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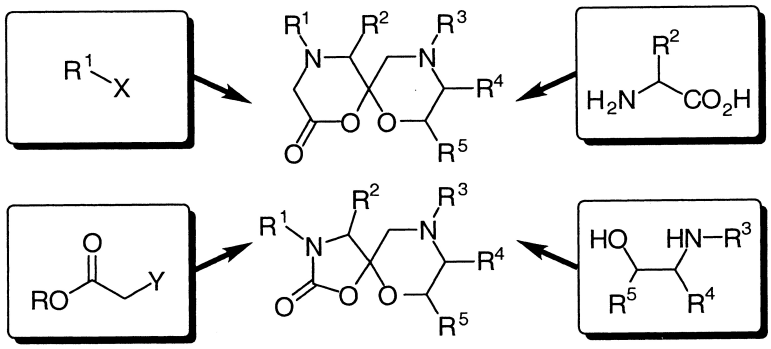

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Amino Acid-Derived Heterocycles as Combinatorial Library Targets: Spirocyclic Ketal Lactones

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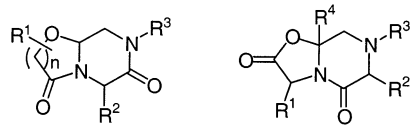
The spirocyclic ketal-lactone frameworks of **3** and **4** were designed as novel structures amenable to combinatorial synthesis. The synthesis of representative analogues was developed in solution and on solid support, the scope of effective input materials was determined, and the stability and stereochemistry of the products was evaluated. The spirocycles are obtained in modest overall yields (5−36%) and excellent purities (>72%) and offer a promising motif for combinatorial prospecting libraries.

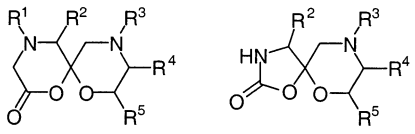
Introduction

The balance of supply and demand between chemistry and biology within drug discovery has seesawed during the past decade as quantum increases in the rate of production of chemical collections have been matched by ultrahigh-throughput screening technologies and by the multitude of new targets promised by genome sequencing. These advances ultimately depend on a source of novel "prospecting libraries" of molecules that are "drug-like"[1−6] and amenable to diversification in the format of parallel or combinatorial synthesis.[7,8] The design of structural motifs and routes for their assembly have typically focused on heterocyclic structures that can be assembled on solid phase.[9−15]

As part of an ongoing program to develop such motifs,[16] we have investigated bicyclic structures that utilize an acetal carbon as the linchpin for cyclization of a precursor assembled from amino acid-derived subunits (e.g., **1** and **2**).[17,18] An attractive feature of the aminal lactone **2** is its formation under basic conditions that involve "cyclative release" from the solid support,[19,20] reducing the need for purification of the final product. We now describe the development of spirocyclic systems **3** and **4**, which embody similar concepts.



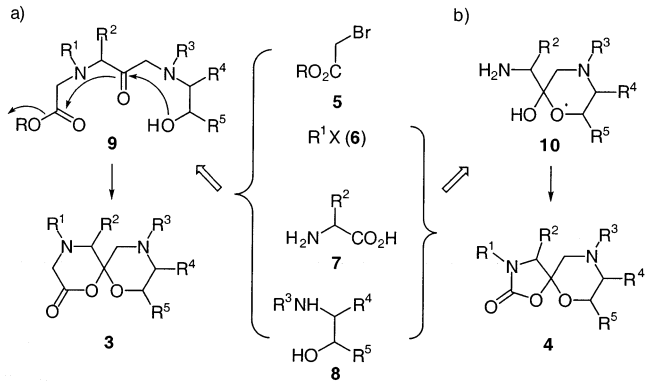
1 **2**



3 **4**

These previously unreported structures offer a number of sites where substituents can be readily varied from amino acid or amino alcohol components and displayed in an unusual orientation. As illustrated in Scheme 1a, the ketone carbon of the linear precursor **9** was envisaged as the linchpin in a base-induced cascade leading to the 6,6 system **3**. The variable input materials: acylating agents (R^1), α-amino acids (R^2), and 1,2-amino alcohols (R^3−R^5) are all available with a large diversity of chemical functionality and often in a chirally pure, protected form. Moreover, attaching the precursor to solid support through the ester leaving group, R, would not only facilitate combinatorial and parallel synthesis, but also ensure high purity of the final product through the cyclative release strategy. As described below, we have reduced this proposal to practice and demonstrated its utility for combinatorial synthetic design. We studied the sequence in solid-phase as well as solution-phase formats, streamlining the latter by using polymeric reagents and scavenging agents. In conjunction with our primary goal to develop the chemistry of the spirocyclic lactones **3**, we also pursued an inverse sequence for assembling the components that facilitated cyclization of the amino-hemiketals **10** to the spirocyclic carbamates **4** (Scheme 1b).

Scheme 1



Results and Discussion

Solution-Phase Chemistry. The feasibility of the synthetic route to the spirocyclic framework of **3** was first explored

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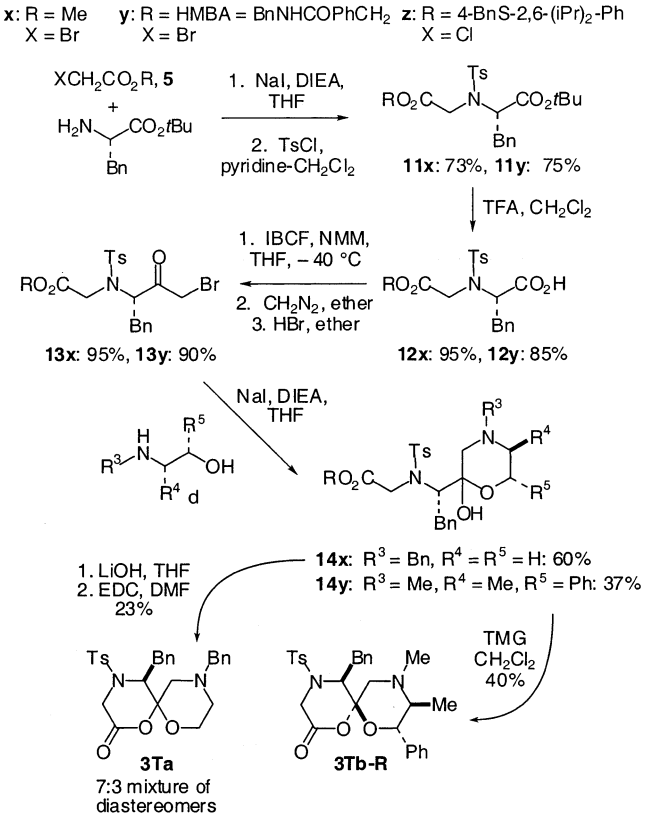
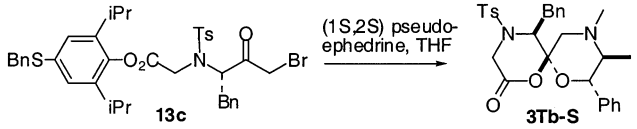
Scheme 2



in solution. As depicted in Scheme 2, phenylalanine *tert*-butyl ester was alkylated with methyl bromoacetate, and the resulting secondary amine was tosylated to give ester **11x**. After cleavage of the *tert*-butyl ester with trifluoroacetic acid (TFA), carboxylic acid **12x** was converted to the α-diazoketone on activation with isobutyl chloroformate (IBCF) and reaction with diazomethane[21] and thence to the α−bromoketone **13x** with HBr. Displacement of the bromide with *N*-benzylethanolamine proceeded with concomitant cyclization to the hemiketal **14x**. As the methyl ester, this material did not cyclize to the spirocyclic lactone with either base or acid. The resistance of methyl ester **14x** toward basic lactonization conditions contrasts with the ready cyclization of the corresponding precursor of aminal lactone **2** with a variety of leaving groups.[18] However, the transformation to **3Ta** could be effected by saponification of the ester with LiOH and subsequent lactonization with EDC. The product is isolated as a 7:3 mixture of diastereomers; the predominant isomer was inferred to have the *R*-configuration at the ketal carbon by analogy to the more substituted analogue **3Tb**−**R**.

Ester leaving groups more reactive than simple methyl or (polymeric) benzyl groups were required to implement the cyclative release strategy; ready incorporation as a linking group for solid-phase synthesis was also important. The electron-deficient benzyl ester derived from *p*-hydroxymethylbenzoic acid (HMBA) derivatives (e.g., amide **14y**) proved to be the most promising. Such esters are known to be activated toward nucleophilic attack as a result of the electron-withdrawing properties of the para carbonyl group,[22] which also provides a convenient point of attachment to a solid support.

Scheme 3



The model precursor **5y** (Scheme 2) was prepared from HMBA pentafluorophenyl ester by reaction with benzylamine and bromoacetic acid. Hemiketal **14y** was formed as described for the methyl ester **14x**, except that the more functionalized (1*S*,2*S*)-pseudoephedrine was employed as the amino alcohol component to aid in stereochemical assignment of the product. With the more reactive HMBA leaving group, spirocyclization occurred directly on treatment with 0.2 M 1,1,3,3-tetramethylguanidine (TMG) in methylene chloride at room temperature. The product **3Tb** was isolated as a single diastereomer and shown to have the (*R*) configuration at the ketal carbon (**3Tb**−**R**), as described below. The HMBA moiety thus offered considerable promise as an ester leaving group and solid-phase linker.

Although we did not explore it extensively, the 4-benzylmercapto-2,6-diisopropylphenyl ester moiety embodied in **5z** warrants discussion. We first evaluated phenyl esters as leaving groups in the lactonization reaction, but found them to be too reactive toward acyl transfer in the early step of halogen displacement leading to intermediate **11**. The 2,6-diisopropyl substituents of **5z** block this side reaction, and the sulfur atom offers a point of attachment to solid support as well as a mechanism for additional activation through oxidation. However, the latter feature proved to be superfluous, since treatment of ester **13z** with (1*S*,2*S*)-pseudoephedrine afforded the spirocycle **3Tb**−**S** directly under the mildly basic displacement conditions (Scheme 3). This level of reactivity poses a problem for solid-phase synthesis, since the product would be released during the displacement step in the presence of an excess of the amino-alcohol component, but it raised the intriguing possibility of stereochemical diversification through control over the ketal configuration. This point is addressed in more detail below.

The stability of spirocycle **3Tb**, and thus the suitability of this ring system for a prospecting library, was evaluated under a variety of conditions. The compound is stable to 50% TFA in methylene chloride and to 0.5 M triethylamine in THF for a period of days. In aqueous solution, spirocycle **3Tb** is stable in the pH range 2−7 with <10% decomposition over 8 h, as measured by ^{1}H NMR. At higher or lower pH, the molecule degrades by hydrolysis of the lactone ring.

Solid-Phase Synthesis. The sequence of Scheme 2 was adapted to solid phase, on the basis of the commercially available polystyrene resin **15** carrying the HMBA linker (Scheme 4). This material is esterified with bromoacetic acid to give polymer **5p**, which undergoes displacement in DMSO with excess amino acid,[23] either as the *tert*-butyl or allyl ester, depending on any side chain protecting group present. This material is acylated or sulfonylated prior to ester deprotection to give **12p**. Conversion of acid **12p** to bromoketone **13p** and displacement with an amino alcohol follow the same protocol employed in solution, except that the reagents are used in excess to ensure conversion. Lactonization of

Scheme 4

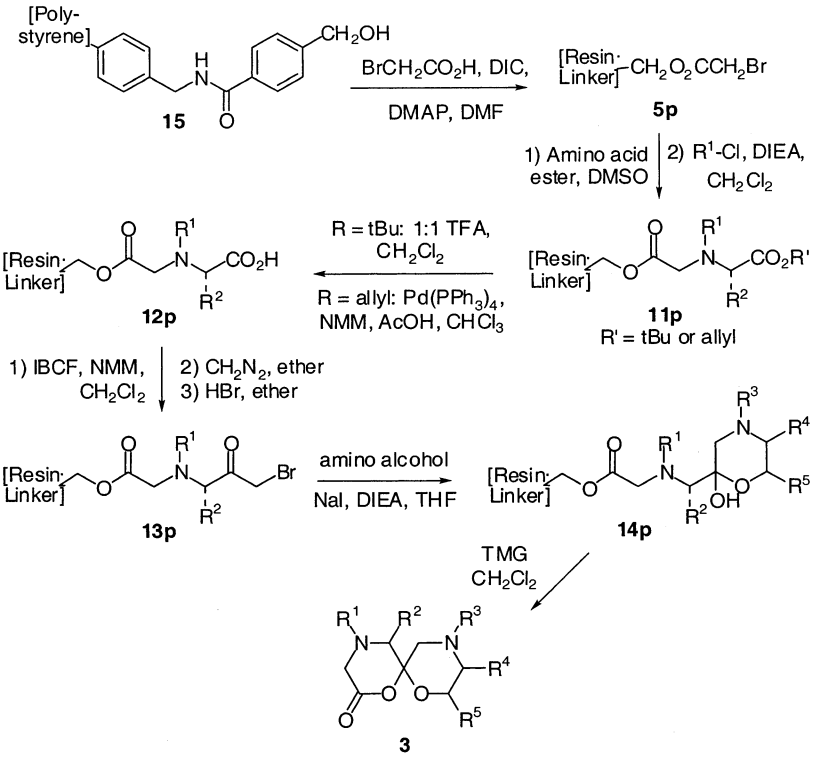
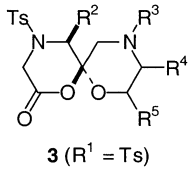


Table 1. Spirocycles 3 Synthesized on Solid Support (Scheme 4)



product	R^2 amino acid	R^3	R^4	R^5	yield, %[a]	purity, %[b]
3Ta	Phe	Bn	H	H	19	72
3Tb	Phe	Me	(*S*)-Me	(*S*)-Ph	36	80
3Tc	Phe	Me	(*S*)-Me	(*R*)-Ph	32	79
3Td	Phe	Me	(*R*)-Me	(*S*)-Ph	31	91
3Te	Phe	Me	(*R*)-Me	(*R*)-Ph	24	90
3Tf	Phe		$-(CH_2)_3-$(*S*)	H	16	82
3Tg	Phe		$-(CH_2)_3-$(*R*)	H	9	80
3Th	Ala	Me	(*S*)-Me	(*S*)-Ph	23	86
3Ti	Val	Me	(*S*)-Me	(*S*)-Ph	29	82
3Tj	Lys-(Boc)	Me	(*S*)-Me	(*S*)-Ph	10	88
3Tk	Asp-(*t*-Bu)	Me	(*S*)-Me	(*S*)-Ph	18	85
3Tl	Thr-(*t*-Bu)	Me	(*S*)-Me	(*S*)-Ph	11	81

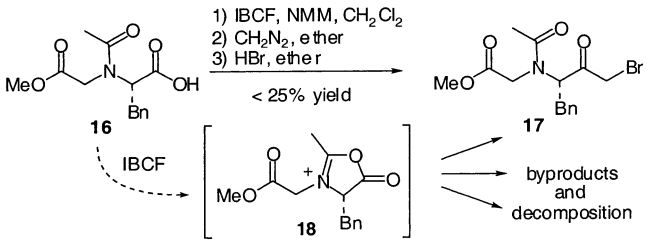
[a] Overall molar yield based on initial loading level of resin **15** and amount of product determined by NMR internal standard. [b] Purity determined from molar and gravimetric yields.

hemiketal **14p** at room temperature with 0.2 M TMG in methylene chloride also proceeds smoothly, with release of spirocycle **3** from the resin. The base can be removed under vacuum or, more conveniently, by passing the crude product through a short plug of silica gel with additional solvent. The derivatives listed in Table 1 were prepared using this protocol. Molar yields of the products were determined with hexamethyldisiloxane as ^{1}H NMR internal standard; purity was then calculated from the weight of material isolated.[24]

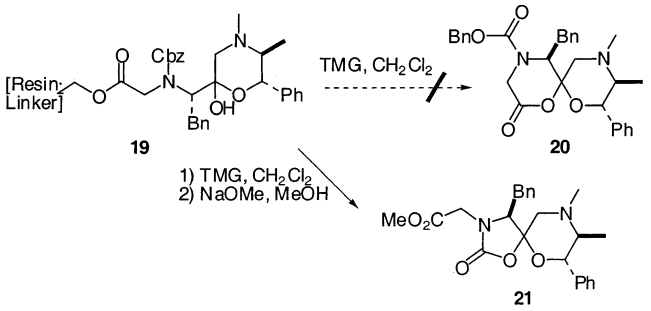
Substitution at R^3, R^4, and R^5. Spirocycles **3Ta**−**3Tg** were synthesized to explore variations at the R^3, R,[4] and R^5 positions. All four pseudoephedrine stereoisomers give good overall yields of the corresponding spirocycles **3Tb**−**3Te**, and each was isolated as a single diastereomer (the configurations at the ketal carbon are discussed below). The yields are reduced when the prolinol enantiomers are employed, reflecting additional strain introduced by the 6,5-ring fusion. In contrast, when primary amino alcohols (i.e., $R^3 = H$) were used, no spirocyclic product could be detected at the end of the sequence. This result is consistent with observations from solution-phase work, in which primary amines reacted with bromoketone **5b** to give a complex mixture of products.

Substitution at R^2. The syntheses of spirocycles **3Th**−**3Tl** demonstrate that amino acid side chains of different steric and electronic characteristics can be incorporated to vary the R^2 substituent. In addition to phenylalanine, alanine, valine,

Scheme 5



Scheme 6



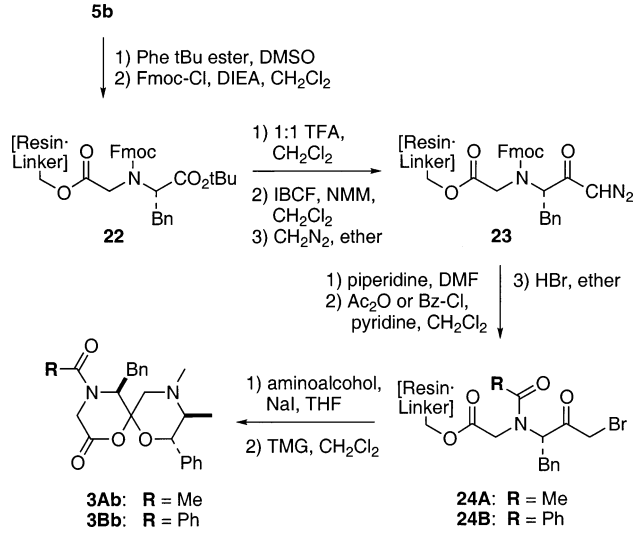
lysine, aspartic acid, and threonine, all give the corresponding spirocycles in acceptable yields and purities. The protecting groups of the side chains of **3Tj**−**3Tl** can all be removed using TFA with preservation of the ketal lactone. Presumably, the protonated amine of the morpholine ring protects the ketal lactone ring system under acidic conditions, as it does for the related aminal lactones **2**.[18]

Substitution at R[1]. Sulfonyl substituents, represented by tosyl, are advantageous R^1 groups, as evidenced by the synthesis of spirocycles **3Ta**−**3Tl**. However, attempts to incorporate acyl groups at this position through the sequence of Scheme 4 were not successful. The basis for this failure was explored in detail in solution, since exclusion of acyl groups at R^1 would significantly limit the diversity of a library based on this motif. We found that the problem lay in generation of the bromomethyl ketone (Scheme 5). Activation of the model amide **16** with isobutyl chloroformate and treatment with diazomethane followed by HBr affords only a low yield of the bromoketone **17**. *N*-Acyl-*N*-alkyl amino acids such as **16** are notoriously difficult to couple with weakly nucleophilic partners as a result of competing products arising from the oxazolone intermediate (e.g., **18**) on activation.[25]

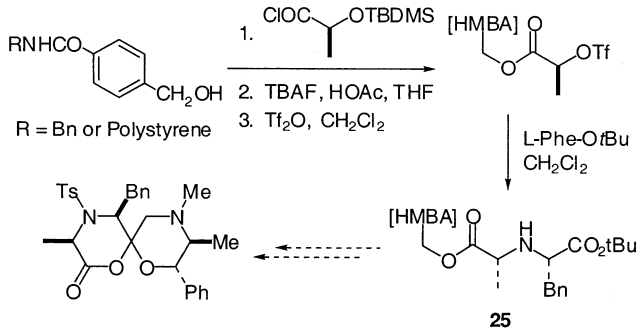
An attempt to carry an *N*-Cbz moiety through the sequence was also unsuccessful. In a solid-supported synthesis, the intermediate **19** released none of the expected ketal-lactone **20**, but afforded a small amount of the ketal-carbamate **21** on subsequent treatment of the resin with methanolic base (Scheme 6).

To avoid the problems of Schemes 5 and 6, we reordered the steps and introduced an R^1 acyl substituent after generation of the diazoketone: the base-labile Fmoc group was used to protect the amine during the carboxyl activation and diazomethane reactions, then replaced prior to formation of the bromoketone (Scheme 7). Acetyl and benzoyl moieties as representative acyl groups afforded the spirocyclic products **3Ab** and **3Bb** in relatively low yield (5−6% overall) but in 80% purity off the solid phase. The poor yields were

Scheme 7



Scheme 8



attributed to the lability of the α-diazoketones and decomposition during deprotection and acylation conditions.

Substitution on the Acetic Acid Moiety. Our attempts to introduce diversity adjacent to the lactone carbonyl group in **3** by using α-substituted α-bromo esters failed as a result of *β*-elimination in the first displacement step. Although this side reaction has been minimized in related systems by employing α-triflates instead of bromides,[26] we obtained low yields in the model system depicted in Scheme 8 in both solution and solid-phase formats; as a consequence, we did not pursue this variation further. In hindsight, in light of the configuration of the ketal stereocenter and the axial orientation of the benzyl side chain in the unsubstituted analogue **3Tb**−**R** (see below), it may have been more fruitful to investigate this sequence starting with the D-lactate enantiomer.

Stereochemistry of the Cyclization. Except for the formation of a 7:3 mixture of diastereomers in cyclization to **3Ta**, all of the products listed in Table 1 were isolated as single diastereomers. Molecular modeling of spirocycle **3Tb** derived from (1*S*,2*S*)-pseudoephedrine suggested that the cyclization would proceed to give the thermodynamically favored diastereomer **3Tb**−**R**, in which each ketal oxygen is axial or pseudoaxial with respect to the other ring, thus maximizing anomeric stabilization (Figure 1). The (*R*) configuration was indeed confirmed for **3Tb** by observing NOE correlations between hydrogens **b** and **c**, as shown in Figure 1. Similar results were obtained for spirocycles **3Td**,

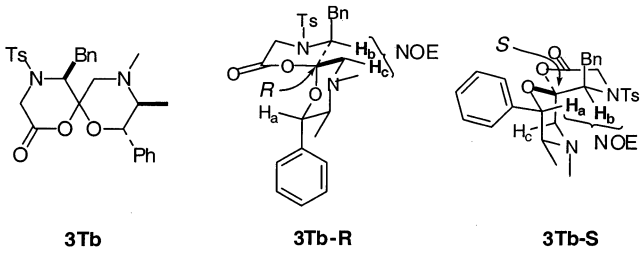


Figure 1. Ketal stereoisomers of **3Tb**.

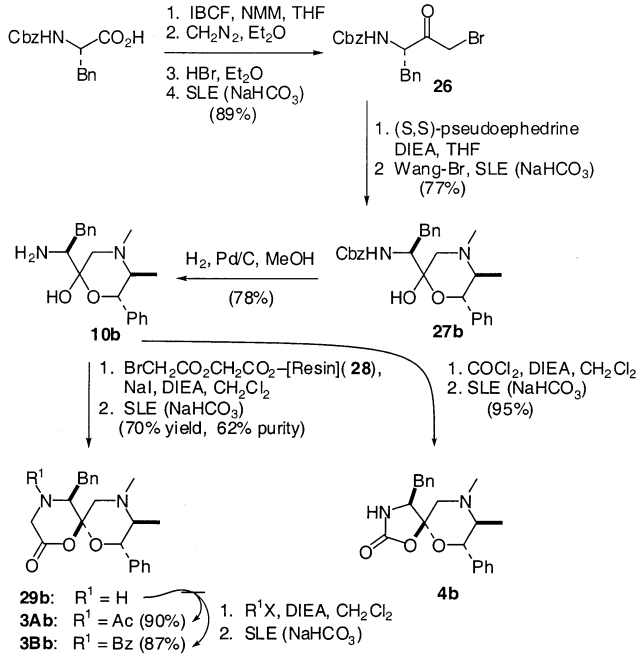
3Te, **3Ab**, and **3Bb**; the ketal configuration of the other spiroketals was assumed to be the same.

Interestingly, however, the choice of leaving group influenced the stereochemical course of the cyclization quite dramatically. The spirocycles from aryl ester **5z** were often diastereomers of those isolated from the analogous solid-phase synthesis using the HMBA linker. For example, the product from treatment of ester **13z** with (1*S*,2*S*)-pseudoephedrine is spirocycle **3Tb**−**S**, as confirmed by an NOE correlation between protons a and b (Figure 1) and by single-crystal X-ray crystallography (Figure 2a). The crystal structure of **3Tb**−**S** is interesting because neither of the ketal oxygens is axial with respect to the other ring; both are equatorial and antiperiplanar to the nitrogen atom in the other ring.

Opposing stereoselection from the two linker systems was also observed in the formation of spirocycles **3Ta** and **3Tc** from (1*R*,2*S*)-pseudoephedrine. Although we presume that the phenolic leaving group favors kinetic control over the cyclization, it is not apparent why the bulky tetrahedral intermediate is more readily attained when it is equatorial to the morpholine ring (indeed, molecular modeling of the tetrahedral intermediates leading to **3Tb**−**R** and **3Tb**−**S** suggests that the former is lower in energy). Moreover, the dichotomy between the leaving groups is not absolute: both give the same ketal stereoisomers with (1*S*,2*R*)- and (1*R*,2*R*)-pseudoephedrine (**3Td** and **3Te**).

Solution-Phase Synthesis. An alternative assembly sequence involving solution-phase chemistry and employing polymeric reagent scavengers and solid−liquid extraction (SLE) for reaction workup was also explored.[27−31] A key feature of this process is the intermediacy of amino hemiketal **10**, which offers not only more flexibility in choice of acyl

Scheme 9



groups (R^1) but also access to a different ring system, the spirocyclic ketal carbamates **4**. This route is exemplified by the phenylalanine−pseudoephedrine combination shown in Scheme 9.

Cbz−phenylalanine was converted to the bromomethyl ketone **26** in 89% yield with the usual reagents (IBCF, CH_2N_2, HBr) using SLE with aqueous $NaHCO_3$ as the only purification step. After displacement with pseudoephedrine and DIEA, excess amine was scavenged with Wang bromopolystyrene resin.[32] The polymeric versions of DIEA and NMM proved less effective than DIEA itself, so SLE (aq $NaHCO_3$) was again used to remove the hydrobromide salt. Hydrogenolysis of the Cbz group then gave the amino hemiketal **10b** in 60% yield from the bromomethyl ketone.

Alkylation of the amino hemiketal **10** and cyclization to the amino ketal lactone **29b** requires a bifunctional reagent with balanced activity: the ester needs to be reactive enough for lactonization to proceed, but not so reactive that acylation competes with alkylation of the amine. In addition, the leaving group has to be removed by extraction or evapora-

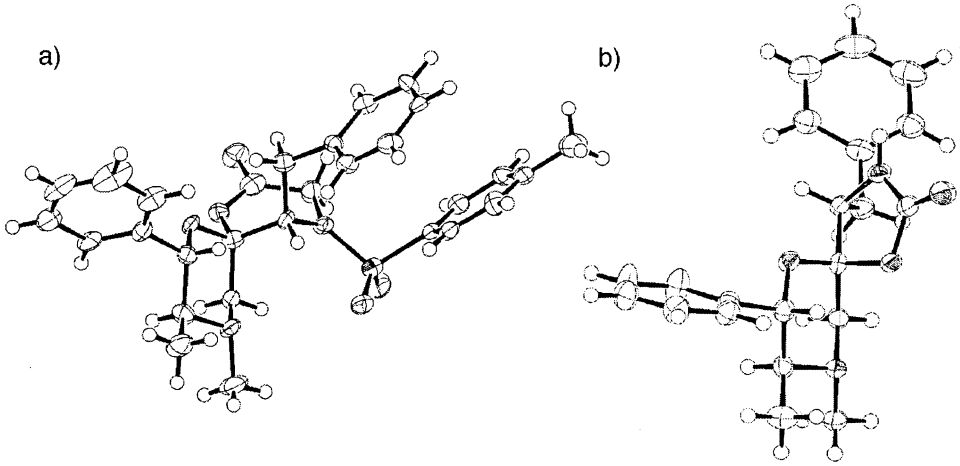
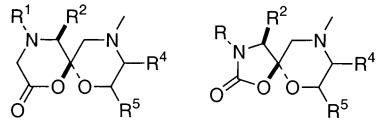


Figure 2. ORTEP plots of crystal structures of (a) **3Tb**−**S** and (b) **4a**.

Table 2. Spirocycles **3** and **4** Synthesized in Solution (Scheme 9)

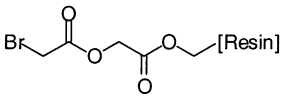


3 (R^3 = Me) **4** (R^3 = Me)

R^1	R^2 amino acid	R^4	R^5	lactone	yield, %[a]	purity, %[b]	carbamate[c]	yield, %[a]	purity, %[b]
Ac	Phe	(*S*)-Me	(*S*)-Ph	**3Ab**	31	64	**4b**	48	67
Bz	Phe	(*S*)-Me	(*S*)-Ph	**3Bb**	27	59			
Ac	Phe	(*S*)-Me	(*R*)-Ph	**3Ac**	21	54	**4c**	40	52
Ac	Phe	(*R*)-Me	(*S*)-Ph	**3Ad**	19	53	**4d**	42	65
Ac	Phe	(*R*)-Me	(*R*)-Ph	**3Ae**	27	48	**4e**	57	78
Ac	Lys(Boc)	(*S*)-Me	(*S*)-Ph	**3Aj**	32	49	**4j**	42	57
Ac	Asp(*t*-Bu)	(*S*)-Me	(*S*)-Ph	**3Ak**	28	41	**4k**	60	72
Ac	Val	(*S*)-Me	(*S*)-Ph	**3Au**	35	58	**4u**	45	67
Me	Phe	(*S*)-Me	(*S*)-Ph	**3Mb**	50	55	**4b-Me**	57	56

[a] Overall molar yield based on starting amino acid and amount of product determined by NMR internal standard. [b] Purity determined from molar and gravimetric yields. [c] For carbamates **4**, R = H except for **4b-Me**, where R = Me.

tion. The most promising reagents were methyl α-(bromoacetoxy)acetate and 2,2,2-trifluoroethyl bromoacetate; the former gave the cleanest product, but the methyl glycolate leaving group is neutral and nonvolatile. The polymeric version of this reagent, **28**, offered the best solution, since it can be used in excess and removed on filtration during workup. Treatment of the phenylalanine−pseudoephedrine derivative **10b** in this manner afforded the spirocyclic amine **29b** in 70% yield and 62% overall purity as measured by an NMR internal standard. The spirocyclic amine can be derivatized with a variety of acylating agents, thus making this position readily available for diversification. This sequence was applied successfully to other amino acids and pseudoephedrine stereoisomers with the results listed in Table 2.



28

The alternative spirocyclic skeleton represented by carbamate **4b** was readily accessible from the amino hemiketal intermediate **10b** by treatment with phosgene (Scheme 9). X-ray crystallography revealed that the ketal stereocenter of **4b** has the (*R*) configuration, with the carbamate oxygen axial with respect to the morpholine ring (Figure 2b). Not surprisingly, when applied to the other amino acids and diastereomeric amino alcohols, the overall yields and purities for this sequence were slightly higher than for the longer route to the corresponding lactones **3** (Table 2). Table 2 records the overall yields and purities of products that were not subjected to any purification procedure. Although the yields of the solution-phase products were slightly higher than the solid-phase products of Table 1, the greater purity of the latter compounds highlights the advantage of the cyclative release strategy.

Conclusion

Location of a ketone or aldehyde carbon within a peptide or peptide-derived framework provides a variety of bicyclization patterns with an aminal or acetal carbon as the linchpin. The resulting novel heterocycles with fused or spirocyclic skeletons and dense functionalization can be prepared on solid phase or in solution by processes that are amenable to parallel synthesis and combinatorial diversification. The routes to the spirocyclic ketals **3** and **4** also provide an example of divergent design, affording different ring systems and potential libraries from a common intermediate.

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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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