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

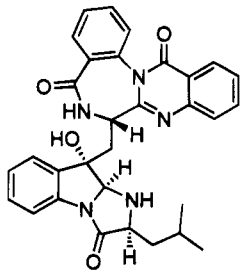
Ronald G. Sherrill* and Elizabeth E. Sugg

Department of Medicinal Chemistry, Glaxo Research Institute, 5 Moore Drive, Research Triangle Park, North Carolina 27707

Received September 13, 1994

Introduction

The gastrointestinal peptide hormone cholecystokinin (CCK) plays a key role in a number of physiological processes including pancreatic and bilary secretion, gallbladder contraction, and gut motility. CCK is also a putative neuromodulator involved in dopaminergic transmission, satiety, and analgesia.[1] Since the isolation of nonpeptidal CCK antagonist asperlicin **1**,[2] the 1,4-benzodiazepine ring system has served as a useful tool for delineating the pharmacological actions of CCK. Modifications of this template led to the development of 3-amino-5-phenyl-1,4-benzodiazepin-2-ones devazepide (**2**, MK-329)[3] and L-365,260 (**3**),[4] selective CCK-A and CCK-B receptor antagonists, respectively.



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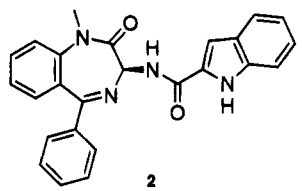

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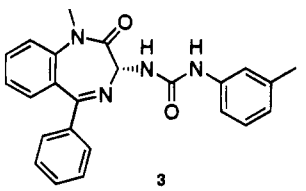

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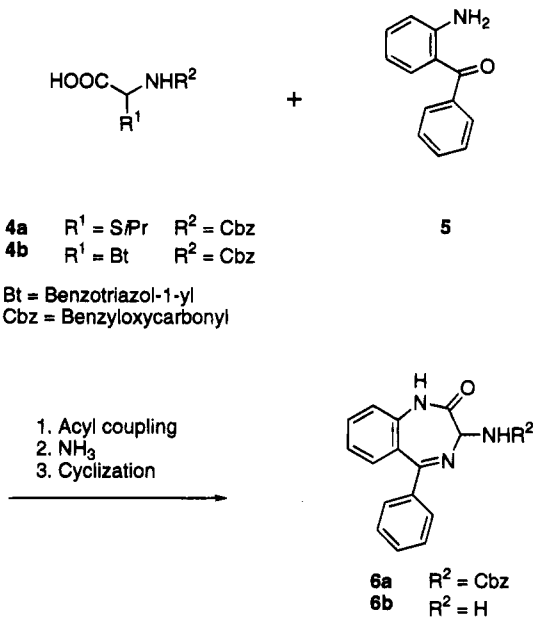
Although early syntheses of 3-amino-benzodiazepin-2-ones suffered from low yielding multistep sequences,[5]

Scheme 1



Bock and co-workers reported two improved preparations in 1987.[6] The first of these routes involved construction of the N1-substituted 1,4-benzodiazepine nucleus followed by introduction of the 3-amino functionality. The two-step amination sequence required oxime formation and subsequent catalytic hydrogenation over a reduced ruthenium catalyst at elevated temperature and pressure. The second of these routes (Scheme 1) employed α-(isopropylthio)-*N*-(benzyloxycarbonyl)glycine (**4a**) as a masked aminoglycine synthon. The key synthetic step involved a novel mercury-mediated displacement of the isopropylthiol group with ammonia to generate the aminal present in the 3-aminobenzodiazepine nucleus **6**. While higher yielding than the oxime route, this process suffers from the use of stoichiometric quantities of highly toxic mercuric chloride and the rather odoriferous nature of the displaced 2-propanethiol.

A recent report by Katritzky,[7a] describing the synthesis of monoacyl aminals from α-benzotriazol-1ylglycine derivatives, prompted the investigation of an alternative approach to the preparation of 3-amino-1,4-benzodiazepin-2-ones (Scheme 1). We reasoned that α-benzotriazol-1-yl-*N*-(benzyloxycarbonyl)glycine (**4b**) would serve as a superior aminoglycine synthon. Simple nucleophilic displacement of the benzotriazole functionality with ammonia would provide the suitably protected aminal of the 3-amino-1,4-benzodiazepine nucleus **6**.

* To whom correspondence should be addressed.

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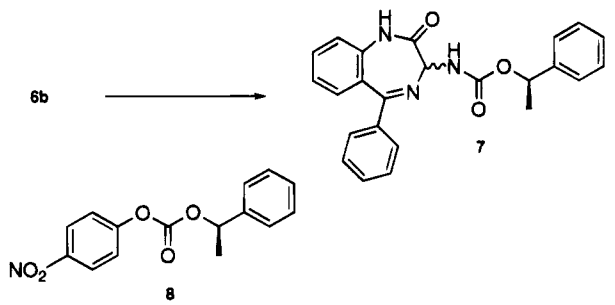
N1-Substituted-3-amino-1,4-benzodiazepin-2-ones have been resolved using classic Edman degradation conditions[8,6a] in satisfactory yields (30% of either enantiomer) as well as through an elegant crystallization-induced asymmetric transformation[19] (91% of a single enantiomer). More recently, the diastereomeric derivatization of N1-unsubstituted-3-amino-1,4-benzodiazepin-2-ones via α-methylbenzyl carbamates was reported.[9] The chiral auxiliary was introduced by initial treatment of 3-aminobenzodiazepine **6b** with carbonyldiimidazole to form the imidazole urea. Subsequent treatment of the activated urea with a 4-fold excess of chiral α-methylbenzyl alcohol at reflux in THF over several days provided each diastereomer in approximately 34% yield.

For our studies in the SAR of these peptide antagonists, it was desirable to have the versatility of resolution prior to functionalization of the N1-postion. Assignment of the absolute stereochemistry of our analogues could then be made using literature precedent.[9] The α-methylbenzyl carbamate moiety was appealing as this group served a dual role of chiral auxiliary and protecting group. In order to employ a stoichiometric quantity of the chiral alcohol, we chose to investigate *p*-nitrophenyl carbonate **8**[13] for the preparation of carbamate **7**.

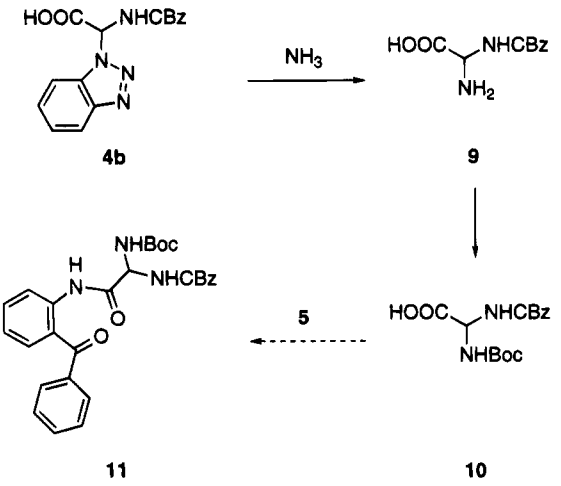


To assess the utility of these approaches toward the synthesis and resolution of N1-unsubstituted-3-aminobenzodiazepines, we now report a comparative synthesis of MK 329[3] and L-365,260.[4]

Results and Discussion

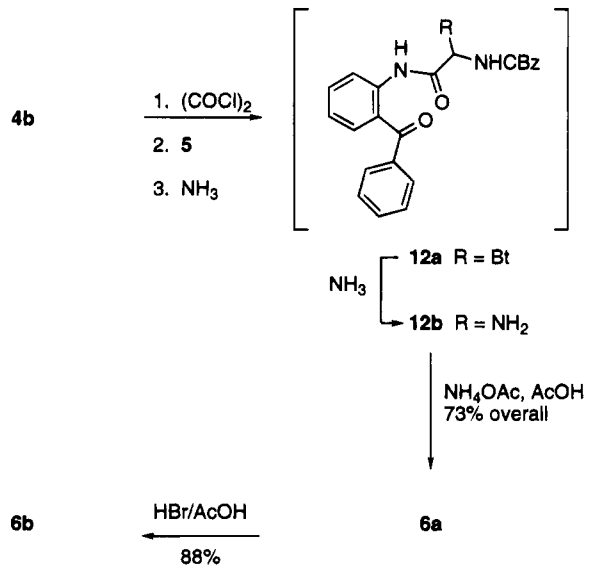
Synthesis of Racemic 3-Amino-1,4-benzodiazepine-2-one. Construction of the protected 3-amino-1,4-benzodiazepin-2-one **6a** centered initially on acyl coupling of differentially protected acid-aminal **10** to 2-aminobenzophenone **5**. This approach provided the versatility of protecting group selection on the 3-amino functionality prior to ring closure. Benzotriazole adduct **4b**, prepared in 95% yield from benzyl carbamate, benzotriazole, and glyoxylic acid,[7b] was treated with saturated methanolic ammonia to provide aminoglycine **9** as reported by Katritzky.[7b] Boc protection of **9** then provided fully protected aminal **10**.

Several attempts to couple aminal **10** to **5** via mixed anhydride or carbodiimide coupling conditions (e.g. DCC, EDC,[17] or BOP[18]) failed. Therefore, we investigated



direct coupling of benzotriazole adduct **4b** (Scheme 2) prior to displacement with ammonia. This approach

Scheme 2



would shorten the synthesis by eliminating the added protection and deprotection of aminal **9**. Due to the poor nucleophilicity observed during the attempted acyl coupling of 2-aminobenzophenone (**5**) with **10**, competing displacement of the benzotriazole functionality with the deactivated aniline seemed unlikely. Furthermore, we anticipated a more facile aminolysis of the benzotriazole moiety when substituted α to an acyl amide.[7b]

Preliminary attempts to couple benzotriazole adduct **4b** to **5** with standard peptide coupling agents or via a mixed anhydride again gave little or no reaction. However, *in situ* formation of the acyl chloride with oxalyl chloride and catalytic DMF followed by treatment with 2-aminobenzophenone (**5**) gave clean conversion to acyl amide **12a**, as assessed by TLC. The crude solution of **12a** was treated directly with ammonia gas in a THF/methanol solvent mixture to provide amino ketone **12b**. Following solvent displacement into ethyl acetate, the benzotriazole byproduct was readily extracted with aqueous base and the crude amino ketone **12b** was cyclized[6] to provide 3-[(benzyloxycarbonyl)amino]-1,4-benzodiazepine **6a** in 73% overall yield from 2-aminobenzophenone (**5**), without chromatography. Removal of the Cbz protecting group by treatment with saturated HBr in acetic

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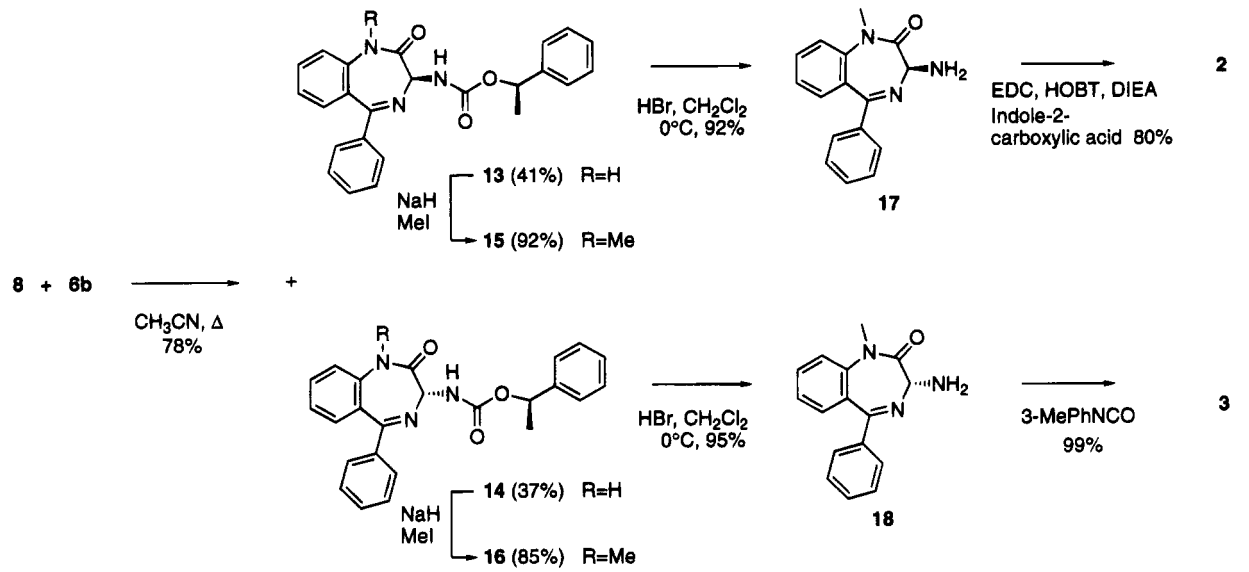
Scheme 3



acid[10] and subsequent neutralization was effected in 88% yield to provide racemic 3-amino-1,4-benzodiazepin-2-one **6b** in 66% overall yield from 2-aminobenzophenone (**5**).

Resolution of 3-Amino-1,4-benzodiazepin-2-one. Intuitively, the most direct synthesis of the chiral carbamate would be through the corresponding chloroformate. Unsubstituted benzyloxy carbamates are typically prepared via the corresponding chloroformate or through an activated carbonate of the alcohol.[11] Chloroformates of α-alkyl-substituted benzyl alcohols, however, are unstable due in large part to the enhanced stability of the substituted benzylic cation formed during decomposition.[12] Attempted preparations of α-methylbenzyl chloroformate at low temperature provide unstable mixtures of the desired compound and the corresponding α-methylbenzyl chloride.[12b] Therefore we chose to investigate the *p*-nitrophenyl carbonate of (*R*)-α-methylbenzyl alcohol **8** for the introduction of the chiral auxiliary onto the benzodiazepine nucleus **6b** (Scheme 3). Although carbonate **8** has been reported,[13] to our knowledge the use of activated carbonates of phenethyl alcohol in the diastereomeric derivatization of amines is unprecedented.

Using a modification of the literature procedure,[13] chiral carbonate **8** was prepared in 85% yield from (*R*)-α-methylbenzyl alcohol and *p*-nitrophenyl chloroformate (Scheme 3). Carbonate **8** was stable at room temperature for several months with no measurable chemical or chiral degradation as assessed by TLC, NMR, and optical rotation. Preparation of diastereomeric carbamates **13** and **14** was accomplished in refluxing acetonitrile in 78% overall yield (41% of **13** and 37% of **14**). The diastereomeric excess of purified isomers **13** and **14** was determined by reversed phase HPLC to be 99.8 and 96.3, respectively. Alkylation of **13** and **14** with sodium hydride and methyl iodide gave **15** and **16** in 93 and 85% yield, respectively.

Separation of diastereomers **13** and **14** prior to alkylation of the N-1 postion extended the combined overall synthesis of enantiomers **17** and **18** by one step. However, the diastereomeric excess of **13** and **14** was easily quantified by reversed-phase analytical HPLC whereas alkylated diastereomers **15** and **16** were inseparable by reversed phase HPLC. Isomers **15** and **16** were, however, readily separable by TLC and flash chromatography. There was no evidence by NMR or TLC of epimerization at the C-3 position during the alkylation step.

Removal of the carbamate auxiliary with HBr in dichloromethane at low temperature followed by recrystallization to remove traces of α-methylbenzyl bromide afforded enantiomers **17** and **18** in 92 and 95% yield, respectively. The absolute configuration of **17** and **18** was assigned as 3*S*-(−) and 3*R*-(+), respectively, based on comparisons with reported optical rotations.[6] Enantiomers **17** and **18** were converted to MK-329 (**2**) and L365,260 (**3**), respectively, and analyzed by reversed-phase and chiral HPLC. Homogeneities greater than 99% and an enantiomeric excess of 96.0 were obtained for each compound.[14]

The enantiomeric purity of the commercially available (*R*)-α-methylbenzyl alcohol was determined by chiral HPLC and used to assess the degree of racemization incurred during the resolution sequence. With the enantiomeric excess of the starting alcohol measured at 98.6, a total of 1.3% racemization was calculated for each analogue in the five step route from formation of the *p*-nitrophenyl carbonate **8** through preparation of CCK antagonists MK-329 (**2**) and L-365,260 (**3**).

Conclusion

We have demonstrated a novel route for the preparation of racemic 3-amino-1,4-benzodiazepin-2-ones in 66% overall yield from 2-aminobenzophenone (**5**) utilizing α-benzotriazol-1-yl-*N*-(benzyloxycarbonyl)glycine **4b** as an aminoglycine synthon. In addition to a modest increase (6−11%) above previously reported yields,[6a] the safety and efficiency of this sequence imparts a substantial improvement over existing routes. With the continuing interest in the pharmacological properties of this class of compounds, an expedient chemical synthesis will play

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(14) A sample of the opposite configuration isomer was prepared in an identical fashion and used for peak verification of the opposite enantiomer.

a critical role in their evaluation as potential therapeutic agents. The generality of this approach toward diverse 5-substituted 3-amino-1,4-benzodiazepines has been investigated and will be published separately.

In addition, we have developed an improved protocol for the diastereomeric resolution of 3-amino-1,4-benzodiazepines which exploits a stable *p*-nitrophenyl carbonate of α-methylbenzyl alcohol.[13] Carbamate derivatives **13** and **14** were prepared in high yield (78% overall) by reaction with a stoichiometric quantity of the activated carbonate **8**. Following alkylation of the N-1 position, removal of the chiral auxiliary provided enantiopure amines **17** and **18** in high yield (81–85% overall). The commercial availability of numerous enantiomerically pure substituted benzyl alcohols coupled with facile deprotection methods make α-substituted benzyl carbamates attractive chiral handles for the diastereomeric resolution of amines. This improved procedure for the introduction of these chiral auxiliaries should find wide application in the resolution of amines.

Experimental Section

General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Anhydrous grade solvents were used without additional drying. Pyridine, diisopropylethylamine, *N*-methylmorpholine, and triethylamine were dried over 4 Å molecular sieves immediately prior to use. ^{1}H NMR chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Coupling constants are reported in hertz (Hz) and resonances are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Mass spectra (MS) were taken in a positive ion mode under chemical ionization (CI) or fast atom bombardment (FAB) methods. All reactions were monitored by thin-layer chromatography on silica gel plates (Merck, 0.25 mm, 60F-254) and visualized by UV light, 7% ethanolic phosphomolybdic acid, or iodine stain. Flash chromatography was performed on flash grade silica gel (230–400 mesh, Merck) as described by Still[15] or TLC mesh silica gel (<230 mesh, EM Science) as described by Taber.[16] Analytical purity was assessed by reversed phase (RP) HPLC using a system equipped with a photodiode array spectrometer (λ range 200–400 nM). Linear gradients over 30 min were used in all cases. The stationary and mobile phase is noted in the experimental protocol. Melting points were determined in open capillaries and are uncorrected.

1,3-Dihydro-5-phenyl-3(*R,S*)-[(benzyloxycarbonyl)amino]-2*H*-1,4-benzodiazepin-2-one (6a). A solution of 2-(benzotriazol-1-yl)-*N*-(benzyloxycarbonyl)glycine (**4b**)[7b] (10.00 g; 30.67 mmol) in anhydrous THF (100 mL) under N_2 was cooled to 0–5 °C with an ice–water bath. Oxalyl chloride (2 M in dichloromethane, 15.3 mL, 30.7 mmol) was added via syringe followed by anyhydrous DMF (0.25 mL). After maintaining the reaction mixture at 0–5 °C for 2 h, a solution of 2-aminobenzophenone (5.445 g, 27.61 mmol) and dry *N*-methylmorpholine (5.90 mL, 61.4 mmol) in anhydrous THF (30 mL) was added dropwise over approximately 20 min. The reaction was allowed to warm to ambient temperature and the reaction slurry was filtered, washing the filter cake with a minimum quantity of anhydrous THF (approximately 25 mL). The mother liquor containing **12a** was saturated with ammonia gas, diluted with methanol (150 mL), and saturated again with ammonia gas over approximately 0.5 h. Following solvent displacement into ethyl acetate, the solution of crude **12b** was washed twice with aqueous sodium hydroxide (1 N). After back-extracting the combined aqueous layers with ethyl acetate, the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*.

The crude amine **12b** (12.6 g) was dissolved in glacial acetic acid (200 mL), combined under N_2 with ammonium acetate (10.00 g, 129.7 mmol), and allowed to stir at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* and suspended in ethyl acetate (50 mL) and diethyl ether (150 mL). Aqueous sodium hydroxide (1 N) was added until the pH of the aqueous layer was greater than 8. The resulting slurry was cooled to 0–5 °C in an ice–water bath and then filtered. The solid was washed consecutively with water and diethyl ether and dried under high vacuum to provide the title compound as a crystalline solid (7.770 g, 73%). Mp 200–203 °C (lit.,[6a] 212–213 °C hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (b, 2H); 5.35 (d, J = 8.4, 1H); 6.60 (d, J = 8.1, 1H); 7.12–7.71 (m, 14H); 8.38 (s, 1H). MS (FAB): $[M + H]^+ = 386$. Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found: C, 71.55; H, 5.00; N, 10.88.

3-Amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (6b). A solution of 1,3-dihydro-5-phenyl-3(*R,S*)-[(benzyloxycarbonyl)amino]-2*H*-1,4-benzodiazepin-2-one (**6a**) (7.00 g, 18.2 mmol) in glacial acetic acid (200 mL) was saturated with HBr gas. The reaction was warmed to 70 °C and held for 20 min. The temperature was raised to 80 °C and maintained for an additional 20 min. The resulting slurry was cooled to ambient temperature, diluted with anhydrous diethyl ether (200 mL), agitated for 0.5 h, and filtered. The solid was washed with diethyl ether and dried at 60 °C under vacuum to provide the dihydrobromide salt (6.836 g, 16.54 mmol). The free base was obtained by partitioning the dihydrobromide (6.100 g, 14.77 mmol) between aqueous potassium carbonate (5% w/v, 50 mL) and ethyl acetate containing approximately 5% v/v 2-propanol and dichloromethane. After separating the phases, the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a solid. The product was dried under high vacuum to provide the title compound as a crystalline solid (3.687 g, 14.26 mmol, 88% overall from **6a**). Mp 153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (b, 2H); 4.51 (s, 1H); 7.12–7.60 (m, 9 H); 8.22 (bs, 1H). MS (FAB): $[M + H]^+ = 252$. Anal. Calcd for $C_{15}H_{13}N_3O \cdot 0.4\ H_2O$: C, 69.70; H, 5.38; N, 16.26. Found: C, 69.80; H, 5.29; N, 16.34.

Carbonic Acid 4-nitrophenyl (*R*)-1-Phenylethyl Diester (8). 1(*R*)-Phenylethanol (2.939 g, 24.06 mmol) and anhydrous pyridine (2.05 mL, 25.3 mmol) were combined under N_2 in dry dichloromethane (10 mL) and cooled to 0–5 °C with an ice–water bath. A solution of 4-nitrophenyl chloroformate (4.849 g, 24.06 mmol) in dry dichloromethane (15 mL) was added dropwise over 15 min. The reaction was allowed to warm to ambient temperature and stirred overnight under N_2. After cooling to 0–5 °C, the reaction was quenched with aqueous hydrochloric acid (1 N). The phases were separated and the organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified on flash grade silica gel using 15% ethyl acetate in n-hexane. Pure fractions were combined and concentrated *in vacuo* to provide the title compound as an oil (5.872 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.70 (d, J = 6.4, 3H); 5.84 (q, J = 6.6, 1H); 7.81–7.47 (m, 7H); 8.25 (d, J = 8.9, 2H). MS (CI): $[M + H]^+ = 288$. $[\alpha]_D$ +126.5 (c = 2.6, $CHCl_3$). Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.83; H, 4.54; N, 4.89.

Chiral HPLC of 1(*R*)-Phenethyl Alcohol. Chiralcel OF (Diacel Chem. Ind., LTD; 0.46 × 25 cm), n-hexane: 2-propanol (98.5/1.5), 1.0 mL/min, t_R = 19.2 min (*S*-isomer t_R = 17.9 min), 98.6 ee.

1,3-Dihydro-5-phenyl-3(*S*)-{[(*R*)-α-methylbenzyloxycarbonyl]amino}-2*H*-1,4-benzodiazepin-2-one (13) and 1,3-Dihydro-5-phenyl-3(*R*)-{[(*R*)-α-methylbenzyloxycarbonyl]amino}-2*H*-1,4-benzodiazepin-2-one (14). 3-Amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (**6b**) (2.100 g, 8.124 mmol), carbonic acid 4-nitrophenyl (*R*)-1-phenylethyl diester (**8**) (2.332 g, 8.124 mmol) and dry triethylamine (1.133 mL, 8.124 mmol) were combined in acetonitrile (25 mL) under N_2 and heated at reflux overnight. After removing the reaction solvent *in vacuo*, the residue was dissolved in ethyl acetate and washed twice with aqueous sodium hydroxide (1 N). The combined aqueous layers were extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified

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by chromatography on TLC mesh silica gel (~100 g) using a step gradient of 30–35% ethyl acetate in n-hexane. The impure fractions were combined, evaporated *in vacuo*, and purified again by chromatography on TLC mesh silica (~100 g) gel using 35% ethyl acetate. The impure fractions were combined, evaporated *in vacuo*, and purified again by chromatography on flash grade silica gel (~75 g) using 30% ethyl acetate in n-hexane. The pure fractions of each diastereomer were combined from previous columns and concentrated *in vacuo* to provide the less polar carbamate **13** (1.345 g, 41%) and the more polar carbamate **14** (1.210 g, 37%) as amorphous solids.

Carbamate **13**: R_f (1:1 ethyl acetate:hexane) 0.47. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.47 (d, J = 6.4, 3H); 4.96–5.02 (m, 1H); 5.68 (q, J = 6.6, 1H); 7.18–7.65 (m, 14H); 8.32 (d, J = 9.0, 1H); 10.81 (s, 1H). MS (FAB): $[M + H]^+$ = 400. $[\alpha]_D$ +27.0 (c = 0.9, $CHCl_3$). Anal. Calcd for $C_{24}H_{21}N_3O_3 \cdot 0.3H_2O$ C, 71.20; H, 5.38; N, 10.38. Found: C, 71.23; H, 5.38; N, 10.30.

Carbamate **14**: R_f (1:1 ethyl acetate:hexane) 0.42. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.46 (d, J = 6.6, 3H); 4.95–5.01 (m, 1H); 5.68 (q, J = 6.5, 1H); 7.18–7.66 (m, 14H); 8.34 (d, J = 8.2, 1H); 10.84 (s, 1H). MS (FAB): $[M + H]^+$ = 400. $[\alpha]_D$ +140.0 (c = 1.2, $CHCl_3$). Anal. Calcd for $C_{24}H_{21}N_3O_3 \cdot 0.3H_2O$ C, 71.20; H, 5.38; N, 10.38. Found: C, 71.33; H, 5.37; N, 10.33.

1,3-Dihydro-1-methyl-5-phenyl-3(*S*)-{[(*R*)-α-methylbenzyloxycarbonyl]amino}-2*H*-1,4-benzodiazepin-2-one (15). Sodium hydride (60% dispersion in mineral oil, 120 mg, 3.00 mmol) was added to a solution of **13** (1.202 g, 3.009 mmol) in anhydrous DMF (10 mL) at 0–5 °C under N_2. After 1.5 h, methyl iodide (196.6 μL, 3.160 mmol) was added via micropipette and the reaction was maintained for 1.5 h. The reaction mixture was added via pipette to a vigorously stirred solution of water (75 mL) containing aqueous sodium hydrogen sulfate (2 mL, 1 N). The resulting slurry was filtered and washed with water, and the residual solid was dried under high vacuum overnight. The crude product was dissolved in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on flash grade silica gel using 35% ethyl acetate in n-hexane. Pure fractions were combined, concentrated *in vacuo*, and dried under high vacuum overnight to provide the title compound as an amorphous solid (1.156 g, 93%). R_f (2:3 ethyl acetate:hexane) 0.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 6.6, 3H); 3.46 (s, 3H); 5.33 (d, J = 8.3, 1H); 5.77 (d, J = 6.5, 1H); 6.82 (d, J = 8.3, 1H); 7.20–7.69 (m, 14H). MS (FAB): $[M + H]^+$ = 414. Mp 203–205 °C. $[\alpha]_D$ +6.1(c = 1.2, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_3O_3 \cdot 0.25H_2O$ C, 71.84; H, 5.67; N, 10.05. Found: C, 71.98; H, 5.71; N, 9.89.

1,3-Dihydro-1-methyl-5-phenyl-3-(*R*)-{[(*R*)-α-methylbenzyloxycarbonyl]amino}-2*H*-1,4-benzodiazepin-2-one (16). Using conditions identical to those described in the synthesis of **15**, the title compound was obtained as a solid from intermediate **14** (1.152 g, 2.884 mmol). The crude product was dissolved in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and then concentrated *in vacuo*. The residue was purified by chromatography on flash grade silica gel using 35–40% ethyl acetate in n-hexane. Pure fractions were combined, concentrated *in vacuo*, and dried under high vacuum overnight to provide the title compound as an amorphous solid (1.013 g, 85%). R_f (2:3 ethyl acetate:hexane) 0.35. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (d, J = 6.7, 3H); 3.49 (s, 3H); 5.38 (d, J = 8.7, 1H); 5.79 (d, J = 6.6, 1H); 6.82 (d, J = 8.7, 1H); 7.21–7.68 (m, 14H). MS (FAB): $[M + H]^+$ = 414. $[\alpha]_D$ +171.3 (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_3O_3$ C, 72.62; H, 5.61; N, 10.16. Found: C, 72.48; H, 5.64; N, 10.08.

1,3-Dihydro-1-methyl-3(*S*)-amino-5-phenyl-2*H*-1,4-benzodiazepin-2-one Hydrobromide (17). A solution of **15** (1.094 g, 2.646 mmol) in dichloromethane (25 mL) at 0–5 °C was saturated with hydrogen bromide. After 30 min, the reaction mixture was concentrated *in vacuo* and dissolved in dichloromethane (10 mL), and the product was precipitated by addition of anhydrous diethyl ether. The resulting slurry was stirred for 30 min and filtered, and the residual solid was dried for 48 h under high vacuum to provide the title compound as a hygroscopic yellow solid (1.040 g, 93%) characterized as a partial imminium salt. A small sample (approximately 25 mg) was removed and dried under vacuum at 56 °C to remove residual HBr. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.46 (s, 3H); 5.30 (s, 1H); 7.19–7.70 (m, 9H), spectra confirms partial solvate. MS (FAB): $[M + H]^+$ = 266. Mp 81–84 °C. Anal. Calcd for $C_{16}H_{15}N_3O \cdot 1.4HBr \cdot 0.2C_4H_{10}O \cdot 1.5H_2O$ (dried at room temperature): C, 47.99; H, 5.13; N, 9.99; Br, 26.61. Found: C, 48.03; H, 4.81; N, 10.37; Br, 26.40. Anal. Calcd for $C_{16}H_{15}N_3O \cdot 0.1C_4H_{10}O \cdot HBr \cdot 0.75H_2O$ (dried at 56 °C): C, 53.65; H, 5.07; N, 11.44. Found: C, 53.65; H, 4.90; N, 11.21.

1,3-Dihydro-1-methyl-3(*R*)-amino-5-phenyl-2*H*-1,4-benzodiazepin-2-one Dihydrobromide (18). Using an identical procedure to that described for the synthesis of **17**, **16** (0.939 g, 2.27 mmol) was converted to **18** (0.922 g, 97%). A small sample (approximately 25 mg) was removed and dried under vacuum at 56 °C to remove residual HBr. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.46 (s, 3H); 5.30 (s, 1H); 7.19–7.70 (m, 9H), spectra confirms partial solvate. MS (FAB): $[M + H]^+$ = 266. Mp 81–84 °C. Anal. Calcd for $C_{16}H_{15}N_3O \cdot 1.4\,HBr \cdot 0.2C_4H_{10}O \cdot 1.4H_2O$ (dried at room temperature): C, 48.20; H, 5.10; N, 10.04; Br, 26.72. Found: C, 48.52; H, 4.84; N, 10.44; Br, 26.50. Anal. Calcd for $C_{16}H_{15}N_3O \cdot 0.1C_4H_{10}O \cdot HBr \cdot 0.75H_2O$ (dried at 56 °C): C, 53.65; H, 5.07; N, 11.44. Found: C, 53.87; H, 5.08; N, 11.19.

(*S*)-*N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide (2). A combination of **17** (950 mg, 2.22 mmol), indole-2-carboxylate (358 mg, 2.22 mmol), 1-hydroxybenzotriazole (341 mg, 2.52 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (426 mg, 2.22 mmol), and diisopropylethylamine (0.852 mL, 4.89 mmol) was combined under N_2 in dichloromethane (20 mL) and allowed to stir at ambient temperature overnight. The reaction mixture was washed consecutively with 1 N HCl and aqueous K_2CO_3 (5% w/v), dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and triturated with anhydrous ether. The resulting slurry was filtered, washed with ether, and dried overnight under high vacuum to provide the title compound as a crystalline solid (725 mg, 80%). Mp 167–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H); 5.83 (d, J = 8.2, 1H); 7.12–7.74 (m, 14 H); 8.26 (d, J = 8.0, 1H); 9.30 (s, 1H). MS (FAB): $[M + H]^+$ = 409. Chiral HPLC: Pirkle Covalent L-Phenylglycine (25 cm × 4.6 mm, 5 μm), n-hexane/2-propanol/acetonitrile (40/57/3), 1.5 mL/min, t_R = 8.35 min (*R*-isomer, t_R = 7.15 min), 96.0% ee.[14] RP HPLC: Vydac C18 (4.6 mm × 250 mm, 5 μm), 36–45% acetonitrile in aqueous TFA (0.1% v/v), 1.5 mL/min, t_R = 17.1 min, 99.1%. $[\alpha]_D$ −107.8 (c = 0.9, CH_3CN), (lit.,[19] −113.7, c = 1, CH_3CN). Anal. Calcd for $C_{25}H_{20}N_4O_2 \cdot 0.25H_2O$: C, 72.71; H, 5.00; N, 13.57. Found: C, 72.71; H, 5.09; N, 13.41.

(*R*)-1-(1-Methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-diazepin-3-yl)-3-*m*-tolylurea (3). A solution of **18** (825 mg, 1.93 mmol) in dichloromethane (20 mL) under N_2 was treated with 3-methylphenyl isocyanate (0.249 mL, 1.93 mmol) followed by disopropylethylamine (0.690 mL, 3.96 mmol). After stirring for 30 min at ambient temperature, the reaction was concentrated *in vacuo* and purified by chromatography on flash grade silica gel using 30–35% ethyl acetate in n-hexane. Pure fractions were combined, concentrated *in vacuo*, and triturated with ether. The resulting slurry was filtered, washed with ether, and dried under high vacuum overnight to provide the title compound as a crystalline solid (0.767 g, 99%). Mp 157–159. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H); 3.39 (s, 3H); 5.21–5.24 (m, 1H); 6.73 (d, J = 7.0, 1H); 7.06–7.77 (m, 13H); 8.96 (s, 1H). MS (FAB): $[M + H]^+$ = 399. Chiral HPLC: Pirkle Covalent L-Phenylglycine (25 cm × 4.6 mm, 5 μm), n-hexane/2-propanol/acetonitrile (70/27/3), 2.5 mL/min, t_R = 8.52 min (*S*-isomer, t_R = 9.92 min), 96.0% ee.[14] RP HPLC: Vydac C18 (4.6 mm × 250 mm, 5 μm), 36–45% acetonitrile in aqueous TFA (0.1% v/v), 1.5 mL/min, t_R = 13.0 min, 99.8%. $[\alpha]_D$ + 101.0 (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{24}H_{22}N_4O_2 \cdot 0.2H_2O$: C, 71.69; H, 5.62; N, 13.93. Found: C, 71.73; H, 5.62; N, 13.91.

Acknowledgment. We thank the efforts of Randy Rutkowske (NMR), Roderick Davis (MS), and Lawrence Shampine (MS) for their invaluable assistance in spectral characterization. We also thank Drs. Marc Rodriguez and Jeffrey Stafford for helpful discussion.

JO941578S

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