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Synthesis of a Polymer-Supported Oxazolidine Aldehyde for Asymmetric Chemistry

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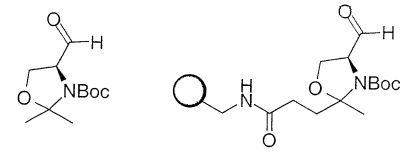
An expedient synthesis of the polymer-supported aldehyde **3**, as a Garner aldehyde equivalent, is described. Oxazolidine **3** may be obtained through preformation of aldehyde linker **4** in solution and loaded onto amine-terminating resin under peptide-coupling conditions, or alternatively via oxidation of polymer-bound alcohol **14**. The integrity of the serine-derived stereocenter is maintained through all steps of the synthesis.

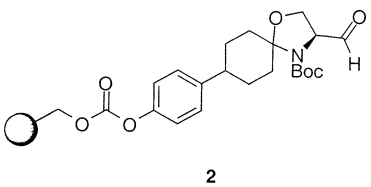
Introduction

Amino acids are used extensively as chiral building blocks in organic synthesis, owing to their availability and optical purity. Suitably protected amino aldehydes have proven exceptionally useful because of their ease of synthesis and manipulation.[1] The optically active oxazolidine **1** first reported by Garner has emerged as one of a number of distinct serine aldehyde derivatives.[2] The acetonide is useful owing to its chemical and optical stability and high enantiopurity. The chiral aldehyde is a versatile synthetic intermediate because the formyl group is a strong electrophile and addition reactions can often display a high degree of asymmetric induction.[3] The contiguous amino-hydroxy functionality along the serine-derived backbone is a common motif within many complex molecules and the oxazolidine has been used expansively as the source for such structures. Furthermore, the ease of deprotection and manipulation of the acetal in downstream products is a definite advantage. This has been demonstrated in the synthesis of a wide range of natural products that range from simple sphingosines[4] to the more complicated cores of structures such as the proteasome inhibitor TMC-95A.[5]

The oxazolidine family has now been expanded to include many other chiral templates that make use of different substitutions to fulfill a wide range of chemistry requirements. Threonine[2a] and α-methylserine[6] derivatives have also been prepared. The nitrogen-protecting group has been varied for reasons of orthogonality and selectivity in later stage chemical manipulation,[7] and a number of examples exist of 2,2-disubstituted derivatives.[8]

Recent attention in the field of solid-phase organic synthesis has been directed toward carbon−carbon bond formation.[9] Asymmetric chemistry has yet to be fully exploited as a particular aspect of organic synthesis on solid support. The creation of a polymer-supported version of the Garner aldehyde would be an extension of its capabilities as a chiral auxiliary and a platform for the creation of further stereogenic centers via solid-phase organic synthesis. *N*,*O*-Acetals have been used on solid phase to link ketones and amino alcohols to resin.[10] The acetal may be cleaved rapidly and easily by exposure to TFA with excellent purity of recovered compound.





In previous work we have established the practicality of the insoluble oxazolidine aldehyde **2** in the stereo-

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(1) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

(2) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18.

(3) For a comprehensive review on the synthesis and application of the Garner aldehyde see: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136.

(4) 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.

(5) Some recent examples include: (a) Ma, D.; Wu, Q. *Tetrahedron Lett.* **2000**, *41*, 9089. (b) Inoue, M.; Furuyama, H.; Sakazaki, H.; Hirama, M. *Org. Lett.* **2001**, *3*, 2863. (c) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1967. (d) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *40*, 512.

(6) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949.

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selective synthesis of a library of β-lactams.[8c] This paper describes a practical synthesis of the chiral oxazolidine aldehyde **3**: a second-generation polymer-supported Garner aldehyde. The linker is based upon a 2,2-disubstituted oxazolidine, the key element of which is a short, flexible tether that connects the oxazolidine component with an amide bond to the polymeric support. The incorporation of these two elements addresses the limitations of the original construct **2**: namely the rigid link from resin to oxazolidine and the chemically vulnerable carbonate group.

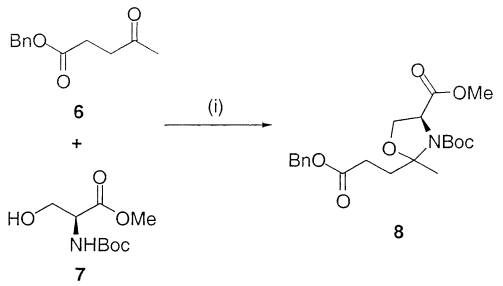
The creation of a differentially 2,2-disubstituted oxazolidine involves the formation of a new stereogenic center. For oxazolidine **3** it was thought that resolution of this center was not necessary. Although changing the steric bulk of 2-substituents on the oxazolidine ring is known to alter the level of asymmetric induction at the formyl group,[8b] we felt that an alkyl spacer, in either configuration about the 2-position, in combination with a methyl group was a good mimic for the Garner aldehyde itself, and hence these substituents would be unlikely to effect the selectivities observed for **1**. From the outset we envisaged synthesizing the aldehyde **4** as the immediate precursor to the polymer-supported oxazolidine aldehyde. An alternative procedure might involve synthesis of the alcohol **5** that would be oxidized to the aldehyde on resin.

Results and Discussion

The oxazolidine ring formation in the synthesis of the Garner aldehyde uses 2,2-dimethoxypropane in combination with a serine-derived amino alcohol and a catalytic amount of Lewis acid (typically $BF_3 \cdot Et_2O$ or pTsOH).[3] We envisaged using the small, simple benzyl ester ketone **6** in place of the hemiacetal. The ketone would serve as the site of oxazolidine formation and the carboxylic acid, revealed after hydrogenolysis of the benzyl ester, as the point of attachement to resin. Ester **6** was obtained directly from levulinic acid.[11] Removal of the benzyl group by hydrogenolysis was seen as a mild method of deprotection that would not interfere with the integrity of the oxazolidine structure.

Ketone **6** was reacted with L-*N*-Boc-serine methyl ester[12] (**7**) under ketalization conditions developed by Kurihara[13] from Noyori[14] (Scheme 1). By using the alkoxysilane isopropoxytrimethylsilane and a catalytic amount of trimethyl trifluoromethanesulfonate (TMSOTf) in the presence of equimolar ketone and diol, the corresponding acetal may be synthesized in high yields at room temperature. We have adapted the reaction to use amino alcohols and have demonstrated this procedure as an alternative route for accessing 1,3-oxazolidines.[8c] However, under these conditions oxazolidine methyl ester **8** was formed in only moderate yield (38%) as a mixture of diastereomers. As with all subsequent oxazolidines synthesized, no separation between diastereomers was observed by TLC. Integration of the methyl ester signals in the ^{1}H NMR spectrum showed the diastereomers to have been formed in equal amount. As with other oxazolidine structures,[2a] line broadening and doubling due to Boc rotamers was observed in the ^{1}H and ^{13}C NMR spectra of all acetals synthesized. The presence of diastereomers within each sample further complicated each spectrum. Recording ^{1}H NMR spectra at elevated temperatures (typically >100 °C) reduced the number and breadth of the signals.[2a]

SCHEME 1[a]



[a] Reagents and conditions: (i) *i*-PrOTMS, TMSOTf, CH_2Cl_2, rt, 24 h (38%).

Accordingly, an alternative approach was investigated. With use of an adaptation of Avenoza's synthesis of the Garner aldehyde,[15] silyl ether **9** was used as the serine component in the acetalization reaction. Differentially protected serinol **9** was synthesized in four steps from D-serine in 80% overall yield[15] and uses the inherent, masked symmetry contained within this amino acid to bring about an apparent inversion of stereochemistry. Thus D-serine was used to make L-serinal. Reaction of ketone **6** with alcohol **9** produced oxazolidine silyl ether **10** in excellent yield (85%) (Scheme 2). Integration of the benzylic methylene signals in the ^{1}H NMR spectrum for each diastereomer gave the ratio of formation to be 1:1. Desilylation of the *tert*-butyldiphenyl siloxy group of **10** with TBAF in THF gave the corresponding alcohol **11** (85%). Prolonged exposure to the desilylating agent produced a number of byproducts as seen by TLC. This was likewise noted when using HF-pyridine where more byproduct than desired product was formed.

Oxidation of primary alcohol **11** to aldehyde **12** under Swern conditions [$(COCl)_2$, DMSO, Et_3N] was straightforward (90%).[16] Oxidation with use of the Dess−Martin periodinane was also found to be a good alternative (80%).[15,17] Removal of the benzyl ester with hydrogen over

(7) (a) Beaulieu, P. *Tetrahedron Lett.* **1991**, *32*, 1031. (b) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron Lett.* **1998**, *54*, 6051. (c) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113.

(8) (a) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194. (b) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673. (c) Gordon, K.; Bolger, M.; Khan, N.; Balasubramanian, S. *Tetrahedron Lett.* **2000**, *41*, 8621.

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(10) (a) Guillier, F.; Orain, D.; Bradley M. *Chem. Rev.* **2000**, *100*, 2091 and references therein. (b) Groth, T.; Meldal, M. *J. Comb. Chem.* **2001**, *3*, 34 and references therein.

(11) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560.

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(13) Kurihara, M.; Miyata, N. *Chem. Lett.* **1995**, 263.

(14) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(15) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Synthesis* **1997**, 1146.

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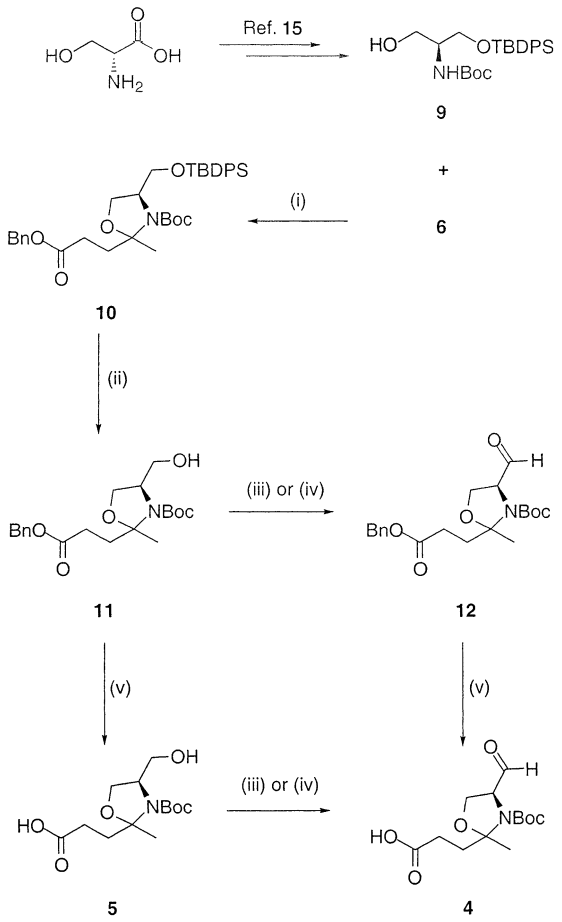
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

SCHEME 2[a]

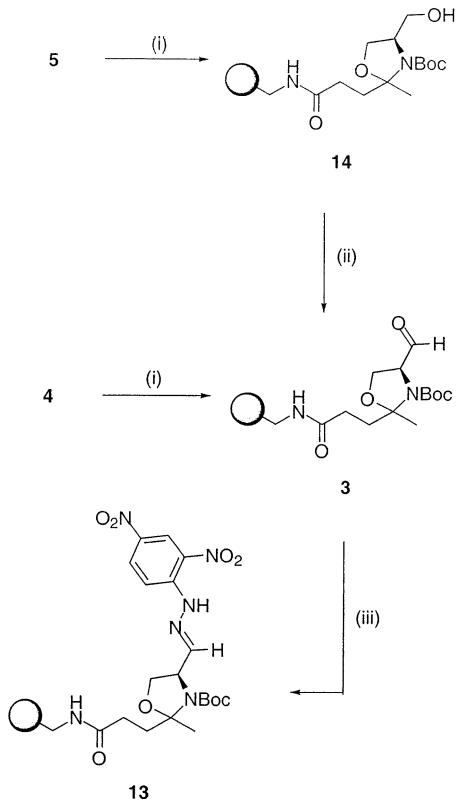


[a] Reagents and conditions: (i) *i*-PrOTMS, TMSOTf, CH_2Cl_2, rt, 24 h (85%); (ii) TBAF, THF, rt, 3 h (86%); (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C to room temperature, 15 min; (iv) Dess−Martin periodinane, CH_2Cl_2, rt, 3 h; (v) 10% Pd−C, H_2, MeOH, rt, 4 h.

a palladium on carbon catalyst gave the target acid aldehyde **4**. Hydrogenation after a sulfur oxidation can be variable due to catalyst poisoning;[18] however, with a careful workup and chromatographic separation, any such problem was avoided. Alternatively, aldehyde **4** may be accessed via alcohol **5** by simply alternating the oxidation−deprotection steps. Thus, hydrogenation of the benzyl ester followed by oxidation gave aldehyde **4**. The oxidation−deprotection pathway was preferred as the removal of the benzyl ester was clean and quantitative and the final product did not require purification prior to immobilization to the solid phase.

Acid **4** was coupled to amino-methylated Merrifield with use of DIC and HOBt (Scheme 3). The gel-phase ^{13}C NMR spectrum of loaded oxazolidine **3** compared favorably with the solution-phase spectrum of aldehyde **4**. To gauge the loading of the aldehyde, **3** was reacted with dinitrophenyl hydrazine to form the corresponding hydrazone **13**. The nitrogen content of a resin sample was determined by elemental analysis and hence the yield of the loading reaction was found to be quantitative.

SCHEME 3[a]



[a] Reagents and conditions: (i) aminomethylated polystyrene (0.75 mmol g^{-1}), DIC, HOBt, CH_2Cl_2/DMF (1:1), rt, 24 h; (ii) Py·SO_3, Et_3N, DMSO, CH_2Cl_2, rt, 12 h; (iii) 2,4-dinitrophenylhydrazine, THF/MeOH (4:1), 75 °C, 8 h.

As an alternative approach alcohol **5** was first loaded onto resin (HOBt, DIC) to give alcohol **14**. The oxidation of **14** to **3** under Swern or Dess−Martin conditions gave unsatisfactory quantities of aldehyde. The oxidation of alcohols on polymeric support has been recognized as often being problematic and unsatisfactory favoring preformation of the aldehyde in solution.[10b] However, sulfur trioxide pyridine complex in combination with DMSO and Et_3N successfully oxidized the polymer-bound alcohol **14** to **3**.[19] Therefore, there are two clear synthetic options to generate **3**.

The integrity of the serine-derived stereocenter through the acetalization, desilylation, and oxidation steps was assured by analysis of the appropriate Mosher ester.[20] The reaction conditions are known to preserve the integrity of the center within the 2,2-dimethyl system[15] and it was thought that this observation would extend to other substituted 1,3-oxazolidines. Alcohol **11** was condensed with (+)-(*R*)-MTPA to give Mosher ester **15** (Scheme 4). The peaks in the ^{19}F NMR spectrum of **15** (Figure 1b) compared favorably with the literature values[2a,15] reported for the enantiomerically pure L-Garner aldehyde-derived ester **16** (Figure 1a): the presence of the diastereomeric center within the ring causes only slight broadening of signals in the ^{19}F NMR spec-

(18) Paterson, I.; Chen, D. Y.; Aceña, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513.

(19) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

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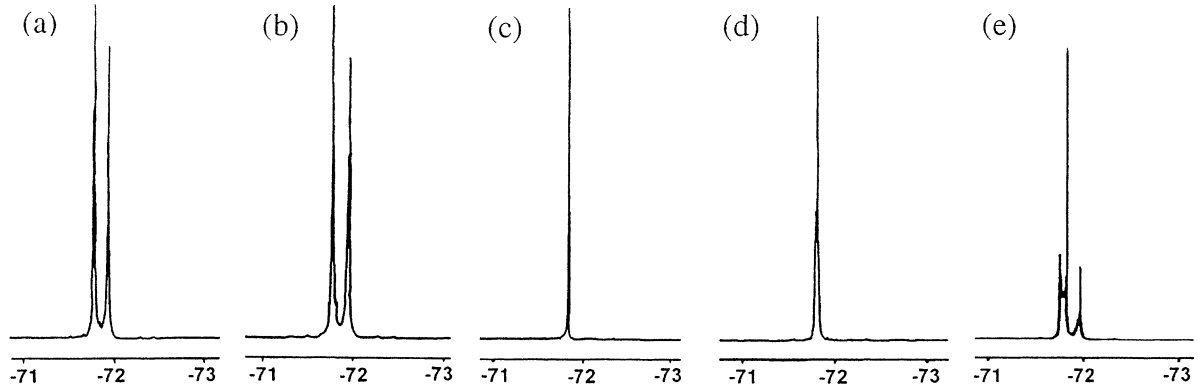
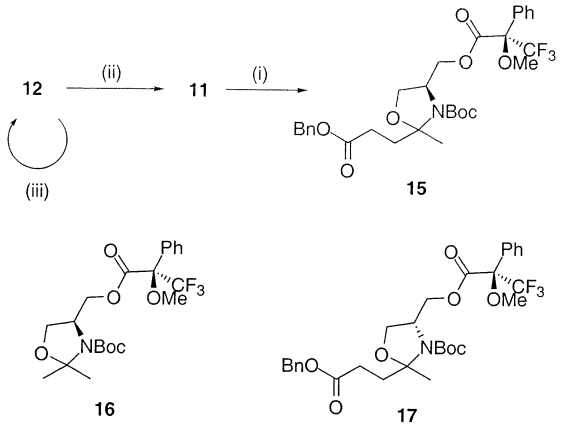


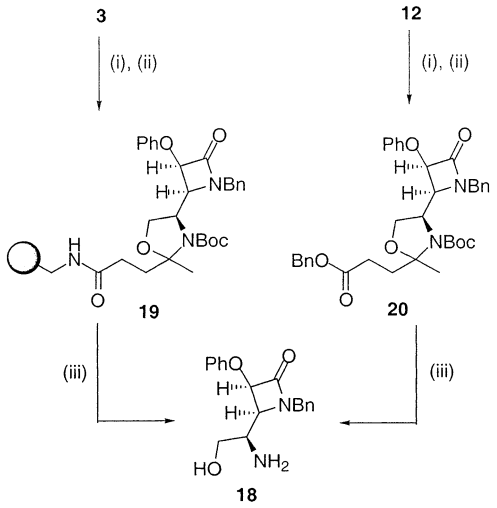
FIGURE 1. The ^{19}F NMR spectra of (a) (*R*)-Mosher ester **16**; (b) (*R*)-Mosher ester **15**; (c) diastereomer of **16**; (d) (*R*)-Mosher ester **17**; and (e) a 1:1 mixture of **15** and **17**.

SCHEME 4[a]



[a] Reagents and conditions: (i) (*R*)-(+)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 12 h (55%); (ii) $NaBH_4$, THF/*i*-PrOH (1:1), 0 °C, 2 h; (iii) identical conditions to those used for coupling of **4** to resin: aminomethylated polystyrene (0.75 mmol g^{-1}), levulinic acid, DIC, HOBt, CH_2Cl_2/DMF (1:1), rt, 24 h.

SCHEME 5[a]



[a] Reagents and conditions: (i) $BnNH_2$, 4 Å MS, CH_2Cl_2, rt, 1 h; (ii) Et_3N, $PhOCH_2COCl$, 0 °C to room temperature, 18 h; (iii) 10% TFA/CH_2Cl_2, rt, 1 h.

trum (Figure 1).[21] As ester **15** was formed in only 55% yield, it was necessary to show that the stereochemical integrity at C-4 was maintained throughout all synthetic steps and not an artifact of diastereoselective Mosher ester formation. Hence the opposite diastereomeric Mosher ester **17** was synthesized from the oxazolidine derived from L-serine, under identical conditions, in 55% yield. The ^{19}F NMR spectrum of **17** (Figure 1d) was clearly that of the opposite diastereomer by comparison with the literature[2a,15] and the spectrum aquired for the opposite diastereomer of **16** (Figure 1c). This confirms that the Mosher ester study was indeed a true reflection of stereochemical integrity.

Aldehyde **12** was reduced ($NaBH_4$) to alcohol **11** and then reacted directly with (+)-(*R*)-MPTA.[2a] The ^{19}F NMR spectrum of the aldehyde-derived ester **15** was identical with the alcohol-derived ester confirming that the oxidation procedures had not caused epimerization of the 4-position. The stereochemical integrity of the serine-derived center under the loading conditions was also evaluated by subjecting model aldehyde **12** to identical amide coupling conditions and converting the aldehyde to Mosher ester **15** as before. The ^{19}F and ^{13}C NMR spectra were identical to those of the Mosher ester derived directly from oxazolidine alcohol **11**.

As final confirmation that the resin-bound aldehyde had not undergone C-4 epimerisation, β-lactam **18** was synthesized from aldehyde **3** with a view to comparing its optical rotation with a sample derived from a solution-phase synthesis (Scheme 5). Treatment of **3** with benzylamine in the presence of molecular sieves followed by phenoxyacetyl chloride and Et_3N gave β-lactam **19**.[8c,22] Cleavage of **19** with 10% TFA in DCM yielded lactam **18** (75% from **3**). The optical rotation of product **18** ($[\alpha]_D$ −25) compared favorably with that of the β-lactam derived from solution-phase analogue **20** ($[\alpha]_D$ −25) and the literature value ($[\alpha]_D$ −26).[8c]

A practical synthesis of a second-generation polymer-supported Garner aldehyde equivalent has been demonstrated. The synthesis is scalable to 20 g without loss of efficiency or stereochemical integrity. This linker should

(21) The most satisfactory resolution of ^{19}F signals is only achieved at ambient temperature where the chemical shift differences of the individual conformers cannot be "averaged out". See ref 2a.

(22) For a discussion on the asymmetric Staudinger reaction see: Palomo, C.; Cossío, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Román, P.; Luque, A.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.

prove to be of significantly broader utility than the previous version.[8c] Studies on the exploitation of this linker system for a range of chemistries will be reported in due course.

Experimental Section

General Methods. Chemicals were purchased from Aldrich Chemical Co. and were used without further purification. Aminomethylated polystyrene resin was purchased from Novabiochem. All anhydrous solvents were distilled in house (THF from $LiAlH_4/CaH_2$ with triphenylmethane as indicator; CH_2Cl_2 and MeOH from CaH_2) or purchased from Aldrich. Infrared spectra of solution samples were obtained from a film on NaCl. FTIR spectra of resin samples were obtained as a CH_2Cl_2 gel. Gel-phase ^{13}C NMR spectroscopic data were acquired in $CDCl_3$ with an acquisition time of 0.1 s, 10 ns delay between pulses, and 3.5×10^5 to 7.0×10^5 scans.

General Procedures. All solution-phase anhydrous experiments were performed under a positive pressure of argon in dried glassware equipped with a rubber septum cap. Anhydrous solvents and other liquid reagents were transferred by syringe or cannulation. Solid-phase reactions were typically carried out in fritted polyethylene filtration tubes fitted with a Teflon cap at the outlet and a rubber septum seal, under a positive pressure of argon with gentle shaking on an orbital shaker. Column chromatography was performed with Merck silica gel (230−400 mesh silica kieselgel) under positive pressure. Resin washing typically used 2 mL of solvent per cycle for 200 mg of resin.

4-Oxo-pentanoic Acid Benzyl Ester, 6. To a solution of levulinic acid (630 mg, 5.4 mmol) and Et_3N (900 μL, 6.5 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added benzyl chloroformate (1.0 mL, 7.0 mmol). The mixture was stirred for 5 min at 0 °C and then DMAP (90 mg, 0.75 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, 0.1 M HCl, and brine, dried with Na_2SO_4, and concentrated in vacuo to give a clear liquid. The crude was purified by flash column chromatography on silica gel (20% EtOAc/hexane, R_f = 0.28). Yield: 880 mg (80%, as a clear liquid). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 172.6, 135.9, 128.6, 128.2, 66.5, 37.9, 29.8, 28.0. ^1H NMR (250 MHz, $CDCl_3$): δ 7.34 (s, 5 H), 5.12 (s, 2 H), 2.77 (t, 2 H, J = 6.1 Hz), 2.63 (t, 2 H, J = 6.1 Hz), 2.18 (s, 3 H). IR (cm^{-1}): 2952, 1736, 1719, 1354, 1156, 1026, 751. HRMS: $[M + Na]^+$ calcd for $C_{12}H_{14}O_3Na$ 229.0841, found 229.0842. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.79. Found: C, 69.97; H, 6.80.

(2*R/S*,4*S*)-2-(2-Benzyloxycarbonylethyl)-2-methyloxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester, 8. To a solution of ketone **6** (65.4 mg, 0.32 mmol), L-*N*-Boc-serine methyl ester (**7**) (84.9 mg, 0.39 mmol), and isopropoxytrimethylsilane (*i*-PrOTMS) (240 μL, 1.35 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C was added TMSOTf (2 μL, 10 μmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched by the addition of pyridine (∼10 μL) and the mixture concentrated in vacuo to yield a yellow oil. The oil was purified by flash column chromatography on silica gel (20% EtOAc/hexane, R_f = 0.33) to yield the product as a 1:1 mixture of diastereomers. Yield: 49.6 mg (38%, as a clear oil). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 173.1, 173.0, 171.4, 171.3, 171.0, 170.9, 151.9, 151.7, 151.2, 151.0, 136.2, 136.1, 136.0, 135.9, 128.5, 128.4, 128.2, 128.1, 128.0, 96.2, 96.1, 95.6, 81.3, 80.6, 66.5, 66.3, 66.2, 66.1, 66.0, 65.7, 59.4, 58.7, 52.4, 52.3, 52.2, 52.1, 33.4, 33.1, 32.4, 32.1, 29.2, 29.1, 28.8, 28.7, 28.2, 23.8, 23.3, 22.8, 22.6. ^1H NMR (400 MHz, DMSO, 140 °C): δ 7.36 (s, 10 H), 5.12 (s, 4 H), 4.45 (dd, 1 H, J = 7.7, 3.4 Hz), 4.43 (dd, 1 H, J = 7.6, 4.5 Hz), 4.21 (dd, 1 H, J = 9.2, 7.7), 4.18 (dd, 1 H, J = 9.0, 7.6), 3.95 (dd, 1 H, J = 9.2, 3.4), 3.89 (dd, 1 H, J = 9.0, 4.5 Hz), 3.71 (s, 3 H), 3.70 (s, 3 H), 2.51−2.11 (m, 8 H), 1.53 (s, 3 H), 1.46 (s, 3 H), 1.40 (s, 18 H). IR (cm^{-1}): 2977, 2889, 1737, 1705, 1455, 1391, 1255, 1206, 1171, 1084. HRMS: $[M + Na]^+$ calcd for $C_{21}H_{29}NO_7Na$ 430.1842, found 430.1840.

(2*R/S*,4*S*)-2-(2-Benzyloxycarbonylethyl)-4-(*tert*-butyldiphenylsilyloxymethyl)-2-methyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester, 10. To a solution of ketone **6** (277 mg, 1.34 mmol), (*S*)-O-*tert*-butyldiphenylsilyl-*N*-Boc-serinol (**9**) (680 mg, 1.58 mmol), and *i*-PrOTMS (847 μL, 4.77 mmol) in anhydrous CH_2Cl_2 (9 mL) at 0 °C was added TMSOTf (14.2 μL, 78.5 μmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched by the addition of pyridine (∼60 μL) and the mixture concentrated in vacuo to yield a clear oil. The oil was purified by flash column chromatography on silica gel (20% EtOAc/hexane, R_f = 0.56) to yield the product as a 1:1 mixture of diastereomers. Yield: 635 mg (78%, as a clear oil). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 151.8, 151.6, 136.0, 135.5, 133.4, 133.2, 130.0, 129.7, 128.5, 128.4, 128.2, 127.8, 127.7, 95.1, 95.0, 94.7, 94.6, 80.3, 79.9, 66.2, 66.1, 65.6, 65.2, 64.9, 63.2, 63.1, 62.7, 61.8, 58.6, 58.2, 58.1, 57.8, 33.7, 32.9, 32.8, 31.0, 29.5, 29.3, 28.8, 28.3, 26.8, 25.0, 24.1, 23.1, 21.6, 19.2. ^1H NMR (400 MHz, DMSO, 140 °C): δ 7.65 (m, 8 H), 7.44−7.31 (m, 22 H), 5.12 (s, 2 H), 5.08 (s, 2 H), 4.01 (m, 6 H), 3.92 (m, 2 H), 3.79 (m, 1 H), 3.66 (m, 1 H), 2.42−2.15 (m, 8 H), 1.45 (m, 6 H), 1.37 (s, 18 H), 1.08 (s, 9 H), 1.07 (s, 9 H). IR (cm^{-1}): 3070, 2959, 2857, 1738, 1694, 1472, 1367, 1264, 1165, 1084, 1021. HRMS: $[M + Na]^+$ calcd for $C_{36}H_{47}NO_6SiNa$ 640.3070, found 640.3065.

(2*R/S*,4*R*)-2-(2-Benzyloxycarbonylethyl)-4-hydroxymethyl-2-methyloxazolidinone-3-carboxylic Acid *tert*-Butyl Ester, 11. Desilylation: To a solution of oxazolidine silyl ether **10** (2.36 g, 3.83 mmol) in THF (4 mL) was added a 1.0 M solution of TBAF in THF (4.97 mL, 4.97 mmol). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc then poured into water. The organic layer was separated, washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give a yellow oil. The oil was purified by flash column chromatography on silica gel (20% EtOAc/hexane, R_f = 0.10) to give the product as a 1:1 mixture of diastereomers. Yield 1.23 g (85% as a clear oil). **Reduction:** To a solution of oxazolidine aldehyde **12** (217 mg, 0.58 mmol) in anhydrous THF/*i*-PrOH (1:1, 7 mL) at 0 °C was added solid $NaBH_4$ (66 mg, 1.74 mmol). The reaction mixture was stirred for 45 min at 0 °C until TLC had shown the consumption of aldehyde. The cold solution was carefully partitioned between 1 N HCl and EtOAc (4×). The combined organics were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude product (198 mg) as a 1:1 mixture of diastereomers. The alcohol was used without further purification. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 173.0, 154.3, 153.9, 135.9, 128.5, 128.3, 128.2, 95.4, 81.6, 66.3, 65.5, 65.2, 60.4, 59.1, 33.4, 32.8, 29.0, 28.8, 28.3, 24.8, 23.1. ^1H NMR (400 MHz, DMSO, 100 °C): δ 7.34 (m, 10 H), 5.11 (s, 4 H), 4.45 (m, 1 H), 3.91 (m, 4 H), 3.81 (m, 2 H), 3.61 (m, 2 H), 3.32 (m, 2 H), 2.45−2.09 (m, 8 H), 1.43 (s, 24 H). IR (cm^{-1}): 3453, 2976, 2884, 1736, 1697, 1455, 1391, 1257, 1166, 1085. HRMS: $[M + Na]^+$ calcd for $C_{20}H_{29}NO_6Na$ 402.1893, found 402.1899. Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.32; H, 7.65; N, 3.69. Found: C, 62.92; H, 7.93; N, 3.89.

(2*R/S*,4*S*)-2-(2-Benzyloxycarbonylethyl)-4-formyl-2-methyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester, 12. To a solution of oxalyl chloride (700 μL, 8.02 mmol) in anhydrous CH_2Cl_2 (4 mL) at −78 °C was added dropwise DMSO (680 μL, 9.58 mmol). The mixture was stirred for 5 min at −78 °C and a solution of oxazolidine alcohol **11** (2.55 g, 6.72 mmol) in anhydrous CH_2Cl_2 (4 mL) at −78 °C was added by cannulation. The solution was stirred for 30 min at −78 °C and Et_3N (4.60 mL, 33.0 mmol) was added. After being allowed to warm to room temperature (∼15 min) the mixture was diluted with EtOAc and poured into water; the organic layer was separated and washed with water, 10% citric acid solution (2 ×), saturated $NaHCO_3$ solution (2 ×), and brine (2 ×), dried with Na_2SO_4, and concentrated in vacuo to yield a yellow oil.

The oil was purified by flash column chromatography on silica gel (20% EtOAc/hexane, $R_f = 0.51$) to yield the product as a 1:1 mixture of diastereomers. Yield 2.22 g (90% as a clear oil). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 199.3, 174.0, 173.9, 153.6, 152.4, 152.2, 137.0, 136.6, 130.6, 129.6, 129.4, 129.3, 128.7, 97.4, 97.2, 96.5, 82.9, 82.6, 82.5, 67.5, 67.4, 67.3, 65.9, 65.4, 65.2, 65.1, 64.8, 64.5, 34.6, 33.8, 33.7, 32.7, 30.2, 30.0, 29.8, 29.3, 25.6, 25.0, 24.7, 23.2. ^{1}H NMR (400 MHz, DMSO, 140 °C): δ 9.57 (d, 1 H, $J = 1.9$ Hz), 9.54 (d, 1 H, $J = 2.3$ Hz), 7.35 (m, 10 H), 5.12 (s, 2 H), 5.11 (s, 2 H), 4.36 (m, 2 H), 4.11 (m, 2 H), 4.03 (dd, 1 H, $J = 9.4$, 3.6 Hz), 3.96 (dd, 1 H, $J = 9.3$, 4.9 Hz), 2.44−2.19 (m, 8 H), 1.53 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 9 H), 1.44 (s, 9 H). IR (cm^{-1}): 2977, 2934, 1736, 1707, 1455, 1390, 1256, 1167, 1084. HRMS: $[M + Na]^+$ calcd for $C_{20}H_{27}NO_6Na$ 400.1736, found 400.1754. Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.66; H, 7.16; N, 3.71. Found: C, 63.32; H, 7.21; N, 3.81.

(2*R/S*,4*R*)-2-(2-Carboxyethyl)-4-hydroxymethyl-2-methyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester, 5. To a round-bottomed flask containing 10% Pd-C (23.3 mg, approximately 10% w/w) under argon was added anhydrous methanol (1 mL) followed by a solution of benzyl ester **11** (102 mg, 0.26 mmol) in methanol (1 mL). The flask was purged twice with hydrogen, then stirred vigorously under 1 atm of hydrogen (balloon) at room temperature. After 4 h, when all of the starting material had been consumed as judged by TLC, the mixture was filtered through a short pad of Celite and the filtrate concentrated in vacuo to give the crude product as a clear oil (70 mg) in a 1:1 mixture of diastereomers. An analytical sample was obtained after purification by flash column chromatography on silica gel (25% hexane/EtOAc, $R_f = 0.29$). ^{13}C NMR (100 MHz, DMSO): δ 175.2, 152.4, 152.2, 152.1, 95.2, 95.1, 80.4, 80.0, 79.9, 66.4, 66.2, 65.7, 65.4, 61.8, 61.6, 60.9, 59.4, 59.1, 59.0, 58.7, 34.4, 33.8, 33.3, 31.8, 29.9, 29.4, 29.0, 28.9, 26.6, 24.9, 23.8, 22.2, 20.6. ^{1}H NMR (400 MHz, DMSO, 140 °C): δ 3.94 (m, 4 H), 3.86 (m, 2 H), 3.66 (m, 2 H), 3.41 (dd, 1 H, $J = 10.7$, 8.1 Hz), 3.35 (dd, 1 H, $J = 10.2$, 8.5 Hz), 2.30−2.11 (m, 8 H), 1.46 (s, 21 H), 1.43 (s, 3 H) [at room temperature 11.7 (br, 1 H) and 4.87 (br, 1 H) disappear upon heating or with a D_2O shake]. IR (cm^{-1}): 3196, 2978, 2676, 1694, 1393, 1255, 1167, 1086. HRMS: $[M + Na]^+$ calcd for $C_{13}H_{23}NO_6Na$ 312.1423, found 312.1424.

(2*R/S*,4*S*)-2-(2-Carboxy-ethyl)-4-formyl-2-methyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester, 4. Hydrogenolysis: To a round-bottomed flask containing 10% Pd-C (200 mg, approximately 10% w/w) under argon was added anhydrous methanol (1 mL) followed by a solution of benzyl ester **12** (1.904 g, 5.0 mmol) in methanol (4 mL). The flask was purged twice with hydrogen, then stirred vigorously under 1 atm of hydrogen (balloon) at room temperature. After 4 h, all of the starting material had been consumed as judged by TLC. The mixture was filtered through a short pad of Celite and the filtrate concentrated in vacuo to give the crude product as a clear oil (1.353 g) in a 1:1 mixture of diastereomers. An analytical sample was obtained after purification by flash column chromatography on silica gel (33% EtOAc/hexane, $R_f = 0.24$). **Oxidation:** To a solution of oxalyl chloride (18.6 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (1 mL) at −78 °C was added dropwise DMSO (22.0 μL, 0.31 mmol). The mixture was stirred for 5 min at −78 °C and a solution of oxazolidine alcohol **5** (44.7 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (1 mL) at −78 °C was added by cannulation. The solution was stirred for 30 min at −78 °C and Et_3N (87 μL, 0.62 mmol) was added. After being allowed to warm to room temperature (∼15 min) the mixture was poured into water and the organic layer was separated and washed with 10% citric acid solution and brine, dried with Na_2SO_4, and concentrated in vacuo to yield a yellow oil. The oil was purified as before. Yield 45.7 mg (100% as a clear oil). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 198.2, 179.1, 152.6, 152.3, 151.4, 151.1, 96.2, 96.0, 95.4, 82.0, 81.6, 64.8, 64.2, 63.9, 63.7, 63.4, 33.3, 32.6, 32.4, 31.5, 28.9, 28.6, 28.2, 24.5, 23.6, 23.2, 22.1. ^{1}H NMR (400 MHz, DMSO, 140 °C): δ 9.58 (d, 1 H, $J = 1.9$ Hz), 9.54 (d, 1 H, $J = 2.3$ Hz), 4.35 (m, 2 H), 4.13 (m, 2 H), 4.06 (dd, 1 H, $J = 9.4$, 3.7 Hz), 3.97 (dd, 1 H, $J = 9.3$, 4.9 Hz), 2.35−2.15 (m, 8 H), 1.54 (s, 3 H), 1.48 (s, 3 H), 1.46 (s, 9 H), 1.45 (s, 9 H) [at room temperature 12.0 (br, 1 H) disappears upon heating or with a D_2O shake]. IR (cm^{-1}): 3409, 2978, 1709, 1393, 1167, 1088. HRMS: $[M + Na]^+$ calcd for $C_{13}H_{21}NO_6Na$ 310.1267, found 310.1255.

Mosher Ester 15. To a solution of oxazolidine alcohol **11** (180 mg, 0.47 mmol), DCC (113 mg, 0.55 mmol), and DMAP (13.8 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (2 mL) was added a solution of (+)-(*R*)-MTPA (121 mg, 0.52 mmol) in anhydrous CH_2Cl_2 (0.65 mL). The mixture was stirred at room temperature for 18 h. The resulting white suspension was filtered and the filtrate concentrated in vacuo to give a clear oil to which diethyl ether (4 mL) was added. The resulting suspension was filtered and the filtrate concentrated in vacuo to give a clear oil. The oil was purified by flash column chromatography on silica gel (15% EtOAc/hexane, $R_f = 0.48$) to give the product as a 1:1 mixture of diastereomers. Yield 153 mg (55% as a clear oil). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 172.7, 165.9, 165.8, 151.9, 151.6, 151.3, 151.1, 135.8, 131.8, 131.7, 129.5, 128.3, 128.1, 128.0, 127.3, 127.0, 126.7, 124.5, 121.6, 118.7, 95.2, 95.1, 94.8, 84.9, 84.6, 84.3, 84.1, 81.0, 80.9, 80.6, 66.0, 65.4, 65.0, 64.5, 64.2, 64.0, 63.5, 55.2, 54.9, 54.7, 54.6, 33.4, 32.6, 32.3, 30.7, 29.2, 29.0, 28.6, 28.0, 24.4, 23.6, 22.6, 21.3. ^{1}H NMR (400 MHz, DMSO, 140 °C): δ 7.46 (m, 10 H), 7.35 (m, 10 H), 5.11 (m, 4 H), 4.55 (m, 2 H), 4.40 (dd, 1 H, $J =$ 10.9, 6.9 Hz), 4.24 (dd, 1 H, $J = 10.6$, 8.0 Hz), 4.09, (m, 2 H), 3.96 (m, 2 H), 3.71 (m, 2 H), 3.50 (s, 6 H), 2.42−2.19 (m, 8 H), 1.46 (s, 18 H), 1.43 (s, 3 H), 1.39 (s, 3 H). ^{19}F NMR (400 MHz, $CDCl_3$, with reference to CDF_3): δ −71.75, −71.95. IR (cm^{-1}): 2978, 2934, 1752, 1696, 1454, 1384, 1257, 1168, 1021. HRMS: $[M + Na]^+$ calcd for $C_{30}H_{36}NO_8F_3Na$ 618.2291, found 618.2277. Anal. Calcd for $C_{30}H_{36}NO_8F_3$: C, 60.49; H, 6.10; N, 2.35. Found: C, 60.23; H, 6.11; N, 2.42.

Mosher Ester 17. 17 was prepared in an identical manner to **15** with *ent*-**11**. *ent*-**11** was prepared from *ent*-**9** in an identical manner to **11**. Yield 55% as a clear oil in a 1:1 mixture of diastereomers. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 172.8, 166.1, 166.0, 152.1, 151.8, 151.4, 151.2, 135.9, 132.0, 129.6, 128.4, 128.2, 127.2, 124.6, 121.7, 118.9, 95.3, 95.2, 94.9, 85.0, 84.7, 84.4, 84.2, 81.3, 81.1, 80.7, 66.2, 65.7, 65.4, 65.3, 65.0, 64.8, 64.5, 64.4, 64.0, 55.3, 55.1, 55.0, 33.6, 32.7, 32.2, 30.7, 29.4, 29.3, 28.7, 28.2, 24.6, 23.7, 22.7, 21.4. ^{1}H NMR (400 MHz, DMSO, 140 °C): δ 7.47 (m, 10 H), 7.35 (m, 10 H), 5.12 (m, 4 H), 4.55 (m, 2 H), 4.40 (dd, 1 H, $J = 10.9$, 6.9 Hz), 4.25 (dd, 1 H, $J = 10.6$, 8.1 Hz), 4.10 (m, 2 H), 3.98 (m, 2 H), 3.70 (m, 2 H), 3.50 (m, 6 H), 2.40−2.18 (m, 8 H), 1.45 (s, 18 H), 1.43 (s, 3 H), 1.39 (s, 3 H). ^{19}F NMR (400 MHz, $CDCl_3$, with reference to CDF_3): δ −71.82. IR (cm^{-1}): 2932, 1746, 1695, 1454, 1384, 1257, 1165, 1084, 1022. HRMS: $[M + Na]^+$ calcd for $C_{30}H_{36}NO_8F_3Na$ 618.2291, found 618.2298. Anal. Calcd for $C_{30}H_{36}NO_8F_3$: C, 60.49; H, 6.10; N, 2.35. Found: C, 60.52; H, 6.20; N, 2.49.

Oxazolidine Aldehyde 3. From 4: to amino-methylated Merrifield resin (0.75 mmol g^{-1}, 200 mg, 0.15 mmol) preswollen in CH_2Cl_2 was added a solution of crude oxazolidine acid **4** (130 mg, 0.45 mmol), HOBt (72 mg, 0.47 mmol), and DIC (72 μL, 0.46 mmol) in anhydrous CH_2Cl_2/DMF (1:1, mL). The mixture was shaken for 18 h at room temperature. The resin was drained, washed with CH_2Cl_2 (3×), MeOH (3×), DMF (3×), MeOH (3×), and CH_2Cl_2 (3×), and then dried in vacuo. **From 14:** To alcohol **14** (0.64 mmol g^{-1}, 200 mg, 0.13 mmol) preswollen in CH_2Cl_2 was added Et_3N (110 μL, 0.79 mmol) in CH_2Cl_2 (2.5 mL) followed by a solution of Py·SO_3 (125 mg, 0.79 mmol) in DMSO (3 mL). The resin was stirred for 12 h at room temperature. The resin was drained, washed with 10% citric acid solution/THF (1:1, 3×), THF (3×), MeOH (3×), and CH_2Cl_2 (3×), and then dried in vacuo. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 198.8, 198.5, 171.8, 95.8, 95.2, 82.0, 81.3, 64.9, 64.3, 63.8, 63.5, 34.0, 33.4, 32.2, 31.0, 28.3, 28.0, 24.6, 23.6, 23.3, 22.3. IR (cm^{-1}, CH_2Cl_2 gel): 3437, 1790, 1673.

Hydrazone 13. A sample of resin **3** (0.64 mmol g^{-1}, 26.3 mg, 33.6 μmol) was refluxed with 2,4-dinitrophenylhydrazine (21.5 mg, 0.11 mmol) in anhydrous MeOH/THF (3 mL, 1:4) for 8 h. The resin was drained, washed with THF/H_2O (1:1, 3×), THF (3×), and CH_2Cl_2 (3×), then dried in vacuo. Anal. Calcd: N, 4.79. Found: N, 4.92.

Oxazolidine Alcohol 14. From 5: To amino-methylated Merrifield resin (0.75 mmol g^{-1}, 200 mg, 0.15 mmol) preswollen in CH_2Cl_2 was added a solution of crude oxazolidine alcohol **5** (130 mg, 0.45 mmol), HOBt (72 mg, 0.47 mmol), and DIC (72 μL, 0.46 mmol) in anhydrous CH_2Cl_2/DMF (1:1, 2.5 mL). The mixture was shaken for 18 h at room temperature. The resin was drained, washed with CH_2Cl_2 (3×), MeOH (3×), DMF (3×), MeOH (3×), and CH_2Cl_2 (3×), and then dried in vacuo. The Kaiser test was negative. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 172.2, 95.6, 81.6, 65.1, 62.9, 60.3, 58.4, 34.1, 33.3, 30.9, 28.3, 28.2, 25.0, 24.1, 23.3, 21.9. IR (cm^{-1}, CH_2Cl_2 gel): 3435, 1667.

***β*-Lactam 19.** To polymer-supported aldehyde **3** (0.64 mmol g^{-1}, 200 mg, 0.13 mmol) preswollen in CH_2Cl_2 was added 4 Å MS and benzylamine (85 μL, 0.77 mmol) in anhydrous CH_2Cl_2 (3 mL). The resin was shaken for 30 min then drained. The resin was then shaken for a further 2 × 30 min with benzylamine (2 × 85 μL) in CH_2Cl_2 (2 × 3 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 anhydrous CH_2Cl_2 (3 mL) and the mixture was cooled to 0 °C. Et_3N (200 μL, 1.43 mmol) was added followed by the dropwise addition of phenoxyacetyl chloride (100 μL, 0.72 mmol). The resin was agitated for 30 min at 0 °C, then allowed to warm to room temperature and shaken for 18 h. The resin was drained, washed with CH_2Cl_2 (3×), THF/sat $NaHCO_3$ (1:1, 3×), THF/H_2O (1:1, 3×), THF (3×), and CH_2Cl_2 (3×), and dried in vacuo. ^{13}C gel-phase NMR (100 MHz, CH_2Cl_2): δ 171.5, 166.2, 157.4, 129.6, 122.7, 116.0, 96.4, 81.3, 80.6, 80.4, 66.3, 65.9, 58.2, 57.9, 34.4, 31.4, 30.9, 30.4, 25.4, 24.7, 23.3. IR (cm^{-1}, CH_2Cl_2 gel): 3435, 1757, 1692. Anal. Calcd: N, 2.35. Found: N, 2.56.

***β*-Lactam 18. From 20:** To β-lactam **20** (52 mg, 87 μmol) was added 10% TFA/CH_2Cl_2 (200 μL). The solution was shaken for 1 h then partitioned between EtOAc and water. The aqueous layer was separated and washed with EtOAc (2×), taken to pH 10 with 0.1 M NaOH, and extracted into EtOAc (2×). The combined organics were concentrated in vacuo to give a white residue. Yield 18 mg (66%). A sample for optical rotation was obtained after partitioning the product between water and EtOAc. The aqueous layer was reduced in vacuo (freeze-dried) to give the β-lactam as the TFA salt: $[\alpha]_D$ −25 (*c* 1.0, CH_2Cl_2) [lit.[8c] $[\alpha]_D$ −26 (*c* 1.0, MeOH) for TFA salt]. **From 19:** To β-lactam **19** (0.54 mmol g^{-1}, 100 mg, 54 μmol) was added 10% TFA/CH_2Cl_2 (2 mL). The resin was shaken for 1 h, drained, and washed with CH_2Cl_2. The filtrate was concentrated in vacuo, then partitioned between EtOAc and water. The aqueous layer was washed with EtOAc (2×), taken to pH 10 with 0.1 M NaOH, and extracted into EtOAc (2×). The combined organics were concentrated in vacuo to give a white residue. Yield 13 mg (75%). A sample for optical rotation was obtained as above: $[\alpha]_D$ −25 (*c* 0.4, CH_2Cl_2 for TFA salt). ^{13}C NMR (100 MHz, MeOD): δ 167.7, 157.5, 135.8, 129.4, 128.6, 128.0, 127.6, 122.2, 115.3, 80.1, 63.3, 59.4, 51.8, 45.5. ^{1}H NMR (400 MHz, MeOD): δ 7.38−7.29 (m, 7 H), 7.09 (dd, 2 H, J = 7.7, 0.9 Hz), 7.02 (app t, 1 H, J = 7.4 Hz), 5.44 (d, 1 H, J = 5.0 Hz), 4.75 (d, 1 H, J = 15.2 Hz), 4.45 (d, 1 H, J = 15.2 Hz), 4.03 (dd, 1 H, J = 5.0, 3.7 Hz) 3.55 (dd, 1 H, J = 10.8, 5.0 Hz), 3.51 (dd, 1 H, J = 10.8, 5.7 Hz), 3.13 (app dd, 1 H, J = 5.4, 3.7 Hz). IR (cm^{-1}): 3756, 3690, 3051, 2987, 1768, 1674, 1419, 1272. HRMS: $[M + Na]^+$ calcd for $C_{18}H_{21}N_2O_3$ 313.1552, found 313.1553.

***β*-Lactam 20.** To a solution of aldehyde **12** (370 mg, 0.98 mmol) in anhydrous CH_2Cl_2 (3 mL) with 4 Å MS was added benzylamine (115 μL, 1.20 mmol). The reaction mixture was stirred for 1 h at room temperature then cooled to 0 °C and Et_3N (630 μL, 4.56 mmol) added followed by dropwise addition of phenoxyacetyl chloride (250 μL, 1.84 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo to yield a clear oil. The oil was purified by flash column chromatography on silica gel (20% EtOAc/hexane, R_f = 0.30) to yield the product as a mixture of diastereomers. Yield: 302 mg (52%, as a clear oil). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 166.6, 157.5, 153.4, 152.7, 136.0, 135.9, 135.4, 129.6, 129.0, 128.6, 128.4, 128.3, 128.2, 128.0, 122.5, 116.0, 116.0, 115.9, 96.1, 95.5, 81.4, 80.5, 66.4, 66.1, 65.9, 58.6, 58.0, 57.9, 44.9, 34.3, 32.1, 30.4, 29.7, 28.5, 25.2, 24.4, 23.1. ^{1}H NMR (400 MHz, DMSO, 140 °C): δ 7.33 (m, 20 H), 7.23 (m, 4 H), 7.13 (m, 4 H), 7.04 (m, 2 H), 5.52 (d, 1 H, J = 5.1 Hz), 5.48 (d, 1 H, J = 5.5 Hz), 5.09 (d, 2 H, J = 10.2 Hz), 5.04 (d, 2 H, 12.6), 4.80 (d, 2 H, J = 15.5 Hz), 4.48 (m, 2 H), 4.02 (m, 4 H), 3.93 (dd, 1 H, J = 9.6, 5.1 Hz), 3.89 (dd, 1 H, J = 9.4, 6.1 Hz), 3.66 (m, 2 H), 2.39−2.03 (m, 8 H), 1.53 (s, 12 H), 1.52 (s, 9 H), 1.49 (s, 3 H). IR (cm^{-1}): 2927, 1755, 1688, 1597, 1494, 1380, 1239, 1162, 1089. HRMS: $[M + Na]^+$ calcd for $C_{35}H_{40}N_2O_7Na$ 623.2733, found 623.2736.

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Supporting Information Available: NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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