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Studies on the Chemical Stability and Synthetic Utility of an Oxazolidine Linker for Solid-Phase Chemistry

A. Jonathan Wills, Montserrat Cano,† and Shankar Balasubramanian*

University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

sb10031@cam.ac.uk

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A chemical stability study on the oxazolidine linker system has been carried out using a dual-linker analytical construct within a parallel reaction scan. The study established the compatibility of the oxazolidine platform with a wide range of commonly employed synthetic reaction conditions including nucleophilic, oxidizing, and reducing conditions. The scan was further used to probe and optimize acidic conditions under which the oxazolidine could release the substrate from the solid-support and to identify reagents that could cleave while retaining other acid-labile groups. The solid-phase synthesis of a small molecular array established the utility of oxazolidine aldehyde **1** as a building block for asymmetric chemistry while exploiting the data generated by the reaction scan.

Introduction

Solid-phase synthesis has grown to become an important and well-established branch of organic methodology, and it remains unrivaled as a method for constructing synthetic peptide and nucleotide sequences.[1] Recent advances in solid-phase methodology have focused on the creation of small molecules, particularly in pharmaceutical research, where libraries of compounds have been used to identify possible drug leads.[2] In an effort to increase the molecular diversity within these compound libraries,[3] new synthetic methods have been sought,[4] and carbon−carbon bond formation has emerged as a powerful approach to the expansion in the diversity of compound libraries.[5] Increasingly, asymmetric synthesis on the solid-phase has been investigated as a means to access new structural entities.

The link between the solid support and the substrate is the foundation for the success of a solid-phase synthesis. The choice of linker is therefore based on a critical examination of the intended chemical transformations. The substrate must be easily loaded onto and released from the linker, yet this connection must remain inert under all the planned reaction conditions. Consequently, a large number of linker systems have been developed that address quite specific synthetic needs.[6] While the majority of linkers are simply structural connections between the support and the substrate, an increasing number also combine characteristics that direct the chemical outcome of a reaction or aid analysis.[7]

We have recently reported the synthesis of the polymer-supported oxazolidine aldehyde linker **1** for use in asymmetric chemistry on solid-phase.[8] The linker system is based on the synthetically important Garner aldehyde (**2**).[9,10] This chiral building block and auxiliary has been used in the successful synthesis of many natural products including simple sphingosines,[11] and the core for more complex structures such as the proteasome inhibitor TMC-95A.[12] The future use of oxazolidine linker **1** for the solid-phase synthesis of natural products and their

* Corresponding author. Tel: +44 1223 336347. Fax: +44 1223 336913.

† Present address: Medicinal Chemistry Department, R&D Center, Ferrer Group, Juan de Sada 32, 08028 Barcelona, Spain.

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(11) Some recent examples include: (a) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979. (b) Jonghe, S. D.; Overmeire, I. V.; Calenbergh, S. V.; Hendrix, C.; Busson, R.; Keukeleire, D. D.; Herewijn, P. *Eur. J. Org. Chem.* **2000**, 3177. (c) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538. (d) Chun, J.; Li, G.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **2002**, *43*, 375.

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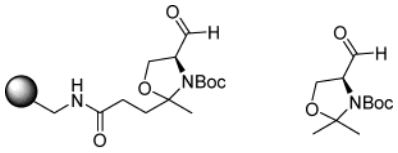
analogues requires a thorough understanding of the capabilities and limitations of this system.



1 2

As a method for testing the stability of new linker systems, we have developed a reaction scan based around a dual-linker analytical construct.[13] Analytical linkers have been produced over the past few years to counter the problems of reaction monitoring and library deconvolution on solid-phase.[14] The dual-linker analytical construct in particular has proven useful in gauging reaction progression and product purity. Systems based on the dual-linker approach have an enhanced spectroscopic tag inserted between the solid support and the substrate-loaded linker (Figure 1). The construct introduces a second, orthogonal linker, and cleavage at this site releases the analytical fragment combined with the linker and substrate. The substrate itself may be released into solution as normal without concomitant removal of the tag, although in practice the scaffold is not typically used quantitatively and is combined only as a small fraction with the normal platform.

Detection of the analytical fragment is frequently performed by LC-MS using dual-linkers that have been designed to incorporate groups that facilitate detection and analysis by this method. A typical dual-linker might include a chromophore to aid UV detection and a mass ionizer and isotope label to give an easily recognizable profile in the mass spectrum.

By combining our benzoin photolabile safety-catch linker[15] with the analytical construct **3** developed by GlaxoSmithKline,[16] we have established a novel system for probing linker stability.[13,17] The dual-linker system was screened against a comprehensive range of solid-phase reaction conditions, and by monitoring the identity of the cleaved analytical fragments, the stability of the benzoin linker could be determined. Thus, the susceptibility of this linker to strong oxidizing and acid conditions was highlighted, hence forewarning future users of this system.

Herein, we report the results of a reaction scan against our oxazolidine linker system. To complement the stability study, we have also performed a cleavage scan to identify conditions that would allow efficient and reproducible removal of the substrate from support. The value of the scan in demonstrating the stability of the linker

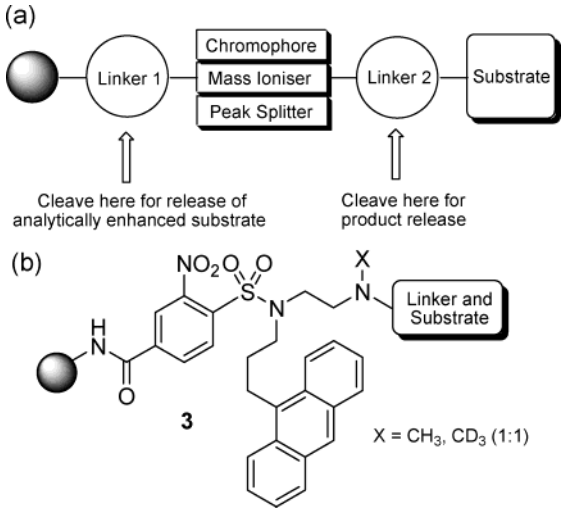


FIGURE 1. (a) Schematic representation of the dual-linker analytical construct. The substrate may be removed by cleavage at linker 2, and an analytically enhanced substrate residue may be obtained by cleavage at the orthogonal linker 1. (b) The GlaxoSmithKline reporter resin platform **3** incorporating all of the elements shown in the schematic dual-linker construct.[16]

system has been demonstrated by the synthesis of various molecules using many of the conditions from the scan. These target molecules also highlight many of the structural motifs accessible from oxazolidine aldehyde **1**.

Results and Discussion

The reaction scan was planned for the purpose of providing information about the stability of an oxazolidine linker-substrate combination typical of the products that might be expected downstream from aldehyde **1**. The aim of the scan was not to probe the reactivity of the formyl group but rather to investigate the stability of the oxazolidine to highlight reagents that might cause the premature release of the substrate from the support.

The oxazolidine linker is comprised of an *N*,*O*-acetal that connects the serine-based substrate to the support-bound levulinic acid-derived spacer. Although the scan was designed in such a way as to detect cleavage at any part of the oxazolidine linker structure, we were primarily interested in identifying conditions that could hydrolyze the *N*,*O*-acetal, the normal site of substrate release from the support. While a great deal is known about the solution-phase reactivity of 1,3-oxazolidines,[18] and indeed *N*,*O*-acetals in general, this is not the case for solid-supported oxazolidines where an alteration in reactivity might be expected due to the effects of the support and its connection to the oxazolidine.

It was a requirement that the dual-linker oxazolidine platform should be simple, and it was essential that the substrate chosen as representative of a typical reaction product was relatively inert so as not to complicate the results of the scan. Because the reaction scan encompassed a broad range of conditions, few groups could be considered entirely immune, hence the choice of substituent reflected, if not a minimum, a predictive reactiv-

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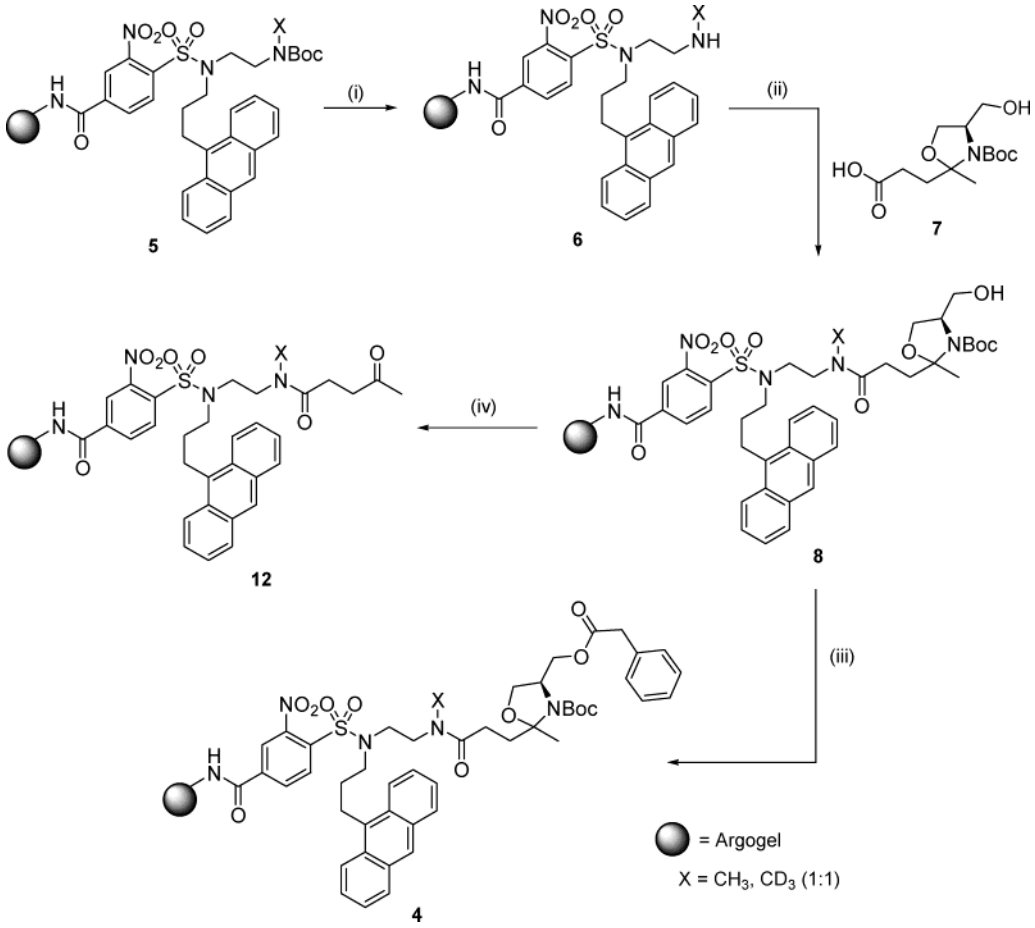
SCHEME 1[a]



[a] Reagents and conditions: (i) 66% TFA/CH_2Cl_2, 30 min, rt, ×2; (ii) **7**, TBTU, HOBt, DIPEA, CH_2Cl_2/DMF (1:1), 18 h, rt; (iii) phenyl acetic acid, DIC, DMAP, CH_2Cl_2, 18 h, rt; and (iv) 50% TFA/CH_2Cl_2, 1 h, rt.

ity profile. Indeed, when we attempted to carry out a reaction scan on the aldehyde (equivalent of **1**), we experienced a complex output owing to reactions at both linker and aldehyde functionality.

Oxazolidine ester **4** was chosen as an appropriate scaffold for the reaction scan. The reporter resin **3**, used successfully in our previous study,[13] formed the backbone of the analytical construct, and the appropriately derivatized oxazolidine linker was attached to it. Although the susceptibility of the ester to nucleophilic attack and reduction was anticipated, its reactivity was considered predictable and the byproducts easily identifiable. A less reactive ether derivative might be imagined, but the synthesis of such compounds has been reported as problematic due to the competing cyclization of the anion generated from the 4-hydroxy methyl group onto the neighboring carbamate.[19] In solution-phase studies, the nature of the 4-substituent has been observed to have only a small effect on the reactivity of the *N*,*O*-acetal.[20] Thus, the data generated from our reaction scan studies are likely to provide a general picture of oxazolidine reactivity for other classes.

The dual-linker structure **4** was assembled from Argogel resin **5** (Scheme 1).[13,16,21] Amine **6** was obtained by exposure of **5** to 66% TFA in CH_2Cl_2. Oxazolidine acid **7**[8] was coupled to **6** using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), HOBt, and DIPEA, and the resulting alcohol **8** was capped with phenyl acetic acid in the presence of DIC and DMAP to yield ester **4**.

The yields and purities of each transformation were judged by cleavage of a small portion of resin and analyzing the resultant residue by LC-MS. Cleavage of the dual-linker to release the analytically enhanced fragment was achieved by treatment of a resin sample with thiophenol and DIPEA in acetonitrile. Reaction of **4**, **6**, and **8** under the cleavage conditions yielded the fragments **9**, **10**, and **11**, respectively (Scheme 2). The LC-MS spectra showed that each transformation occurred in greater than 95% yield and purity. Furthermore, the spectra demonstrated that the oxazolidine platform itself was stable to the analytical cleavage conditions; hence, any modification of the linker in the scan could only be attributed to a reaction with the reagents and not as an artifact of analysis. The spectrum obtained from each cleavage was used as a standard to identify compounds in the reaction scan. Ketone **12**, an expected hydrolysis product, was obtained by exposure

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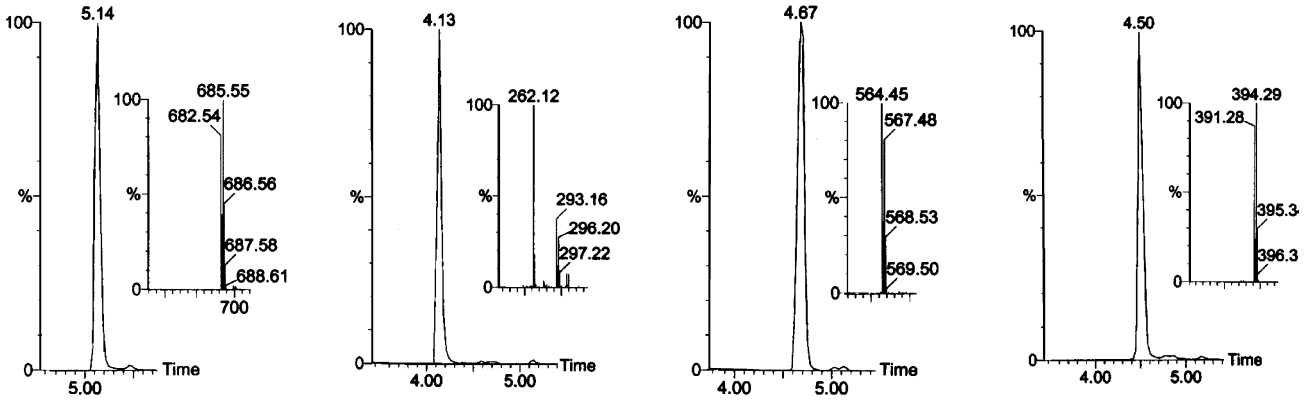
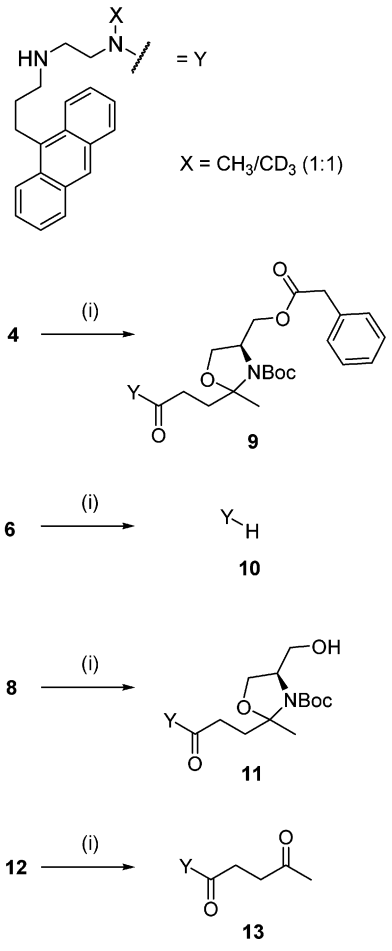


Ester **9** Amine **10** Alcohol **11** Ketone **13**

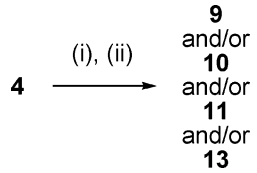
FIGURE 2. LC-MS spectra of the standards used for comparison in the reaction scan. Each fragment has a unique LC-MS profile allowing the products of the scan to be easily identified and quantified. LC-MS analyses were performed on the cleaved residues with UV detection at 386 nm and electrospray ionization in +ve mode.

SCHEME 2[a]



[a] Reagents and conditions: (i) PhSH, DIPEA, MeCN, 30 min, rt.

SCHEME 3[a]



[a] Reagents and conditions: (i) reaction scan: see Table 1 for conditions and (ii) PhSH, DIPEA, MeCN, 30 min, rt.

of **13** to 50% TFA in CH_2Cl_2 (Scheme 1). All four compounds had distinct retention times and mass spectral profiles (Figure 2), allowing the products of the reactivity survey to be easily identified.

The scan comprised a series of reaction conditions that were representative of the types of transformations common in organic synthesis (e.g., oxidation, reduction, amide bond formation etc). Moreover, the reagents were chosen to reflect the synthetic methodology typically used on the solid phase, which may be different from their solution-phase counterpart.[17,22]

We foresaw four different outcomes in the reaction scan: (i) the linker system would remain inert to reaction conditions; hence, only fragment **9** would be detected after cleavage; (ii) the phenyl acetic acid ester could be cleaved, yielding **8**, but the linker system would remain inert, and hence, upon cleavage, **11** would be detected; (iii) the *N*,*O*-acetal could be hydrolyzed giving ketone **12**. Fragment **13** would be detected in this case, and (iv) the amide bond could be hydrolyzed to give amine **6**. Fragment **10** would indicate this event. Of course, a mixture of the results could equally be envisaged when the reaction has not had time to run to completion in the time scale of the reaction scan, or in situations where two differing reaction pathways are competing. In practice, we observed no other reactivity other than that described.

The scan was performed in parallel, treating small resin quantities (~20 mg) of **4** with the reagents shown in Table 1 for typically 5 h (Scheme 3). Each resin was drained, washed, cleaved to release the analytical fragment, and analyzed by LC-MS for comparison against the previously generated standards. The outcome of each reaction is shown in Table 1.

The results from the study revealed that the oxazolidine linker was stable to a wide range of reaction conditions, particularly amide and ester coupling protocols, oxidizing and basic conditions, and Wittig and Mitsunobu reagents. As expected, the alkylating, nucleophilic, and reductive conditions cleaved the phenyl acetic

(22) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, 1998.

TABLE 1. Reaction Scan against the Oxazolidine Linker Construct 4

entry	reaction conditions[a]	≥90% of ester[b]	product obtained
	Amide/Ester Coupling Protocols		
1	DIC, HOBt, AcOH, DMAP, DIPEA	√	
2	DIPEA, DMAP cat, Ac_2O	√	
3	AcCl, pyr	√	
4	$PhCH_2Br$, $CsCO_3$	√	
5	$PhCH_2OH$, PPh_3, DEAD	√	
	Alkylating/Nucleophilic Conditions		
6	NaH, $PhCH_2Br$	×	**11**
7	$CH_2CHMgBr$ in Et_2O (1 M)	×	**11**
8	TBAF/THF (1 M)	×	**11**
9	TBAF/THF (1 M), MeI	×	**11**
	Carbon−Carbon Bond-Forming Reactions		
10	$Ph_3P{=}CH(CO)Me$	√	
	Reductive Conditions		
11	$BnNH_2$, $NaBH(OAc)_3$	√	
12	$NaBH_4$	×	**11**
	Oxidizing Conditions		
13	H_2O_2 (10%)	√	
14	Pyr·SO_3, Et_3N	√	
15	NMO, TPAP	√	
16	$NaIO_4$	√	
	Bases		
17	20% piperidine in DMF	√	
18	KHMDS, BnBr	√	
	Acids		
19	AcOH	√	
20	TsOH	×	**13**
21	HF·pyr	√	
22	HCOOH (neat)	×	**13**
23	HCl, dioxane	×	**13**
24	$BF_3{\cdot}OEt_2$	×	**13**
25	TFA/CH_2Cl_2 (1:1)	×	**13**

[a] Resin aliquots (∼20 mg) were incubated with reagents (5−10 equiv) in sealed 1 mL pipet tips at room temperature for 5 h, then washed, and cleaved with PhSH and DIPEA in CH_3CN. LC-MS analyses were then performed on the cleaved residues. See Experimental Procedures for details. [b] √ indicates ≥90% by peak area in the LC-MS.

acid ester, but the oxazolidine linker itself remained unaffected. The stability of the linker to the wide variety of reagents considered in the scan emphasizes the potential of the oxazolidine platform in natural product and library synthesis.

N,*O*-Acetals are highly acid labile, and it was not surprising that under the acidic conditions of the scan, hydrolysis of the oxazolidine was observed. Although acetic acid has been used previously to hydrolyze the acetal,[23] no cleavage was observed under the conditions of the scan (rt, 6 h), which were milder than the conditions described for hydrolysis (e.g., 50 °C, overnight).[23a] The high acid lability of the *N*,*O*-acetal may be used to its advantage, for the substrate may be removed from the support under relatively mild conditions without necessarily affecting other acid sensitive protecting groups and functionalities.

The difference in acid lability between the oxazolidine *N*,*O*-acetal and the *N*-Boc protecting group has been used to great effect in many natural product syntheses where retention of the nitrogen protecting group was required in the subsequent synthetic transformations.[23] The second element of the reaction scan was focused on identifying conditions that could be used to release the substrate from the support with or without concomitant removal of the Boc group. As the acid reaction scan was concerned only with the identity of the substrate cleaved from resin, it was not necessary to use the dual-linker analytical construct **4**, and the simpler oxazolidine ester **14** was used instead. The ester was synthesized from the previously described oxazolidine alcohol **15** (Scheme 4).[8] Acid hydrolysis of **14** would yield the amino alcohol **16** and the Boc-protected serine derivative **17**. The ratio of these in the cleaved mixture would be dependent on the acids and conditions used.

TABLE 2. Acid Reaction Scan against the Oxazolidine Linker 14

	product[b]	
acids and conditions[a]	**16**	**17**
1% TFA/CH_2Cl_2, rt, 15 min		√
pTsOH, MeOH, rt, 18 h		√
20% TFA/CH_2Cl_2, rt, 30 min	√	
1 M HCl in dioxane, rt, 6 h	√	
formic acid, rt, 6 h	√	
AcOH, 100 °C, 6 h	30%	70%

[a] See Experimental Procedures for details. [b] √ indicates ≥95% by peak area in the LC-MS at 260 nm and integration of peaks in the ^{1}H NMR spectrum.

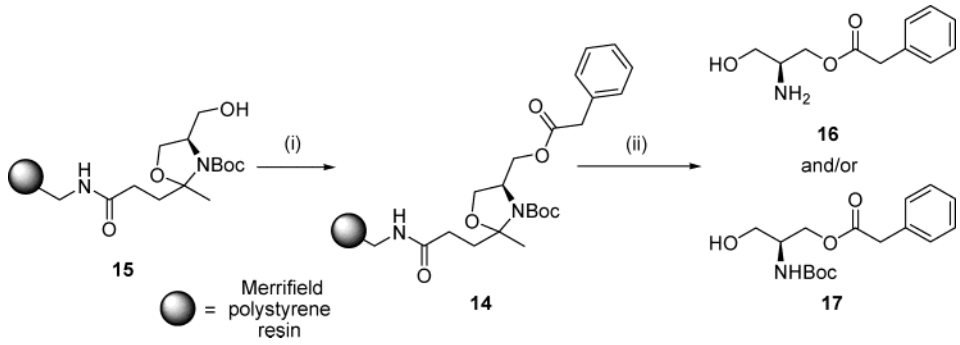
Resin samples (∼25 mg) of **14** were treated with an appropriate acid and drained, and the collected filtrate was analyzed by LC-MS and ^{1}H NMR to establish the proportion of **16** and **17**. Because of the ease and rapidity of analysis, it was possible to carry out many iterations of the scan varying temperature, concentration, and reaction time, and in this manner an optimized set of acid cleavage conditions was obtained (Table 2).

Using only mild acid conditions (e.g., 1% TFA/CH_2Cl_2), it was possible to reproducibly hydrolyze the *N*,*O*-acetal without concomitant removal of the Boc protecting group; hence, alcohol **17** could be obtained in high yield and purity. Under harsher conditions (e.g., 1 M HCl), cleavage of the oxazolidine occurred alongside Boc deprotection, and consequently, amino alcohol **16** was the only product. Under intermediate conditions, mixtures of the cleavage products **16** and **17** were obtained. For instance, using 5% TFA/CH_2Cl_2 over 20 min gave a ∼1:1 mixture of **16** and **17**. No cleavage was observed after treatment of **14** with acetic acid at room temperature. Upon elevating the temperature and extending the reaction time, it was possible to detect increasing quantities of **17**. However, under the conditions necessary to give high yields of substrate (100 °C, 6 h), significant amounts of amino alcohol **16** were obtained. Overall, TFA was the best acid for cleavage, requiring only a short reaction time to give high yields of either compound.

To demonstrate the utility of the oxazolidine aldehyde **1**, a diverse array of small molecules was synthesized (Scheme 5). Each member of the array was chosen to highlight a structural type that is easily accessible from the aldehyde. The reaction sequences used in their construction feature many of the reagents included in the

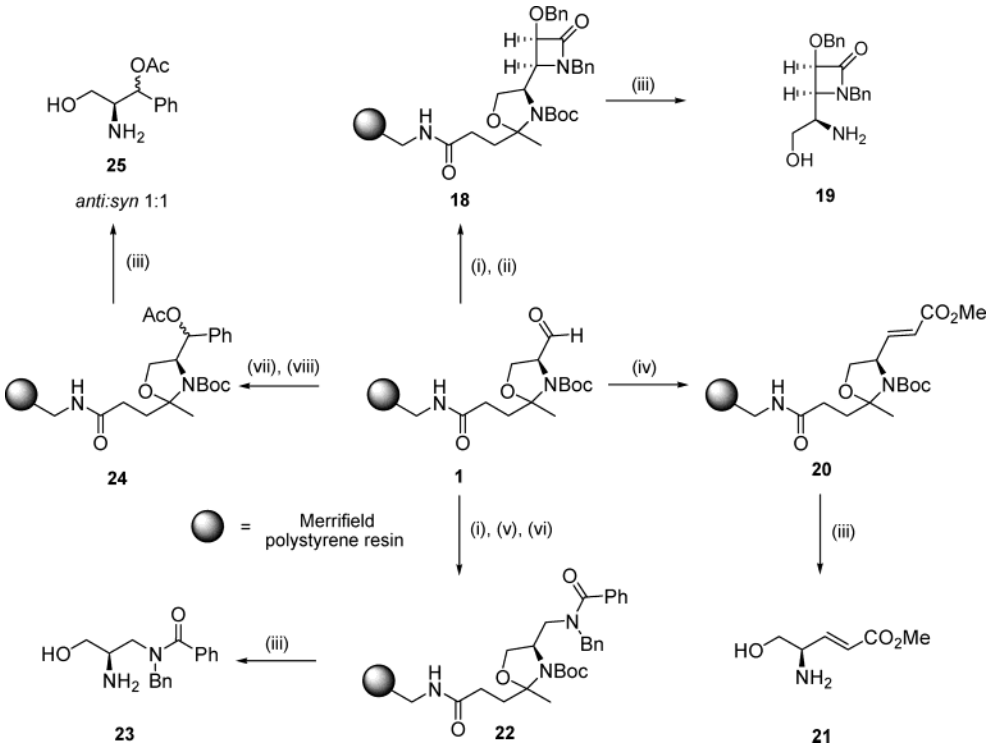
(23) Examples include: (a) Qui, X.; Qing, F. *J. Chem. Soc., Perkin Trans.* **2002**, 2052. (b) Dondoni, A.; Mariotti, G.; Marra, A. *J. Org. Chem.* **2002**, *67*, 4475. (c) Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951. (d) Nevalainen, M.; Kauppinen, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **2001**, *66*, 2061.

SCHEME 4[a]



[a] Reagents and conditions: (i) phenyl acetic acid, DIC, DMAP, CH_2Cl_2, 18 h, rt and (ii) reaction scan: see Table 2 for conditions.

SCHEME 5[a]



[a] Reagents and conditions: (i) $BnNH_2$, 4 Å mol sieves, CH_2Cl_2, 30 min, rt, ×3; (ii) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 18 h, 0 °C to rt; (iii) 20% TFA/CH_2Cl_2, 30 min, rt; (iv) Ph_3PCHCO_2Me, benzene, 18 h, rt; (v) $NaBH(OAc)_3$, 1% AcOH/DMF, 30 min, rt, ×3; (vi) BzCl, Et_3N, CH_2Cl_2, 18 h, rt; (vii) 0.69 M PhMgBr in THF, THF, 12 h, −78 °C; and (viii) Ac_2O, DMAP, CH_2Cl_2, 18 h, rt.

reaction scan that illustrates the value of this method in demonstrating reagent-linker compatibility. The array also typifies the classes of reaction commonly used in solution-phase Garner aldehyde (**2**) chemistry.

Cycloaddition reactions feature significantly in the chemistry of the Garner aldehyde and have been used extensively as the foundation for syntheses toward complex natural products such as calicheamicin.[24] We have previously demonstrated the use of the Staudinger reaction on solid phase as a means of accessing β-lactams.[8,25,26] The [2 + 2] cycloaddition between an aldehyde-derived resin-bound imine and a solution-generated ketene has been used to generate a wide variety of stereochemically pure β-lactams. Treatment of aldehyde **1** with benzylamine in the presence of molecular sieves gave the intermediate imine that was reacted directly with the ketene generated from benzyloxyacetyl chloride and triethylamine to yield β-lactam **18** (Scheme 5). Amino alcohol **19** was obtained in good yield (60%) and purity (>97%) after cleavage of **18** from the resin with 20% TFA in CH_2Cl_2. The optical rotation of the product β-lactam **19** ($[\alpha]_D = -37$) was in good agreement with the values previously reported ($[\alpha]_D = -38$).[25a,26]

Olefination reactions have been used successfully to generate new carbon−carbon bonds to the Garner aldehyde, and Wittig reagents in particular have been used

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to create a wide range of interesting scaffolds. Methyl-(triphenylphosphoranylidene) acetate was reacted with aldehyde **1** to give the polymer-bound alkene **20**. Compounds of this type are important because of their potential to undergo Diels−Alder, epoxidation, dihydroxylation, and Michael-type addition reactions, many of which have been observed as occurring stereoselectively. Cleavage from resin gave amino alcohol **21** in excellent purity (>97%) in exclusively the E configuration, as expected.[10]

Use of the oxazolidine aldehyde is not purely restricted to carbon−carbon bond-forming reactions. The synthesis of differentially substituted amines is possible through a sequence demonstrated by the transformation of **1** to oxazolidine **22**. Aldehyde **1** was reacted with benzylamine in the presence of molecular sieves, and the resultant imine was reduced with sodium triacetoxyborohydride in 1% AcOH/DMF. The secondary amine produced from the reductive amination step was capped with benzoyl chloride to give the oxazolidine **22**. Amino alcohol **23** was obtained after cleavage form the resin.

Reactions of the Garner aldehyde with organometallic reagents frequently proceed with good to excellent diastereoselectivities, and consequently, a significant amount of research has been undertaken in an attempt to rationalize and optimize the ratios of syn- and anti-addition products.[19,27] Grignard, organolithium, and zinc reagents often react with the Garner aldehyde to give products with modest to excellent diastereomeric ratios, and simple versions of these nucleophiles have been used to study the effect of solvent, temperature, additives, and concentration on addition stereoselectivity. The reaction of aldehyde **1** with phenylmagnesium bromide was studied to compare the reactivity and selectivity of the solid-phase oxazolidine linker against the Garner aldehyde. Following the literature precedent,[19] aldehyde **1** was reacted with 3 equiv of Grignard in THF for 3 h at −78 °C. Monitoring the reaction by gel-phase ^{13}C NMR and IR spectroscopy, it was clear that a significant amount of aldehyde remained, and despite extending the reaction time significantly (up to 24 h), product formation was still minimal. The reaction was investigated in some detail, and a parallel reaction study was performed to identify the effect of solvent, temperature, and resin on reactivity. In moving from THF to diethyl ether, no improvement in reactivity was noted. Indeed, product formation appeared to reduce in this solvent, presumably due to the change in resin solvation preventing access of the Grignard into the active sites of the support.[28] After increasing the reaction temperature, significant bronzing of the resin was observed, and upon cleavage, numerous unidentifiable products were obtained. Changing the support had no effect on the reactivity, and similar product mixtures were obtained from different capacity Merrifield resins and Tentagel and Argogel supports. Ultimately, it was found that a greater concentration of Grignard reagent was required to produce the highest quantity of addition product. By adding 9 equiv of phenylmagnesium bromide over 12 h, the complete consumption of aldehyde was observed by gel-phase ^{13}C NMR and IR spectroscopy. The alcohol resulting from the addition was capped with acetic anhydride in the presence of DMAP. The amino alcohol **25** was obtained after acid cleavage and HPLC purification to remove the minor byproducts.

An anti/syn ratio of 1:1 was observed (HPLC, ^{1}H NMR) as compared to ratios of 3:1[29] and 5:1[19] reported in solution for the Garner aldehyde. Differences in selectivity between similar solution- and solid-phase α-chiral aldehydes in reaction with Grignard reagents have been reported.[30] The reason for the differences in reactivity and selectivity may be related to the diffusion of the charged organometallic reagent into the hydrophobic support[31] and also the behavior of the resin matrix at −78 °C where a frozen gel-phase may restrict the interactions between the resin-bound aldehyde and the Grignard.[32]

Although changing the steric bulk of the oxazolidine 2-substituents is known to alter the level of asymmetric induction at the formyl group,[19] it was felt that the flexible alkyl spacer of the linker, in either configuration about the 2-position, in combination with a methyl group was a good mimic for the Garner aldehyde itself; hence, these substituents are unlikely to be the cause of the differences in reaction selectivity between **1** and **2**.

Conclusion

A stability and reactivity study of the oxazolidine linker system was successfully performed using a rapid reaction scan based on the analytically enhanced dual-linker platform. The scan allowed the susceptibility of the oxazolidine scaffold to acid hydrolysis to be evaluated and highlighted the stability of the linker to a comprehensive range of reaction classes including oxidizing, reducing, and basic conditions. A second, acid scan was used to identify conditions that allowed the release of the substrate from the support with or without the concomitant removal of other acid-labile groups. The reagent compatibility information gained from the scans facilitated the construction of a diverse small molecule array, and this collection of useful chiral building blocks realized the synthetic potential of he oxazolidine linker.

The Garner aldehyde has proven to be an extremely important building block in organic chemistry. The oxazolidine aldehyde linker **1** is a useful solid-phase alternative owing to the successful transfer of many of the solution-phase reactions.

Experimental Procedures

General Procedure for Analytical Cleavage of Resin Containing Oxazolidine Linker. A small resin sample was incubated for 15 min at room temperature with 200 μL of a solution made from thiophenol (25 μL) and DIPEA (50 μL) in MeCN (250 μL). After filtration, the filtrate was diluted to a final volume of 500 μL with MeCN prior to analysis. LC-MS

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analyses were performed on a Hewlett-Packard HP 1050 instrument (diode array detection at 386 nm) and a Micromass Platform mass spectrometer using electrospray ionization in +ve mode.

Amine Reporter Resin 6. Resin **5**[13,16,21] (450 mg, 0.13 mmol) preswollen in CH_2Cl_2 was treated for 30 min with a solution of 66% TFA/CH_2Cl_2 (3 mL). The resin was drained and treated with a further 66% TFA/CH_2Cl_2 (3 mL) for 30 min, then washed with CH_2Cl_2 (3×), and dried in vacuo. An analytical sample of resin was cleaved and showed the formation of **6** at the expense of **5**. LC-MS (386 nm): $R_t = 4.13$ min (100%). MS $[M + H]^+ = 293$ when X = CH_3.

Oxazolidine Alcohol on Reporter Resin 8. To resin **6** (400 mg, 0.13 mmol) preswollen in CH_2Cl_2 was added a solution of oxazolidine acid **7**[8] (80 mg, 0.28 mmol), TBTU (90 mg, 0.28 mmol), HOBt (43 mg, 0.32 mmol), and DIPEA (90 μL, 66 mg, 0.51 mmol) in CH_2Cl_2/DMF (1:1, 4 mL). The resin was shaken at room temperature for 18 h, then drained, washed with DMF (3×) and CH_2Cl_2 (3×), and dried in vacuo. An analytical sample of resin was cleaved and showed the formation of **8** at the expense of **6**. LC-MS (386 nm): $R_t = 4.67$ min (100%). MS $[M + H]^+ = 564$ when X = CH_3.

Oxazolidine Ester on Reporter Resin 4. To resin **8** (400 mg, 0.13 mmol) preswollen in CH_2Cl_2 was added a solution of phenyl acetic acid (70 mg, 0.51 mmol), DIC (80 μL, 64 mg, 0.51 mmol), and DMAP (8 mg, 65 μmol) in CH_2Cl_2 (2 mL). The resin was shaken for 18 h; then drained; washed with CH_2Cl_2 (3×), DMF (3×), MeOH (3×), and CH_2Cl_2 (3×); and dried in vacuo. An analytical sample of resin was cleaved and showed the formation of **4** at the expense of **8**. LC-MS (386 nm): $R_t = 5.14$ min (100%). MS $[M + H]^+ = 682$ when X = CH_3.

Ketone on Reporter Resin 12. Resin **8** (20 mg, ~5 μmol) was treated with 50% TFA/CH_2Cl_2 (300 μL) for 30 min, then drained, washed with DMF (3×) and CH_2Cl_2 (3×), and dried in vacuo. An analytical sample of resin was cleaved and showed the formation of **12** at the expense of **8**. LC-MS (386 nm): $R_t = 4.50$ min (100%). MS $[M + H]^+ = 391$ when X = CH_3.

Ester 14. To polymer-supported alcohol **15**[8] (0.64 mmol g^{-1}, 200 mg, 0.13 mmol) preswollen in CH_2Cl_2 was added DMAP (82 mg, 0.67 mmol) and phenylacetic acid (91 mg, 0.67 mmol) then DIC (104 μL, 83 mg, 0.66 mmol) in CH_2Cl_2 (3 mL). The resin was shaken at room temperature for 18 h; then drained; washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×); then dried in vacuo. ^{13}C gel-phase NMR (100 MHz): δ 172.3, 171.1, 151.9, 133.7, 129.2, 128.6, 95.3, 81.1, 80.6, 65.6, 65.2, 64.9, 63.7, 63.5, 55.9, 55.5, 55.2, 41.3, 34.3, 33.9, 31.5, 28.4, 25.1, 24.0, 23.1, 21.6. IR (cm^{-1}, CH_2Cl_2 gel): 3438, 1739, 1692.

Phenyl Acetic Acid (*S*)-2-Amino-3-hydroxy-propyl Ester (16) TFA Salt. TFA method: to resin-bound ester **14** (0.58 mmol g^{-1}, 141 mg, 0.082 mmol) was added 20% TFA/CH_2Cl_2 (3 mL). The resin was shaken for 30 min, then drained, and washed with CH_2Cl_2 (3×). The combined filtrate was concentrated in vacuo to give the product as a clear film (26 mg, 100% from **15**). LCMS (260 nm): $R_t = 2.25$ min (100%). $ES^+ = 210.2$ $[M + H]^+$. HRMS: $[M + Na]^+$ calcd for $C_{11}H_{15}NO_3Na$ 232.0950, found 232.0961. ^{13}C NMR (100 MHz, MeOD): δ 171.4, 133.7, 129.0, 128.2, 127.0, 61.6, 58.5, 51.8, 39.9. ^1H NMR (400 MHz, MeOD): δ 7.28 (m, 5 H), 4.33 (dd, $J = 12.1$, 4.5 Hz, 1 H), 4.26 (dd, $J = 12.1$, 6.8 Hz, 1 H), 3.77 (dd, $J = 11.7$, 4.4 Hz, 1 H), 3.72 (s, 2 H), 3.67 (dd, $J = 11.7$, 6.0 Hz, 1 H), 3.51 (m, 1 H). IR (cm^{-1}): 3387, 3034, 1740, 1673, 1203. $[\alpha]_D$ +1.3 ($c = 0.04$, MeOH).

Phenyl Acetic Acid (*S*)-2-*t*-Butoxycarbonylamino-3-hydroxy-propyl Ester (17). TFA method: to resin-bound ester **14** (0.58 mmol g^{-1}, 220 mg, 0.127 mmol) was added 1% TFA/CH_2Cl_2 (5 mL). The resin was shaken for 15 min, then drained, and washed with CH_2Cl_2 (3×). The resin was treated with 1% TFA/CH_2Cl_2 (5 mL) for a further 15 min, then drained, and washed with CH_2Cl_2 (3×) as before. The combined filtrates were concentrated in vacuo to give the product as a clear film (40 mg, 100% from **15**). LCMS (260 nm): $R_t = 3.91$ min (100%). $ES^+ = 210.2$ $[M + H - Boc]^+$. HRMS: $[M + Na]^+$ calcd for $C_{16}H_{23}NO_5Na$ 332.1474, found 332.1475. ^{13}C NMR (100 MHz, MeOD): δ 171.9, 134.2, 129.0, 128.1, 126.6, 78.9, 63.4, 60.7, 51.3, 40.4, 27.3. ^1H NMR (500 MHz, MeOD): δ 7.28 (m, 5 H), 4.20 (dd, $J = 11.1$, 5.0, 1 H), 4.07 (dd, $J = 11.1$, 6.5, 1 H), 3.80 (m, 2 H), 4.56 (s, 2 H), 3.51 (app t, $J = 6.1$, 2 H), 1.43 (s, 9 H). IR (cm^{-1}): 3399, 2925, 1717. $[\alpha]_D$ −0.3 ($c = 0.02$, MeOH).

β-Lactam 18. To polymer-supported aldehyde resin **1** (0.64 mmol g^{-1}, 235 mg, 0.15 mmol) preswollen in CH_2Cl_2 was added benzylamine (63 μL, 61 mg, 0.58 mmol) in CH_2Cl_2 (2 mL) and 4 Å molecular sieves. The resin was shaken for 30 min and then drained. The resin was then shaken for a further 2 × 30 min with benzylamine (2 × 63 μL, 61 mg, 0.58 mmol) in CH_2Cl_2 (2× 2 mL) until IR showed the disappearance of the aldehyde carbonyl stretch. After draining, the resin was washed with CH_2Cl_2 (3×). To the resin was added CH_2Cl_2 (2 mL), and the mixture was cooled to 0 °C. Triethylamine (167 μL, 121 mg, 1.20 mmol) was added followed by the dropwise addition of benzyloxyacetyl chloride (94 μL, 110 mg, 0.596 mmol). The resin was agitated for 30 min at 0 °C. The mixture was then allowed to warm to room temperature and shaken for 18 h. The resin was drained; washed with CH_2Cl_2 (3×), THF:aq sat $NaHCO_3$ (1:1, 3×), THF:H_2O (1:1, 3×), THF (3×), and CH_2Cl_2 (3×); and then dried in vacuo. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 172.0, 97.9, 95.8, 80.8, 80.7, 73.2, 65.9, 64.9, 64.3, 63.8, 58.2, 57.8, 34.0, 33.4, 32.2, 31.6, 30.9, 30.4, 28.6, 28.3, 28.0, 27.8, 27.7, 24.7, 24.6, 23.4, 22.3. IR (cm^{-1}, CH_2Cl_2 gel): 3436, 1753, 1674. Anal. cald N 2.28%, found N 2.28%.

(3*R*,4*S*)-4-((*R*)-1-Amino-2-hydroxy-ethyl-1-benzyl-3-benzyloxy-azetidine-2-one (19).[25a,26] To polymer-supported β-lactam **18** (0.56 mmol g^{-1}, 250 mg, 0.14 mmol) was added 20% TFA/CH_2Cl_2 (3 mL). The resin was shaken for 30 min, then drained, and washed with CH_2Cl_2. The combined filtrate was concentrated in vacuo, and the resulting residue was partitioned between water and EtOAc. The aqueous layer was separated and washed with EtOAc (1×), then made basic (pH 9−10) with aq 1 M NaOH. The aqueous layer was extracted with EtOAc (3×), and the combined organics were dried with Na_2SO_4 and concentrated in vacuo to give the product as a clear residue (33 mg, 72% from **1**). LC-MS (260 nm): $R_t = 2.41$ min (100%). $ES^+ = 327.2$ $[M + H]^+$. HRMS: $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_3$ 327.1708, found 327.1693. ^{13}C NMR (100 MHz, MeOD): δ 169.5, 137.1, 135.9, 128.5, 128.2, 127.9, 127.8, 127.7, 127.5, 81.4, 73.4, 63.4, 59.6, 52.0, 45.2. ^1H NMR (400 MHz, MeOD): δ 7.36−7.27 (m, 10 H), 4.85 (d, $J = 11.5$ Hz, 1 H), 4.77 (d, $J = 5.0$ Hz, 1 H), 4.69 (d, $J = 11.5$ Hz, 1 H), 4.68 (d, $J = 15.2$ Hz, 1 H), 4.36 (d, $J = 15.2$ Hz, 1 H), 3.79 (dd, $J = 5.0$, 3.7 Hz, 1 H), 3.51 (dd, $J = 10.8$, 5.0 Hz, 1 H), 3.47 (dd, $J = 10.8$, 5.8 Hz, 1 H), 3.02 (m, 1 H). IR (cm^{-1}): 3351, 2927, 1752, 1674, 1202, 1134. $[\alpha]_D = -37.0$ ($c = 0.1$, MeOH).

Ester 20. To polymer-supported aldehyde resin **1** (0.64 mmol g^{-1}, 350 mg, 0.225 mmol) preswollen in benzene was added methyl(triphenylphosphoranylidene)acetate (150 mg, 0.45 mmol) and benzene (3 mL). The resin was shaken at room temperature for 18 h; then drained; and washed with benzene (3×), DMF (3×), MeOH (3×), and CH_2Cl_2 (3 ×); then dried in vacuo. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 172.2, 166.5, 95.9, 95.6, 81.4, 80.7, 67.9, 67.4, 58.3, 57.8, 51.8 34.5, 34.0, 31.4, 31.1, 25.2, 24.2, 23.3, 22.0. IR (cm^{-1}, CH_2Cl_2 gel): 3438, 1721, 1693.

(*E*)-(*R*)-5-Amino-6-hydroxy-hex-2-enoic Acid Methyl Ester (21) TFA Salt. To polymer-supported ester **20** (0.62 mmol g^{-1}, 100 mg, 0.062 mmol) was added 20% TFA/CH_2Cl_2 (2 mL). The resin was shaken for 20 min, then drained, and washed with CH_2Cl_2 (3×). The combined filtrate was concentrated in vacuo, and the resulting residue was partitioned between water and CH_2Cl_2. The aqueous layer was separated and washed with CH_2Cl_2 (1×), then concentrated in vacuo (freeze-dried) to give the product TFA salt as a clear residue (9 mg, 55% from **1**). HRMS: $[M + Na]^+$ calcd for $C_{17}H_{20}N_2O_2Na$ 307.1422, found 307.1436. ^{13}C NMR (100 MHz, MeOD): δ 167.5, 163.3 (q, $J = 34.4$) 141.4, 126.7, 62.7, 55.2, 52.9. ^1H NMR

(400 MHz, MeOD): δ 6.88 (dd, J = 16.0, 6.8 Hz, 1 H), 6.18 (dd, J = 16.0, 1.3 Hz, 1 H), 4.02 (m, 1 H), 3.82 (dd, J = 11.6, 4.3 Hz, 1 H), 3.75 (s, 3 H), 3.67 (dd, J = 11.6, 6.3 Hz, 1 H). IR (cm^{-1}): 3370, 2923, 1718, 1673. $[\alpha]_D = +6.3$ (c = 0.03, MeOH).

Amide 22. To polymer-supported aldehyde resin **1** (0.64 mmol g^{-1}, 0.225 mg, 0.144 mmol) preswollen in CH_2Cl_2 was added benzylamine (121 μL, 119 mg, 1.11 mmol) in CH_2Cl_2 (3 mL) and 4 Å molecular sieves. The resin was shaken for 30 min and then drained. The resin was then shaken for a further 2 × 30 min with benzylamine (2 × 121 μL, 119 mg, 1.11 mmol) in CH_2Cl_2 (2 × 3 mL) until IR spectroscopy showed the disappearance of the aldehyde carbonyl stretch. After draining, the resin was washed with CH_2Cl_2 (3×). To the resin was added 1% AcOH/DMF (2.5 mL) followed by $NaBH(OAc)_3$ (143 mg, 0.67 mmol) powder. The resin was shaken for 90 min and then drained. The resin was treated once more with $NaBH(OAc)_3$ (143 mg, 0.67 mmol) in 1% AcOH/DMF (2.5 mL) for 90 min. The resin was drained and washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×). To the resin was added CH_2Cl_2 (3 mL) followed by benzoyl chloride (130 μL, 157 mg, 1.12 mmol) and Et_3N (156 μL, 113 mg, 1.12 mmol). The resin was shaken at room temperature for 18 h and then drained; washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×); then dried in vacuo. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 172.7, 96.2, 95.6, 80.7, 65.9, 64.8, 64.3, 63.9, 55.8, 54.4, 53.1, 52.5, 33.9, 32.8, 31.3, 30.4, 25.3, 24.6, 23.7, 23.3. IR (cm^{-1}, CH_2Cl_2 gel): 3436, 1680, 1632, 1601. Anal. cald N 2.41%, found N 2.34%.

***N*-((*R*)-2-Amino-3-hydroxy-propyl)-*N*-benzyl-benzamide (23).** Amide **22** was cleaved from resin and worked up in an identical manner to β-lactam **19**. Hence, from amide **22** (0.56 mmol g^{-1}, 400 mg, 0.225 mmol), the product was obtained as a clear residue (28 mg, 45% from **1**). LC-MS (260 nm): R_t = 2.82 min, ES+ 285.3 (100%). HRMS: $[M + Na]^+$ calcd for $C_{17}H_{20}N_2O_2Na$ 307.1422, found 307.1436. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 136.6, 136.0, 130.3, 129.3, 129.0, 128.3, 127.3, 127.0, 64.2, 54.2, 51.3, 48.0. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.22 (m, 8 H), 7.17−7.13 (m, 2 H), 4.63 (d, J = 16.1 Hz, 1 H), 4.51 (d, J = 16.1 Hz, 1 H), 3.74 (bm, 1 H), 3.53 (bm, 2 H), 3.27 (dd, J = 13.8, 5.5, 1 H), 3.00 (bm, 1 H), 2.20 (b, 3 H). IR (cm^{-1}): 3358, 2970, 1622, 1453, 1202. LC-MS: R_t = 2.80 min (100%). ES^+ = 285.3 $[M + H]^+$. $[\alpha]_D = -48.8$ (c = 0.03, MeOH).

Ester 24. To polymer-supported aldehyde resin **1** (0.64 mmol g^{-1}, 230 mg, 0.149 mmol) was added THF (2.5 mL), and the mixture was cooled to −78 °C. Phenylmagnesium bromide in THF (0.69 M, 647 μL, 0.446 mmol) was added dropwise over 30 min, and the mixture was stirred for 4 h at −78 °C. A second portion of phenylmagnesium bromide in THF (0.69 M, 647 μL, 0.446 mmol) was then added, followed by a third (0.69 M, 647 μL, 0.446 mmol) after another 4 h. The mixture was stirred for a further 4 h and then warmed to 0 °C and quenched with aq sat. NH_4Cl solution. The resin was drained; washed with H_2O THF/H_2O (1:1, 3×), THF (3×), DMF (3×), MeOH (3×), and CH_2Cl_2 (3×); and then dried in vacuo. To the resin preswollen in CH_2Cl_2 was added DMAP (92 mg, 0.753 mmol), followed by CH_2Cl_2 (2 mL) and Ac_2O (140 μL, 151 mg, 1.483 mmol). The resin was shaken overnight; drained; washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×); and then dried in vacuo. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 172.3, 169.6, 145.2, 128.0, 125.7, 97.7, 95.8, 80.9, 73.2, 69.7, 65.9, 64.1, 63.5, 61.5, 59.6, 53.4, 33.9, 33.2, 31.2, 28.4, 27.9, 24.7, 23.4, 21.2. IR (cm^{-1}, CH_2Cl_2 gel): 3437, 1744, 1673.

(1*R*/*S*,2*S*)-2-Amino-3-hydroxy-1-phenyl-propyl Ester (25) TFA Salt. To polymer-supported ester **20** (0.58 mmol g^{-1}, 260 mg, 0.149 mmol) was added with 20% TFA/CH_2Cl_2 (4 mL). The resin was shaken for 30 min, then drained, and washed with CH_2Cl_2 (3×). The combined filtrate was concentrated in vacuo to give the crude product as a clear residue. The residue was purified by HPLC using a C_{18} 5 micron column (10 × 250 mm) on an HPLC machine with UV detection at 260 nm. The elution conditions were solvent A (0.1% TFA/H_2O) and solvent B (0.1% TFA/MeCN) with a gradient of 95:5 A/B going to 100% B over 30 min. R_t =13.56 min (53%), 13.78 (47%). The product was obtained as a clear residue in a ∼1:1 mixture of diastereomers (26 mg, 55% from **1**). LCMS (260 nm): R_t = 2.16 min (45%), 2.30 (55%), ES+ 210.1 $[M + H]^+$. HRMS: $[M + H]^+$ calcd for $C_{11}H_{16}N_1O_3$ 210.1130, found 210.1131. ^{13}C NMR (125 MHz, MeOD): δ 171.9, 171.2, 141.4, 137.4, 136.7, 130.4, 130.0, 129.9, 129.5, 128.5, 127.6, 127.5, 127.0, 75.1, 73.8, 72.3, 62.5, 59.2, 58.7, 57.7, 57.5, 20.8, 20.5. ^1H NMR (500 MHz, MeOD): δ 7.44−7.36 (m, 10 H), 6.03 (d, J = 4.7 Hz, 1 H), 5.86 (d, J = 7.87 Hz, 1 H), 3.69 (m, 2 H), 3.65 (m, 2 H), 3.56 (dd, J = 11.7, 4.5 Hz, 1 H), 3.34 (dd, J = 11.7, 4.8, 1 H), 2.10 (s, 3 H), 2.08 (s, 3 H). IR (cm^{-1}): 3376, 3064, 1674, 1202.

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Supporting Information Available: LC-MS traces for representative analytical cleavage of resins, full experimental details for reaction scans, and NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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