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The Synthesis of *N*-Aryl-5(*S*)-aminomethyl-2-oxazolidinone Antibacterials and Derivatives in One Step from Aryl Carbamates

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Abstract:

Since 1993, a significant process research and development effort directed towards the large-scale synthesis of oxazolidinone antibacterial agents has been ongoing in both Early Chemical Process Research and Development, and Chemical Process Research and Development at Pharmacia. This work has led to the successful development of the current commercial process to produce Zyvox (linezolid), recently approved by the FDA as an antibacterial. While this synthesis is appropriate for the preparation of linezolid in particular, a more convergent and versatile synthesis was developed for the rapid preparation of numerous other oxazolidinone analogues. Toward this end, economical methods for the large-scale preparation of *N*-[(2*S*)-2-(acetyloxy)-3-chloropropyl]acetamide 3 and *tert*-butyl [(2*S*)-3-chloro-2-hydroxypropyl]carbamate 27 from commercially available (*S*)-epichlorohydrin via the common intermediate (2*S*)-1-amino-3-chloro-2-propanol hydrochloride 2a were developed. Also, general methods for coupling these reagents with *N*-aryl carbamates to give *N*-aryl-5(*S*)-aminomethyl-2-oxazolidinone derivatives in one step were developed. These reagents and procedures have proven widely applicable in the preparation of a diverse array of oxazolidinone analogues such as 23 and 28 in both process and medicinal chemistry research.

Introduction

Linezolid represents the first antibacterial with a new mechanism of action to be approved by the FDA in over 30 years. The oxazolidinones have a novel mechanism of action that involves inhibition of protein synthesis at an early and unique step.[1] Initial preparations of the active *S*-isomers were done using the elegant chemistry developed by Manninen in which an aryl carbamate in THF is deprotonated with butyllithium and reacted with (*R*)-glycidyl butyrate to give the corresponding 5(*S*)-hydroxymethyloxazolidinone.[2] While developing this chemistry, Manninen observed that the lithium anion of the carbamate was required to obtain a useful yield of the desired oxazolidinone. Using potassium or sodium cations leads to formation of a mixture of 5- and 4-hydroxymethyl oxazolidinones as well as an unusual 4-arylaminomethyl-2-oxazolidinone.[3] It was subsequently found that (*S*)-chloropropanediol could be used as a substitute for (*R*)-glycidyl butyrate with lithium *tert*-butoxide as base and DMF or DMAc as solvent. Numerous methods of activating the resulting hydroxyl and displacing with an amine have been developed. The best method from a commercial standpoint uses 3-nitrobenzenesulfonyl chloride for the activation and a large excess of ammonia for the subsequent displacement reaction.[4] The nosylate leaving group sufficiently accelerates the ammonia displacement reaction to allow it to proceed at atmospheric pressure and low temperature (40−50 °C). The low cost of aqueous ammonia allows it to be used in large excess (∼100 equiv), thus suppressing competing dimer formation and eliminating the need for nitrogen protection and deprotection steps.

To reduce the number of steps from the aryl carbamate to the desired 5(*S*)-aminomethyloxazolidinones, we began exploring convergent early amination approaches. In these routes a protected nitrogen is substituted for the hydroxyl in the glycidol used in Manninen's procedure, thus obviating the need for the hydroxyl activation and ammonia displacement steps. The benzylidene **1**, was synthesized from commercial Daiso (*S*)-epichlorohydrin, generally following a literature procedure for preparing the racemate (Scheme 1).[5] Monoacetylation and base treatment yielded the epoxyacetamide **5**. We were then pleased to find that coupling epoxide **5** (in racemic form) with 1.3 equiv of the methyl carbamate **7**[6] under the Manninen conditions gave a 78% yield of linezolid based upon **5**. The requirement for an excess of urethane and the moderate yield was attributed to the competitive formation of the oxazoline **6**. These convergent routes were not explored extensively until 1999 in favor of the linear chloropropanediol/nosylate route due to the then prohibitive cost of commercial (*S*)-epichlorohydrin.

In 1996, Jacobsen published an alternative synthesis of **5** using a kinetic resolution approach with azide as the

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(1) Shinabarger, D. *Expert Opin. Invest. Drugs* **1999**, *8*, 1195. Aoki, H.; Ke, L. Z.; Poppe, S. M.; Poel, T. J.; Weaver, E. A.; Gadwood, R. C.; Thomas, R. C.; Shinabarger, D. L.; Ganoza, M. C. *Antimicrob. Agents Chemother.* **2002**, *46*, 1080.
(2) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
(3) Manninen, P. R.; Little, H. A.; Brickner, S. J. *Book of Abstracts;* 212th ACS National Meeting, Orlando, FL, August 25−29, 1996; American Chemical Society: Washington, DC, 1996; ORGN-389. AN 1996: 415294.
(4) Pearlman, B. A.; Perrault, W. R.; Barbachyn, M. R.; Manninen, P. R.; Toops, D. S.; Houser, D. J.; Fleck, T. J. U.S. Patent 5,837,870, November 17, 1998.
(5) Paul, R.; Williams, R. P.; Cohen, E. *J. Org. Chem.* **1975**, *40*, 1653−1656.
(6) Pearlman, B. A. U.S. Patent 6,107,519, August 22, 2000.

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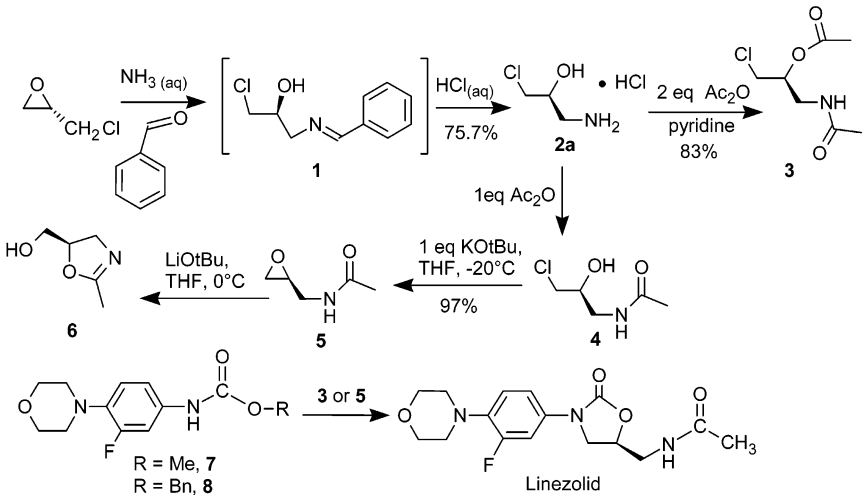
Scheme 1



nucleophile.[7] In his report, Jacobsen also demonstrated the conversion of an aryl carbamate to a 5(*S*)-acetamidomethyloxazolidinone using the reagent **5**, obtaining a 95% yield in the coupling reaction using 2 equiv of **5** relative to carbamate. An excess of epoxide was tolerable in Jacobsen's approach since his method should arguably make it the less expensive reagent. Also, significantly, Jacobsen demonstrated that the intermediate **3** was crystalline in enantiopure form making it an attractive synthetic target for large-scale synthesis.

In 1999, Chirex began making tonne quantities of (*S*)-epichlorohydrin from cheap racemic epichlorohydrin using Jacobsen's hydrolytic kinetic resolution technology (HKR).[8] Our interest in early amination routes to the oxazolidinones was thus renewed due to the cheap cost of (*S*)-epichlorohydrin and the crystallinity of **3**.

Results and Discussion:

(2*S*)-1-Amino-3-chloro-2-propanol Hydrochloride, 2a: Process Development. With minor variation, we have continued to use the original benzaldehyde/ammonia process for the preparation of **2a** (Scheme 1). The yield, although not ideal, has remained consistent at ~70% as the process has been scaled up as long as the original stoichiometries were used. Variations in time and temperature do not seem to greatly affect the yield. A pilot-scale reaction was done at 35−40 °C for 90 min and then 20−25 °C for 3 days, a subsequent larger pilot run was done at 35−41 °C for 12 h, and both gave a similar yield (67 and 74%). In some early runs, we tried using excesses of ammonia or benzaldehyde to try to improve the yield. However, these tended to give lower yields, presumably due to competing direct condensation of ammonia with benzaldehyde to form hydrobenzamide.[9] Due to the low cost of (*S*)-epichlorohydrin and the high throughput of the process (7.1 L/kg, 1.5 M peak volume), it remains the most economical method for the preparation of **2a**. Our highest lab yield for the preparation of **2a** (77%) was obtained by running the ammonia displacement at 35−40 °C.

The most significant difficulty seen in the largest pilot-scale run was that by cooling to −28 °C to precipitate all of the product, some impurities came out which caused the product cake to be hard and difficult to package. Also some product may have transiently dissolved in the residual mother liquor, perhaps contributing to the hard cake. This also led to a long drying time with room-temperature nitrogen (4 days to reach 1.73% LOD). An approach to improving the crystallization is to form other salts besides the hydrochloride, **2a**. Six salts were prepared in a parallel reactor and isolated by solvent swap from water to acetonitrile or 2-propanol. We had hopes that one of these might prove significantly more crystalline than **2a** and thus lead to a higher yield due to reduced filtrate losses. However, none gave better yields, although the mesylate gave a near equivalent yield. The camphorsulfonate salts were tried mainly with an eye towards possibly doing a diastereomeric salt resolution of racemic **2**. However, considering the low cost of (*S*)-epichlorohydrin, it is unlikely that a resolution approach will ever be competitive.

Process Development for Preparing *N*-[(2*S*)-2-(Acetyloxy)-3-chloropropyl]acetamide, 3. In our initial attempt to prepare reagent **3** by scalable means, **2a** was diacylated with triethylamine and acetic anhydride in THF. Unfortunately, some of the starting **2a** was occluded by the precipitated triethylamine hydrochloride in this system, resulting in only a 53.8% isolated yield of **3**. We therefore repeated the acetylation in acetonitrile. An homogeneous solution was obtained on warming the reaction mixture to 44 °C. After removal of triethylamine hydrochloride via precipitation from toluene/THF and an extractive workup, an isolated yield of 90.0% was obtained. A small demonstration pilot run was done which gave a 92.5% yield.

In the process of considering further scale-up, some difficulties presented themselves. The waste triethylamine hydrochloride that is filtered off gives a voluminous cake which would have required excessive filtering capacity. Also, running the acylation in acetonitrile solvent would have

(7) (a) Jacobsen, E. N.; Schaus, S. E. *Tetrahedron Lett.* **1996**, *37*, 7937. (b) Jacobsen, E. N.; Schaus, S. E. U.S. Patent 5,929,232, July 27, 1999.
(8) Jacobsen, E. N.; Tokunaga, M. WO 0009463, February 24, 2000.
(9) Karupaiyan, K.; Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1998**, *54*, 4375.

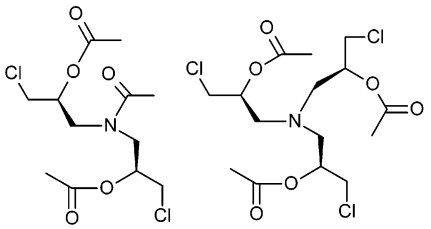


Figure 1.

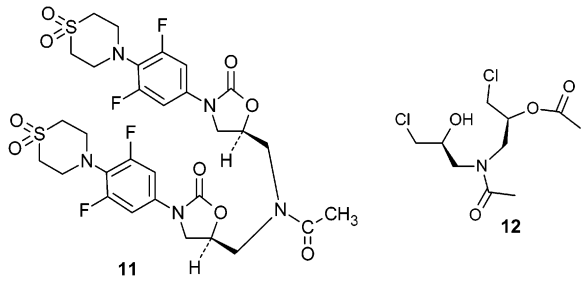


Figure 2.

required a tedious solvent swap to arrive at the desired methylene chloride solution for the extractive isolation. We tried to address all of these concerns via a Schotten−Bauman type diacylation of **2a** that would have allowed us to omit the troublesome **2a** crystallization and lead directly to a solution of **3** in methylene chloride. Acylation of a secondary alcohol in the presence of water is normally not achievable, and this secondary alcohol is expected to be relatively unreactive as proximate amides reduce the nucleophilicity of alcohols.[10] Still, we had hoped that running in a two-phase system could have made the process feasible for this case. Thus far, we have been unsuccessful at fully diacylating **2a** in the presence of significant amounts of water.

In another approach, we speculated it might be possible to selectively diacylate **2a** in 2-propanol as solvent. A diacylation of **2a** in methylene chloride and 2-propanol (3 mL/g each) and triethylamine as base was tried. With 2.5 equiv of acetic anhydride, the reaction stalled at 4.4% monoacetylated intermediate, showing that the 2-propanol was competing to a certain extent. However, adding another 1 equiv of acetic anhydride (3.5 equiv total) gave complete conversion. Therefore, it was practical to consider the one isolation process from epichlorohydrin to **3**. Thus, a slurry of crude **2a** in 2-propanol, prepared without isolation from (*S*)-epichlorohydrin, was treated with pyridine (2.5 equiv) and acetic anhydride (3.5 equiv) in methylene chloride to give, after extractive workup, a solution of crude **3** in toluene. Crystallization by addition of isooctanes afforded a poor 57.1% yield of **3**, of only 93.3 wt % purity by external standard GC analysis. The mother liquor was chromatographed and an additional 23.2% yield of **3** obtained (total yield = 76.5%) along with the dimeric and trimeric byproducts **9** and **10** in impure form (Figure 1). Analysis of the mixture by GC indicated 6.9 area % **9** and 1.4 area % **10** total were formed, for a mass balance of about 85% overall from (*S*)-epichlorohydrin. Clearly, isolating at the **2a** stage is better for removal of these overalkylation products, and we thus abandoned the one-pot process.

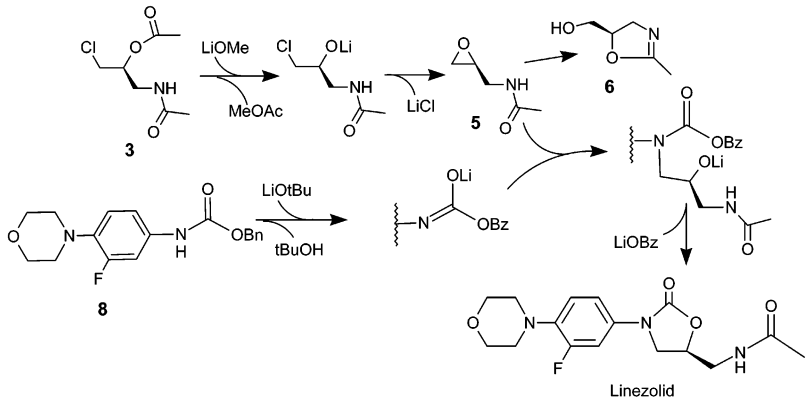
To simplify the workup due to the high water solubility of reagent **3** we chose to use methylene chloride as solvent. Thus, to avoid occlusion, a base whose hydrochloride salt is soluble in methylene chloride was needed. Reactions using tributylamine as base gave complex mixtures by GC; however, clean conversion was seen with as little as 1.5 equiv of pyridine. Upon scale-up of the pyridine process, however, a difficulty was observed. During drying in a nitrogen stream, the product cake became difficult to break up, and a brown oil collected in the filter flask. NMR and GC analysis of this oil showed it to contain 5.4% in yield of **3** along with acetic acid and pyridine in a molar ratio of 1.9:0.5:1.0 acetic acid:pyridine:**3**. Clearly some acetic acid carried through the extractions and prevented complete azeotropic removal of pyridine with toluene during the isolation. Crystallizations spiked with a high level of acetic acid also gave a sticky oil. Thus, a higher pH extraction was done during the isolation to ensure complete acetic acid removal, and this eliminated the oiling problem.

During further development work, we succeeded in isolating the principal impurity responsible for oiling during the final crystallization of **23** (see below) and showed it to be the bis-adduct **11** (Figure 2). A correlation was then found between the level of this impurity in a given lot of compound **23** and the level of a 12.4-min retention time impurity (GC 15 M-DB-1, 70 °C 2 min, then 10 °C/min) in the lot of reagent **3** used to prepare it. Attempts to isolate this 12.4-min impurity by chromatography and fully characterize it have so far been unsuccessful due to its high polarity and its instability to silica gel. However, we are fairly confident it is the incompletely acetylated dimer **12** (Figure 2) as GC data suggests that the 12.4-min impurity is an intermediate in the triacetate's formation. This incompletely acetylated impurity partitions preferentially in the aqueous phases. Thus, an extra aqueous sodium chloride wash was added to the isolation of **3**, reducing the level of this impurity from the 2.0% obtained with the original procedure to only 0.36% in a pilot lot. GC analysis of this extra waste stream showed it contained only 2.5% reagent **3**. A use test then showed this new material gave only 0.25% dimer in crude **23**, instead of about 1.0% with the original procedure.

One-Pot Conversion of *N*-Aryl Carbamates to *N*-Aryl-5(*S*)-acetamidomethyl-2-oxazolidinones. A general method for the preparation of *N*-aryl-5(*S*)-acetamidomethyl-2-oxazolidinones from *N*-aryl carbamates was then developed (Scheme 2). While Jacobsen had chosen to preform and chromatograph **5** by treating **3** with methanol and potassium carbonate, we chose to form **5** in situ and thus avoid the isolation of this unstable intermediate. We chose to apply the lithium *tert*-butoxide/DMF chemistry developed for the reaction of (*S*)-chloropropanediol with aryl carbamates as we believed this would give the simplest process. Methanol was added to act as a nucleophile for the in situ deacetylation. We used 2 equiv of **3** to increase the conversion following the precedent of Jacobsen. Thus, a solution of **8**[2] in DMF (2 mL/g), methanol (2.02 equiv), and lithium *tert*-butoxide (3.0 equiv, in THF) was simply treated at 5−21 °C for 21 h with

(10) Szabò, L.; Li, Y.; Polt, R. *Tetrahedron Lett.* **1991**, *32*, 585.

Scheme 2



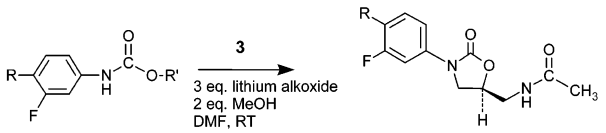
3 (2.00 equiv). HPLC showed a clean 87% conversion to linezolid. After extractive workup and crystallization from xylenes, a 72.1% yield of 98.0 wt % purity linezolid was obtained. HPLC analysis of the filtrate showed an additional 9.7% recoverable linezolid.

Pilot-Scale Preparation of Oxazolidinone 15. The first large-scale application of this convergent oxazolidinone synthesis was in the preparation of **15**. When we substituted sulfone **13** for the linezolid substrate **8** in the corresponding reaction with **3**, a lower yield was obtained (68.4 norm % vs 80.3 norm %). The yield in this reaction was considerably increased by substituting solid lithium *tert*-amylate for lithium *tert*-butoxide in THF to increase the desired coupling reaction rate (second order) in the face of the undesired decomposition of **5** to **6** (first order) by taking advantage of the concentration effect. This reaction gave an 84% conversion of starting material and a 75% HPLC external standard yield of **15**[12] after extractive workup. Numerous unknowns observed by HPLC accounted for the balance of the yield. Results for other substrates and conditions appear in Table 1.

On the basis of the results of these experiments, it appears that a para nitrogen substituent on the aromatic ring of the linezolid substrate was increasing the yield relative to the sp^3 carbon substituent in the **15** series substrates. Changing to an sp^2 hybridized center by using the unsaturated substrate **17** increased the yield about 8−9%. We had hoped to use a reduced substrate in the coupling to avoid performing a hydrogenation as the last step in the synthesis; however, the increased yield seen with **17** outweighed this concern.

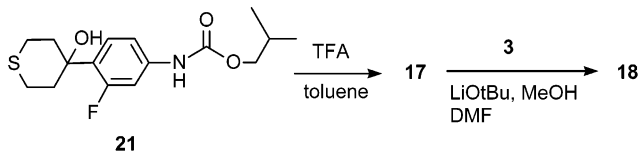
A simple, high-yielding, streamlined procedure for the coupling of **3** with **17** to give **18** (a known intermediate in the synthesis of **15**)[12] was then developed (Scheme 3). Tertiary alcohol **21**[13] was dehydrated with trifluoroacetic acid and the water and trifluoroacetic acid removed via azeotropic distillation with toluene. To this solution was then added a solution of **3** in DMF, followed by 2 equiv of methanol. The toluene was then extracted into a separate phase by the addition of isooctanes. Lithium *tert*-butoxide in isooctanes (3 equiv) was then added to effect the desired oxazolidinone

Table 1: **Substrate and concentration effects on reactions with 3**



Entry	R	R'	Substrate	Product	Yield by HPLC	Notes
1		Benzyl	**8**	linezolid	80.3%	1.95 M LiOtBu in THF
2		isobutyl	**13**	**15**	68.4%	1.95 M LiOtBu in THF
3		isobutyl	**13**	**15**	75.0%	lithium t-amylate solid
4		isobutyl	**14**	**16**	74.3%	lithium t-amylate solid
5		isobutyl	**17**	**18**	83.4%	lithium t-amylate solid
6	H	isobutyl	**19**	**20**	83.2%	lithium t-amylate solid
7	H	isobutyl	**19**	**20**	81.8%	4.3 M lithium t-amylate slurry in hexanes

Scheme 3

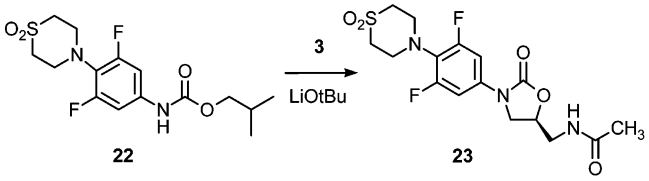


formation. Acetic acid was added to quench the reaction, and the product was extracted from the upper nonpolar phase with methanol and water. The product was then extracted from the methanol/water phase with methylene chloride. After a solvent swap to methanol, the product was precipitated with toluene and water. Our best laboratory run of this process afforded a 76.4% purity corrected isolated yield of **18** from **21**. Only 1.9% product was lost to the isolation, and 13.5% was lost as residual **17**. A variety of low-level unknown impurities accounted for the remaining 8.1% in yield. Upon piloting, this process afforded a 75% yield of **18**, in accord with laboratory expectations.

Several important variables were identified in the reaction of carbamate **17** with reagent **3**. It is important to add a sufficient amount of an immiscible hydrocarbon to the crude **17** solution to extract out the toluene from the DMF phase

(11) Mbappe, M. A.; Sicsic, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1035.
(12) Thomas, R. C.; Poel, T. J. U.S. Patent 6,358,942, March 19, 2002.
(13) (a) Gage, J. R.; Perrault, W. R.; Poel, T. J.; Thomas, R. C. *Tetrahedron Lett.* **2000**, *41*, 4301. (b) Herrinton, P. M.; Owen, C. E.; Gage, J. R. *Org. Process Res. Dev.* **2001**, *5*, 80.

Scheme 4



where the reaction occurs, or else lower yields are obtained. Also, we tried to substitute commercial 2 M lithium *tert*-butoxide in THF for lithium *tert*-butoxide in hexanes. Although this was observed to reduce the yield in earlier experiments, we had hoped that adding isooctanes would extract enough of the THF out of the reactive phase to restore the yield. However, the yield was still depressed by over 6% to 69.9%. In one run, we also tried adding all of the lithium *tert*-butoxide in one portion at <0 °C and then warming to 13 °C; we obtained a conversion nearly identical to that from the normal slow-addition process. This was not a useful variant for the pilot-plant processing, but it did simplify the laboratory procedure considerably. A preparation of **18** was done in which the lithium *tert*-butoxide was added in 12 portions, instead of a constant syringe pump addition, and a normal yield (77.2%) was obtained. This showed that minor changes in the flow rate during the lithium *tert*-butoxide addition do not affect the yield in this reaction.

Pilot-Scale Preparation of Oxazolidinone 23. Our convergent oxazolidinone synthesis was also applied on pilot scale to the sulfone **23**, using the isobutyl carbamate **22**[14] as substrate (Scheme 4). Our initial oxazolidinone preparation conditions closely mimicked those developed for the preparation of **18** above. However, the increased acidity of the carbamate proton caused by the additional aromatic fluorine substituent on **22** resulted in conversions as high as 92%, as opposed to 88% with **17**. The reactions were also cleaner, giving none of the minor byproducts seen with **17**. The higher conversions proved somewhat irreproducible, and conversions as low as 82% were also obtained. We then found that we could reproducibly obtain conversions of 92−95% by adding the lithium *tert*-butoxide to the carbamate **22** and then adding **3** slowly as a solution in DMF.

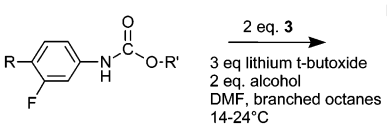
To further explore this inverse addition observation, several oxazolidinone formation reactions were run on a parallel reactor using variants of this inverse addition and several different substrates (Table 2). In all of the runs except entries 2, 7, and 8, the reactions were slurries prior to beginning the addition of reagent **3** due to the small amount of DMF used to dissolve the substrate. Reactions 2 and 7 gave the highest conversions, suggesting that substrate solubility is the key variable in achieving high conversions with this procedure. It is not surprising that entry 8 gave a somewhat poor conversion despite the substrate solubility as 2-propanol should be slow to transesterify reagent **3**. Little effect was seen upon varying methanol from 1 to 3 equiv, showing that the process is robust with respect to the amount of alcohol used for the transesterification.

In an initial pilot run to prepare compound **23** using DMF as solvent, several challenges were encountered. A significant amount of solids were formed at the bottom of the reactor, which was not evident during lab development. The removal of DMF proved very tedious and challenging during product isolation. To improve the process for this step and circumvent these challenges, we had hoped to eliminate the use of DMF and increase reaction solubility to prevent the solid precipitation. Subsequently, it was found that THF could be substituted for DMF in the coupling reaction, though with a slight reduction in conversion. Also, it was found that this THF procedure is applicable to less acidic substrates as applying it to **8** yielded linezolid with a 91% conversion and a 73% isolated yield.

A series of reactions involving different solvents were then studied; as Table 3 indicates, the highest level of conversion was obtained with acetonitrile as solvent. However, a sticky salt plug was observed during the reaction. By using a 1:1 mixture of acetonitrile/THF as solvent, a slightly lower level of conversion was obtained compared to using only acetonitrile (83.4% vs 86.2%) but the reaction was completely homogeneous throughout the reaction. All

(14) Chen, J. J.; Lu, C. V. WO 02085865, October 31, 2002.

Table 2: **Order of addition and substrate effects on reactions with reagent 3**



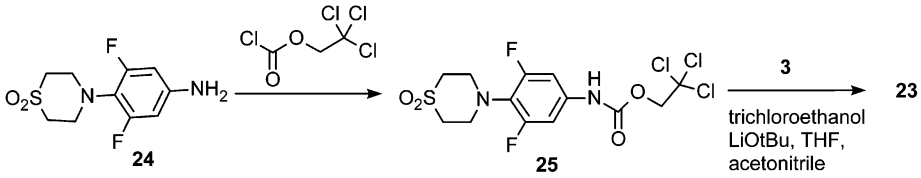
Entry	R	R'	Alcohol	Conversion (**3** added last)	Conversion (LiOtBu added last)
1		iBu	2 eq methanol	83.5%	87.6%[a]
2		iBu	2 eq methanol	85.5%	78.8%[b]
3		Bz	2 eq methanol	79.2%	83.2%
4		Bz	3 eq methanol	81.1%	
5		Bz	1 eq methanol	78.5%	
6		Bz	2 eq methanol	80.9%	
7		Bz	2 eq ethanol	84.8%	
8		Bz	2 eq isopropanol	77.8%	

[a] 3 equiv of lithium *tert*-butoxide solid added last at 0−5 °C, then reaction warmed to rt. [b] 3 equiv of lithium *tert*-butoxide in THF added last at 0−5 °C, then reaction warmed to rt.

Table 3: **Solvent effects in the preparation of 23**

solvent	ratio **23**:**22**	observations
THF	81:19	sticky LiCl plug formed
CH_3CN	86:14	sticky LiCl plug formed
CH_2Cl_2	72:28	substrate forms sticky ball
2-propanol	N/A	unstirrable sludge formed
ethanol	4:96	substrate insoluble
1:1 CH_3CN:THF	83:17	homogeneous solution
1:1 CH_3CN:CH_2Cl_2	79:21	LiCl precipitates, but not sticky
1:1 THF:CH_2Cl_2	83:17	sticky LiCl plug formed
sec-BuOH	22:78	substrate insoluble
glyme	63:37	substrate marginally soluble

Scheme 5



of the runs in Table 3 were done at 10 mL total volume/g of **22** at 4−22 °C overnight. The lithium *tert*-butoxide (3 equiv) was added last in one portion to a mixture of **22**, reagent **3** (2 equiv), and methanol (2 equiv) dissolved in the indicated solvent.

Upon scaling up to 20 g starting material, using 1:1 THF/acetonitrile under lower temperature (16 °C) and higher concentration (5 mL/g total volume), the level of conversion increased to 87.4% by calibrated HPLC. At this concentration, towards the end of the reaction and especially after the acetic acid quench, the reaction mixture became somewhat viscous and sticky. To avoid this problem, a lower concentration reaction was performed at 6.9 mL/g at 16 °C overnight. As expected, the viscosity, after the acid quench, was greatly reduced without any significant conversion loss (87.0% vs 87.4%). Other conditions for the oxazolidinone formation were also screened. The use of lithium ethoxide as the base under standard conditions resulted in a significantly decreased level of conversion (76% vs 90−95%). It was rationalized that the reduced basicity of lithium methoxide relative to ethoxide was increasing the stability of the epoxyacetamide **5**. Also, the use of additional methanol (3 equiv) was found to not significantly increase the level of conversion but did provide a sticky reaction mixture.

After switching to the THF/acetonitrile solvent system, conditions for the removal of unreacted starting material still needed to be defined. Through partitioning studies, we found that **23** partitions preferentially at ca. 85% in the aqueous phase of a toluene/water mixture. However, the processing volume required was too large (ca. 60 L/kg) due to the low water solubility of **23**. By using a water miscible cosolvent, we had hoped to increase the solubility of the product to decrease the processing volume. At the refluxing temperatures needed to dissolve the product, methanol was found to be the best cosolvent with our toluene/water system. Under the new toluene/water/methanol system, nonpolar impurities such as **22** and most of the colored impurities were effectively removed. The preferential partitioning of **22** for the toluene layer also allowed the starting material to be recovered for reuse.

Residual toluene needed to be removed from the aqueous product-containing layer to meet ICH toluene specifications for the final product. Computer simulations[15] involving the distillation of toluene from a mixture of water and methanol showed that toluene removal was extremely efficient in this system. After reducing the total volume of the crude extracts by ∼10%, analysis of the mixture by GC indicated no detectable toluene remaining in the still residue. However, upon rapid cooling and crystallization of the anhydrous product, an unfilterable solid was obtained. By slowing the cooling rate to ca. 5 °C per hour and utilizing seed crystals, nice filterable solids were obtained. Two multikilogram pilot campaigns proceeded as expected using the new procedure with no major problems, and 80% isolated yields were obtained in each.

In hopes of increasing the yield and reducing the amount of excess **3** required in the reaction, we explored the use of other carbamates besides the isobutyl carbamate **22** for preparing **23**. We speculated that, since the acidity of the carbamate is key to favoring alkylation over isoxazoline formation, using a more acidic carbamate should favor the desired reaction. However, this proved generally not to be the case, at least in this series. One modest success we did have was in substituting trichloroethanol for methanol and the trichloroethyl carbamate, **25**, for the isobutyl carbamate **22** (Scheme 5). Here we saw a minor conversion increase to 66% with 1.25 equiv of **3** vs a 58% conversion with the standard reagents. Other combinations of carbamates and alcohols did not give an improvement. Carbamates tried included isopropenyl, trifluoroethyl, and phenyl. The carbamates were prepared via reaction of the aniline **24**[14] with the corresponding commercially available chloroformate. Most of these alternative carbamates gave poor results. For example, the phenyl carbamates gave gross mixtures when reacted with isolated **5** and lithium *tert*-butoxide. When the phenyl carbamates were reacted with methanol and **3**, the methyl carbamate was formed, and it reacted to give poor yields of **23**.

Recently, (*S*)-*N*-[2-(acetyloxy)-3-bromopropyl]acetamide has become commercially available from Samsung Fine Chemicals,[16] and we have shown that it performs equivalently to **3** in the synthesis of **23**.

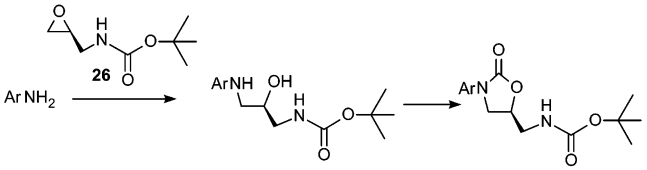
Preparation and Use of *tert*-Butyl [(2*S*)-3-Chloro-2-hydroxypropyl]carbamate, 27. We also desired a reagent which would be useful for the synthesis of 5(*S*)-aminomethyloxazolidinone derivatives other than acetamide. Several other amines besides acetamide were explored as substrates for the Manninen conditions and all of these substrates failed to give useful yields. However, Bayer recently found that the BOC-protected (*S*)-glycidylamine **26** could be used to alkylate anilines, and the resulting amino alcohols cyclized to the desired oxazolidinones with CDI, although only in poor to moderate yields (Scheme 6).[17]

(15) The commercial BDIST-SimOpt software from Batch Process Technologies (www.bptech.com) and the freeware VLECALC by William D. Kovats (my.net-link.net/∼wdkovats) gave qualitatively similar predictions.

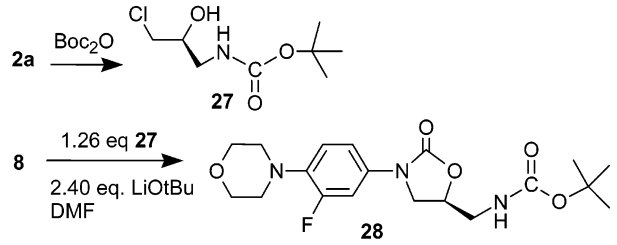
(16) Roh, K. R.; Lee, J. H.; Hwang, D. I.; Lee, W. J.; Kim, K. I. WO 9952855, October 21, 1999.

(17) Raddatz, S.; Bartel, S.; Guarnieri, W.; Rosentreter, U.; Ruppelt, M.; Wild, H.; Endermann, R.; Kroll, H. P.; Henninger, K. WO 9940094, August 12, 1999; Bartel, S.; Guarnieri, W.; Habich, D.; Raddatz, S.; Riedl, B.; Rosentreter, U.; Ruppelt, M.; Stolle, A.; Wild, H.; Endermann, R.; Kroll, H. P. WO 9937641, July 29, 1999.

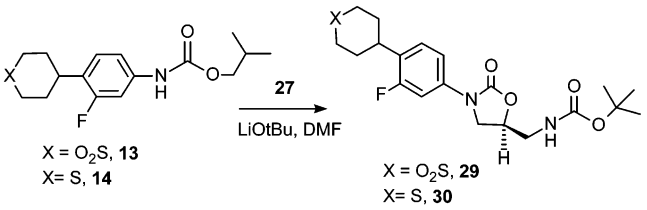
Scheme 6



Scheme 7



Scheme 8



We therefore tried the corresponding chlorohydrin reagent **27** and found that it performed very well using DMF as the solvent and lithium *tert*-butoxide as the only base (Scheme 7). We obtained the desired BOC-protected linezolid derivative **28** analytically pure in 87.5% yield after chromatography. With 2 equiv of **27**, the reaction was driven to 99.5% conversion and 94 crude HPLC area % **28** as compared to only 86.8% conversion with 2 equiv of **3**. This prompted us to try reducing the equivalents of **27** to only 1.26, and this very low loading still gave a 95% conversion.

Compounds **29** and **30**, potential intermediates for preparing thiopyran oxazolidinone **15**, were also prepared with reagent **27** (Scheme 8). Both compounds **13** and **14**[13] were somewhat poorer substrates for this chemistry with reagent **27** than they were for reagent **3** (Table 1). With 1.26 equiv of **27**, only 83.0 area % **29** and 85.0 area % **30**, respectively, were formed under conditions which had afforded 94 area % **28** in the linezolid series. This was due both to lower conversion and to an increase in the level of some unknowns.

In the preparation of **27**, a scalable procedure for the clean bocylation of **2a** with 1.05 equiv of di-*tert*-butyldicarbonate in methanol/aqueous potassium bicarbonate proved simple to develop. However, subsequent crystallization of the product after extractive isolation was somewhat problematic. Even with seeding (~50 mg of seeds for 20 g run), the product precipitated very slowly from toluene/heptane (overnight stirring was required to reach complete precipitation at room temperature). When the isolated material was recrystallized, the precipitation was complete within a matter of hours suggesting that the impurities in the crude reaction mixture were causing the slow crystallization. GC analysis of various lots of the crude product showed them to contain 1−4% of a late-eluting impurity, which did not affect use of the reagent. This impurity was isolated and identified as fully BOC-protected 1,3-diamino-2-propanol, obviously derived from the corresponding diamine in the starting material. Apparently, the expected impurities derived from the dialkylation of ammonia with epichlorohydrin, which were difficult to remove from diacetate **3**, were easily removed while crystallizing reagent **27**. This diamino impurity was slowing the crystallization, as lower levels of it were associated with faster precipitations of **27**.

Conclusions

Methods were developed for the preparation and use of the valuable reagents **3** and **27**.[18] In addition to the pilot-scale preparations described herein, these reagents have proven widely applicable to the rapid synthesis of numerous other pharmaceutically active aryl oxazolidinone analogues in medicinal chemistry at Pharmacia.[19]

Experimental Section

(2*S*)-1-Amino-3-chloro-2-propanol Hydrochloride (2a). To a solution of benzaldehyde (59.54 g, 0.561 mol, 1.03 equiv) in ethanol (150 mL) at 18 °C was added aqueous ammonia (28.8 wt %, 49.9 g, 0.861 mol, 1.58 equiv) followed by an ethanol rinse (6 mL). (*S*)-Epichlorohydrin (50.5 g, 0.546 mol) was added, and rinsed in with ethanol (22 mL). The reaction mixture was allowed to exotherm from 19 to 40 °C over 1 h; it was then stirred at 35−40 °C for 6 h and then at 20−25 °C for 13.5 h. GC showed 1.4% residual (*S*)-epichlorohydrin and 80.7% compound **1** (identity confirmed vs racemic GC standard[5]). The solution was concentrated in vacuo to 133 mL, and toluene (115 mL) was added. While a temperature of 36−41 °C was maintained, a solution of hydrochloric acid (37 wt %, 80.6 g, 0.827 mol, 1.52 equiv) and water (77 mL) was added over 5 min. The two-phase mixture was stirred at 35−45 °C for 3 h, and the phases were settled and separated. The upper phase was washed with water (28 mL), the aqueous was combined, and ethanol (28 mL) was added. The mixture was concentrated to 95 mL, and ethanol (7 × 38 mL) was added, concentrating to 95 mL after each addition. Ethanol (95 mL) was added, and the slurry was warmed to reflux and then cooled to and maintained at −25 °C for 18 h. The product was collected by vacuum filtration, washed with −28 °C ethanol (28 mL) and dried in a room-temperature nitrogen stream to afford a white solid (61.4 g, 77.0%, mp = 125−136 °C): ^{1}H NMR (CD_3OD, 400 MHz) δ 4.85 (s, 4H), 4.2−4.0 (m, 1H), 3.66−3.57 (m, 2H), 3.22 (dd, J = 17.2, 3.6 Hz, 1H), 2.94(dd, J = 12.4, 16.8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) d 43.53 (t), 46.90 (t), 68.74 (d); MS (CI, NH_3) *m*/*z* (relative intensity) 112 (43), 110 (100); $[\alpha]^{25}_D = -22$ (c = 1.02, water); Anal. Calcd for $C_3H_9Cl_2NO$: C, 24.68; H, 6.21; N, 9.59; found: C, 24.30; H, 6.36; N, 10.01; GC for **1** (t_R= 17.5 min) and (*S*)-epichlorohydrin (t_R = 1.23 min): 15 M-DB-1 capillary column, T_{inj} = 250 °C, T_{ini} = 28 °C for 2 min, T_{fin} = 250 °C, rate = 10 °C/min.

(18) Perrault, W. R.; Gadwood R. C. WO 0232857, April 25, 2002; Perrault, W. R.; Pearlman, B. A.; Godrej, D. B. WO 0285849, October 31, 2002.
(19) Johnson, P. D.; Aristoff, P. A.; Poel, T. J.; Thomasco, L. M. WO 0259115, August 1, 2002.; Barbachyn, M. R.; Zurenko, G. E. WO 0198297, December 27, 2001.

Table 4: **Alternative (2*S*)-1-amino-3-chloro-2-propanol salts**

salt	acid	yield/ g	% of theory	crystallization solvent	crystallization temperature
2b	methanesulfonic	5.3	75	acetonitrile	−23
2c	benzenesulfonic	6.6	72	acetonitrile	−23
2d	(1*R*)-10-camphorsulfonic	8.1	70	2-propanol	0
2e	(1*S*)-10-camphorsulfonic	6.8	58	2-propanol	0
2f	*p*-toluenesulfonic	5.6	59	2-propanol	−23

(2*S*)-1-Amino-3-chloro-2-propanol Salts. To a sample of crude **1** concentrate (9.0 g) derived from (*S*)-epichlorohydrin (3.15 g, 34 mmol) following the procedure for preparing **2a** above was added toluene (20 mL), water (20 mL), and the indicated acid (41 mmol, 1.2 equiv, Table 4). The mixture was stirred at room temperature for ∼18 h on a parallel synthesizer, and the phases were separated. The upper was washed with water (10 mL). The aqueous phase was concentrated to an oil in vacuo and the crystallization solvent added twice, concentrating to a thick slurry or oil after each addition. The crystallization solvent was added, and the slurries were cooled to the indicated temperatures; the products were collected by vacuum filtration and dried in a nitrogen stream to give a white solid in the indicated amounts.

2b: ^{1}H NMR (300 MHz, CD $_3$OD) δ 1.19 (s, 3 H), 1.42 (t, J = 12 Hz, 1 H), 1.67 (d, J = 13 Hz, 1 H), 2.08 (dd, J = 3, 6 Hz, 2 H), 2.52 (m, 1 H), 3.32 (s, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 38.49 (q), 42.45 (t), 45.86 (t), 67.67 (d); $[\alpha]^{25}_D = -16$ (c = 0.92, water); Anal. Calcd for $C_3H_8ClNO\cdot CH_4O_3S$: C, 23.36; H, 5.88; N, 6.81. Found: C, 22.86; H, 6.04; N, 6.76.

2c: ^{1}H NMR (300 MHz, CD_3OD) δ 1.35 (t, J = 12 Hz, 1 H), 1.60 (d, J = 13 Hz, 1 H), 2.00 (dd, J = 4, 6 Hz, 2 H), 2.45 (m, 1 H), 3.35 (s, 4 H), 5.86 (d, J = 5 Hz, 3 H), 6.26 (t, J = 5 Hz, 2 H); ^{13}C NMR (75 MHz, CD_3OD) δ 42.40 (t), 45.77 (t), 67.61 (d), 125.77 (d), 128.27 (d), 130.33 (d), 144.96 (s); $[\alpha]^{25}_D = -12$ (c = 0.95, water). Anal. Calcd for $C_6H_6O_3S\cdot C_3H_8ClNO$: C, 40.38; H, 5.27; N, 5.23. Found: C, 38.97; H, 5.42; N, 4.53.

2d: ^{1}H NMR (300 MHz, CD_3OD) δ 0.86 (s, 3 H), 1.11 (s, 3 H), 1.42 (m, 1 H), 1.64 (td, J = 6, 9 Hz, 1 H), 1.90 (d, J = 18 Hz, 1 H), 2.07 (m, 2 H), 2.31 (m, 1 H), 2.62 (m, 1 H), 2.78 (d, J = 15 Hz, 1 H), 2.96 (dd, J = 12, 15 Hz, 1 H), 3.23 (dd, J = 12, 15 Hz, 1 H), 3.29 (d, J = 15 Hz, 1 H), 3.61 (m, 2 H), 4.05 (m, 1 H), 4.83 (s, 4 H);^{13}C NMR (75 MHz, CD_3OD) δ 19.05 (q), 19.24 (q), 24.69 (t), 26.71(t), 42.50 (t), 42.58 (t), 42.95 (d), 45.89(t), 47.70 (t), 58.48 (s), 67.69 (d), 217.38 (s); $[\alpha]^{25}_D = -24$ (c = 0.96, water). Anal. Calcd for $C_{10}H_{16}O_4S\cdot C_3H_8ClNO$: C, 45.67; H, 7.08; N, 4.10. Found: C, 43.70; H, 7.21; N, 3.98.

2e: ^{1}H NMR (300 MHz, CD_3OD) δ 0.86 (s, 3 H), 1.11 (s, 3 H), 1.42 (m, 1 H), 1.64 (m, 1 H), 1.90 (d, J = 18 Hz, 1 H), 2.07 (m, 2 H), 2.31 (m, 1 H), 2.62 (m, 1 H), 2.78 (d, J = 15 Hz, 1 H), 2.96 (m, 1 H), 3.23 (m, 1 H), 3.29 (d, J = 15 Hz, 1 H), 3.61 (m, 2 H), 4.05 (m, 1 H), 4.83 (s, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 19.05 (q), 19.24 (q), 24.70 (t), 26.71(t), 42.51 (t), 42.58 (t), 42.95 (d), 45.89(t), 47.10 (t), 58.48 (s), 67.69 (d), 217.35 (s); $[\alpha]^{25}_D = 5$ (c = 0.98, water). Anal. Calcd for $C_{10}H_{16}O_4S\cdot C_3H_8ClNO$: C, 45.67; H, 7.08; N, 4.10. Found: C, 45.36; H, 7.11; N, 4.07.

2f: ^{1}H NMR (300 MHz, CD_3OD) δ 1.23 (s, 3 H), 1.78 (t, J = 12 Hz, 1 H), 2.05 (d, J = 13 Hz, 1 H), 2.44 (m, 2 H), 2.87 (m, 1 H), 3.70 (s, 4 H), 6.10 (d, J = 6 Hz, 2 H), 6.58 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, CD_3OD) δ 20.24 (q), 42.43 (t), 45.79 (t), 67.66 (d), 125.84 (d), 128.79 (d), 140.74 (s), 142.29 (s); $[\alpha]^{25}_D = -13$ (c = 0.86, water). Anal. Calcd for $C_7H_8O_3S\cdot C_3H_8ClNO$: C, 42.63; H, 5.72; N, 4.97. Found: C, 42.59; H, 5.76; N, 4.96.

***(S)*-*N*-[2-(Acetyloxy)-3-chloropropyl]acetamide (3).** To a slurry of **2a** (200.2 g, 1.371 mol) in methylene chloride (465 mL) was added acetic anhydride (322 g, 3.153 mol, 2.30 equiv). The slurry was warmed to 38 °C, and pyridine (140 g, 1.731 mol, 1.26 equiv) was added while maintaining the temperature at 36−38 °C, followed by a methylene chloride (32 mL) rinse. The resulting solution was stirred at 37−40 °C for 5 h and then at 20−25 °C for 14 h. GC [(15 M-DB-1 capillary column, T_{inj} = 250 °C, T_{ini} = 70 °C for 2 min, T_{fin} = 250 °C, rate = 10 °C/min; t_R (**3**) = 8.66 min; t_R (**4**) = 6.87 min] showed 0.90% residual intermediate **4**. The mixture was cooled to 25 °C, and water (240 mL) was added. The mixture was cooled to 6 °C, and a solution of aqueous potassium carbonate (47 wt %, 800 g, 2.72 mol, 1.98 equiv) was added over 7 min, while maintaining the temperature at 5−7 °C. Water (622 mL) and methylene chloride (240 mL) were added; the phases were separated, and the aqueous was washed with methylene chloride (2 × 120 mL). The combined organics were washed with a solution of sodium chloride (26 g) in water (792 mL). The wash was back-extracted with methylene chloride (2 × 120 mL), and the combined organics were concentrated in vacuo to 540 mL. Toluene (2 × 400 mL) was added and the mixture concentrated to 540 mL after each addition. The solution was cooled to 28 °C to give a slurry, and 900 mL of isooctanes was added. The slurry was cooled to 3 °C and the product collected by pressure filtration, washed with isooctanes (280 mL), and dried in a nitrogen stream to give a white solid (220.3 g, 82.9%): mp = 66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.20 (bs, 1H), 5.09 (p, J = 4.8 Hz, 1H), 3.70 (dd, J = 12.0, 4.8 Hz, 1H), 3.64−3.47 (m, 3H), 2.12 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.93 (q), 23.12 (q), 40.52 (t), 43.53 (t), 71.98 (d), 170.46 (s), 170.63 (s). $[\alpha]^{25}_D = -10$ (c = 0.94, methylene chloride) Anal. Calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.37; H, 6.29; N, 7.18. GC for: DSC: stable to 152 °C.

***N*-(3-Chloro-2-hydroxypropyl)acetamide [(±) 4].** To a slurry of **(±)-2a** (47.71 g, 326.7 mmol) in THF at −40 °C was added triethylamine (36.50 g, 360.8 mmol, 1.10 equiv) followed by acetic anhydride (35.01 g, 342.9 mmol, 1.05 equiv) while maintaining <−30 °C. The mixture was stirred 15 min at −30 °C, then allowed to warm to 20 °C over 1 h. The mixture was stirred at 20−25 °C for 3 h, and then the precipitate was removed by vacuum filtration and the product rinsed through with THF (175). The filtrate was concentrated to 80 g net weight, toluene (195 mL) was added, and the mixture was concentrated to 86 g and toluene (250 mL) added. The mixture was concetrated to 68 g and toluene (250

mL), methanol (40 mL), and ethyl acetate (10 mL) were added. The mixture was cooled to −20 °C, seeded, and cooled to −30 °C, and heptane (200 mL) was added. The precipitate was collected by vacuum filtration at −33 °C, washed with heptane (100 mL), and dried. The crude solid was redissolved in toluene (250 mL) and methanol (120 mL) and was concentrated under reduced pressure to 233 g net weight. The solution was cooled to −30 °C and seeded, and heptane (180 mL) was added. The precipitate was collected by vacuum filtration at −30 °C, washed with heptane (100 mL), and dried in a nitrogen stream to give a white solid (32.25 g, 66.3%); silica gel TLC (95:5 methylene chloride: methanol, iodine char) R_f = 0.23; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3 H), 3.33 (p, J = 6 Hz, 1 H), 3.54 (d, J = 6 Hz, 2 H), 3.95 (s, 1 H), 4.73 (s, 1 H), 6.94 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.01, 43.32, 46.46, 70.72, 172.37; MS (Cl, NH_3) 154 (34); 152 (100) Anal. Calcd for $C_5H_{10}ClNO_2$: C, 39.62; H, 6.65; N, 9.24. Found: C, 39.63; H, 6.69; N, 9.13.

(±)-*N*-(Oxiranylmethyl)acetamide [(±)-5]; (±)-(2-Methyl-4,5-dihydro-1,3-oxazol-5-yl)methanol [(±)-6]. To a solution of (±)1-acetamido-2-hydroxy-3-chloropropane, (±)-**4** (1.00 g, 6.59 mmol), in THF (2.0 mL) at −40 °C was added potassium *tert*-butoxide in THF (1.0 M, 6.3 mL, 6.3 mmol, 0.95 equiv). The mixture was warmed to 0 °C; then the solution was filtered through silica gel (1.7 g) and rinsed through with 10 mL of 5:95 methanol:methylene chloride. The filtrate was concentrated to dryness, redissolved in methylene chloride, then chromatographed on 34 g of silica gel, eluting with 880 mL of ethyl acetate then 220 mL each of 5, 10, and 20% methanol in ethyl acetate. The appropriate fractions were combined and concentrated to give two compounds **(±)-5** (0.487 g, 64.2%): silica gel TLC R_f = 0.50 (iodine char, 95:5 methylene chloride:methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.59 (dd, J = 3, 5 Hz, 1 H), 2.80 (t, J = 5 Hz, 1 H), 3.11 (m, 1 H), 3.25 (dt, J = 6, 15 Hz, 1 H), 3.70 (ddd, J = 3, 6, 15 Hz, 1 H), 6.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.01, 40.75, 45.21, 50.63, 170.69; MS (CI^+) 116 $(M + H)^+$ and **(±)-6** (0.071 g, 9.4%): silica gel TLC R_f = 0.30 (iodine char, 95:5 methylene chloride:methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 3 H), 3.53−3.84 (m, 5 H), 4.60−4.65 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92, 55.88, 63.87, 80.19, 165.39; MS (CI^+) 116 $(M + H)^+$. Note: Treating a solution of **(±)-5** (0.1532 g, 1.331 mmol) in THF (1.54 mL) at 0 °C with lithium *tert*-butoxide (0.1199 g, 1.498 mmol, 1.13 equiv) for 1 h gave **(±)-6** as the major product by TLC.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide: Linezolid: Zyvox. (DMF as solvent) To a solution of **8**[2] (1.032 g, 3.125 mmol) in DMF (2.0 mL) and methanol (0.202 g, 6.32 mmol, 2.02 equiv) at 20 °C was added a solution of lithium *tert*-butoxide in THF (4.16 g of an 18.1 wt % solution, 9.39 mmol, 3.00 equiv) while keeping less than 24 °C with an ice bath. The solution was cooled to 5 °C and **3** (1.207 g, 6.234 mmol, 2.00 equiv) was added. The resulting solution was allowed to stand at 21 °C for 21 h at which point HPLC showed an 86.8% conversion of **8** to linezolid. Saturated aqueous ammonium chloride (5.0 mL) was added followed by water (30 mL), saturated aqueous sodium chloride (20 mL), and methylene chloride (20 mL). The phases were separated and the aqueous washed with methylene chloride (3 × 20 mL). The organics were dried on magnesium sulfate and concentrated to an oil in vacuo (4.209 g). Xylenes A.R. (25 mL) was added, and the product was crystallized by seeding and sonicating (initially gave a gel which broke up to give a slurry). The product was collected by vacuum filtration, washed with xylenes A.R. (10 mL) and dried in a nitrogen stream to afford a white solid (0.6509 g, 61.8%). The filtrate was concentrated in vacuo to an oil and xylenes (15 mL) added. The second crop was crystallized by seeding and sonicating (initially gave a gel which broke up to give a slurry). The product was collected by vacuum filtration, washed with xylenes A.R. (10 mL), and dried in a nitrogen stream to a white solid (0.1085 g, 10.3%). HPLC analyses showed the first and second crops to be 98.9 and 94.6 wt % linezolid, respectively, with <0.2% enantiomer in each; also, an additional 9.7% yield of linezolid was detected in the filtrate by external standard HPLC (total = 80.6%). Analysis data for 1st crop material: mp = 73−76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, J = 14.4, 2.4 Hz, 1H), 7.07 (dd, J = 8.8, 2.0 Hz, 1H), 6.91 (t, J = 8.8 Hz, 1H), 6.43 (br t, 1H), 4.77 (m, 1H), 4.02 (t, J = 9.2 Hz, 1H), 3.86 (t, J = 4.4 Hz, 4H), 3.76 (dd, J = 8.8, 6.8 Hz, 1H), 3.66 (m, 2H), 3.05 (t, J = 4.8 Hz, 4H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.07 (q), 41.93 (t), 47.66 (t), 51.00 (t), 66.95 (t), 71.99 (d), 107.56 (dd, J_{C-F} = 26.16 Hz), 113.97 (dd, J_{C-F} = 3.02 Hz), 118.85 (dd, J_{C-F} = 4.03 Hz), 132.90 (sd, J_{C-F} = 4.03 Hz), 136.58 (sd, J_{C-F} = 9.06 Hz), 154.42 (s), 155.50(sd, J_{C-F} = 246.53 Hz), 171.19 (s) MS (EI) *m*/*z* (relative intensity) 337 (90), 293 (81), 209 (100); $[\alpha]^{25}_D$ = −16 (c = 1.05, ethanol). Anal. Calcd for $C_{16}H_{20}FN_3O_4$: C, 56.97; H, 5.97; N, 12.46; found: C, 56.86; H, 6.05; N, 12.44.

Linezolid (THF as solvent)**.** To **8** (5.006 g, 15.15 mmol) and lithium *tert*-butoxide (3.621 g, 45.23 mmol, 2.99 equiv) was added THF (15 mL) yielding a beige solution after a moderate exotherm from 24 to 31 °C. The mixture was cooled to 14 °C and methanol (0.9691 g, 30.25 mmol, 2.00 equiv) added with an exotherm to 20 °C. The resulting solution was cooled to 7 °C, yielding a thick slurry. **3** (5.885 g, 30.39 mmol, 2.01 equiv) was added and the mixture stirred at 15−18 °C for 15 h at which point HPLC showed a 90.9% conversion of **8** to linezolid. Acetic acid (1.73 mL, 30.22 mmol, 2.00 equiv) was added with an exotherm from 13 to 27 °C, followed by water (20 mL) and methylene chloride (20 mL). The phases were separated and the aqueous washed with methylene chloride (2 × 10 mL). The combined organics were dried on magnesium sulfate and then concentrated in vacuo to a net weight of 18 g. The resulting oil was seeded and ethyl acetate (28 g) added to yield a thin slurry. The slurry was concentrated to 29 g and ethyl acetate (30 g) added. The slurry was cooled to −25 °C and the product collected by vacuum filtration, washed with −25 °C ethyl acetate (2 × 5 mL), and dried in a nitrogen stream to give a white solid (3.725 g, 72.9%): HPLC (99.0 wt %, 98.9 area % linezolid, t_R 1.60 min) conditions: Inertsil

ODS-2 5.0 μm 150 mm × 4.6 mm, flow rate = 2.0 mL/min, gradient elution from 40:60 A:B to 80:20 A:B over 10 min; A = acetonitrile; B = water. External standard HPLC analysis of the filtrate showed 12.9% and 7.6% yield of linezolid and **8**, respectively.

(1*S*)-2-{Acetyl[(2*S*)-2-(acetyloxy)-3-chloropropyl]amino}-1-(chloromethyl)ethyl Acetate(9); (1*S*)-2-{Bis[(2*S*)-2-(acetyloxy)-3-chloropropyl]amino}-1-(chloromethyl)ethyl Acetate (10). A crude slurry of **2a** in 2-propanol was prepared by the procedure above starting with (*S*)-epichlorohydrin (19.34 g, 209 mmol) and substituting 2-propanol for ethanol in the final solvent exchange. The crude slurry was concentrated to 34 g net weight and methylene chloride (92 mL) was added. The mixture was cooled to <0 °C and acetic anhydride (69 mL, 731 mmol, 3.5 equiv) was added followed by pyridine (42 mL, 519 mmol, 2.48 equiv). The mixture was allowed to exotherm to 46 °C, stirred 1.5 h at 42 °C, and then cooled to 18 °C. GC showed a mixture of 91.7% **3** (t_R = 8.5 min), 6.9% **9** (t_R = 14.7 min), and 1.4% **10** (t_R = 17.4 min); conditions: 15 M-DB-1 capillary column, T_{inj} = 250 °C, T_{ini} = 70 °C for 2 min, T_{fin} = 250 °C, rate = 10 °C/min. A solution of potassium bicarbonate (50.08 g, 495.3 mmol, 2.37 equiv) in water (166 mL) was added. The phases were separated and the aqueous washed with methylene chloride (3 × 50 mL). The organics were concentrated to an oil and chased with toluene (4 × 80 g). The oil was dissolved in toluene (93 g), seeded with **3** and isooctanes (44 g added) to give a slurry. The precipitate was collected at room temperature and washed with isooctanes to give **3** (23.11 g, 57.1%) (98.1 area % **3** by GC, 1.5 area % **9**, 0.4 area % **10**. The mother liquour was concentrated to an oil and loaded on a silica gel column (287 g) packed with methylene chloride and eluted with 1000 mL each of 0, 1, 2, 4, 8, 16% methanol in methylene chloride, collecting 14 fractions. Fraction 8 was concentrated to yield **9** (77 area % purity, 553 mg, 1.6%) MS (CI^+) *m*/*z* 234 (100), 236 (49), 328 (65), 330 (43), 332 (8.7); fraction 2 was concentrated to yield **10** (78 mg, 0.27%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 9 H), 2.76 (dd, *J* = 6, 14 Hz, 3 H), 2.93 (dd, *J* = 6, 14 Hz, 3 H), 3.65 (dd, *J* = 5, 7 Hz, 3 H), 3.70 (dd, *J* = 5, 7 Hz, 3 H), 5.10−5.17 (m, 3 H); MS (CI^+) *m*/*z* 292 (100), 294 (42), 298 (56), 300 (52), 326 (48), 328 (40), 330 (11), 420 (54), 422 (57), 424 (16) Anal. Calcd for $C_{12}H_{19}Cl_2NO_5$: C, 43.92; H, 5.84; N, 4.27. Found: C, 44.08; H, 6.01; N, 4.71.

***N*,*N*-Bis({(5S)-3-[4-(1,1-dioxidothiomorpholin-4-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-acetamide (11).** The preparation of **23** below (run in DMF as solvent) was repeated on 27 g of carbamate **22** (74.5 mmol) with minor changes. The lot of reagent **3** used was assayed by GC as containing 2.1 area % **12** and 0.45 area % **9**. When the crude product **23** was redissolved in refluxing water/toluene a small amount of an oily third phase was observed. The water and toluene phases were decanted off to leave behind the oil which was chromatographed on silica gel with acetonitrile eluent to afford a solid (10 mg) HPLC (82 area % **11** t_R = 4.51 min) procedure: Inertsil ODS-2 5.0 μm 150 mm × 4.6 mm, flow rate = 1.0 mL/min, detection at 254 nm, isocratic elution solvent: 479.5 of g buffer (1 L of water, 1.57 g of ammonium formate, formic acid to pH = 3.2) and 409.1 g of acetonitrile; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 3.17 (s, 8 H), 3.61 (s, 8 H), 3.6−4.2 (m, 8 H), 4.93 (q, *J* = 9 Hz, 2 H), 7.1−7.2 (m, 4 H); MS (CI, NH_3) *m*/*z* 748 [100, $(M + H)^+$], 765 [31, $(M + NH_4)^+$].

***N*-{[(5S)-3-(3-Fluoro-4-tetrahydro-2H-thiopyran-4-yl-phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (16).** To a slurry of **14** (1.9543 g, 6.275 mmol) and **3** (2.4312 g, 12.555 mmol, 2.00 equiv) in DMF (3.00 mL) and methanol (0.3974 g, 12.403 mmol, 1.98 equiv) was added lithium *tert*-amylate (1.7765 g, 18.88 mmol, 3.01 equiv) at 2 °C. The mixture was warmed and stirred at 18−23 °C for 18 h. The solution was cannulated into a mixture of saturated ammonium chloride (10 mL) and water (10 mL) while maintaining 5−15 °C and rinsed in with toluene (20 mL) and water (10 mL). Heptane (15 mL) was added and the mixture cooled to 2 °C. The precipitate was collected by vacuum filtration, washed with water (20 mL) and heptane (5 mL), and dried in a nitrogen stream to give a white solid (1.634 g, 73.9%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (q, *J* = 10 Hz, 2 H), 1.84 (s, 3 H), 1.99 (d, *J* = 12 Hz, 2 H), 2.65 (d, *J* = 14 Hz, 2 H), 2.82 (t, *J* = 12 Hz, 3 H), 3.41 (t, *J* = 6 Hz, 2 H), 3.73 (dd, *J* = 6, 9 Hz, 1 H), 4.10 (t, *J* = 9 Hz, 1 H), 4.73 (m, 1 H), 7.23 (dd, *J* = 8, 10 Hz, 1 H), 7.33 (t, *J* = 8 Hz, 1 H), 7.44 (dd, *J* = 2, 13 Hz, 1 H), 8.23 (t, *J* = 6 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) d 22.38 (q), 28.21 (t), 33.49 (t), 35.90 (d), 41.36 (t), 47.13 (t), 71.59 (d), 105.11 (dd, J_{C-F} = 28), 113.76 (dd, J_{C-F} = 3), 127.88 (sd, J_{C-F} = 15), 128.25 (dd, J_{C-F} = 4), 137.89 (sd, J_{C-F} = 12), 153.96 (s), 159.46 (dd, J_{C-F} = 241), 169.97 (s); MS (EI) *m*/*z* (relative intensity) 352 (100); $[\alpha]^{25}_D$ = −13 (*c* = 0.80, methylene chloride). Anal. Calcd for $C_{17}H_{21}FN_2O_3S$: C, 57.94; H, 6.01; N, 7.95. Found: C, 57.64; H, 6.13; N, 7.65.

(*S*)-*N*-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (18). To a slurry of **21** (21.9 g, 66.89 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (150 mg, 0.68 mmol, 0.01 equiv) in toluene (120 mL) was added trifluoroacetic acid (14.07 g, 123.4 mmol, 1.85 equiv. The solution was stirred at 35−37 °C for 6 h. The solution was concentrated in vacuo to 60 mL and toluene (4 × 56 mL) added, concentrating to 50 mL after each addition, then to a final volume of 56 mL. Reagent **3** (24.36 g, 125.80 mmol, 1.88 equiv), DMF (37.5 mL), and isooctanes (38 mL) were added followed by methanol (3.994 g, 124.5 mmol, 1.86 equiv). A solution of lithium *tert*-butoxide (15.00 g, 187.4 mmol, 2.80 equiv) in isooctanes (141 mL) was added over 2 h while maintaining 15 °C and was rinsed in with isooctanes (10 mL). The mixture was stirred for 12 h at 15−19 °C at which point HPLC showed 12% residual **17**. Acetic acid (7.57 g, 126.06 mmol, 1.89 equiv) was added followed by methanol (32 mL). The phases were separated and the upper phase washed twice with a mixture of methanol (32 mL) and water (10 mL). To the combined lower phases were added water (80 mL) and methylene chloride (80 mL). The phases were separated, and the upper was washed twice with methylene chloride (32

mL). The combined lower phases were concentrated in vacuo to 122 mL, and methanol (2 × 75 mL) was added, concentrating to 80 mL after each addition. Toluene (71 mL) was added; then water (71 mL) was added dropwise over 0.5 h while maintaining 21 °C. Isooctanes (61 mL) was added and the slurry cooled to −1 °C. The product was collected by vacuum filtration, washed with water (24 mL) and isooctanes (24 mL), and dried in a nitrogen stream to afford a brown solid (19.43 g, 76.9%): (HPLC: 90.2 wt % **18**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3 H), 2.62 (s, 2 H), 2.85 (t, J = 6 Hz, 2 H), 3.32 (s, 2 H), 3.67 (t, J = 5 Hz, 2 H), 3.79 (t, J = 9 Hz, 1 H), 4.05 (t, J = 9 Hz, 1 H), 4.80 (m, 1 H), 6.00 (s, 1 H), 6.59 (s, 1 H), 7.13 (dd, J = 2 Hz, J = 9 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.37 (dd, J = 2 Hz, J = 13 Hz, 1 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 22.97 (q), 25.05 (t), 25.82 (t), 29.28 (t), 41.78 (t), 47.37 (t), 72.04 (d), 106.15 (dd, J_{C-F} = 29 Hz), 113.23 (dd, J_{C-F} = 3 Hz), 124.58 (d), 126.95 (dd, J_{C-F} = 15 Hz), 129.73 (dd, J_{C-F} = 5 Hz), 134.14(s), 137.99 (sd, J_{C-F} = 10 Hz), 154.25 (s), 159.73 (sd, J_{C-F} = 245 Hz), 171.29 (s); MS (EI) m/z 350 (M^+, 100); $[\alpha]^{25}_D$ = −14 (c = 0.90, methylene chloride). Anal. Calcd for $C_{17}H_{19}FN_2O_3S$: C, 58.27; H, 5.47; N, 7.99. Found: C, 58.27; H, 5.52; N, 7.92. HPLC for **18** (t_R = 2.70 min); **17** (t_R = 8.75 min); **21** (t_R = 5.60 min): Phenomenex Luna 5.0 μm C-8(12) 150 mm × 4.6 mm, flow rate = 2.0 mL/min, gradient elution from 40:60 A:B to 73.3:26.7 A:B over 15 min; A = acetonitrile; B = water.

(*S*)-*N*-[[3-(3-Fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide (20). To a mixture of **19**[13a] (300.0 g, 1.42 mol), **3** (556.1 g, 2.87 mol, 2.02 equiv), methanol (90.03 g, 2.81 mol, 1.98 equiv), and DMF (500 mL) was added a slurry of lithium *tert*-amylate (401.3 g, 4.27 mol, 3.00 equiv) in heptane (1 L) while maintaining −4 to 7 °C, followed by heptane (100 mL). The mixture was then stirred at 19−20 °C for 21 h. The reaction mixture was then added to a mixture of ammonium chloride (228 g, 4.26 mol, 3.00 equiv), water (2.0 L), and toluene (1.0 L) while maintaining 8−10 °C. The reaction mixture was rinsed in with a mixture of water (100 mL), saturated ammonium chloride (50 mL), and toluene (100 mL). The precipitate was collected by vacuum filtration and washed with heptane (1 L) and water (1 L) and dried in a nitrogen stream to give 252.4 g of crude product. This was triturated in acetonitrile (1 kg) at 90 °C and the slurry concentrated under reduced pressure to 800 mL total volume. Toluene (1900 mL) was added while concentrating to maintain 800 mL total volume. Water (1 L) and heptane (1 L) were added, and the precipitate was collected by vacuum filtration, washed with water (750 mL) and heptane (250 mL), and dried in a nitrogen stream to give a white solid (225.7 g, 63.0%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 3 H), 3.35 (s, 1 H), 3.43 (t, J = 6 Hz, 2 H), 3.76 (dd, J = 6, 9 Hz, 1 H), 4.13 (t, J = 9 Hz, 1 H), 4.75 (m, 1 H), 6.96 (td, J = 2, 8 Hz, 1 H), 7.31 (dd, J = 1, 8 Hz, 1 H), 7.43 (q, J = 8 Hz, 1 H), 7.50 (dt, J = 2, 14 Hz, 1 H), 8.25 (t, J = 6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.36 (q), 41.33 (t), 71.62 (d), 104.91 (dd, J_{C-F} = 27), 109.86 (dd, J_{C-F} = 21), 113.52 (dd, J_{C-F} = 2), 130.53 (dd, J_{C-F} = 10), 140.10 (dd, J_{C-F} = 11), 153.95 (s), 161.22 (sd, J_{C-F} = 241), 169.97 (s). Anal. Calcd for $C_{12}H_{13}FN_2O_3$: C, 57.14; H, 5.19; N, 11.11; found: C, 56.99; H, 5.21; N, 11.09; $[\alpha]^{25}_D$ = −40 (c = 1.05, acetonitrile). A second crop was collected from the filtrates (46.8 g, 13.1%, total yield = 76.1%).

***N*-[[(5*S*)-3-[4-(1,1-Dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (23).** *(DMF as Solvent).* To a mixture of **22** (330 g, 910 mmol) and lithium *tert*-butoxide (218.7 g, 2.73 mol, 3.00 equiv) were added isooctanes (1200 mL), DMF (300 mL), and methanol (58.4 g, 1.82 mol, 2.00 equiv). A solution of reagent **3** (353 g, 1.82 mol, 2.00 equiv) in DMF (300 mL) was added over 4 h while maintaining 15−20 °C. The mixture was stirred at 20 °C for 17 h at which point HPLC showed a 91% conversion of **22** to **23**. Acetic acid (104 mL, 1.82 mol, 2.0 equiv) was added while maintaining 14−20 °C followed by methanol (900 mL) and water (150 mL). The phases were separated, and the upper was washed twice with a mixture of methanol (488 mL) and water (163 mL). To the combined lower extracts were added methylene chloride (1 L) and water (1 L). The phases were separated, and the upper was washed with methylene chloride (3 × 1 L). The extracts were concentrated in vacuo to 300 mL total volume. 2-Propanol (2000 mL) was added, and the resultant slurry was stirred at 20−25 °C for 5 h and the product collected by vacuum filtration, washed with 2-propanol (1500 mL), and dried in a 50 °C vacuum oven to afford crude **23** as a yellow solid (259.4 g). Crude **23** was slurried in water (6.0 L); the slurry was warmed to 100 °C and then cooled to 25 °C; the product was collected by vacuum filtration, washed with water (2 × 500 mL), and dried in a 60 °C vacuum oven to afford an off-white solid (230.2 g, 62.7%): HPLC: 99.5 area % **23**, t_R = 2.96 min; **11**, 0.13%, t_R = 3.87 min; **22**, 0.26%, t_R = 10.83 min (HPLC procedure: Inertsil ODS-2 5.0 μm 150 mm × 4.6 mm, flow rate = 1.0 mL/min, detection at 254 nm, isocratic elution solvent: 409.1 g of acetonitrile and 479.5 g of a mixture of 1 L of water, 1.57 g of ammonium formate, and formic acid to pH = 3.2); ^{1}H NMR (300 MHz, DMSO) δ 1.83 (s, 3H), 3.20−3.24 (m, 4H), 3.40 (t, J = 5.6 Hz, 2H), 3.47−3.51 (m, 4H), 3.70 (dd, J = 9.0 Hz, J = 7.9 Hz, 1H), 4.09 (t, J = 9.0 Hz, 1H), 4.69−4.78 (m, 1H), 7.29 (s, 1H), 7.32 (s, 1H), 8.21 (t, J = 5.6 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 22.32 (s), 41.23 (s), 47.08 (s), 49.79 (s), 51.89 (s), 71.63 (s), 101.95 (d, J_{C-F} = 29.1 Hz), 121.93 (dd, J_{C-F} = 14.5 Hz), 135.71 (dd, J_{C-F} = 14.5 Hz), 153.76 (s), 157.92 (dd, J_{C-F} = 244.95 Hz), 169.90 (s); IR (mull) 1741, 1643, 1558, 1520, 1421, 1311, 1289, 1279, 1245, 1233, 1224, 1211, 1134, 1123, 849 cm^{-1}; KF = 0.00%; $[\alpha]^{25}_D$ = −23 (c = 0.96, DMSO); UV Σ_{max} 253 (17500, 95% EtOH); Melt Solvate: 0.06% DMF; ROI 0.04%. Anal. Calcd for $C_{16}H_{19}F_2N_3O_5S$: C, 47.64; H, 4.75; N, 10.42; S, 7.95; F, 9.42. Found: C, 47.58; H, 4.77; N, 10.41; S, 7.94; F, 9.36.

Alternate Preparation of 23 *(THF/Acetonitrile as solvent).* To a slurry of **22** (300 g, 828 mmol) and **3** (321 g, 1.656 mol, 2.00 equiv) in acetonitrile (600 mL) and methanol (53 g, 1.656 mol, 2.0 equiv) was added a slurry of lithium *tert*-butoxide (199.6 g, 2.48 mol, 3.00 equiv) in THF (500

mL) over 0.5 h while maintaining 4−11 °C followed by a THF (100 mL) rinse. The reaction mixture was then stirred for 15 h at 16 °C, and a solution of glacial acetic acid (95 mL, 1.656 mol, 2.0 equiv) in water (1.33 L) was added over 15 min at 5 °C followed by water (330 mL). The mixture was concentrated in vacuo to 2.4 L. Toluene (1.8 L) and methanol (600 mL) were added and the phases separated at 70 °C. The organic was washed with water (1.2 L) and methanol (300 mL) at 67 °C. The combined aqueous layers were washed with toluene (1.8 L) at 67 °C. The upper toluene layer was re-extracted with water (1.2 L) and methanol (300 mL) at 60−65 °C. The combined aqueous layers were extracted with methylene chloride (2 × 1.5 mL). The organcics were clarified, and water (5.0 L) and methanol (2.5 L) were added. The mixture was concentrated via atmospheric distillation to a pot temperature of 85 °C. The solution was then cooled to 65 °C, seeded, and then slowly cooled at 5−10 °C/h to 2 °C. The white slurry was then filtered; the cake was washed with a mixture of water (1.1 L) and methanol (360 mL) and dried at 60 °C for ca. 3 days to give a white solid (259.2 g, 77.6%) HPLC t_R = 3.06 min (98.7% **23**) (column = Inertsil OSD-2, 150 mm × 4.6 mm, flow rate: 1.0 mL/min, detection at 254 nm, isocratic elution solvent: 409.1 g of acetonitrile and 479.5 g of a mixture of 1 L of water, 1.57 g of ammonium formate, and formic acid to pH = 3.2).

Alternate Preparation of 23 *(Bromo Analogue of **3** as Reagent).* **22** (2.5 g, 6.9 mmol), (*S*)-*N*-[2-(acetyloxy)-3-bromopropyl]acetamide (3.27 g, 13.8 mmol, 2.0 equiv), and methanol (0.56 mL, 13.8 mmol, 2.0 equiv) were stirred in acetonitrile (5 mL). A slurry of lithium *tert*-butoxide (1.7 g, 20.7 mmol, 3.0 equiv) in THF (5 mL) was prepared and added to the carbamate/acetamide mixture while maintaining a temperature less than 20 °C. The cloudy light yellow/brown solution was stirred at 15−16 °C for 16 h. The reaction was quenched with a solution of concentrated acetic acid (0.8 mL, 13.6 mmol, 2.0 equiv) in THF (1.8 mL) while maintaining a temperature less than 20 °C. Water (7 mL) was added to the mixture. The mixture was concentrated to approximately 20 mLvolume and washed with toluene (15 mL) and methanol (7 mL) while maintaining temperature above 60 °C. The phases were separated, and the upper layer was washed twice with a mixture of water (20 mL) and methanol (5 mL) while maintaining temperature above 60 °C. The combined lower phases were washed twice with methylene chloride (2 × 20 mL) and were concentrated to approximately 25 mL volume. Water (35 mL) was added, and the slurry was concentrated to approximately 45 mL volume and slowly cooled to 0 °C. The precipitate was collected by vacuum filtration, washed with a cold solution of water (10 mL) and methanol (2.5 mL), and dried in a nitrogen stream to give a white solid (2.32 g, 83%). HPLC t_R = 1.83 min (column = Phenomenex IB-SIL Phenyl BD, 150 mm × 4.6 mm, flow rate: 1.0 mL/min, detection at 254 nm, isocratic elution solvent: 350 mL of acetonitirile and 650 mL of a solution of 0.7 mL of triethylamine in 1 L of water adjusted to pH 3.5 with phosphoric acid).

Alternate Preparation of 23 *(Carbamate **25** as Substrate).* To a solution of **25** (0.971 g, 2.22 mmol), **3** (0.539 g, 2.78 mmol, 1.26 equiv), and trichloroethanol (0.31 mL, 3.23 mmol, 1.45 equiv) in acetonitrile (2 mL) and THF (2 mL) at 0 °C was added lithium *tert*-butoxide (0.402 g, 5.02 mmol, 2.27 equiv). The mixture was allowed to warm to room temperature and stir for 16 h. HPLC analysis showed 66% **23**, 26.5% **25**: t_R (**23**) = 1.7; t_R (**25**) = 13.9 min, Inertsil ODS-2 5.0 μm 250 mm × 4.6 mm, flow rate = 2.0 mL/min, detection at 254 nm, isocratic elution solvent: 479.5 g buffer (1 L of water, 1.57 g of ammonium formate, formic acid to pH = 3.2) and 409.1 g of acetonitrile.

2,2,2-Trichloroethyl 4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenylcarbamate (25). To a slurry of **24** hydrochloride salt (4.06 g, 13.59 mmol) and potassium carbonate (3.38 g, 24.4 mmol, 1.80 equiv) in THF (40 mL) was added 2,2,2-trichloroethyl chloroformate (2.44 mL, 17.7 mmol, 1.31 equiv) and the mixture warmed to 45 °C. Methylene chloride (30 mL) was added, and the salts were filtered off with a methylene chloride wash (40 mL). The filtrate was washed with saturated sodium bicarbonate solution, and the aqueous was back-extracted with methylene chloride (50 mL). The organics were dried on magnesium sulfate; 100 mL of isooctanes was then added, and the mixture was concentrated to a slurry. Isooctanes (100 mL) was again added, and the precipitate was collected by vacuum filtration and dried in a nitrogen stream to give a white solid (5.54 g, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (t, J = 5 Hz, 4 H), 3.46 (s, 4 H), 4.95 (s, 2 H), 7.21 (d, J = 11 Hz, 2 H), 10.46 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.82, 51.94, 73.46, 95.55, 102.28 (J_{C-F} = 29 Hz), 121.71, 136.02, 151.53, 158.06(J_{C-F} = 243 Hz, J_{C-F} = 9 Hz).

[(2*S*)-Oxiranylmethyl]carbamic Acid, 1,1-Dimethylethyl Ester (26). To a solution of **27** (19.98 g, 95.29 mmol) in methanol (50.0 mL) at 13 °C was added lithium *tert*-butoxide (8.40 g, 104.9 mmol, 1.10 equiv) while maintaining less than 22 °C. The mixture was stirred at 8−20 °C for 15 min, and water (200 mL) followed by methylene chloride (200 mL) was added. The phases were separated, and the aqueous was washed with methylene chloride (135 mL). The combined organics were dried on magnesium sulfate and concentrated to an oil. Column chromatography on silica gel (0 to 4% methanol in methylene chloride eluent) gave the title compound as a white solid (14.26 g, 86.4%): mp = 45−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.448 (s, 9 H), 2.59 (s, 1 H), 2.78 (t, J = 4 Hz, 1 H), 3.09 (s, 1 H), 3.20 (dt, J = 14, 6 Hz, 1 H), 3.53 (d, J = 15 Hz, 1 H), 4.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.28 (q), 41.72 (t), 45.04 (t), 50.85 (d), 79.61 (s), 155.96 (s); MS (CI^+) for $C_8H_{15}NO_3$ *m/z* 174 $(M + H)^+$; $[\alpha]^{22}_D$ (−13, C = 1.0, methylene chloride). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.17; H, 8.54; N, 8.00.

***tert*-Butyl-(2*S*)-3-chloro-2-hydroxypropylcarbamate (27).** To a slurry of **2a** (900 g, 6.16 mol) and di-*tert*-butyldicarbonate (1.470 kg, 6.74 mol, 1.09 equiv) in methanol (3.6 L) was added a solution of potassium bicarbonate (702 g, 7.01 mol, 1.14 equiv) in water (2.1 L) over 45 min while maintaining 28−30 °C. The mixture was stirred at 28 °C

for 1 h at which point GC showed 3.4 area % residual di-*tert*-butyl dicarbonate. Methylene chloride (3.6 L) and water (1.8 L) were added and the phases separated. The organic was washed with water (900 mL), and both aqueous were serial back-extracted with methylene chloride (2.25 L). The combined organics were concentrated in vacuo to 2.7 L total volume. Toluene (2.7 L) was added and the solution concentrated to 3.0 L total volume. Isooctanes (4.2 L) was added, the resultant two-phase solution seeded with **27** and stirred at 22 °C for 20.5 h. The resultant slurry was cooled to 4 °C and stirred for 3 h. The product was collected by vacuum filtration and washed with isooctanes (900 mL) and dried in a 30 °C vacuum oven to afford a white solid (1162 g, 90.0%): GC 96.0 area % **27**; mp = 48−52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.13 (bs, 1H), 3.92 (m, 1H), 3.76 (bs, 1H), 3.60−3.51 (m, 2H), 3.42 (m, 1H), 3.24 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.26 (q), 43.81 (t), 46.42 (t), 71.19 (d), 80.09 (s), 157.17 (s); $[\alpha]^{25}_D = -22$ (*c* = 0.94, methylene chloride). Anal. Calcd for $C_8H_{16}ClNO_3$: C, 45.83; H, 7.69; N, 6.68; Cl, 16.91. Found: C, 46.12; H, 7.73; N, 6.76; GC for **27** (t_R= 8.3 min): 15 M-DB-1 capillary column, T_{inj} = 250 °C, T_{ini} =70 °C for 2 min, T_{fin} = 250 °C, rate = 10 °C/min.

***tert*-Butyl-{(5*S*)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate (28).** To a solution of **8** (0.8758 g, 2.651 mmol) and **27**, (0.7011 g, 3.344 mmol, 1.26 equiv) in DMF (1.7 mL) in an ice bath was added a solution of lithium *tert*-butoxide in THF (2.82 g of an 18.1 wt % solution, 6.37 mmol, 2.40 equiv). The resultant solution was allowed to stand at 20 °C for 44 h (HPLC showed 95.0% conversion after 20 h and 97.8% conversion after 44 h). Saturated aqueous ammonium chloride (5.0 mL), water (10 mL), and methylene chloride (12 mL) were added and the phases separated. The aqueous was washed with methylene chloride (12 mL), and the combined organics were dried on magnesium sulfate and concentrated to an oil (2.4574 g). External standard HPLC showed the oil to contain 0.9397 g (89.6%) of **28**. HPLC retention time = 4.97 min (column = Zorbax SB-C8 3.5 μm 150 mm × 4.6 mm, flow rate = 2.0 mL/min, gradient elution from 30:70 A:B to 90:10 A:B over 15 min; A = 969:30:1 acetonitrile:THF:trifluoroacetic acid; B = 949:50:1 water:THF:trifluoroacetic acid). An analytical sample of **28** isolated by column chromatography (ethyl acetate/hexanes eluent) had the following physical properties: mp = 46.2−48.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, *J* = 14.4, 2.4 Hz, 1H) 7.09 (dd, *J* = 8.8, 2.0 Hz), 6.92 (t, *J* = 9.2, 1H) 5.11 (bs, 1H), 4.73 (bs, 1H), 4.00 (t, *J* = 8.8, 1H), 3.86 (t, *J* = 4.4, 4H), 3.80 (t, *J* = 6.8, 1H), 3.50 (m, 2H), 3.04 (t, *J* = 4.8, 4H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.25 (q), 43.27 (t), 47.53 (t), 51.03 (dt, J_{C-F} = 3.02 Hz), 66.95 (t), 71.99 (d), 80.19 (s), 107.50 (dd, J_{C-F} = 26.16 Hz), 113.93 (dd, J_{C-F} = 3.02 Hz), 118.83 (dd, J_{C-F} = 4.03 Hz), 133.18 (sd, J_{C-F} = 11.07 Hz), 136.45 (sd, J_{C-F} = 9.06 Hz), 154.29 (s), 155.55 (sd, J_{C-F} = 241.50 Hz), 156.30 (s). MS (EI) *m*/*z* (relative intensity) 395 (100), 339 (85); $[\alpha]^{25}_D$ = −36 (*c* = 0.71, acetonitrile). Anal. Calcd for $C_{19}H_{26}FN_3O_5$: C, 57.71; H, 6.63; N, 10.63; found: C, 57.63; H, 6.81; N, 10.32.

***tert*-Butyl-{(5*S*)-3-[4-(1,1-dioxohexahydro-1lambda^6-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate (29).** To a slurry of **13**[13a] (1.0037 g, 2.92 mmol), and **27**, (0.7608 g, 3.629 mmol, 1.24 equiv) in DMF (1.80 mL) in an ice bath was added lithium *tert*-butoxide in THF (18.07 wt % solution, 2.7465 g, 6.20 mmol, 2.12 equiv). The mixture was allowed to stand at 20−25 °C for 37 h. Toluene (10 mL), saturated aqueous ammonium chloride (5 mL), water (5 mL) and heptane (10 mL) were added and the precipitate collected by vacuum filtration, washed with water (13.2 g) and toluene (10.2 g) and dried in a nitrogen stream to give a white solid, 1.1507 g (89.0%): HPLC t_R = 3.0 min (column = Phenomenex Luna C8 5 μm, 150 mm × 4.6 mm, flow rate = 2.0 mL/min, gradient elution from 40:60 A:B to 100:0 A:B over 15 min; A = acetonitrile; B = water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (s, 9 H), 2.07 (m, 2 H), 2.17 (q, *J* = 13 Hz, 2 H), 3.10 (d, *J* = 12 Hz, 2 H), 3.20 (t, *J* = 12 Hz, 1 H), 3.28 (t, *J* = 5 Hz, 1 H), 3.30 (m, 3 H), 3.80 (dd, *J* = 6, 9 Hz, 1 H), 4.11 (t, *J* = 9 Hz, 1 H), 4.71 (m, 1 H), 7.20 (t, *J* = 6 Hz, 1 H), 7.24 (d, *J* = 8 Hz, 1 H), 7.37 (t, *J* = 9 Hz, 1 H), 7.47 (dd, *J* = 2, 13 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.05 (q), 29.91 (t), 33.49 (d), 42.88 (t), 47.06 (t), 50.45 (t), 71.53 (d), 78.07 (s), 105.18 (dd, J_{C-F} = 28 Hz), 113.78 (d), 125.32 (sd, J_{C-F} = 15), 128.13 (dd, J_{C-F} = 6), 138.41 (sd, J_{C-F} = 11), 153.98 (s), 157.17 (sd, J_{C-F} = 241), 160.8 (s); MS (EI) *m*/*z* (relative intensity) 442 (2), 342 (21), 243 (31), 151 (100); $[\alpha]^{25}_D$ = −23 (*c* = 0.93, methylene chloride). Anal. Calcd for $C_{20}H_{27}FN_2O_6S$: C, 54.29; H, 6.15; N, 6.33. Found: C, 54.09; H, 6.20; N, 6.41.

[[(5*S*)-3-[3-Fluoro-4-(tetrahydro-2H-thiopyran-4-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]carbamic Acid 1,1-Dimethylethyl Ester (30). To a solution of **14**[13a] (0.915 g, 2.94 mmol) and **27** (0.768 g, 3.66 mmol, 1.25 equiv) in DMF (1.8 mL) and THF (3.0 mL) at 0 °C was added lithium *tert*-butoxide (0.697 g, 8.71 mmol, 2.97 equiv). The mixture was allowed to room to room temperature over 16 h. Saturated aqueous ammonium chloride (5 mL), water (5 mL), toluene (10 mL) and isooctanes (20 mL) were added and the phases separated. The aqueous was washed with toluene (10 mL) and the combined organics dried on $MgSO_4$ and concentrated to an oil. Column chromatography (gradient from 0 to 70% ethyl acetate in hexanes) afforded a hard oil (0.920 g, 76.3%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 1.86 (q, *J* = 13 Hz, 2 H), 2.06 (d, *J* = 15 Hz, 2 H), 2.69 (d, *J* = 14 Hz, 2 H), 2.86 (t, *J* = 14 Hz, 3 H), 3.52 (m, 2 H), 3.83 (t, *J* = 7 Hz, 1 H), 4.01 (t, *J* = 9 Hz, 1 H), 4.75 (s, 1 H), 5.03 (s, 1 H), 7.14−7.22 (m, 2 H), 3.39 (d, *J* = 12 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.16, 29.17, 33.80, 36.35, 47.33, 71.98, 80.20, 105.96 (J_{C-F} = 29 Hz), 113.54 (J_{C-F} = 3 Hz), 127.89 (J_{C-F} = 6 Hz), 129.02 (J_{C-F} = 15 Hz), 137.37(J_{C-F} = 11 Hz), 154.18, 156.22, 160.18 (J_{C-F} = 243 Hz). Anal. Calcd for $C_{20}H_{27}FN_2O_4S$: C, 58.52; H, 6.63; N, 6.82. Found: C, 58.20; H, 6.74; N, 6.66.

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