Postcondensation Modifications of Ugi Four-Component Condensation Products: 1-Isocyanocyclohexene as a Convertible Isocyanide. Mechanism of Conversion, Synthesis of Diverse Structures, and Demonstration of Resin Capture

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Abstract: The concept of a "universal isocyanide" that enables postcondensation modification of Ugi four-component condensation products is introduced. This strategy is suited for the synthesis of libraries. By using 1-isocyanocyclohexene as the isocyanide input in the Ugi reaction, the product cyclohexenamides can be converted to a variety of products. From the original α-(acylamino) amides, new carboxylic acids, esters, and thioesters are produced from acid-activated conversion of the cyclohexenamide moiety. It has been determined that the intermediate in conversion of this type is an oxazolinium-5-one (münchnone) that reacts with many nucleophiles to yield the products above. The münchnone can also undergo cycloaddition with acetylenic dipolarophiles to form pyrroles. Through internal nucleophilic attack, Ugi products are shown to convert to a protected monosaccharide derivative and to 1,4-benzodiazepine-2,5-diones. All of the conversions described consist of a single step. Resin capture of Ugi products is demonstrated, in which a solution condensation reaction is followed by trapping of the products onto solid support resin. Both the trapping step and subsequent cleavage of products from the resin occur in very high yield.

Introduction

Combinatorial chemistry has received much attention lately as a tool for drug discovery.[1,2] Unlike traditional approaches which involve separate synthesis of each individual analog or desired compound, combinatorial synthesis aims to yield large numbers of compounds based on a common core structure with a minimum of time and effort. This may be accomplished through parallel synthetic methods and readily available, diverse starting materials. Ideally, complete automation of the synthetic process would be achieved, thus taking maximum advantage of the parallel process.

Early work on combinatorial libraries used technologies readily adaptable to parallel synthesis. Peptides[3] and oligonucleotides[4,5] were exploited for combinatorial synthesis both because of the well-developed solid-supported synthetic methodology for each and because each offered a readily available pool of inputs for each coupling step. For example, for the creation of a library of all possible tetranucleotides (which encompasses $4^4 = 256$ members), all monomers are readily available, and the linear coupling techniques are quite standard.

More recently, published work has appeared[6−12] on libraries of small-molecule organic compounds, perhaps the most desired class of potential drug candidates. Development of libraries of these compounds is a more challenging endeavor in that (1) the synthesis should be efficient, (2) the synthesis should offer ample opportunites for the introduction of input diversity, and (3) the synthesis should be adaptable to solid support resin or high throughput solution arrays. Because standard peptides and oligonucleotides have limitations as bioavailable therapeutics, the payoff for development of small-molecule libraries is potentially great.

While very impressive results have been registered in this area, the strategies to date have been almost exclusively linear.[6,7,9−12] We believe that an important tool of combinatorial chemistry, the multiple-component condensation (MCC), is currently being underexploited.[13,14,17] A multiple-component condensation brings three or more reactants together in a single event to produce a final product that contains aspects of all inputs. An MCC thus offers greater possibilities for molecular diversity per step with reduced synthetic time and effort as compared to linear synthesis. For rapid combinatorial synthesis, this is a clear advantage.

We have recently focused our efforts on the Ugi four-component condensation (4CC) (Figure 1).[15] The Ugi reaction[16] brings together a carboxylic acid, an amine, an aldehyde or

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1996.

(1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251.
(2) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401.
(3) Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367−383.
(4) Latham, J. A.; Johnson, R.; Toole, J. J. *Nucleic Acids Res.* **1994**, *22*, 2817−2822.
(5) Chen, H.; Gold, L. *Biochemistry* **1994**, *33*, 8746−8756.
(6) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997−10998.
(7) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4708−4712.
(8) Chen, C.; Ahlberg Randall, L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2662.
(9) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909−6913.
(10) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172.
(11) Baldwin, J. J.; Burbaum, J. J.; Henderson, I.; Ohlmeyer, M. H. J. *J. Am. Chem. Soc.* **1995**, *117*, 5588−5589.
(12) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029−7030.
(13) For a recent example, see: Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819−7822.
(14) For a discussion of MCCs in library synthesis, see: Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115−123.
(15) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842−7843.

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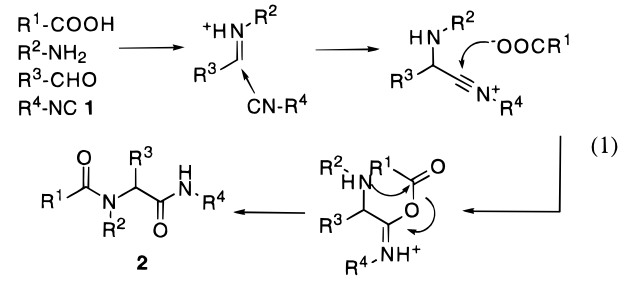


Figure 1.

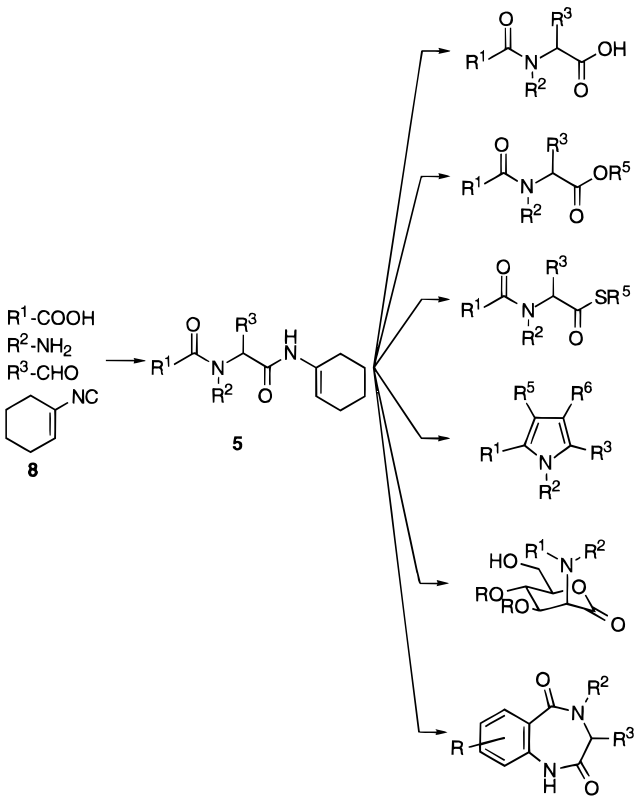


Figure 2. Single-step conversions of cyclohexenamide Ugi product **5**.

ketone, and an isocyanide in a one-pot condensation reaction to yield an α-(acylamino) amide (**2**). While the Ugi reaction is an excellent tool for a library synthesis of this core structure, it suffers from a lack of commercially available isocyanides **1**. Unlike the other three readily available components, somewhat fewer than two dozen isocyanides can be purchased, limiting potential libraries at the R^4 position. One possible solution is the creation of a sublibrary of isocyanides as inputs into a Ugi 4CC library.[17] Another approach will be described herein: we envisioned the concept of a "universal isocyanide," an input for the Ugi 4CC that can be converted, postcondensation, into different functionalities, thereby circumventing the lack of commercial isocyanide inputs as well as avoiding the need to synthesize and store a large number of isocyanides should commercial sources prove insufficient. The isocyanide that we present here, 1-isocyanocyclohexene (**8**), is a remarkably versatile substrate (see Figure 2) whose 4CC product **5** *can be converted in a single step to a variety of products* under acidic conditions, including many products that are otherwise inaccessible from the Ugi reaction.

(16) Gokel, G.; Lüdke, G.; Ugi, I., In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic: New York, 1971; pp 145−199.

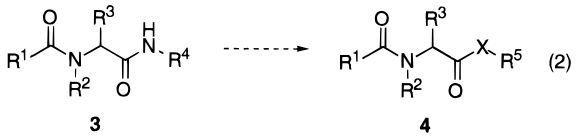
(17) Tempest, P. A.; Brown, S. D.; Armstrong, R. W. *Angew. Chem., Int. Ed. Engl.*, in press.

As effective as **8** has proven to be in 4CC product modifications, it should be noted that other universal isocyanides may turn out to be suited for different and more extensive conversions. For example, the convertible isocyanide strategy described here is acid activated. We are investigating other isocyanide inputs that can be activated for conversion by basic, neutral, or metal-mediated conditions. Of major importance to us at this point, however, is the idea of reducing the impact of a relatively unavailable input in library synthesis by introducing that input in a convertible form.

We present here evidence for the mechanism of transformation offered in our initial communication,[15] as well as new uses of Ugi 4CC products for the synthesis of pyrroles, sugars, and 1,4-benzodiazepine-2,5-diones. Finally, we demonstrate the *resin capture* of 4CC products of a solution reaction, which can be a useful tool in solid-supported library synthesis. In this strategy, a solution phase reaction is followed by trapping the reaction products onto functionalized resin. This method can combine the best features of both modes of synthesis—ease of monitoring and reduced need for multiple equivalents of reactants (solution reactions) with ease of isolation and purification (solid-supported reactions).

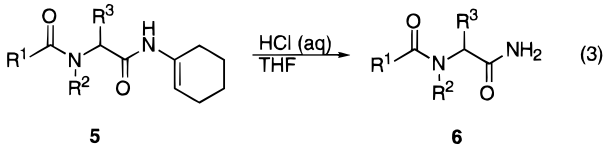
Results and Discussion

Cyclohexenamide Conversions. Our initial work in this area demonstrated transformation of Ugi products of type **3** to new products **4** (eq 2). Ugi has published work[18,19] on cleavable



carbonamide moieties R^4, but the methods to date require conversion of the amide group into another, more labile functionality, and involve at least three steps from the 4CC product **3**. In addition, these methods yield only the carboxylic acid derivative of **4** ($-XR^5 = -OH$).

However, Ugi had earlier demonstrated[20] the use of 1-isocyanocyclohexene (**8**) in a 4CC and had converted the enamide product **5** to the primary amide **6** (eq 3) through acidic hydrolysis. We decided to reinvestigate this transformation,



prompted by a report[21] that an enamide could be selectively cleaved to the corresponding methyl ester under acidic methanol conditions.

Synthesis of 1-isocyanocyclohexene (**8**) was straightforward and proceeded as shown in Scheme 1. Ugi's original procedure for synthesis of **8** was modified only in that better yields were obtained when **7** was purified prior to dehydration and triphosgene was used as the dehydrating agent in place of phosphorus oxychloride. Other syntheses of **8** have appeared in the literature.[22,23] 1-Isocyanocyclohexene can be stored

(18) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810−819.

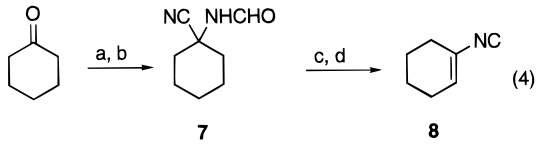
(19) Geller, J.; Ugi, I. *Chem. Scr.* **1983**, *22*, 85−89.

(20) Rosendahl, F. K.; Ugi, I. *Ann. Chem.* **1963**, *666*, 65−67.

(21) Fukuyama, T. Presented at the 35th Annual Buffalo Medicinal Chemistry Symposium, Buffalo, NY, May 1994.

(22) Barton, D. H. R.; Bowles, T.; Huisnec, S.; Forbes, J. E.; Llobera, A.; Porter, A. E. A.; Zard, S. Z. *Tetrahedron Lett.* **1988**, *29*, 3343−3346.

Scheme 1[a]



[a] Reagents and conditions: (a) NaCN(aq), NH_4Cl(aq), Et_2O, 61%; (b) HCOOH, Ac_2O, 44%; (c) ^tBuOK, THF; (d) triphosgene, DABCO, CH_2Cl_2, 50% (two steps).

indefinitely at −30 °C under an inert atmosphere, but darkens in a short time upon exposure to air. We have succeeded in easily preparing multigram quantities.

Ugi four-component condensations with **8** proceeded smoothly and in good yield (ca. 50−85%) for a variety of examples illustrated herein (see the Experimental Section). Conversions of the cyclohexenamide moiety were then attempted with various conditions and nucleophiles. When the isolated 4CC products were treated with the acidic conditions detailed in the footnotes to Table 1, the products listed were obtained in high isolated yield. As can be seen, the cyclohexenamide moiety has been converted under mild conditions to a variety of carboxylic esters, thioesters, and carboxylic acids. Not only are products that are not accessible via the Ugi reaction (i.e., esters) obtained, but amides can be synthesized from the carboxylic acids via standard carbodiimide coupling techniques to afford new Ugi products without requiring the appropriate isocyanide. This result greatly expands the scope of the 4CC and reduces the impact of its weakest component, the isocyanide input.

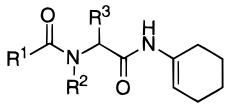
We next turned to in situ conversions of the cyclohexenamide. The goal was to perform some of the conversions of Table 1 without isolation of initial cyclohexenamide 4CC product. It was expected that simple acidification of a crude reaction mixture that contained the appropriate nucleophile would result in the cyclohexenamide being converted regardless of other species present. Results are shown in Table 2. After monitoring the Ugi reaction in methanol solution and judging it complete, the introduction of acetyl chloride (to generate HCl) and subsequent heating resulted in the product methyl esters listed in Table 2. Hydrolysis products (i.e., carboxylic acids), which might have arisen from the single equivalent of water produced in the 4CC, were not observed. By performing the cyclohexenamide conversion in a one-pot process, an overall five-component condensation is achieved, with the isocyanide input contributing only a single carbonyl carbon atom to the final structure.

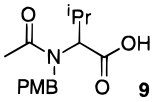
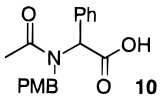
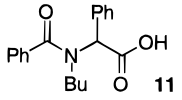
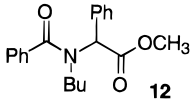
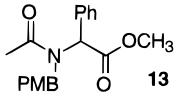
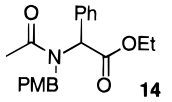
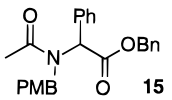
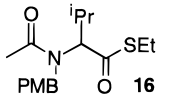
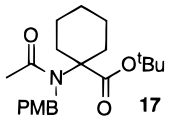
We next focused on the mechanism for this transformation. It is unusual that a carboxylic acid would result from acidic hydrolysis of an enamide, as shown in Table 1. One would expect instead the primary amide, because under aqueous acidic conditions, protonation of the cyclohexenamide would typically be followed by hydrolysis of the resulting *N*-acyliminium species to the amide and cyclohexanone.[24] While cyclohexanone is indeed observed as a product of these reactions, the primary amide is not.

A clue to the mechanism of transformation is given in Scheme 2. In attempts to convert **24** to the methyl ester under the acidic methanol conditions of both Tables 1 and 2, only the deformylated primary amide was isolated. This is the expected product on the basis of a mechanism of hydrolysis of an *N*-acyliminium species, but does not fit with the results in Tables 1 and 2. In additional experiments on **26** and **27**, it was not only established that deformylation under these acidic conditions[25] was very rapid (<30 min) but also that the absence of an acylated amine altogether (**28**) precludes formation of carboxylic acid as per Table 1. Thus, it appears that an *N*-acyl group is essential for the conversions shown in Tables 1 and 2, and its loss before the crucial step prevents the formation of the Table 1 products. This led us to propose[15] the mechanism detailed in Figure 3, which involves an oxazolinium-5-one (münchnone) intermediate. Protonation of the enamide gives the activated species **22**, which then cyclizes to the münchnone[26−29]**30** and eliminates cyclohexanimine. The reactive münchnone then is opened by

Table 1. Results of Cleavage of Cyclohexenamide 4CC Products

Condensation Product[a]



R^1	R^2	R^3	Nu:	Cond.[b]/ Yield[c]	Product
Me-	PMB-	^{i}Pr-	H_2O	A/56%	 **9**
Me-	PMB-	Ph-	H_2O	A/83%	 **10**
Ph-	Bu-	Ph-	H_2O	A/25%	 **11**
Ph-	Bu-	Ph-	MeOH	B/98%	 **12**
Me-	PMB-	Ph-	MeOH	B/100%	 **13**
Me-	PMB-	Ph-	EtOH	B/57%	 **14**
Me-	PMB-	Ph-	BnOH	C/75%	 **15**
Me-	PMB-	^{i}Pr-	EtSH	D/68%	 **16**
Me-	PMB-	-$(CH_2)_5$-	^{t}BuOH	E/64%	 **17**

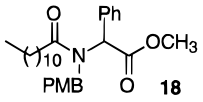
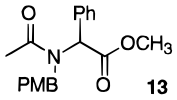
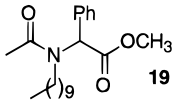
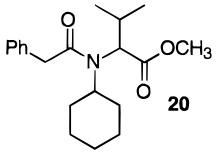
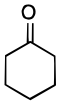
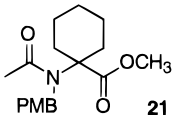
[a] PMB = *p*-MeO-benzyl. [b] Reaction conditions: (A) 1.7% HCl in THF, 23 °C, overnight; (B) indicated alcohol as solvent, 5 equiv of AcCl, 55 °C, 3 h; (C) 5 equiv of AcCl, 10 equiv of BnOH in THF, 55 °C, 3 h; (D) EtSH as solvent, 10 equiv of AcCl, 23 °C, overnight; (E) 5 equiv of AcCl, 10 equiv of ^{t}BuOH in THF, 55 °C, 48 h. [c] All yields are of isolated, purified product.

(23) Baldwin, J. E.; Yamaguchi, Y. *Tetrahedron Lett.* **1989**, *30*, 3335−3338.

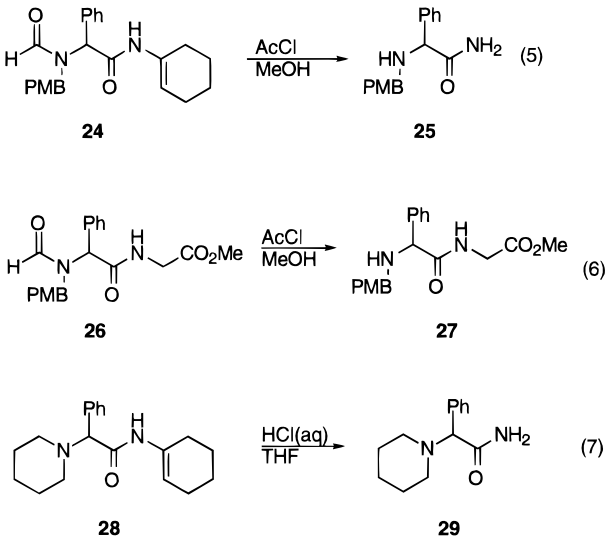
(24) Brossi, A.; Dolan, L. A.; Teitel, S. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 1−4.

(25) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991; pp 349−350.

Table 2. Results of In situ Acidic Methanolyses of Four Component Condensation Products

R^1COOH	R^2NH_2	R^3CHO	Product	Isol. Yld.
1-undecyl-	PMB-	Ph-	 **18**	65%
CH_3-	PMB-	Ph-	 **13**	79%
CH_3-	1-decyl	Ph-	 **19**	99%
$PhCH_2$-	C_6H_{11}-	^{i}Pr-	 **20**	67%
CH_3-	PMB-		 **21**	55%

Scheme 2



a nucleophile to yield the product **23**. Lack of an acylated amine (**28**), or its rapid loss (**24**), prevents the formation of **30**.

Pyrroles. While these experiments offered some evidence for the intermediacy of a münchnone in the cyclohexenamide conversion, more compelling proof would result from a 1,3-dipolar cycloaddition of a dipolarophile to the proposed intermediate. It is well-known that the anhydro-5-hydroxyoxazolium hydroxide species **31** (Figure 4), which are members of a larger class of azomethine ylides, undergo cycloadditions with a wide variety of dipolarophiles.[30] Perhaps the most common method of generating such species is the cyclodehydration of *N*-acyl-*N*-alkylamino acids using acetic anhydride and a nitrogenous base at elevated temperatures.[31]

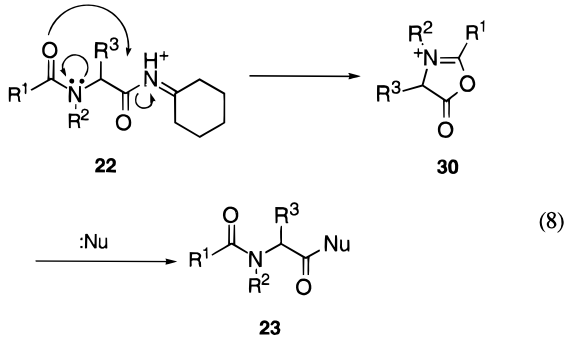


Figure 3. Proposed mechanism of cyclohexenamide conversions.

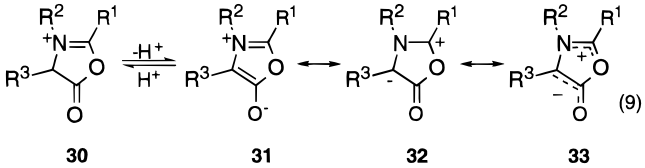
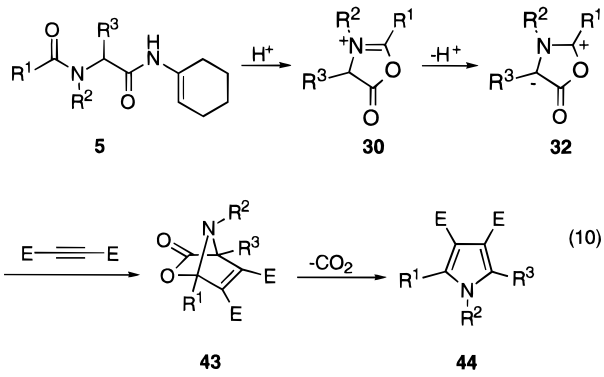


Figure 4. Resonance structures of active 1,3-dipoles derived from Ugi products.

Scheme 3



Therefore, we attempted cycloaddition of cyclohexenamide Ugi products under various acidic conditions with a selection of acetylenic dipolarophiles, with the expectation that the reaction would proceed as depicted in Scheme 3. Protonation of **5** is followed by cyclization and loss of cyclohexanimine to **30**, which loses a proton to form 1,3-dipole **32**. This 1,3-dipole undergoes a [3+2] cycloaddition reaction with the acetylene to **43**, which rapidly aromatizes with loss of CO_2 to the pyrrole **44**. Results of these reactions are shown in Table 3. Several general trends can be observed. First, unlike cyclodehydration procedures, which are typically run at 50−60 °C, higher temperatures and toluene as a solvent were necessary for improved or even observable yields. Second, the more electron withdrawing the acetylenic dipolarophile, the better the yields. Steric hinderance plays a role, as seen in the product ratios of **36** to **37**,[26] the failure of diphenylacetylene to react to form the tetraphenylpyrrole,[31] and the failure to form the bicyclic pyrrole expected from the γ-lactam 4CC product. Optimization of yields by further variation of conditions has not been attempted. While cycloaddition of münchnones with electron deficient nitriles such as ethyl cyanoacetate has also been reported,[32] we were unable to observe any predicted imidazole products with a variety of conditions and substrates.

(26) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Il Abdon, R. L.; Trost, B. M. *Tetrahedron* **1994**, *50*, 93−116.
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(31) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 136−137.
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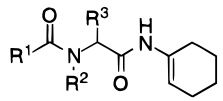
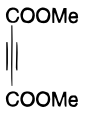
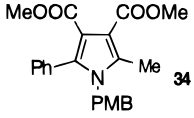
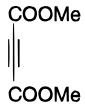
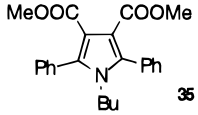
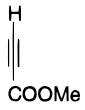
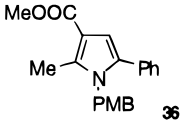
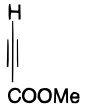
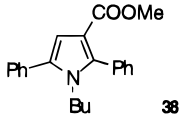
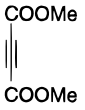
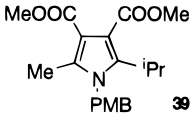
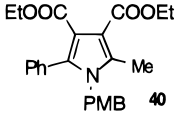
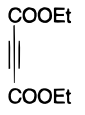
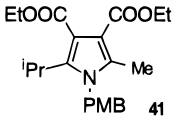
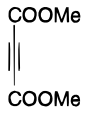
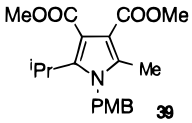
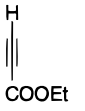
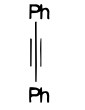
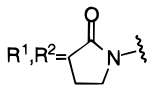
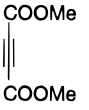
Table 3. 1,3-Dipolar Cycloadditions of Acetylenic Dipolarophiles with Ugi Products

Condensation Product						
						
R^1	R^2	R^3	Dipolarophile	Cond.[a]/ Yield[b]	Product	
Me-	PMB-	Ph-		A/63%		**34**
Ph-	Bu-	Ph-		A/35%		**35**
Me-	PMB-	Ph-		A/24%	 (3.3)	**36**
Ph-	Bu-	Ph-		A/24%		**38**
Me-	PMB-	^{i}Pr-		A/13%		**39**
Me-	PMB-	Ph-		A/19%		**40**
Me-	PMB-	^{i}Pr-		B/9%		**41**
Me-	PMB-	^{i}Pr-		B/5%		**39**
Me-	PMB-	Ph-		B/0%	N.R.	
Ph-	Bu-	Ph-		A/0%	N.R.	
Ph-	Bu-	Ph-		A/0%	N.R.	
				A/0%	N.R.	

[a] Reagents and conditions: (A) 5 equiv of dipolarophile, 3 equiv of HCl, toluene, 100 °C; (B) 5 equiv of dipolarophile, 3 equiv of HCl, THF, 55 °C. [b] Purified, isolated yield.

This 1,3-dipolar cycloaddition reaction represents a novel synthesis of pyrroles, which are important pharmacophores in their own right.[33] There are several notable advantages to this method. Instead of reliance upon acylated amino acids as precursors for münchnones **30**, the larger and more diverse pool of carboxylic acids, amines, and aldehydes can be called upon to furnish the 1-, 2-, and 5-substituents of pyrrole **44** resulting from cycloaddition. Thus, even though the cyclohexenamide class of Ugi 4CC products can be seen as precursors of acylated amino acids (as per **9**, **10**, and **11** in Table 1), it is not necessary to convert them to the free carboxylic acid to access the standard acetic anhydride methods of generating active 1,3-dipoles for cycloaddition; the cyclohexenamide itself is a substrate for münchnone formation. Once again, the cyclohexenamide functionality has been erased in the product pyrrole, with even the single carbon atom present in products **9**−**21** lost as CO_2. Finally, the stereocenter created at the α-carbon in the Ugi 4CC (resulting in an enantiomeric mixture of products) is removed by aromatization after cycloaddition, resulting in a single product.

Internal Nucleophile. As an extension of the work on nucleophilic opening of münchnone intermediates to yield products **9**−**21**, we investigated tethered nucleophiles as a means of forming rings (Figure 5). The concept in Figure 5a is illustrated by using D-arabinose as an aldehyde input in a Ugi reaction followed by cyclization to form the corresponding 2-acetamido-2-deoxyhexose (Scheme 4).

Protected D-arabinose **46** was prepared using standard procedures.[34−36] This aldehyde reacted smoothly under standard Ugi conditions to furnish **47** in high yield as a 3.4:1 mixture of inseparable diastereomers at the α-carbon (as determined by ^{1}H NMR). We expected that acidic treatment of **47** would cleave the isopropylidene protecting group, protonate the enamide, promote münchnone formation, and either open the münchnone with methanol or the newly deprotected secondary hydroxyl, with the exact sequence of events dependent upon the relative rates. Lactonization should occur under these

(33) For a recent representative example, see: Santiago, B.; Dalton, C. R.; Huber, E. W.; Kane, J. M. *J. Org. Chem.* **1995**, *60*, 4947−4950.

(34) Horton, D.; Varela, O. *Carbohydr. Res.* **1984**, *134*, 205−214.

(35) Armstrong, R. W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *56*, 915−922.

(36) Teegarden, B. R. Ph.D. Thesis, University of California, Los Angeles, 1991.

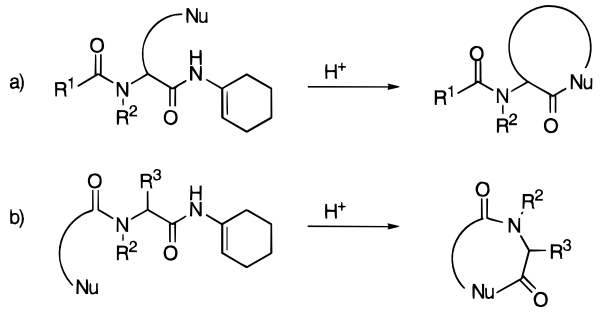
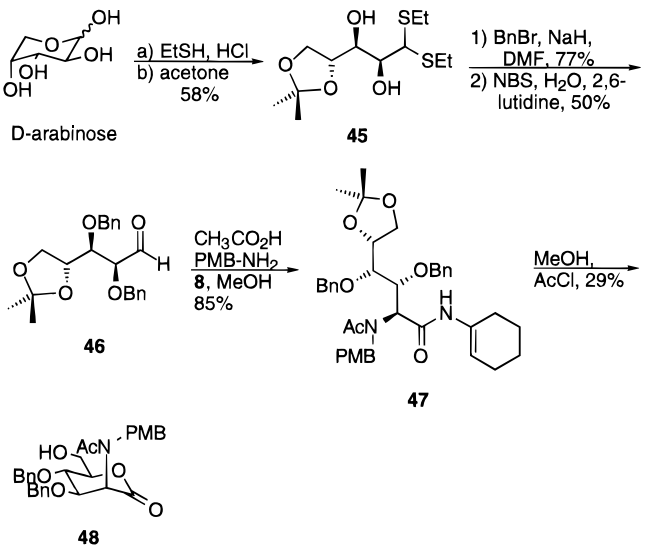


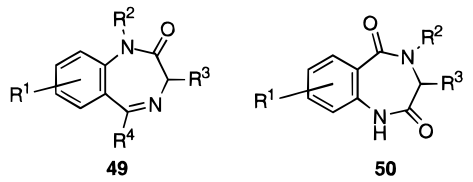
Figure 5.

Scheme 4

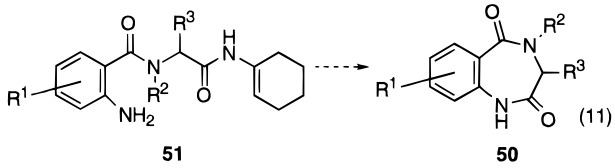


conditions whether or not the methyl ester is initially formed, and cyclization should occur via the secondary hydroxyl to form a six-membered ring rather than via the primary hydroxyl (seven-membered ring). Treatment of **47** with acidic methanol conditions (0.1 M HCl, 23 °C) yielded the protected 2-acetamido-2-deoxy-D-mannono-δ-lactone **48** in 29% yield. Attempts to improve the yield through either elevated temperatures or increased acidicity resulted in β-elimination and formation of the α,β-unsaturated 2-acetamido lactone. The *p*-methoxybenzyl amide protecting group could be oxidatively removed using ceric ammonium nitrate, and the benzyl ethers by catalytic hydrogenation over Pearlman's catalyst.

1,4-Benzodiazepine-2,5-diones. 1,4-Benzodiazepines[37] **49** have been the target of several solid phase combinatorial strategies.[6,7,9,38] The structurally similar 1,4-benzodiazepine-2,5-diones, however, have been reported as important pharmacophores in their own right, as anticonvulsants,[39] as antitumor agents,[40] and as glycoprotein antagonists.[41] 1,4-Benzodiazepine-2,5-diones have appeared very recently in several solid and solution phase syntheses.[42−44]



Synthesis of this class of compounds would represent an intramolecular cyclization of the type shown in Figure 5b. If a Ugi product of type **51** could be synthesized, cleavage of the cyclohexenamide to an ester or acid and subsequent lactamization with the anthranilic nitrogen would yield the corresponding 1,4-benzodiazepine-2,5-dione **50** (eq 11), in either one or two steps from the Ugi product. The commercially available inputs for a library of such compounds would then consist of over 40 substituted anthranilic acids, and the legion of amines and aldehydes. As before, the isocyanide input would be erased except for a single carbon atom.



In the interests of ease of synthesis, we wished to avoid employing a protecting group for the anthranilic acid nitrogen in the Ugi 4CC. This would allow the use of anthranilic acids "off-the-shelf" and obviate the need for protecting group removal later. We expected that the precondensation of the amine and aldehyde components, along with the reduced nucleophilicity of the anthranilic nitrogen, would avoid this problem. The results are shown in Scheme 5.

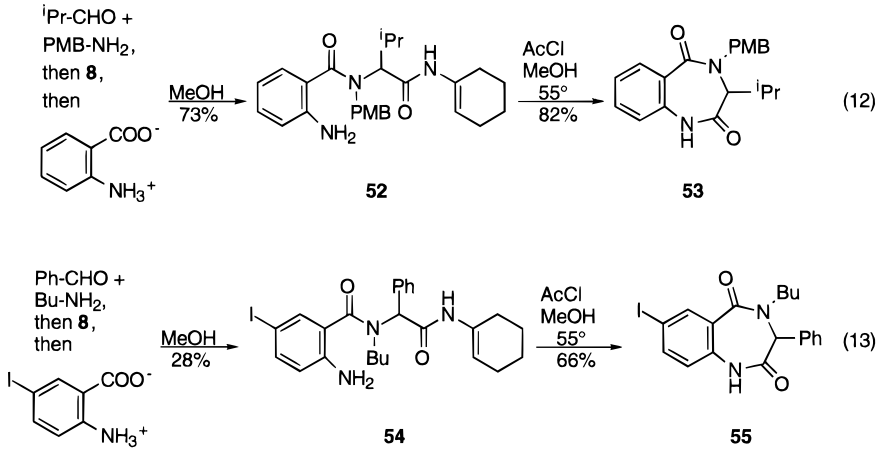
By combining isobutyraldehyde and *p*-methoxybenzylamine in methanol with 4 Å molecular sieves and stirring for 1 h, followed by isocyanide and finally anthranilic acid addition, a 73% isolated yield of 4CC product **52** was obtained, with some recoverable starting materials, but no observable side products. Treatment of this product with acetyl chloride in methanol resulted in 1,4-benzodiazepine-2,5-dione **53** as a single isolable product in 82% yield. A second example with different inputs is shown in eq 13. Aside from sluggishness of the 4CC, the reactions proceeded similarly. This accomplishes the synthesis of 1,4-benzodiazepine-2,5-diones extremely rapidly, in good yield, and with remarkable possibilities for diverse functionality.

Resin Capture. As a final exmple of the versatility of the cyclohexenamide conversion, we demonstrate here the *resin capture* of Ugi products onto a solid support. We believe that this can represent a valuable strategy for library synthesis, in which *a solution reaction is followed by capture of the products onto a solid support* for further transformation, eventually leading to removal of the final products from the resin. Although library generation has traditionally followed an either/or approach to solid and solution phase synthesis, a mixed strategy in which difficult to monitor or low-yielding reactions are performed in solution, and then the following reactions on a solid support, could prove superior.

We employed the Wang[45] *p*-(benzyloxy)benzyl alcohol resin as the nucleophile in cyclohexenamide conversion (Scheme 6), which was expected to perform similarly to benzyl alcohol in product **15**. An excess of Ugi 4CC products **5** was incubated

(37) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
(38) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306−3307.
(39) Cho, N. S.; Song, K. Y.; Párkányi, C. *J. Heterocycl. Chem.* **1989**, *26*, 1807−1810.
(40) Jones, G. B.; Davey, C. L.; Jenkins, T. C.; Kamal, A.; Kneale, G. G.; Neidle, S.; Webster, G. D.; Thurston, D. E. *Anti-Cancer Drug Des.* **1990**, *5*, 249.
(41) McDowell, R. S.; Blackburn, B. K.; Gadek, T. R.; McGee, L. R.; Rawson, T.; Reynolds, M. E.; Robarge, K. D.; Somers, T. C.; Thorsett, E. D.; Tischler, M.; Webb, R. R., II; Venuti, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 5077−5083.
(42) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742−5743.
(43) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5744−5745.
(44) Karp, G. M. *J. Org. Chem.* **1995**, *60*, 5814−5819.
(45) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

Scheme 5



Scheme 6

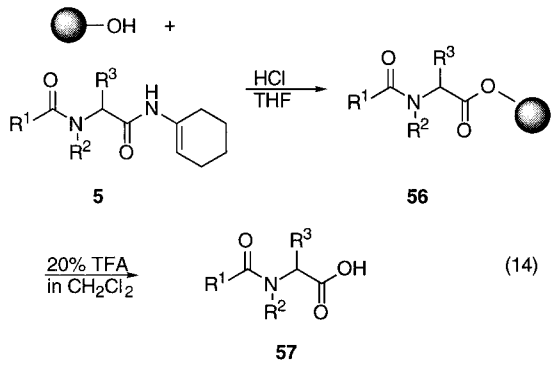


Table 4. Results of Resin Capture of 4CC Products and Subsequent Cleavage

Condensation Product					
R^1	R^2	R^3	eq of 4CC Prod.	Conditions	Prod./ Yield
Me-	PMB-	Ph-	4	HCl, toluene, 100°	**10**/100%
Ph-	Bu-	Ph-	4	HCl, toluene, 100°	**11**/62%
Me-	PMB-	Ph-	4	HCl, THF, 55°	**10**/100%
Me-	PMB-	iPr	4	HCl, THF, 55°	**9**/100%
Me-	PMB-	iPr	1.5	HCl, THF, 55°	**9**/96%

with Wang resin under anhydrous acidic THF conditions, and then the resin was washed repeatedly with methanol and CH_2Cl_2. Cleavage from the resin was with a 20% (v/v) trifluoroacetic acid in methylene chloride solution. The products were characterized without purification and were >95% pure by TLC and ^{1}H NMR. Perhaps most remarkable, as displayed in Table 4, are the yields of products recovered from the resin. The yields were calculated on the basis of the manufacturer's stated loading level of the Wang resin. We initially employed a 4-fold excess of 4CC products, but discovered that high yields of recovered carboxylic acid were maintained even when the excess of Ugi products was reduced to 1.5 equiv! Inspection of the solution washes of the resin prior to cleavage revealed a mixture of carboxylic acid and methyl ester derivatives arising from hydrolysis/methanolysis of the excess 4CC starting material during these washes.

Interestingly, when we attempted to capture 1,4-benzodiazepine-2,5-dione precursors **52** and **54** on Wang resin, subsequent cleavage yielded no product. Characterization of the wash solutions revealed high yields of the 1,4-benzodiazepine-2,5-diones. Apparently, the cyclization to produce the 1,4-benzodiazepine-2,5-diones from their 4CC precursors is facile enough that the initially formed Wang benzyl ester is very rapidly displaced by the anthranilic nitrogen; thus, the product cleaves itself off the resin.[9] This was observed even under milder temperatures and acidity.

Conclusions

The Ugi four-component condensation and multiple-component condensations in general are powerful tools for the generation of libraries of diverse compounds based on a common core. There are several advantages to MCCs over linear synthesis: fewer steps, greater diversity at each step from higher numbers of inputs,[46] and (in some cases) more readily available starting materials. The drawbacks to MCCs are not trivial: the libraries are wedded to a single core functionality, and in the case of the Ugi 4CC, some inputs have only limited availability. We have sought to address these shortcomings specifically. Use of 1-isocyanocyclohexene as the isocyanide input yields products that can enjoy great variability at a formerly restricted site; not only are different amide functionalities possible, but also heretofore inaccessible moieties. The pyrrole synthesis presented above represents transformation into an entirely new class of compounds. But the scope of the cyclohexenamide conversion is not limited to external nucleophiles. We have demonstrated nucleophiles attached to both the aldehyde and acid inputs, which resulted in a monosaccharide and benzodiazepinediones, respectively. More generally, we believe the concept of a universal isocyanide can extend beyond the 1-isocyanocyclohexene presented here. Although 1-isocyanocyclohexene is remarkably versatile, different isocyanides can potentially lead to further modifications that open access to

(46) In a linear strategy, *bifunctional* or *bireactive* inputs are required at each step in order to provide reactive sites for succeeding steps. On the other hand, an MCC can proceed successfully with *monofunctional* and *monoreactive* inputs. This concept is illustrated by comparison of peptide synthesis with the Ugi 4CC. Each amino acid input for linear peptide synthesis incorporates two orthogonally reactive sites—one to couple to the existing peptide and the other to provide a site for further attachment. However, the four inputs for the Ugi reaction all require only one reactive site. Thus, the 4CC reaction can employ a greater number and variety of inputs than can a linear strategy.

classes of compounds beyond those shown here. For instance, we have investigated metal-mediated transformations of Ugi products incorporating a 2-isocyanopyridine input.

Finally, polymer capture of activated cyclohexenamides, while not fully exploited for library synthesis here, represents a new strategy for solid phase synthesis: beginning not with attachment of the first input to the solid support, but rather with a solution reaction whose products are amenable to being subsequently attached to the resin. Careful inspection of the system presented here reveals that the only species trappable on the resin is the fully-formed Ugi 4CC product; unreacted starting materials and potential side products are inert to the capture because they lack the required cyclohexenamide functionality which is only present in the 4CC product. Furthermore, while it has not been attempted here, "captured" 4CC products are available to undergo further synthetic transformations on a solid support prior to being cleaved from the resin. We believe this method can lead to hybrid strategies for library generation that combine the ease of solution *synthesis* with the ease of solid-supported *isolation and purification*.

Experimental Section

General Procedures. All reactions unless otherwise indicated were performed in oven- or flame-dried glassware under an inert atmosphere. Solvents were distilled immediately prior to use: THF from sodium/benzophenone ketyl, methanol from magnesium turnings, CH_2Cl_2 from P_2O_5, and toluene from calcium hydride. Anhydrous DMF was purchased from Aldrich and used directly. Wang *p*-(benzyloxy)benzyl alcohol resin (100−200 mesh) was purchased from Advanced ChemTech. The loading level was 0.9 mmol/g. The resin was dried prior to use by azeotropically removing water with toluene. Thin layer chromatography was performed on silica gel with precoated glass plates (E. Merck Brinkman, Kieselgel 60 F_{254}, 0.25 mm) and visualized with UV light, *p*-anisaldehyde, and/or ninhydrin staining. NMR spectra were obtained with a Bruker ARX-500, ARX-400, or AM-360 spectrometer in a $CDCl_3$ solvent and referenced to residual $CHCl_3$. Coupling constants are listed in hertz. IR spectra were obtained with a Nicolet 510P FT-IR spectrometer. Absorbances are stated in inverse centimeters. Optical rotations were obtained with a Perkin-Elmer 241MC polarimeter. Concentrations are reported in grams per milliliter.

General Procedure for Ugi Four-Component Condensation. The carboxylic acid (1.25 equiv), amine (1.25 equiv), and aldehyde (1.0 equiv) are dissolved in methanol to an approximate concentration of 1 M in each. This solution is allowed to stand for 10 min, and then is added in one portion to a flask containing the isocyanide (1.0 equiv). The resulting solution is allowed to stir at room temperature for 12 h. When reaction is complete by TLC (1−5% methanol in CH_2Cl_2), the solvent is removed in vacuo, and the residue purified by flash column chromatography on silica gel, eluting with a 0−5% methanol in CH_2Cl_2 gradient.

General Procedure for Ugi Reaction Followed by in Situ Methanolysis. The carboxylic acid (1.25 equiv), amine (1.25 equiv), and aldehyde (1.0 equiv) are dissolved in methanol to an approximate concentration of 1 M in each. This solution is allowed to stand for 10 min, and then is added in one portion to a flask containing the isocyanide (1.0 equiv). The resulting solution is allowed to stir at room temperature for 12 h. When reaction is complete by TLC (1−5% methanol in CH_2Cl_2), the methanol volume is doubled and acetyl chloride (10 equiv) is added in one portion. The flask is equipped with a reflux condenser and heated to 55 °C for 3 h. When TLC shows complete conversion to methyl ester, the reaction is cooled to room temperature, the solvent removed in vacuo, and the residue taken up in CH_2Cl_2 and filtered. Purification is by flash column chromatography on silica gel, eluting with a 0−5% methanol in CH_2Cl_2 gradient.

General Procedure for Acidic Hydrolysis of Cyclohexenamide Products. The starting cyclohexenamide (0.1 mmol) is dissolved in 1 mL of a stock solution of 0.5 mL concentrated HCl in 9.5 mL of THF. This reaction mixture is stirred for 12−18 h, neutralized with solid sodium bicarbonate, and then filtered. The solvent is removed in vacuo and the residue dissolved in pH 10 water and washed with methylene chloride. The aqueous layer is then acidified and reextracted with methylene chloride. The organics are combined and dried over sodium sulfate, and the solvent is evaporated.

General Procedure for Pyrrole Synthesis (Method A). The cyclohexenamide (0.05 mmol) is azeotropically dried with toluene, and then dissolved in 1 mL of toluene. The acetylene (0.25 mmol, 5 equiv) is then added, followed by HCl (3 equiv as a 1.0 M solution in anhydrous ether). The flask is then capped and heated to 100 °C for 4 h. The solvent is then evaporated after cooling, the residue taken up in methylene chloride and filtered, and the soluble portion purified by preparative TLC (0.5 mm thickness, 20 cm × 20 cm, 1−5% MeOH in methylene chloride as eluent).

General Procedure for Pyrrole Synthesis (Method B). This procedure is identical to that above except that THF is substitued for toluene as solvent and the reaction is heated to 55 °C.

General Procedure for Polymer Capture and Cleavage Using Wang Resin. The cyclohexenamide (0.11 mmol) is azeotropically dried with toluene, dissolved in THF, and then added to a flask containing Wang resin (0.027 mmol, 0.25 equiv, or 0.073 mmol, 0.67 equiv). HCl (0.55 mmol as a 1 M solution in anhydrous ether) is added and the flask capped and then heated to 55 °C for 5 h. After cooling, the resin is filtered off and washed three times with methylene chloride, three times with methanol, and three times with methylene chloride again. The carboxylic acid product is cleaved from the resin by incubating with a 20% trifluoroacetic acid in methylene chloride solution for 20 min, at which point the pink to dark purple resin is washed three times with methylene chloride. The solvent is evaporated, and the product is characterized.

Characterization and experimental data for compounds **9**−**10**, **13**−**21**, and **25** have been previously reported.[15] Data for these compounds include full experimental details, complete listings of proton and carbon-13 magnetic resonances, IR absorbances, results of high-resolution mass spectrometric analysis, and copies of ^{1}H NMR and ^{13}C NMR spectra.

1-Amino-1-cyanocyclohexane.[20] Cyclohexanone (103 mL, 1.0 mol) was dissolved in 33 mL of diethyl ether in a 1 L flask. Ammonium chloride (60.4 g, 1.13 mol) was then added in 183 mL of water. The solution was cooled in an ice bath, followed by sodium cyanide (50.5 g, 1.03 mol) addition in 133 mL of water dropwise via addition funnel. The biphasic solution was stirred overnight at 23 °C, and then the aqueous layer was acidified to pH 1 with concentrated HCl. (CAUTION: Hydrogen cyanide is liberated.) The hydrochloride salt of the product was filtered and washed with ether. The remaining aqueous solution was extracted with ether three times to remove unreacted cyclohexanone, and then the pH was raised to 12 with 1 M NaOH and the solution extracted with ether three times to collect the remaining product. Organics were combined and dried over Na_2SO_4 and the solvent removed in vacuo to leave a clear oil. The hydrochloride salt was dissolved in 1 M NaOH and extracted with ether; after repeating the above procedures, the oils were combined to yield 76 g (61%) of product.

1-Cyano-1-formamidocyclohexane (7).[20] To 1-amino-1-cyanocyclohexane (76 g, 613 mmol) in an ice bath cooled flask was added 107 mL of 98% formic acid. To this stirred, cooled solution was added a mixture of 107 mL of 98% formic acid and 63.5 mL of acetic anhydride dropwise via addition funnel. (CAUTION: Formation of the mixed anhydride occurs with considerable heat evolution and should be performed slowly and in a cooled flask.) After stirring for 12 h at 23 °C, the reaction was quenched with 10 mL of water, and as much solvent as possible was removed with a rotary evaporator. The resulting yellow oil was dissolved in methylene chloride and washed with pH 10 water. This aqueous layer was extracted with fresh methylene chloride twice, and the combined organics were washed with pH 1 water to remove starting material. Neutralization of the acidic water and CH_2Cl_2 extraction yielded, after standard drying and solvent removal, 5.0 g (6.5%) of starting material. The former organic portions yielded 55 g of crude product, which was recrystallized from benzene to provide 40 g (53%) of shiny, white leaves. The title compound exists as two rotamers in a 7.7:1 ratio at room temperature in chloroform. ^{1}H NMR (400 MHz): (major rotamer) δ 8.13 (d, 1 J = 1.1), 6.88 (br, 1), 2.32 (m, 2), 1.73−1.58 (m, 8); (minor rotamer) δ 8.49 (d, 1, J = 11), 7.02 (d, 1, J = 11), 2.15 (m, 2), 1.31−1.27 (m, 8).

1-Formamidocyclohexene.[22] 1-Cyano-1-formamidocyclohexane (**7**) (2.0 g, 13.2 mmol) and anhydrous potassium *tert*-butoxide (5.9 g, 52.6 mmol) were dissolved in 50 mL of THF. After heating to reflux for 6 h, the reaction mixture was poured into 200 mL of 0.5 M Na_2CO_3. The layers were separated and extracted 3× with ethyl acetate. The organics were combined and dried over Na_2SO_4. Silica gel chromatography (1:1 to 1:2 hexanes/ethyl acetate) yielded 1.22 g (74%) of a white crystalline solid along with 177 mg (9%) of starting material. The title compound exists as two rotamers in a 3:1 ratio at room temperature in chloroform. ^{1}H NMR (400 MHz): (major rotamer) δ 8.35 (d, 1, J = 11.5), 7.55 (br, 1), 5.30 (t, 1, J = 3.9), 2.15−2.07 (m, 4), 1.73−1.58 (m, 4); (minor rotamer) δ 8.21 (d, 1, J = 13.5), 8.15 (d, 1, J = 1.6), 6.12 (t, 1, J = 3.9), 2.33 (m, 4), 1.85 (m, 4).

1-Isocyanocyclohexene (8).[20,22,23] 1-Formamidocyclohexene (6.0 g, 48.0 mmol) and diazabicyclo[2.2.2]octane (DABCO, triethylenediamine) (16.2 g, 144.0 mmol) were dissolved in 120 mL of CH_2Cl_2. To the cooled solution (0 °C), 10% w/v triphosgene in CH_2Cl_2 (95 mL, 32.0 mmol) was added dropwise. After stirring for 0.5 h, the reaction mixture was poured into 500 mL of a 0.5 M Na_2CO_3 solution. This was extracted 3× with CH_2Cl_2, dried over Na_2SO_4, and rapidly chromatographed on triethylamine-deactivated silica gel (9:1 hexanes/ethyl acetate) to yield 3.1 g (60%) of a clear, colorless oil. The product is conveniently stored under argon at −30 °C as a 1 M solution in hexanes. ^{1}H NMR: δ 6.05 (m, 1), 2.23 (m, 2), 2.11 (m, 2), 1.69 (m, 2) 1.57 (m, 2).

(*R*,*S*)-2-(*N*-Butylbenzamido)phenylacetic Acid (11). NMR spectra of the title compound suffer extreme peak broadening due to rotational isomerism. This compound was characterized by ^{1}H NMR and HRMS, and by conversion into **12**. ^{1}H NMR (400 MHz): δ 7.47−7.38 (m, 5), 5.67 (s, 1), 3.38 (br, 1), 3.24 (br, 1), 1.41 (br, 1), 1.24 (br, 1), 0.96−0.86 (br, 2), 0.67 (br, 3). HRMS (EI): *m/z* (M^+) calcd 311.1521, found 311.1521.

(*R*,*S*)-2-(*N*-Butylbenzamido)phenylacetic Acid Methyl Ester (12). Yield: 98%. IR (neat): 2957, 1748, 1638. ^{1}H NMR (500 MHz): δ 7.44−7.38 (m, 10), 5.97 (br, 1), 3.80 (s, 3), 3.17 (br, 2), 1.63 (br, 2), 0.81 (br, 2), 0.52 (br, 3). ^{13}C NMR (126 MHz): δ 170.9, 136.5, 134.4, 129.5, 128.8, 128.7, 128.4, 126.5, 62.0, 52.4, 47.5, 31.5, 19.6, 13.2. HRMS (EI): *m/z* (M^+) calcd 325.1678, found 325.1681.

(*R*,*S*)-*N*-(1-Cyclohexenyl)-2-(*N*′-(4-methoxybenzyl)formamido)-phenylacetamide (24). Yield: 72%. IR (neat): 3308, 2932, 1655, 1514, 1248. The title compound exists at room temperature as a 1.3:1 mixture of rotamers. When peaks corresponding to the same proton(s) from each rotamer can be identified, they are listed separately as major and minor. ^{1}H NMR (400 MHz): (major rotamer) δ 8.23 (s, 1), 7.28−7.27 (m, 5), 7.13 (d, 2, J = 8.4), 6.71 (d, 2, J = 8.4), 6.03 (br, 1), 5.77 (s, 1), 4.51 (d, 1 J = 15.4), 4.29 (d, 1, J = 15.3), 3.73 (s, 3), 2.30 (t, 1, J = 6.4), 2.06−1.52 (m, 7); (minor rotamer) δ 8.15 (s, 1), 7.28−7.27 (m, 5), 6.89 (d, 2 J = 7.5), 6.81 (d, 2, J = 7.5), 6.03 (br, 1), 4.97 (s, 1), 4.71 (d, 1, J = 14.7), 4.27 (d, 1 J = 14.9), 3.75 (s, 3), 2.06−1.52 (m, 8). ^{13}C NMR (101 MHz): δ 167.0, 166.6, 163.8, 159.0 (2), 134.6, 134.1, 132.3, 132.2, 129.9 (2), 129.5, 129.3, 129.0 (2), 128.7, 128.6, 128.5 (2), 128.3, 128.2, 114.2, 114.0, 113.8, 113.6, 64.8, 61.0, 55.1, 49.7, 46.6, 41.8, 27.6, 27.5, 26.9, 24.9, 23.9, 23.8, 22.3 (2), 21.8, 21.7. HRMS (EI): *m/z* (M^+) calcd 378.1943, found 378.1939.

(*R*,*S*)-Methyl 2-(2-(*N*-(4-Methoxybenzyl)formamido)phenylacetamido)acetate (26). Yield: 43%. IR (neat): 3304, 2953, 1754, 1663, 1514, 1250, 1211, 1179. The title compound exists at room temperature as a 1:1 mixture of rotamers. When peaks corresponding to the same proton(s) from each rotamer can be identified, they are listed together. ^{1}H NMR (400MHz): δ 8.19 and 8.11 (s, 1), 7.28−7.25 (m, 5), 7.15 and 7.04 (br t, 1), 7.12 and 6.89 (d, 2, J = 8.7 and 8.6), 6.80 and 6.70 (d, 2, J = 8.5 and 8.6), 5.75 and 5.04 (s, 1), 4.77 and 4.48 (d, 1, J = 14.7 and 15.4), 4.24 and 4.21 (d, 1, J = 15.3 and 14.7), 4.02−3.86 (m, 2), 3.74 and 3.72 (s, 3), 3.68 and 3.67 (s, 3). ^{13}C NMR (101 MHz): δ 169.8, 169.7, 169.2, 169.1, 163.8, 163.7, 159.0, 158.9, 134.1, 133.8, 129.9, 129.4, 129.0, 128.9, 128.7, 128.6 (2), 128.6, 128.2, 128.1, 113.9, 113.8, 64.0, 60.2, 55.1, 52.2, 52.1, 49.6, 46.5, 41.2, 41.1. HRMS (EI): *m/z* (M^+) calcd 370.1529, found 370.1532.

(*R*,*S*)-Methyl 2-(2-((4-Methoxybenzyl)amino)phenylacetamido)-acetate (27). IR (neat): 3322, 2926, 1752, 1671, 1514, 1248. ^{1}H NMR (400MHz): δ 7.86 (br t, 1), 7.42−7.30 (m, 5), 7.27 (d, 2, J = 8.5), 6.87 (d, 2, J = 8.6), 4.37 (s, 1), 4.12 (dd, 1, J = 18.3, 6.0), 4.00 (dd, 1, J = 18.3, 5.3), 3.82 (d, 1, J = 13.0), 3.80 (s, 3), 3.78 (d, 1, J = 13.0), 3.77 (s, 3), 2.45 (br, 1). HRMS (EI): *m/z* (M^+) calcd 343.1658, found 343.1659.

(*R*,*S*)-1-(1-Piperidino)phenylacetamide (29). IR (neat): 3403, 3185, 2934, 1661. ^{1}H NMR (500 MHz): δ 7.35−7.27 (m, 5), 7.16 (br, 1), 5.51 (br, 1), 3.85 (s, 1), 2.39 (br, 4), 1.63 (br, 4), 1.42 (br, 2). HRMS (EI): *m/z* [$(M + H)^+$] calcd 219.1497, found 219.1499.

Dimethyl 1-(4-Methoxybenzyl)-2-methyl-5-phenylpyrrole-3,4-dicarboxylate (34). Yield: 63%. IR (neat): 1707, 1514, 1248, 1175. ^{1}H NMR (400 MHz): δ 7.33−7.24 (m, 5), 6.80 (d, 2, J = 8.7), 6.77 (d, 2, J = 8.9), 4.91 (s, 2), 3.83 (s, 3), 3.79 (s, 3), 3.65 (s, 3), 2.37 (s, 3). ^{13}C NMR (101 MHz): δ 166.1, 165.4, 158.9, 135.6, 135.3, 130.4, 130.3, 128.6, 128.2, 126.8, 115.0, 114.2, 112.1, 55.2, 51.6, 51.4, 47.2, 11.4. HRMS (EI): *m/z* [$(M + H)^+$] calcd 394.1654, found 394.1652.

Dimethyl 1-butyl-2,5-diphenylpyrrole-3,4-dicarboxylate (35). Yield = 35%. IR (neat): 2953, 1717, 1198, 1167. ^{1}H NMR (400 MHz): δ 7.45−7.40 (m, 10), 3.68 (t, 2, J = 7.7), 3.65 (s, 6), 1.14 (tt, 2, J = 7.5, 7.5), 0.83 (tq, 2, J = 7.5, 7.5), 0.49 (t, 3, J = 7.4). ^{13}C NMR (101 MHz): δ 165.4, 136.5, 131.0, 130.5, 128.7, 128.2, 114.3, 51.6, 44.6, 32.3, 19.3, 13.1. HRMS (EI): $(M+H)^+$ calcd 392.1862, found 392.1866.

Methyl 1-(4-Methoxybenzyl)-2-methyl-5-phenyl-3-pyrrolecarboxylate (36). Yield: 24% (isolated as a 3.3:1 mixture with **37**). Assignment of major and minor regioisomers was on the basis of ^{1}H NMR chemical shifts, coupling constants, observed NOE of the pyrrole proton from irradiation of the pyrrole methyl in the minor regioisomer, and published data on analogous compounds.[27,28] IR (neat): 2928, 1701, 1514, 1248. ^{1}H NMR (400 MHz): δ 7.33−7.26 (m, 5), 6.84 (s, 4), 6.65 (s, 1), 5.07 (s, 2), 3.82 (s, 3), 3.79 (s, 3), 2.46 (d, 3, J = 3.3). HRMS (EI): *m/z* (M^+) calcd 335.1521, found 335.1526.

Methyl 1-(4-Methoxybenzyl)-5-methyl-2-phenyl-3-pyrrolecarboxylate (37). Yield: 24% (isolated as a 1:3.3 mixture with **36**). IR (neat): 2928, 1701, 1514, 1248. ^{1}H NMR (400 MHz): δ 7.33−7.26 (m, 5), 6.80 (d, 2, J = 8.9), 6.75 (d, 2, J = 8.9), 6.47 (d, 1, J = 0.7), 4.85 (s, 2) 3.78 (s, 3), 3.65 (s, 3), 2.12 (d, 2, J = 0.6). HRMS (EI): *m/z* (M^+) calcd 335.1521, found 335.1526.

Methyl 1-Butyl-2,5-diphenyl-3-pyrrolecarboxylate (38). Yield: 24%. IR (neat): 2957, 2928, 1717, 1475, 1196. ^{1}H NMR (400 MHz): δ 7.46−7.36 (m, 10), 6.67 (s, 1), 3.83 (t, 3, J = 7.5), 3.65 (s, 3), 1.18 (tt, 2, J = 7.3, 7.3), 0.85 (tq, 2, J = 7.4, 7.4), 0.53 (t, 3, J = 7.4). ^{13}C NMR (101 MHz): δ 165.2, 139.7, 134.6, 133.1, 132.3, 130.7, 129.2, 128.5, 128.3, 128.0, 127.6, 113.0, 110.5, 50.8, 44.7, 32.5, 19.3, 13.2. HRMS (EI): *m/z* (M^+) calcd 333.1719, found 333.1722.

Dimethyl 2-Isopropyl-1-(4-methoxybenzyl)-5-methylpyrrole-3,4-dicarboxylate (39). Yield: 13% (method A), 5% (method B). IR (neat): 2951, 1705, 1514, 1215. ^{1}H NMR (400 MHz): δ 6.84 (d, 2, J = 8.9), 6.80 (d, 2, J = 8.9), 5.03 (s, 2), 3.84 (s, 3), 3.78 (s, 6), 3.01 (qq, 1, J = 7.1, 7.1), 2.35 (s, 3), 1.19 (d, 6, J = 7.1). ^{13}C NMR (101 MHz): δ 168.1, 165.3, 159.0, 138.8, 134.3, 128.4, 126.6, 114.3, 111.1, 55.3, 51.9, 51.2, 46.4, 29.7, 26.1, 21.7, 11.1. HRMS (EI): *m/z* (M^+) calcd 359.1733, found 359.1735.

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-arabinose Diethyl Dithioacetal. 4,5-*O*-Isopropylidene-D-arabinose diethyl dithioacetal[34] (2.0 g, 6.75 mmol) was dissolved in anhydrous DMF (50 mL). Deoiled sodium hydride (324 mg, 13.5 mmol) was added in one portion to the stirred solution. After 1 h, the solution was cooled in an ice bath, and benzyl bromide (3.2 mL, 27.0 mmol) was added slowly. Another 324 mg of sodium hydride was added after 1 h, and the solution was stirred for an additional 12 h. The reaction was quenched with methanol and then with saturated aqueous ammonium chloride. As much solvent as possible was removed with a rotary evaporator, and then the residue was partitioned between saturated aqueous ammonium chloride and methylene chloride. The aqueous layer was extracted three times with methylene chloride, and then the organic extracts were combined and dried over sodium sulfate. After removal of solvent in vacuo, purification was via flash column chromatography (silica, hexanes to 3:1 hexanes/ethyl acetate gradient), to obtain 2.48 g (77%) of the title compound. ^{1}H NMR (360 MHz): δ 7.41−7.27 (m, 10), 4.93 (d, 1, J = 10.9), 4.80 (d, 1, J = 11.4), 4.76 (d, 1, J = 11.5), 4.75 (d, 1, J = 11.0), 4.25 (dd, 1, J = 12.7, 6.4), 4.18−4.09 (m, 2), 4.04 (dd, 1, J =

8.3, 6.3), 3.90 (dd, 1, J = 8.3, 6.7), 3.81 (dd, 1, J = 6.5, 4.4), 2.75−2.62 (m, 4), 1.43 (s, 3), 1.34 (s, 3), 1.26 (t, 3, J = 7.4), 1.24, t, 3, J = 7.5).

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-arabinose (46).[36] The diethyl dithioacetal of the title compound (766 mg, 1.61 mmol) was dissolved in 41 mL of acetonitrile and 11 mL of water. 2,6-Lutidine (1.31 mL, 11.3 mmol) that had been passed through basic alumina was added. To the stirred solution was added a slurry of *N*-bromosuccinimide (1.72 g, 9.65 mmol) in acetonitrile (7.5 mL). The solution turned orange-brown. After 10 min, the reaction was quenched by dropwise addition of aqueous $NaHSO_3$ until the color disappeared. The reaction mixture was diluted with saturated aqueous sodium bicarbonate and extracted with methylene chloride three times. The organic layers were combined and dried over sodium sulfate, and the solvent was removed in vacuo. Purification was via flash column chromatography (silica, hexanes to 3:1 hexanes/ethyl acetate gradient). Yield: 296 mg (50%). ^{1}H NMR (400 MHz): δ 9.72 (d, 1, J = 1.3), 7.37−7.27 (m, 10), 4.77 (d, 1, J = 11.8), 4.65 (d, 1, J = 11.8), 4.57 (s, 2), 4.25 (dd, 1, J = 12.6, 6.3), 4.07 (dd, 1, J = 8.5, 6.3), 4.03 (dd, 1, J = 3.1, 1.3), 3.98 (dd, 1, J = 6.4, 3.1), 3.94 (dd, 1, J = 8.5, 6.2), 1.42 (s, 3), 1.35 (s, 3). ^{13}C NMR (101 MHz): δ 203.0, 137.3, 136.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 108.9, 83.9, 79.6, 75.1, 74.3, 73.6, 66.5, 26.5, 25.1.

D-Arabinose 4CC Product 47. Compound **47** was prepared using the general procedures described above for 4CC, except that the reaction was run at 0 °C for 18 h in order to improve the diastereoselectivity. Yield: 85% of a 3.4:1 mixture of inseparable diastereomers at the C-2 position. IR (neat): 2934, 1684, 1638, 1514, 1248. NMR data are listed for each diastereomer, when resonances from each can be identified. ^{1}H NMR (500 MHz): (major diastereomer) δ 7.41−7.27 (m, 10), 7.10 (d, 2, J = 8.8), 6.80 (d, 2, J = 8.6), 5.96 (br, 1), 4.95 (dd, 1, J = 15.5, 11.6), 4.79−4.26 (m, 6), 4.25−4.00 (m, 4), 4.08 (td, 1, J = 7.7, 2.1), 3.80 (s, 3), 2.11 (s, 3), 2.12−1.97 (m, 4), 1.66−1.55 (m, 4), 1.49 (s, 3), 1.38 (s, 3); (minor diastereomer) δ 7.56 (br, 1), 7.41−7.27 (m, 10), 6.89 (d, 2, J = 7.2), 6.87 (d, 2, J = 7.2), 6.05 (br, 1), 5.22 (d, 1, J = 11), 4.79−4.26 (m, 6), 4.25−4.00 (m, 3), 3.82 (s, 3), 3.69 (d, 1, J = 6.3), 3.60 (dd, 1, J = 7.0, 2.0), 2.07 (s, 3), 2.12−1.97 (m, 4), 1.66−1.55 (m, 4), 1.48 (s, 3), 1.35 (s, 3). ^{13}C NMR (126 MHz): (both diastereomers) δ 173.1, 172.9, 167.2, 167.1, 166.9, 166.6, 159.0, 158.8, 138.6, 138.3, 137.8, 137.7, 132.3, 132.1, 128.3 (2), 128.2 (2), 128.1 (4), 127.9, 127.8, 127.7, 127.5 (2), 127.4, 127.3, 114.2, 114.1 (2), 113.4, 113.1, 112.8, 112.6, 109.1, 108.4, 108.2, 80.1, 78.9, 77.4, 76.3, 76.0, 75.1, 74.7, 74.6, 74.5, 74.1, 73.1, 72.4, 66.6, 66.5, 66.2, 60.0, 55.1 (2), 50.7, 27.7 (2), 26.6, 26.4, 25.2, 25.1, 24.8, 23.9, 23.8, 22.6, 22.4 (3), 22.3, 22.9, 21.8. HRMS (EI): m/z [(M + H)$^+$] calcd 657.3495, found 657.3516.

2-(*N*-(4-Methoxybenzyl)acetamido)-2-deoxy-3,4-di-*O*-benzyl-D-mannono-δ-lactone (48). Compound **47** (3.4:1 mixture of diastereomers, 63 mg, 0.10 mmol) was azeotropically dried with toluene and then dissolved in 4.4 mL of methanol. Distilled acetyl chloride (34 μL, 0.48 mmol) was then added and the solution stirred at 23 °C for 2 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. After drying with sodium sulfate, the solvent was removed in vacuo, and the residue was purified by preparative TLC (silica, 0.5 mm thickness, 20 cm × 20 cm) with 1:2 hexanes/ethyl acetate as eluent. Yield: 14 mg (29%) of the major diastereomer. $[\alpha]^{22}_D$ = +44.2° (c = 0.013, $CHCl_3$). IR (neat): 3418, 2930, 1748, 1642, 1514, 1248. ^{1}H NMR (400 MHz): δ 7.39−7.27 (m, 12), 6.84 (d, 2, J = 8.7), 4.89 (d, 1, J = 11.7), 4.86 (d, 1, J = 11.0), 4.79 (d, 1, J = 11.0), 4.64 (d, 1, J = 11.7), 4.40 (d, 1, J = 15.6), 4.37 (dt, 1, J = 9.5, 2.3), 4.29 (d, 1, J = 16.1), 4.28 (t, 1, J = 9.3), 3.96 (dd, 1, J = 12.8, 2.3), 3.84 (dd, 1, J = 12.8, 2.4), 3.82−3.77 (m, 1), 3.77 (s, 3), 3.55 (d, 1, J = 8.8), 1.95 (s, 3). ^{13}C NMR (101 MHz): δ 170.9, 167.1, 159.2, 137.9, 137.5, 129.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.4, 114.0, 80.1, 78.3, 75.9, 75.0, 74.9, 62.1, 60.2, 55.2, 54.5, 21.3. HRMS (FAB): m/z [(M + H)$^+$] calcd 520.2335, found 520.2328.

(*R*,*S*)-*N*-(1-Cyclohexenyl)-2-(*N*′-(4-methoxybenzyl)-2-aminobenzamido)-3-methylbutanamide (52). Isobutyraldehyde (9 μL, 0.1 mmol) and *p*-methoxybenzylamine (16 μL, 0.125 mmol) were combined in 500 μL of methanol with 4 Å molecular sieves. The solution was stirred at 23 °C for 1 h, and then **8** (100 μL of 1 M solution in hexanes, 0.1 mmol) was added, followed by anthranilic acid (14 mg, 0.1 mmol). After stirring at 23 °C for 18 h, the solution was filtered through Celite, the solvent removed in vacuo, and the residue purified via flash column chromatography (silica, hexanes to 1:1 hexanes/ethyl acetate gradient) to yield 32 mg (73%) of a clear glass. Characterization by NMR was made difficult by amide rotational isomerism that broadened all peaks. IR (neat): 2934, 1684, 1615, 1514, 1246. ^{1}H NMR (400 MHz): δ 8.25 (br, 1), 7.20−6.72 (br, 8), 5.94 (br, 1), 4.7 (br d, 1), 4.44 (d, 1, J = 14.9), 4.15 (br d, 1), 3.74 (s, 3), 2.65 (br, 1), 2.05 (br, 4), 1.63−1.54 (m, 4), 0.97−0.86 (m, 6). HRMS (EI): m/z (M^+) calcd 435.2522, found 435.2528.

(*R*,*S*)-3-Isopropyl-4-(4-methoxybenzyl)-1,4-benzodiazepine-2,5-dione (53). Compound **52** (33 mg, 0.076 mmol) was azeotropically dried with benzene and then dissolved in 1 mL of methanol. After adding distilled acetyl chloride (27 μL, 0.38 mmol), the flask was capped and then heated to 55 °C for 6 h. After removal of solvent in vacuo, the residue was purified via flash column chromatography (silica, 2:1 hexanes/ethyl acetate to 1:2 gradient). Yield: 21 mg (82%) of a clear glass. IR (neat): 3220, 2967, 1686, 1632, 1514, 1248. ^{1}H NMR (500 MHz): δ 8.77 (s, 1), 8.00 (dd, 1, J = 7.9, 1.5), 7.43 (td, 1, J = 7.9, 1.5), 7.32 (d, 2, J = 8.6), 7.23 (td, 1, J = 7.8, 0.9), 6.88 (d, 1, J = 8.0), 6.83 (d, 2, J = 8.6), 5.15 (d, 1, J = 14.4), 4.45 (d, 1, J = 14.4), 3.74 (s, 3), 3.62 (d, 1, J = 11.5), 1.71−1.63 (m, 1), 0.82 (d, 3, J = 6.6), 0.65 (d, 3, J = 6.6). ^{13}C NMR (126 MHz): δ 171.9, 166.1, 159.3, 134.6, 132.5, 131.5, 130.2, 128.6, 126.8, 124.8, 119.7, 114.0, 71.0, 55.2, 54.7, 27.5, 19.6, 19.4. HRMS (EI): m/z (M^+) calcd 338.1630, found 338.1633.

(*R*,*S*)-*N*-(1-Cyclohexenyl)-2-(*N*′-butyl-2-amino-5-iodobenzamido)-phenylacetamide (54). See the procedures for **52**. Yield: 28%. IR (neat): 3349, 2930, 1680, 1613, 1483, 1424. ^{1}H NMR (400 MHz): δ 7.44−7.37 (m, 8), 6.63 (br, 1), 6.46 (d, 1, J = 10.3), 6.02 (br, 1), 5.77 (br, 1), 4.57 (br, 1), 3.45−3.33 (m, 1), 3.24−3.21 (m, 1), 2.09−2.04 (m, 4), 1.66−1.63 (m, 2), 1.57−1.53 (m, 2), 0.90−0.86 (m, 4), 0.53 (m, 3). ^{13}C NMR (101 MHz): δ 170.2, 168.0, 143.6, 138.7, 135.4, 134.8, 132.3, 129.9, 129.1, 129.0, 123.5, 117.9, 114.4, 64.8, 48, 31.6, 27.8, 23.9, 22.4, 21.8, 19.6, 14.2. HRMS (EI): m/z (M^+) calcd 531.1383, found 531.1374.

(*R*,*S*)-4-Butyl-7-iodo-3-phenyl-1,4-benzodiazepine-2,5-dione (55). See the procedures for **53**. Yield: 66%. IR (neat): 3214, 2957, 1688, 1620, 1480. ^{1}H NMR (500MHz): δ 8.49 (s, 1), 8.04 (s, 1), 7.44 (d, 1, J = 8.0), 7.18−7.07 (m, 5), 6.46 (d, 1, J = 8.4), 5.36 (s, 1), 4.08 (br, 1), 3.66 (ddd, 1, J = 13.7, 9.0, 5.5), 1.81 (br, 1), 1.75−1.70 (m, 1), 1.43 (tq, 2, J = 7.4, 7.4), 0.98 (t, 3, J = 7.3). ^{13}C NMR (126 MHz): δ 171.2, 165.4, 140.6, 139.6, 133.6, 132.9, 129.6, 129.0, 128.7, 128.2, 124.4, 121.4, 88.1, 66.8, 30.1, 20.0, 13.8. HRMS (EI): m/z (M^+) calcd 434.0491, found 434.0480.

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Supporting Information Available: Text giving characterization data for compounds **40** and **41** and figures showing ^{1}H NMR spectra of compounds **11**, **12**, **24**, **26**, **27**, **29**, **34**−**41**, **46**−**48**, and **52**−**55** and several unnumbered intermediates (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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