Synthesis of Oxazolidinones by a Solid-Phase/Activation Cycloelimination (SP/ACE) Methodology

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A versatile method for the solid-phase synthesis of oxazolidinones is described. An appropriate 1,2-diol is attached to immobilized sulfonyl chloride, resulting in the selective activation of one of the alcohol functions. The subsequent reaction of the other alcohol group with an isocyanate, followed by a base-promoted cycloelimination gives an oxazolidinone. By proper choice of isocyanates, functionalities can be introduced which are essential for antibiotic activity.

Introduction

Oxazolidinones are synthetic antibacterials that exhibit activity against many antibiotic-resistant strains of Gram-positive bacteria.[1] They represent the only completely new class of antibiotics licensed over the past 30 years.[2] Structure-activity relationship (SAR) studies have revealed the most important features that are responsible for their biological activity, as summarized in Figure 1.[3]

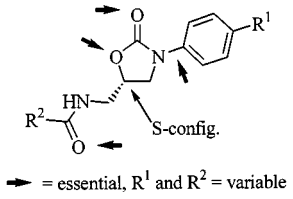

Figure 1. Structural entities that are essential and those that are variable for biological activity

Despite the considerable synthetic attention given to these 3,5-disubstituted 1,3-oxazolidin-2-ones during the last decade, the vast majority of reported synthetic routes are still performed in solution.[4] This information encouraged us to develop a novel solid-phase synthetic route leading to oxazolidinones which possess the general structure that is necessary for antibiotic activity (as in Figure 1). We report here on the synthesis of oxazolidinones by a solid-phase/activation cycloelimination (SP/ACE) process, which makes use of an S_N2-type cyclization/cleavage (C/C) strategy. SP/ACE enables the preparation of oxazolidinones by attaching a 1,2-diol to immobilized sulfonyl chloride, followed by reaction with isocyanate, and subsequent base-promoted cycloelimination with concurrent detachment from the resin (Scheme 1). Our approach enables the efficient introduction of defined chirality at C-5 by employing a D-mannitol-derived enantiomerically pure 1,2-diol.

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Results and Discussion

SP/ACE: The Concept

To investigate the scope of this solid-phase/activation cycloelimination principle, a set of three commercially available 1,2-diols (**2a**−**c**) were attached to the polymer-bound sulfonyl chloride **1**[5,6] in a parallel fashion (Scheme 1), giving the polymer-bound sulfonates **3a**−**c**. In this manner, a selective activation of the primary alcohol was attained, leaving the secondary alcohol function untouched. The subsequent reaction of the secondary alcohol group with *p*-toluenesulfonyl isocyanate gave the highly activated carbamates **4a**−**c**, which appeared to be especially susceptible to base-promoted cycloelimination. This nucleophilic cyclocleavage is exceptional, as it proceeds by direct S_N2 substitution,[7] in contrast to the extensively studied nucleophilic removal by means of an S_{AE}-type reaction.[8] The cycloelimination was accomplished with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as the base and gave the oxazolidinones **5a**−**c** in an overall yield of 39−43%.[9]

Along with the target compounds **5a** and **5b**, the formation of a minor amount (<1%) of the corresponding 3,4-disubstituted oxazolidinones was observed. These regioisomers, however, were readily removed by recrystallization of the products. Despite the ambident nucleophilic character of the polymer-bound carbamates **4**, *O*-alkylation was only observed during the cycloelimination of **4c**, giving the corresponding cyclic carbonate by-product **9** (about 25%). This alternative mode of cyclization/cleavage can most likely be attributed to steric factors (R^1 = *t*Bu).

Synthesis of the Target Oxazolidinones

The oxazolidinones **5d**−**g** were synthesized by employing the 1,2-diol **2d** in the SP/ACE procedure (Scheme 1). Diol **2d** was prepared from commercially available solketal according to the literature.[10−12] Tosylation of the alcohol group, followed by substitution with azide, and subsequent deprotection, afforded **2d** in good overall yield (68%). The

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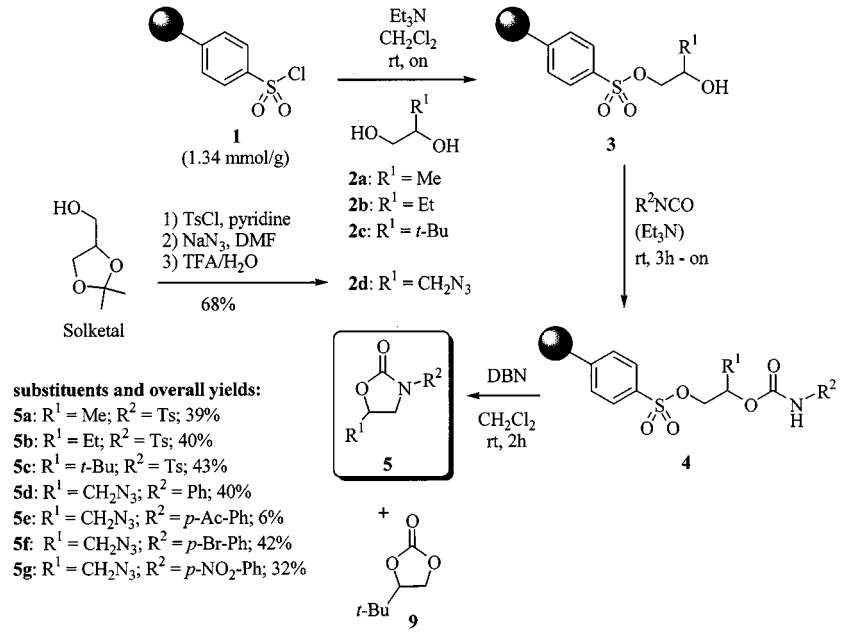
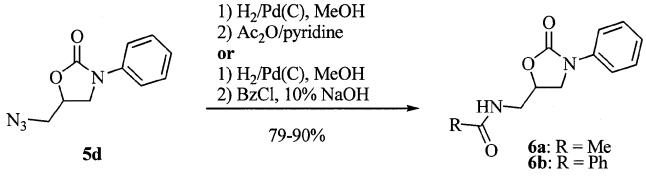


Scheme 1. Synthesis of substituted oxazolidinones by SP/ACE

coupling of diol **2d** to the immobilized arenesulfonyl chloride **1** was accomplished with triethylamine in dichloromethane. The remaining secondary alcohol was then reacted with a series of *N*-aryl isocyanates, giving the polymer-bound *N*-aryl carbamates **4d**−**g**. The lower reactivity of aryl isocyanates compared to the aforementioned tosyl isocyanate necessitated the use of triethylamine (0.1−1 equiv.) to allow the reaction to occur. The carbamates prepared in this manner were then treated with DBN (2 equiv.) in dichloromethane. Cyclization to oxazolidinones **5d**−**g** occurred in spite of the less-activated N−H bond of the *N*-aryl carbamate. The observed overall yield of **5e** (R = *p*-Ac-Ph) was disappointingly low (6%), which is most likely due to the poor solubility of the isocyanate. However, the yield of the cycloeliminated compounds **5d**, **5f** and **5g** was more satisfactory (32−42%). The purity of the detached material was in all cases high (>85% by GC analysis).

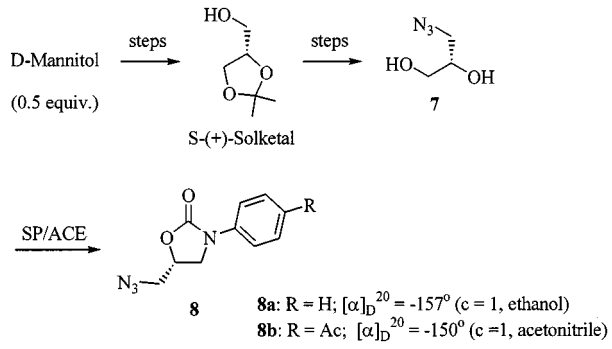
The thus acquired *N*-aryl-5-azidomethyl oxazolidinones **5d**−**g** were expected to be suitable for conversion into the corresponding *N*-aryl-5-amidomethyl oxazolidinones (as in Figure 1) by successive reduction and acylation of the azide group. For this reason, *N*-phenyl-5-azidomethyl oxazolidinone **5d** was subjected to catalytic hydrogenation [H_2/Pd(C)] and subsequent acetylation (Ac_2O/pyridine) giving **6a** (Scheme 2). These steps proceeded smoothly in good overall yield (90%). Additionally, a sample of **5d** was hydrogenated and subsequently converted into the benzamidomethyl-substituted oxazolidinone **6b** under Schotten−Baumann conditions (80% overall; Scheme 2) showing that variation in the amidomethyl moiety can be readily attained.



Scheme 2. Conversion of the azidomethyl moiety into amidomethyl substituents

Enantiopure Oxazolidinones

Since compound **5d** appeared to be an excellent candidate to be converted into the amidomethyl-substituted oxazolidinones **6**, we decided to prepare *N*-aryl-5-azidomethyl oxazolidinones with the correct and unambiguous stereochemistry (*R*-configuration) at C-5. The desired stereogenicity can be introduced in the target oxazolidinones by employing the optically pure 1,2-diol **7** (Scheme 3). Diol **7** was prepared from *S*-(+)-solketal, analogous to the synthesis of racemic diol **2d**.[10−12] *S*-(+)-Solketal can be prepared by successive protection, oxidative cleavage ($NaIO_4$) and subsequent reduction ($NaBH_4$) of D-mannitol as has been reported previously.[13−15] The optical rotation of the oxazolidinones **8a** {$[\alpha]_D^{20} = -157$ (c = 1, ethanol)} and **8b** {$[\alpha]_D^{20} = -150$ (c = 1, acetonitrile)} was found to be in



Scheme 3. Synthesis of enantiopure oxazolidinones by SP/ACE

good agreement with the values reported in the literature.[16] Chiral HPLC of **8a** (Chiralcel OD, 2-propanol/hexane, 20:80) and **8b** (Chiralpak AD, 2-propanol/hexane, 30:70), demonstrated that only one enantiomer was present in the sample, as was proved by simultaneous runs of these samples with the corresponding racemates **5d** and **5e**, which showed complete separation under these conditions.

Conclusion

The present study describes a convenient solid-phase method for the preparation of 3,5-disubstituted oxazolidin-2-ones employing the SP/ACE methodology. The synthesis of the target compounds by SP/ACE is accomplished with high purity and in good overall yields. Enantiopure products are easily attained by using *S*-(+)-solketal as starting material.

Experimental Section

General: Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin−Elmer automatic polarimeter, model 241 MC, using concentrations *c* in g/100 mL at 20 °C in the solvents indicated. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX-500, a Bruker AM-400, or a Bruker AC-300 spectrometer in $CDCl_3$. The chemical shift δ is denoted in ppm relative to the internal standard (TMS for ^{1}H NMR, $CDCl_3$ for ^{13}C NMR). FTIR spectra were recorded on an ATI Mattson − Genesis Series FTIR spectrophotometer. The wavenumbers are listed in cm^{-1}. For high-resolution mass spectra a double focussing VG7070E mass spectrometer was used. Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Polymer loading values, that were used as a starting point for following reactions, were established assuming quantitative preceding reactions. The overall yields of detached products were calculated according to the theoretical value, based on the loading of the original PS-TsCl (1.34 mmol/g). For this purpose, the amount of resin obtained was weighed after each reaction step and a known part of this amount of product was then set up for the successive reaction. These values, together with the amounts of detached product, allow the calculation of the correct overall yields.

Polymer-Bound Alcohols 3a−g. − General Procedure: Dichloromethane (5 mL), the 1,2-diol (3.35 mmol) and Et_3N (0.37 mL, 2.68 mmol) were added to the polymer-bound sulfonyl chloride **1** (1.00 g, 1.34 mmol), and the mixture was allowed to stir overnight room temperature. The resin was filtered and washed with dichloromethane (50 mL, 3×), methanol (50 mL, 3×), and dichloromethane (50 mL, 3×), and dried in vacuo for 6 h to give **3a−g**. − FTIR (KBr): $\tilde{\nu}$ = 3410 (OH), 2910 (C−H stretch), 1590 (arom.), 1365 ($-SO_2-$), 1171 ($-SO_2-$).

Polymer-Bound Carbamates 4a−c. − General Procedure: Resin **3a−c** (1.15 mmol) was treated with tosyl isocyanate (0.35 mL, 2.30 mmol) for 3 h at room temperature in dichloromethane (5 mL). The resin was filtered off, washed with methanol (50 mL, 5×), dichloromethane (50 mL, 3×), methanol (50 mL, 5×) and dichloromethane (50 mL, 3×) and dried in vacuo for 6 h to afford carbamates **4a−c**. − FTIR (KBr): $\tilde{\nu}$ = 3300 (NH, broad), 2910 (C−H stretch), 1740 (carbamate, linear), 1595 (arom.), 1365 ($-SO_2-$), 1175 ($-SO_2-$).

Polymer-Bound Carbamates 4d−g. − General Procedure: Resin **3d−g** (1.15 mmol) was treated with *p*-R-phenyl isocyanate (R = H, Ac, Br, NO_2; 3.45 mmol) and triethylamine (0.02 mL, 0.14 mmol) overnight at room temperature in dichloromethane (5 mL). The resin was filtered off, washed with dimethyl sulfoxide (dimethyl formamide in the case of R = Ac; 50 mL, 3×), water (50 mL, 3×), methanol (50 mL, 3×), and dichloromethane (50 mL, 3×) and dried in vacuo for 6 h to afford carbamates **4d−g**. − FTIR (KBr): $\tilde{\nu}$ = 3300 (NH, broad), 2915 (C−H stretch), 2100 (N_3) 1700 (carbamate, linear), 1680 (C=O for R = Ac) 1590 (arom.), 1365 ($-SO_2-$), 1175 ($-SO_2-$).

Cycloelimination to 3,5-Disubstituted 1,3-Oxazolidin-2-ones 5a−g. − General Procedure: A sample of **4a−g** (1.00 mmol) was suspended in dichloromethane (5 mL) and DBN (0.14 mL, 1.13 mmol) was added. The mixture was stirred at room temperature for 2 h and the resin was filtered, washed with dichloromethane (50 mL, 3×), methanol (50 mL, 3×), dichloromethane (50 mL, 3×), and methanol (50 mL, 3×). The filtrate was concentrated under reduced pressure, and filtered through a short plug of silica gel (ethyl acetate/heptane, 1:1). Evaporation of the solvent gave oxazolidinones **5a−f** as a white solid and **5g** as a slightly yellow solid. Crystallization of the product (**5a−c**: ethyl acetate/hexane, **5d−g**: ethanol/hexane) gave pure **5a−f** as colorless crystals and **5g** as slightly yellow crystals. The polymer-supported sulfonyl chloride starting material **1** could be regenerated by treatment of the remaining polymer with 1 N sulfuric acid, followed by reaction with thionyl chloride (3 equiv.) in DMF.[4b]

5-Methyl-3-tosyl-1,3-oxazolidin-2-one (5a): Yield 112 mg (0.44 mmol, 39% overall) white solid. Colorless crystals from ethyl acetate/hexane; m.p. 144−145 °C. − ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.42 (d, *J* = 6.3 Hz, 3 H), 2.46 (s, 3 H), 3.57 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{BX} = 7.1 Hz, 1 H), 4.14 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{AX} = 7.8 Hz, 1 H), 4.69 (m, part of ABX, 1 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.93 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.78, 21.62, 50.91, 71.18, 128.15, 129.84, 133.82, 145.67, 151.61. − MS (CI): *m*/*z* = 256 (14) [M^+ + 1], 191 (34) [$M^+ - SO_2$], 155 (13) [$C_7H_7SO_2$], 91 (100) [C_7H_7]. − $C_{11}H_{13}NO_4S$ (255.29): calcd. C 51.75, H 5.13, N 5.49; found C 51.75, H 4.97, N 5.55.

5-Ethyl-3-tosyl-1,3-oxazolidin-2-one (5b): Yield 122 mg (0.45 mmol, 40% overall) white solid. Colorless crystals from ethyl acetate/hexane; m.p. 116−118 °C. − ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (t, *J* = 7.4 Hz, 3 H), 1.72 (m, 2 H), 2.45 (s, 3 H), 3.62 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{BX} = 7.1 Hz, 1 H), 4.12 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{AX} = 8.0 Hz, 1 H), 4.49 (m, part of ABX, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 8.33, 21.52, 27.11, 49.09, 75.56, 127.99, 129.75, 133.79, 145.59, 151.60. − MS (CI): *m*/*z* = 270 (9) [M^+ + 1], 205 (21) [$M^+ - SO_2$], 155 (28) [$C_7H_7SO_2$], 91 (100) [C_7H_7]. − $C_{12}H_{15}NO_4S$ (269.31): calcd. C 53.52, H 5.61, N 5.20; found C 53.14, H 5.59, N 4.92.

5-*tert*-Butyl-3-tosyl-1,3-oxazolidin-2-one (5c): Yield 126 mg (0.49 mmol, consisting of both **5c** (75%) and cyclic carbonate (25%), 43% overall) white solid. Colorless crystals of **5c** from ethyl acetate/hexane; m.p. 121−122 °C. − ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.89 (s, 9 H), 2.45 (s, 3 H), 3.75 (dd, part of ABX, J_{AB} = 9.4 Hz, J_{BX} = 7.5 Hz, 1 H), 3.98 (dd, part of ABX, J_{AB} = 9.4 Hz, J_{AX} = 8.6 Hz, 1 H), 4.22 (dd, part of ABX, J_{AX} = 8.6 Hz, J_{BX} = 7.5 Hz, 1 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H). − ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.63, 24.00, 33.64, 45.42, 81.13, 128.02, 129.81, 134.04, 145.63, 151.73. − MS (CI): *m*/*z* =

298 (43) [$M^+ + 1$], 233 (29) [$M^+ - SO_2$], 155 (68) [$C_7H_7SO_2$], 91 (100) [C_7H_7]. – $C_{14}H_{19}NO_4S$ (297.37): calcd. C 56.55, H 6.44, N 4.71; found C 56.78, H 6.58, N 4.73.

5-Azidomethyl-3-phenyl-1,3-oxazolidin-2-one (5d): Yield 94 mg (0.43 mmol, 40% overall) white solid. Colorless crystals from ethanol/hexane; m.p. 82–84 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.60 (dd, part of ABX, J_{AB} = 13.2 Hz, J_{BX} = 4.5 Hz, 1 H), 3.69 (dd, part of ABX, J_{AB} = 13.2 Hz, J_{AX} = 4.7 Hz, 1 H), 3.87 (dd, part of ABX, J_{AB} = 9.0 Hz, J_{BX} = 6.2 Hz, 1 H), 4.10 (t, part of ABX, J_{AB} = J_{AX} = 9.0 Hz, 1 H), 4.78 (m, part of ABX, 1 H), 7.16 (t, J = 7.4 Hz, 1 H), 7.39 (t, J = 8.0 Hz, 2 H), 7.54 (d, J = 8.1 Hz, 1 H). – ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 47.5, 53.1, 70.6, 118.3, 124.4, 129.1, 137.9, 153.9. – MS (CI): m/z = 190 (20) [$M^+ - N_2$], 71 (44) [C_3H_5NO], 43 (100) [C_2H_3O]. – $C_{10}H_{10}N_4O_2$ (218.21): calcd. C 55.04, H 4.62, N 25.68; found C 55.06, H 4.58, N 25.32. Spectroscopic data are in agreement with those reported previously.[16]

3-*p*-Acetylphenyl-5-azidomethyl-1,3-oxazolidin-2-one (5e): Yield 17 mg (0.07 mmol, 6% overall) white solid. Colorless crystals from ethanol/hexane; m.p. 80–81 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.59 (s, 3 H), 3.62 (dd, part of ABX, J_{AB} = 13.3 Hz, J_{BX} = 4.3 Hz, 1 H), 3.74 (dd, part of ABX, J_{AB} = 13.3 Hz, J_{AX} = 4.4 Hz, 1 H), 3.92 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{BX} = 6.2 Hz, 1 H), 4.15 (t, part of ABX, J_{AB} = J_{AX} = 9.1 Hz, 1 H), 4.83 (m, part of ABX, 1 H), 7.65 (d, J = 8.9 Hz, 2 H), 7.98 (d, J = 8.9 Hz, 2 H). – ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.4, 47.1, 52.9, 70.7, 117.3, 129.6, 132.7, 141.9, 153.6, 196.8. – MS (CI): m/z = 232 (15) [$M^+ - N_2$], 71 (47) [C_3H_5NO], 43 (100) [C_2H_3O]. – $C_{12}H_{12}N_4O_3$ (260.25): calcd. C 55.38, H 4.65, N 21.53; found C 55.03, H 4.44, N 21.48. Spectroscopic data are in agreement with those reported previously.[17]

5-Azidomethyl-3-*p*-bromophenyl-1,3-oxazolidin-2-one (5f): Yield 138 mg (0.46 mmol, 42% overall) white solid. Colorless crystals from ethanol/hexane; m.p. 92–93 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.58 (dd, part of ABX, J_{AB} = 13.2 Hz, J_{BX} = 4.38 Hz, 1 H), 3.69 (dd, part of ABX, J_{AB} = 13.2 Hz, J_{AX} = 4.6 Hz, 1 H), 3.84 (dd, part of ABX, J_{AB} = 8.9 Hz, J_{BX} = 6.2 Hz, 1 H), 4.07 (t, part of ABX, J_{AB} = J_{AX} = 8.9 Hz, 1 H), 4.79 (m, part of ABX, 1 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.50 (d, J = 9.0 Hz, 2 H). – ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 47.3, 53.0, 70.6, 117.2, 119.7, 132.1, 137.0, 153.7. – MS (CI): m/z = 268 (17) [$M^+ - N_2$], 71 (51) [C_3H_5NO], 43 (100) [C_2H_3O]. – HRMS (EI): m/z = 295.9905 ($C_{10}H_9BrN_4O_2$ requires 295.9909).[18]

5-Azidomethyl-3-*p*-nitrophenyl-1,3-oxazolidin-2-one (5g): Yield 98 mg (0.37 mmol, 32% overall) slightly yellow solid. Slightly yellow crystals from ethanol/hexane; m.p. 115–116 °C. – ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.65 (dd, part of ABX, J_{AB} = 13.4 Hz, J_{BX} = 4.2 Hz, 1 H), 3.79 (dd, part of ABX, J_{AB} = 13.4 Hz, J_{AX} = 4.2 Hz, 1 H), 3.96 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{BX} = 6.2 Hz, 1 H), 4.19 (dd, part of ABX, J_{AB} = J_{AX} = 9.0 Hz, 1 H), 4.89 (m, part of ABX, 1 H), 7.73 (d, J = 9.3 Hz, 2 H), 8.24 (d, J = 9.3 Hz, 2 H). – ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 47.0, 52.8, 70.8, 117.4, 119.9, 124.9, 125.1, 153.4. – MS (CI): m/z = 235 (18) [$M^+ - N_2$], 71 (37) [C_3H_5NO], 43 (100) [C_2H_3O]. – $C_{10}H_9N_5O_4$ (263.21): calcd. C 45.63, H 3.45, N 26.61; found C 45.79, H 3.42, N 26.55. – HRMS (EI): m/z = 263.0651 ($C_{10}H_9N_5O_4$ requires 263.0655).

5-Acetamidomethyl-3-phenyl-1,3-oxazolidin-2-one (6a): A sample of **5d** (62 mg, 0.28 mmol) was dissolved in methanol (10 mL) and palladium (10% on activated carbon; 12 mg, 0.01 mmol Pd) was added under nitrogen atmosphere. Subsequently, the mixture was shaken under a hydrogen atmosphere (1 h) and filtered through a plug of hyflo. The solvent was removed under reduced pressure giving the primary amine as a colorless oil (99%), which was dissolved in a mixture of pyridine (0.5 mL) and acetic anhydride (0.05 mL, 0.53 mmol), and stirred at room temperature (1 h). Ice (25 mL) and aqueous HCl (36%; 0.6 mL, 6 mmol) were added, and the mixture was extracted with dichloromethane (5× 20 mL). The organic fractions were collected, dried (Na_2SO_4) and concentrated giving 60 mg (90% overall) of **6a** as a white solid. Colorless crystals from ethanol: m.p. 130–131 °C. – ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.01 (s, 3 H), 3.64 (m, 2 H), 3.81 (dd, part of ABX, J_{AB} = 9.2 Hz, J_{BX} = 6.8 Hz, 1 H), 4.06 (dd, part of ABX, J_{AB} = J_{AX} = 9.2 Hz, 1 H), 4.78 (m, 1 H), 6.60 (m, 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 7.37 (t, J = 8.6 Hz, 2 H), 7.50 (d, J = 8.4 Hz, 2 H). – ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 23.0, 41.9, 47.5, 72.0, 118.4, 124.3, 129.1, 137.8, 154.6, 171.2. – MS (CI): m/z = 235 (7) [$M^+ + 1$], 190 (18) [$M^+ - CO_2$], 43 (100) [CH_3CO]. – $C_{12}H_{14}N_2O_3$ (234.25): calcd. C 61.53, H 6.02, N 11.96; found C 61.36, H 5.79, N 11.62. Spectroscopic data are in agreement with those reported previously.[16]

5-Benzamidomethyl-3-phenyl-1,3-oxazolidin-2-one (6b): A sample of **5d** (151 mg, 0.68 mmol) was dissolved in methanol (10 mL) and palladium (10% on activated carbon; 12 mg, 0.01 mmol Pd) was added under nitrogen atmosphere. Subsequently, the mixture was shaken under a hydrogen atmosphere (1 h) and filtered through a plug of hyflo. The solvent was removed under reduced pressure giving the primary amine as a colorless oil (99%). The amine and benzoyl chloride (0.09 mL, 0.77 mmol) were dissolved in 10% aqueous NaOH (8 mL), and the solution was stirred vigorously (15 min.) in a sealed vessel. The white precipitate was filtered off, rinsed with water, and dried in vacuo yielding 162 mg (80%) of **6b** as a white solid. Colorless crystals from ethanol; m.p. 168 °C. – ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 3.80 (ddd, part of ABMX, J_{AB} = 14.7 Hz, J_{BM} = J_{BX} = 6.1 Hz, 1 H), 3.88 (dd, part of ABX, J_{AB} = 9.1 Hz, J_{BX} = 6.7 Hz, 1 H), 3.94 (ddd, part of ABMX, J_{AB} = 14.7 Hz, J_{AM} = 3.4 Hz, J_{AX} = 6.4 Hz, 1 H), 4.11 (dd, part of ABX, J_{AB} = J_{AX} = 9.1 Hz, 1 H), 4.88 (m, 1 H), 6.94 (t, J = 6.4 Hz, 1 H), 7.13 (t, J = 7.5 Hz, 1 H), 7.35 (t, J = 8.0 Hz, 2 H), 7.41 (t, J = 8.0 Hz, 2 H), 7.50 (m, 3 H), 7.78 (d, J = 7.0 Hz, 2 H). – ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 42.5, 47.7, 72.0, 118.4, 124.3, 127.1, 128.6, 129.1, 131.9, 133.5, 137.8, 154.5, 168.3. – MS (CI): m/z = 297 (4) [$M^+ + 1$], 252 (15) [$M^+ - CO_2$], 105 (90) [C_6H_5CO], 77 (100) [C_6H_5]. – $C_{17}H_{16}N_2O_3$ (296.32): calcd. C 68.91, H 5.44, N 9.45; found C 68.55, H 5.16, N 9.07. – HRMS (EI): m/z = 296.1162 ($C_{17}H_{16}N_2O_3$ requires 296.1161).

(*R*)-5-Azidomethyl-3-phenyl-1,3-oxazolidin-2-one (8a): Yield 89 mg (0.41 mmol, 38% overall) white solid. Colorless crystals from ethyl acetate/hexane; m.p. 76–78 °C. – $[\alpha]_D^{20}$ = −157 (c = 1, ethanol). ^{1}H and ^{13}C NMR spectra are identical to those of **5d**. Melting point and spectroscopic data are in agreement with those reported previously.[16]

(*R*)-5-Azidomethyl-3-*p*-acetylphenyl-1,3-oxazolidin-2-one (8b): Yield 16 mg (0.06 mmol, 5% overall) white solid. Colorless crystals from ethyl acetate/hexane; m.p. 79–81 °C. – $[\alpha]_D^{20}$ = −150 (c = 1, acetonitrile). ^{1}H and ^{13}C NMR spectra are identical to those of **5e**. Melting point and spectroscopic data are in agreement with those reported previously.[16,17]

[1] D. L. Shinabarger, K. R. Marotti, R. W. Murray, A. H. Lin, E. P. Melchior, S. M. Swaney, D. S. Dunyak, W. F. Demyan, J. M. Buysse, *Antimicrob. Agents Chemother.* **1997**, *41*, 2132–2136.

[2] *Chem. Eng. News*, May 29, **2000**, p. 12.
[3] A general structure-activity relationship was defined by Brickner: S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, G. E. Zurenko, *J. Med. Chem.* **1996**, *39*, 673−679.
[4] To the best of our knowledge, only two papers on the solid-phase synthesis of 3,5-disubstituted 1,3-oxazolidin-2-ones have appeared in the literature:[4a] H.-P. Buchstaller, *Tetrahedron* **1998**, *54*, 3465−3470. − [4b] A first outline of our methodology was published in a previous communication: P. ten Holte, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.* **1998**, *39*, 7407−7410.
[5] PS-TsCl, 1.34 mmol/g. Purchased from Argonaut Technologies Inc.
[6] For recent reviews on linkers for SPOS, see: [6a] I. W. James, *Tetrahedron* **1999**, *55*, 4855−4946. − [6b] F. Guillier, D. Orain, M. Bradley, *Chem. Rev.* **2000**, *100*, 2091−2157.
[7] Only a few other examples of S_N2-type cyclization/cleavages are known: [7a] T. Takahashi, S. Tomida, H. Inoue, T. Doi, *Synlett* **1998**, 1261−1263. − [7b] M. C. Pirrung, L. N. Tumey, *J. Comb. Chem.* **2000**, *2*, 675−680.
[8] For a recent review on cyclization/cleavage methodologies, see: J. H. van Maarseveen, *Comb. Chem. High Throughput Screening* **1998**, *1*, 185−214.
[9] The average overall yield of 70% reported in the previous communication (ref. 4b) was obtained in a multi-gram scale experiment with Dowex 50X2−400 ion-exchange resin-derived sulfonyl chloride.
[10] E. Baer, H. O. L. Fischer, *J. Am. Chem. Soc.* **1948**, *70*, 609−610.
[11] U. Schmidt, R. Meyer, V. Leitenberger, F. Stäbler, A. Lieberknecht, *Synthesis* **1991**, 409−413.
[12] S. F. Martin, Y.-L. Wong, A. S. Wagman, *J. Org. Chem.* **1994**, *59*, 4821−4831.
[13] C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear, C. S. Vianco, *J. Org. Chem.* **1991**, *56*, 4056−4058.
[14] G. J. F. Chittenden, *Carbohydr. Res.* **1991**, *222*, 283−287.
[15] S. Takano, H. Numata, K. Ogasawara, *Heterocycles* **1982**, *19*, 327−328.
[16] W. A. Gregory, D. R. Brittelli, C.-L. J. Wang, M. A. Wuonola, R. J. McRipley, D. C. Eustice, V. S. Eberly, P. T. Bartholomew, A. M. Slee, M. Forbes, *J. Med. Chem.* **1989**, *32*, 1673−1681. Optical rotations reported: Compound **8a**: $[\alpha]_D^{25} = -160.0 \pm 0.9$ ($c = 0.93$, ethanol); compound **8b**: $[\alpha]_D^{25} = -150.0 \pm 0.9$ ($c = 0.93$, acetonitrile).
[17] C.-L. J. Wang, W. A. Gregory, M. A. Wuonola, *Tetrahedron* **1989**, *45*, 1323−1326.
[18] The 400-MHz ^{1}H NMR and 100-MHz ^{13}C NMR of sample **5f** did not reveal any impurities; nevertheless no reliable elemental analysis of compound **5f** could be obtained.

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