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Efficient Synthesis of *N-tert*-Butyl-2-{3(*R*)-[3-(3-chlorophenyl)ureido]-8-methyl-2-oxo-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-1-yl}acetamide and Related CCK_B Antagonists

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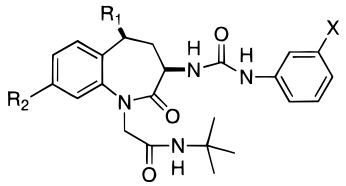
Abstract:

An efficient synthesis of the CCK_B antagonist *N-tert*-butyl-2-{3(*R*)-[3-(3-chlorophenyl)ureido]-8-methyl-2-oxo-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-1-yl}acetamide [(*R*)-1a] in optically active form is presented. The synthesis of the core 3-amino-5-phenylbenzazepin-2-one moiety started with the coupling of 2-amino-4-methylbenzophenone (6a) and diethyl 3-phosphono-2-(methoxyimino)propionic acid (8). The resulting amide diethyl 2-[3-phosphono-2-(methoxyimino)propionamido]-4-methylbenzophenone (9a) underwent intramolecular benzazepinone ring formation in tetrahydrofuran with 2 equiv of potassium *tert*-butoxide to provide 8-methyl-5-phenyl-1*H*-benz[*b*]azepine-2,3-dione 3-(*O*-methyloxime) (10a) in high yield. Hydrogenation over Raney nickel in methanol reduced both the *O*-methyloxime and the 4,5-double bond, giving *cis*-3-amino-8-methyl-5-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one (7a) with high selectivity. A classical resolution of amino lactam 7a and attachment of the N-1 and C-3 side chains afforded the title compound. The sequence was repeated with other 2-aminophenyl ketones and was shown to work well for C-5 substituents such as methyl and cyclohexyl or as part of a fluorenyl group, thus providing an easy access to these molecules from readily available starting materials.

Recently, John Lowe described the synthesis and biological activity of a series of 5-aryl(5-alkyl)-3-ureidobenzazepin-2-ones which were potent antagonists of the cholecystokinin-B receptor.[1] These compounds have potential for the treatment of panic disorder and anxiety,[2] pain,[3] and control of dopaminergic function.[4] The two compounds of most interest were the 5-phenyl analogue **1a** and 5-cyclohexyl derivative **2**, which featured an ionizable group on the ureido sidechain to provide a water-soluble salt. This paper describes a new approach to the synthesis of these benzazepin-2-ones by a general method which allows control of the 3,5-cis stereochemistry in these systems.



1a, R_1 = phenyl, R_2 = methyl, X = Cl
2, R_1 = cyclohexyl, R_2 = methyl, X = CO_2H

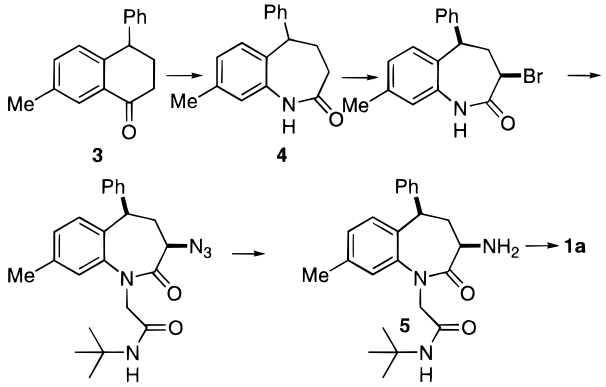
The synthesis of the benzazepin-2-one fragment in **1a** and **2** used by Lowe was based on the classical approach to 5-substituted benzazepinones, the Beckmann ring expansion of a 4-substituted tetralone as shown for compound **1a** in Scheme 1. For **1a**, the synthesis of tetralone **3** required seven steps. Introduction of the N-1 and C-3 side chains was based on literature procedures involving bromination, alkylation at N-1, azide displacement, and reduction.[5] It was this portion of the route which was considered questionable for scale-up. Both the initial bromo lactam and the azide precursor to **5** which had the C-3 moiety cis to the C-5 phenyl group were prone to equilibration to the thermodynamically more stable trans isomers. Successful preparations required rapid workup and purification of these intermediates by column chromatography, which was not suitable for large-scale work. Finally, the resolution of *rac*-**5** was achieved through a derivatization and chromatographic separation requiring four chemical steps and a careful chromatography.[6] In view of these problems, a new approach to these compounds was sought.

We have published an annelation process to the racemic 4,5-dehydrobenzazepin-2-one 3-benzamide derivative of lactam **7a**, *N*-(8-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benz[*b*]azepin-3-yl)benzamide.[7] Starting from benzophenone **6a,** the C-4 carbon was introduced with methylmagnesium chloride to provide 5-methyl-2-(1-phenylvinyl)phenylamine after loss of water. Following the attachment of *N*-benzoyl-2-methoxyglycine, a two-carbon amino acid, an intramolecular amidoalkylation provided the unsaturated benzazepin-2-one. This option was not pursued further due to the extra process steps to introduce a single carbon atom, the moderate yield of the amidoalkylation, and especially the lack of a stereospecific hydrogenation of the 4,5-olefin to provide the cis diastereomer cleanly.

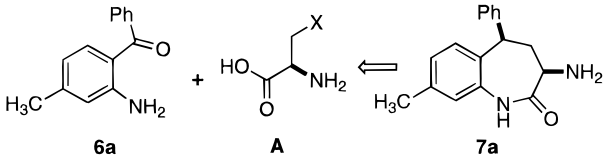
For the current process, our retrosynthetic analysis to amino lactam **7a** from a three-carbon amino acid equivalent **A** is shown in Scheme 2. The generic amino acid moiety **A** could be derivable ideally from serine and would provide

(1) (a) Lowe, J. A.; Hageman, D. L.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Bordner, J. *J. Med. Chem.* **1994**, *37*, 3789. (b) Lowe, J. A.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Appleton, T. A.; Lombardo, F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1933.
(2) Dooley, D. J.; Klamt, I. *Psychopharmacology* **1993**, *112*, 452.
(3) Noble, F.; Derrien, M.; Roques, B. P. *Br. J. Pharmacol*. **1993**, *109*, 1064.
(4) Rasmussen. K.; Czachura, J. F.; Stockton, M. E.; Howbert, J. J. *J. Pharmacol. Exp. Ther*. **1993**, *264*, 480.
(5) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Snyder, J. P.; Springer, J. P.; Hirshfield, J.; Tristram, E. W.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem.* **1986**, *29*, 251.
(6) Rittle, K. E.; Evans, B. E.; Bock, M. G.; DiPardo, R. M.; Whitter, W. L.; Hommick, C. F.; Veber, D. F.; Freidinger, R. M. *Tetrahedron Lett*. **1987**, *28*, 521.
(7) Urban, F. J.; Breitenbach, R.; Gonyaw, D.; Kelly, S. E. *Synth. Commun*. **1996**, *26*, 2241.

Scheme 1



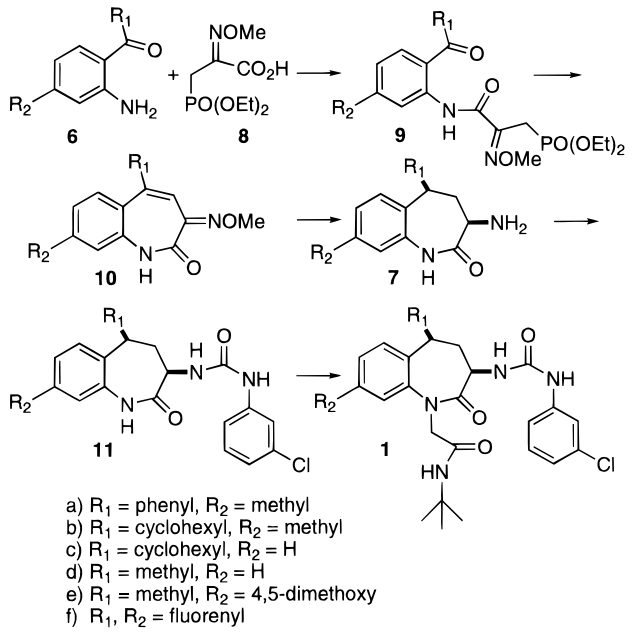
Scheme 2



the absolute stereochemistry at C-3 while readily available 2-amino-4-methylbenzophenone (**6a**) again would complete the required carbon skeleton of **1a**. In the event, a serine-based route was not reduced to practice but diethyl 3-phosphono-2-(methoxyimino)propionic acid (**8**) served as an amino acid surrogate. This provided a short, convergent process to 3-aminobenzazepin-2-one **7a** via an acylation, intramolecular Wadsworth−Horner−Emmons reaction and a stereoselective cis hydrogenation.

The ethyl ester of **8**, triethyl 3-phosphono-2-(methoxyimino)propionate, had been introduced by Elder for the synthesis of vinylglycines.[8] The hydrolysis of triethyl 3-phosphono-2-(methoxyimino)propionate with potassium hydroxide in aqueous ethanol provided acid **8** in 90% yield as a low-melting solid. 2-Amino-4-methylbenzophenone (**6a**), available from Aldrich Chemical Company, was coupled with **8** in methylene chloride with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride in 41% yield (Scheme 3).[9] The low reactivity of *o*-aminobenzophenones was well-known, and the modest yield for the acylation step was not optimized.[10] The yields listed in Table 1 for the acylation were done with the water-soluble carbodiimide. However, in one experiment, the acid chloride of **8** was prepared in situ with oxalyl chloride in methylene chloride and afforded a 70% yield of **9a**. This was not developed further when it was decided not to scale up the synthesis of **1a**. The phosphonate amides **9a**−**f** were crystalline compounds in each of the substrates examined and could be purified by recrystallization. While the Wadsworth−Horner−Emmons reaction has been used often for ring formation,[11] few examples with secondary amides were known. The primary example was that of Stork for the formation of five- and six-membered lactams.[12] Treatment of **9a** with 2 equiv of potassium *tert*-butoxide in tetrahydrofuran and refluxing the resulting solution for 30 min caused formation

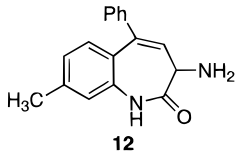
Scheme 3



a) R_1 = phenyl, R_2 = methyl
b) R_1 = cyclohexyl, R_2 = methyl
c) R_1 = cyclohexyl, R_2 = H
d) R_1 = methyl, R_2 = H
e) R_1 = methyl, R_2 = 4,5-dimethoxy
f) R_1, R_2 = fluorenyl

of oxime lactam **10a** in 90% yield. The crystalline product **10a** was shown by single-crystal X-ray analysis to consist of a single oxime isomer with the methoxy group anti to the lactam carbonyl while the NMR spectrum had only one methoxy resonance.

The next step was the hydrogenation of both the oxime ether and the olefin in **10a**. The catalyst chosen for this reaction was Raney nickel (RaNi). The reduction with RaNi in methanol at 50 psi caused the complete reduction of **10a** to provide **7a** in 88% yield as essentially one isomer. By NMR, only the cis isomer shown was observed in the crude product. However, after formation of the urea **11a**, the NMR of the filtrate showed weak signals for the trans isomer (<3% of total). While detailed study of the mechanism of this selective hydrogenation has not been done, examining reaction mixtures before the reduction was complete showed 3-amino-4,5-dehydrobenzazepin-2-one **12** as the only observable intermediate. An authentic sample of this material was available from hydrolysis of the corresponding *N*-benzamide of this compound from our earlier work.[7] This indicated that the amino group was directing the addition of hydrogen to the double bond.



With *rac*-**7a** in hand, a resolution with (+)-dibenzoyltartaric acid provided the desired enantiomer for **1a** in 40% yield. Since **1a** had not been isolated in crystalline form, its absolute configuration had been assigned on the basis of its biological activity. A single-crystal X-ray structure of the resolved salt of **7a** determined it to be the 3*R*,5*R* enantiomer, thus confirming the earlier assignment (Figure 1).[13]

(8) Bicknell, A. J.; Burton, G.; Elder, J. S. *Tetrahedron Lett.* **1988**, *29*, 3361.
(9) While compounds **7**, **11**, and **1** are drawn as one enantiomer, only the intermediates for **1a** were prepared in optically active form in this work; the other compounds were racemates.
(10) Ellman, J. A.; Bunin, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997.
(11) Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.
(12) Stork, G.; Matthews, R. *J. Chem. Soc., Chem. Commun.*, **1970**, 445.

Table 1. **Yields (%) for compounds listed in Scheme 3**

	a	b	c	d	e	f
9	41	52	66	41	75	39
10	87	52	53	52	52	61
7	88	79	86		73	80
11	89	62	91		82	67
1	71		59			

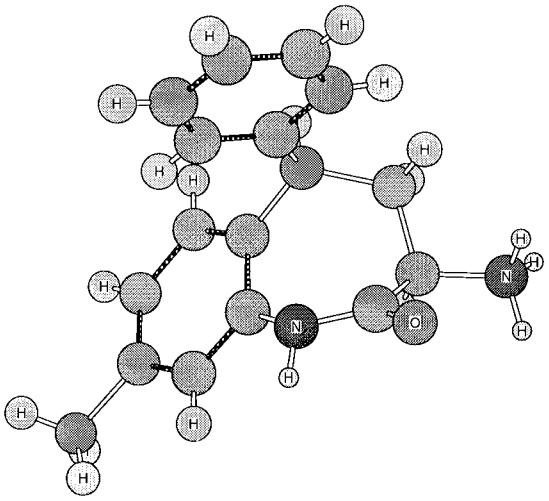


Figure 1. **Single-crystal X-ray structure of (*R*)-7a.**

To complete the synthesis of **1a**, amino lactam (*R*)-**7a** was treated with 3-chlorophenyl isocyanate in 1,2-dichloroethane at room temperature. The desired urea (*R*)-**11a** precipitated directly from the reaction mixture and was isolated by filtration in 89% yield. The final step involved attachment of the N-1 side chain. The conditions of Watthey were used.[14] The urea (*R*)-**11a** was treated with *N-tert*-butyliodoacetamide and powdered potassium hydroxide in tetrahydrofuran in the presence of catalytic tetrabutylammonium bromide at room temperature to provide (*R*)-**1a** in 71% yield after chromatography. The chromatography was required to remove a small amount of bis-alkylated material (<5%). There was no indication of any trans isomer under these conditions.

After completion of this six-step process from **6a** to (*R*)-**1a** with all crystalline intermediates, compared with 20 steps for the original synthesis and multiple chromatographic purifications, the scope of the process was probed. Starting with either commercially available 1-amino-9-fluorenone, 2-aminoacetophenones, or (2-aminophenyl)cyclohexyl-methanones, which were readily prepared from 2-aminobenzonitriles and cyclohexylmagnesium chloride,[15] the process was found to provide the fluorenyl derivative as well as both 5-methyl- and 5-cyclohexyl-3-aminobenzazepin-2-ones in good yields (Table 1). In each case, only traces of *trans*-3-amino-5-(alkyl or aryl)benzazepin-2-ones were observed in the key hydrogenation step. Compound **7c** was taken through to **1c**, while **7b**, **7e**, and **7f** were elaborated to **11b**, **11e**, and **11f**, respectively.

In conclusion, a short, efficient process to a variety of 3-amino-5-(aryl or alkyl)benzazepin-2-ones has been described. Since compound **1a** did not enter full development, the process has not been optimized further for large-scale work. The easy access to the structures provided by this work should facilitate further study of these benzazepine derivatives as receptor antagonists.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer in deuteriochloroform or dimethyl sulfoxide-d_6. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Diethyl 3-Phosphono-2-(methoxyimino)propionic Acid (8). Triethyl 3-phosphono-2-(methoxyimino)propionate[8] (11.6 g, 41 mmol) was dissolved in ethanol (30 mL) and treated with 1 N NaOH (45 mL, 45 mmol). After being stirred at room temperature for 5 h, the reaction mixture was extracted twice with ether, then acidified with 1 N HCl (50 mL), and extracted three times with methylene chloride. The methylene chloride layers were combined, washed with brine, and dried over sodium sulfate. Filtration of the drying agent and evaporation in vacuo provided the acid as an oil, which crystallized upon refrigeration. This was used without further purification: 9.4 g, 90%; mp 37−40 °C; IR (KBr) ν 1716, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1, CO_2H), 4.20−4.05 (m, 7), 3.34 (d, 2, J = 24 Hz), 1.30 (t, 6); ^{13}C NMR ($CDCl_3$) δ 163.4, 143.5, 143.3, 63.6, 63.0, 62.9, 24.7, 22.9, 16.2, 16.1; mass spectrum, *m/z* 254 (M + 1).

Diethyl 2-[3-Phosphono-2-(methoxyimino)propionamido]-4-methylbenzophenone (9a). Propionic acid **8** (1.7 g, 7.17 mmol), 2-amino-4-methylbenzophenone (**6a**) (1 g, 5 mmol), and 1-[3-(dimethylamino)propyl]- 3-ethylcarbodiimide hydrochloride (1.5g, 7.8 mmol) were refluxed in methylene chloride (20 mL) for 8 h. The reaction mixture was washed with water, 2 N HCl, aqueous sodium bicarbonate, and brine. The solution was dried over magnesium sulfate and evaporated in vacuo to an oil. This was purified by column chromatography over silica gel with 5% ethyl acetate in chloroform to remove unreacted benzophenone. The product was isolated as a crystalline solid: 0.91 g, 41%; mp 115−8 °C; IR (KBr) ν 1687, 1640, 1611, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.97 (s, 1), 8.59 (s, 1), 7.70−7.42 (m, 6), 6.90 (d, 1), 4.19 (s, 3), 4.13 (q, 4), 3.40 (d, 2, J = 24 Hz), 2.42 (s, 3), 1.32 (t, 6); ^{13}C NMR ($CDCl_3$) δ 198.9, 160.8, 145.5, 139.9, 139.2, 133.9, 132.0, 129.6, 128.2, 123.2, 121.6, 121.4, 63.7, 62.4, 62.3, 23.6, 22.1, 21.8, 16.3, 16.2; mass spectrum, *m/z* 446 (M^+).

Anal. Calcd for $C_{22}H_{27}N_2O_6P$: C, 59.18; H, 6.09; N, 6.27. Found: C, 59.11; H, 6.17; N, 6.53.

Under similar conditions, the following phosphonate amides were prepared from the readily available 2-aminophenyl ketones.

(13) The structure of compound **7a** was drawn in CSC Chem3D Plus with the experimentally determined X-ray coordinates. The molecule of (+)-dibenzoyltartaric acid was deleted for clarity. The X-ray data for compound **7a** has been submitted to the Cambridge Crystallographic Centre.

(14) Watthey, W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511.

(15) Chambers, M. S.; Hobbs, S. C.; Fletcher, S. R.; Matassa, V. G.; Mitchell, P. J.; Watt, A. P.; Baker, R.; Freedman, S. B.; Patel, S.; Smith, A. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1919.

{2-[[2-(Cyclohexylcarbonyl)-5-methylphenyl]carbamoyl]-2-(methoxyimino)ethyl}phosphonic acid diethyl ester (9b): R_1 = cyclohexyl; R_2 = methyl; 3.14 g, 52% yield; mp 64−6 °C; IR (KBr) ν 1680, 1643, 1612, 1570, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.66 (s, 1), 8.63 (d, 1), 7.80 (d, 1), 6.93 (d, 1), 4.20 (s, 3), 4.12 (q, 4), 3.39 (d, 2), 3.28 (m, 1), 2.38 (s, 3), 1.90−1.19 (m with t at 1.27, 16); ^{13}C NMR ($CDCl_3$) δ 207.0, 161.0, 146.0, 145.8, 145.5, 140.4, 130.5, 123.5, 121.5, 119.6, 63.6, 62.3, 62.2, 61.0, 46.5, 29.7, 25.9, 25.8, 23.6, 22.1, 21.8, 16.3, 16.2.

Anal. Calcd for $C_{22}H_{33}N_2O_6P$: C, 58.40; H, 7.35; N, 6.19. Found: C, 58.44; H, 7.46; N, 6.24.

{2-[[2-(Cyclohexylcarbonyl)phenyl]carbamoyl]-2-(methoxyimino)ethyl}phosphonic acid diethyl ester (9c): R_1 = cyclohexyl; R_2 = H; 5.65 g, 66% yield; mp 96−8 °C; IR (KBr) ν 1682, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.56 (s, 1), 8.77 (d, 1), 7.92 (d, 1), 7.54 (t, 1), 7.15 (t, 1), 4.22 (s, 3), 4.14 (m, 4), 3.40 (d, 2), 3.30 (m, 1), 1.92−1.20 (m, 16); ^{13}C NMR ($CDCl_3$) δ 207.4, 161.0, 145.9, 145.8, 140.2, 134.2, 130.4, 122.6, 122.1, 121.2, 63.6, 62.4, 62.3, 60.9, 46.7, 29.7, 25.9, 25.8, 23.5, 21.7, 16.3, 16.2.

Anal. Calcd for $C_{21}H_{31}N_2O_6P$: C, 57.53; H, 7.13; N, 6.39. Found: C, 57.60; H, 7.37; N, 6.31.

Diethyl 2-[3-phosphono-2-(methoxyimino)propionamido]-acetophenone (9d): R_1 = methyl; R_2 = H; 1.5 g, 41% yield; ^1H NMR ($CDCl_3$) δ 12.62 (s, 1), 8.79 (d, 1), 7.89 (d, 1), 7.55 (t, 1), 7.11 (t, 1), 4.19 (s, 3), 4.10 (m, 4), 3.40 (d, 2, J = 25 Hz), 2.66 (s, 3), 1.27 (t, 6).

Diethyl 2-[3-phosphono-2-(methoxyimino)propionamido]-4,5-dimethoxyacetophenone (9e): R_1 = methyl; R_2 = 4,5-dimethoxy; 4.62 g, 75% yield; mp 103−4 °C. IR (KBr) ν 1675, 1646, 1609, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.88 (s, 1), 8.56 (s, 1), 7.29 (s, 1), 4.20 (s, 3), 4.20 (q, 4), 3.99 (s, 3), 3.90 (s, 3), 3.40 (d, 2), 2.61 (s, 3), 1.28 (t, 6); ^{13}C NMR ($CDCl_3$) δ 161.0, 154.3, 145.9, 145.8, 143.7, 136.7, 115.1, 113.7, 103.6, 63.6, 62.4, 62.3, 56.3, 56.2, 28.4, 23.6, 21.8, 16.3, 16.2.

Anal. Calcd for $C_{18}H_{27}N_2O_8P$: C, 50.23; H, 6.32; N, 6.51. Found: C, 50.36; H, 6.37; N, 6.73.

Diethyl 1-[3-phosphono-2-(methoxyimino)propionamido]fluorenone (9f): 1.68 g, 39% yield; mp 104−7 °C; IR (KBr) ν 1695, 1653, 1614, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.25 (s, 1), 8.41 (d, 1), 7.62 (d, 1) 7.51−7.41 (m, 3), 7.28 (dt, 1), 7.20 (d, 1), 4.24 (s, 3), 4.11 (m, 4), 3.40 (d, 2, J = 25 Hz), 1.29 (t, 6); ^{13}C NMR ($CDCl_3$) δ 160.7, 145.4, 145.2, 144.1, 143.7, 138.3, 136.6, 134.6, 134.0, 129.2, 124.0, 120.6, 120.2, 118.8, 115.4, 63.8, 62.4, 62.3, 23.4, 21.6, 16.3, 16.2.

Anal. Calcd for $C_{21}H_{23}N_2O_6P \cdot 0.25H_2O$: C, 58.00; H, 5.45; N, 6.44. Found: C, 57.93; H, 5.33; N, 6.45.

8-Methyl-5-phenyl-1*H*-benz[*b*]azepine-2,3-dione 3-(*O*-Methyloxime) (10a). Phosphono amide **9a** (17.6 g, 39.5 mmol) was dissolved in tetrahydrofuran (160 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was cooled with ice water to 4 °C and potassium *tert*-butoxide (9.32 g, 79 mmol) was added in one portion. The cooling bath was removed, and the reaction mixture was heated to reflux for 0.5 h. The cooled reaction mixture was diluted with ethyl acetate (100 mL) and washed with water and brine. After drying over magnesium sulfate, the solvent was evaporated in vacuo to afford a solid, which was crystallized from 2-propanol: 10 g, 87% yield; mp 234−7 °C; IR (KBr) ν 1676, 1615, 1574, 1552, 1545, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.71 (s, 1 NH), 7.38 (bs, 5), 7.05 (s, 1), 6.96 (d, 1, J = 8.1 Hz), 6.84 (d, 1, J = 8.1 Hz), 6.67 (s, 1, vinyl), 4.13 (s, 3, $NOCH_3$), 2.35 (s, 3); ^{13}C NMR ($CDCl_3$) δ 167.5, 149.1, 144.7, 141.7, 140.3, 135.0, 131.5, 129.1, 128.5, 128.4, 126.1, 125.1, 122.3, 118.7, 63.6, 21.1.

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.22; H, 5.69; N, 9.52. The structure was confirmed by single-crystal X-ray analysis.

Under similar conditions, the following benzazepinone oximes were prepared from the phosphono amides described above.

5-Cyclohexyl-8-methyl-1*H*-benz[*b*]azepine-2,3-dione 3-(*O*-methyloxime) (10b): R_1 = cyclohexyl; R_2 = methyl; 0.41 g, 52% yield; mp 222−226 °C; IR (KBr) ν 1679, 1631, 1617, 1563 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.53 (s, 1), 7.49 (d, 1), 6.99 (m, 2), 6.34 (s, 1), 4.02 (s, 3), 2.66 (t, 1), 2.33 (s, 3), 1.91−1.69 (m, 5), 1.44−1.12 (m, 5); ^{13}C NMR ($CDCl_3$) δ 168.4, 149.8, 148.8, 139.3, 134.3, 127.1, 125.6, 122.7, 116.0, 89.0, 63.4, 43.0, 33.2, 26.8, 26.2, 20.9; mass spectrum, *m/z* 298 (M^+), 267 (M^+ − OMe).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.42; H, 7.51; N, 9.45.

5-Cyclohexyl-1*H*-benz[*b*]azepine-2,3-dione 3-(*O*-methyloxime) (10c): R_1 = cyclohexyl; R_2 = H; 1.7 g, 53% yield; mp 192−200 °C; IR (KBr) ν 1675, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.50 (s, 1), 7.50 (d, 1), 7.39 (t, 1), 7.29 (m, 2), 6.40 (s, 1), 4.04 (s, 3), 2.69 (bt, 1), 1.95−1.70 (m, 5), 1.47−1.18 (m, 5); ^{13}C NMR ($CDCl_3$) δ 168.6, 149.6, 148.8, 134.5, 129.9, 129.0, 127.1, 124.6, 122.6, 116.8, 63.42, 43.1, 33.2, 26.7, 26.2; mass spectrum, *m/z* 285 (M + 1).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.80; H, 7.37; N, 9.96.

5-Methyl-1*H*-benz[*b*]azepine-2,3-dione 3-(*O*-methyloxime) (10d): R_1 = methyl; R_2 = H; 0.45 g, 52% yield; mp 190−3 °C; IR (KBr) ν 1669, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.61 (s, 1), 7.48 (d, 1), 7.33−7.13 (m, 3), 6.54 (s, 1), 4.06 (s, 3), 2.35 (s, 3); ^{13}C NMR ($CDCl_3$) δ 167.3, 148.7, 139.5, 134.2, 129.6, 129.0, 127.8, 124.4, 122.3, 118.7, 63.5, 23.8; mass spectrum, *m/z* 217 (M + 1).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.71; H, 5.72; N, 13.05.

5-Methyl-7,8-dimethoxy-1*H*-benz[*b*]azepine-2,3-dione 3-(*O*-methyloxime) (10e): R_1 = methyl; R_2 = 4,5-dimethoxy; 1.68 g, 52% yield; mp 233−5 °C; IR (KBr) ν 1659, 1627, 1615, 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.80 (s, 1), 6.88 (s, 1), 6.73 (s, 1), 6.41 (s, 1), 4.00 (s, 3), 3.90 (s, 3), 3.85 (s, 3), 2.31 (s, 3); ^{13}C NMR ($CDCl_3$) δ 166.9, 149.9, 148.8, 145.6, 139.1, 128.5, 121.5, 117.1, 110.0, 105.2, 63.3, 56.2, 56.1, 23.9.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.84; N, 10.14. Found: C, 61.07; H, 5.91; N, 10.34.

4*H*-Fluorene[1,9-*bc*]azepine-5,6-dione 6-(*O*-methyloxime) (10f): 0.59 g, 61% yield; mp 254−61 °C. IR (KBr) ν 1681, 1667, 1637, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.75 (s, 1), 7.70 (d, 1), 7.75 (s, 1), 7.69 (d, 1), 7.46−7.31 (m, 4), 6.82 (d, 1), 4.28 (s, 3); ^{13}C NMR ($CDCl_3$) δ 160.7, 149.1, 140.9, 140.0, 139.3, 137.4, 134.8, 132.3, 130.6, 128.4, 122.4, 122.2, 121.2, 118.1, 115.7, 110.0, 63.8.

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.05; H, 4.51; N, 10.40.

***cis*-3-Amino-8-methyl-5-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one (*rac*-7a).** Raney nickel (Aldrich, 40 g of aqueous slurry) was washed once with water and three times with methanol; each time the excess solvent was drawn off by syringe under nitrogen. Benzazepine-2,3-dione **10a** (10 g, 34 mmol) was added as a slurry in methanol with the final volume being ca. 600 mL. This was shaken at 50 psi of hydrogen pressure for 24 h. TLC of an aliquot showed that the reduction was complete at this point. The hazy solution was filtered through Celite twice to give a clear solution, which was evaporated in vacuo to provide the amine as a white solid: 8 g, 88% yield; mp 212−15 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1), 7.80−7.05 (m, 6), 6.96 (d, 1), 6.71 (s, 1), 4.30 (q, 1), 3.61 (q, 1), 2.82 (m, 1), 2.50 (m, 1), 2.32 (s, 3), 1.70 (bs, 2, NH_2).

(+)-*cis*-3(*R*)-Amino-8-methyl-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one (+)-Dibenzoyltartrate [(*R*)-7a (+)-Dibenzoyltartrate]. *cis*-3-Amino-5-phenylbenzazepin-2-one *rac*-**7a** (7.81 g, 29 mmol) and D-(+)-dibenzoyltartaric acid (10.5 g, 29.3 mmol) were combined in acetone (300 mL) and stirred at room temperature. This initially gave a clear solution followed by crystallization. After stirring for 4 h, the solids were collected, washed with acetone, and dried in vacuo at 40 °C; 7.89 g. This initial salt (6.74 g) was dissolved in methanol (75 mL) with heating to give a clear solution. Ethyl acetate (205 mL) was added to the hot solution over 5 min. This caused crystallization. The slurry was heated with distillation of the solvent at atmospheric pressure while additional ethyl acetate was introduced to maintain the original volume until a total of 280 mL of distillate was collected. The slurry was allowed to cool to room temperature over 1 h, and the solids were collected and washed with ethyl acetate. The yield of the recrystallization was 6.2 g, 92%, or 40% for the overall resolution. The material was a white solid: mp 193−4 °C dec; $[\alpha]_D$ 180.6° (c = 0.205, MeOH).

Anal. Calcd for $C_{35}H_{32}N_2O_9$: C, 67.30; H, 5.16; N, 4.48. Found: C, 67.64; H, 4.96; N, 4.43.

The structure and absolute stereochemistry were confirmed by single-crystal X-ray analysis.

(+)-*cis*-3(*R*)-Amino-8-methyl-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one [(*R*)-7a]. The dibenzoyltartrate salt (6.98 g, 11.2 mmol) was dissolved in a mixture of 0.5 N NaOH (70 mL) and methylene chloride (50 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (30 mL). The organic layers were combined, washed with water, and dried over magnesium sulfate. This was filtered and concentrated in vacuo to ca. 25 mL, and hexanes (50 mL) were added slowly. This process was repeated with more hexanes, and the product was collected and dried in vacuo: 2.9 g, 98% yield; mp 177−80 °C dec; $[\alpha]_D$ 259.5° (c = 0.264, MeOH); ^{1}H NMR ($CDCl_3$) same as racemic amine; ^{13}C NMR ($CDCl_3$) δ 177.0, 143.5, 138.0, 135.8, 133.1, 131.6, 128.3, 127.2, 126.6, 126.2, 123.7, 61.1, 51.3, 45.8, 42.0, 20.9.

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.70; H, 7.02; N, 10.61.

Under hydrogenation conditions similar to those described above, the following benzazepinone oximes were reduced to the *cis*-3-amino-5-substituted-benzazepin-2-ones.

***cis*-3-Amino-8-methyl-5-cyclohexyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one (7b):** R_1 = cyclohexyl; R_2 = methyl; 0.22 g, 79% yield; ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1), 6.99 (d, 1), 6.90 (d, 1), 6.75 (s, 1), 3.50 (q, 1), 2.61−2.42 (m, 2), 2.30 (s, 3), 1.98 (m, 2), 1.78−1.45 (m, 6), 1.26−0.73 (m, 5), 0.51 (m, 1).

***cis*-3-Amino-5-cyclohexyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one (7c):** R_1 = cyclohexyl; R_2 = H; 0.78 g, 86% yield; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1), 7.27−7.18 (m, 1), 7.10 (d, 2), 6.92 (d, 1), 3.50 (q, 1), 2.63−2.49 (m, 2), 2.01 (m, 2), 1.78−1.47 (m, 6), 1.30−0.78 (m, 5), 0.55 (m, 1).

***cis*-3-Amino-7,8-dimethoxy-5-methyl-1,3,4,5-tetrahydrobenz[*b*]azepin-2-one (7e):** R_1 = methyl; R_2 4,5-dimethoxy; 0.33 g, 73% yield; ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1), 6.69 (s, 1), 6.50 (s, 1), 3.88 (s, 3), 3.84 (s, 3), 3.49 (q, 1), 3.00 (m, 1), 2.74 (m, 1), 1.71 (dt, 1), 1.60 (bs, 2), 1.30 (d, 3).

***cis*-6-Amino-7,7a-dihydro-4*H*-fluoreno[1,9-*bc*]azepin-5(6*H*)-one (7f):** 0.29 g, 80% yield; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1), 7.75 (d, 1), 7.60 (d, 1), 7.49−7.30 (m, 4), 6.93 (d, 1), 4.10 (t, 1), 3.61 (q, 1), 2.71 (q, 1), 2.40 (m, 1), 1.70 (bs, 2).

(+)-3(*R*)-[3-(3-Chlorophenyl)ureido]-8-methyl-2-oxo-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepine [(*R*)-11a]. Benzazepin-2-one (***R*)-7a** (2 g, 7.52 mmol) was suspended in 1,2-dichloroethane (40 mL) and stirred under nitrogen while 3-chlorophenyl isocyanate (1.2 g, 7.9 mmol) in 1,2-dichloroethane (10 mL) was added dropwise over 2 min. This gave initial solution and then a thick precipitate. The mixture was heated at a gentle reflux for 1 h, which gave a solution, which then was allowed to cool to room temperature. The precipitate was collected, washed with dichloroethane and then hexanes, and dried in vacuo: 2.82 g, 89% yield; mp 133−40 °C; $[\alpha_D]$ 49.6° (c = 0.42, MeOH); IR (KBr) ν 1669, 1619, 1593, 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$ with several drops of DMSO-d_6) δ 8.83 (s, 1), 8.48 (s, 1), 7.30 (s, 1), 6.90−6.71 (m, 8), 6.61 (d, 1), 6.54−6.38 (m, 3), 4.20 (q, 1), 4.03 (q, 1), 2.70 (m, 1), 2.15 (m, 1), 1.96 (s, 3); ^{13}C NMR (DMSO-d_6) δ 172.5, 154.6, 144.5, 142.3, 137.7, 137.0, 133.6, 133.1, 132.1, 130.7, 128.6, 127.5, 126.4, 126.3, 124.2, 121.3, 117.4, 116.4, 84.7, 56.1, 49.5, 44.8, 20.9.

Anal. Calcd for $C_{24}H_{22}N_3O_2Cl\cdot0.2H_2O$: C, 68.07; H, 5.33; N, 9.92. Found: C, 68.21; H, 5.16; N, 9.79.

Under conditions similar to those described above, the following *cis*-3-amino-5-substituted-1,3,4,5-tetrahydrobenzazepin-2-ones were reacted with 3-chlorophenyl isocyanate to provide the corresponding ureas.

3-[3-(3-Chlorophenyl)ureido]-8-methyl-2-oxo-5-cyclohexyl-1,3,4,5-tetrahydrobenz[*b*]azepine (11b): R_1 = cyclohexyl; R_2 = methyl; 0.193 g, 62% yield; mp 162−9 °C; IR (KBr) ν 1674, 1619, 1592, 1554, 1515 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.78 (s, 1), 8.96 (s, 1), 7.59 (s, 1), 7.20 (t, 1), 7.10 (d, 1), 7.04 (d, 1), 6.90 (d, 2), 6.76 (s, 1), 6.58 (d, 1), 4.19 (m, 1), 2.51 (m, 3), 2.27 (s, 3), 1.90 (m, 2), 1.71−1.43 (m, 4), 1.18−0.72 (m, 5), 0.48 (m, 1); ^{13}C NMR (DMSO-d_6) δ 172.9, 154.5, 142.2, 137.1, 136.9, 133.6, 133.1, 132.3, 130.7, 126.1, 123.8, 121.2, 117.3, 116.3, 49.3, 46.9,

45.5, 38.7, 31.9, 26.4, 26.2, 20.9; mass spectrum, *m/z* 426 (M + 1).

Anal. Calcd for $C_{24}H_{28}N_3O_2Cl \cdot 0.2\ ClCH_2CH_2Cl$: C, 65.75; H, 6.51; N, 9.43. Found: C, 65.67; H, 6.57; N, 9.55.

3-[3-(3-Chlorophenyl)ureido]-2-oxo-5-cyclohexyl-1,3,4,5-tetrahydrobenz[*b*]azepine (11c): R_1 = cyclohexyl; R_2 = H; 1.17 g, 91% yield; mp 222−5 °C; IR (KBr) ν 1694, 1651 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.88 (s, 1), 8.99 (s, 1), 7.60 (t, 1), 7.30−7.06 (m, 5), 6.98 (d, 1), 6.90 (d, 1), 6.60 (d, 1), 4.20 (m, 1), 2.58 (m, 2), 1.96 (m, 2), 1.76−1.43 (m, 4), 1.22−0.77 (m, 5), 0.53 (m, 1); ^{13}C NMR (DMSO -d_6) δ 172.8, 154.5, 142.2, 137.2, 136.2, 133.6, 132.4, 130.7, 127.9, 125.4, 123.3, 121.2, 117.3, 116.3, 56.4, 49.2, 47.4, 38.8, 31.9, 31.8, 26.4, 26.2; mass spectrum, *m/z* 412 (M + 1).

Anal. Calcd for $C_{23}H_{26}N_3O_2Cl$: C, 67.06; H, 6.36; N, 10.20. Found: C, 66.72; H, 6.36; N, 9.82.

3-[3-(3-Chlorophenyl)ureido]-7,8-dimethoxy-2-oxo-5-methyl-1,3,4,5-tetrahydrobenz[*b*]azepine (11e): R_1 = methyl; R_2 = 4,5-dimethoxy; 0.33 g, 82% yield; mp 208−10 °C; IR (KBr) ν 1725, 1707, 1696, 1676 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.68 (s, 1), 9.00 (s, 1), 7.60 (t, 1), 7.20 (t, 1), 7.10 (dd, 1), 6.91 (dd, 1), 6.85 (s, 1), 6.61 (s, 1), 6.55 (d, 1), 4.19 (m, 1), 3.78 (s, 3), 3.71 (s, 3), 3.04 (m, 1), 2.72 (m, 1), 1.63 (t, 1), 1.20 (d, 3); ^{13}C NMR (DMSO-d_6) δ 173.0, 154.4, 148.0, 146.4, 142.2, 133.6, 130.7, 130.0, 129.3, 121.2, 117.3, 116.3, 114.2, 108.3, 56.2, 56.0, 49.3, 43.5, 34.7, 22.5.

Anal. Calcd for $C_{20}H_{22}N_3O_4Cl \cdot 0.5\ CH_3CH(OH)CH_3$: C, 59.51; H, 6.04; N, 9.68. Found: C, 59.28; H, 6.25; N, 9.76.

6-[3-(3-Chlorophenyl)ureido]-7,7a-dihydro-4*H*-fluoreno-[1,9-*bc*]azepine-5(6*H*)-one (11f): 0.28 g, 67% yield; mp 221−5 °C; IR (KBr) ν 1663, 1617, 1593, 1552 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.29 (s, 1), 9.04 (s, 1), 7.90 (d, 1), 7.71 (d, 1), 7.56 (m, 2), 7.48−7.33 (m, 3), 7.20 (t, 1), 7.09 (d, 1), 6.99 (d, 1), 6.90 (d, 1), 6.76 (d, 1), 4.30−4.14 (m, 2), 2.80 (q, 1), 2.30 (m, 1).

Anal. Calcd for $C_{23}H_{18}N_3O_2Cl \cdot 0.5\ (H_2O)$: C, 66.91; H, 4.64; N, 10.18. Found: C, 66.80; H, 4.78; N, 9.99.

***N-tert*-Butyl-2-{3(*R*)-[3-(3-chlorophenyl)ureido]-8-methyl-2-oxo-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepin-1-yl}acetamide [(*R*)-1a].** (+)-3(*R*)-[3-(3-Chlorophenyl)-ureido]-8-methyl-2-oxo-5(*R*)-phenyl-1,3,4,5-tetrahydrobenz[*b*]azepine [(*R*)-**11a**] (2.5 g, 6 mmol), *N-tert*-butyliodoacetamide (1.72 g, 7.15 mmol), and tetrabutylammonium bromide (0.2 g, 0.6 mmol) were dissolved in dry tetrahydrofuran (50 mL) under a nitrogen atmosphere. Powder potassium hydroxide (0.45 g, 8 mmol) was added in one portion, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate (50 mL) and was washed with water and brine. After drying over magnesium sulfate, the solvent was removed in vacuo to provide a foam, which was purified by flash chromatography over silica gel with 1:1 ethyl acetate/hexanes. The fractions with the product spot were combined, and the material was crystallized from methanol and water to provide a white solid: 2.2 g, 71% yield; mp 156−170 °C; $[\alpha]_D$ 124.5° (c = 0.52, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.01 (s, 1), 7.60 (s, 1), 7.32 (d, 1), 7.24 (m, 2), 7.15 (m, 4), 7.02 (m, 2), 6.90 (d, 1), 6.83 (d, 1), 6.75 (bs, 1), 5.88 (s, 1), 4.63 (t, 1), 4.29 (d, 1), 3.88 (d, 1), 3.02 (d, 2), 2.89 (d, 1), 2.39 (s, 3), 1.32 (s, 9).

***cis-N-tert*-Butyl-2-{3-[3-(3-chlorophenyl)ureido]-2-oxo-5-cyclohexyl-1,3,4,5-tetrahydrobenz[*b*]azepin-1-yl}-acetamide (1c).** Following the previous experimental procedure, benzazepinone **11c** (0.4 g, 1 mmol) was alkylated with *N-tert*-butyliodoacetamide (0.28 g, 1.2 mmol) to provide the title compound as a white solid: 0.3 g, 59% yield; mp 222−5 °C (lit. mp 223−6 °C); ^1H NMR ($CDCl_3$) δ 8.03 (s, 1), 7.59 (t, 1), 7.34−7.15 (m, 3), 7.10 (d, 1),7.01 (t, 1), 6.91 (d, 1), 6.83 (d, 1), 6.43 (bd, 1), 6.31 (s, 1), 4.95 (d, 1), 4.54 (m, 1), 3.59 (d, 1), 2.66 (m, 1), 2.53 (t, 1), 2.18 (bd, 1), 1.78 (m, 1), 1.59 (m, 1), 1.4 (s, 9), 1.29−0.78 (m, 6), 0.58 (m, 1).

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