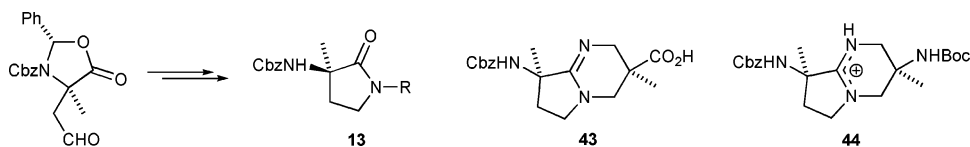# JOC*Article*

Preparation of Diazabicyclo[4.3.0]nonene-Based Peptidomimetics

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Several functionalized diazabicyclo[4.3.0]nonenes and other heterocycles have been prepared as potential peptidomimetic scaffolds. A novel and efficient method has been developed for the preparation of *N*-substituted γ-lactams **13**. Preparation of amidine-containing 1,5-diazabicyclo[4.3.0]nonenes **43** and **44** has been achieved through Hg-mediated cyclization of the precursor *N*-aminopropyl-γ-thiolactams and subsequent functional group manipulation. Bicycle **43** represents a novel scaffold for potential peptide turn mimetics, whereas **44** could potentially be employed as an α-helix template attached to the C-terminus of peptides. These compounds are novel additions to the current range of small-molecule constrained peptidomimetics.

Introduction

Functionalized monocyclic and bicyclic compounds are highly useful scaffolds in the rational design and synthesis of peptidomimetics.[1-5] These conformationally restricted heterocyclic frameworks have been used to generate mimics and templates of a variety of peptide secondary structural elements, particularly β-turns,[6-17] but also γ-turns,[18-20] β-strands,[21-26] and α-helices.[27-31] Such scaffolds have been employed to constrain the backbone geometry and/or side-chain conformations of appended peptides to investigate the structural basis of peptide–protein and protein–protein interactions and to develop potent

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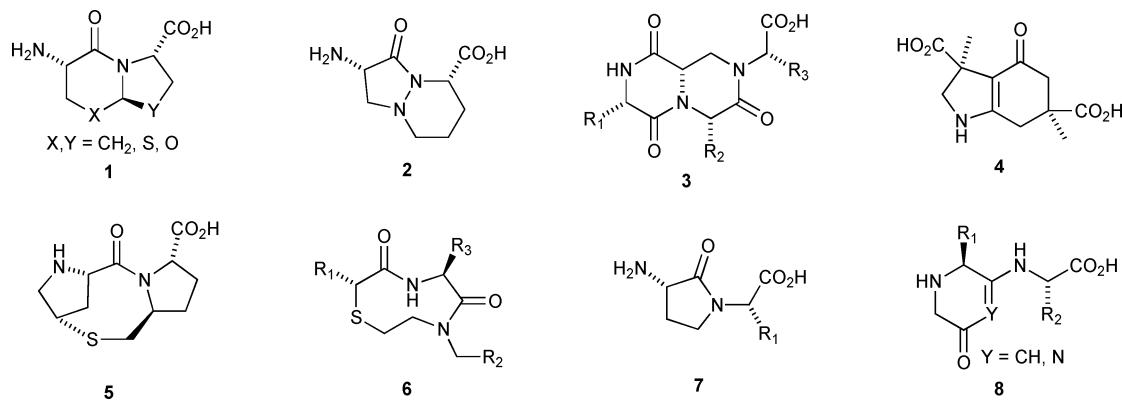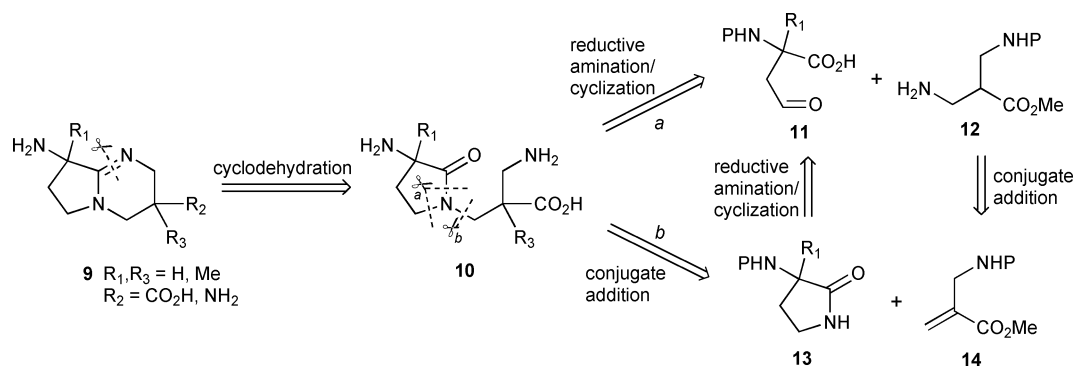
FIGURE 1. Cyclic small molecule peptidomimetic scaffolds.

SCHEME 1

and selective peptidomimetic therapeutic agents. Notable examples of constrained cyclic peptidomimetic scaffolds include the 6,5-fused azabicycloalkane–type β-turn mimetics, exemplified by the Nagai mimetic **1** (X = CH$_2$, Y = S),[32] 5,6-fused bicyclic hydrazones, e.g., **2**,[23,33] diketopiperazine β-turn mimetics **3**,[8,12,13,15] the aza[4.3.0]bicyclononene and diproline-based α-helix templates **4**[27] and **5**,[28,29] respectively, medium-ring β-turn mimetics, e.g., **6**,[3,9,10,17] γ-lactam-constrained dipeptide surrogates **7**,[1,34] and the β-strand templates **8**[21,22] (Figure 1).

We were interested in expanding the range of fused 5,6-bicyclic heterocycles available as peptidomimetic scaffolds. The diazabicyclo[4.3.0]nonene **9** represents such a novel peptidomimetic scaffold, in which incorporation of a carboxylate substituent (R$_2$ = CO$_2$H) affords a dipeptide surrogate that could act as a turn mimetic. Alternatively, incorporation of an amino substituent (R$_2$ = NH$_2$) affords a potential α-helix template related to the *N*-terminal α-helix template **4** developed by Bartlett.[27] Bicyclic amidine **9** (R$_2$ = NH$_2$), in the protonated state, has a geometry matching that of **4** but with the three

hydrogen-bond acceptor carbonyl groups replaced with donor N–H groups and represents a potential C-terminal α-helix template.

Results and Discussion

Retrosynthetic analysis of the bicyclic amidine **9** suggested that the bicycle could be formed by cyclodehydration of an *N*-(3-aminopropyl)-γ-lactam **10** (Scheme 1).[35] While Freidinger[1] has developed methods for the preparation of γ-lactam peptidomimetics, we envisaged a novel route to the γ-lactam **10** through reductive amination of an aspartate semialdehyde derivative **11** with amine **12**, followed by cyclization. Alternatively, **10** could be accessed by Michael-type addition of γ-lactam **13** to substituted acrylate **14**. With the γ-lactam **13** accessible from **11** through a similar reductive amination–cyclization process, and the amine **12** accessible from acrylate **14**, the required starting materials for this strategy are the aldehyde **11** and acrylate **14**. We chose to incorporate α-methyl substituents (**9**, R$_1$, R$_3$ = Me) for additional conformational constraint. Accordingly, our synthesis was initiated with oxazolidinone **16**, prepared via condensation of Cbz-L-alanine **15** with benzaldehyde dimethyl acetal according to Shrader's modification[36] of the procedure of Karady et al.[37] Alkylation of the oxazolidinone **16** was achieved in 91% yield by treatment with lithium hexamethyldisilazide followed by addition of allyl iodide (Scheme 2). Only the (2*S*,4*S*)-isomer was detected by ^{1}H NMR

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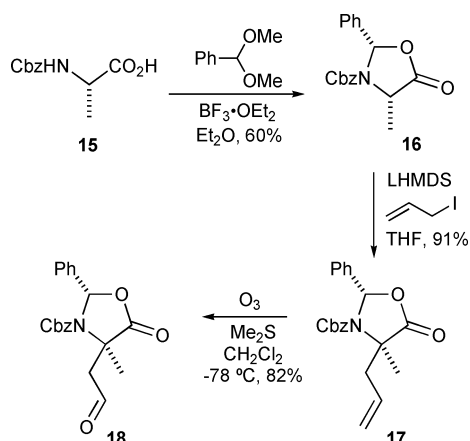
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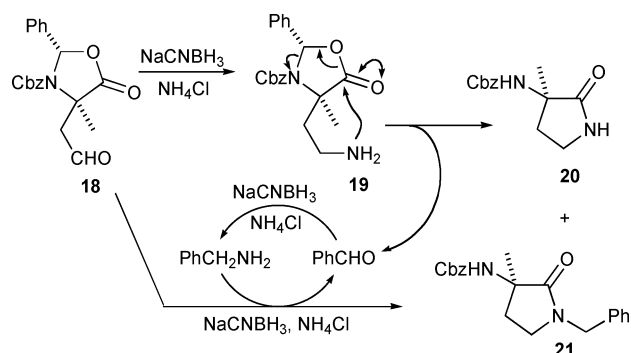(35) Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, *11*, 591–598.

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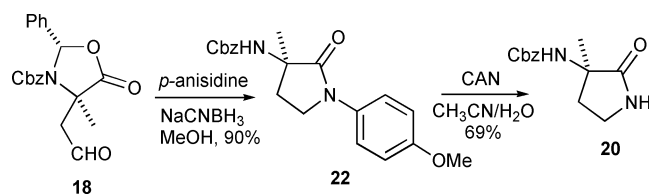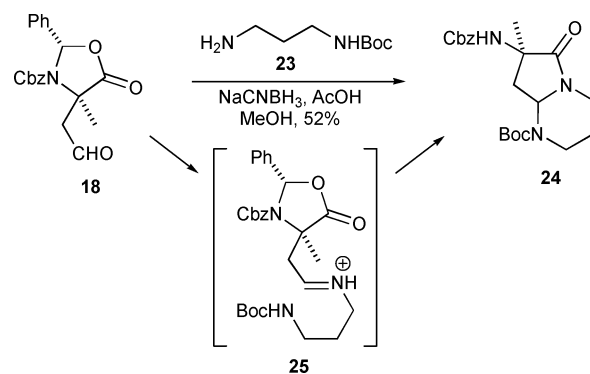
SCHEME 2

SCHEME 3

SCHEME 4

spectroscopy, indicating that the reaction had proceeded to give the allyloxazolidinone **17** in >95:5 diastereomeric ratio. Ozonolysis of the allyloxazolidinone **17** gave the requisite aldehyde **18** in 82% yield (Scheme 2).

A. Preparation of γ-Lactam. A reductive amination/cyclization strategy from **18** was investigated as a route to γ-lactam scaffolds. Treatment of the aldehyde **18** with ammonium chloride and sodium cyanoborohydride gave the γ-lactam **20** directly, presumably via cyclization of intermediate amine **19** with concomitant release of benzaldehyde (Scheme 3). However, the γ-lactam **20** was produced in low yield, with the *N*-benzyl lactam **21** isolated as the major product. The *N*-benzyl lactam **21** presumably forms by reductive amination of the benzaldehyde byproduct generating benzylamine, which then undergoes reductive amination/cyclization with aldehyde **18**. An efficient preparation of the lactam **20** was ultimately achieved using *p*-anisidine as the amine partner in the reductive amination of **18**. Under these conditions, PMP-lactam **22** was produced in 90% yield, which upon treatment with ceric ammonium nitrate gave γ-lactam **20** in good yield (Scheme 4).
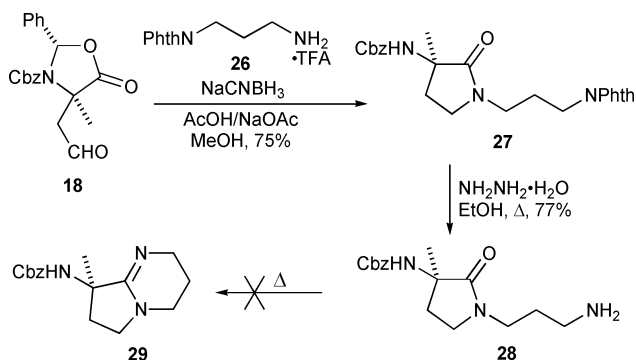
B. Synthesis of Diazabicyclo[4.3.0]nonene Ring System. Extension of the reductive amination/cyclization methodology was then investigated using functionalized diamines as a route
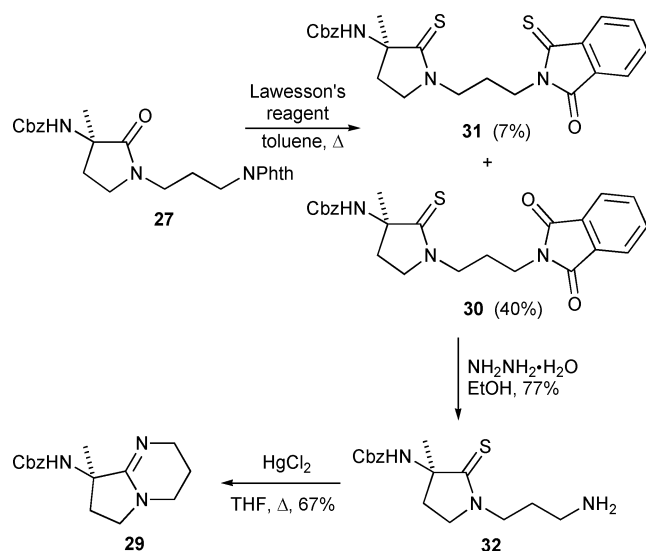
SCHEME 5

SCHEME 6

toward the diazabicyclo[4.3.0]nonene ring system. Treatment of the aldehyde **18** with Boc-diaminopropane **23** under reductive amination conditions gave the bicyclic compound **24** in 52% yield as a 1:1 ratio of diastereomers (Scheme 5). Formation of the bicyclic compound **24** presumably occurs via the initially formed iminium species **25**, with two cyclization events and elimination of benzaldehyde yielding the bicyclic product **24**.

It was anticipated that replacement of Boc-protected diamine **23** with the corresponding phthaloyl-protected compound **26** would prevent intramolecular attack of the intermediate iminium species, thereby preventing formation of the bicyclic compound. Accordingly, treatment of the aldehyde **18** with 1.5 equiv of the phthaloyl-protected diaminopropane **26** in the presence of sodium cyanoborohydride gave the phthalimidopropyl-γ-lactam **27** in 75% yield (Scheme 6). A slight excess of amine **26** is required for optimum yields of **27**, as some of the amine undergoes reductive amination with the benzaldehyde byproduct formed concurrently with production of the γ-lactam **27**.

Removal of the phthaloyl group from **27** was effected by treatment with hydrazine hydrate in ethanol to generate the amine **28**. Subsequent attempts to cyclodehydrate the aminopropyl-γ-lactam **28** to the bicyclic amidine **29**, including refluxing in high boiling point solvents with catalytic acid and via the corresponding *O*-silyl- and *O*-alkylimidates, were unsuccessful.[35] Accordingly, γ-lactam **27** was converted to the corresponding thiolactam **30** by treatment with Lawesson's reagent.[38] The phthalimidopropyl thiolactam **30** was isolated in moderate yield, together with varying amounts of a byproduct, presumed to be the dithio compound **31** (Scheme 7). Various conditions were employed in an attempt to improve the yield of the thiolactam **30**; however, variation of the amount of

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SCHEME 7

SCHEME 8
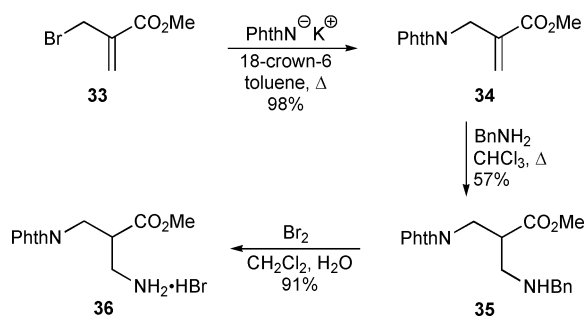
Lawesson's reagent and the reaction time did not result in significant improvements in the yield of **30** (optimum 40%, with 20% unreacted starting material). Treatment of the thiolactam **30** with hydrazine hydrate gave the free amine **32** in 77% yield. The amine was then treated with mercuric chloride in THF[34,39] to give the bicyclic amidine **29** in 67% yield. The amidine **29** was found to be unstable as its free base and was therefore purified and stored as its trifluoroacetate salt.

C. Synthesis of Functionalized Diazabicyclo[4.3.0]nonene Ring System. With a method for preparing the alanine-derived diazabicyclo[4.3.0]nonene derivative **29** in hand, preparation of the carboxylate-functionalized bicycle **41** via the corresponding carboxylate-functionalized phthalimidopropyl-γ-lactam **37** was investigated. Initial attempts to prepare **37** by Michael-type addition of γ-lactam **20** to phthalimidomethacrylate **34** were unsuccessful. Hence, the reductive amination−cyclization route was followed as for the preparation of amidine **29**, which necessitated preparation of amine **36**. Phthalimidomethylacrylate **34** was prepared from the corresponding bromide **33** and then treated with 1 equiv of benzylamine to give the amine **35** in 57% yield (76% based on recovered starting material) (Scheme 8). Use of excess benzylamine in attempts to increase the yield of the amine **35** only resulted in the formation of increasing amounts of *N*-benzylphthalimide, presumably via transimidation of either the acrylate **34** or the amine **35** with excess benzylamine.

Removal of the benzyl group from the amine **35** was initially attempted by hydrogenation in the presence of Pearlman's

SCHEME 9
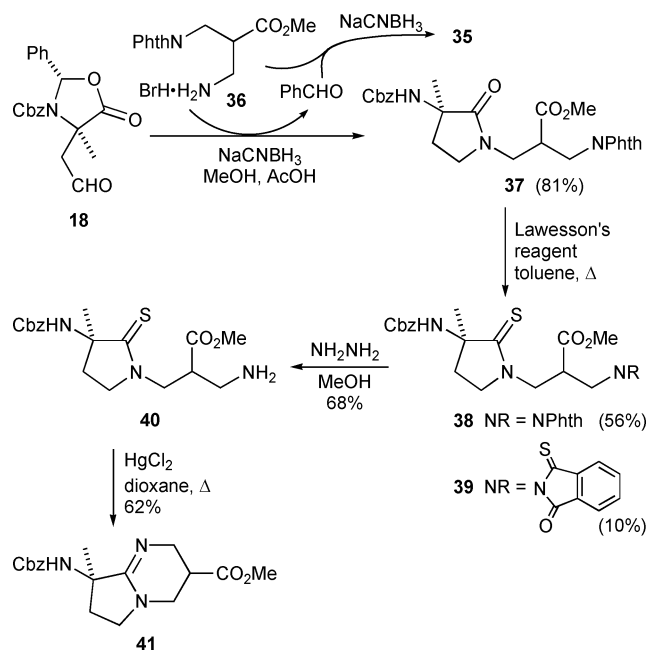
catalyst; however, the procedure was not reproducible and normally resulted in the recovery of the benzyl-protected amine **35**. Alternative debenzylation conditions were therefore investigated, and ultimately treatment of the *N*-benzylamine **35** with *N*-bromosuccinimide (NBS) or bromine in methylene chloride/water was found to give the amine as its hydrobromide salt **36**, in high yield (Scheme 8).[40] While *N*-debenzylation under these conditions has been employed sporadically, the use of this procedure is most common with *N*-benzylamides,[41,42] with the *N*-debenzylation of amines[40,43]—particularly secondary amines[44]—being rare. The use of NBS and bromine were equally effective, with the use of bromine being the method of choice on large scale as removal of the succinimide byproduct is avoided.

Synthesis of the bicyclic amidine **41** then followed the protocol outlined in Scheme 7 for the synthesis of the model compound **29**. Reductive amination of the aldehyde **18** with the amine hydrobromide salt **36** gave the γ-lactam **37** in 71% yield, as a 1:1 ratio of diastereomers. The diastereomers were separable by chromatography and independently characterized, but in subsequent reactions a 1:1 mixture of the diastereomers of **37** was employed. As with the conversion of aldehyde **18** and amine **26** to give γ-lactam **27** (Scheme 6), conversion of **18** and amine **36** to give γ-lactam **37** required an excess of the amine due to the competing reductive amination with the benzaldehyde byproduct (Scheme 9). It should be noted, however, that in this case this secondary reductive amination process converts excess amine **36** into its corresponding *N*-benzyl derivative **35**, which is the immediate precursor of the amine **36**. The use of 1.5 equiv of amine **36** in the reductive amination of **18** gave, in addition to 81% yield of the desired

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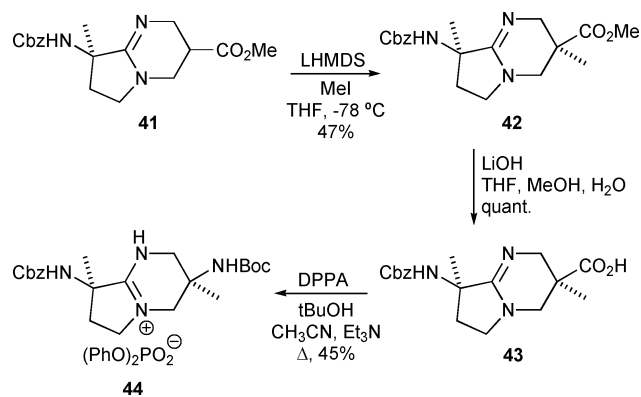(41) Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331−332.

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SCHEME 10

lactam **37**, the *N*-benzylamine **35** in 24% yield (72% recovery of excess amine, which can be recycled back to the amine **36**, thereby improving the overall efficiency of the process).

Formation of the thiolactam **38** was performed by treatment of the *γ*-lactam **37** with 0.55 equiv of Lawesson's reagent in refluxing toluene (Scheme 9). The thiolactam **38** was isolated in 56% yield, and the dithio compound **39** in 10% yield. The yield of the thiolactam **38** was higher than for the corresponding reaction in the model series (**27** → **30**), presumably because the methoxycarbonyl group sterically shields the phthaloyl group, thereby slowing formation of the dithio compound **39**.

Initial attempts to remove the phthaloyl group of **38** by hydrazinolysis with hydrazine hydrate in refluxing ethanol were unsuccessful, and the starting material was recovered. After experimentation with various methods it was found that treatment of the thiolactam **38** with anhydrous hydrazine in methanol gave a satisfactory yield of the free amine **40**.

With the functionalized aminopropyl-thiolactam **40** in hand, synthesis of the bicyclic amidine was investigated. Treatment of the thiolactam **40** with mercuric chloride in refluxing THF proceeded slowly, with some starting material still remaining after 2 days. Dioxane was therefore substituted for THF, and the corresponding reaction using dioxane as solvent was found to be complete in 24 h (Scheme 9). Purification of the amidine **41** proved troublesome, with the solvent system used in chromatographic purification of the model amidine **29** (CHCl$_3$/MeOH/TFA) proving ineffective. The dilemma was solved through the use of either reversed-phase column chromatography or normal-phase silica chromatography eluting with CH$_2$Cl$_2$/MeOH/isopropylamine, with the amidine **41** isolated in 62% yield as a 1:1 mixture of diastereomers (Scheme 9).

Alkylation of the amidine **41** adjacent to the ester moiety was then investigated in order to introduce further conformational restraint to the bicyclic scaffold.[27] Treatment of the amidine **41** with 5.5 equiv of LHMDS and 3.5 equiv of methyl iodide gave a moderate yield of the alkylated compound **42** (Scheme 10). Only one diastereomer was detectable by ^{1}H NMR spectroscopy of the crude product, indicating that the reaction proceeds stereoselectively to give **42** in >95:5 diastereomeric ratio. While the stereochemical identity of the product was not established definitively, it is presumed to arise from approach of the electrophile from the side opposite to the bulky, pseudoaxial CbzNH group. This is also in accord with the reported *α*-methylations of cyclohexane carboxylate esters in which the methyl groups are installed in a cis manner in equatorial positions.[45]

Alkaline hydrolysis of ester **42** gave the corresponding acid **43** in quantitative yield. Acid **43** was then transformed through

a Curtius rearrangement to the corresponding Boc-protected amine **44**, isolated in good yield as the diphenylphosphate salt.

Conclusion

Several functionalized diazabicyclo[4.3.0]nonenes and other heterocycles have been prepared as peptidomimetic scaffolds. A novel and efficient method has been developed for the preparation *N*-substituted *γ*-lactams, which have previously been utilized as constrained dipeptide surrogates. A rapid assembly of the 1,5-diazabicyclo[4.3.0]nonan-9-one ring system **24** has been achieved through a one-pot reductive amination–tandem cyclization process. Preparation of amidine-containing 1,5-diazabicyclo[4.3.0]nonenes **29** and **41**−**44** has been achieved through Hg-mediated cyclization of the precursor *N*-aminopropyl-*γ*-thiolactams and subsequent functional group manipulation. C3-Carboxylate-functionalized compound **43**, containing a fused 5,6-bicyclic ring system and the combination of a protected amino group and carboxylic acid, represents a novel scaffold for potential peptide turn mimetics. C3-Amino-functionalized compound **44**, containing a protonated amidine and two differentially protected amino groups, could potentially be employed as an *α*-helix template attached to the C-terminus of peptides. The three N−H hydrogen bond donors of **44** are positioned in an analogous arrangement to the three carbonyl group hydrogen bond acceptors of the N-terminal template **4** and therefore mimic the hydrogen-bonding pattern of the first turn at the C-terminus of an *α*-helix. These compounds are novel additions to the current range of small-molecule constrained peptidomimetics.

Experimental Section

General procedures are available in the Supporting Information.

(2S,4S)-3-Benzyloxycarbonyl-4-methyl-2-phenyl-4-(prop-2-enyl)oxazolidin-5-one 17. A solution of the oxazolidinone **16**[36] (15.0 g, 48.2 mmol) in dry THF (80 mL), under an atmosphere of argon, was cooled to −78 °C. A solution of lithium hexamethyldisilazide in THF (1.0 M, 63 mL) was added slowly, and the mixture was stirred for 15 min. Allyl iodide (6.3 mL, 68.9 mmol), which had been passed through a short column of alumina, was then added, and the mixture was stirred at −78 °C for 3 h. The mixture was allowed to warm to room temperature and was stirred for a further 18 h. The mixture was diluted with ether (250 mL) and was quenched by the addition of satd NH$_4$Cl (250 mL). The organic layer was separated and washed with satd NH$_4$Cl. The combined aqueous layers were extracted with ether, and then the organic layers were combined and dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica to give the oxazolidinone **17** (15.45 g, 91%) as a clear, viscous oil: ^{1}H NMR (400 MHz, CDCl$_3$) (major rotamer) *δ* 1.81 (3H, s), 2.54 (1H, dd, *J* 6.3 13.5), 3.27 (1H, dd, *J* 8.9 13.5), 4.96 (2H, m), 5.16 (2H, m), 5.67 (1H, m), 6.28 (1H, s, NH), 6.87 (1H, m), 7.18−7.41 (9H, m); (minor rotamer) *δ* 1.72 (3H, s), 2.54 (1H, dd, *J* 6.3 13.5), 2.92 (1H, dd, *J* 8.5 13.5), 4.96 (2H, m), 5.16 (2H, m), 5.60 (1H, m), 6.34 (1H, s, NH), 6.87 (1H, m, ArH), 7.18−7.41 (9H, m, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 23.6, 39.4, 63.1, 67.2, 89.4, 121.3, 126.8, 127.8, 128.1, 128.3, 128.7, 129.8, 130.9, 135.2, 137.0, 151.7, 174.1; MS (FAB) *m/z* 352 (100, M + H$^+$).

(2S,4S)-3-Benzyloxycarbonyl-4-methyl-4-(2-oxoethyl)-2-phenyloxazolidin-5-one 18. A solution of the allyloxazolidinone **17** (7.8 g, 22.2 mmol) in methylene chloride (200 mL) was cooled to −78 °C, and then ozone was bubbled through the solution until it

(45) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426−2431.

turned blue (ca. 45 min). Oxygen was bubbled through the solution until it became colorless. Dimethyl sulfide (33 mL) was added, and the solution was stirred at −78 °C for 30 min. The solution was allowed to warm to room temperature, and then the solvent was removed under reduced pressure. The residue was purified by chromatography on silica and was recrystallized from hexanes/ethyl acetate to give the aldehyde **18** (6.44 g, 82%) as colorless prisms: mp 109−110 °C; ^{1}H NMR (400 MHz, CDCl$_3$) (major rotamer) δ 1.76 (3H, s), 3.07 (1H, d, J = 15.5 Hz), 4.04 (1H, d, J = 15.5 Hz), 4.84 (1H, d, J = 9.9 Hz), 4.97 (1H, d, J = 9.9 Hz), 6.57 (1H, s), 6.79 (1H, m), 7.16−7.48 (9H, m), 9.92 (1H, s); ^{13}C NMR (100 MHz, CDCl$_3$) (major rotamer) δ 24.4, 48.4, 57.8, 67.3, 89.9, 127.1, 127.5, 128.0, 128.3, 128.6, 129.8, 135.1, 136.6, 151.8, 173.6, 198.6; MS (FAB) m/z 354 (100, M + H$^+$). Anal. Calcd for C$_{20}$H$_{19}$NO$_5$: C, 68.0; H, 5.4; N, 4.0. Found: C, 68.0; H, 5.5; N, 4.1.

(3R)-3-Benzyloxycarbonylamino-3-methyl-1-(3-phthalimidopropyl)pyrrolidin-2-one 27. To a solution of the aldehyde **18** (1.0 g, 2.83 mmol) and the amine salt **26** (1.35 g, 4.25 mmol) in methanol (25 mL) were added NaCNBH$_3$ (267 mg, 4.25 mmol) and NaOAc (100 mg). Acetic acid was added dropwise to lower the pH to 6.0. The solution was then stirred at room temperature for 36 h, and then the solvent was removed under reduced pressure. The residue was taken up in ether/methylene chloride (5:1) and was washed with water, then dilute HCl, then water. The organic phase was dried, and the solvent was removed under reduced pressure. Purification of the residue by chromatography on silica gave the lactam **27** (0.92 g, 75%) as a colorless oil, which solidified after storage at −20 °C: mp 73−75 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.41 (3H, s), 1.93 (1H, m), 1.97 (1H, m), 2.35 (1H, m), 2.45 (1H, m), 3.32 (1H, m), 3.39 (2H, m), 3.48 (1H, m), 3.66 (1H, m), 3.71 (1H, m), 5.04 (1H, d, J = 12.2 Hz), 5.09 (1H, d, J = 12.2 Hz), 5.42 (1H, br s), 7.32 (5H, m), 7.71 (2H, m), 7.83 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.2, 25.9, 32.7, 35.3, 40.5, 43.4, 57.8, 66.4, 123.1, 127.8, 127.9, 128.3, 132.0, 133.9, 136.3, 154.9, 168.0, 174.5. Anal. Calcd for C$_{24}$H$_{25}$N$_3$O$_5$: C, 66.2; H, 5.8; N, 9.7. Found: C, 66.5; H, 6.0; N, 9.9.

(3R)-3-Benzyloxycarbonylamino-3-methyl-1-(3-phthalimidopropyl)pyrrolidin-2-thione 30. To a solution of the lactam **27** (400 mg, 0.92 mmol) in dry toluene (5 mL) was added Lawesson's reagent (124 mg, 0.31 mmol), and the mixture was heated at reflux for 2 h. The mixture was cooled, and the solvent was removed under reduced pressure. The residue was chromatographed on silica to give the dithio compound **31** (28 mg, 7%) and the thiolactam **30** (165 mg, 40%) as a white solid: mp 55−57 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.45 (3H, s), 2.07 (2H, m), 2.42 (1H, m), 2.61 (1H, m), 3.70 (4H, m), 3.74 (1H, m), 3.97 (1H, m), 5.07 (2H, s), 6.00 (1H, s), 7.28−7.35 (5H, m), 7.72 (2H, m), 7.83 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.6, 25.3, 34.2, 35.2, 45.9, 51.4, 66.3, 66.6, 123.2, 127.8, 127.9, 128.4, 131.9, 134.0, 136.4, 154.7, 168.1, 204.1. Anal. Calcd for C$_{24}$H$_{25}$N$_3$O$_4$S: C, 63.8; H, 5.6; N, 9.3. Found: C, 64.1; H, 5.8; N, 9.5.

(3R)-1-(3-Aminopropyl)-3-benzyloxycarbonylamino-3-methylpyrrolidin-2-thione 32. To a solution of the thiolactam **30** (1.1 g, 2.4 mmol) in ethanol (20 mL) was added a solution of hydrazine hydrate in ethanol (2 M, 2.4 mL). The solution was heated at reflux for 2.5 h and then was allowed to cool, and the solvent was removed under reduced pressure. The residue was suspended in dilute HCl (30 mL), and the mixture was heated at 50 °C for 15 min. The mixture was cooledc and the precipitate was removed by filtration. The filtrate was washed with methylene chloride, and then the aqueous layer was made basic (pH >11) by the addition of 6 N NaOH. The solution was extracted twice with ethyl acetate, and then the combined organic phases were dried and the solvent was removed under reduced pressure to give the amine **32** (605 mg, 77%) as a pale yellow oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.41 (3H, s), 1.67 (2H, br s), 1.77 (2H, m), 2.41 (1H, m), 2.49 (1H, m), 2.67 (2H, m), 3.56 (1H, m), 3.63 (1H, m), 3.78 (1H, m), 3.86 (1H, m), 5.07 (2H, s), 6.21 (1H, br s), 7.31 (s, 5H); ^{13}C NMR (100 MHz,

CDCl$_3$) δ 24.9, 27.9, 33.8, 37.9, 45.7, 51.4, 66.4, 66.8, 127.9, 128.0, 128.4, 136.3, 154.8, 204.0; MS (FAB) m/z 322 (100, M + H$^+$).

(S)-7-Amino-7-methyl-1,5-diazabicyclo[4.3.0]non-5-ene 29. To a solution of the amine **32** (600 mg, 1.87 mmol) in dry THF (10 mL) was added HgCl$_2$ (760 mg, 2.80 mmol). The mixture was heated at reflux for 18 h, and then the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography on silica, eluting with CHCl$_3$/MeOH/TFA (70:30:1) to give the bicyclic amidine **29** as its trifluoroacetate salt (502 mg, 67%) as a clear oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.64 (3H, s), 2.02 (2H, m), 2.09 (1H, m), 2.75 (1H, m), 3.39 (2H, m), 3.44 (2H, m), 3.63 (1H, m), 3.80 (1H, m), 5.02 (1H, d, J = 12.5 Hz), 5.10 (1H, d, J = 12.5 Hz), 7.32 (5H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.4, 24.7, 32.8, 38.0, 43.3, 51.2, 61.3, 67.0, 127.6, 128.0, 128.4, 136.2, 156.8, 167.3; MS (FAB) m/z 288 (100, M + H$^+$); HRMS (FAB) m/z 288.1704, C$_{16}$H$_{22}$N$_3$O$_2$ requires 288.1712.

Methyl 3-Benzylamino-2-(phthalimidomethyl)propanoate 35. To a solution of the acrylate **34**[46] (5.0 g, 20.4 mmol) in chloroform (25 mL) was added benzylamine (2.2 g, 20.5 mmol). The solution was refluxed for 2 d and then cooled and the solvent removed under reduced pressure. Purification of the residue by chromatography on silica recovered some acrylate **34** (1.23 g, 25%) and gave the amine **35** (4.42 g, 57%) as a white solid: mp 82−83 °C; IR ν 3470, 3326, 1773, 1734, 1715, 1398, 1367, 1201 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.81 (1H, br s), 2.83 (1H, dd, J = 5.7, 12.3 Hz), 2.89 (1H, dd, J = 6.7, 12.3 Hz), 3.03 (1H, m), 3.67 (3H, s), 3.77 (2H, s), 3.97 (1H, dd, J = 6.7, 14.0 Hz), 4.00 (1H, dd, J = 7.0, 14.0 Hz), 7.20 (1H, m), 7.27 (4H, m), 7.71 (2H, m), 7.83 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.3, 44.5, 47.7, 51.9, 53.6, 123.3, 126.8, 128.0, 128.2, 131.9, 133.4, 140.0, 168.1, 173.0; MS (FAB) m/z 353 (100, M + H$^+$). Anal. Calcd for C$_{20}$H$_{20}$N$_2$O$_4$: C, 68.2; H, 5.7; N, 8.0. Found: C, 68.1; H, 5.9; N, 7.8.

Methyl 3-Amino-2-(phthalimidomethyl)propanoate Hydrobromide 36. To a solution of the amine **35** (23.0 g, 65.3 mmol) in methylene chloride (300 mL) was added water (40 mL), and the mixture was stirred vigorously. Bromine (11.0 g, 68.8 mmol) in methylene chloride (60 mL) was added dropwise over ca. 30 min, after which vigorous stirring was continued for 4 h. The mixture was extracted with water (300 mL), and the aqueous layer was lyophilized to give the amine salt **36** (20.4 g, 91%) as a white powder. Recrystallization from ether/methanol gave the amine salt **36** as fine crystals: mp 184−186 °C dec; ^{1}H NMR (400 MHz, D$_2$O) δ 3.33 (2H, m), 3.42 (1H, m), 3.78 (3H, s), 4.00 (1H, dd, J = 5.4 14.7 Hz), 4.07 (1H, dd, J = 6.3 14.7 Hz), 7.83 (4H, s); ^{13}C NMR (100 MHz, D$_2$O) δ 37.0, 38.0, 42.1, 53.2, 123.6, 130.8, 135.1, 170.0, 172.6; MS (FAB) m/z 263 (100, M + H$^+$). Anal. Calcd for C$_{13}$H$_{15}$BrN$_2$O$_2$: C, 45.5; H, 4.4; N, 8.2. Found: C, 45.7; H, 4.5; N, 8.0.

(3R)-3-Benzyloxycarbonylamino-3-methyl-1-((2RS)-2-methoxycarbonyl-3-phthalimido)propyl)pyrrolidin-2-one 37. To a solution of the aldehyde **18** (13.7 g, 38.8 mmol) in methanol (250 mL) were added the amine salt **36** (20.0 g, 58.3 mmol) and sodium cyanoborohydride (3.7 g, 58.9 mmol). The solution was stirred at room temperature for 3 d, with acetic acid being added to keep pH ~6 (ca. 2 mL). The solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate and water, and the aqueous phase was re-extracted with ethyl acetate. The combined organic phases were dried, and the solvent was removed under reduced pressure. The residue was subject to chromatography on silica, eluting with 3:1 ethyl acetate/hexanes, to give the *N*-benzylamine **35** (4.85 g, 24%), and the lactam **37** (15.5 g, 81%) as a foam, as a 1:1 mixture of diastereomers. Further chromatography enabled isolation of pure samples of each of the diastereomers of **37**. The first eluting diastereomer was obtained as a glassy solid: mp 66−71 °C; IR ν 3420, 3403, 1774, 1718 (br), 1503, 1398, 1072 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.41 (3H, s), 2.33 (1H, m), 2.46 (1H, m), 3.19 (1H, m), 3.35 (2H, m), 3.48 (1H,

(46) Sibi, M. P.; Patil, K. *Angew. Chem., Int Ed.* **2004**, *43*, 1235−1238.

dd, J = 8.4, 17.1 Hz), 3.68 (3H, s), 3.74 (1H, dd, J = 5.1, 14.1 Hz), 3.88 (1H, dd, J = 7.0, 14.0 Hz), 4.02 (1H, dd, J = 8.3, 14.1 Hz), 5.05 (1H, d, J = 12.3 Hz), 5.08 (1H, d, J = 12.3 Hz), 5.42 (1H, br s), 7.32 (5H, m), 7.72 (2H, m), 7.84 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.2, 32.9, 37.2, 42.7 (2 C's), 44.4, 52.4, 57.7, 66.5, 123.4, 127.9, 128.0, 128.4, 131.8, 134.1, 136.3, 154.9, 167.9, 172.0, 175.0; MS (FAB) m/z 494 (100, M + H$^+$). Anal. Calcd for C$_{26}$H$_{27}$N$_3$O$_7$·0.5H$_2$O: C, 62.1; H, 5.6; N, 8.4. Found: C, 62.4; H, 5.7; N, 8.1. The second eluting diastereomer was obtained as a viscous oil: IR ν 3423, 3405, 1775,1718 (br), 1503, 1399, 1075 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.37 (3H, s), 2.31 (1H, m), 2.43 (1H, m), 3.30 (2H, m), 3.45 (1H, m), 3.61 (2H, m), 3.67 (3H, s), 3.87 (1H, dd, J = 5.1, 13.0 Hz), 4.00 (1H, dd, J = 7.5, 13.0 Hz), 5.04 (1H, d, J = 12.3 Hz), 5.05 (1H, d, J = 12.3 Hz), 5.36 (1H, br s), 7.32 (5H, m), 7.71 (2H, m), 7.84 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.1, 30.8, 37.3, 42.4, 42.8, 44.0, 52.3, 57.7, 66.5, 123.4, 127.9, 128.0, 128.4, 131.8, 134.1, 136.3, 154.9, 167.9, 171.9, 174.9; MS (FAB) m/z 494 (100, M + H$^+$).

(3R)-3-Benzyloxycarbonylamino-3-methyl-1-((2RS)-2-methoxycarbonyl-3-phthalimido)propyl)pyrrolidin-2-thione 38. To a solution of the lactam **37** (1:1 mixture of diastereomers) (11.6 g, 23.5 mmol) in toluene (250 mL) was added Lawesson's reagent (5.4 g, 13.4 mmol). The mixture was refluxed for 1.5 h and then was allowed to cool and the solvent removed under reduced pressure. Chromatography of the residue on silica, eluting with 3:2 ethyl acetate/hexanes, gave the dithio compound **39** (1.2 g, 10%), the starting lactam **37** (2.8 g, 24%), and the thiolactam **38** (6.7 g, 56%, 74% based on recovered starting material) as a white foam as a 1:1 mixture of diastereomers: IR ν 3433, 3360, 1774, 1720 (br), 1511, 1496, 1398, 1088 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.40 (1.5H, s), 1.41 (1.5H, s), 2.38 (1H, m), 2.55 (1H, m), 3.48 (0.5H, m), 3.62 (2.5H, m), 3.69 (1.5H, s), 3.70 (1.5H, s), 3.84 (1H, m), 3.91 (1H, m), 4.03 (1.5H, m), 4.40 (0.5H, m), 5.05 (2H, s), 5.95 (0.5H, br s), 6.00 (0.5H, br s), 7.30 (5H, m), 7.71 (2H, m), 7.83 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.8, 24.3, 24.5, 34.2, 34.3, 37.0, 37.2, 41.7, 47.5, 47.6, 52.3, 52.6, 66.1, 66.4, 123.2, 127.7, 127.8, 128.2, 131.6, 134.0, 136.2, 154.5, 167.8, 171.8, 204.7; MS (FAB) m/z 510 (100, M + H$^+$). Anal. Calcd for C$_{26}$H$_{27}$N$_3$O$_6$S: C, 61.3; H, 5.3; N, 8.2. Found: C, 61.6; H, 5.7; N, 7.8.

(3R)-3-Benzyloxycarbonylamino-3-methyl-1-((2RS)-3-amino-2-methoxycarbonyl)propyl)pyrrolidin-2-thione 40. To a solution of the thiolactam **38** (6.44 g, 12.7 mmol) in dry methanol (80 mL) was added anhydrous hydrazine (445 mg, 13.9 mmol). The solution was stirred under argon at room temperature for 24 h, after which time a white precipitate had formed. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was partitioned between methylene chloride and 2 N HCl. The aqueous layer was made basic (pH 10) by the addition of 6 N NaOH and then was then extracted with methylene chloride. The combined organic phases were dried, and the solvent was removed under reduced pressure to give the amine **40** (3.27 g, 68%) (1:1 mixture of diastereomers) as a pale yellow oil: IR ν 3431, 3356, 1717 (br), 1515, 1497, 1443, 1088 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.40 (1.5H, s), 1.42 (1.5H, s), 1.47 (2H, br s), 2.41 (1H, m), 2.52 (1H, m), 2.87 (0.5H, m), 2.95 (1H, m), 3.00 (1H, m), 3.09 (0.5H, m), 3.63 (2H, m), 3.70 (1.5H, s), 3.72 (1.5H, s), 3.74 (0.5H, m), 3.95 (0.5H, dd, J = 7.6, 13.4 Hz), 4.06 (0.5H, m), 4.25 (0.5H, dd, J = 6.6, 13.4 Hz), 5.07 (2H, s), 6.01 (0.5H, br s), 6.05 (0.5H, br s), 7.33 (5H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.6, 34.0, 34.1, 41.1, 41.2, 45.0, 45.3, 47.3, 47.5, 52.0, 52.1, 52.7, 66.3, 66.5, 66.6, 127.8, 127.9, 128.3, 136.2, 154.6, 173.1, 173.3, 204.4, 204.7; MS (FAB) m/z 380 (100, M + H$^+$); HRMS (FAB) m/z 380.1650, C$_{18}$H$_{26}$N$_3$O$_4$S requires 380.1644.

(3RS,7S)-7-Benzyloxycarbonylamino-3-methoxycarbonyl-7-methyl-1,5-diazabicyclo[4.3.0]non-5-ene 41. To a solution of the amine **40** (1.0 g, 2.6 mmol) in dioxane (25 mL) was added mercuric chloride (1.07 g, 3.9 mmol). The mixture was stirred at reflux for 24 h and then was allowed to cool to room temperature. The mixture was filtered through Celite, washed with acetone, and the filtrate

was concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with a gradient of CH$_2$Cl$_2$/MeOH/isopropylamine (90:10:1−80:20:1), to give the bicyclic amidine **41** (567 mg, 62%) as a colorless oil. Further chromatography enabled isolation of pure samples of each of the diastereomers of amidine **41**. The first eluting diastereomer was obtained as a colorless oil: IR ν 3408, 3275, 1738, 1717, 1692, 1508, 1310, 1275, 1089 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.66 (3H, s), 2.16 (1H, ddd, J = 2.9, 7.9, 12.7 Hz), 2.61 (1H, ddd, J = 8.8, 9.2, 12.7 Hz), 3.22 (1H, m), 3.64 (2H, m), 3.70 (3H, s), 3.79 (4H, m), 5.06 (1H, d, J = 12.7 Hz), 5.12 (1H, d, J = 12.7 Hz), 7.28 (1H, m), 7.35 (2H, m), 7.44 (2H, m), 7.74 (1H, br s); ^{13}C NMR (100 MHz, acetone-d_6) δ 23.2, 32.9, 34.2, 39.5, 44.5, 50.7, 52.0, 61.3, 66.0, 127.5, 127.6, 128.3, 137.0, 155.4, 166.2, 170.5; MS (FAB) m/z 346 (100, M + H$^+$); HRMS (FAB) m/z 346.1773, C$_{18}$H$_{24}$N$_3$O$_4$ requires 346.1767. Anal. Calcd for C$_{18}$H$_{23}$N$_3$O$_4$·HCl·2H$_2$O: C, 51.7; H, 6.8; N, 10.1. Found: C, 51.7; H, 6.7; N, 10.4. The latter eluting diastereomer was obtained as a colorless oil: IR ν 3412, 3278, 1739, 1717, 1691, 1508, 1311, 1279, 1091 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.76 (3H, s), 2.15 (1H, ddd, J = 3.3, 8.3, 12.7 Hz), 2.57 (1H, ddd, J = 7.8, 9.3, 12.7 Hz), 3.42 (1H, m), 3.59 (2H, m), 3.66 (3H, s), 3.75 (2H, m), 3.90 (2H, m), 5.08 (2H, m), 7.28 (1H, m), 7.36 (2H, m), 7.44 (2H, m), 7.72 (1H, br s); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 23.8, 32.9, 34.6, 39.1, 44.1, 50.7, 52.0, 61.3, 65.8, 127.3, 127.5, 128.3, 137.0, 155.3, 166.1, 170.0; MS (FAB) m/z 346 (100, M + H$^+$); HRMS (FAB) m/z 346.1764, C$_{18}$H$_{24}$N$_3$O$_4$ requires 346.1767.

(3S,7S)-7-Benzyloxycarbonylamino-3-methoxycarbonyl-3,7-dimethyl-1,5-diazabicyclo[4.3.0]non-5-ene 42. The amidine **41** (1:1 mixture of diastereomers) (1.0 g, 2.9 mmol) was dissolved in dry THF, and the solution was cooled to −78 °C. Lithium hexamethyldisilazide (1.0 M in THF, 10.2 mL) was added slowly, and the solution was stirred for 2 h, at which time methyl iodide (1.0 g, 7.0 mmol) was added. The solution was stirred for 3 h at −78 °C and then was allowed to warm to ca. 0 °C and stirred for 1 h. The solution was cooled to −78 °C, a further 2 equiv of LHMDS was added (5.8 mL), and stirring was continued for 30 min. Methyl iodide (1 equiv, 185 μL) was added, and the solution was stirred at −78 °C for 3 h. The solution was then allowed to warm to ambient temperature overnight. Methanol (ca. 50 mL) was added to quench the reaction, and the solution was evaporated to dryness under reduced pressure. The crude product was purified by chromatography on silica, eluting with CH$_2$Cl$_2$/MeOH/isopropylamine (80:20:1) to give the product **42** (487 mg, 47%) as a colorless oil: IR ν 3395, 3293, 1738, 1717, 1690, 1538, 1375, 1261, 1219, 1090 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.27 (3H, s), 1.65 (3H, s), 2.08 (1H, m), 2.62 (1H, m), 3.11 (1H, d, J = 13 Hz), 3.29 (1H, d, J = 13 Hz), 3.58−3.87 (4H, m), 3.64 (3H, s), 5.05 (2H, m), 7.28 (5H, m), 7.35 (1H, br s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.7, 24.3, 30.8, 32.9, 38.9, 46.6, 50.3, 52.8, 60.4, 66.1, 127.1, 127.6, 128.3, 136.5, 156.0, 166.2, 172.9; MS (FAB) m/z 360 (100, M + H$^+$); HRMS (FAB) m/z 360.1915, C$_{19}$H$_{26}$N$_3$O$_4$ requires 360.1923.

(3S,7S)-7-Benzyloxycarbonylamino-3-carboxy-3,7-dimethyl-1,5-diazabicyclo[4.3.0]non-5-ene 43. The amidine ester **42** (300 mg, 0.84 mmol) was dissolved in 1:1:1 THF/MeOH/1.0 M LiOH$_{aq}$ (5 mL). The solution was stirred at room temperature for 18 h and lyophilized to give a white foam. The residue was taken up in methanol (5 mL), and 3 N HCl (ca. 0.3 mL) was added to lower the pH to 6. The mixture was filtered, and the filtrate was evaporated under reduced pressure to give the acid **43** (288 mg, 100%) as a white solid: ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.20 (3H, s), 1.56 (3H, s), 2.17 (1H, m), 2.58 (1H, m), 3.24 (2H, m), 3.53 (1H, m), 3.75 (3H, s), 5.09 (2H, s), 7.36 (5H, m); ^{13}C NMR (100 MHz, MeOH-d_4) δ 20.1, 22.5, 32.7, 39.1, 46.0, 50.1, 50.9, 60.7, 66.4, 127.5, 127.7, 128.1, 155.6, 165.4, 177.2; MS (FAB) m/z 368 (8, M + Na$^+$), 352 (38, M + Li$^+$), 346 (44, M + H$^+$), 313 (100); HRMS (FAB) m/z 346.1773, C$_{18}$H$_{24}$N$_3$O$_4$ requires 346.1767.

(3*S*,7*S*)-7-Benzyloxycarbonylamino-3-*tert*-butoxycarbonylamino-3,7-dimethyl-1,5-diazabicyclo[4.3.0]non-5-ene Diphenylphosphate 44. To a solution of the acid **43** (100 mg, 0.29 mmol) in dry *tert*-butyl alcohol/acetonitrile (2:1, 4.5 mL) in a screw-capped pressure bottle were added DPPA (112 mg, 0.41 mmol) and triethylamine (32 mg, 0.32 mmol). The bottle was flushed with argon before affixing the cap and then was placed in a sand bath at ca. 110 °C. The solution was heated for 36 h and then was allowed to cool. Ether (8 mL) was added, and the solution was stored at 4 °C overnight. The precipitate (diphenyl phosphate) was removed by filtration, the solid was washed with ether, and the filtrate evaporated under reduced pressure. The residue was purified by chromotography on silica to give the amidine diphenyl phosphate salt **44** (84 mg, 45%): ¹H NMR (400 MHz, MeOH-d_4) δ 1.41 (3H, s), 1.43 (9H, s), 1.52 (3H, s), 2.15 (1H, ddd, J = 3.5, 7.0, 12.7 Hz), 2.59 (1H, m), 3.16 (1H, d, J = 13 Hz), 3.35 (1H, d, J = 13 Hz), 3.73 (2H, m), 3.79 (1H, d, J = 13 Hz), 3.89 (1H, d, J = 13 Hz), 5.07 (1H, d, J = 12.4 Hz), 5.14 (1H, d, J = 12.4 Hz), 7.34 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 24.6, 28.2, 31.7, 33.3, 45.8, 51.2, 53.8, 60.8, 66.6, 79.7, 120.3*, 120.3*, 122.9*, 127.7, 128.3, 129.0, 136.4, 153.1*, 155.0, 156.2, 166.7 [* = (PhO)₂PO₂−]; MS (FAB) m/z 417 (100, M + H⁺); HRMS (FAB) m/z 417.2512, $C_{22}H_{33}N_4O_4$ requires 417.2502.

Supporting Information Available: Experimental methods and spectroscopic data for compounds **16**, **20**, **22**, **24**, **26**, **28**, and **34**; spectroscopic data for compounds **31** and **39**; ¹H spectra for compounds **17**, **18**, **20**, **22**, **24**, **26−30**, **32**, **35−38**, and **40−44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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