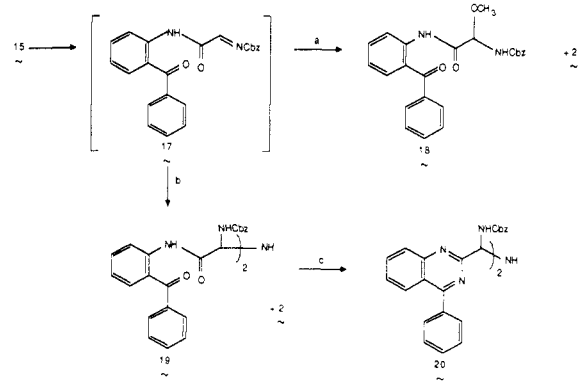
Scheme I[a]



Cbz ≡ benzyloxycarbonyl

[a] (a) *i*-BuOCOCl, *N*-methylmorpholine, CH_2Cl_2, 0 °C, 15 min; 0–23 °C, 12 h; (b) NH_3 (g), $HgCl_2$, THF, 0–23 °C; (c) NH_4OAc, HOAc, 23 °C; (d) H_2, 10% Pd/C, HCO_2H–CH_3OH, 40–50 °C, 3 h; (e) CH_3I, NaH, DMF, 23 °C, 2 h.

Scheme II[a]



[a] (a) CH_3OH, 65 °C, 2–6 h; (b) toluene, 110 °C, 2–12 h; (c) NH_3, 110 °C, pressure bomb.

For example, ammonia or other ammonium salts (e.g., NH_4OH, NH_4Cl, $(NH_4)_2SO_4$) and solvent combinations (e.g., THF, DMF) while workable in the extreme were substantially less effective, affording yields of **16** below 35%. Surprisingly, heating **15** in methanol gave only traces of **16**; the major product in this reaction was characterized as the methoxy analogue **18**[26] (Scheme II). Alternatively, when **15** was heated in toluene the major isolable product proved to be the dimer **19**, presumably arising from the addition of **15** to the acyl imine **17**. An almost identical product distribution of dimer **19** to benzodiazepine **16** was obtained when **15** was treated with trimethylaluminum in THF. Frustrating from a practical viewpoint was the fact that the formation of **19** represented a synthetic dead end since suitable reaction conditions could not be developed to convert **19** to **16**. Eventually, **19** reacted with ammonia under forcing conditions to afford the quinazoline dimer **20**.

The sequence of events leading from **15** to **16** is open to some speculation. It is likely that the α-amino group in **15** simply condenses with the benzophenone carbonyl

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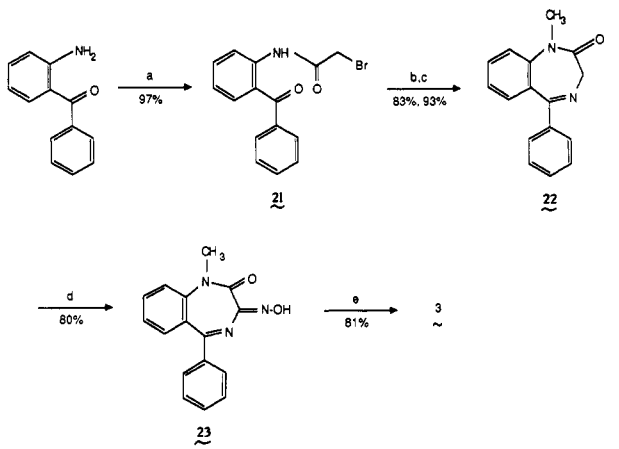
(26) Cf. ref 10: 2-(*N*-acetoxyacetamido)acetanilide when reacted with ammonia in ethanol afforded 3-acetamido-1,4-benzodiazepine; no report of the detection of the corresponding 2-acetamido-2-ethoxyacetanilide was made.

Scheme III[a]



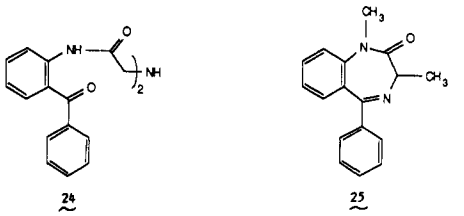
[a] (a) $BrCOCH_2Br$, CH_2Cl_2–H_2O, −10–23 °C, 4 h; (b) NH_3 (g), CH_3OH, −10–15 °C, 2 h, then 65 °C, 2 h; (c) CH_3Cl, NaOH (aq), toluene, Aliquat 336, 0–25 °C, 4 h; (d) *t*-BuOK, *i*-AmONO, toluene, −20–0 °C, 45 min; (e) H_2, 5% Ru/C, CH_3OH, 68–74 °C, 40 psi, 24 h.

to form the seven-membered cycle. However, it is equally plausible that ammonium acetate reacts with the benzophenone carbonyl[27] to form the corresponding primary imine, which in turn cyclizes to give **16**.

With the skeletal framework of the target compound in place, the synthesis was completed without incident. Removal of the benzyloxycarbonyl (Cbz) protecting group under transfer hydrogenation conditions in methanol–aqueous formic acid afforded **2** as its formate salt. The free amine could be isolated after neutralization of the salt with sodium carbonate solution (10%) in ethyl acetate in 86% yield. In this way, the synthesis of **2** was accomplished in 55–60% overall yield requiring no purification of intermediates **14** and **15**. Alternatively, methylation of **16** with sodium hydride and iodomethane in DMF, followed by similar deprotection of the 3-amino group, afforded **3** in 77% yield.

(3) Amination of the 1,4-Benzodiazepin-2-one Ring. Although the synthetic approach devised for **2** (vide supra) lends itself to the preparation of a large variety of analogues for structure–activity studies, the reliance on mercury salts in the cyclization step was deemed to be a major drawback of the method. This is particularly the case, from a safety and disposal standpoint, if kilogram quantities of this material are required for preparing structural analogues for indepth biological evaluation. An alternative route was therefore developed which relies in part on some classical benzodiazepine chemistry.[28] The process is outlined in Scheme III.

Employing a minor modification of the published procedure, 2-aminobenzophenone was acylated with bromoacetyl bromide in a methylene chloride–water mixture to give **21** in 97% isolated yield. Bromoacetamide **21** was then converted to the *N*-methyl-1,4-benzodiazepin-2-one **22** in 77% overall yield by utilizing a sequence that included (a) amination in methanol at 0 °C, followed by (b) cyclization of the intermediate glycinanilide at refluxing temperatures, and (c) alkylation of the amide nitrogen with methyl iodide under phase-transfer conditions. The major contaminant produced in 5–8% yield in this sequence was the amine **24**, resulting from the reaction of the intermediate glycinanilide with **21**. Use of the corresponding iodoacetamide resulted in significantly higher levels (15–25%) of **24**, whereas the chloroacetamide required higher temperatures in a pressurized vessel to complete the amination. In any event, **24** was easily removed by recrystallization. In the N-1 alkylation step, methyl chloride was employed to prevent competing C,N-dimethylation to give **25**, a compound detected in varying quantities when the reaction was carried out with methyl iodide.



The identification of a C,N-dimethylated byproduct demonstrated the ability to form a carbanion at C-3 of the benzodiazepine nucleus under phase-transfer conditions. Since it had already been shown that diazepam can be metalated under aprotic conditions and can subsequently be modified at the C-3 position, we proceeded along similar lines.[29] After several trial experiments in which we attempted to introduce an amino group directly at the C-3 position of **22** (e.g., azidophenyl methyl sulfide, phenylmagnesium bromide;[30] tosyl azide;[31] *p*-dodecylbenzenesulfonyl azide;[32] *O*-(2,4-dinitrophenyl)hydroxylamine;[33] *O*-(diphenylphosphinyl)hydroxylamine[34]) the following solution was devised. The *N*-methylbenzodiazepinone **22** was metalated with potassium *tert*-butoxide in toluene (−20 °C) and reacted with isoamyl nitrite to give the oxime **23** in 80% yield. Catalytic reduction of **23** was achieved efficiently with dry, reduced 5% ruthenium on carbon catalyst[35] in warm methanol. In this way, **3** was isolated in 81% yield as a crystalline salt of >98% purity (HPLC). Alternative reduction conditions of **23** were also briefly explored. These included catalytic reduction with rhodium/carbon (5%), nickel boride, and Raney nickel catalysts, as well as, chemical reduction with zinc in acetic acid and stannous chloride in hydrochloric acid; these methods were all inferior relative to the reduction of **23** with ruthenium catalyst.

(4) Resolution of 3-Amino-1,4-benzodiazepin-2-ones. For the synthesis of the CCK antagonist **1** and structurally related analogues we required the individual enantiomers of **3**. Initial attempts to resolve **3** by conventional diastereomeric salt crystallization techniques were uniformly unsuccessful. In these studies, we examined the gamut of commercially available chiral reagents with the result that no diastereomeric salt could be crystallized. Further, when the mother liquors were allowed to stand for prolonged periods of time, **3**, in the presence of chiral acids, gradually decomposed to yield multicomponent mixtures. Accordingly, an alternative method of resolving **3** was developed, the salient features of which are summarized in Scheme IV.[36,37]

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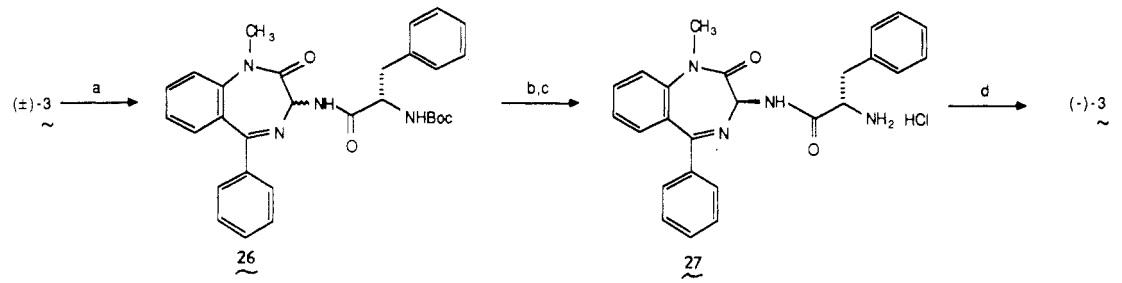
(35) The oxime reduction proceeds to only 25% completion with unreduced catalyst.

Scheme IV[a]



[a] (a) Boc-D-Phe, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HBT), DMF, 23 °C, 30 min; (b) HCl (g), EtOAc, 0 °C, 30 min; (c) crystallize; (d) C_6H_5NCS, CH_2Cl_2, 40 °C, 10 min, then CF_3CO_2H, 50 °C, 20 min.

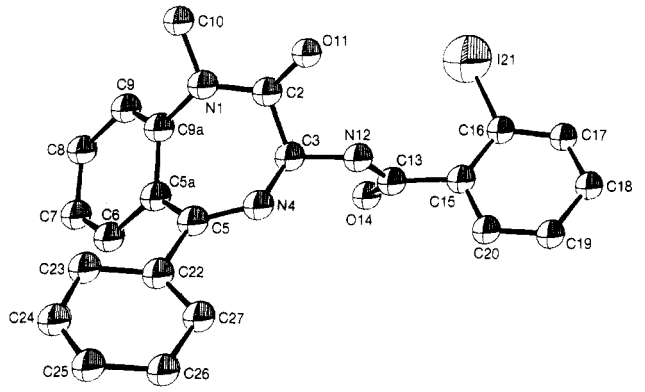


Figure 1. A computer-generated drawing of one molecule of **28** derived from the X-ray coordinates with hydrogens omitted for clarity.

Racemic **3** was coupled with Boc-D-phenylalanine by utilizing a standard peptide coupling protocol to afford **26** as a mixture of diasteromers. Removal of the Boc protecting group with gaseous HCl provided the hydrochloride salts of the diastereomeric amides **27**. Gratifyingly, the desired 3*S* isomer then crystallized from absolute ethanol in diastereomerically pure form (100% HPLC). With the separation of diastereomeric amides **27** complete, the remaining task was the retrieval of chiral **3**. This was accomplished via the classical Edman degradation[38,39] by heating the 3*S* diastereomer of **27** with phenyl isothiocyanate to give the corresponding thiourea, which in turn was briefly exposed to warm trifluoroacetic acid. In this way, the 3*S*-(−) enantiomer of **3** was obtained enantiomerically pure in 30% overall yield (60% of theory). In a similar manner, the 3*R*-(+) enantiomer of **3** was obtained by using L-phenylalanine as the resolving agent.

The enantiomeric integrity of 3*S*-(−)-**3** was assessed by HPLC on a chiral support and found to be 98% ee.[40] The absolute configuration was assigned by X-ray crystallographic analysis of the *o*-iodobenzamide derivative **28** (Figure 1).

Summary. Two efficient synthetic routes to the valuable 3-amino-1,4-benzodiazepines **2** and **3** were developed. The preparation of **2** was accomplished by using a novel mercuric ion assisted ammonia displacement of the *N*-Cbz-(alkylthio)glycinamide **14**. The sequence was carried out in 55–60% overall yield (based on 2-aminobenzophenone) requiring no purification of intermediates **14** and **15**. The fact that a multitude of other 3-(acylamino)-1,4-benzodiazepines, irrespective of aromatic substituents, are accessible via this convergent approach lends additional practicality and scope to the method. The second approach features a two-step amination of the 1,4-benzodiazepine ring system and represents a practical solution for preparing large quantities of 3-amino-1,4-benzodiazepines such as **3** with speed and economy. With this method, the synthesis of **3** was carried out in 49% overall yield (based on 2-aminobenzophenone).

The resolution of **3** was accomplished via the separation of the corresponding diastereomeric phenylalaninamides.[29] While the overall procedure requires several steps, they are operationally straightforward and proceed in high chemical yield. In addition, the use of Boc-D-Phe or Boc-L-Phe in the coupling step allows access to either the *R* or *S* enantiomer of **3** in high chiral purity. As such, this method not only fulfilled our immediate requirements but may also find broader application in the resolution of amines as an alternative to traditional diastereomeric salt crystallization or as an adjunct, providing chirally pure seed crystals.

Experimental Section

Melting points were determined in open capillaries on a ThomasHoover Unimelt apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian EM 390 (90 MHz) spectrometer with tetramethylsilane as an internal standard and a Varian XL300 (300 MHz, FT mode) spectrometer and a Nicolet NT-360 (360 MHz, FT mode) spectrometer, both instruments with an internal lock on the deuterium resonance of the solvent. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constant, assignment). Electron impact (EI) mass spectra were determined on a VG 7035 spectrometer and fast atom bombardment (FAB) mass spectra were run on a Finnigan-MAT 731 instrument. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. X-ray diffraction measurements were made with a CAD-4 diffractometer using CuKα radiation.

Flash chromatography was performed as described by Still[41] on silica gel (E. Merck 40–63 μm). Thin-layer chromatography (TLC) and preparative thick-layer chromatography (PLC) were carried out on E. Merck 60F-254 precoated silica gel plates (0.25, 0.5, and 2 mm thickness) by using UV light, iodine vapors, or 5% phosphomolybdic acid reagent in 95% ethanol to visualize the chromatograms.

(36) Communicated in preliminary form: Rittle, K. E.; Evans, B. E.; Bock, M. G.; DiPardo, R. M.; Whitter, W. L.; Homnick, C. F.; Veber, D. F.; Freidinger, R. M. Presented at the 20th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, MD, September 1986. Rittle, K. E.; Evans, B. E.; Bock, M. G.; DiPardo, R. M.; Whitter, W. L.; Homnick, C. F.; Veber, D. F.; Freidinger, R. M. *Tetrahedron Lett.* **1987**, *28*, 521.

(37) Compound **3**, resolved by this method, provided the seed crystals for the corresponding 3(*S*)-amino-(1*S*)-(+)-10-camphorsulfonic acid salt which served as the basis of an alternative resolution method; cf.: Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 955.

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(40) Composition was determined after reaction of **3** with phenyl isothiocyanate and analysis of the corresponding thiourea on a Pirkle covalent phenylglycine column using hexane/2-propanol.

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All reactions, except those performed in aqueous solvents, were carried out with use of standard techniques for the exclusion of moisture. Commercial chemicals were used as obtained without further purification, except for solvents, which were purified and dried, where appropriate, before use by standard methods.

2-[*N*-(α-(Isopropylthio)-N^{α}-(benzyloxycarbonyl)-glycinyl)amino]benzophenone (14). α-(Isopropylthio)-N^{α}-(benzyloxycarbonyl)glycine[23] (10.54 g, 37.2 mmol) was dissolved in 400 mL of dry methylene chloride in a three-neck flask equipped with magnetic stirrer, addition funnel, and nitrogen inlet tube. The solution was cooled to 0 °C and treated with *N*-methylmorpholine (4.1 mL, 37.2 mmol) followed by isobutyl chloroformate (4.8 mL, 37.2 mmol). The resulting reaction mixture was stirred at 0 °C for 15 min more and then was heated to reflux. The refluxing reaction mixture was treated dropwise over 20 min with a solution of 2-aminobenzophenone (6.97 g, 35.3 mmol) in 50 mL of dry methylene chloride. After the addition was complete, the reaction was refluxed 20 min more and then stirred at room temperature overnight. The reaction mixture was washed in succession with 10% citric acid solution (2 × 100 mL), saturated sodium bicarbonate solution (2 × 100 mL), and brine. The dried (magnesium sulfate) organic phase was concentrated to give 20 g of crude product. The analytical sample was obtained by PLC (4:1 hexane–ethyl acetate elution) as a glassy oil: R_f 0.30 (3:1 hexane–ethyl acetate); IR ($CHCl_3$, partial) 1710, 1690, 1580, 1485, 1450, 1410, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, 7 Hz), 1.44 (d, 3 H, 7 Hz), 3.26 (hept, 1 H, 7 Hz), 5.16 (AB q, 2 H, OCH_2), 5.57 (d, 1 H, 8 Hz, glycine α proton), 5.95 (d, 1 H, 8 Hz, NHCbz), 7.13 (t, 1 H, 6 Hz), 7.35 (m, 5 H), 7.50 (t, 2 H, 7 Hz), 7.58 (m, 3 H), 7.71 (d, 2 H, 7 Hz), 8.58 (d, 1 H, 7 Hz), 11.45 (br s, 1 H, NH); MS, *m/e* 462 (M^+), 280 (M^+ –benzophenone), 278, 250, 207, 175, 146, 108 (100%), 105.

Anal. Calcd for $C_{26}H_{26}N_2O_4S$: C, 67.51; H, 5.67; N, 6.06. Found: C, 67.63; H, 5.74; N, 6.15.

2-[*N*-(α-Amino-N^{α}-(benzoxylcarbonyl)glycinyl)amino]-benzophenone (15). The crude (isopropylthio)glycinamide **14** (14.0 g, 30.3 mmol) was dissolved in 200 mL of dry tetrahydrofuran. This solution was cooled to 0 °C and saturated with ammonia. Mercuric chloride (9.07 g, 33.4 mmol) was then added in one portion to the stirred mixture, while a continuous stream of ammonia gas was bubbled into the reaction flask. After 3 h, the suspended solids were removed, and the solvent was rotary evaporated to give crude **15** as an oil (16 g), which was used immediately without further purification. (Note: all operations should be confined to a well ventilated hood.) A portion of **15** was chromatographed for characterization: R_f 0.24 (1:1 hexane–ethyl acetate); ^1H NMR ($CDCl_3$) δ 2.2 (2 H, exchangeable, NH_2), 5.01 (d, 1 H, 4 Hz, glycine α proton), 5.20 (s, 2 H, Cbz), 6.35 (br s, 1 H, NHCbz), 7.20 (t, 1 H, 6 Hz), 7.4 (m, 5 H), 7.50 (m, 2 H), 7.6 (m, 3 H), 7.75 (d, 2 H, 7 Hz), 8.58 (d, 1 H, 7 Hz), 11.45 (1 H, s).

1,3-Dihydro-5-phenyl-3(*R*,*S*)-[(benzloxycarbonyl)-amino]-2*H*-1,4-benzodiazepin-2-one (16). Crude α-aminoglycinamide **15** (16 g, 39.66 mmol) was dissolved in 300 mL of glacial acetic acid and was treated with ammonium acetate (14.4 g, 187 mmol). The resulting reaction mixture was then protected from moisture and stirred at room temperature overnight (or for 2.5 h at 55 °C). The heterogeneous reaction mixture was concentrated under reduced pressure to remove the acetic acid, and the residue was partitioned between ethyl acetate (175 mL) and 1 N sodium hydroxide solution (40 mL). After the mixture was stirred for approximately 30 min the solids were collected and washed with ethyl acetate to afford 7.1 g of analytically pure **16**. The ethyl acetate washings (containing mercury salts) were further processed (flash chromatography, 1:1 hexane–ethyl acetate) to afford an additional 4.3 g of product (75% yield from 2-aminobenzophenone): mp 212–213 °C; R_f 0.38 (1:1 hexane–ethyl acetate); IR ($CHCl_3$, partial) 1695, 1605, 1500, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (AB q, 2 H), 5.36 (d, 1 H, 9 Hz, CHNH), 6.60 (d, 1 H, 9 Hz, CHNHCO), 7.16 (d, 1 H, 7 Hz), 7.21 (t, 1 H, 8 Hz), 7.4 (m, 9 H), 7.55 (m, 3 H), 8.65 (br s, 1 H), spectrum confirms solvate; MS, *m/e* 385 (M^+), 277 ($M^+ - OCH_2C_6H_5$), 248, 235, 223, 207, 108 (100%).

Anal. Calcd for $C_{23}H_{19}N_3O_3 \cdot 0.3H_2O$: C, 70.68; H, 5.05; N, 10.75. Found: C, 70.53; H, 4.79; N, 11.16.

3(*R*,*S*)-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (2). The benzodiazepinone **16** (19.6 g, 50.9 mmol) was dissolved in 2 L of hot methanol containing 90% aqueous formic acid (4.5% by volume). A 3-L three-neck flask fitted with reflux condenser and addition funnel was carefully charged with 4.8 g of palladium/carbon (10%) catalyst and with 300 mL of the above solvent system under nitrogen. The solution containing **16** was then added within 5 min to the stirred catalyst suspension. The resulting reaction mixture was stirred rapidly at 40–50 °C for 3 h, taking care that unreacted **16** did not precipitate from solution. The reaction mixture was cooled and filtered, and the recovered catalyst was washed with acetone. The combined washings and filtrate were rotary evaporated to give **2** as its formate salt in crude form. Recrystallization from tetrahydrofuran afforded the analytical sample as a solvate: mp 150–151 °C; R_f 0.19 (90:10:1:1 methylene chloride–methanol–acetic acid–water); IR (KBr, partial) 3100, 1700, 1600, 1310, 1090, 765, 700, 680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.30 (s, 1 H), 4.7 (br s, exchangeable), 7.21 (t, 1 H, 8 Hz), 7.27 (d, 1 H, 7 Hz), 7.46 (m, 5 H), 7.60 (t, 1 H, 8 Hz), 8.25 (br s, amide NH), spectrum confirms solvate.

Anal. Calcd for $C_{15}H_{13}N_3O \cdot CH_2O_2 \cdot 0.75H_2O$: C, 61.82; H, 5.35; N, 13.52. Found: C, 62.19; H, 5.11; N, 13.16.

The free base was generated by partitioning the formate salt **2** between ethyl acetate (200 mL) and 10% sodium carbonate solution (35 mL). The phases were separated, and the organic layer was dried with sodium sulfate (magnesium sulfate must be avoided since poor product recoveries result) and concentrated to afford 11 g (86% yield) of **2** as the free amine: ^1H NMR ($CDCl_3$) δ 2.0 (br s, 2 H, NH_2), 4.52 (s, 1 H, C-3 proton), 7.16 (d, 1 H, 8 Hz), 7.19 (t, 1 H, 8 Hz), 7.4 (m, 4 H), 7.55 (m, 3 H), 8.37 (br s, 1 H, NHCO); MS, *m/e* 251 (M^+).

2-[(2-Bromoacetyl)amino]benzophenone (21). To a 3-L three-neck flask equipped with a mechanical stirrer, thermometer, and addition funnel were added 1300 mL of dichloromethane, 100 mL of water, and 197.2 g (1.00 mol) of 2-aminobenzophenone. The resulting slurry was cooled to −10 °C and treated with a solution of bromoacetyl bromide (100 mL, 232 g, 1.15 mol) in 300 mL of dichloromethane. The reaction mixture was agitated while allowing the temperature to warm to 20–25 °C over 3 h. The phases were separated, and the organic layer was washed with water (2 L) and then concentrated to 800 mL by distillation (atm). Dry dichloromethane (1 L) was added and the volume again reduced to 800 mL. Hexane was added (800 mL), and the distillation was continued until the final volume was 800 mL and the temperature of the distillate vapors reached 60–65 °C. The resulting hexane slurry was cooled to 5 °C and filtered. The filter cake was washed with cold hexane (400 mL) to yield 309 g (97%) of the analytical product: mp 94.5–95.5 °C (lit.[28] mp 94–95 °C).

1,3-Dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (22). To a 12-L three-neck flask fitted with a mechanical stirrer, gas addition tube (sparge), and condenser were added 6 L of methanol and 300 g (0.943 mol) of **21**. The resulting slurry was agitated and saturated with gaseous ammonia via subsurface addition while the reaction temperature was maintained between −10 and 10 °C (125–160 g ammonia/L of methanol). The slurry was agitated, while the temperature was allowed to reach 15 °C. During this time (1.5 h) the reaction mixture became homogeneous. Upon completion of the amination the reaction was heated to reflux for 2 h, cooled, and concentrated to 900 mL in vacuo. The residual slurry was warmed to 40 °C and treated with 900 mL of water. This mixture was stirred at 20–25 °C for 12 h and filtered, and the filter cake was washed (3 × 300 mL of 1:1 methanol–water). The vacuum-dried (50 °C) solid 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, mp 177–178.5 °C (lit.[28] mp 178–179 °C) attained in 83% yield, was 98% pure (HPLC) and was methylated as follows: into a cold (0–5 °C) mixture of toluene (6–8 L) and Aliquat 336 (20 mL), contained in a 22-L three-neck flask equipped with mechanical stirrer, thermometer, and gas inlet tube (sparge), was introduced gaseous methyl chloride (892.3 g). While the mixture was agitated, powdered benzodiazepin-2-one (513.4 g, 2.17 mol) and 50% aqueous sodium hydroxide (2.5 L) were added to the reaction mixture. The gas inlet tube was replaced by a mercury bubbler, and while the reaction temperature gradually rose to 20–25 °C, the two-phase system was stirred vigorously for 3–4 h. The phases were separated, and the aqueous layer was extracted with toluene (2.5 L). The combined organic extracts were washed with cold water (1.7 L) and concentrated

to 2.5 L. The resulting slurry was cooled to 0–5 °C and treated with hexane to complete the crystallization of **22**, 506 g (93%), mp 154.5–155.5 °C (lit.[28] mp 154–156 °C), which was >98% pure (HPLC).

1,3-Dihydro-1-methyl-3-oximido-5-phenyl-2*H*-1,4-benzodiazepin-2-one (23). To a 22-L three-neck flask equipped with mechanical stirrer, thermometer, and addition funnel were added 10 L of toluene and 506 g (2.02 mol) of **22**. The reaction mixture was cooled to −20 °C (internal) and with good stirring was treated with potassium *tert*-butoxide (567 g, 5.05 mol) under nitrogen. After 15 min, the cold suspension was treated with isoamyl nitrite (325 mL, 2.42 mol) at such a rate as to maintain the temperature below 0 °C. The reaction was quenched after 30 min by rapid addition of the reaction mixture to a stirred mixture of ice-cold water (20 L), acetic acid (1 L), and ethyl acetate (20 L). After the reaction was mixed throughly, the layers were separated, and the aqueous phase was extracted with ethyl acetate (20 L). The combined organic layers were washed with water (10 L) and concentrated in vacuo; repetition of the cycle assured removal of all water, ethyl acetate, and acetic acid. The resulting toluene slurry of **23** was cooled to 0 °C, aged for 1 h, and filtered. The washed filter cake was dried in vacuo (50 °C) to yield 461 g (81.6%) of **23**: mp 239–241 °C; IR (KBr, partial) 3300, 1650, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.44 (s, 3 H, CH_3), 7.15–7.88 (m, 9 H, Ar); MS, *m/e* 279 (M^+, 100%), 263, 249, 236, 222, 177.

Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.67; H, 4.62; N, 15.08.

3(*R*,*S*)-Amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one ((±)-3). An evacuated 5-gal stirred autoclave was charged with a suspension of dry, reduced 5% ruthenium on carbon catalyst (119 g; 25 wt % of **23**) in 4 L of methanol and then with a suspension of **23** (475 g, 1.70 mol) in 4 L of methanol. The inlet line was flushed with 2 L of methanol, and the closed, evacuated system was warmed to 50 °C with agitation. Hydrogen was introduced and 40 psi of pressure maintained while the temperature was increased to 68–74 °C. The heterogeneous mixture was stirred for 19–24 h, cooled, and filtered through Solka-Flok. The autoclave was flushed with methanol (2 × 4 L); these rinsings were used to wash the catalyst and Solka-Flok cake. The combined methanol filtrates were concentrated in vacuo to 4 L volume and turned over to acetonitrile by adding 4 L acetonitrile, concentrating, and repeating the cycle twice more. The acetonitrile solution (4 L) containing **3** was transferred to a 12-L three-neck flask equipped with mechanical stirrer, addition funnel, and thermometer. After cooling to 10 °C, the solution was treated with a 1.0 M solution of benzenesulfonic acid (260 g, 1.64 mol) in acetonitrile (1.6 L). The resulting suspension was aged at 20–24 °C for 8 h, filtered, and washed with acetonitrile (2 × 2 L) and hexane (2 × 2 L). Vacuum-drying at 25 °C gave 579 g (80.4%) of (±)-**3** as its benzenesulfonate salt. (A wash of the catalyst/Solka-Flok cake with 4 L of methylene chloride gave an additional 20 g, 2.8% of free amine.) (±)-**3** free base: mp 110–112 °C; IR (KBr, partial) 3380, 3310, 1675, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.4 (br s, 2 H, NH_2), 3.47 (s, 3 H, CH_3), 4.47 (s, 1 H, C-3 proton), 7.18–7.64 (m, 9 H, Ar). (±)-**3** benzenesulfonate salt: mp 224–227 °C.

Anal. Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.40; H, 5.00; N, 9.92; S, 7.57. Found: C, 62.09; H, 4.88; N, 10.07; S, 7.67.

1,1-Dimethylethyl [(*R*)-2-[(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)amino]-2-oxo-1-(phenylmethyl)ethyl]carbamate (26). A solution of dry dimethylformamide (350 mL) containing 50.4 g (0.190 mol) of racemic **3** was treated in succession with Boc-D-phenylalanine (52.9 g, 0.200 mol), 1-hydroxybenzotriazole (27.0 g, 0.200 mol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (38.2 g, 0.200 mol) with exclusion of moisture. The pH of the reaction mixture was adjusted to approximately 9.5 with triethylamine (27.6 mL, 0.2 mol). The resulting suspension was stirred for 15 min, and the solvent was removed under reduced pressure. The oily residue was partitioned between ethyl acetate and 10% citric acid solution. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with 10% sodium hydroxide solution, water, and brine. The dried (magnesium sulfate) extracts were rotary evaporated to yield 90 g of crude **26** as a yellow foam. Flash chromatography (15% ethyl acetate–methylene chloride) afforded the analytical sample as a 1:1 mixture of diastereomers: R_f 0.48 (180:10:1:1 methylene chloride–methanol–acetic acid–water); mp 117–120 °C (soften); IR (KBr, partial) 1670, 1600, 1490, 1170, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 and 1.42 (s, 9 H, Boc), 3.19 (dd, 1 H, 9 and 6 Hz); 3.27 (dd, 1 H, 9 and 6 Hz), 3.46 (s, 3 H), 4.6 (br s, 1 H), 5.01 (br t, 1 H), 5.47 and 5.50 (d, 1 H, 7 Hz), 7.25–7.50 (m, 10 H), 7.6 (m, 4 H), 7.80 (br d, 1 H, 7 Hz); MS, *m/e* 512 (M^+), 456, 421, 321, 293, 265, 250, 225, 222.

Anal. Calcd for $C_{30}H_{32}N_4O_4$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.99; H, 6.32; N, 10.81.

α-Amino-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)benzenepropanamide (27). The Boc amine **26** (65.2 g, 0.158 mol) was dissolved in 300 mL of ethyl acetate and cooled to 0 °C. This solution was then saturated with hydrogen chloride gas. After 30 min the resulting precipitate was collected and washed with ethyl acetate (2 × 50 mL). This solid was dissolved in hot absolute ethanol (950 mL), and the solution was filtered and cooled with stirring to induce crystallization. The solid was collected, washed with 60% diethyl ether in ethanol and finally with diethyl ether to give 17.70 g of the desired diastereomer **27**. Further processing of the mother liquors yielded an additional 5.6 g of **27** as diastereomerically homogeneous material (100%, HPLC). The free base was prepared by dissolving the amine HCl salt in water, basifying with 10% sodium hydroxide solution and extracting with ethyl acetate: $[\alpha]^{25}_D$ −35.1° (*c* 0.85, CH_2Cl_2); R_f 0.24 (90:10:1:1 methylene chloride–methanol–acetic acid–water); mp 97–108 °C (shrink, soften); IR (KBr, partial) 3370, 1670, 1600, 1495, 1330, 1110, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (br s, 2 H, NH_2), 2.69 (dd, 1 H, 14 and 11 Hz), 3.37 (dd, 1 H, 14 and 4 Hz), 3.49 (s, 3 H), 3.76 (dd, 1 H, 11 and 3 Hz), 5.55 (d, 1 H, 9 Hz, C-3 proton), 7.25–7.50 (m, 11 H), 7.6 (m, 3 H), 8.97 (d, 1 H, 9 Hz, N*H*CO); MS, *m/e* 412 (M^+), 321 (100%), 293, 265, 250, 223, 222, 208, 193.

Anal. Calcd for $C_{25}H_{24}N_4O_2$: C, 72.79; H, 5.87; N, 13.58. Found: C, 72.44; H, 5.85; N, 13.48.

3(*S*)-Amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one ((−)-3). A solution of 50 mL of methylene chloride containing 16.74 g (40.6 mmol) of **27** was treated with 5.33 mL (44.6 mmol) of phenyl isothiocyanate and heated on the steam bath for 10 min. The reaction mixture was rotary evaporated to dryness, and the residue was flash chromatographed on silica gel (15% ethyl acetate in methylene chloride) to give the intermediate thiourea as a white foam (25 g). The thiourea was dissolved in 20 mL of trifluoroacetic acid and warmed to about 50 °C for 20 min. The reaction mixture was concentrated in vacuo, and the residual trifluoroacetic acid was chased with methylene chloride (2 × 50 mL). Flash chromatography of the crude reaction product (90:10:1:1 methylene chloride–methanol–acetic acid–water) gave 9.75 g homogeneous product, which was converted to the free base with 10% sodium hydroxide solution in methylene chloride. Concentration of the dried (sodium sulfate) organic phase and trituration of the corresponding residue with ether afforded (−)-**3** as a foam: $[\alpha]^{25}_D$ −236° (*c* 0.33, CH_2Cl_2); R_f 0.31 (90:10:1:1 methylene chloride–methanol–acetic acid–water); IR (KBr, partial) 3300, 1680, 1605, 1490, 1440, 1325, 1110, 1005, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.9 (br s, 2 H, NH_2), 3.48 (s, 3 H), 4.49 (br s, 1 H, C-3 proton), 7.21 (t, 1 H, 7 Hz), 7.4 (m, 5 H), 7.58 (t, 1 H, 7 Hz), 7.63 (m, 2 H), spectrum verifies that (−)-**3** is partially solvated; MS, *m/e* 265 (M^+, 100%), 248 (M − NH_3), 237, 223.

Anal. Calcd for $C_{16}H_{15}N_3O{\cdot}0.15C_4H_{10}O{\cdot}0.15H_2O$: C, 71.43; H,6.07; N, 15.06. Found: C, 71.44; H, 5.95; N, 15.11.

X-ray Crystal Structure Analysis of (3*S*)-(−)-*N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-iodobenzenecarboxamide (28). Suitable crystals ($C_{23}H_{18}N_3O_2I$) for X-ray diffraction studies formed from ethyl acetate with space group symmetry of $P2_12_12_1$ and cell constants of a = 15.623 (9) Å, b = 20.752 (5) Å, and c = 14.785 (5) Å for Z = 8. Of the 3678 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2767 were ($I > 3\sigma I$). Standard data corrections were applied including absorption. The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined using full-matrix least-squares techniques.[42] A badly disordered molecule

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of ethyl acetate was found in the crystal lattice. The absolute configuration was determined from the anomalous scattering effects that showed the correct enantiomer to have an R factor of 0.093 while the other was 0.121. This difference was significant at the 0.005 level[43] and was confirmed by careful remeasurement of 13 enantiomorph sensitive reflections. Hydrogens were put in calculated positions and assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.087. The conformations of the two crystallographically distinct molecules were different primarily in the amide side chain. For instance, the dihedral angle for N12–C13–C15–C16 was -92.4°, while the angle for N12′–C13′–C15′–C16′ was 114.1°. No abnormally short intermolecular contacts were noted. Tables I–III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **28** from the final X-ray coordinates.

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Kinetics and Mechanism of the Oxidation of Unsaturated Carboxylic Acids by Methyltributylammonium Permanganate in Methylene Chloride Solutions

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The product obtained when permanganate is reduced by unsaturated carboxylic acids under anhydrous conditions is manganese(III). The rate of reaction, which is subject to acid catalysis, exhibits a Hammet ρ value of 1.11 and inverse secondary isotope effects (k_H/k_D = 0.96–0.98) when the hydrogens on the double bond are replaced by deuterium. The involvement of a free-radical process is indicated by the formation of polymer during the oxidation of acrylic and methacrylic acids. The reaction is believed to be initiated by formation of an organometallic complex in which the double bond is a η^2 ligand on manganese. Rearrangement of this complex results in the formation of a reactive manganate(V) cyclic diester, which undergoes a rapid (free-radical) reduction to manganese(III).

The oxidation of unsaturated carboxylic acids (and their salts) by aqueous potassium permanganate has received considerable attention. For example, the oxidations of cinnamic acids,[1-4] cinnamate ion,[5,6] crotonic acid,[7] oleic acid,[9,10] oleate ion,[5,11,12] butenoate ions,[1,5] pentenoate ions,[1] propenoate ions,[1] 3-thienyl-2-propenoate ions,[13] and 2-pyridinyl-2-propenoate ions[13] have been described in the literature. More recently, however, it has become common to carry out permanganate oxidations, with the aid of phase-transfer agents, in nonaqueous solvents.[14] Despite the usefulness of this procedure, practically no kinetic or mechanistic information is available with respect to the oxidation of unsaturated carboxylic acids, although a closely related reaction—the oxidation of cinnamate esters—has been studied.[15]

As the results presented in this paper indicate, the oxidation of unsaturated carboxylic acids in nonaqueous solvents contrasts in several ways, both with the corresponding aqueous phase oxidations and with the oxidation of unsaturated esters.

Experimental Section

The solvent used in all of the experiments, anhydrous methylene chloride, was purified by double distillation over 4-Å molecular sieves. The oxidizing agent, methyltributylammonium permanganate, was obtained by precipitation from an aqueous mixture of methyltributylammonium bromide and potassium permanganate.[16] Because of its instability, it was stored in the dark and at low temperatures. With the exception of the deuteriated derivatives of cinnamic acid, the reducing agents were obtained commercially and purified by either fractional distillation or crystallization. Cinnamic-α-d and -β-d acids were prepared according to the procedure previously reported.[17] Crotonic acid and all the derivatives of cinnamic acid were used in the trans form.

The kinetic experiments were all carried out in the presence of excess alkene. The reaction rates were followed by use of a Hewlett-Packard 8450A UV–vis spectrophotometer, provided with a thermostated cuvette holder. The permanganate band at 526

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