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Solid-Phase Synthesis of Multiple Classes of Peptidomimetics from Versatile Resin-Bound Aldehyde Intermediates

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Abstract: A wide variety of highly substituted lactam containing peptidomimetic scaffolds are prepared by solid-phase synthesis from a single, versatile class of resin-bound aldehyde intermediates (**1**). These include monocyclics **3**, bicyclics **4**, tricyclics **5**, and tetracyclics **6**. The key intermediate **1** is readily synthesized from resin-bound natural or unnatural α-amino acids. The synthetic procedures permit the construction of a large diversity of substitution patterns for ready use in combinatorial chemistry. In every case, the release of final products from resin is by a cyclitive cleavage process. Since this depends on successful completion of multiple intermediate synthetic steps, the products are often quite pure, even though previous steps involve only a filtration workup. The mild conditions for many of these synthetic procedures offer the promise of using this chemistry in peptide fragment condensations to produce modified peptides, at either the N-terminus or C-terminus, or as individually assembled peptide segments with a wide variety of conformationally restricted peptidomimetic linkers at the point of juncture.

1. Introduction

The substituted lactam scaffolds "**A**" and "**B**" are frequently found in peptidomimetic structures.[1−5] In the absence of the secondary and tertiary structure imposed by extended peptide sequences on local regions of a peptide or protein, they are one of the simplest ways of creating, in a small space, conformational constraints on amino acid side chains. They also increase the enzymatic stability of the internal amide link, an important aspect when converting small peptides, subject to ready enzymatic hydrolysis, into "non-peptide" analogues that can maintain activity under physiological conditions.

This article reports the preparation, via solid-phase synthesis, of a wide variety of highly substituted lactam containing

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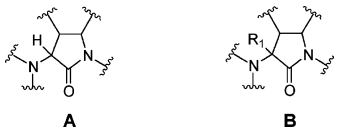
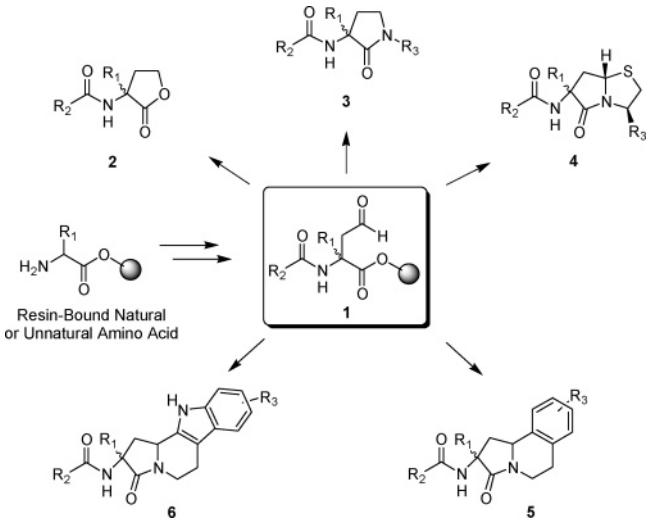


peptidomimetic scaffolds based on **A** or **B**, including many cases of an underrepresented class of derivatives in which the position alpha to the amine and lactam carbonyl is functionalized (e.g., R_1 in structure **B**). This is accomplished through the synthesis and use of a remarkably stable and versatile class of resin-bound aldehyde intermediates (**1**).[6] The multipotent nature of **1** is demonstrated by preparing a representative series of five peptidomimetic scaffolds: lactones **2**, lactams **3**, bicyclics **4**, tricyclics **5**, and tetracyclics **6** (Scheme 1). The importance of the scaffolds formed from **1**, well documented in the solution literature, will be discussed in more detail in the appropriate sections of this article. The simple synthetic procedures reported permit a wide diversity of substitution patterns and are, in this sense, combinatorial chemistry[7] enabled. In every case, the release of final products from resin is by a cyclitive cleavage process.[8] This removes the need for "resin-linker handles" that remain on the products. Since cyclitive cleavage depends on successful completion of multiple intermediate synthetic steps, the products are often quite pure, even though previous steps involve only a filtration workup.

With solid-phase based chemistry[9,10] the multiple step sequences described in this report are quickly carried out on a micromole scale. Even peptidomimetic scaffold syntheses requiring as many as 10 steps provide good overall yields. Resin

Scheme 1. Peptidomimetic Scaffolds Available from Versatile Aldehyde Intermediates **1**



1 is prepared under achiral conditions and the resulting products are racemic, which is compatible with their use at the beginning stages of a discovery process. When **1** is combined, in subsequent convergent syntheses, with chiral reagents, the diaster-

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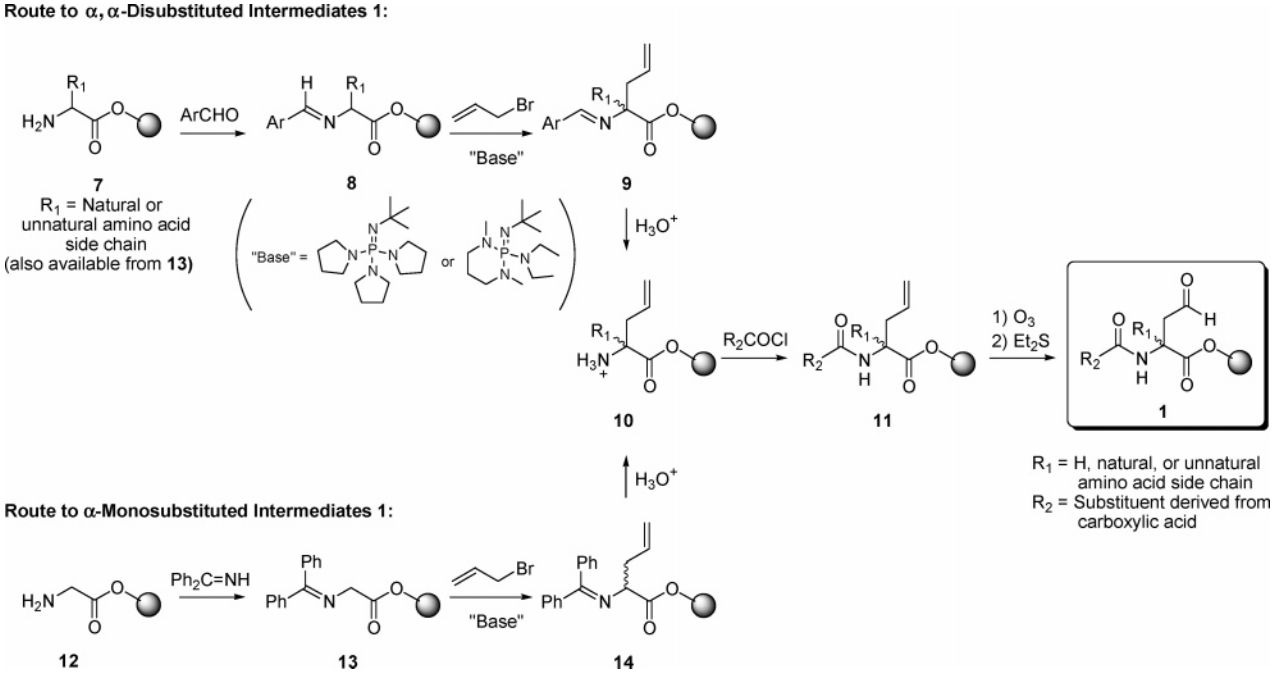
Scheme 2. Synthesis of Aldehyde Intermediates **1**



eomeric products are nonracemic. Finally, in the preparation of the bicyclic scaffold **4**, solid-phase chemistry allows formation of each of two stereoisomers through temperature controlled sequential release in the final cyclitive cleavage.

1.1. Preparation of Versatile Aldehyde Intermediates 1. At the core of this report is the preparation and use of resin-bound **1**. The starting material is a standard Merrifield resin,[9] chosen for its versatility and low cost. The stability of the polystyrene-based Merrifield resin to acids, non-nucleophilic bases, and oxidation allows the use of all these conditions in the course of the resin-bound chemistry. In addition, since all scaffolds are released from resin by a cyclitive cleavage process[8] there is no need for alternative linkers to permit specialized cleavage conditions. Scheme 2 outlines the syntheses of aldehyde intermediates **1**.

The intermediates are all made by ozonolysis of the α-allyl substituted derivatives **11** derived from resin-bound natural or unnatural α-amino acids **7** or **12**.[11] These, in turn, are synthesized by chemistry based on earlier solution-phase work, including the first general synthesis of α-amino acids by phase-transfer catalysis (PTC), which involved α-alkylation of the benozphenone imine of glycine ethyl ester, reported in 1978.[12] The benzophenone imines of glycine alkyl esters have been used in a variety of synthetic studies during the intervening years.[13] Solid-Phase Unnatural Amino Acid and Peptide Synthesis (UPS),[14] an integrated technique that extends the scope of the solution-phase chemistry to a general solid-phase synthesis of unnatural α-amino acids, peptides, and peptidomimetics was reported in 1996.[14a] This chemistry involves addition of three steps to the normal Merrifield peptide synthesis in order to attach an unnatural side chain to a resin-bound α-amino acid or

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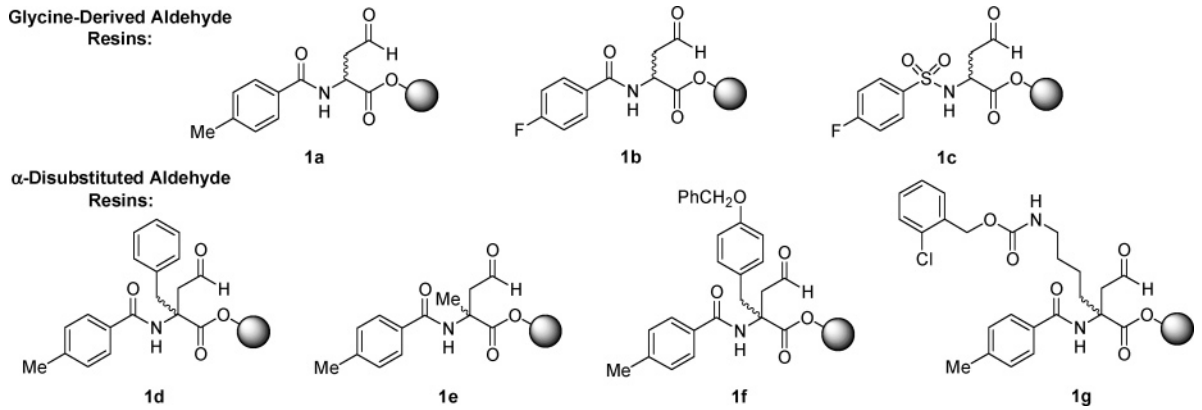

Figure 1. Seven aldehyde resins **1** used in the synthesis of peptidomimetic scaffolds **2**−**5**.

peptide: (a) activation of the N-terminal residue by conversion into a Schiff base (Scheme 2, **7** to **8**, $R_1 \neq H$; or **12** to **13**); (b) removal of the proton on the carbon α to the newly introduced imine functionality and reaction of the resulting carbanion with an electrophile (**8** to **9**, $R_1 \neq H$; or **13** to **14**); (c) removal of the Schiff base activating group (**9** to **10**, $R_1 \neq H$; or **14** to **10**, $R_1 = H$).

Alkylation of resin-bound starting materials **13** (derived from glycine) or **8** (prepared from an α-substituted α-amino acid) lead, respectively, to mono-[14a] or dialkylated[14b] products such as **14** or **9**. Alkylations with activated and unactivated halides[14c] are readily accomplished, and reactions with Michael acceptors lead to various glutamic acid derivatives.[14e] Tandem dialkylation from **13** also gives α,α-dialkylated α-amino acids.[14d] On-resin enantioselective alkylations[14g] and Michael additions[14j] can be accomplished using *Cinchona* alkaloid-derived phase-transfer catalysts. Boron alkylation of a resin-bound glycine cation equivalent derived from **13** yields various products often difficult to prepare from the anionic equivalents.[14f] All these routes provide multiple means of introducing substituents into **7** or **12**. This makes possible numerous variations on R_1 in structure **1**, expanding the potential combinatorial synthesis of arrays of substituted target scaffolds **2**−**6** (Scheme 1).

2. Results and Discussion

In the current work, Merrifield-bound aldehyde precursor **10**, $R_1 = H$, was prepared from resin-bound glycine **12**. For **10**, $R_1 \neq H$ (i.e., α,α-dialkyl α-amino acid derivatives), procedures from **7** to **10** previously reported for Wang resin[14b] were adapted to Merrifield resin.[15,16] For most of the α-substituted cases, commercially available resin-bound Boc-protected amino acid derivatives of **7** were used as starting materials. The exception was the resin-bound *O*-benzyl protected tyrosine starting material (leading to **1f**, see Figure 1), which was prepared from chloromethylated Merrifield resin by conventional means.

Group R_2 in **2**−**6** (Scheme 1) is envisioned as a key location in scaffold derivatives for modifications of functionality inter-

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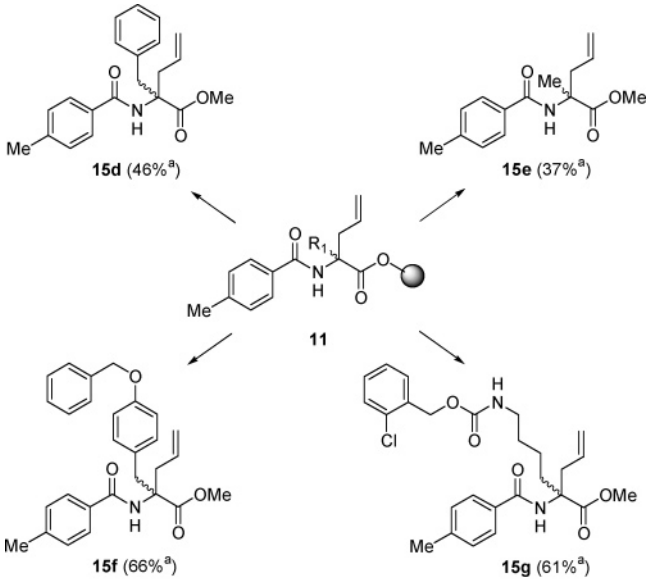
Scheme 3. Characterization of Resin-Bound Olefins by Methanolysis with NaOMe



[a] Yields reported here and in all subsequent Schemes, Figures, and Tables are based on purified products and resin-bound amino acids as starting materials.

acting with receptor binding or enzyme active sites. Often R_2 fragments will be introduced from carboxylic acid starting materials. Therefore initial work focused on producing amide derivatives for R_2 (with the exception of one sulfonamide) in the final products. After hydrolyzing **9** or **14** to **10**, the second site of diversity, R_2, was incorporated by reaction of **10** with acid chlorides or a sulfonyl chloride. All the resulting resin-bound α-substituted olefins **11** were characterized by cleavage with methoxide to afford methyl esters **15** (Scheme 3).

Ozonolysis[17,18] of resin-bound substrates is still not a commonly used solid-phase reaction, even though it was first reported more than 30 years ago as a means to form aldehydes. There have been subsequent reports of ozonolyses of resin-bound olefins, both to transform substrates and to cleave olefins serving as linkers to resins. In the present study ozone generation was calibrated to ensure complete reaction without over-

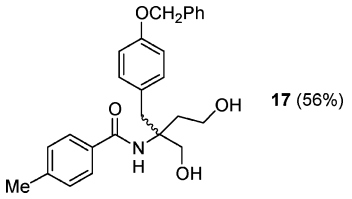


Figure 2. Diol product from $NaBH_4$ reduction of **1f**.

oxidation. The procedure is straightforward and gives good conversions, as determined by the yields and purities of products subsequently produced.[19] Figure 1 lists the resin-bound aldehydes **1** prepared and used in subsequent scaffold formation.

2.1. Multiple Uses of Versatile Intermediates 1. 2.1.1. Preparation of Lactones 2. One of the simplest scaffolds available from **1** is lactone **2** (Scheme 1).[20,21] An example of the biological significance of this scaffold is the *N*-acyl-L-homoserine lactone signal molecule and its analogues used by Gram-negative bacteria to activate quorum sensing.[20f] The lactone scaffold synthesis, with representative examples, is outlined in Scheme 4 (yields given here and in subsequent schemes, figures, and tables are based on resin-bound α-amino acids **7** and **12** and are for purified products). Since these lactones required base and elevated temperature for the final cyclitive cleavage, it was possible, after reduction and prior to release, to wash away excess reagents and obtain, after cleavage, crude products in 90 to 98% purity. Purification and complete characterization of these lactones also substantiated the nature of the resin-bound aldehyde intermediates **1**.

Sodium cyanoborohydride[22] was routinely used as a reducing agent after observing, in one case (the reduction of **1f**), that $NaBH_4$ led to the diol product **17** (Figure 2). 2-Amino-2-alkyl substituted-1,4-butanediols such as **17** are highly functionalized molecules, and this alternate synthetic pathway should afford access to a variety of such derivatives from intermediates **1**.

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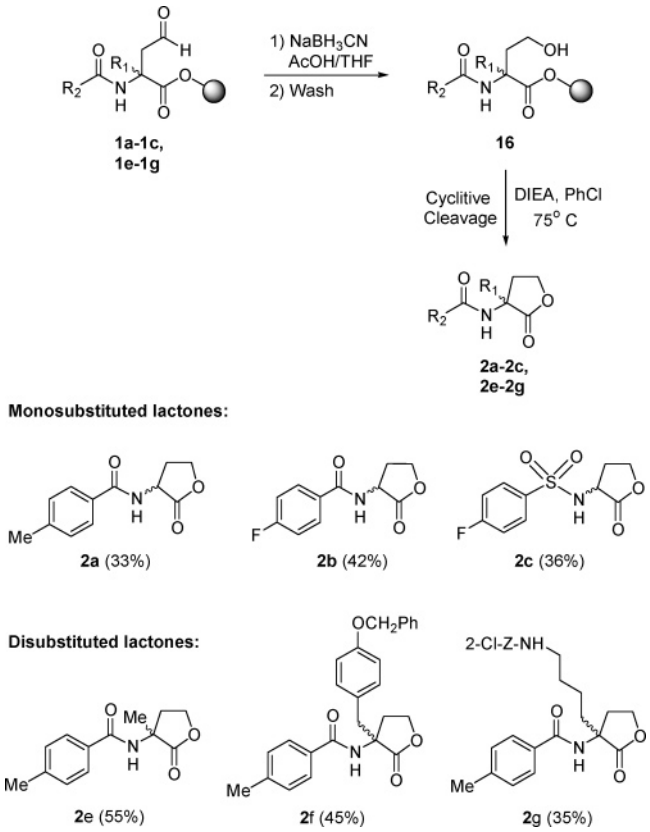
(19) See Supporting Information for experimental details.

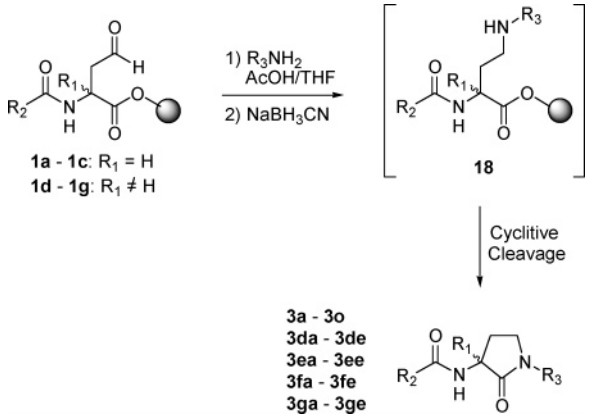
(20) Early references and recent examples of α-amino-γ-lactones (homoserine lactones): (a) Baldwin, J. E.; North, M.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3167−3168. (b) Schwab, J. M.; Ray, T. *Chem. Commun.* **1988**, 29−31. (c) Baldwin, J. E.; North, M.; Flinn, A. *Tetrahedron* **1988**, *44*, 637−642. (d) Son, J.-K.; Kalvin, D.; Woodard, R. W. *Tetrahedron Lett.* **1988**, *29*, 4045−4048. (e) Rolland-Fulcrand, V.; Rolland, M.; Roumestant, M.-L.; Martinez, J. *Eur. J. Org. Chem.* **2004**, 873−877. (f) Geske, G. D.; Wezeman, R. J.; Siegel, A. P.; Blackwell, H. E. *J. Am. Chem. Soc.* **2005**, *127*, 12762−12763. (g) Annedi, S. C.; Biabani, F.; Poduch, E.; Mannargudi, B. M.; Majumder, K.; Wei, L.; Khayat, R.; Tong, L.; Kotra, L. P. *Bioorg. Med. Chem.* **2006**, *14*, 214−236.

(21) Early references and recent examples of α-alkyl-α-amino-γ-lactones: (a) Pedersen, M. L; Berkowitz, D. B. *Tetrahedron Lett.* **1992**, *33*, 7315−7318. (b) Hayes, J. F.; Tavassoli, A.; Sweeney, J. B. *Synlett* **2000**, 1208−1209. (c) Reference 17k. (d) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907−2918. (e) Kiuchi, M.; Adachi, K.; Kohara, T.; Minoguchi, M.; Hanano, T.; Aoki, Y.; Mishina, T.; Arita, M.; Nakao, N.; Ohtsuki, M.; Hoshino, Y.; Teshima, K.; Chiba, K.; Sasaki, S.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 2946−2961. (f) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985−1987. (g) Ma, D.; Zhu, W. *J. Org. Chem.* **2001**, *66*, 348−350. (h) Mazal, C.; Jonas, J.; Zák, Z. *Tetrahedron* **2002**, *58*, 2729−2733. (i) Brouillette, W. J.; Bajpai, S. N.; Ali, S. M.; Velu, S. E.; Atigadda, V. R.; Lommer, B. S.; Finley, J. B.; Luo, M.; Air, G. M. *Bioorg. Med. Chem.* **2003**, *11*, 2739−2749. (j) Gasperi, T.; Loreto, M. A.; Tardella, P. A.; Veri, E. *Tetrahedron Lett.* **2003**, *44*, 4953−4956. (k) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115−2118. (l) Reference 3e.

Scheme 4. Representative Lactones Prepared through Reduction and Cyclitive Cleavage



Scheme 5. Synthetic Scheme for Syntheses of Lactams **3**



2.1.2. Preparation of Lactams 3. As noted in the introduction, lactam scaffolds are a frequent theme in peptidomimetic structures,[1−5] providing one of the simplest scaffolds for recreating, in a small space, some of the conformational constraints present in larger peptides or proteins. Early examples are the Freidinger lactams[23] **3** (R_1 = H), which were developed in the early 1980s. More recently a number of groups have reported examples of **3** in which R_1 is either hydrogen or a variety of other substituents.[1−5] In the present case, both α-monosubstituted and α,α-disubstituted lactams **3** were prepared by reductive amination of **1** with primary amines (R_3-NH_2) and $NaBH_3CN$ to give intermediate **18**, followed by cyclitive cleavage (Scheme 5).

Sodium cyanoborohydride and the alternative reducing agent sodium triacetoxyborohydride have been used extensively in reductive aminations of amines both in solution[22,24] and on solid phase.[25] Sodium triacetoxyborohydride is widely used for reductive amination under mild conditions.[24d,f] However, the preferred solvent for $NaBH(OAc)_3$ reductions is dichloroethane. For reactions with aldehyde resins **1**, $NaBH_3CN$ was used because of its efficiency, solvent compatibility, and selectivity. The chemoselectivity in reductions with $NaBH_3CN$ broadly depends on solvent and pH, thus allowing a careful selection of reducing capability versus tolerability toward diverse functional groups. Acetic acid has been reported as the acidic component in reductive aminations with sodium cyanoborohydride performed on resin, as mixtures of $NaBH_3CN$ and acetic acid, in either DMF or THF.[25b,25e] Interestingly, it was reported that when THF was used as the solvent the presence of a small amount of water did not negatively impact reductions,[25b] which makes similar conditions an attractive choice for applications in solid-phase chemistry. Ultimately, the best results were achieved with $NaBH_3CN$ dissolved in a 0.3−0.5 M solution of AcOH in dry THF, DMF, or mixtures of these two solvents, depending on the solubility of the amine component.

Partial cyclitive cleavage often occurred during the room-temperature reductive aminations. In the case of the reaction between unreactive amines (aniline) and aldehyde resins with R_1 = H, heating in toluene at 65−75 °C for 6−15 h was necessary to optimize yields. For aldehyde resins with R_1 = alkyl, the optimal results were obtained after heating the preformed reductive amination products in chlorobenzene, in the presence of DIEA, at 80−85 °C for 18 h. These results may reflect an interplay between the Thorpe−Ingold effect,[26] the lowered nucleophilicity of phenyl-substituted amines, and the steric hindrance which the preformed amines encounter, to varying degrees, upon the approach to the ester carbonyl cleavage site. Following aqueous workup the lactams thus formed were purified from any excess reagents or reduction byproducts by chromatography and crystallization.[19]

2.1.3. Multiple Site Variations on Lactam 3 Scaffold. For the lactam scaffold **3** the combinatorial potential of **1** was exemplified by preparing a series of lactams in which R_1, R_2, and R_3 were varied. These cases are discussed in the following sections.

(22) (a) Borch, R. F; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897−2904. (b) Review: Hutchins, R. O.; Hutchins, M. K. Sodium Cyanoborohydride. In *Encyclopedia of Reagents for Organic Synhesis;* Paquette, L. A., Ed.; John Wiley: Chichester, U.K., 1995; Vol. 7, pp 4539−4542.

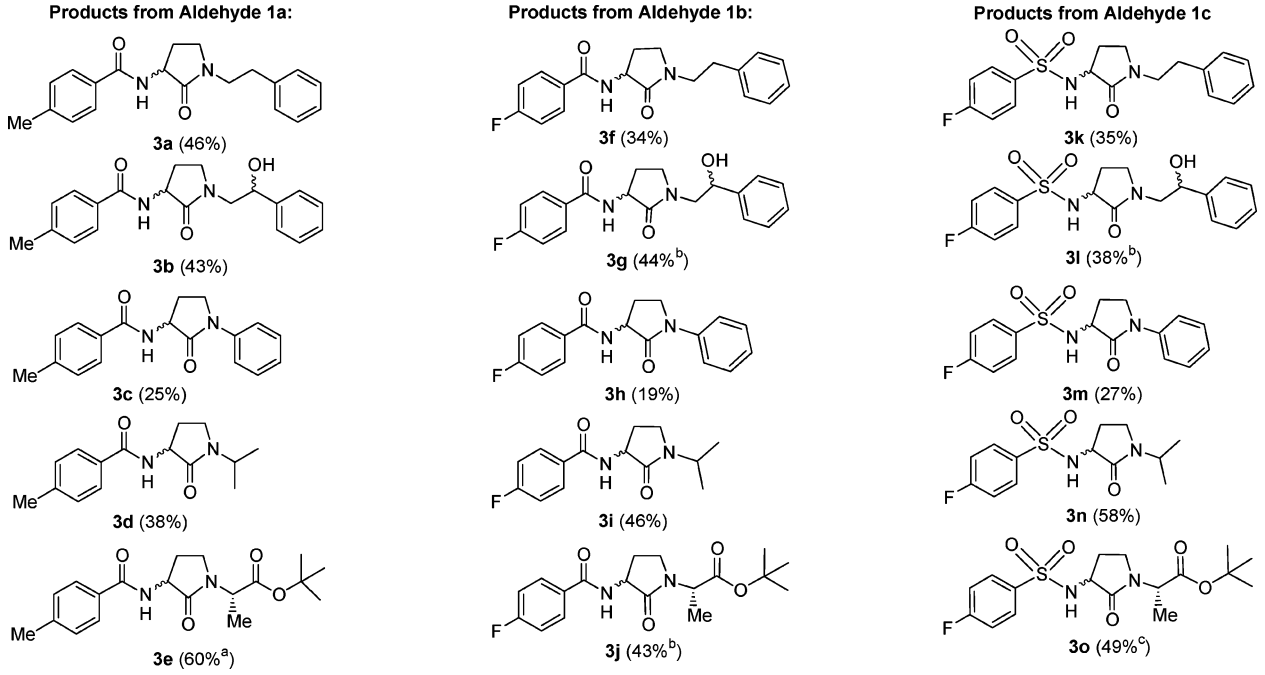
(23) Reviews and early references to Freidinger lactams: (a) Reviews: references 1o and 1u. (b) References 2d, 2e, and 5a.

(24) Review and selected examples of solution-phase reductive aminations: (a) Review: Baxter, E. W.; Reitz, A. B. in *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, 2002; Vol. 59, Chapter 1, pp 1−697. (b) Nutaitis, C. F.; Schultz, R. A.; Obaza, J.; Smith, F. X. *J. Org. Chem.* **1980**, *45*, 4606−4608. (c) Manescalchi, F.; Nardi, A. R.; Savoia, D. *Tetrahedron Lett.* **1994**, *35*, 2775−2778. (d) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862. (e) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367−2373. (f) Chen, Z.; Kende, A. S.; Colson, A.-O.; Mendezandino, J. L; Ebetino, F. H.; Bush, R. D.; Hu, X. E. *Synth. Commun.* **2006**, *36*, 473−479.

(25) Selected examples of reductive aminations on solid phase: (a) Esser, C. K.; Kevin, N. J.; Yates, N. A.; Chapman, K. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2639−2644. (b) Brown, E. G.; Nuss, J. M. *Tetrahedron Lett.* **1997**, *38*, 8457−8460. (c) Kung, P.-P.; Swayze, E. *Tetrahedron Lett.* **1999**, *40*, 5651−5654. (d) Jefferson, E. A.; Swayze, E. E. *Tetrahedron Lett.* **1999**, *40*, 7757−7760. (e) Forns, P.; Sevilla, S.; Erra, M.; Ortega, A.; Fernández, J.-C.; de la Figuera, N.; Fernández-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2003**, *44*, 6907−6910.

(26) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080−1106. (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1766.

Table 1. Amines (R_3NH_2) and Amides (R_2) as Variables in the Reductive Amination/Cyclization Sequence to Lactams **3**



[a] Combined yield of two diasteroemers. [b] Isolated as a mixture of diastereomers. [c] Isolated yield of diastereomeric mixture as 1:1 complex with alanine *tert*-butyl ester.

2.1.3.1. Amine Survey (R_3NH_2) in Lactam Formation. We first chose to survey five primary amines (R_3NH_2) for reaction with a single aldehyde intermediate, **1a** (R_1 = H, R_2 = 4-methylbenzoyl). These would probe the scope of amine compatibility with the reduction/cyclitive cleavage conditions in lactams where there was only monosubstitution α to the lactam carbonyl. Simple phenethyl amine was used, along with potentially more problematic amines. For example, 2-amino-1-phenylethanol was chosen because it has polyfunctionality; aniline is a less reactive amine; isopropyl amine is more hindered; and alanine *tert*-butyl ester demonstrates the ability to incorporate amino acids. The results of this survey are summarized in Table 1, column 1.

As expected, a variety of conditions were required, but the desired product was obtained in all cases. Starting from commercial BocGly Merrifield resin, this eight-step reaction sequence typically gave products in 30−50% overall purified yield. When diastereomeric products were formed (as in **3b** and **3e**) they were in equal proportions. The lactam **3e** is an example of a conformationally restricted peptidomimetic. Its synthesis here provides an alternative to another solid-phase based route we recently published to this important class of molecules.[4e]

The long-term stability of aldehyde intermediates **1** is noteworthy. As reported in the Supporting Information, various derivatives of resin **1** (R_1 = H), stored for more than 12 years at room temperature in a capped bottle (and not under an inert atmosphere), gave, in all cases examined, the expected products.[27]

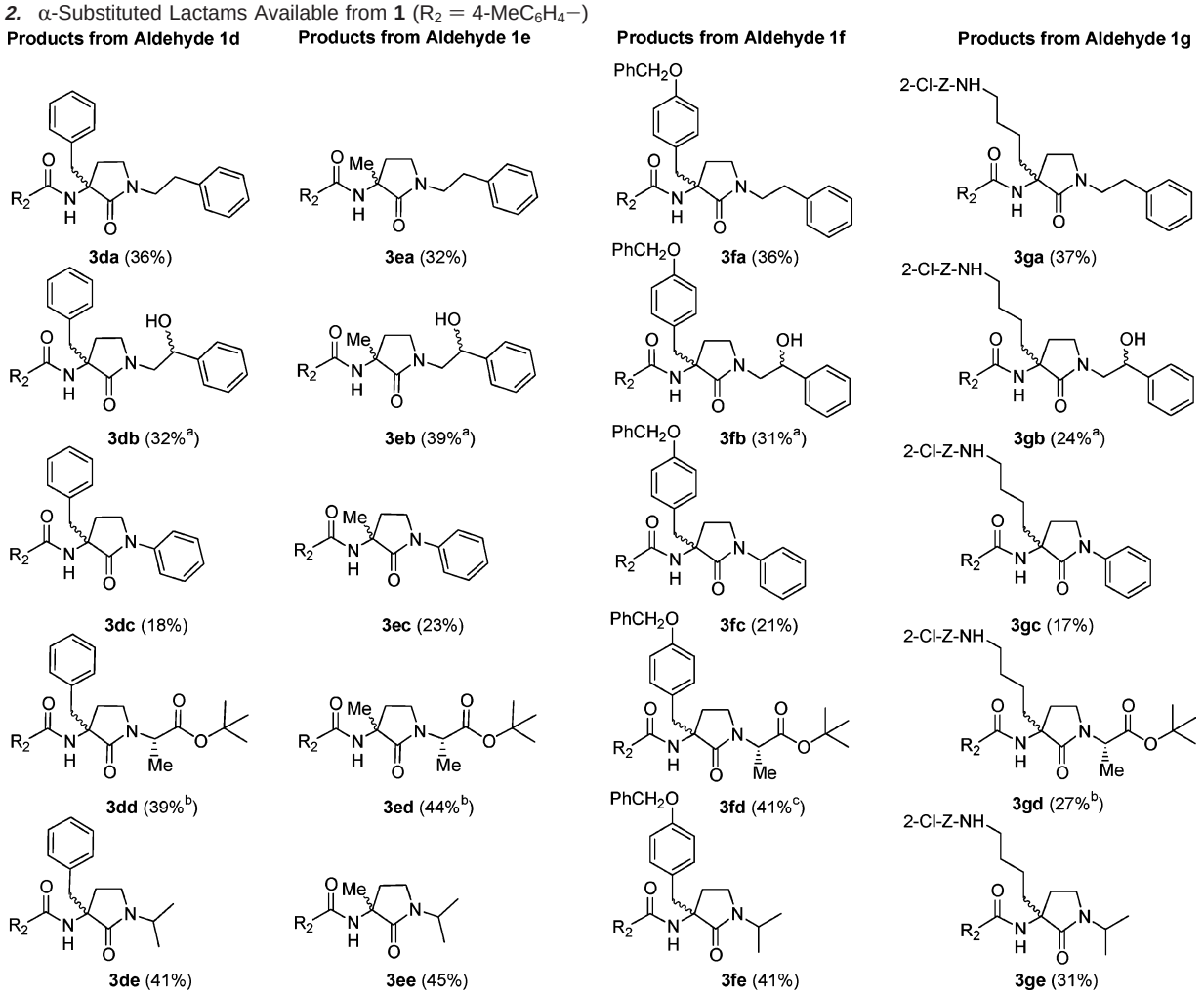
2.1.3.2. Other Amides (R_2) in Lactam Formation with Amines R_3NH_2. These same amines were reacted with two other amide derivatives of aldehyde **1** (R_1 = H: **1b** and **1c**), to give an additional 10 lactams (Table 1, columns 2 and 3). The data show that the synthetic sequence is compatible with other amide substituents. A special case is the sulfonamide precursor (**1c**), which afforded sulfonamide derivatives (**3k**−**3o**). These compounds fall into a class of lactam sulfonamide derivatives with known biological activity.[5l] For sulfonamide lactam **3o**, the acidity of the sulfonamide hydrogen led to formation of a one-to-one complex of product with excess alanine *tert*-butyl ester, which was isolated and characterized after chromatography.

2.1.3.3. Preparation of α-Substituted Lactams (Variations of R_1). Finally, it was shown that α-disubstituted lactams (**3**, $R_1 \neq$ H) can be readily made by this reductive amination/cyclization route (Table 2). This highly functionalized, compact, conformationally restricted peptidomimetic scaffold has been the focus of numerous studies.[1−5]

An unstated driving force for earlier development of the resin-bound, α-disubstitution chemistry (reported in 1998 and shown as part of Scheme 2, compounds **7** to **10**)[14b] was to provide synthetic access to the resin-bound olefin **10** required for multiple variations of R_1 in peptidomimetic **3**. This would allow, through subsequent conversion to aldehyde **1**, the synthesis of multiple scaffolds with large variations in R_1 (Scheme 5, $R_1 \neq$ H). Earlier attempts to make **10** by synthesizing, in solution, an α-disubstituted protected α-amino acid precursor (e.g., Boc-α-methyl-α-allylglycine), and then linking its carboxylate salt to chloromethylated Merrifield resin, gave very poor conversions. Presumably this was due to the hindrance to attack imposed by the adjacent sterically encumbered quaternary center. This was the primary reason for subsequently developing a simple route to prepare these α,α-disubsituted α-amino acids on-resin.[14b] Using this procedure, there is now access to multiple R_1 in **10**, with these R_1 groups, in turn, present in **7** either from

(27) A direct comparison of new vs old resin was made by preparing five compounds (**3a**−**3d** and **3h**) from samples of resins **1a** and **1b** that were over 12 years old. Additionally, 10 new compounds (**3p**−**3y**) were prepared and fully characterized from aged resins **1h**−**1j** (for full details see Table 1, experimental procedures, and NMR spectra in the Supporting Information).

Table 2. α-Substituted Lactams Available from **1** (R_2 = 4-MeC_6H_4−)



[a] Isolated as a racemic mixture of diastereomers. [b] Isolated as a mixture of two diastereomers. [c] Combined yield of two isolated diastereomers.

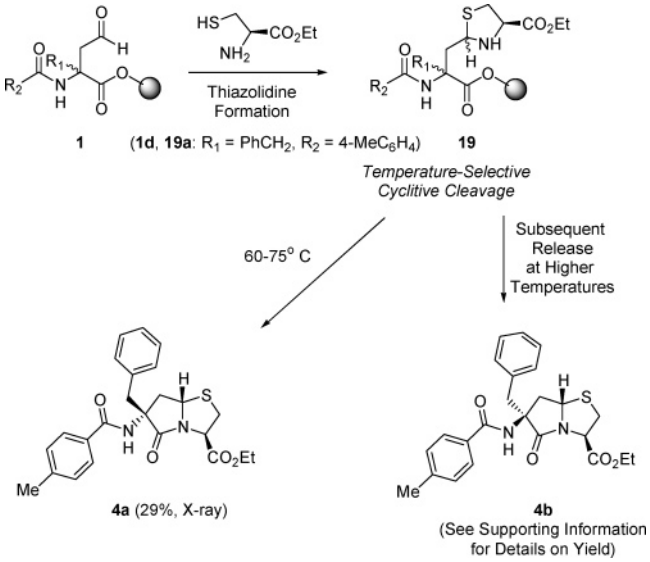
natural α-amino acids or by introduction, on-resin, by previously reported procedures.[14]

With α-disubstituted **1** ($R_1 \neq H$) available, it was now possible to make intensively funtionalized scaffolds. The first exemplification was in the synthesis of α-disubstituted monocyclic lactams **3**. It was gratifying that this could be accomplished as easily as in the monosubstituted cases, using the same reductive amination/cyclization route (Scheme 5, $R_1 \neq H$). This was done, in a comprehensive fashion, with a series of four α-disubstitued aldehyde intermediates (Figure 1) **1d**−**1g** (columns) and five different amines (rows), to make multiply substituted γ-lactams (Table 2).

The route proved to be very general and was compatible with functionalized side chains R_1, such as those present in the protected tyrosine and lysine derivatives (see products **3fa**−**3fe** and **3ga**−**3ge**), along with a combination of R_3's derived from R_3NH_2. When R_3NH_2 is an amino acid (compounds **3dd**, **3ed**, **3fd**, and **3gd**), it is possible to construct a series of conformationally restricted dipeptidomimetics, in these cases of the dipeptides (*R*,*S*)-Phe-(*S*)-Ala, (*R*,*S*)-Ala-(*S*)-Ala, (*R*,*S*)-Tyr-(*S*)-Ala, and (*R*,*S*)-Lys-(*S*)-Ala, respectively. There are only a limited number of published solution-phase routes to these scaffolds. We recently published a general, alternative solid-phase route which also makes them accessible.[4e] While complementary to the route reported here, it is limited to amine containing substrates that can be remotely linked to resins (as with the carboxylic acid of amino acids). In the present work there is no requirement for this remote link since the amine incorporation is an integral part of the final steps leading to cyclitive cleavage.

The wide range of structures synthesized provided an opportunity to observe some interesting effects of substituents on the NMR chemical shifts of diastereomeric pairs of compounds. Of particular note was the strong influence of a benzyl or a 4-benzyloxybenzyl R_1 group in the α position of the γ-lactam ring on the ^{1}H NMR chemical shifts of methyl groups when present in the R_3 side chain. For example, a $\Delta = 0.4$ ppm was found for the α-methyl protons in the alanine derived compounds **3dd** and **3fd**, and a $\Delta = 0.25$ ppm was observed for the methyl protons in isopropylamine derived **3de** and **3fe**. The observed differences of chemical shifts between two diastereomers were similar in magnitude to the anisochrony of isopropyl methyl groups in chiral molecules reported by others.[28a] Moreover, in the ^{1}H NMR spectra of the 2-Cl-Z-lysine derivatives **3ga**−**3ge**, many signals showed some splitting or line broadening, on the order of 1−2 Hz, which is attributable to the slow exchange of rotamers of the urethane C−N bond in the 2-Cl-Z group.[28b,28c]

Scheme 6. Selective Formation of Diastereomeric Bicyclics **4** through Controlled Release from Resin



2.1.4. Preparation of Bicyclic γ-Lactams 4. There is a rich history regarding the preparation and importance of bicyclic scaffolds **4**. In the 1940s they were considered analogues of nature's beautiful peptidomimetic, penicillin.[2a] Years later they experienced a resurgence of interest, both as β-turn peptidomimetics and as conformationally restricted scaffolds for analogues of both natural and synthetic molecules with a range of biological activities.[1,29−31] There are many reports of solution-phase syntheses of derivatives and analogues of bicyclic scaffold **4**, including those with non-hydrogen substitution at R_1.[30] There is also a report of a synthesis on resin.[31] The majority, both in solution and on solid phase, rely on the formation of a thiazolidine intermediate (paralleling an approach first reported by duVigneaud,[2a] and then by Sheehan[32] in his classic synthesis of penicillin) through the reaction of β-amino thiols with the solution equivalent of **1**. This was followed by intramolecular cyclization, through either attack of the thiazolidine nitrogen on an ester link or attack on an activated carboxylic acid. In an analogous way, but from resin **1d**, bicyclics **4** were prepared by reaction with (*R*)-cysteine ethyl ester to form intermediate thiazolidine **19** followed by cyclitive cleavage (Scheme 6). By virtue of solid-phase methodology and a final cyclitive cleavage step, this multistep synthesis (seven steps from starting resin **7**) directly provides high quality diastereomeric products **4a** and **4b** in good overall yield.

Along with the high purities obtained directly by this solid-phase synthesis, there are a number of interesting stereochemical observations to report. First of all, this synthesis gave (predominantly) only two (**4a** and **4b**) of the four diastereomers possible. The stereochemistry was confirmed by X-ray structure for **4a** and NMR analysis for **4b**. Second, **4a** and **4b** could be released from the resin with temperature controlled selectivity.

X-ray structure of **4a**

The presence of two of the four diastereomers was not surprising in light of the observation by others, in solution chemistry, that, in spite of the mixture of thiazolidine diastereomers presumably present in intermediate **19**, the bicyclic products formed with (*R*)-cysteine derivatives have predominantly the (*S*)-stereochemistry at the ring fusion. This is assumed to be a function of either selective cyclization of one of the two isomers in the thiazolidine precursor (which is equilibrating under the reaction conditions) or subsequent equilibration of the ring fusion to a more thermodynamically stable product.[30i] Of note in this current work is that it is possible to selectively obtain each of the two diastereomers **4a** and **4b** using a temperature regulated sequential cyclitive release. After the initial reaction of **1d** with (*R*)-cysteine ethyl ester the resin was thoroughly washed. Heating at 60−75 °C then provided **4a** in high purity. Raising the temperature to 115 °C then released increasing amounts of **4b** (see Table 2 on page 56 of the Supporting Information for full details of this experimental observation).

2.1.5. Preparation of Tricyclics 5 and Tetracyclics 6. Up to this point a key feature in the use of **1** has been its conversion into an amine intermediate (e.g., **18**, Scheme 5, or **19**, Scheme 6) that proceeds to form the final scaffold while simultaneously undergoing cyclitive cleavage from the resin. This overall process is chemically efficient and produces samples that are quite pure, since the cyclitive cleavage[8] is unlikely to occur from most resin impurities produced, either from incomplete reaction or as side products at earlier steps.

The Pictet−Spengler reaction is a widely used approach for the synthesis of amine containing cyclic structures, both in solution[33] and on solid phase,[34] from aldehyde precursors. It offered another synthetic route from aldehyde **1** to a key amine intermediate **20** and the opportunity to form highly functionalized multicyclic lactam containing scaffolds through a subsequent cyclitive cleavage process (Scheme 7). Again, solid-

(28) (a) Pourahmady, N.; Palaniswamy, V. A.; Eisenbraun, E. J. *Org. Magn. Reson.* **1983**, *21*, 670−671. (b) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 2nd ed.; VCH: New York, 1993; pp 287−315. (c) See Supporting Information in: Jensen, K. J.; Alsina, J.; Songster, M. F.; Vágner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441−5452.

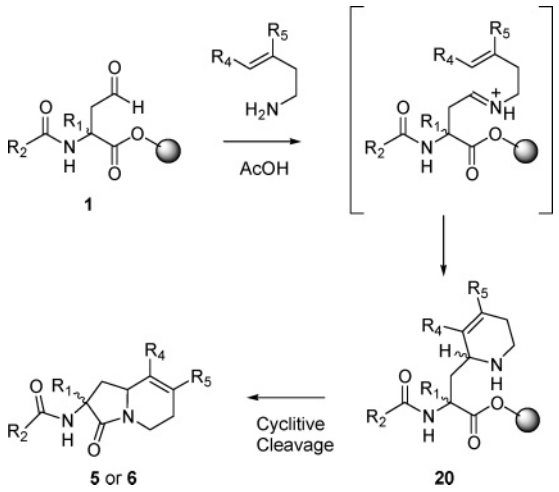
(29) Early references and recent examples of the formation of bicyclic thiazolidine lactams **4** (R = H) in solution: (a) Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647−650. (b) Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577−3592. (c) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145−148. (d) Ndungu, J. M.; Gu, X.; Gross, D. E.; Cain, J. P.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2004**, *45*, 4139−4142.

(30) Early references and recent examples of the formation of bicyclic thiazolidine lactams **4** (R ≠ H) in solution: (a) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Heterocycles* **1992**, *34*, 903−906. (b) Genin, M. J.; Johnson, R. L. *J. Am. Chem. Soc.* **1992**, *114*, 8778−8783. (c) Genin, M. J.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 3481−3483. (d) Chalmers, D. K.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 5927−5937. (e) Subasinghe, N. L.; Khalil, E. M.; Johnson, R. L. *Tetrahedron Lett.* **1997**, *38*, 1317−1320. (f) Takeuchi, Y.; Marshall, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 5363−5372. (g) Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 628−637. (h) Khalil, E. M.; Pradhan, A.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 2977−2987. (i) Somu, R. V.; Johnson, R. L. *J. Org. Chem.* **2005**, *70*, 5954−5963.

(31) Solid-phase synthesis of a bicyclic thiazolidine lactam: Johannesson, P.; Erdélyi, M.; Lindeberg, G.; Frändberg, P.-A.; Nyberg, F.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **2004**, *47*, 6009−6019.

(32) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957**, *79*, 1262−1263.

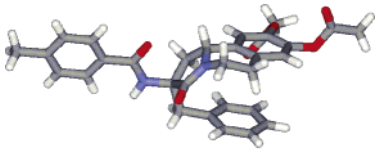
Scheme 7. Formation of Polycyclic Peptidomimetics from **1** via Pictet−Spengler Reactions



phase methodology with a final cyclitive cleavage step enabled this multistep synthesis (seven steps from starting resin **7**), providing high quality products **5** or **6** in good overall yield.

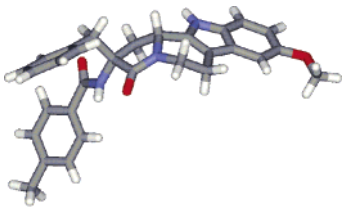
This expanded scope and potential was demonstrated by synthesizing the representative tricyclic **5** and tetracyclic **6** through amine intermediates **21** and **23** (Schemes 8 and 9, respectively). To our knowledge there are no published examples, either in solution or through solid-phase synthesis, of the α-amino, α-alkyl disubstituted lactam scaffolds exemplified by **5** and **6**.[35] The formation of **5a** and **5b**, by reaction of **1d** with dopamine, proceeded uneventfully under very mild conditions (Scheme 8).

The Pictet−Spengler was catalyzed by acetic acid, and the cyclitive cleavage proceeded at room temperature. Due to the oxidative instability, polarity, and acidity of the catechol containing products, the mixture of diastereomers was immediately converted to the bis-acetate derivatives **22a** and **22b**, for chromatographic purification and characterization by NMR (**22a**) and X-ray (**22b**) analysis.



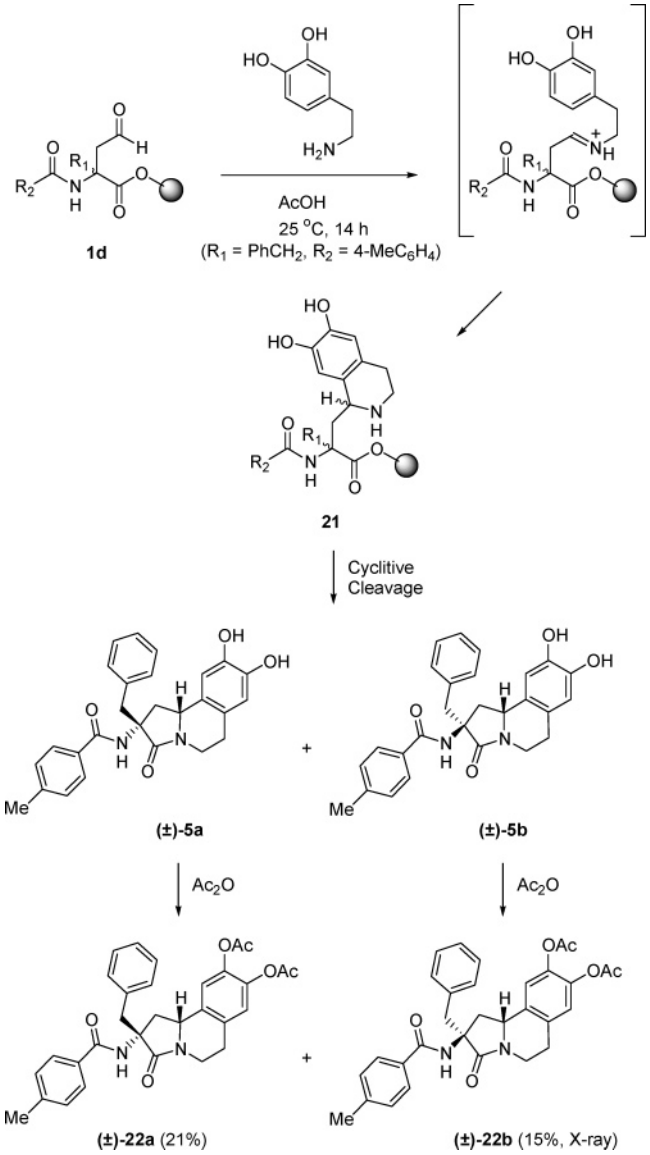
X-ray Structure of (±)-**22b**

In an analogous fashion, the use of **1** to form a tetracyclic scaffold through the Pictet−Spengler intermediate was exemplified by reacting **1d** with 5-methoxytryptamine (Scheme 9) to yield the highly substituted tetracyclic peptidomimetics **6a** and **6b**.



X-ray Structure of (±)-**6a**

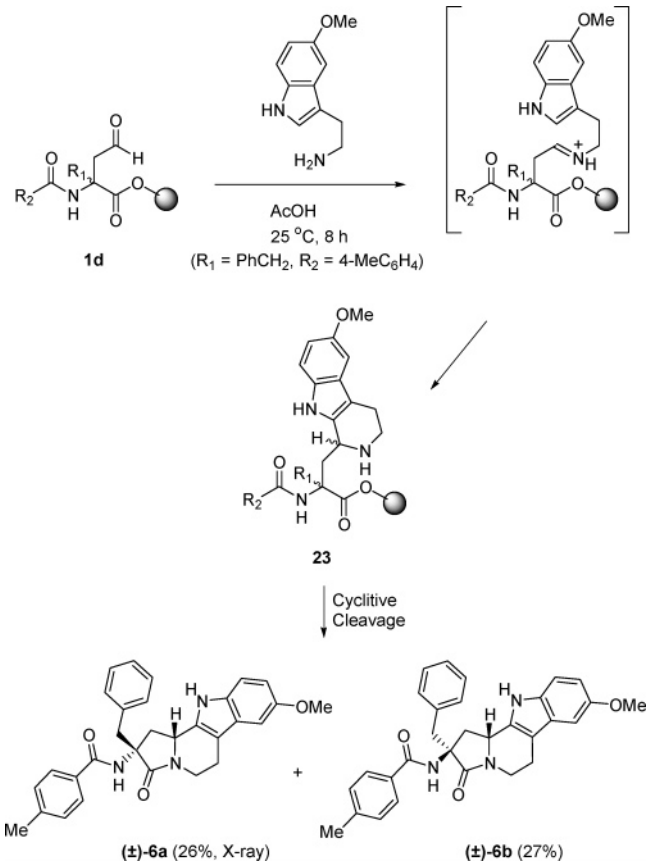
Scheme 8. Formation of Tricyclic Scaffold from **1d**



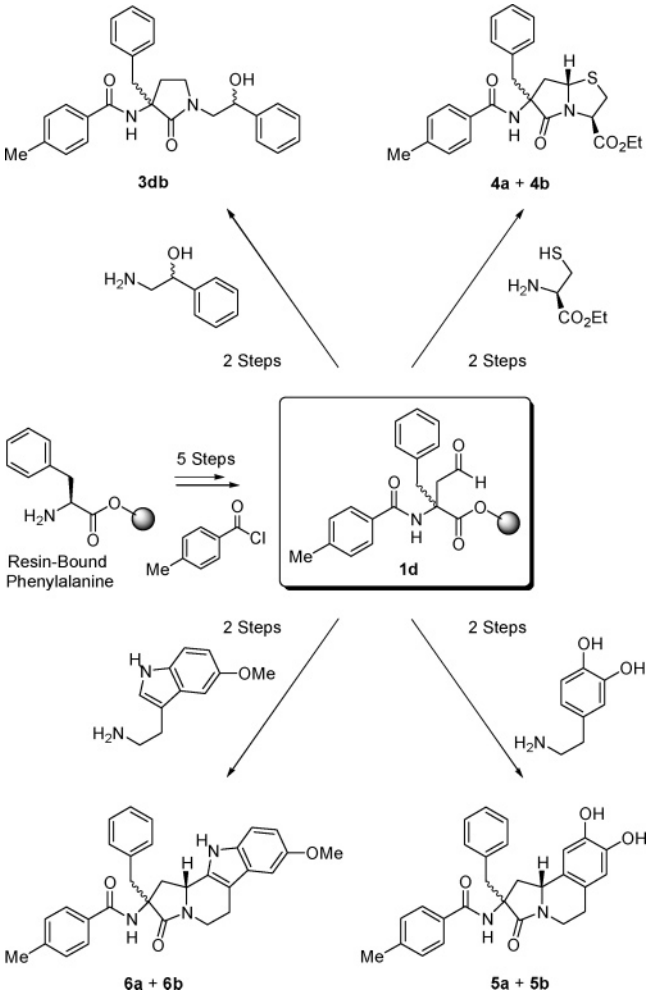
As in the tricyclic case, the reaction took place uneventfully under very mild conditions, with acetic acid catalysis, and the cyclitive cleavage proceeded at room temperature. Products were characterized by X-ray, LC/MS, and NMR analysis.

(33) Review, early references, and recent examples of Pictet−Spengler reactions in solution: (a) Review: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842. (b) Review: Reference 1q. (c) Review: Larghi, E. L.; Amongero, M.; Bracca, A. B. J.; Kaufman, T. S. *Arkivok* **2005**, 98−153. (d) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030−2036. (e) de la Figuera, N.; Rozas, I.; Garcia-López, M. T.; González-Muñiz, R. *Chem. Commun.* **1994**, 613−614. (f) De la Figuera, N.; Alkorta, I.; García-López, M. T.; Herranz, R.; González-Muñiz, R. *Tetrahedron* **1995**, *51*, 7841−7856. (g) Andreu, D.; Ruiz, S.; Carreño, C.; Alsina, J.; Albericio, F.; Jiménez, M. A.; de la Figuera, N.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Am. Chem. Soc.* **1997**, *119*, 10579−10586. (h) de la Figuera, N.; Martín-Martínez, M.; Herranz, R.; García-López, M. T.; Latorre, M.; Cenarruzabeitia, E.; del Río, J.; González-Muñiz, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 43−48. (i) Martín-Martínez, M.; De la Figuera, N.; Latorre, M.; Herranz, R.; García-López, M. T.; Cenarruzabeitia, E.; Del Río, J.; González-Muñiz, R. *J. Med. Chem.* **2000**, *43*, 3770−3777. (j) D'Alessio, S.; Gallina, C.; Gavuzzo, E.; Giordano, C.; Gorini, B.; Mazza, F.; Paradisi, M. P.; Panini, G.; Pochetti, G. *Eur. J. Med. Chem.* **2001**, *36*, 43−53. (k) González-Muñiz, R.; Martín-Martínez, M.; Granata, C.; de Oliveira, E.; Santiveri, C. M.; González, C.; Frechilla, D.; Herranz, R.; García-López, M. T.; Del Río, J.; Jiménez, M. A.; Andreu, D. *Bioorg. Med. Chem.* **2001**, *9*, 3173−3183. (l) Martín-Martínez, M.; Latorre, M.; García-López, M. T.; Cenarruzabeitia, E.; Del Río, J.; González-Muñiz, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 109−112. (m) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255−16262.

Scheme 9. Formation of Tetracyclic Scaffold from **1d**



Scheme 10. Representative Synthesis of All Four Scaffolds from a Common Intermediate **1d**



3. Summary

A wide variety of highly substituted lactam containing peptidomimetic scaffolds can now be prepared by solid-phase synthesis from a single, versatile class of resin-bound aldehyde intermediates (**1**). These include monocyclics **3**, bicyclics **4**, tricyclics **5**, and tetracyclics **6**. Scheme 10 summarizes the power of this general approach through the synthesis, in just two steps, of each of these scaffolds from a representative common intermediate **1d**. The synthetic procedures permit the construction of a large diversity of substitution patterns for ready use in combinatorial chemistry. In every case, the release of final products from resin is by a cyclitive cleavage process. Since this depends on successful completion of multiple intermediate synthetic steps, the products are often quite pure, even though previous steps involve only a filtration workup. Solid-phase chemistry permits these multistep syntheses to be successfully carried out on a micromole scale.

The mild conditions for many of these synthetic procedures are noteworthy, as they offer the promise of using this chemistry in peptide fragment condensations[36] to produce modified peptides, at either the N-terminus or C-terminus, or as individually assembled peptide segments with a wide variety of conformationally restricted peptidomimetic linkers at the point of juncture. For example, reductive aminations to lactams **3** (Scheme 5) could be done with the amine component R_3 coming from the N-terminus of a peptide in solution (N-terminal modification), a peptide as the "amide" functionality R_2 in Scheme 5 (C-terminal modification), or peptides as components of both R_3 and R_2 (segment condensation). Similarly, by a process closely analogous to known peptide fragment condensation work, a peptide fragment possessing at its N-terminus a cysteine residue could be reacted with **1** to create a bicyclic lactam unit (analagous to the bicyclic lactam in structures **4**, Scheme 6) at the point of juncture. Finally, fragment and segment condensations may be possible from **1** in which the amide functionality is part of a peptide, and the other peptide

(34) Review and selected examples of Pictet−Spengler reactions on solid phase: (a) Review: Nielsen, T. E.; Diness, F.; Meldal, M. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 801−814. (b) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647−1649. (c) Groth, T.; Meldal, M. *J. Comb. Chem.* **2001**, *3*, 45−63. (d) Orain, D.; Koch, G.; Giger, R. *Chimia* **2003**, *57*, 255−261. (e) Grimes, J. H., Jr.; Angell, Y. M.; Kohn, W. D. *Tetrahedron Lett.* **2003**, *44*, 3835−3838. (f) Kunda, B.; Sawant, D.; Chhabra, R. *J. Comb. Chem.* **2005**, *7*, 317−321. (g) Danieli, B.; Giovanelli, P.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A. *J. Comb. Chem.* **2005**, *7*, 458−462. (h) Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2005**, *7*, 599−610. (i) Reference 18g. (j) Lee, S.-C.; Park, S. B. *J. Comb. Chem.* **2006**, *8*, 50−57. (k) Chang, W.-J.; Kulkarni, M. V.; Sun, C.-M. *J. Comb. Chem.* **2006**, *8*, 141−144.

(35) Based on SciFinder Scholar and Beilstein CrossFire searches of generic scaffolds.

(36) Selected peptide fragment condensation reviews: (a) Benz, H. *Synthesis* **1994**, 337−358. (b) Albericio, F.; Lloyd-Williams, P.; Giralt, E. *Meth. Enzymol.* **1997**, *289*, 313−336. (c) Barlos, K.; Gatos, D. *Biopolymers (Peptide Science)* **1999**, *51*, 266−278. (d) Borgia, J. A.; Fields, G. B. *Trends Biotechnol.* **2000**, *18*, 243−251. (e) Dawson, P. E.; Kent, S. B. H. *Ann. Rev. Biochem.* **2000**, *69*, 923−960. (f) Coltart, D. M. *Tetrahedron* **2000**, *56*, 3449−3491. (g) Okada, Y. *Curr. Org. Chem.* **2001**, *5*, 1−43. (h) Tam, J. P.; Xu, J.; Eom, K. D. *Biopolymers (Peptide Science)* **2001**, *60*, 194−205. (i) Nilsson, B. L.; Soellner, M. B.; Raines, R. T. *Ann. Rev. Biophys. Biomol. Struct.* **2005**, *34*, 91−118. (j) Durek, T.; Becker, C. F. W. *Biomol. Eng.* **2005**, *22*, 153−172. (k) Papas, S.; Strongvis, C.; Tsikaris, V. *Curr. Org. Chem.* **2006**, *10*, 1727−1744.

fragment (in solution) has, at its N-terminus, a residue (e.g., tryptophan) capable of undergoing a Pictet−Spengler reaction (Scheme 7).

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Supporting Information Available: Full experimental details, characterization data, and proton NMRs of all products are provided. Crystallographic data are given for products **4a**, **22b**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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