Synthetic Design for Combinatorial Chemistry. Solution and Polymer-Supported Synthesis of Polycyclic Lactams by Intramolecular Cyclization of Azomethine Ylides

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Abstract: The rapidly expanding field of combinatorial chemistry has stimulated the development of new methods and synthetic strategies for assembly of compound libraries. We propose four criteria that are desirable for synthetic routes to such libraries: (1) the sequence involves a small number of steps; (2) no more than one variable is introduced in any step; (3) starting materials are readily obtained with a diverse selection of substituents, and (4) cyclic, nonoligomeric structures represent the most interesting targets. Guided by these criteria, we have explored an intramolecular version of the azomethine ylide cycloaddition reaction which utilizes readily available amino acids, aldehydes, and 2° amines as inputs. We prepared a number of cycloadducts in solution to optimize conditions and examine the scope of the process and to identify a synthetic strategy that would be amenable to solid-phase synthesis of these compounds. Transfer of the sequence to solid phase was demonstrated by the synthesis of a number of representative compounds, indicating that the chemistry is suitable for construction of a combinatorial library.

The utility of combinatorial chemistry for the production of organic compound libraries is widely recognized.[1−9] The advent of techniques for the parallel and combinatorial assembly[10] of large compound libraries is revolutionizing synthesis design, just as it is altering how compounds are screened for biological activity. Library candidates are chosen for their ready synthesis on polymer beads or by automated methods, and "combinatorial synthetic design" is governed less by retrosynthetic analysis and more by considerations of what input materials are available and what can be made from them.[8,27,28] Some traditional strategies for target-directed synthesis are not applicable in this new context; for example, convergence in a synthetic scheme cannot be implemented readily when assembly proceeds on a solid support. This milieu also has profound effects on fundamental experimental issues such as reagent stoichiometry, reaction conditions, and removal of side products. The input materials should embody relatively simple functional group classes that can be obtained with a broad range of substituents, and they should not themselves require multistep preparation. Synthetic libraries were first developed with peptides[11,12,29,30] and the related "peptoids"[31−33] for just these reasons. However, the library concept has been extended to hetero- and polycyclic structures, and it has stimulated the adaptation to solid support of many procedures for carbon−carbon and carbon−heteroatom bond formation (*inter alia*:[34−38]).

Within this context, three criteria for synthetic design appropriate for assembly of a combinatorial library by the mix-and-split strategy can be offered.

(1) *The sequence involves a small number of steps which are amenable to solid phase*. The synthesis of a large number of compounds simultaneously is impractical if conventional purification steps are required in individual reaction workups. As a result, provision must be made for convenient removal of reagents and byproducts, and syntheses must be relatively short. While the syntheses of oligopeptides and oligonucleotides have been optimized to the point that multistep sequences can be undertaken effectively, relatively few transformations approach the efficiency demanded by a procedure that does not allow purification of the intermediates. Several protocols have been described for preparation of libraries in solution by short sequences;[8] however, most multistep combinatorial and parallel synthesis strategies are carried out in a polymer-supported format. Solid-phase synthesis avoids many common limitations of solution-phase chemistry: excess reagent(s) can be used because the product is isolated by simple filtration, and side reactions can be tolerated if the byproducts are not bound to the solid support.

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

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(10) We differentiate (1) "combinatorial synthesis", which generates a library containing all combinations of the components but in discrete fashion, for example, on solid support beads, (2) "mixture synthesis", in which compounds are produced as molecular mixtures by including multiple variants of the starting components in each reaction, and (3) "parallel synthesis", in which individual compounds are prepared in isolated reaction vessels or wells. Combinatorial synthesis is exemplified by the Furka "mix-and-split" strategy,[11,12] mixture synthesis as described by Carell et al.,[13] and parallel synthesis by the "Diversomer" technology of DeWitt et al.;[14] many additional examples can also be found. A large library can be assembled with fewer individual reactions by the combinatorial and mixture strategies, in contrast to the parallel approach, but the former methods require decoding,[15−20] indexing,[21,22] deconvolution,[23−25] or affinity selection[26] steps to identify active compounds.

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(2) *No more than one variable is introduced in any step*. If several variables are introduced in one step, then separate reactions for each combination are required if all are to be generated without producing molecular mixtures. This criterion is particularly important for combinatorial syntheses that rely on encoding strategies for compound identification.[15,17−19]

(3) *Starting materials are readily obtained with a diverse selection of substituents*. Exotic functional group classes for which few examples are available, or input materials that must be synthesized individually, are clearly less practical.

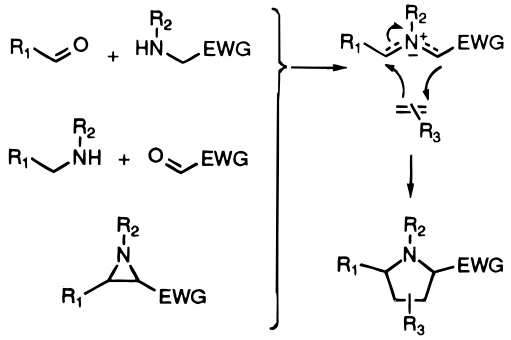
To these three, self-evident criteria, we would add a fourth, more subjective one.

(4) *Cyclic, nonoligomeric structures represent the most interesting targets*. At the current stage of development in this field, the assembly of polycyclic molecules on solid-phase poses a greater challenge than that of acyclic or oligomeric compounds; such targets therefore provide more opportunity for the development of synthetic strategies and methods. Furthermore, conformationally constrained molecules are generally more attractive as lead structures from a biological assay, since they provide more information about the three-dimensional requirements for ligand binding.

In this report, we describe methods for the synthesis of polycyclic compounds that were devised specifically for application to combinatorial chemistry.

The Azomethine Ylide Cycloaddition. The [3 + 2] cycloaddition of stabilized azomethine ylides to alkenes and alkynes (Scheme 1)[39,40] meets all of the criteria offered above:

Scheme 1



it provides a highly substituted, cyclic product under mild conditions from readily available starting materials such as aldehydes, amino acids, and alkenes. The mechanism of the transformation has been studied extensively, and many variations have been explored in synthesis. Indeed, the use of this cycloaddition reaction in an intermolecular format has been described for the parallel synthesis of a number of pyrrolidine libraries.[41−44]

Although there are several methods for generating azomethine ylides, the strategy pioneered by Grigg[45] and Tsuge[46] is particularly attractive (Scheme 1). Condensation of an amino acid with an aldehyde is followed by 1,2-prototropy, in the case of primary amines, or loss of a proton from the iminium ion intermediate, when a secondary amine is involved.[47] Proton loss from the tautomeric iminium ion, formed on condensation of an amine with an α-dicarbonyl compound, is also a logical route to the stabilized ylide, although few examples of this process have been described.[48] A third route to these ylides via ring opening of the isomeric aziridines is well-known.[49−52] When the ylide is generated by aldehyde-amine condensation in the presence of the dipolarophile, three components are brought together in a single reaction. As a result, in a combinatorial synthesis where one of the components is tethered to a solid support, the other components cannot be varied independently, unless the sequence is limited to stabilized imines that can be carried through the mix-and-split steps. This limitation is removed if the [3 + 2] cycloaddition is carried out in an *intramolecular* format, in which the dipolarophile is attached to one of the other components (Scheme 2). The intramolecular reaction has several other attractive features: significant stereocontrol is anticipated, and the polycyclic products are capable of a high degree of functionalization and skeletal variation. Moreover, while the intermolecular reaction of stabilized ylides is limited to electron-deficient dipolarophiles,[45] it appears that the intramolecular reaction is feasible with a wide range of unactivated alkenes and alkynes as the olefinic partner.[40]

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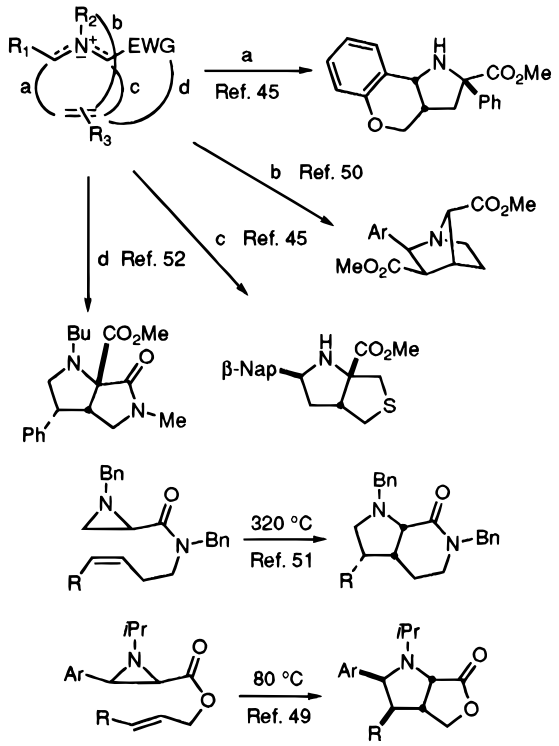
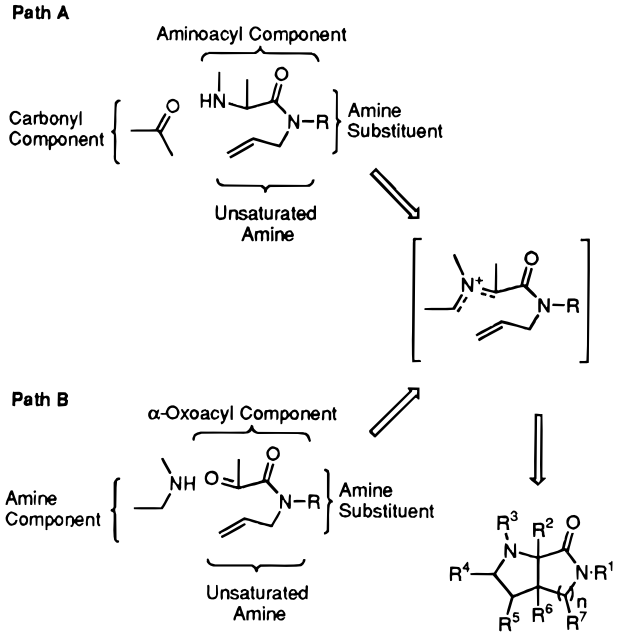
Scheme 2



Intramolecular cycloadditions that represent all of the ways in which the dipolarophile can be connected to the ylide have been described (Scheme 2).[45,50,53,54] As specific examples in which the olefin has been tethered via the stabilizing moiety (connection d), the Weinreb[51] and Heathcock[52,55] groups have shown that amide-linked ylides, generated by thermolysis of the aziridine precursors, cyclize to the bicyclic lactams. Padwa[50] and DeShong[49] and their co-workers have reported a similar reaction of aziridine esters to give bicyclic lactones. While aziridine synthesis and pyrolysis may not be an attractive sequence for solid support, the success of the cycloadditions themselves suggested that an alternative method for generation of the ylides would make this reaction applicable to combinatorial synthesis. This report describes the development of sequences A and B depicted in Scheme 3 for this purpose, with an exploration of the various possibilities for substitution of the bicyclic nucleus and adaptation of the chemistry to solid support. The two routes are complementary in providing routes to cycloadducts with different substitution patterns.

Design of a Combinatorial Library. To assemble a combinatorial library on solid support, with introduction of no more than one variable in each step, requires that one of the variable components be linked to the solid phase before the next variable is introduced. For the sequence of Scheme 3, path A,

Scheme 3



a number of strategies can be devised for construction of secondary allylic and homoallylic amines on solid phase by alkylation or reductive amination; however, to drive the reaction to completion without polyalkylation requires that the electrophile be attached to the support and the amine be the soluble component used in excess. The scope of the intramolecular cycloaddition reaction was explored in solution using a number of secondary allylic amines that are commercially available or were synthesized by conventional methods. These substrates allowed us to evaluate aryl and primary and secondary alkyl substituents at R^1 and a number of allylic and homoallylic groups for the unsaturated component.

The third variable, the secondary amino acid, can be incorporated as a single unit (e.g., sarcosine and other *N*-alkylamino acids, or a cyclic amino acid such as proline) or itself assembled on solid phase (e.g., by amine displacement of an α-bromoacylamide). A number of cyclic and acyclic amino acids were evaluated in the present study. The final variable component is a nonenolizable carbonyl derivative; aromatic aldehydes provide the richest source, but potentially reactive ketones such as isatin and other stabilizing aldehydes such as glyoxylate offer additional possibilities that were explored.

Both paths A and B lead to the bicyclic pyrrolidino-lactam skeleton and allow similar variations in the unsaturated secondary amine component. Where these two routes differ most significantly is in the tri- and tetracyclic skeleta that can be formed. In path A, cyclic amino acyl components (R^2 and R^3 linked) afford structures with the 3,8-diazatricyclo[6.3.0.$0^{1,5}$]-2-undecanone backbone (and higher homologs), while cyclic amines in sequence B (R^3 and R^4 linked) lead to 1,4-diazatricyclo[6.3.0.$0^{2,6}$]-3-undecanone as the simplest tricyclic skeleton.

The potential size of libraries constructed according to these schemes with full variation of all the components is vast, hence an important element in the work we report here was to explore the limits of this variability. We first examined the scope and limitations of the intramolecular cycloadditions of Scheme 3, paths A and B, in solution. Having demonstrated their feasibility, we then carried out a number of examples on solid-phase to demonstrate the utility of these sequences for combinatorial chemistry.

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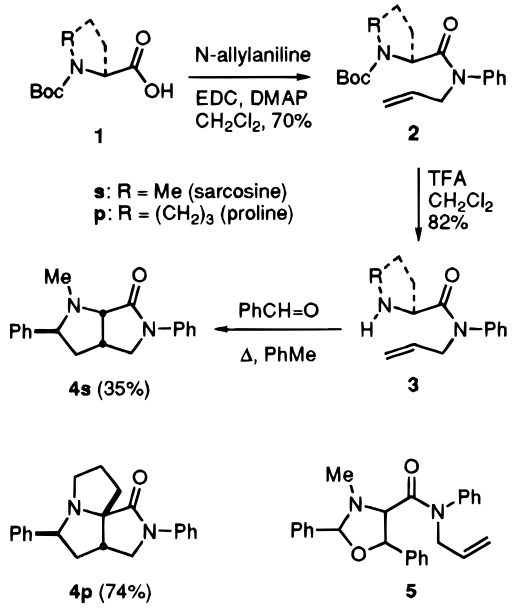
Scheme 4



Results and Discussion

Solution-Phase Chemistry: Demonstration of the Cycloaddition via Path A. The feasibility of the cycloaddition was first demonstrated by combining three commercially available components: *N*-allylaniline, *N*-Boc-sarcosine, and benzaldehyde (Scheme 4). An equimolar solution of amine **3s** and benzaldehyde in toluene was heated at reflux under a Dean-Stark trap to provide the bicyclic lactam **4s** in 35% yield after 20 h. The sequence with proline proceeded similarly to give the tricyclic lactam **4p** in 74% yield. Small-scale reactions (ca. 0.5 mmol of amine) in the presence of molecular sieves or without any explicit water removal showed no effect on the yield; therefore, subsequent reactions were run without rigorously anhydrous reaction conditions. The choice of solvent, however, had a dramatic effect on the rate of reaction. Reactions carried out in refluxing benzene proceeded much more slowly than those in toluene, and attempted reactions in acetonitrile or ethylene glycol dimethyl ether returned only starting materials. Furthermore, the addition of amine bases such as triethylamine or DBU did not affect the reaction outcome. However, since an added amine base was found to be crucial for success of the glyoxamide strategy (Scheme 3, path B, described below), an equivalent of triethylamine was generally included to maintain complementarity between the two protocols.

A byproduct of the cyclization of **3s** with benzaldehyde is the 2:1 adduct **5**. With a 2:1 ratio of benzaldehyde to amine and a concentration of 0.5 M amine in toluene, the 2:1 adduct is produced in approximately equivalent amount to the desired bicyclic product. Submission of oxazolidine **5** and bicycle **4p** individually to refluxing toluene, with or without catalytic tosic acid, showed that their formation is irreversible under the reaction conditions. Analysis of the ^{1}H NMR spectra arising from a study of the concentration dependence of this reaction revealed that a 2:1 molar mixture of aldehyde to amine and a reaction concentration of 0.5−0.6 M (of amine in toluene) provided the most consistent results, with the 2:1 and the 1:1 adduct being produced in approximately equimolar amounts and with total mass balances of 60−70%.

The cycloadducts **4s** and **4p** are formed as single diastereomers, with the *cis* ring fusion and the *exo* configuration of the C-phenyl substituent according to 1D ^{1}H NOE difference spectroscopy. These assignments were confirmed with crystal structures of the analogs **6** and **7** (Figure 1). The relative

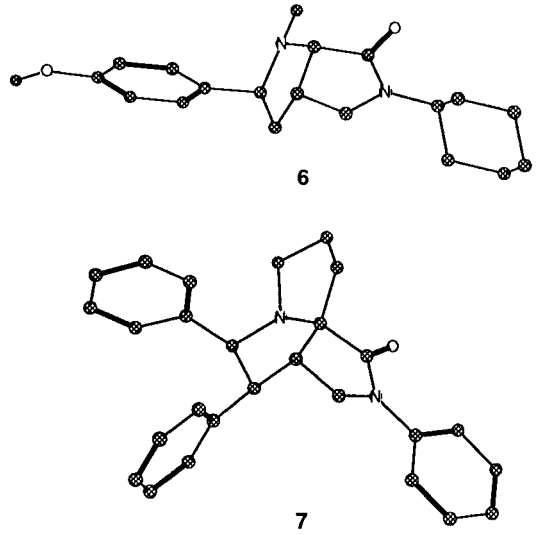


Figure 1. Crystal structures of bi- and tricyclic products.

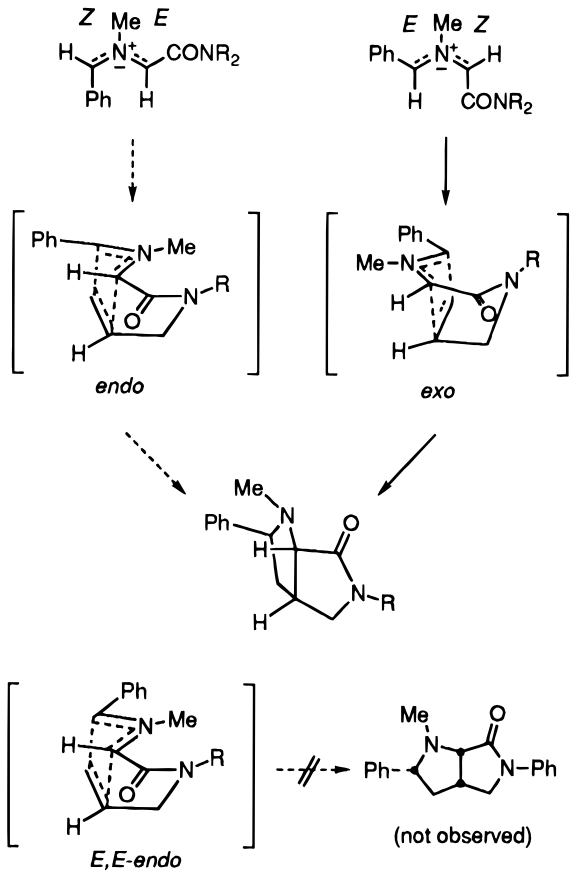
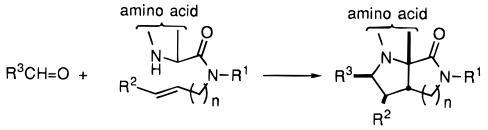


Figure 2. Possible Ylide and Transition State Geometries.

stereochemistry is consistent with two possibilities for the transition state structure of the sarcosine substrate: the *Z,E*- and *E,Z*-ylide geometries, with *endo* and *exo* orientations of the allyl group, respectively (Figure 2). However, only the *E,Z-exo* geometry is possible for the proline substrate or, in the alternative glyoxamide format, for cyclic amines like tetrahydroisoquinoline (see below). Moreover, if the *endo* transition state were possible for the acyclic substrates, one might expect some of the other C-phenyl stereoisomer from the *E,E*-ylide, although that isomer is less reactive.[39]

Variation of the Amine Substituent. Using sarcosine as the secondary amino acid and a simple allyl group as the unsaturated component, we found that the reaction tolerates primary and secondary alkyl substituents on the amide nitrogen, in addition to aryl (entries 1−3, Table 1), but not hydrogen

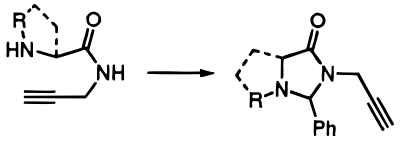
Table 1. Solution-Phase Cyclization of Unsaturated α-Aminoacylamides (Path A)



entry	R^1	amino acid	*n*	R^2	R^3	yield (%)	(compd)
1	Ph	Sar	1	H	Ph	35	**4s**
2	benzyl	Sar	1	H	Ph	50	
3	cyclohexyl	Sar	1	H	Ph	57	
4	Ph	Pro	1	H	Ph	74	**4p**
5	Ph	Sar	1	phenyl	Ph	49	
6	Ph	Pro	1	phenyl	Ph	63	**7**
7	benzyl	Sar	2	H	Ph	45	
8	benzyl	Pro	2	H	Ph	32	
9	Ph	Sar	2	H	Ph	16	
10	benzyl	*N*-methylalanine	1	H	Ph	66[a]	
11	cyclohexyl	Sar	1	H	*p*-F-phenyl	60	
12	cyclohexyl	Sar	1	H	*p*-MeO-phenyl	47	**6**
13	Ph	Sar	1	H	*p*-NO_2-phenyl	30	
14	Ph	Sar	1	H	2-naphthyl	27	
15	Ph	Pro	1	H	*p*-MeO-phenyl	75	
16	Ph	Sar	1	H	furyl	26	
17	Ph	Sar	1	H	BuO_2C	30	
18	Ph	Sar	1	H	MeO_2C, Me	21[b]	**18**
19	Ph	Sar	1	H	2-oxoindolin-3-ylidene	27	**19**

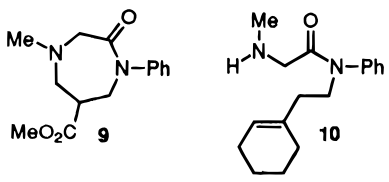
[a] Reaction carried out in refluxing xylenes. [b] Product isolated as a 1.1:1 mixture of isomers.

itself. Although azomethine ylides derived from secondary amides by aziridine thermolysis undergo intramolecular cycloaddition,[52] condensation of the sarcosyl or prolyl propargyl amides with benzaldehyde simply leads to the imidazolidinones **8**.

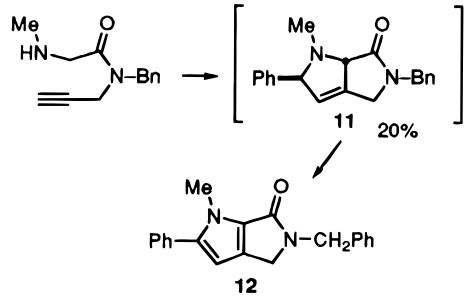


8s R = Me,H 50%
8p R = $(CH_2)_3$ 63%

Variation of the Unsaturated Component. In addition to the simple allyl group, several substituted allyl, homoallyl, and propargyl derivatives were investigated as the unsaturated component. Among the allyl analogs, phenyl substitution at the terminal position is well tolerated (entries 5 and 6, Table 1); the ready availability of cinnamyl amines indicates that this particular substitution pattern provides a rich opportunity for diversity. Neither methyl nor methoxycarbonyl are tolerated at the 2-position, the former because of apparent lack of reactivity (no reaction observed in refluxing toluene) and the latter because of intramolecular cycloaddition to give **9** on deprotection of the secondary amine (84% yield). The 3-butenyl group affords bicyclic lactams with the 5,6-ring system (entries 7 and 8), but when combined with the *N*-phenyl substituent and sarcosine (entry 9), the cyclization proceeds in poor yield with formation of considerable amounts of the 2:1 adduct. Cycloaddition was not observed with the substituted homoallylic derivative **10**.



Substituted acetylenes are also effective dipolarophiles for intermolecular azomethine ylide cycloadditions;[49,56] however, the propargyl and 3-butenyl groups were not successful in the present context, leading to decomposition. The sarcosine analog did afford a low yield of the unsaturated adduct **11**, which aromatized to the pyrrole **12** on standing, as DeShong et al. observed for the related lactones.[49] We also prepared the sarcosyl amide of benzylmethylamine to investigate the aromatic ring itself as the dipolarophile. Although we had seen no evidence for cyclization onto the benzene ring in any of the other benzylamine analogs we had studied, we were prompted by the observations of Heathcock and co-workers[52] of cycloaddition of related ylides to the benzene ring. However, no cyclic product was apparent in the ^{1}H NMR spectrum of the crude reaction mixture from sarcosyl *N*-benzyl-*N*-methylamide.



Variation of the Amino Acid. Aside from sarcosine and proline, only modest variation in the amino acid component appears to be tolerated. *N*-Allylaniline and benzaldehyde were employed as the amine and carbonyl components, respectively. The *N*-methylalanine derivative (Table 1, entry 10) required higher temperatures than the sarcosine analog; however, the reaction proceeded in better yield, and no evidence of an oxazolidine byproduct was observed. Furthermore, the reaction results in the stereospecific formation of a tetrasubstituted carbon atom, as also occurs in cyclizations with proline (entries 4, 6, and 8). Interestingly, pipecolinic *N*-allylanilide was unreactive under the normal conditions, indicating that formation of the iminium ion may be sterically disfavored in this case. Four *N*-alkylglycines in addition to sarcosine were also evaluated,

(56) Grigg, R.; Gunaratne, H. Q. N.; Kemp, J. *Tetrahedron* **1990**, *46*, 6467−6482.

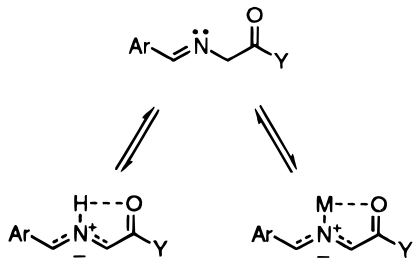
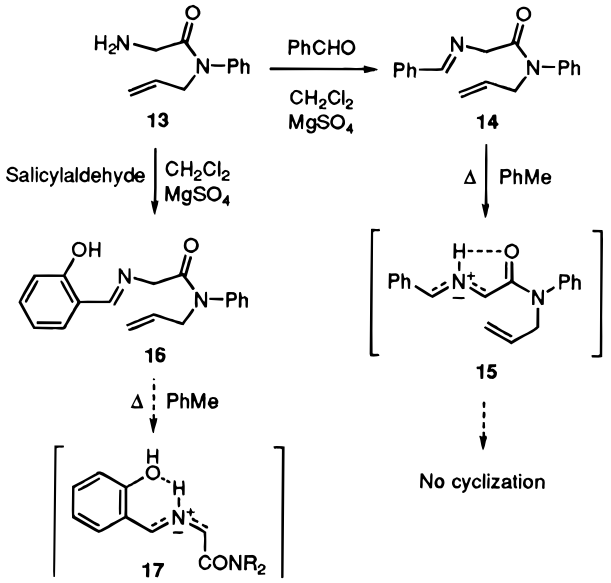


Figure 3. Azomethine Ylide Formation by Prototropy or Metal-Cation Complexation.

Scheme 5



since they are readily accessible by the strategy employed by the Chiron group for the "submonomer" assembly of peptoids.[32] However, the *N*-phenyl, *N*-benzyl, *N*-cyclohexyl, and *N*-butyl analogs all failed to give cyclic products under the standard conditions. Complex product mixtures were observed, and no starting material was recovered, which led us to believe that the imine was being formed but that ylide formation or cyclization was for some reason disfavored in these cases.

Attempted Reactions with Primary Amino Acids. The abundance of commercially available primary amino acid derivatives as well as the opportunity for further derivatization that the secondary amine in the cycloadduct would afford prompted us to try to incorporate these analogs in the synthetic sequence. Grigg and co-workers have demonstrated ylide formation from primary amino acid imines both by prototropy and by metal complexation; in these cases, the imine is activated by protonation or complexation in concert with the carbonyl oxygen, as shown in Figure 3.[45,57]

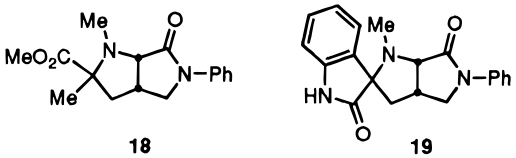
Reaction of the glycine-derived amide **13** with benzaldehyde under dehydrating conditions readily afforded imine **14** (Scheme 5); however, we were unable to induce this material to undergo cyclization, either thermally, in the presence of silver acetate or lithium bromide or with triethylamine as catalyst. Reaction of **14** with benzaldehyde in the presence of silver acetate or lithium bromide, as reported by Grigg for related intermolecular reactions,[45] resulted in decomposition at high temperatures and recovery of starting material at lower temperatures. Combination of **14** directly with benzaldehyde in toluene at reflux produced similar results, either with or without a catalyst.

Although an ylide is probably forming under these conditions, it is likely to have the *E*,*E*-geometry depicted in **15**; as discussed above, this appears to be the wrong configuration for the desired cyclization reaction. In an attempt to provide an alternative means of stabilizing the iminium hydrogen, we investigated salicylaldehyde as the carbonyl component; we reasoned that the hydrogen-bonding scheme of **17** would allow the *E*,*Z*-ylide to be formed. Unfortunately, all attempted cyclization reactions involving imine **16** resulted in decomposition of the starting material. It is clear that an alternative strategy will be required to employ primary amino acids in this intramolecular cyclization process.

Variation of the Carbonyl Component. We examined the cyclization with a number of different carbonyl components using the sarcosine-derived *N*-phenyl (**3s**) and *N*-cyclohexylallyl amides and in one case proline derivative **3p** (Table 1, entries 11−19). A number of the products are particularly noteworthy. The bicyclic adduct **6** crystallized from the reaction mixture, and an X-ray structure verified the *cis*-relationship of the ring junction protons and the aryl substituent (Figure 1).

In addition to the aromatic aldehydes (Table 1, entries 1−16), which were generally effective in the cyclization, three nonaromatic carbonyl components, butyl glyoxylate, methyl pyruvate, and isatin (entries 17−19) also provided cyclic products. In all of these compounds, the carbonyl group is activated by conjugation to an aromatic ring or an α-carbonyl group; in our hands, formaldehyde (as paraformaldehyde) or alkyl aldehydes failed to afford cycloadducts. The reactions of **3s** with butyl glyoxylate and methyl pyruvate (entries 17 and 18) provide points of cross-reference with the alternative strategy of path B (Scheme 3), since the same ylides are available from condensation of the *N*-allylglyoxamide with sarcosine and *N*-methylalanine esters (see below).

The two ketones, methyl pyruvate and isatin, afford cycloadducts with a quaternary center. In the reaction with methyl pyruvate (entry 18), **18** is formed as a mixture of stereoisomers, while isatin affords a single spirocycle **19** of undetermined geometry (entry 19). Cyclization of the pyruvyl and isatin derivatives prompted an investigation of the reactivity of a number of other ketones, such as cyclohexanone and benzophenone; however, in each case, unreacted starting material was recovered from the reaction mixture. Steric as well as electronic factors presumably inhibited formation of the iminium ion intermediate.



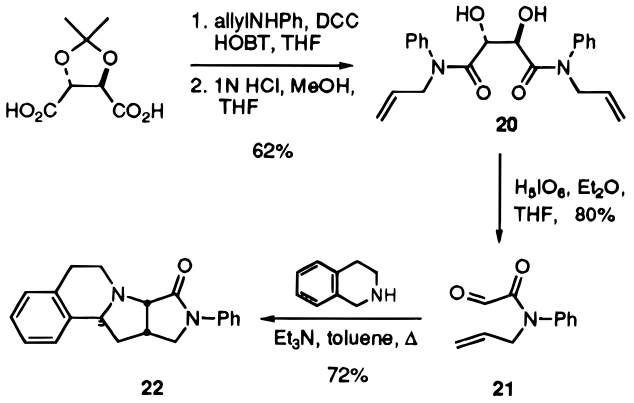
Cycloaddition via Path B: Glyoxamide Synthesis, Azomethine Ylide Generation, and Cyclization. As described above for path A, the feasibility of the condensation and cyclization steps of path B (Scheme 3) were first verified in solution phase experiments.[58] The symmetrical tartramide **20** was prepared from diethyl tartrate as shown in Scheme 6 and cleaved with periodic acid to afford the glyoxamide **21**.[59] This oxidation is most conveniently carried out in 1:1 tetrahydrofuran/ether from which the inorganic byproducts precipitate at the end of the reaction; the crude glyoxamide is obtained in 80% yield and can then be carried on without further purification. Combination of this material with 1 equiv of 1,2,3,4-tetrahy-

(57) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5887−5989.

(58) The phenylglyoxamide analog (PhCOCON(allyl)Ph) was studied briefly as another readily accessible, nonenolizable α-ketoamide; however, no reaction of this compound was observed even on prolonged heating with the activated 2° amines that are successful with the simple glyoxamide analogs.

(59) Stetter, H.; Skobel, H. *Chem. Ber.* **1987**, *120*, 643−645.

Scheme 6



droisoquinoline in refluxing toluene for 16 hours afforded the tetracyclic lactam **22** as a single diastereomer in 50% yield. Addition of one equivalent of triethylamine to the reaction mixture increased the yield to 72%; however, the yield was not affected when molecular sieves were added; these yields are based on the symmetrical tartramide and encompass the oxidation, condensation, and cyclization steps.

The geometry of this alternative process was revealed by the stereochemistry of two homoallyl and substituted allyl analogs **23** and **24** (Figure 4). NOE and coupling interactions established the *anti* relationship between the ring fusions, which arises from the same *anti*,*syn-exo* transition state demonstrated for the related cycloadditions of Scheme 3, path A (see above). The versatility of this sequence was determined by examining the cycloaddition reaction with a variety of glyoxamides and amines.

Variation of the Amine Component. The variability tolerated in the amine component was evaluated with *N*-allyl-*N*-phenylglyoxamide **21** as the dicarbonyl partner. As illustrated by Table 2 (entries 1−7), cyclic and acyclic α-amino acid esters are effective in this cyclization procedure. The acyclic amino esters afford the same ring system and some of the same products that are available from the alternative sequence of path A; indeed, the butyl ester of **25** (entry 2) is described above (Table 1, entry 17). Steric hindrance plays an important role in this condensation: while sarcosine ethyl ester affords the bicyclic product **25** in 65% yield (as a 5:1 mixture of the *exo*:*endo* isomers, Table 2, entry 2), the *N*-methylalanine ester gives the quaternary product **26** in only 25% yield (entry 3). The yield of the latter process is reduced by transamination of the iminium intermediate to produce ethyl pyruvate and the sarcosine amide, which then condenses with starting glyoxamide to give **27** (Scheme 7).

The condensation with methyl glycinate itself requires refluxing xylene and only gives the bicyclic adduct in poor yield (Table 2, entry 4). This result is similar to that obtained with unsubstituted amino acids in the alternative path A, which we attribute to preferential formation of the unproductive, *anti*−*anti* isomer of the ylide (see above).[39] In an attempt to expand the scope of the methodology, we investigated the generation of azomethine ylides via decarboxylation.[60,61] We first attempted to react glyoxamide **21** with sarcosine in the presence of triethylamine, but the condensation was stymied because the amino acid is insoluble. However, the reaction can be accomplished with the trimethylsilyl ester, as shown in entry 5; condensation with bis(trimethylsilyl)sarcosine affords the bicyclic pyrrolidine lactam **28** without any substituent at the 7-position (Scheme 8). This strategy appears to have limited

(60) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chem. Lett.* **1986**, 973−976.

(61) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. I* **1988**, 2703−2713.

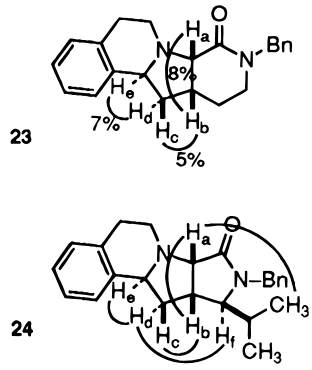
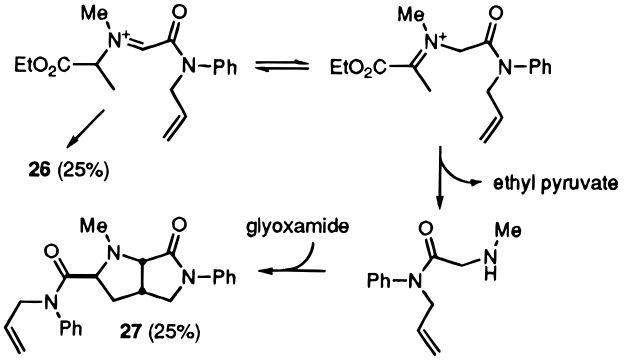
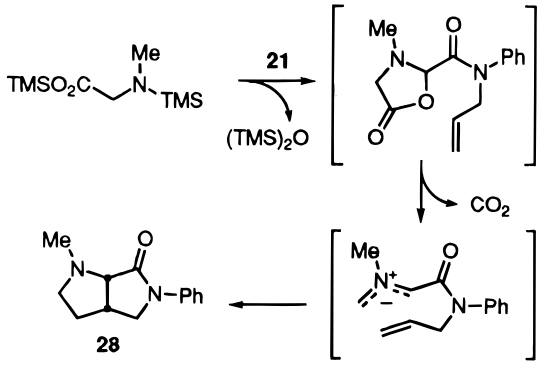


Figure 4. NOE Interactions Observed for Cycloadducts.

Scheme 7



Scheme 8



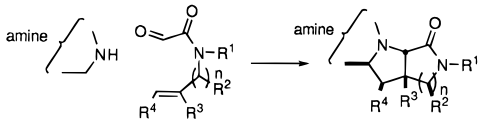
generality, however, since no cycloadduct was obtained with the *N*-methylalanine analog.

Perhaps the most interesting among the secondary amine condensations are those involving cyclic derivatives, since these components lead to novel ring systems that are not accessible by path A (Table 2, entries 1, 6, and 7). We were not successful in inducing unactivated amines such as pyrrolidine or piperidine to react. In spite of the electron withdrawing effect of the amide carbonyl, ylide formation in refluxing toluene requires an additional activating substituent α to the nitrogen, such as the carboxyl group of the amino esters or the aromatic ring of tetrahydroisoquinoline. Moreover, cycloadducts were not obtained from the acyclic analogs, benzyl amine, or methyl benzyl amine.

Variation of the Amine Substituent. In addition to phenyl, benzyl and cyclohexyl groups were evaluated as the nonparticipating amide substituent (Table 2, entries 8 and 9). Good yields were obtained on condensation of the *N*-phenyl and *N*-benzyl amides with tetrahydroisoquinoline, although the yield of cycloadduct was significantly lower when the cyclohexyl derivative was condensed with sarcosine ethyl ester.

Variation of the Unsaturated Component. The unsaturated component proved to be a fruitful position for introducing

Table 2. Solution-Phase Cyclization of Unsaturated Glyoxamides (Path B)



entry	R^1	*n*	R^2	R^3	R^4	amine	yield (%)	(compd)
1	Ph	1	H	H	H	THIQ	72	**22**
2	Ph	1	H	H	H	sarcosine Et ester	65[a]	**25**
3	Ph	1	H	H	H	*N*-Me-Ala Et ester	25[b]	**26**
4	Ph	1	H	H	H	Gly Me ester	25[c]	
5	Ph	1	H	H	H	*N*-TMS-sarcosine TMS ester	40	**28**
6	Ph	1	H	H	H	Pro Me ester	61	
7	Ph	1	H	H	H	picolinic Me ester	40	
8	benzyl	1	H	H	H	THIQ	72	
9	cyclohexyl	1	H	H	H	THIQ	37	
10	Ph	**2**	H	H	H	THIQ	58	
11	benzyl	**2**	H	H	H	THIQ	64	**23**
12	benzyl	**2**	H	H	H	sarcosine Et ester	66[d]	
13	benzyl	1	isopropyl	H	H	THIQ	56	**24**
14	Ph	1	H	methyl	H	sarcosine Et ester	62	
15	Ph	1	H	methyl	H	Pro Me ester	52	
16	Ph	1	H	CO_2Me	H	THIQ	35	
17	Ph	1	H	CO_2Me	H	Pro Me ester	56	
18	Ph	1	H	H	phenyl	THIQ	50	

[a] 5:1 *exo:endo*. [b] Accompanied by 25% of **27**. [c] This reaction carried out in refluxing xylenes. [d] 2.6:1 *exo:endo*.

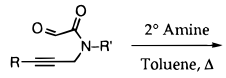
diversity into the target molecules, because considerable variation in this unit is allowed (Table 2, entries 10−18). The homoallyl analogs (entries 10−12) cyclized with comparable efficiency to the lower homologs (entries 1 and 2), affording the 5,6-bicyclic lactams. On the allyl group itself, substitution is tolerated at the allylic (entry 13), central (entries 14−17), and terminal positions (entry 18). In the α-isopropyl analog (entry 13), the stereocenter directs the course of the cycloaddition so that this group adopts the *exo*-configuration in the product, as assigned from NOE difference experiments (Figure 4). Successful cyclization of the carbomethoxy-substituted analog (entries 16 and 17) contrasts with the results obtained in the alternative route to ylide formation, in which intramolecular Michael addition from the aminoacyl group intervened on *N*-deprotection (see above).

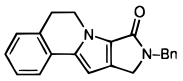
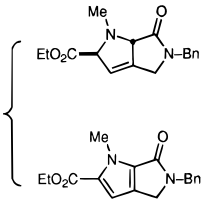
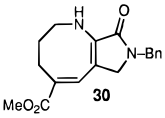
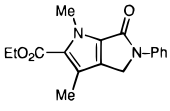
Cyclization is also achieved with propargylic substituents (Table 3), but a variety of side reactions lowered the isolated yields of pyrroline product. Condensation of sarcosine ethyl ester or THIQ with the simple propargyl and 2-butynyl glyoxamides afforded low yields of pyrrolines, accompanied by significant amounts of the pyrrole oxidation products. The proline ester, in contrast, affords a pyrroline intermediate that undergoes ring-opening to the azacyclooctadiene isomer **30** (entry 3), perhaps via electrocyclic ring-opening of ylide **29** (Scheme 9).

Alternative Method for Glyoxamide Preparation. Although oxidative fragmentation of symmetrical tartramides is an efficient source of glyoxamides for scouting solution phase cycloadditions, it was not suitable for solid phase synthesis. An effective alternative was Swern oxidation of the corresponding glycolamides, which in turn are available from coupling the unsaturated amine with acetoxyacetic acid, followed by methanolysis of the ester (Scheme 10). The crude product, submitted without purification to the condensation with THIQ, afforded tetracyclic material in 64% yield, based on the glycolamide. The slightly lower yield may be due to contamination of the glyoxamide with triethylamine salts from the oxidation.

Comparison of the Two Methods of Ylide Generation. We were curious whether the unsymmetrical, *anti*−*syn* ylide required for cyclization was fully equilibrated prior to ring formation or whether a kinetic preference is manifested on condensation of equivalent components, e.g., a sarcosine amide with a glyoxamide such that one carbonyl takes the *syn* position and the other the *anti*. The latter possibility was ruled out by two parallel experiments: condensation of sarcosine *N*-(allyl)-aniline with *N*-(homoallyl)glyoxanilide versus condensation of sarcosine *N*-(homoallyl)anilide with *N*-(allyl)glyoxanilide (Scheme 11). Both reactions gave the same 5,5-product in comparable yields, thus showing that the ylides are fully equilibrated and also that cyclization onto the allyl group occurs more rapidly than onto the homoallyl moiety.

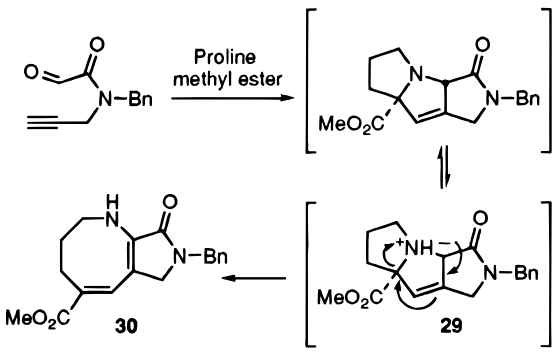
Table 3. Cyclization of Propargylic Amides



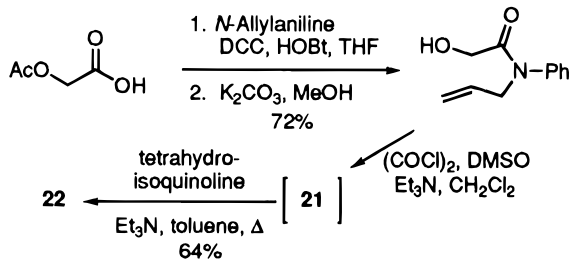
Entry	R	2° Amine	Cycloadduct	Yield
1	H	Tetrahydro-isoquinoline		30%
2	H	Sarcosine ethyl ester		35% 20%
3	H	Proline methyl ester	 **30**	20%
4	Me	Sarcosine ethyl ester		45%

Solid-Phase Chemistry. The results of the solution-phase experiments outlined above served to delineate the general steric and electronic requirements of the cyclization reactions and provided guidelines for choosing the unsaturated amines, amino acids, and carbonyl components or secondary amines that could

Scheme 9



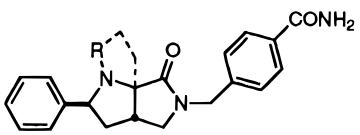
Scheme 10



go into a library. The next step was to demonstrate that the general reaction schemes could be adapted to the solid-phase format. This "transfer" involves two distinct stages: first, devising a strategy for the assembly that would provide the greatest flexibility (and maximize diversity) and that would take advantage of the particular benefits of solid-phase format; second, preparing individual compounds in a batchwise fashion to find resins and conditions that would ultimately be suitable for library construction.

A number of strategies are available for linking a synthetic substrate to the solid phase. Two potential routes for construction of the secondary amines on the solid support are shown in Scheme 12. While the commercial availability of a wide variety of unsaturated bromides makes alkylation of a resin-bound amine attractive, this sequence would not take advantage of one of the primary advantages of the solid-phase format, namely the ability to use an excess of reagent, since quaternization of the resin-bound amines would present a problem. We therefore pursued the alternative: displacement of a resin-bound halide.

Cycloadducts from path A (Scheme 3) were synthesized on solid phase as outlined in Scheme 13. Initial experiments were performed with the Rink amide derivatives of both conventional polystyrene resin[62] and the poly(ethyleneglycol)-derivatized (Tentagel) resin.[63] Although these resins were ultimately abandoned in favor of the Wang resin,[64] our initial studies led to the formation of compounds **31s** and **31p** and indicated the feasibility of the reaction scheme. The Wang resin, in which the functionality is a *p*-alkoxybenzyl alcohol,[64] is commercially available and inexpensive, and it can be obtained with high loading levels (1 mmol/g).



31s R = Me,H 50%
31p R = $(CH_2)_3$ 63%

Ester **32** was prepared by esterification of Wang resin with *p*-chloromethylbenzoic acid and diisopropylcarbodiimide (DIC) in the presence of 4-(dimethylamino)pyridine (DMAP). Displacement with an excess of allylamine afforded the secondary amine **33**, which was coupled to Fmoc-proline with DIC to give the amide **34**; small samples of this resin (ca. 10 mg) were treated with piperidine to determine the Fmoc loading level by colorimetric analysis.[65] In addition, after each of the chemical steps described above, small portions (ca. 50 mg) of functionalized resin were treated with TFA and the material liberated was analyzed by ^{1}H NMR; at each point, the major product visible in the spectrum of the crude material was the desired compound.

The free aminoamide resin **35** was carried on to the cycloaddition reaction. Use of either 2 or 10 equiv of benzaldehyde in refluxing toluene did not change the amount of tricyclic compound isolated upon cleavage. Moreover, although the Kaiser test[66,67] was not suitable for monitoring the disappearance of the secondary amine, the chloranil test[68,69] proved to be quite effective and allowed us to determine the reaction progress qualitatively. Cleavage of the tricyclic product from the resin afforded free acid **37** as a red oil; however, analysis of the ^{1}H NMR spectrum of the crude material clearly indicated the presence of a single cycloadduct, with only minor amounts of other products. To facilitate purification of the zwitterionic product, the methyl ester was prepared using EDC/DMAP/MeOH and purified by chromatography to give **38** as an analytically pure solid in 60% overall yield from **34**.

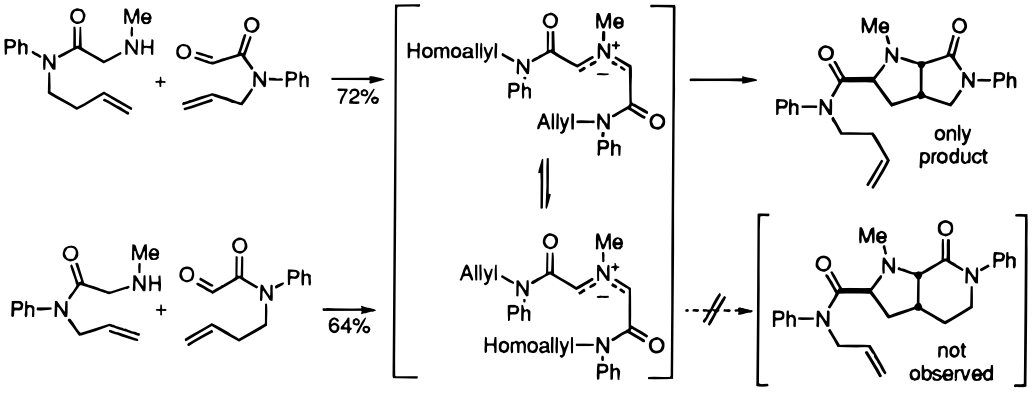
One practical aspect of these reactions is noteworthy. While the coupling and deprotection steps are carried out in standard peptide synthesis flasks and agitated with a wrist-action shaker, the amine displacement and cycloaddition reactions are carried out in conventional round-bottom flasks equipped with magnetic stirrers and warmed with heating mantles. Although we were concerned about the mechanical stability of these resins, examination of an aliquot of resin beads after each of these steps using a dissection microscope revealed that fewer than 1% of the beads had fractured during the course of the reaction.

This synthesis indicated that the solution-phase methodology could be transferred readily to the solid phase and afford comparable yields of cycloadducts. Using the strategy outlined in Scheme 14, we prepared a small library of compounds using the [3 + 2] cycloaddition reaction. These compounds were prepared in batch syntheses using a combination of two amines, two amino acids, and two carbonyl components to give eight separate compounds.

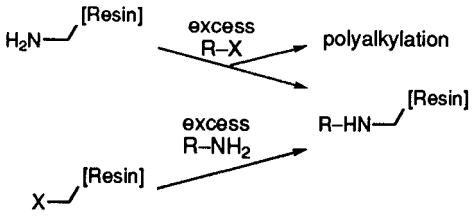
A single batch of Wang resin was functionalized with chloromethylbenzoic acid, split in half, and allowed to react with either allyl- or homoallylamine to give **33** (allyl) and **33** (homoallyl). Although this step was not monitored directly, prolonged reaction times (>12 h) and vigorous stirring proved to be important in ensuring that this step proceeded in >90% yield, as determined by Fmoc quantitation after the subsequent aminoacylation step. Each of these resin portions was split and coupled with either Fmoc-Sar-OH or Fmoc-Pro-OH, affording the four cyclization precursors **34**. Fmoc quantitation of samples from each of the four resin batches at this point indicated that the loading levels were about half of the nominal loading. Each batch of the free amines **35** was then split and reacted with 2-furaldehyde or benzaldehyde to give **36**, which was cleaved from the resin and treated with MeOH/EDC/DMAP or with diazomethane to form the methyl esters **38**. The yields for the eight cycloadducts shown in Table 4 represent the yield of purified material, based on the resin loading at the Fmoc-amino acid step. Although the yields for the esters isolated from the

(62) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787−3790.
(63) Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 113−129.
(64) Lu, G.-S.; Mosjov, S.; Tam, J. P.; Merrifield, R. B. *J. Org. Chem.* **1981**, *46*, 3433−3436.

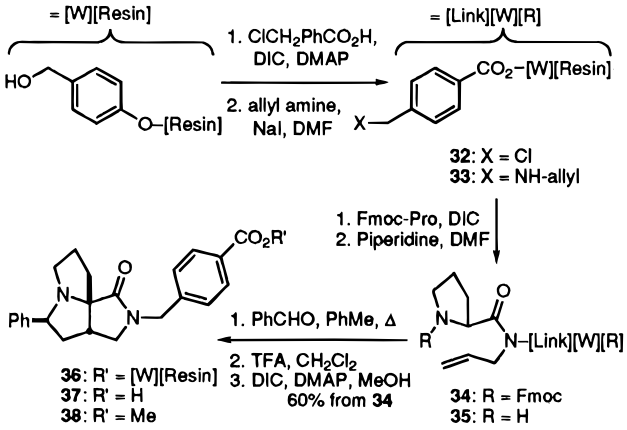
Scheme 11



Scheme 12



Scheme 13

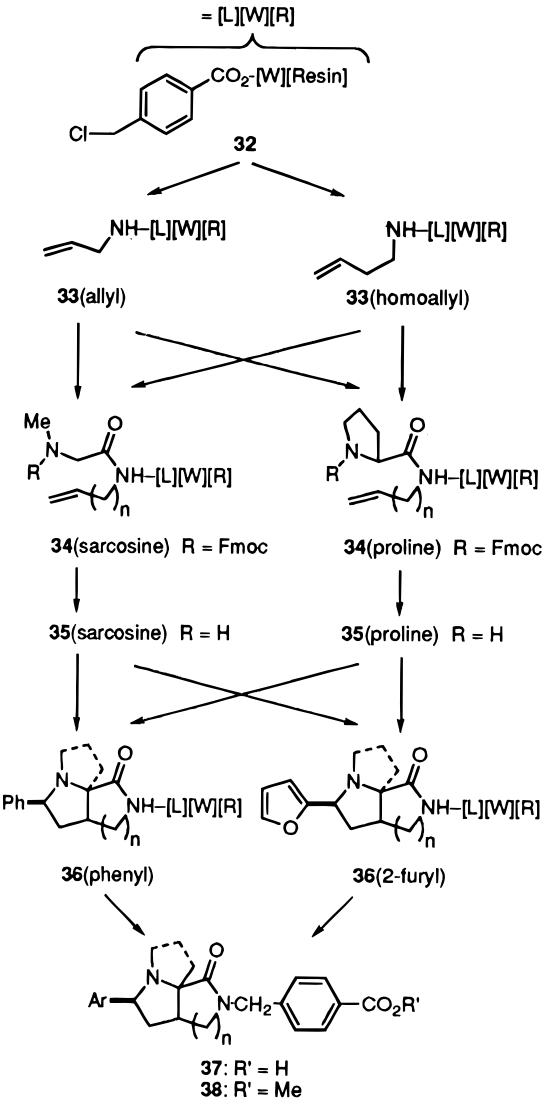


above sequence are variable, they are comparable to or slightly better than those obtained in solution. Some of this variability may result from the esterification and isolation steps after cleavage from the resin.

For translation of the cycloadditions via path B to solid phase, we chose polystyrene resin with the Rink linker, an acid-labile trialkoxybenzhydryl amine, as the tether point. The possibility of an ester linkage to a Wang resin (*p*-alkoxybenzyl alcohol as the tether point)[64] was abandoned when it proved to be labile to the conditions for methanolysis of the acetate prior to oxidation. The sequence for solid-phase assembly was therefore demonstrated as illustrated in Scheme 15, which involved the same steps for formation of the secondary allylic amine as employed for path A.

p-(Chloromethyl)benzoic acid was coupled to the Rink linker[62] with DIC and DMAP, and the halide was displaced with excess allylamine with iodide catalysis. Acetoxyacetic acid was then coupled to the resin-bound allylic amine **40** with DIC and DMAP. Acetate hydrolysis was accomplished with potassium carbonate in methanol and DMF, with the latter solvent required to swell the polystyrene resin. The resin-bound

Scheme 14



hydroxyacet amide **42** was oxidized cleanly to the glyoxamide **43** using the conditions developed by Swern.[70] The dimethyl sulfide and amine salt byproducts of this oxidation were removed by washing the resin with several portions of dichloromethane. Treatment of the resulting glyoxamide-derivatized resin with THIQ and triethylamine in refluxing toluene for 18

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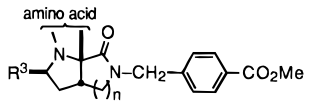
(70) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

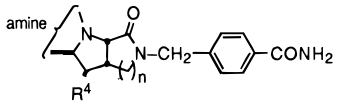
Table 4. Yields of Cycloadducts from Solid-Phase Synthesis, Path A



entry	amino acid	*n*	R^3	yield[a] (%)
1	Sar	1	phenyl	32
2	Sar	2	phenyl	29
3	Pro	1	phenyl	63
4	Pro	2	phenyl	35
5	Sar	1	furyl	75
6	Sar	2	furyl	39
7	Pro	1	furyl	49
8	Pro	2	furyl	52

[a] Yield of purified product, based on resin loading of Fmoc-amino acid; post cleavage esterification with diazomethane except for entries 5, 7, and 8 (MeOH/EDC/DMAP).

Table 5. Cycloadducts from Solid-Phase Synthesis, Path B



	unsaturated amine		
yield[a] (%) secondary amine	**A**: allyl ($n = 1$, $R^4 = H$)	**B**: homoallyl ($n = 2$, $R^4 = H$)	**C**: cinnamyl ($n = 1$, R^4 = phenyl)
1: tetrahydroisoquinoline	45	30	18
2: sarcosine Et ester	48[b]	30[c]	25
3: proline Me ester	34	38	20

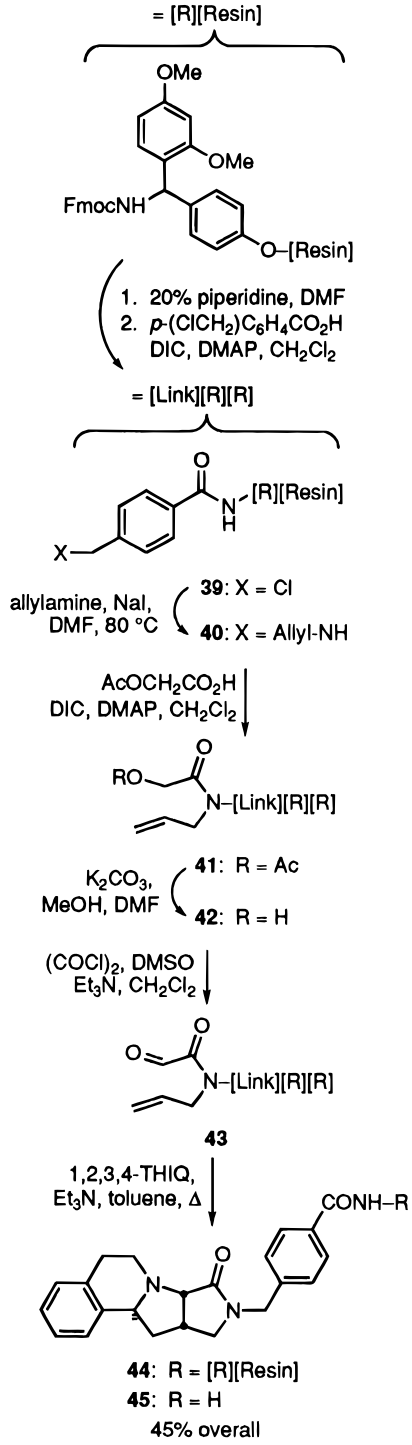
[a] Yields reported for material purified by column chromatography and based on the nominal loading on the commercial resin. [b] 12:1 *exo: endo*. [c] 3:1 *exo:endo*.

h, followed by trifluoroacetic acid-mediated release of the products from the resin afforded bicyclic lactam **45** in 45%, based on the nominal loading of the commercial resin, after purification by column chromatography. This yield translates into an average 89% per step, demonstrating that the sequence illustrated in Scheme 8 was readily adapted to solid-phase synthesis. The potential utility of the reaction sequence for construction of a library of bicyclic lactams was evaluated by synthesizing nine analogs in parallel fashion, as illustrated in Scheme 16.

A sample of the *p*-(chloromethyl)benzoyl resin was divided in three portions, and each was treated with one of three unsaturated primary amines: allylamine, homoallylamine, and cinnamylamine. The resin samples were coupled with α-acetoxyacetic acid, deacetylated to afford the glycolamide resins, and then further subdivided into three portions. The nine resin batches were oxidized separately and condensed with one of three secondary amines: THIQ, sarcosine ethyl ester, and proline methyl ester. The final products were isolated by cleavage from the resin with 95% TFA−water to give the bicyclic lactams shown in Table 5.

The crude products were analyzed by ^{1}H NMR, which, for the allyl- and homoallylamine-derived products (Table 5, columns 1 and 2), showed the exclusive presence of the cycloaddition products. The yields for these cases were determined after column chromatography and correspond to 80−90% per step for the six reactions from commercial resin to TFA-cleavage. In contrast, the yields were lower for the cinnamylamine-based products (column 3). In these cases, ^{1}H NMR analysis of the crude products revealed the presence of significant amounts of uncyclized materials, suggesting that conversion of the substituted alkene requires a longer reaction time than the unsubstituted derivatives.

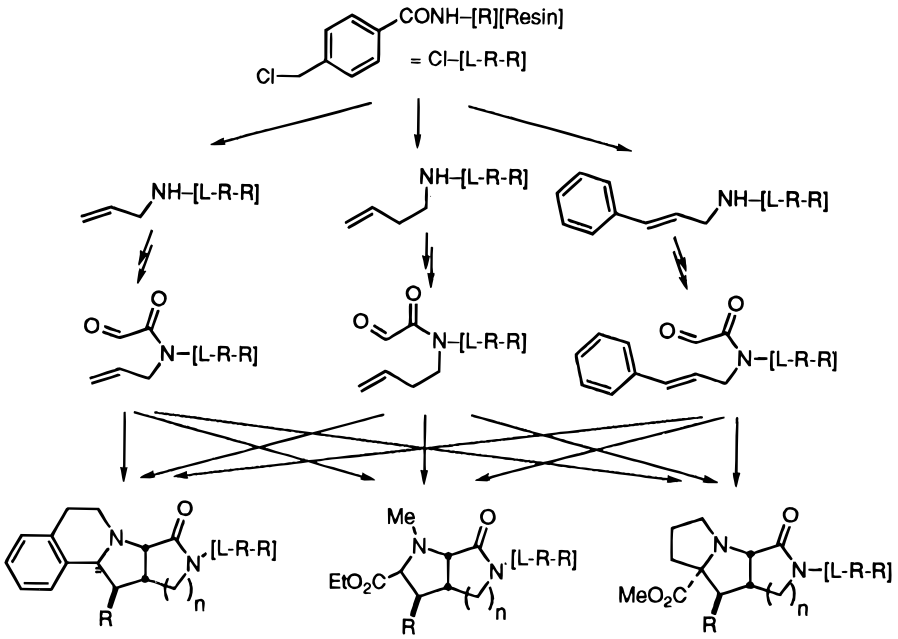
Scheme 15



Conclusions

The implementations of the intramolecular [3 + 2] azomethine ylide cycloaddition described above afford a variety of functionalized, polycyclic lactams in solution and on solid phase. The starting components are simple materials that are readily available, the cyclization process tolerates considerable variability among the substituents, and the two routes provide a number of ring systems and substitution patterns on the bicyclic pyrrolidine skeleton. Ten different ring systems with the pyrrolidinolactam core have been prepared by these methods, of which to our knowledge only the two bicyclic examples[51,52] are represented in compounds previously described (Figure 5). The two assembly sequences satisfy the criteria proposed for an effective combinatorial synthesis and show considerable

Scheme 16



promise for the preparation of libraries of interesting and previously unknown structures.

Experimental Section[71]

General Procedures. Standard Procedure for Cycloadditions of Aminoacyl Amides in Solution. The amine (1 equiv), carbonyl derivative (2 equiv), and Et_3N (1 equiv) are dissolved in toluene to give a final concentration of approximately 0.1 M in amine. The resulting solution is heated at reflux until no starting amine remains by TLC analysis (typically 16 h). The solution is transferred to a separatory funnel using CH_2Cl_2, diluted with CH_2Cl_2, and washed with 1 N NaOH, and the aqueous layer is extracted with additional CH_2Cl_2. The combined organic layers are washed with brine, dried, and concentrated, and the products are purified by chromatography (EtOAc/hexanes) or recrystallization.

Representative Syntheses. [3a*R-(3aσ,5σ,9a*R**)]-Hexahydro-2,5-diphenyl-2*H*,7*H*-pyrrolo[3,4-*d*]pyrrolizin-1-one (4p).** A solution of amine **3p** (76 mg, 0.33 mmol; see Supporting Information) and benzaldehyde (70 mg, 0.66 mmol) in toluene (10 mL) was heated at reflux for 16 h and then concentrated to an oil which was purified by chromatography (1:1 hexanes/EtOAc) to give tricycle **4p** as a solid (74 mg, 74%) after evaporation of the solvent: mp 131−132 °C; TLC R_f = 0.27 (1:1 hexanes/EtOAc); IR 1691, 1496, 1402, 1304 cm^{-1}; ^{1}H NMR δ 7.76 (m, 2), 7.55−7.11 (m, 8), 4.38 (dd, 1, J = 5.1, 11.5), 4.09 (m, 1), 3.50 (dd, 1, J = 4.1, 10.1), 2.75 (m, 1), 2.66 (m, 1), 2.53 (m, 1), 2.45 (m, 1), 2.34 (m, 1), 2.04 (m, 2), 1.75 (m, 2); ^{13}C NMR δ 175.9, 139.4, 138.6, 128.7, 128.5, 128.0, 127.2, 124.5, 119.7, 79.8, 64.4, 51.8, 49.1, 40.1, 35.9, 35.5, 26.4; HRMS (FAB) calcd for $C_{21}H_{23}N_2O$ (MH^+): 319.1810. Found 319.1802.

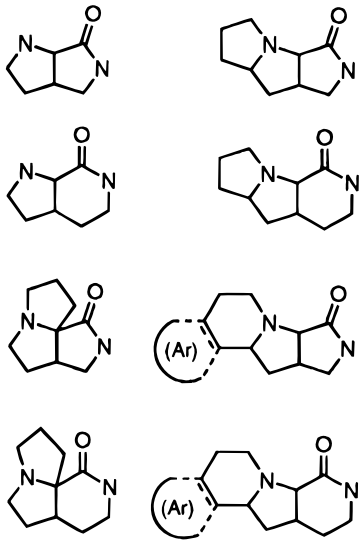


Figure 5. Polycyclic pyrrolidino-lactam ring sytems prepared by intramolecular azomethine ylide cycloaddition.

***N*-Allyl-*N*-phenyl 3-Methyl-2,5-diphenyl-4-oxazolidinecarboxamide (5).** A mixture of amine **3s** (83 mg, 0.40 mmol; see Supporting Information), benzaldehyde (84 mg, 0.80 mmol), and Et_3N (55 μL, 0.40 mmol) in toluene (3 mL) was treated according to the general cyclization procedure to yield an oil which was purified by chromatography (3:2 hexanes/EtOAc v:v) to give two products. The slower-eluting fraction (21 mg, 25%) was bicycle **4s**; the more quickly eluting fraction (39 mg, 46%), 2:1 adduct, **5**, was obtained as an inseparable mixture of isomers: TLC R_f = 0.63 (3:2 hexanes/EtOAc v:v); IR 1663, 1493 cm^{-1}; ^{1}H NMR δ 7.60 (d, J = 6.5) and 7.57−7.17 (m) (15 total); 6.03−5.77 (m, 1), 5.42 (d, J = 8.5) and 5.35 (d, J = 5.0) (one total); 5.15−4.69 (m, 2); 4.34 (d, J = 6.2), 4.32 (dd, J = 6.4, 15.6) and 4.22 (dd, J = 6.5, 14.4) (two total); 3.28 (d, 0.5, J = 8.5), 2.32 (s), 2.18 (s), 2.16 (s), and 2.13 (s) (three total); ^{13}C NMR δ 167.7, 140.9, 138.9, 138.8, 134.2, 132.4, 129.6, 129.3, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 127.8, 127.7, 127.0, 126.6, 118.3, 108.7, 99.9, 97.1, 83.3, 79.0, 72.8, 52.9, 52.5, 36.3, 26.0; HRMS (FAB) calcd for $C_{26}H_{27}N_2O_2$ (MH^+) 399.2072, found 399.2064.

[2*R-(2α,3aα,6aα)]-5-Cyclohexylhexahydro-2-(4-methoxyphenyl)-1-methyl-1*H*-pyrrolo[3,4-*b*]pyrrol-6-one (6).** A solution of sarcosine *N*-cyclohexyl-*N*-2-propenyl amide (210 mg, 1.00 mmol) and *p*-anisaldehyde (272 mg, 243 μL, 2.00 mmol) in toluene (10 mL) was heated at reflux for 3 h. Crystals formed on cooling to room temperature; these crystals were collected by filtration, and the remaining oil was purified by chromatography (4:1 EtOAc/hexanes) to yield a white solid which was recrystallized from EtOAc to give

(71) **General**. Secondary amines were prepared, when necessary, by the method of McCann and Overman.[72] Unless otherwise noted: reaction workups culminated in drying the solution over $MgSO_4$ and evaporating the solvent under reduced pressure; flash chromatography was performed by the method of Still, Kahn, Mitra,[73] using 60-mesh silica gel; NMR spectra were recorded in $CDCl_3$ and reported as chemical shift (multiplicity, number of hydrogens, coupling constants in Hz) referenced to tetramethylsilane or to the residual solvent peak (4.63 for *H*OD, 3.30 for CD_2*H*OD, 7.24 for C*H*Cl_3, 49.0 ppm for *C*D_3OD, or 77.0 ppm for *C*DCl_3).

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bicycle **6** as X-ray quality crystals (153 mg, 47% overall yield): mp 138−140 °C; IR 1677 cm^{-1}; ^1H NMR δ 7.20 (d, 2, J = 8.7), 6.86 (d, 2, J = 8.7), 3.98 (m, 1), 3.92 (d, 1, J = 7.8), 3.80 (s, 3), 3.54 (dd, 1, J = 8.2, 10.0), 3.46 (dd, 1, J = 6.3, 9.8), 3.08 (dd, 1, J = 2.2, 10.0), 2.95 (m, 1), 2.43 (s, 3), 2.14 (m, 1), 1.91 (ddd, 1, J = 2.5, 6.3, 13.0), 1.81−1.70 (m, 5), 1.47−1.32 (m, 4), 1.12 (m, 1); ^{13}C NMR δ 171.2, 158.9, 133.6, 128.5, 113.8, 68.1, 66.6, 55.3, 50.5, 48.8, 44.2, 35.1, 32.5, 30.8, 29.9, 25.5, 25.4; MS (EI) 312.8 (100, M^+); Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.27; H, 8.50; N, 8.55.

[3a*R-(3aσ,4α,5σ,9a*R**)]-2,4,5-Triphenylhexahydro-2*H*,7*H*-pyrrolo[3,4-*d*]pyrrolizin-1-one (7).** A solution of proline *N*-phenyl-*N*-(*E*)-3-phenyl-2-propenyl amide (195 mg, 0.64 mmol), benzaldehyde (135 mg, 1.30 mmol), and Et_3N (89 μL, 0.64 mmol) in toluene (5 mL) was reacted according to the general cyclization procedure. Chromatography (4:1 hexanes/EtOAc) gave tricycle **7** as a white solid (160 mg, 63%). A small sample was recrystallized from EtOAc/hexanes to provide an X-ray quality analytical sample: mp 203−204 °C; TLC R_f = 0.20 (4:1 hexanes/EtOAc); IR 1700, 1494 cm^{-1}; ^1H NMR δ 7.72 (d, 2, J = 8.0), 7.34 (dd, 2, J = 7.8, 7.8), 7.29−6.99 (m, 7), 6.92 (d, 2, J = 7.1), 6.88 (d, 2, J = 7.2), 4.76 (d, 1, J = 7.5), 4.13−4.08 (m, 2), 3.47 (d, 1, J = 10.0), 3.29 (dd, 1, J = 6.1, 11.9), 3.10 (m, 1), 2.88 (m, 1), 2.52 (m, 1), 2.24 (m, 1), 2.11−2.03 (m, 2); ^{13}C NMR δ 177.9, 139.7, 137.5, 137.0, 129.6, 128.7, 128.1, 127.9, 127.8, 127.0, 126.5, 124.4, 119.5, 79.7, 72.3, 58.1, 47.9, 47.6, 41.9, 34.1, 28.3; MS (FAB) *m*/*z* 395 (100, MH^+); Anal. Calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 81.83; H, 6.71; N, 6.95.

***N*,*N*′-Diallyl-*N*,*N*′-diphenyltartramide (20).** To a solution of 3.00 g (15.8 mmol) of tartaric acid acetonide[74] and 4.21 g (31.6 mmol) of *N*-allylaniline in 160 mL of THF stirred at 0 °C was added successively 0.434 g (31.6 mmol) of 1-hydroxybenzotriazole and 6.52 g (31.6 mmol) of dicyclohexylcarbodiimide. The mixture was stirred at room temperature for 20 h, filtered and concentrated in vacuo. The crude yellow oil was purified by column chromatography over 150 g of silica gel (EtOAc/hexanes, 1:5) to afford 5.71 g (86%) of the diamide as a white solid after evaporation of the solvent: mp 73−74 °C; ^1H NMR δ 1.20 (s, 6), 4.19 (dd, 2, J = 14.6, 6.2), 4.29 (dd, 2, J = 14.6, 6.0), 4.70 (s, 2), 5.03−5.11 (m, 4), 5.75−5.85 (m, 2), 7.18−7.20 (m, 4), 7.33−7.40 (m, 6); ^{13}C NMR δ 26.2, 52.9, 75.9, 112.1, 118.2, 128.1, 128.3, 129.3, 132.4, 141.0, 167.6. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.64; H, 6.81; N, 6.68.

To a solution of 5.50 g (12.6 mmol) of the tartramide acetonide in 60 mL of THF was added 60 mL of 1 M HCl. The mixture was heated at reflux for 24 h, allowed to cool to room temperature, neutralized by addition of saturated $NaHCO_3$, and extracted with four 80-mL portions of EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude brown solid was recrystallized from EtOAc/hexanes to afford 3.37 g (71%) of tartramide **20** as a white solid after evaporation of the solvent: mp 126−127 °C; ^1H NMR δ 3.26 (br s, 2), 3.65 (s, 2), 4.10 (dd, 2, J = 14.7, 6.0), 4.35 (dd, 2, J = 14.7, 5.6), 5.03−5.09 (m, 4), 5.73−5.80 (m, 2), 6.90 (br s, 4), 7.15−7.27 (m, 6); ^{13}C NMR δ 53.8, 69.7, 118.4, 128.0, 128.4, 129.7, 132.1, 139.8, 169.7. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.47; H, 6.47; N, 7.36.

General Procedure for Formation of Glyoxamides and Condensation with Amine Components. A solution of the symmetrical tartramide precursor (0.25−0.5 mmol) in 1 mL of diethyl ether and 0.5 mL of THF is stirred at 0 °C and 1 equiv of periodic acid dihydrate is added in two portions over 30 min. Stirring at 0 °C is continued for an additional 45 min during which time a white solid precipitates. The supernatant is decanted, dried over 4Å molecular sieves, and concentrated in vacuo to afford the glyoxamide and its hydrate as a pale yellow oil. This material is not purified but carried on directly into subsequent reactions.

A solution of the crude glyoxamide and 1−1.25 equiv of the amine in toluene with 1−2 equiv of Et_3N is heated at reflux for 18 h, cooled, diluted with CH_2Cl_2, and washed with saturated $NaHCO_3$. The aqueous wash is back-extracted with CH_2Cl_2, and the combined organic extracts are dried ($MgSO_4$) and concentrated on a rotary evaporator. The residue is purified by chromatography (EtOAc/hexanes) to afford the cycloadduct. The following compounds were prepared in this fashion, with the amount and yield of the purified product indicated.

***N*-Allyl-*N*-phenylglyoxamide (21).** To a solution of 190 mg (0.5 mmol) of diol **20** in 1 mL of diethyl ether and 0.5 mL of THF stirred at 0 °C was added 114 mg (0.5 mmol) of periodic acid dihydrate in two portions over 30 min. Stirring at 0 °C was continued for an additional 45 min after which time a white solid had precipitated. The supernatant was decanted, dried over 4Å molecular sieves, and concentrated in vacuo to afford 164 mg (80%) of the glyoxamide **21** and its hydrate as a pale yellow oil: ^1H NMR δ 4.40 (m, 2), 5.12−5.24 (m, 2), 5.81−5.91 (m, 1), 7.15−7.45 (m, 5), 9.36 (s, 1). This material was not purified but carried on directly into subsequent reactions.

[7aR*-(7aα,10aα,11aβ)]-5,6,7a,9,10,10a,11,11a-Octahydro-9-phenyl-8*H*-pyrrolo[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinolin-8-one (22). A solution of 133 mg (1 mmol) of 1,2,3,4-tetrahydroisoquinoline, 101 mg (1 mmol) of Et_3N, and the crude preparation of glyoxamide **21** and its hydrate (0.8 mmol) in 2 mL of toluene was stirred under nitrogen at 110 °C for 20 h. After cooling, the solution was diluted with 30 mL of CH_2Cl_2 and washed with 15 mL of saturated $NaHCO_3$. The aqueous wash was extracted with two 20-mL portions of CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexanes, 2:1) to afford 174 mg (72%) of tetracycle **22** as a white solid after evaporation of the solvent: mp 165−166 °C; ^1H NMR δ 2.24−2.38 (m, 2), 2.87 (dt, 1, J = 15.6, 4.4), 3.02−3.08 (m, 2), 3.24−3.30 (m, 1), 3.44 (dt, 1, J = 17.2, 4.9), 3.66 (dd, 1, J = 10.1, 2.3), 3.98 (d, 1, J = 8.5), 4.10 (dd, 1, J = 10.1, 8.1), 4.26 (t, 1, J = 7.0), 7.04−7.07 (m, 1), 7.11−7.19 (m, 4), 7.36−7.40 (m, 2), 7.67−7.69 (m, 2); ^{13}C NMR δ 26.9, 32.5, 39.8, 45.7, 53.2, 61.2, 68.2, 120.1, 124.9, 126.0, 126.1, 126.4, 128.86, 128.88, 134.4, 137.1, 139.1, 172.2. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.66; H, 6.72; N, 9.12.

***N*-(3-Butenyl)-*N*-phenyl[2*R**-(2α,3aα,6aα)]-Hexahydro-1-methyl-6-oxo-5-phenyl-1*H*-pyrrolo[3,4-*b*]pyrrole-2-carboxamide (Scheme 11).** To a solution of 102 mg (0.25 mmol) of the di(*N*-homoallyl-*N*-phenyl)tartramide in 0.5 mL of THF and 1 mL of diethyl ether stirred in an ice bath was added 57 mg (0.25 mmol) of periodic acid dihydrate in two portions over 30 min. Stirring was continued for an additional 45 min, at which time a white solid had deposited on the bottom of the flask. The clear supernatant was decanted, dried (4Å molecular sieves), concentrated in vacuo, diluted with 1 mL of toluene, and added dropwise to a solution of 96 mg (0.47 mmol) of sarcosine *N*-allylanilide and 66 μL (0.47 mmol) of Et_3N in 1 mL of toluene. The mixture was heated at 110 °C for 5 h, diluted with 40 mL of CH_2Cl_2, and washed with 20 mL of saturated $NaHCO_3$. The $NaHCO_3$ wash was extracted with two 20-mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over 30 g of silica gel (hexanes/EtOAc, 1:1 then 1:2) to afford 128 mg (72%) of the 5,5-bicyclic adduct as a pale yellow oil: ^1H NMR δ 1.73−1.80 (m, 1), 2.23−2.33 (m, 3), 2.69 (s, 3), 3.34−3.39 (m, 2), 3.71−3.75 (m, 1), 3.77−3.85 (m, 2), 3.92 (m, 1, J = 8.9), 3.98 (dd, 1, J = 10.3, 8.7), 5.04−5.11 (m, 2), 5.73−5.83 (m, 1), 7.09−7.13 (m, 3), 7.29−7.36 (m, 3), 7.39−7.43 (m, 2), 7.53−7.55 (m, 2); ^{13}C NMR δ 32.2, 33.7, 36.9, 37.7, 48.3, 52.7, 64.2, 69.5, 116.8, 120.2, 124.7, 128.2, 128.4, 128.7, 129.9, 135.2, 139.3, 141.8, 172.1, 176.0. Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 74.21; H, 7.10; N, 10.65. The same compound was isolated in 62% yield on combination of sarcosine *N*-homoallylanilide and *N*-allylglyoxanilide.

[3a*R-(3aα,6aα)]-Hexahydro-1-methyl-5-phenyl-1*H*-pyrrolo[3,4-*b*]pyrrol-6-one (28, Table 2, Entry 5).** A mixture of 45 mg (0.5 mmol) of sarcosine and 272 μL (1.1 mmol) of bis-trimethylsilylacetamide in 0.5 mL of acetonitrile was stirred at room temperature for 1 h and at 40 °C for 30 min and then combined with a solution of glyoxamide **2** derived from 90 mg (0.25 mmol) of the tartramide precursor **2** in 1 mL of toluene. The resulting mixture was heated at reflux for 18 h and worked up as described for the general procedure to give 40 mg (40%) of the bicyclic product as a pale yellow oil: ^1H NMR δ 1.74−1.83 (m, 1), 2.19−2.26 (m, 1), 2.49 (dt, 1, J = 9.4, 6.4), 2.65 (s, 3), 2.93−3.02 (m, 1), 3.06−3.10 (m, 1), 3.19 (d, 1, J = 9.1), 3.59 (dd, 1, J = 9.9, 3.9), 4.00 (dd, 1, J = 9.9, 8.6), 7.11−7.15 (m, 1), 7.32−7.37 (m, 2), 7.61−7.64 (m, 2); ^{13}C NMR δ 32.5, 34.5, 41.3, 53.8, 57.3, 85.0, 120.2, 124.7, 128.8, 139.3, 172.8; HRMS calcd for $C_{13}H_{17}N_2O$ (MH^+) *m*/*z* 217.1341, found *m*/*z* 217.1346.

Methyl [3a*R-(3aα,7a*β*,8aα)]-octahydro-3-oxo-2-phenylpyrrolo-[3,4-*b*]pyrrolizine-7a-carboxylate (Table 2, Entry 6):** 148 mg (61%) as a pale yellow oil: ^{1}H NMR δ 1.61 (dd, 1, J = 13.1, 10.4), 1.77 (m, 1), 1.82−1.95 (m, 2), 2.21 (dt, 1, J = 12.6, 7.0), 2.78 (dd, 1, J = 13.1, 7.9), 3.06 (dt, 1, J = 11.0, 6.8), 3.11−3.19 (m, 1), 3.48 (dd, 1, J = 10.1, 0.8), 3.72 (s, 3), 3.91 (dd, 1, J = 10.1, 6.6), 4.01 (m, 1), 4.08 (d, 1, J = 7.8), 7.12−7.16 (m, 1), 7.32−7.37 (m, 2), 7.54−7.56 (m, 2); ^{13}C NMR δ 27.1, 36.1, 37.5, 41.5, 47.9, 49.8, 52.4, 66.3, 77.5, 120.1, 124.9, 128.8, 139.0, 171.9, 176.3; HRMS calcd for $C_{17}H_{21}N_2O_3$ (MH^+) m/z 301.1552, found m/z 301.1548.

[7a*R-(7aα,10α,10aα,11a*β*)]-5,6,7a,9,10,10a,11,11a-Octahydro-10-(1-methylethyl)-9-(phenylmethyl)-8*H*-pyrrolo[3′,4′:4,5]pyrrolo-[2,1-*a*]isoquinolin-8-one (Table 2, Entry 13).** To a solution of 165 μL (1.86 mmol) of oxalyl chloride in 4 mL of CH_2Cl_2 was added a solution of 268 μL (3.72 mmol) of dimethyl sulfoxide in 4 mL of CH_2Cl_2. The mixture was stirred at −78 °C for 20 min, and a solution of 115 mg (0.47 mmol) of the glycolamide precursor in 4 mL of CH_2Cl_2 was added. After 30 min of stirring, 0.66 mL (4.70 mmol) of Et_3N was added, and the mixture was stirred at room temperature for 1 h. The solution was then concentrated in vacuo to afford the desired glyoxamide, which was diluted with 1 mL of toluene and added dropwise to a solution of 58 μL (0.47 mmol) of 1,2,3,4-tetrahydroisoquinoline and 157 μL (1.13 mmol) of Et_3N in 1 mL of toluene stirred at room temperature under nitrogen. The mixture was heated at 110 °C for 18 h, cooled to room temperature, diluted with 30 mL of CH_2Cl_2, and washed with 15 mL of saturated $NaHCO_3$. The aqueous wash was extracted with two 20-mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexanes, 2:1) to afford 95 mg (56%) of the cycloadduct as a colorless oil: ^{1}H NMR δ 0.72 (d, 3, J = 6.9), 0.82 (d, 3, J = 6.9), 1.86−1.92 (m, 1), 2.05−2.17 (m, 2), 2.51−2.56 (m, 1), 2.81−2.88 (dt, 1, J = 16.5, 4.6), 2.96−3.04 (m, 1), 3.09 (m, 1), 3.19−3.25 (m, 1), 3.37−3.43 (m, 1), 3.78 (d, 1, J = 8.2), 3.79 (d, 1, J = 15.0), 4.02 (t, 1, J = 6.9), 5.15 (d, 1, J = 15.0), 6.96−6.98 (m, 1), 7.09−7.14 (m, 3), 7.26−7.34 (m, 5); ^{13}C NMR δ 14.1, 14.5, 18.3, 27.1, 27.8, 33.8, 40.0, 44.0, 45.8, 60.9, 67.2, 125.8, 125.9, 126.1, 127.5, 128.1, 128.6, 128.8, 134.6, 136.3, 137.5, 173.3; HRMS calcd for $C_{25}H_{28}N_2O$ (MH^+) m/z 361.2280, found m/z 361.2272.

5,6,9,10-Tetrahydro-9-(phenylmethyl)-8*H*-pyrrolo[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinolin-8-one (Table 3, entry 1): 80 mg (25%) of the pyrrole as a beige solid after evaporation of the solvent: mp 145−146 °C; ^{1}H NMR δ 3.10 (t, 2, J = 6.7), 4.09 (s, 2), 4.41 (t, 2, J = 6.7), 4.71 (s, 2), 6.39 (s, 1), 7.17−7.36 (m, 8), 7.53 (m, 1); ^{13}C NMR δ 28.9, 41.3, 46.0, 46.7, 97.7, 123.3, 127.2, 127.3, 127.4, 127.9, 128.3, 128.7, 128.9, 131.3, 133.1, 137.3, 138.0, 162.3. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found C, 80.32; H, 5.90; N, 8.92.

Ethyl [2*R-(2α,6aα)]-2,4,5,6a-tetrahydro-1-methyl-6-oxo-5-(phenylmethyl)-1*H*-pyrrolo[3,4-*b*]pyrrole-2-carboxylate (Table 3, entry 2):** 74 mg (35%) of the pyrroline as a pale yellow oil: ^{1}H NMR δ 1.27 (t, 3, J = 7.1), 2.77 (s, 3), 3.69 (d, 1, J = 12.7), 3.85 (dq, 1, J = 12.7, 1.8), 4.12−4.20 (m, 2), 4.43 (m, 3), 4.50 (m, 1), 5.75 (m, 1), 7.21−7.33 (m, 5); ^{13}C NMR δ 14.4, 36.2, 45.5, 46.6, 60.8, 71.9, 75.8, 122.4, 127.7, 128.0, 128.8, 135.8, 141.7, 171.0, 171.5; HRMS calcd for $C_{17}H_{21}N_2O_3$ (MH^+) m/z 301.1552, found m/z 301.1554.

Methyl 2,3,4,7,8,9-hexahydro-9-oxo-8-(phenylmethyl)-1*H*-pyrrolo[3,4-*b*]azocine-5-carboxylate (30, Table 3, entry 3): 67 mg (20%) of the ring-expanded product **30** as a bright yellow solid after evaporation of the solvent: mp 155−156 °C; ^{1}H NMR δ 1.39−1.46 (m, 2), 2.86−2.89 (m, 2), 3.52−3.55 (m, 2), 3.64 (s, 2), 3.72 (s, 3), 4.63 (s, 2), 4.70 (br s, 1), 7.09 (s, 1), 7.23−7.34 (m, 5); ^{13}C NMR δ 17.3, 25.2, 41.8, 46.7, 50.2, 51.7, 106.0, 126.3, 127.7, 128.1, 128.8, 134.8, 136.6, 140.1, 166.8, 167.8; HRMS calcd for $C_{18}H_{20}N_2O_3$ m/z 312.1474, found m/z 312.1476.

Syntheses on Solid Support. Preparation of *p*-(Allylaminomethyl)benzoyl Wang Resin (Allyl-Substituted Wang Resin). Wang resin (5.0 g, 0.71 mmol/g, 3.55 mmol), DMAP (ca. 100 mg), and 4-(chloromethyl)benzoic acid (1.2 g, 7.1 mmol) were suspended in CH_2Cl_2 (40 mL) in a solid-phase synthesis vessel. To this suspension was added DIC (2.2 mL, 14 mmol), and the resulting mixture was shaken for 24 h at room temperature. The resin was collected by filtration, washed with DMF (50 mL) and CH_2Cl_2 (10 × 50 mL), and transferred to a round-bottomed flask equipped with a magnetic stir bar. DMF (30 mL), NaI (ca. 100 mg), and allylamine (1.32 mL, 17.8 mmol) were added, and the resulting mixture was heated at 60 °C for 4 h and cooled to room temperature, and the resin was collected by filtration. This amination reaction was repeated. The resin was washed with CH_2Cl_2 (2 × 50 mL), Et_3N (50 mL), CH_2Cl_2 (3 × 50 mL), and Et_2O (50 mL) to give 6.02 g of allyl-functionalized resin.

Preparation of Homoallyl-Substituted Wang Resin. Wang resin (7.11 g, 0.71 mmol/g, 5.04 mmol) was converted in the same fashion to 8.67 g of the homoallyl functionalized resin.

Preparation of Sarcosyl-Allyl Wang Resin. Allyl-substituted resin (2.89 g, ≤1.70 mmol, based on nominal resin loading), Fmoc-Sar-OH (1.58 g, 5.10 mmol), and DMAP (ca. 50 mg) were placed in a solid-phase synthesis flask, and CH_2Cl_2 (20 mL) was added. DIC (797 μL, 5.10 mmol) was added to this suspension, and the resulting mixture was shaken for 12 h. The resin was collected, washed with DMF (50 mL), CH_2Cl_2 (10 × 50 mL), and Et_2O (50 mL), giving 2.69 g of Fmoc-protected sarcosyl resin with a loading of 0.32 mmol/g (by Fmoc quantitation). This resin was shaken in 20 mL of a 20% solution of piperidine in DMF (v:v) for 5 min. The resin was collected, and the reaction was repeated for 30 min. The collected resin was washed with CH_2Cl_2 (10 × 50 mL) and Et_2O (50 mL) to afford 2.51 g of sarcosyl-allyl resin (0.86 mmol based on the Fmoc quantitation).

Preparation of Sarcosyl-Homoallyl, Prolyl-Allyl, and Prolyl-Homoallyl Wang Resins. In a similar fashion, allyl- and homoallyl-substituted resins were converted to the sarcosyl-homoallyl (3.88 g, 2.05 mmol by Fmoc quantitation), prolyl-allyl (2.33 g, 0.74 mmol), and prolyl-homoallyl (4.03 g, 1.91 mmol) resins.

Cleavage of Cycloadducts from Wang Resin. A sample of functionalized resin is stirred in a 95:5 solution (v:v) of TFA/H_2O (10 mL/g of functionalized resin) for 1 h at room temperature. The resin is then collected by filtration and washed with 50 mL of CH_2Cl_2. Concentration of the combined filtrates affords the crude cycloadduct.

Esterification of Cycloadducts from Solid Phase. EDC/MeOH. The crude material resulting from cleavage from the resin is dissolved in CH_2Cl_2 (0.1−0.2 M) at room temperature, and EDC (3 equiv), MeOH (3 equiv), and a catalytic amount of DMAP are added. The resulting mixture is allowed to stir for 18 h, diluted with CH_2Cl_2, and washed with 1 N NaOH. The aqueous layer is further extracted with CH_2Cl_2, and the combined organic layers are washed with brine, dried, and concentrated to afford an oil which is purified by chromatography using EtOAc as eluent.

Diazomethane. The crude material resulting from cleavage from the resin is taken up in THF and treated with an excess of diazomethane at 0 °C. The solution is stirred overnight at room temperature to allow evaporation of the excess diazomethane and then concentrated to afford an oil which is purified by chromatography using EtOAc as eluent.

Representative Syntheses, Path A. Methyl 4-[[[3a*R-(3a*σ*,5*σ*,-9a*R**)]-Hexahydro-1-oxo-5-phenyl-2*H*,7*H*-pyrrolo[3,4-*d*]pyrrolizin-2-yl]methyl]benzoate (Table 4, Entry 3).** Prolyl-allyl Wang resin (1.27 g, 0.66 mmol based on Fmoc-quantitation) was placed in a 25-mL round-bottomed flask, and benzaldehyde (695 mg, 6.6 mmol), Et_3N (92 μL, 0.66 mmol), and toluene (17 mL) were added. The suspension was heated at reflux for 24 h, and the resin was collected and washed with CH_2Cl_2 (50 mL) and Et_2O. Cleavage of the acid from the resin followed by esterification with diazomethane according to the general procedures provided 161 mg of the methyl ester (63% based on the loading of the Fmoc-prolyl functionalized resin) as an oil: IR 1718, 1680, 1280 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.97 (d, 2, J = 8.1), 7.40−7.22 (m, 7), 4.60 (d, 1, A of AB, J = 15.0), 4.49 (d, 1, B of AB, J = 15.0), 4.17 (dd, 1, J = 4.7, 12.1), 3.85 (s, 3), 3.54 (dd, 1, J = 10.1, 10.1), 3.02 (dd, 1, J = 4.2, 16.5), 2.52 (m, 1), 2.45−2.30 (m, 4), 1.93−1.77 (m, 4); ^{13}C NMR (CD_3OD) δ 176.5, 166.6, 141.6, 137.7, 129.5, 129.3, 128.2, 127.8, 127.6, 127.1, 78.9, 64.4, 51.0, 48.7, 46.1, 41.1, 40.7, 35.0, 33.9, 25.7; HRMS (FAB) calcd for $C_{24}H_{27}N_2O_3$ (MH^+) 391.2021, found: 391.2020.

Methyl 4-[[[2*R-(2α,3aα,6aα)]-2-(2-Furanyl)hexahydro-1-methyl-6-oxo-1*H*-pyrrolo[3,4-*b*]pyrrol-5-yl]methyl]benzoate (Table 4, Entry 5).** Sarcosyl-allyl Wang resin (800 mg, 0.28 mmol based on Fmoc-quantitation) was suspended in toluene (10 mL) in a round-bottomed flask. Furaldehyde (46 μL, 0.56 mmol) and Et_3N (39 μL, 0.28 mmol) were added to this solution, and the resulting mixture was heated at reflux for 18 h. The mixture was cooled to room temperature, and the resin was collected and washed with CH_2Cl_2 (10 × 5 mL). The

products were cleaved from the resin and esterified (EDC/MeOH) according to the general procedures to give 74 mg of the methyl ester (75% based on the loading of Fmoc-sarcosyl resin) as an oil: TLC R_f = 0.30 (EtOAc), IR 1722, 1677, 1277 cm^{-1}; ^1H NMR δ 8.00 (d, 2, J = 8.3), 7.35−7.32 (m, 1), 7.31 (d, 2, J = 8.3), 6.30 (dd, 1, J = 1.9, 3.2), 6.18 (dd, 1, J = 0.6, 3.1), 4.52 (d, 1, J = 14.9), 4.45 (d, 1, J = 14.9), 3.93−3.89 (m, 1), 3.90 (s, 3), 3.70 (d, 1, J = 8.5), 3.45 (dd, 1, J = 8.3, 10.0), 3.13 (m, 1), 2.99 (dd, 1, J = 2.7, 10.0), 2.50 (s, 3), 2.36 (ddd, 1, J = 5.8, 9.3, 12.8), 1.89 (ddd, 1, J = 5.5, 5.5, 12.8); ^{13}C NMR δ 172.8, 166.6, 153.9, 141.9, 141.4, 129.9, 129.5, 127.9, 109.8, 107.8, 67.2, 61.3, 52.0, 52.0, 46.2, 38.7, 36.0, 33.3; HRMS (FAB) calcd for $C_{20}H_{23}N_2O_4$ (MH^+) 355.1657, found 355.1654.

Representative Syntheses: Path B. *p*-(Chloromethyl)benzoyl Rink Resin (39). A sample of 4.00 g (2.20 mmol) of Rink amide resin (0.55 mmol/g nominal loading) was swelled in 86 mL of DMF. The solvent was drained and 86 mL of a 20% solution of piperidine in DMF was added to the resin. The mixture was shaken for 5 min, the solvent was drained, and another 86 mL of a 20% solution of piperidine in DMF was added. The mixture was shaken for 20 min at room temperature and drained. The resin was washed with seven 80-mL portions of DMF and dried in vacuo. To the resin in 68 mL of CH_2Cl_2 were added successively 788 mg (4.40 mmol) of 4-chloromethylbenzoic acid, 2.054 g (4.40 mmol) of PyBroP, and 765 μL (4.40 mmol) of diisopropylethylamine. The mixture was shaken at room temperature for 2 h, and the solution was drained. The procedure was repeated once. The resin was washed with six 40-mL portions of CH_2Cl_2 and dried in vacuo. A ninhydrin test performed on a sample of the dried beads was negative (no blue color observed), indicating that acylation had proceeded to completion.

***p*-(*N*-Glycolyl)-*N*-(2-Propenyl)aminomethyl)benzoyl Rink Resin (42).** To a suspension of 1.79 g (0.98 mmol) of acylated resin **39** in 10 mL of DMF in a round-bottomed flask were added 0.74 mL (9.8 mmol) of allylamine and a catalytic amount of sodium iodide. The mixture was heated at 75 °C for 3 h, and the resin was collected by filtration. The procedure was repeated a second time, and heating was prolonged overnight. The resin was collected on a fritted glass, washed with five 20-mL portions of CH_2Cl_2, and dried. A chloranil test performed on a sample of the dried beads was positive (blue color observed), indicating the presence of a secondary amine.

To a suspension of 1.63 g (0.89 mmol) of aminated resin **40** in 15 mL of CH_2Cl_2 were added successively 210 mg (1.78 mmol) of acetoxyacetic acid, 0.42 mL (2.67 mmol) of DIC, and a catalytic amount of DMAP. The mixture was shaken at room temperature for 3 h, and the resin was collected by filtration. The acylation reaction was repeated once with shaking overnight. The resin was collected on a fritted funnel, washed with five 20-mL portions of CH_2Cl_2, and dried. A chloranil test performed on a sample of the dried beads was negative (no blue color observed), indicating that acylation had proceeded to completion.

A suspension of 1.53 g (0.84 mmol) of acylated resin **41** and 1.16 g (8.4 mmol) of K_2CO_3 in 15 mL of methanol and 30 mL of DMF was shaken at room temperature for 18 h. The resin was collected, washed successively with water, methanol, and CH_2Cl_2, and dried in vacuo.

***p*-(*N*-Glycolyl)-*N*-(3-butenyl)- and -(cinnamyl)aminoethyl)benzoyl Rink Resins.** In a similar fashion, resin **39** was substituted with 3-butenylamine or cinnamylamine, acetoxyacetylated, and hydrolyzed to give the homoallyl- and cinnamyl-glycolamide resins.

4-[[[7aαR*,10aα,11a*β*]-[5,6,7a,9,10,10a,11,11a-Octahydro-8-oxo-8*H*-pyrrolo[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinolin-9-yl]methyl]benzamide (45). A solution of 96 μL (1.10 mmol) of oxalyl chloride and 157 μL of dimethyl sulfoxide in 5 mL of CH_2Cl_2 was stirred at −78 °C for 30 min, and 498 mg (0.33 mmol) of allyl-glycolamide Rink resin **42** in 5 mL of CH_2Cl_2 was added. The mixture was stirred at −78 °C for 1 h and allowed to warm to room temperature, and 0.38 mL (2.74 mmol) of Et_3N was added. The mixture was stirred at room temperature for 2 h. The resin was collected on a Buchner funnel, washed with five 10-mL portions of CH_2Cl_2, and placed in a round-bottomed flask containing 5 mL of toluene. After addition of 76 μL (0.55 mmol) of Et_3N and 68 μL (0.55 mmol) of 1,2,3,4-tetrahydroisoquinoline, the mixture was heated at 110 °C for 18 h. After cooling to room temperature, the resin was collected on a Buchner funnel and washed with two 10-mL portions of toluene and five 10-mL portions of CH_2Cl_2. The resin was then placed in 10 mL of 95% TFA/H_2O. The red mixture was stirred at room temperature for 1 h and filtered. The filtrate was neutralized by addition of saturated $NaHCO_3$ and extracted with two 50-mL portions of CH_2Cl_2 and one 50-mL portion of EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. ^1H NMR analysis of the crude product indicated the presence of one major product. Purification by chromatography (CH_2Cl_2/methanol, 20:1 then 15:1) afforded 45 mg (45% based on nominal loading) of tetracycle **45** as a yellow oil: ^1H NMR δ 2.02−2.11 (m, 1), 2.16−2.25 (m, 1), 2.84−2.89 (m, 2), 2.95−2.99 (m, 1), 3.04 (dd, 1, J = 10.3, 2.3), 3.18−3.24 (m, 1), 3.33−3.38 (m, 1), 3.46 (dd, 1, J = 10.2, 8.2), 3.89 (d, 1, J = 8.6), 4.13 (t, 1, J = 6.9), 4.35 (d, 1, J = 14.8), 4.61 (d, 1, J = 14.8), 6.05 (br s, 1), 6.60 (br s, 1), 6.99−7.02 (m, 1), 7.08−7.14 (m, 3), 7.29−7.35 (m, 2), 7.77−7.82 (m, 2); ^{13}C NMR δ 27.0, 32.9, 39.7, 45.9, 46.5, 51.7, 61.3, 67.3, 126.1, 126.5, 128.0, 128.3, 128.9, 132.9, 134.2, 140.3, 169.0, 172.5; HRMS calcd for $C_{22}H_{23}N_3O_2$ (MH^+), m/z 362.1869, found m/z 362.1872.

General Procedure for the Synthesis of Compounds of Table 5. A mixture of oxalyl chloride (4 equiv) and dimethyl sulfoxide (8 equiv) in CH_2Cl_2 (at 0.25 M) was stirred at −78 °C for 30 min, and the glycolamide Rink resin in CH_2Cl_2 (0.11 g/mL) was added. The suspension was stirred at −78 °C for 1 h, Et_3N (10 equiv) was added, and the mixture was stirred at room temperature for 2 h. The resin was collected on a fritted funnel, washed with five 20-mL portions of CH_2Cl_2, and dried briefly. To the resin in toluene (0.11 g/mL) was added the amine (1.5 equiv) and Et_3N (to neutralize amine-hydrochloride if necessary, plus 1.5 equiv), and the mixture was heated at reflux for 18−20 h. The resin was collected on a fritted funnel, washed with five 20-mL portions of CH_2Cl_2, dried, then suspended in 95% trifluoroacetic acid in water, and stirred at room temperature for 1 h. The mixture was filtered, and the filtrate was neutralized with saturated $NaHCO_3$ and extracted with two 80-mL portions of CH_2Cl_2 and one 80-mL portion of EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by chromatography on silica (eluted with CH_2Cl_2−methanol, 20−30:1) to afford the indicated amount of product. The reported yields are based on the nominal loading of the commercial Rink amide resin.

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Supporting Information Available: Experimental Procedures and characterization of synthetic intermediates and final products not described above; ^1H NMR spectra of crude products off resin (Table 4); and products for which melting points, but not recrystallization solvents, are reported (40 pages). See any current masthead page for ordering and Internet access instructions.

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