JOURNAL OF combinatorial CHEMISTRY

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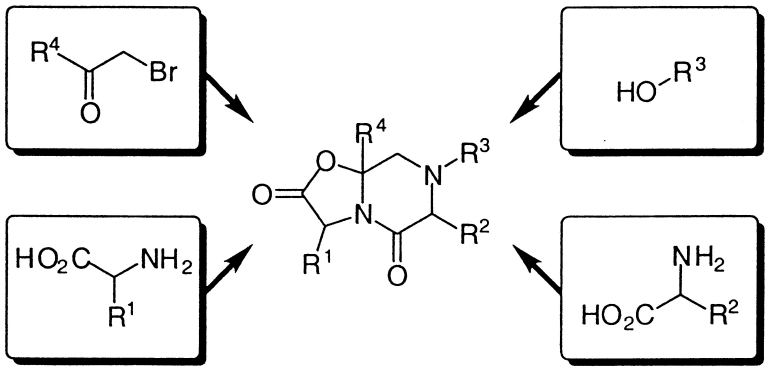
J. Comb. Chem., **2003**, 5 (3), 278-284• DOI: 10.1021/cc020082i • Publication Date (Web): 11 February 2003



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Amino Acid-Derived Heterocycles as Combinatorial Library Targets: Bicyclic Aminal Lactones

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Received September 10, 2002

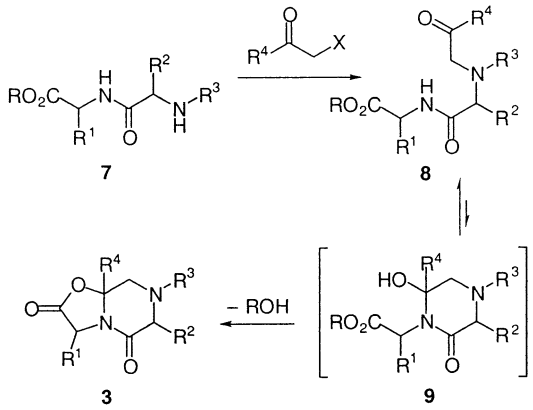
The incorporation of α-amino acids into heterocyclic structures is an effective strategy for generating peptidomimetics and combinatorial library scaffolds. This report describes the synthesis of novel bicyclic aminal lactones **3** by base-catalyzed cyclization of *N*-(2-oxoalkyl)-dipeptide esters **8**. Assembly of the acyclic precursor **8** can be carried out on solid phase, with variation at four positions; cyclative release ensures high product purity in the final step. Cyclization affords the exo isomer stereospecifically when one chiral center is present in the precursor, or when both amino acids have the same configuration.

Introduction

As a source of input materials for the synthesis of combinatorial libraries, α-amino acids occupy a special position. Historically, they served as the starting materials for the first combinatorial libraries, which consisted of oligopeptides.[1−3] They remain unmatched as a source of diverse starting materials: densely functionalized, commercially available in protected form, as pure enantiomers, as the natural as well as a myriad of "unnatural" derivatives. Although libraries of peptides and other linear oligoamides continue to play an important role in bioorganic and medicinal chemistry,[4−6] more compact, conformationally constrained—in short: heterocyclic[7−9]—scaffolds hold greater appeal for lead discovery prospecting libraries[10−12] and represent a greater challenge for synthetic design.[13] Moreover, there is continuing interest in rigid molecules that position amino acid functionality in 3-dimensional mimicry of peptide secondary structure, such as β-turns.[14,15] In this and the following article, we describe synthetic sequences that convert α-amino acids or compounds readily derived from them into novel heterocycles.[16,17] These routes are applicable to either solid phase or solution synthesis and are, thus, appropriate for library construction.

Hydroxyl OH and amide NH functions share the ability to condense with aldehyde and ketone carbonyl groups to form acetal, aminal, and *gem*-diamido derivatives. Appropriate location of an aldehyde (or ketone) relative to a peptide backbone provides a number of opportunities for ring closure to bicyclic structures, with the aldehyde carbon serving as the linchpin (Figure 1). Considerable variability in ring structure is possible, depending on whether the carbonyl function in the peptide starting material is a substituent on nitrogen or part of a side chain, and whether the proximal backbone NH lies toward the amino or the carboxy terminus (ring systems **1**−**6**, Figure 1). In addition to *gem*-diamides, in which the second heteroatom is nitrogen, aminal and thioaminal hybrids, in which the second heteroatom is oxygen or sulfur, are readily envisaged and in many cases known. Moreover different heterocycles and ring sizes are obtained from β- and γ-amino acids and from closure of the second ring from the backbone or a side chain. Many examples of heterocycles **1**, **2**, **4**, and **5** are known,[18] but none, to our knowledge, of the α-amino acid-derived ring systems of **3** and **6**.

Scheme 1



In this article, we describe facile access to 1,4-diaza-7-oxabicyclo[4.3.0]-2,8-nonanediones, **3** ($n = 1$, X = O). These bicyclic aminal lactones are generated on base-catalyzed cyclization of ketone-containing dipeptide esters, **8**, which in turn are obtained by alkylation of *N*-alkyl dipeptides with halomethyl ketones (Scheme 1).

Results and Discussion

Solution-Phase Chemistry. The viability of the sequence was first demonstrated by alkylation of sarcosyl-L-phenylalanine methyl ester with α-bromoacetophenone, followed by treatment with DBU in toluene at 80 °C to produce the bicyclic lactone **3a** in good yield as a single diastereomer. Weaker bases, such as triethylamine, were ineffective, and

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10.1021/cc020082i CCC: $25.00
Published on Web 02/11/2003

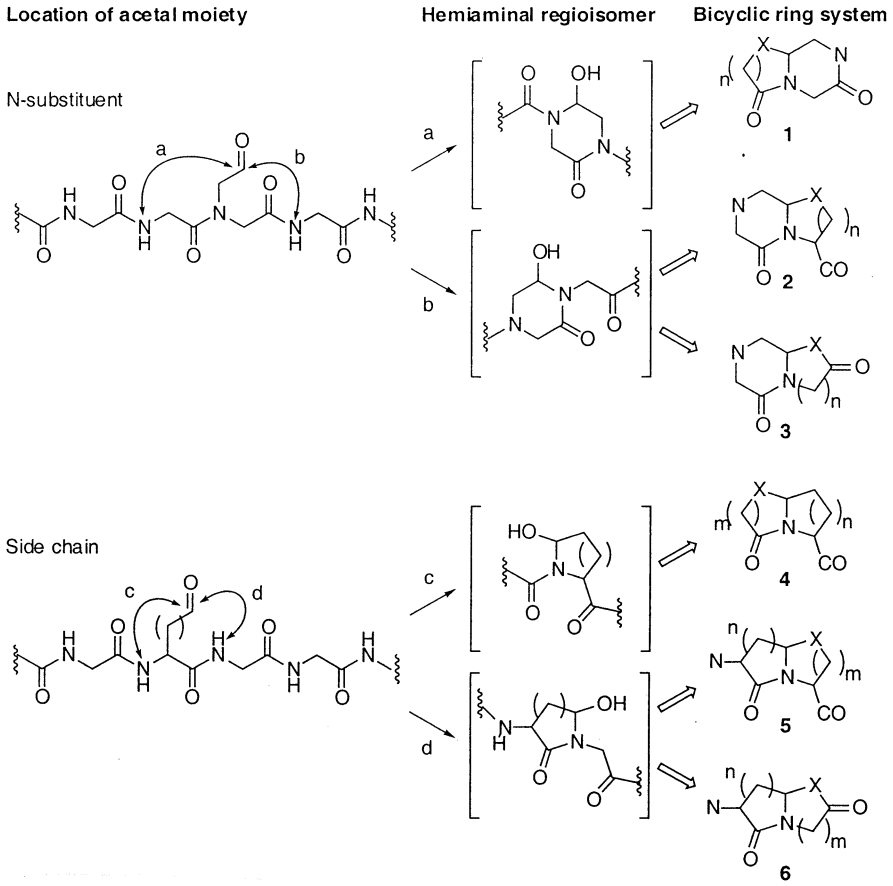
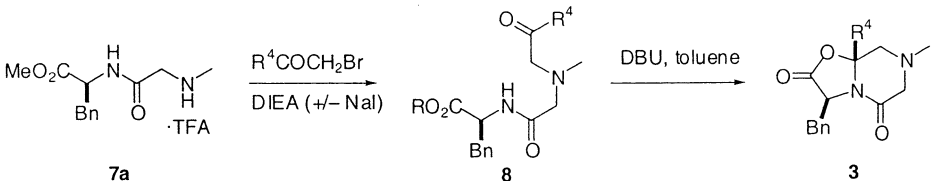


Figure 1. Different heterocyclic motifs from cyclization of a peptide via an acetal carbon.

Table 1. Alkylation and Cyclization of Sarcosyl-Phenylalanine Methyl Ester



series	R^4	alkylation method[a]	yield of **8, %**	reaction time for cyclization, h	yield of **3, %**
a	Ph	B	84	18	84
b	4-NO_2Ph	A	24	1	dec
c	4-ClPh	B	62	10	66
d	4-Ph-Ph	B	82	18	66
e	4-MeOPh	A	53	24	61
f	*t*-Bu	A	19	24	no reaction
g	Me	B	80	8	97

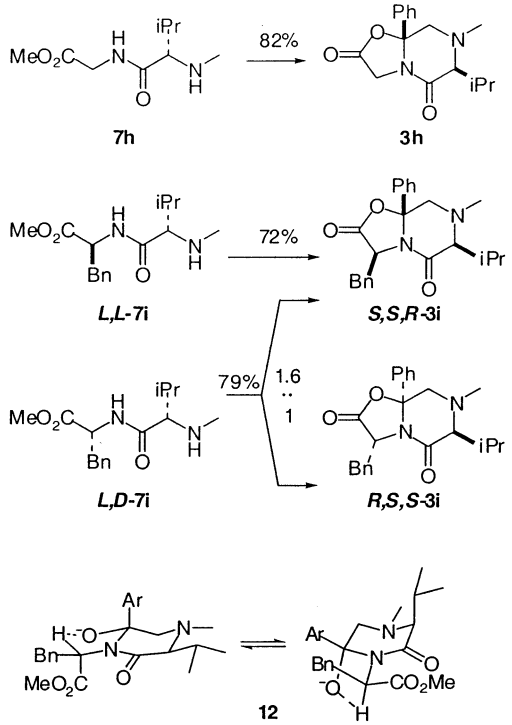
[a] Alkylation method A: 1.1 equiv of α-bromoketone + 2 equiv of DIEA in acetonitrile; Method B = method A + 1 equiv of NaI.

protic or Lewis acid-catalyzed conditions left the aminoketone **8a** unchanged. The need for strong base suggested that the equilibrium **8** ↔ **9** is unfavorable with R^4 = aryl and must be driven by deprotonation. The ketone substituent R^4 exerts electronic as well as steric effects, as illustrated in Table 1.

Both electron-rich and -deficient aryl substituents are permitted, with the exception of the nitrophenyl analogue (series b, Table 1). The poor yield and decomposition observed with this substituent in the alkylation reaction and under cyclization conditions reflect the ready enolization of the bromoketone precursor and, presumably, the ketoamine intermediate **8b**. Although the methyl ketone cyclizes rapidly (series g), the bulky *tert*-butyl substituent blocks cyclization entirely (series f). The reaction sequence is otherwise quite tolerant; over-alkylation of the tertiary amine was not observed to any significant extent, even when an excess of halomethyl ketone was employed, and a range of aromatic and aliphatic groups can be introduced at the acetal carbon.

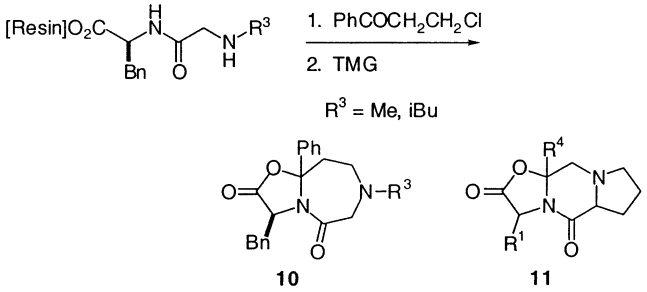
We explored a number of bases as an alternative to DBU, seeking one that could be removed from the product without extraction or chromatography. Other guanidine bases, such as DBN and tetramethylguanidine (TMG), were also effective in catalyzing cyclization, but tertiary amine bases, such as quinuclidine, DIEA, or *N*-methylpyrrolidine, were not. A polymer-supported derivative of phosphazine P2[19] gave low yields and low purity. TMG (bp 115 °C/50 mmHg)

Scheme 2



proved to be the most convenient because it can be removed from the product by evaporation.

Alternative Ring Systems. In addition to aryl and alkyl bromomethyl ketones, we also assessed phenyl vinyl ketone (introduced as the chloroethyl ketone precursor) as the fourth variable input in the synthesis. Cyclization of the β-aminoketone adducts led to the 5,7-aminal lactone **10**, albeit in low overall yield (~20%). Presumably, formation of the intermediate hemiaminal, unfavorable even for the six-membered ring leading to **3**, is further disfavored in the case of the homologue.



An attempt to prepare tricyclic analogues, such as **11**, with proline as the R^2,R^3-component did not prove fruitful. We attribute this limitation to the additional ring strain in the hemiaminal intermediate from the 6,5-ring fusion.

Stereochemistry. The single stereocenter in Sar-L-Phe served to control the course of the cyclization such that the R^1 and R^4 substituents in the bicyclic product adopt the cis (exo) relationship. The same result is observed when R^2 is the only stereocenter in the ketoamine: *N*-methyl-L-Val-Gly-OMe affords the cis product **3h** in 82% yield (Scheme 2). Not surprisingly, the substituents in an L,L-dipeptide act in concert to give the all-cis isomer (e.g., *S*,*S*,*R*-3i). However, the L,D-diastereomer affords two products, with the major

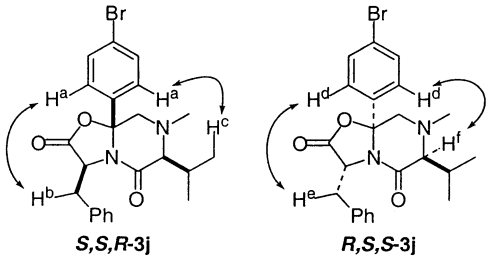
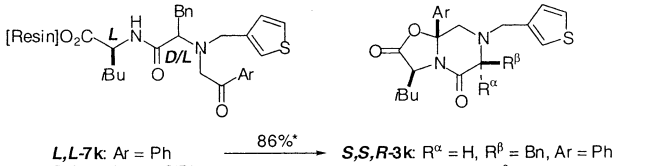


Figure 2. Intramolecular nOe interactions observed for isomers of **3j**.

isomer identical to the product from the L,L-dipeptide in both relative and absolute configurations. The L,D-substrate, thus, undergoes epimerization adjacent to the ester prior to lactonization, perhaps through intramolecular catalysis from the hemiaminal anion **12**. The configuration of the minor product from cyclization of the L,D-substrate was shown to be *R*,*S*,*S* by nOe NMR analysis of the analogous products with a 4-bromophenyl substituent, (*S*,*S*,*R*)- and (*R*,*S*,*S*)-**3j** (Figure 2), which were obtained in 47 and 29% yields after chromatography, respectively. Attempts to form the isomers in which the R^1 and R^4 substituents are trans (e.g., *R*,*S*,*R*- or *S*,*R*,*S*-) by epimerization with DBU (toluene at 80 °C for 56 h) or by deprotonation/reprotonation with potassium hexamethyldisilazide in THF followed by methanol quench were unsuccessful.

Epimerization on cyclization of L,D (or D,L) substrates was not universally observed, however. During the course of the solid-phase studies discussed below, the D,L-diastereomer of the resin-bound Phe-Leu derivative D,L-**7l** underwent clean conversion to a single product whose configuration was assigned as (*S*,*R*,*R*)-**3l** by comparison to the related analogue (*S*,*S*,*R*)-**3k**. Confirmation of the all-cis configuration of the latter compound was later obtained by single-crystal X-ray analysis.

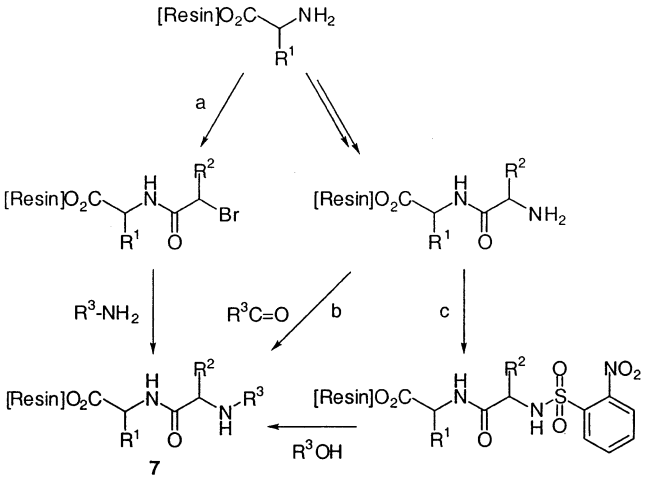


Synthesis on Solid Support. Because assembly of the bicyclic aminal lactones is readily adaptable to solid support, the versatility of the synthesis was explored in this format, starting with commercially available Merrifield polystyrene resin loaded with *N*-Boc amino acids.

Cyclative Release. A key advantage to the solid-phase version of the sequence is the concomitant release from resin of the final product, and *only* the final product, in the cyclization step.[20−23] As noted previously, this feature of the process ensures that side products and partially reacted species are retained on the resin, greatly simplifying and in most cases obviating the need for subsequent purification. The volatility of TMG, in contrast to DBU or DBN, thus took on added importance.

Side Chain Protection and Base Lability. Base-stable protecting groups, such as benzyl or *tert*-butyl esters and

Scheme 3

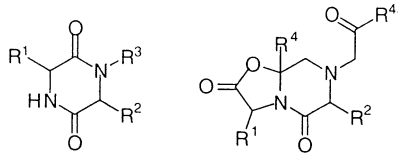


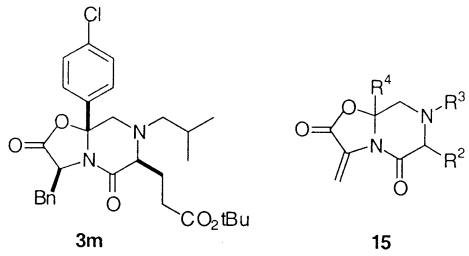
ethers, are carried through the synthesis intact, but base-labile Fmoc groups are not. As noted below, protected serine derivatives do not make good inputs at the first amino acid position because the β-alkoxy moiety undergoes elimination during the cyclization step.

N-Alkylation. Three methods to introduce the *N*-alkyl R^3 substituent in a general fashion were explored: (a) displacement of a bromoacyl amino acid with a primary amine (in analogy to the "submonomer" approach to peptoid synthesis[5]) and (b) reductive amination or (c) monoalkylation of a resin-bound dipeptide (Scheme 3). Bromoacylation followed by displacement avoids a deprotection step and imposes little limitation on the structure of the R^3 substituent; however, this method severely limits R^2 because of competing elimination in the displacement step.

In solid-supported synthesis, in which reagents are generally used in excess to drive reactions to completion, formation of an unsymmetrical dialkylamine by reductive amination is frequently complicated by dialkylation to give the tertiary amine. This problem was partly overcome in route (b) by conducting the reaction in trimethyl orthoformate, as advocated by Campbell et al.[24] However, except for introduction of secondary alkyl groups, such as cyclohexyl, alkylation via a modified Gabriel approach (c) proved to be more effective. Fukuyama has demonstrated the versatility of the 2-nitrobenzenesulfonyl (Ns) moiety as a highly acidifying yet readily removed nitrogen substituent.[25] With a pK_a of 9.5, Ns dipeptides are alkylated on the terminal nitrogen by primary alcohols under Mitsunobu conditions[26] or by alkyl halides in the presence of $CsCO_3$. Removal of the Ns group with thiophenol in DMF in the presence of K_2CO_3 (solution) or DBU (solid phase)[27] does not perturb the ester linkage or side chain protecting groups. This process is less effective with hindered alcohols: no alkylation was obtained with 2-propanol or cyclohexanol, and the reaction with 2-methyl-1-propanol is sufficiently sluggish that a significant amount of N-ethylated material is isolated as a side product. Formation of this material, which presumably arises from ethanol produced by decomposition or ester exchange of the diethyl azodicarboxylate reagent, can be prevented by using diisopropyl azodicarboxylate instead.

Two byproducts were typically observed at the end of the synthesis, prior to optimization of the alkylation reactions. One was the diketopiperazine **13** resulting from release of unalkylated dipeptide **7** under the basic cyclization conditions. Contamination of the desired product with this material was readily suppressed by the simple expedient of capping any unreacted **7** with acetic anhydride prior to treatment of **8** with TMG. The other byproduct that was occasionally observed turned out to be **14**, the product from incomplete reaction on incorporation of R^3 and subsequent dialkylation by the halomethyl ketone. This material was more abundant when hindered R^3 substituents, such as isobutyl, were introduced, and its formation was solvent-dependent. In the synthesis of bicycle **3m**, for example, the byproduct corresponding to **14** constituted 43% of the crude product when dichloromethane was used in the Fukuyama−Mitsunobu alkylation step, 23% when DMF was used, and 21% in *N*-methylpyrrolidone (NMP). The latter solvent was thus used routinely because of its superior resin-swelling properties.





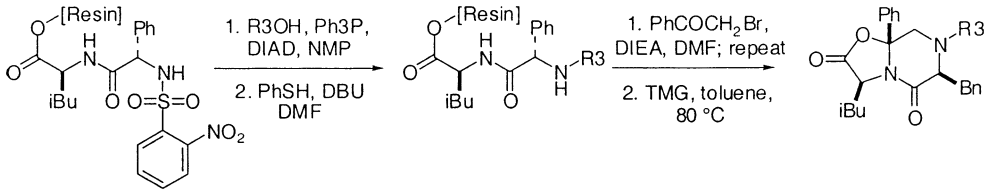
In the course of evaluating reaction conditions, parallel synthesis formats, etc., we observed several trends that reflected on the suitability of various input materials. Yields were typically evaluated over the 8-step synthesis after cyclative release.

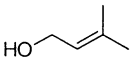
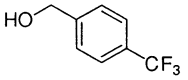
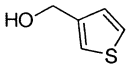
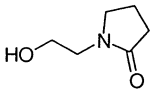
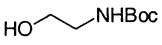
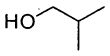
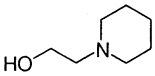
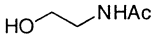
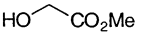
R^1 and R^2 Substituents. Glycine as the first amino acid (R^1 = H) gives low yields because the *N*-alkyl-dipeptide intermediate readily cyclizes to the diketopiperazine. *O*-Benzylserine at this position (R^1 = $BnOCH_2$) undergoes β-elimination during the cyclization step to give the α-methylene lactone **15**.

R^3 Substituents. With resin-linked L-Phe-L-Leu and α-bromoacetophenone as the common components, a variety of alcohol inputs for R^3 were evaluated (Table 2). Benzylic and similarly activated primary alcohols work well in this sequence. Alcohols subject to steric hindrance, for example, from β-branching, give lower yields. Alcohols that give activated intermediates prone to side reactions, either through cyclization (e.g., *N*-(hydroxyethyl)acetamide, but interestingly, not *N*-(hydroxyethyl)pyrrolidinone) or elimination (e.g., 2-(methanesulfonyl)ethanol, methyl 2-hydroxypropanoate) also lead to lower yields or no product.

Substituent Evaluation by Parallel Synthesis. On the basis of the information developed from these initial scouting experiments, a 48-member library was assembled in parallel

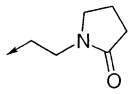
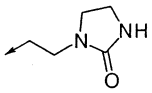
Table 2. Evaluation of R^3 Alcohol Inputs



Entry	R^3OH	Overall yield[a]
1		83% (71%)
2		79%
3		76% (63%)
4		64% (54%)
5		79% (41%)
6		43%
7		41% (21%)
8		-
9		-

[a] First number represents yield of crude material of >80% purity isolated from cyclative release, on the basis of loading of initial Boc-Leu-resin; second number represents yield after chromatographic purification.

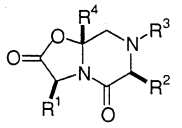
Table 3. Average Mass Recovery from Solid Phase Synthesis[a]

R^1	%	R^2	%	R^3	%	R^4	%
Ala	48	Glu(*t*Bu)	55		52	4-ClPh	67
Leu	37	Tyr(*t*Bu)	44	4-(CF_3)Bn	47	Ph	50
Tyr(2,6-Cl_2Bn)	36	D-Phe	38	$BocNHCH_2CH_2$	46	4-PhPh	43
Phe	34	Lys(Boc)	35	Dimethallyl	43	2,5-$(MeO)_2$Ph	37
		Ser(*t*Bu)	31	3-ThienylCH_2	40	Me	33
		Trp(Boc)	28	*t*$BuOCH_2CH_2$	38	4-(Et_2N)Ph	15
				Me	34		
					31		
				*i*Bu	28		

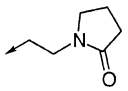
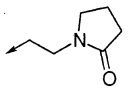
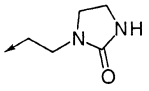
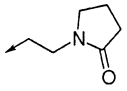
[a] For R^1 and R^2, the substituent is indicated by the amino acid used as input, with side chain protecting group in parentheses.

fashion using 4−6 inputs at each of the four variable positions. The reactions were carried out manually using a custom synthesis block that enabled common temperature control, an inert atmosphere, and either fritted plastic filter cartridges or glass test tubes as reaction vessels. The performance of each component was assessed from the

Table 4. Yield and Purity of Bicyclic Aminal Lactones from Solid Phase Parallel Synthesis



3

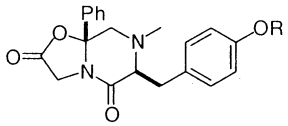
Compound	R^1	R^2	R^3	R^4	Mass yield[a] (%)	NMR purity[b] (%)	Corrected yield (%)
3n	Bn	4-(*t*BuO)Bn	$tBuOCH_2CH_2$	4-ClPh	100	51	51
3o	Bn	$tBuO_2CCH_2CH_2$		2,5-$(MeO)_2$Ph	61	67	41
3p	*i*Bu	*N*-Boc-Indol-3-yl-CH_2		2,5-$(MeO)_2$Ph	22	86	19
3q	*i*Bu	$BocNH(CH_2)_4$		4-ClPh	55	86	47
3r	*i*Bu	4-(*t*BuO)Bn	$BocNHCH_2CH_2$	Ph	81	91	74
3s	*i*Bu	*N*-Boc-Indol-3-yl-CH_2	Me	4-PhPh	61	93	57
3t	*i*Bu	4-(*t*BuO)Bn	Propargyl	4-(Et_2N)Ph	23	95	22
3u	Me	*N*-Boc-Indol-3-yl-CH_2	$BocNHCH_2CH_2$	4-PhPh	69	88	61
3v	Me	$tBuO_2CCH_2CH_2$	Dimethallyl	2,5-$(MeO)_2$Ph	31	75	23
3w	*i*Bu	$tBuOCH_2$	3-ThienylCH_2	4-PhPh	41	91	37
3x	*i*Bu	$tBuOCH_2$	4-(CF_3)Bn	Ph	55	98	54
3y	Me	D-Bn		4-PhPh	38	63[c]	24

[a] Based on initial amino acid loading of resin. [b] Determined by integration against hexamethyldisiloxane as internal standard. [c] Isolated as a 6:1 mixture of diastereomers.

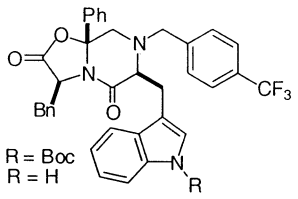
average mass recovery for each compound in which it was incorporated, as shown in Table 3. The mass recoveries were generally good across the range of substituents evaluated, in view of the eight separate reactions involved. One of the most clear-cut trends is that for the electron density of the R^4 substituent, with lower recoveries for the more electron-rich aryl groups than for the neutral or electron-poor analogues. Steric bulk seems to play a modest role at the R^1 position, but no particular relationship is apparent among the R^3 groups evaluated in this library.

A second parallel library was synthesized, and compound purity was evaluated to determine overall yield (Table 4). Purity was assessed by NMR in $CDCl_3$ with a known concentration of hexamethyldisiloxane as internal standard. These data demonstrate the advantage of the cyclative release strategy, since the compound purities are generally high, even when mass recovery is variable.

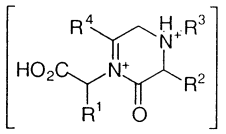
Deprotection of Side Chain Functional Groups. The bicyclic aminal lactone scaffold proved to be stable to both hydrogenolytic and acidic (trifluoroacetic acid) deprotection conditions. The benzyl-protected ether of **3z**, for example, was removed cleanly with hydrogen over 10% Pd/C to give the phenol **3aa** in 91% yield. The Boc-protected indole side chain of **3bb** was cleaved in 69% purified yield on treatment with 18:1:1 trifluoroacetic acid/dimethyl sulfide/water for 2 h at room temperature. The tertiary amine, as the protonated ammonium ion, serves to stabilize the ring system under these conditions, since cleavage of the aminal function would involve introduction of a second cationic center in the molecule (e.g., **16**).



3z: R = Bn
3aa: R = H



3bb: R = Boc
3cc: R = H



16

Conclusions

The cyclization of *N*-(2-oxoalkyl)-dipeptide esters provides a novel bicyclic ring system for which considerable variation is possible. The synthetic strategy can take advantage of the enormous diversity of α-amino acids and primary alcohols and the moderate diversity of commercially available α-haloketones. Chiral products are formed stereospecifically in the absence of antagonistic influences, and the cyclative

release strategy for solid-supported synthesis ensures that products of acceptable purity are obtained even without final purification.

Acknowledgment. Support for this work was provided by the National Institutes of Health (Grant no. GM30759). We also thank the Bristol-Myers Squibb Pharmaceutical Research Institute for the gift of a parallel synthesis reaction system. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member and Novartis Pharma as a Supporting Member.

Supporting Information Available. Experimental procedures and characterization of intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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