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Convenient Synthesis of the Antibiotic Linezolid via an Oxazolidine-2,4-dione Intermediate Derived from the Chiral Building Block Isoserine

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Dedicated to C.I.N.M.P.I.S. on the occasion of its 20th anniversary

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We describe a new synthesis of the 5-(aminomethyl)oxazolidin-3-one core of linezolid in enantiomerically pure form. The expedient cyclization of the α-hydroxy amide derived from isoserine and 3-fluoro-4-morpholinoaniline to give the corresponding (aminomethyl)oxazolidine-2,4-dione, followed by its mild selective reduction at the C(4)-position, gave linezolid in almost quantitative overall yield.

Introduction

The development of bacterial resistance to currently available antibacterial agents is a growing global health problem.[1] Indeed, infections caused by multidrug-resistant pathogens are responsible for significant morbidity and mortality in both hospital and community settings.[2] One possible approach to face this problem is to design new classes of antibacterial agents that employ new mechanisms of action. Such agents should exhibit a lack of cross-resistance with existing antimicrobial drugs. However, from the early 1970s to 1999 the innovative antibiotic pipeline dried up. All newly launched antibiotics were analogues of existing drugs except for mupirocin, an antibiotic active against Gram-positive bacteria launched in 1985. Since 2000, the situation has improved, with five more new classes of antibiotics approved and launched: linezolid (LZD, **1**),[3] daptomycin, retapamulin, fidaxomicin, and bedaquiline.[2]

Discovered in the 1990s and approved in the U.S. by the FDA in 2000, LZD (Figure 1) is currently the only commercially available antibiotic in the oxazolidinone class. Compounds containing the oxazolidinone moiety are interesting because their spectrum of activity covers the important Gram-positive pathogens, particularly those that have been the cause of resistance development.[2,3]

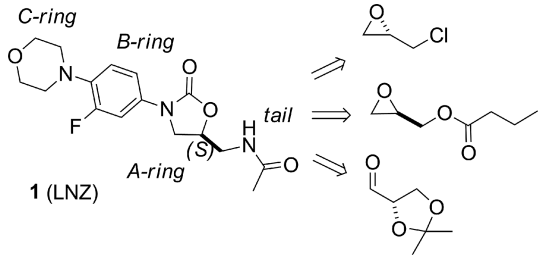

Figure 1. The syntheses of LZD (**1**) utilize chiral building blocks.

LZD selectively inhibits bacterial protein synthesis by binding the peptidyltransferase center on the bacterial ribosome, thus preventing the bacterial translation process.[4] This action mechanism is unique among protein synthesis inhibitors and explains why LZD retains antibacterial activity against Gram-positive organisms that are resistant to members of other classes.

When LZD came onto the market, it was claimed that there would be no cross-resistance to this antibiotic and that resistance would be rare and difficult for the bacteria to develop.[5] Nevertheless, with the increased wide use of LZD and abuse to some degree in clinics in recent years, some clinically resistant strains to LZD have been found worldwide. These include *S. aureus* and *Enterococcus sp.*,[6] and although the LZD-resistant strains (LinR) appear relatively infrequently in the clinic, the infections caused by them were found to be life-threatening.

Consequently, several researchers have recently focused on modifying the oxazolidinone structure to seek analogues with an extended spectrum of antibacterial activity covering

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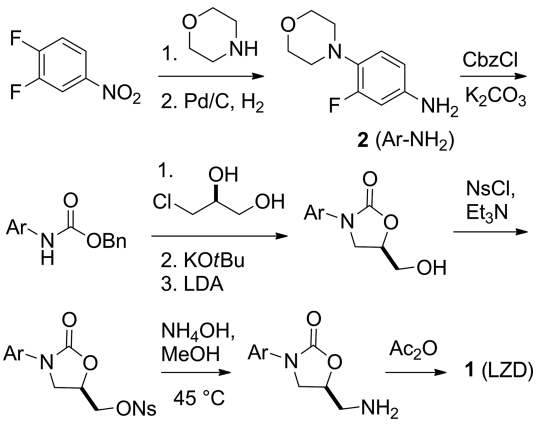
Gram-negative organisms, activity against LinR strains, and an improved safety profile. At present, only four oxazolidinones have entered clinical development.[7] As a consequence, the identification of new synthetic protocols to obtain the 5-(aminomethyl)oxazolidin-3-one core in enantiomerically pure form can be regarded of great interest for the preparation of LZD and analogues.

The key step in LZD synthesis is the formation of the *S*-configured 5-substituted oxazolidinone A-ring. Most protocols described in patents or publications made use of chiral oxiranes[3,7,8] such as epichlorohydrin[9] (Figure 1) or of other building blocks such as glyceraldehyde[10] (Figure 1), whereas very few papers have reported approaches based on asymmetric protocols.[11] The optimized large-scale synthesis of LZD involves a total of nine steps, with the oxazolidinone ring being built by adding enantiomerically pure (*S*)-3-chloropropane-1,2-diol to an appropriate Cbz-protected aniline (Scheme 1).[3,8]



Scheme 1. Synthesis of LZD (**1**) on a process scale.

The large majority of LZD analogues reported in the literature display modifications at the B or C ring and/or in the C(5)-side chain.[2,3,7] In contrast, replacement of the oxazolidinone ring A with other heterocycles has been described only a very few times.[12]

In this context, here we report an expedient synthesis of the oxazolidinone core from the very convenient chiral reagent isoserine, taking advantage of a synthetic strategy that is also suitable for furnishing new LZD analogues bearing diverse substituents on the A-ring.

Results and Discussion

In the last few years we have been interested in the rapid and simple formation of 1,3-oxazolidin-2-one scaffolds for the design of β-turn-like peptidomimetics[13] or as chiral auxiliaries for the stereoselective synthesis of unusual amino acids.[14] Very recently, we observed that treatment of peptide sequences containing the α-hydroxy-β^2-amino acid[15] isoserine (Isoser) with carbonate gave rise to 5-(aminomethyl)oxazolidine-2,4-dione rings.[16]

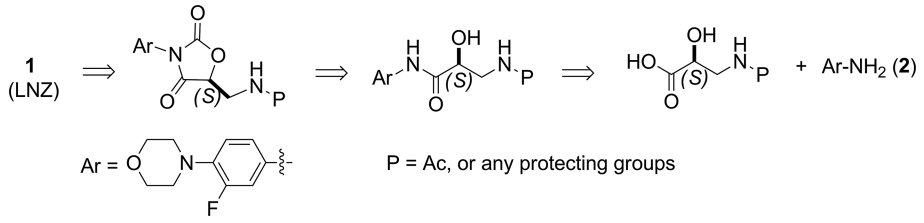
These heterocycles have been described and utilized only occasionally in organic and medicinal chemistry.[17] Our result prompted us to design a plausible retrosynthetic pathway for the synthesis of optically pure LZD (**1**) via the intermediate 5-(aminomethyl)oxazolidine-2,4-dione, taking advantage of the very convenient commercially available chiral reagent (*S*)-isoserine (Scheme 2). The rationale for the other steps of the proposed strategy is discussed in the following sections.

The approach depicted in Scheme 2 could be exploited in the preparation of a number of unprecedented LZD derivatives bearing diverse substituents on the A-ring and/or on the methylacetamide tail (see Figure 1). Isoser can also be purchased in the *R* configuration, and several enantiomerically pure Isoser derivatives are commercially available.[18] Furthermore, many nonracemic substituted isoserines can be obtained from chiral starting materials or by enzymatic resolution, by the use of chiral auxiliaries,[19] or by asymmetric catalysis, such as through catalytic enantioselective Henry reactions.[20] These synthetic alternatives will be developed in due course.

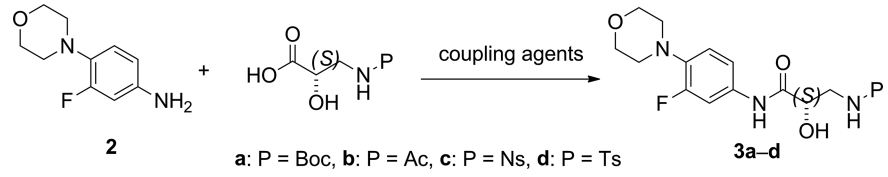
According to the retrosynthetic plan, the first step corresponded to the coupling of 3-fluoro-4-morpholin-4-ylphenylamine (**2**), prepared as reported in the literature,[3] and Isoser. Initially, we optimized the conditions for the coupling of Isoser bearing different protecting groups at the N terminus. The reaction between **2** and *N*-Boc-IsoserOH (Scheme 3) was attempted according to a protocol for the coupling of anilines with chiral α-hydroxy acids described in the literature. This strategy appeared to be a suitable process for the synthesis of the enantiomerically pure α-hydroxy amide **3a**.[21] Arylamine **2** was treated with $SOCl_2$/IMD (imidazole) to give the corresponding *N*-sulfinylarylamine, and treatment of this with *N*-Boc-IsoserOH was performed in the presence of 1,2,4-triazole. Despite several modifications designed to optimize the procedure (see the Supporting Information), in our hands the reaction afforded the expected amide **3a** only in moderate yields of up to 40% (Table 1, Entry 1).

Consequently, reactions between **2** and *N*-Boc-IsoserOH were conducted under various conditions (Table 1) and in different solvents (only the best results are reported in Table 1). All runs were monitored by tlc and terminated after the disappearance of the reagents, or in any case after 12 h. The reaction between **2** and the mixed anhydride obtained from *N*-Boc-IsoserOH and ethyl chloroformate/TEA gave only traces of **3a** after 12 h (Table 1, Entry 2). The use of EDC and HOBt as coupling activating agents in the presence of DIPEA (or TEA, not shown) at room temp. afforded **3a** only in low yield (15%, Entry 3). The use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave a 40% yield (Entry 4), whereas NMM (*N*-methylmorpholine) gave a more satisfactory 60% yield (Entry 5).

On the other hand, the use of the activating agents HBTU/HOBt/NMM or HATU/HOBt/NMM at room temp. for 12 h led to very good yields of 96% and 94% (Entries 6 and 7 in Table 1), respectively. These two reactions were then accelerated by heating for 10 min at 80 °C



Scheme 2. Retrosynthetic approach to LZD (**1**) via an oxazolidine-2,4-dione intermediate, readily obtained in turn from the chiral building block isoserine.



Scheme 3. Coupling of **2** and Isoser.

Table 1. Coupling reactions of isoserine derivatives and **2** to afford amides **3a**–**d**.

Entry	P	Coupling agents	Temperature [°C]	Solvent	3	Yield [%][a]
1	Boc	1. $SOCl_2$/IMD 2. triazole	1. –30 2. room temp.	CH_2Cl_2/DMF	**a**	40[b]
2	Boc	EtOCOCl/TEA	–20 to room temp.	CH_2Cl_2/DMF	–	–[b,c]
3	Boc	EDC/HOBt/DIPEA	0 to room temp.	CH_2Cl_2/DMF	**a**	15[b]
4	Boc	EDC/HOBt/DBU	0 to room temp.	CH_2Cl_2/DMF	**a**	40[b]
5	Boc	EDC/HOBt/NMM	0 to room temp.	CH_2Cl_2/DMF	**a**	60[b]
6	Boc	HBTU/HOBt/NMM	0 to room temp.	CH_2Cl_2/DMF	**a**	96[b]
7	Boc	HATU/HOBt/NMM	0 to room temp.	CH_2Cl_2/DMF	**a**	94[b]
8	Boc	HBTU/HOBt/NMM	80 (MW)	DMF	**a**	98[d]
9	Boc	HATU/HOBt/NMM	80 (MW)	DMF	**a**	98[d]
10	Ac	HBTU/HOBt/NMM	0 to room temp.	CH_2Cl_2/DMF	**b**	97
11	Ac	HATU/HOBt/NMM	80 (MW)	DMF	**b**	98[d]
12	Ac	EDC/HOBt/NMM	0 to room temp.	CH_2Cl_2/DMF	**b**	20
13	Ts[e]	HATU/HOBt/NMM	80 (MW)	DMF	**c**	97[d]
14	Ns[e]	HATU/HOBt/NMM	80 (MW)	DMF	**d**	96[d]

[a] Determined after isolation by flash chromatography over silica gel. [b] Reaction time 12 h. [c] Traces. [d] Reaction time 10 min. [e] Not further examined.

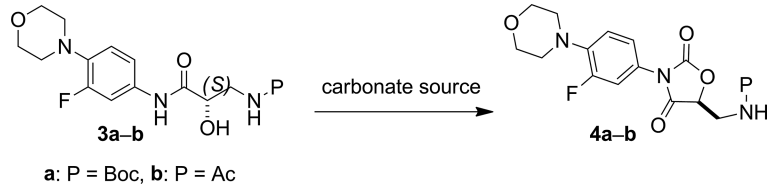
by MW irradiation, giving **3a** in quantitative yields after isolation by flash chromatography over silica gel (Entry 8 with HBTU and Entry 9 with HATU).

Notably, Isoser was incorporated without any need for protection of the OH function. Under the reaction conditions reported above,[13] the acylation of the OH function and thus the formation of isoserine-isoserine side products was not observed, as confirmed by the ^{1}H NMR and RP-HPLC ESI MS analyses of the crude reaction mixtures.

The availability of *N*-Ac-IsoserOH offered the opportunity to synthesize a direct precursor of LZD (**1**) already equipped with the desired methylacetamide tail (Scheme 2). Therefore, we treated **2** and *N*-Ac-IsoserOH under the best-yielding conditions determined for the preparation of **3a** either at room temp. (Entry 6 in Table 1) or with MW activation (Entry 9 in Table 1). In particular, the use of HBTU/HOBt/NMM at room temp. gave **3b** in 97% yield after 12 h (Entry 10), whereas HATU/HOBt/NMM at 80 °C under MW irradiation gave the same product quantitatively in 10 min (Entry 11). As a reference control, we repeated the coupling with EDC/HOBt/NMM (see Entry 5) and obtained a low yield (20%, Entry 12). This observation confirms the efficacy of HATU/HOBt/NMM as coupling reagents and MW activation.

We observed that *N*-Ts- and *N*-Ns-IsoserOH (*N*-nosyl-IsoserOH) behaved similarly to *N*-Boc- and *N*-Ac-IsoserOH in the coupling with **2** under the same reaction conditions as used in Entry 9 (Table 1), giving the corresponding α-hydroxy arylamides **3c** and **3d** in almost quantitative yields (Entries 13 and 14). The arylsulfonyl protecting groups might be of some interest for future developments of LZD analogues. Thanks to its simpler cleavage, the Boc protecting group represents the most convenient option.[22] Nevertheless, the literature reports several methods for the mild cleavage of arylsulfonyl groups.[23]

The next synthetic step of the strategy depicted in Scheme 2 consisted of the cyclization of the Isoser arylamides **3** to the five-membered heterocycles **4** (Scheme 4). As anticipated, we observed that oligopeptides containing Isoser underwent cyclization to 5-(aminomethyl)oxazolidine-2,4-diones on treatment with 1.1 equiv. of DSC (*N*,*N*′-disuccinimidyl carbonate) and a catalytic amount of



Scheme 4. Cyclization of **3a** and **3b** to 3-aryl-5-(aminomethyl)-1,3-oxazolidine-2,4-diones **4a** and **4b**.

DIPEA in DMF at room temp. for 1 h.[16] Under these conditions, **3a** and **3b** gave the corresponding **4a** and **4b** in very good yields of 96% (Entry 1 in Table 2) and 92% (Entry 2 in Table 2), respectively, after purification by flash chromatography over silica gel.

Table 2. Cyclization of **3a** and **3b** to **4a** and **4b**: reagents and yields.

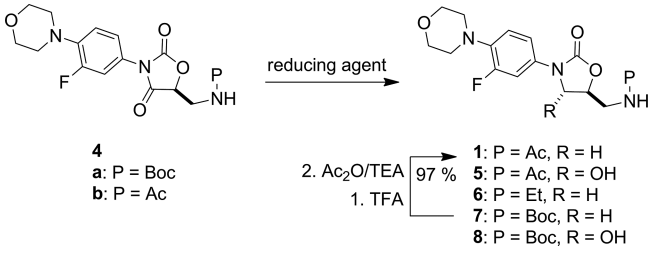
Entry	3	Carbonate	4	Yield [%][a]
1	**a**	DSC	**a**	96[b]
2	**b**	DSC	**b**	92[b]
3	**a**	Boc_2O	**a**	15[c]
4	**a**	triphosgene	**a**	35[c]
5	**a**	CDI	**a**	30[c]
6	**a**	*p*NO_2-phenyl chloroformate	**a**	45[c]

[a] Determined after isolation by flash chromatography over silica gel. [b] Reaction time 1 h. [c] Reaction time 12 h.

Other carbonates or dicarbonates converted **3a** into the 1,3-oxazolidine-2,4-dione **4a** in lower yields: 15% with Boc_2O (Table 2, Entry 3),[24] 35% with triphosgene (Entry 4),[24] 30% with CDI (1,1′-carbonyldiimidazole)[25] (Entry 5), or 45% with *p*-nitrophenyl chloroformate[26] (Entry 6). All reactions were conducted at room temp. for 12 h; increasing the equivalents of the reagents, time, and temperature, in different solvents, had little effect on the reactions.

With the Boc-aminomethyl compound **4a** and the acetamidomethyl compound **4b** to hand, the last step to LZD (**1**) consisted of the reduction of the carbonyl group at C(4) (Scheme 5 and Table 3). This step raised some concerns with regard to the risk of simultaneous reduction of the acetamide segment. The reduction of amides to amines under mild conditions is regarded as a highly valuable but challenging transformation; many of the reported procedures utilize costly or harmful heavy metal catalysts, high pressure, and/or high temperatures.[27] The convenience of the strategy depicted in Scheme 2 was substantiated by the observations reported in the literature that in a 1,3-oxazolidine-2,4-dione, the *N*-carbamate moiety increases the reactivity of the internal amide bond towards reduction by $NaBH_4$.[17] This precedent motivated us to attempt conversion of **4b** into LZD (**1**) by identification of a suitable reducing agent (Table 3).

Indeed, the 5-methylacetamide **4b** was regioselectively reduced with 1.5 equiv. of $NaBH_4$ in H_2O/THF at 0 °C, giving exclusively the 5-aminomethyl-4-hydroxy compound **5** (Scheme 5) with *trans* relative stereochemistry (Table 3, Entry 1). This LZD derivative might be successfully utilized for the introduction of substituents at C(4) in the oxazolidinone ring. Yields improved to 95% in MeOH/THF (Entry 2), whereas other solvents gave inferior results (not shown). The *trans* relationship was confirmed by the very small coupling constant $J(H^4,H^5)$ in the ^1H NMR spectra; *trans*-4,5-disubstituted 1,3-oxazolidin-2-ones are characterized by coupling constants much lower than those of *cis* stereoisomers.[24] Interestingly, the RP-HPLC and NMR analyses ruled out an equilibrium between anomers at C(4).



Scheme 5. Reduction of the carbonyl bond at C(4) of the 1,3-oxazolidine-2,4-dione: synthesis of LZD (**1**).

Table 3. Mild reductions of **4a** and **4b** at C(4) with several reducing agents.

Entry	4	Reducing agent	Temp. [°C]	Solvent	Prod.	Yield [%][a]
1	**b**	$NaBH_4$	0	H_2O/THF	**5**	50[b]
2	**b**	$NaBH_4$	0	MeOH/THF	**5**	95[b]
3	**b**	$LiAlH_4$	0	THF	–	–[b,c]
4	**b**	H_2/Pd-C	r.t.	MeOH	–	–[d]
5	**b**	$HCOO^-NH_4^+$/Pd-C	60	*i*PrOH	–	–[d]
6	**b**	NH_2NH_2	100	$(HOCH_2)_2$	–	–[d]
7	**b**	$Zn(OAc)_2$/$(EtO)_3SiH$	r.t. to 40	THF	–	–[d]
8	**b**	BH_3/OEt_2	0 to r.t.	THF	–	–[d]
9	**b**	BH_3·DMS	0	THF	**1**	55[e]
10	**b**	BH_3·DMS/MS	0	THF	**1**	88[b]
11	**a**	BH_3·OEt_2	0 to r.t.	THF	–	–[d]
12	**a**	BH_3·DMS	0	THF	**7**	64[b,f]
13	**a**	BH_3·DMS/MS	0	THF	**7**	97[b]

[a] Determined after isolation by flash chromatography over silica gel. [b] Reaction time 2 h. [c] Traces of **1**, with **6** as the major byproduct. [d] Reaction time 24 h; **4** was recovered almost quantitatively. [e] Compounds **5** and **6** were the major byproducts. [f] Compound **8** was the major byproduct.

Not unexpectedly, treatment with $LiAlH_4$ at 0 °C resulted in the reduction of both the carbonyl at C(4) and the *N*-Ac function, giving a small amount of **1**, together with the 5-ethylaminomethyl compound **6** (Scheme 5) as the major byproduct (Table 3, Entry 3). Catalytic hydrogenation (Entries 4 and 5),[27] Wolff–Kishner reduction (Entry 6),[28] $Zn(OAc)_2$-catalyzed reduction with $(EtO)_3SiH$ (Entry 7),[27d] or use of 2 M borane in diethyl ether (Entry 8)[27] gave only traces of the desired product after 24 h.

On the other hand, use of borane dimethyl sulfide complex in anhydrous THF at 0 °C gave **1**, which was easily isolated in 55% yield by flash chromatography (Entry 9 in Scheme 5). Analysis of the crude reaction mixture by RP-HPLC ESI revealed the presence of significant amounts of byproducts **5** and **6** (not isolated). When the reaction was repeated in the presence of activated (dried) 4 Å molecular sieves, which effectively prevented the formation of 4-hydroxy compound **5**, product **1** was obtained in the very satisfactory yield of 88% (Entry 10), whereas **6** was present in traces. Use of an increased reaction temperature resulted in larger amounts of *N*-ethylamino **6**.

Finally, we examined the reduction of **4a** under the conditions described in Entries 8–10 in Scheme 5 and Table 3. Use of borane in diethyl ether was again almost ineffective (Entry 11), whereas use of borane dimethyl sulfide complex gave the 1,3-oxazolidin-4-one **7**[29] (64%, Entry 12) and traces of 4-hydroxy-1,3-oxazolidin-4-one **8** (Scheme 5, not isolated). In contrast, in the presence of molecular sieves, use of borane dimethyl sulfide complex afforded **7** quantitatively (Entry 13). Subsequent treatment with TFA followed by acetic anhydride/TEA afforded **1** in 97% yield (Scheme 5).

The enantiomeric purities of the reported compounds and intermediates were confirmed by HPLC analysis on a chiral stationary phase. Analyses of compounds **1**, **3a**, **3b**, **4a**, **4b**, **5**, and **7** performed on a CHIRALPAK IC column were compared with analyses of the corresponding racemates obtained from *rac*-isoserine (see the Supporting Information). In the cases of compounds **1** (LZD) and **7** the spectroscopic characterization and specific optical rotations nicely matched the data reported in the literature (**1**,[3,11a] **7**;[29] see Exp. Sect.).

Conclusions

We have demonstrated the feasibility of a new approach to the synthesis of LZD, based on the use of the chiral starting material *N*-acetylisoserine, which was efficiently coupled to 3-fluoro-4-morpholinoaniline. Cyclization of the resulting α-hydroxy β-acetamido arylamide provided a 5-(acetamidomethyl)-1,3-oxazolidine-2,4-dione intermediate, which was reduced regioselectively to give LZD in very good yield under mild reaction conditions. The use of *N*-Boc-protected isoserine further improved the efficiency of the reduction, requiring only an extra deprotection/acetylation step to afford LZD. Further work directed towards the synthesis of optically pure substituted α-hydroxy β-amino acids of β^2-, β^3-, $\beta^{2,3}$-, and $\beta^{3,3}$-types, suitable precursors of a diverse range of LZD analogues substituted in ring A, is currently ongoing.

Experimental Section

General Methods: Standard chemicals, including (*S*)- and *rac*-isoserine, were purchased from commercial sources and used without further purification. Compound **2** was prepared as reported in the literature (see also the Supporting Information). Flash chromatography was performed with silica gel (230–400 mesh) and mixtures of distilled solvents. Compounds' purities were assessed by analytical RP-HPLC and elemental analysis. Analytical RP-HPLC was performed with an Agilent 1100 series apparatus and a RP column Phenomenex mod. Gemini 3μ C18 110A 100 × 3.0 mm (P/No 00D-4439-Y0); column description: stationary phase octadecyl carbon chain-bonded silica (C18) with TMS endcapping, fully porous organo-silica solid support, particle size 3 μm, pore size 110 Å, length 100 mm, internal diameter 3 mm; DAD 210 nm; mobile phase: from H_2O/CH_3CN (9:1) to H_2O/CH_3CN (2:8) in 20 min at a flow rate of 1.0 mL min^{-1}, followed by 10 min at the same composition. Epimerization of intermediates and products was ruled out by chiral HPLC analysis, performed with an Agilent 1200 series apparatus and a CHIRALPAK IC column (P/No 83325); column description: chiral stationary phase cellulose tris(3,5-dichlorophenylcarbamate) immobilized on silica, particle size 5 μm, length 250 mm, internal diameter 4.6 mm, DAD 210/254 nm; mobile phase: *n*-hexane/propan-2-ol (1:1), at 0.8 mL min^{-1}. The synthetic procedures involving MW irradiation were performed with a microwave oven (MicroSYNTH Microwave Labstation for Synthesis) equipped with a built-in ATC-FO advanced fiber-optic automatic temperature control. ^{1}H NMR spectra were recorded with a Varian Gemini apparatus at 400 MHz in 5 mm tubes, with use of 0.01 M peptide at room temperature. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts are reported as δ values relative to residual $CHCl_3$ δH (7.26 ppm), DMSO δH (2.50 ppm), and $CDCl_3$ δC (77.16 ppm) as internal standards. The unambiguous assignment of ^{1}H NMR resonances was performed with 2D gCOSY.

***N*-Protected Isoserine-Arylamides 3:** 3-Fluoro-4-morpholinoaniline (**2**, 1.0 mmol) was added at 0 °C to a stirred solution of the appropriate *N*-protected isoserine (1.05 mmol) in CH_2Cl_2/DMF (9:1, 5 mL). After 15 min, HOBt (1.1 mmol) and NMM (2.0 mmol) were added, followed after 30 min by either HBTU or HATU (1.1 mmol). The mixture was stirred at room temp. for 12 h. Alternatively, the reaction was performed under MW irradiation for 10 min, with an initial irradiation power of 150 W and monitoring of the internal reaction temperature at 80 °C. Then the reaction mixture was concentrated at reduced pressure, and the residue was diluted with AcOEt (30 mL) and washed with HCl (0.1 M, 5 mL) and a saturated solution of $NaHCO_3$ (5 mL). The organic layer was dried with Na_2SO_4 and the solvent was evaporated at reduced pressure, to afford the appropriate compound **3** as a crude residue, which was purified (yields: see Table 1) by flash chromatography over silica gel (eluent: cyclohexane/EtOAc 40:60).

Compound 3a: $[\alpha]_D^{20}$ = –98.6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H, *t*Bu), 3.12 (t, *J* = 4.4 Hz, 4 H, morph$H_{3,5}$), 3.59 (ddd, *J* = 2.2, 5.8, 14.8 Hz, 1 H, CH_2N), 3.69 (ddd, *J* = 2.2, 5.8, 14.8 Hz, 1 H, CH_2N), 3.92 (t, *J* = 4.4 Hz, 4 H, morph$H_{2,6}$), 4.30 (m, 1 H, CH_2CH), 5.19 (br. t, 1 H, BocNH), 5.72 (br. d, 1 H, OH), 6.93 (t, *J* = 8.8 Hz, 1 H, ArH_2), 7.16 (m, 1 H, ArH_5), 7.58 (dd, *J* = 2.4, 14 Hz, 1 H, ArH_6), 8.85 (s, 1 H, CONH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2, 44.8, 51.0, 66.9, 71.8, 81.1, 108.6, 108.8, 115.5 118.7, 118.8, 132.3, 132.4, 136.6, 136.7, 154.2, 156.6, 170.1 ppm. MS (ESI) calcd. 384.2 $[M + H]^+$; found 384.2. $C_{18}H_{26}FN_3O_5$ (383.42): calcd. C 56.39, H 6.84, F 4.96, N 10.96; found C 56.67, H 6.89, F 5.02, N 10.90.

Compound 3b: $[\alpha]_D^{20}$ = –77.1 (*c* = 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 3 H, Ac), 3.07 (t, *J* = 4.4 Hz, 4 H, morph$H_{3,5}$), 3.68 (ddd, *J* = 2.2, 5.8, 14.8 Hz, 1 H, CH_2N), 3.82 (ddd, *J* = 2.2, 5.8, 14.8 Hz, 1 H, CH_2N), 3.89 (t, *J* = 4.4 Hz, 4 H, morph$H_{2,6}$), 4.32 (m, 1 H, CH_2CH), 6.07 (br. s, 1 H, OH), 6.45 (br. t, 1 H, AcNH),

6.95 (t, J = 8.6 Hz, 1 H, ArH_2), 7.15 (m, 1 H, ArH_5), 7.55 (m, 1 H, ArH_6), 8.89 (s, 1 H, CONH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.7, 44.8, 51.1, 66.9, 74.2, 108.6, 108.8, 115.5, 119.0, 127.0, 128.3, 154.2, 170.1, 174.7 ppm. MS (ESI) calcd. 326.2 $[M + H]^+$; found 326.3. $C_{15}H_{20}FN_3O_4$ (325.34): calcd. C 55.38, H 6.20, F 5.84, N 12.92; found C 55.71, H 6.25, F 5.87, N 13.00.

5-(Aminomethyl)oxazolidine-2,4-diones 4: DSC (1.1 mmol) was added at room temp. under inert atmosphere to a stirred solution of the appropriate compound **3** (1.0 mmol) in CH_2Cl_2/DMF (3:1, 4 mL), followed by DIPEA (0.1 mmol). After 1 h, the solvent was distilled at reduced pressure, the residue was diluted with HCl (1 M, 5 mL), and the aqueous phase was extracted three times with AcOEt (3× 15 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated at reduced pressure. The oily residue was purified by flash chromatography over silica gel (eluent: cyclohexane/EtOAc 60:40) to give the appropriate product **4** (yields: see Table 2).

Compound 4a: $[\alpha]_D^{20}$ = –32.4 (c = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, tBu), 3.13 (t, J = 4.4 Hz, 4 H, morph$H_{3,5}$), 3.75–3.85 (m, 2 H, CH_2N), 3.88 (t, J = 4.4 Hz, 4 H, Morph$H_{2,6}$), 4.90 (t, J = 6.0 Hz, 1 H, CH_2CH), 5.00 (br. t, 1 H, BocNH), 7.01 (t, J = 8.4 Hz, 1 H, ArH_2), 7.16–7.19 (m, 2 H, $ArH_{5,6}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2, 40.4, 40.7, 50.5, 66.7, 82.2, 113.8, 118.6, 118.7, 121.7, 124.3, 124.4, 140.4, 140.6, 153.6, 153.7, 156.1, 169.8, 172.9 ppm. MS (ESI) calcd. 410.2 $[M + H]^+$; found 410.1. $C_{19}H_{24}FN_3O_6$ (409.41): calcd. C 55.74, H 5.91, F 4.64, N 10.26; found C 56.01, H 6.05, F 4.68, N 10.32.

Compound 4b: $[\alpha]_D^{20}$ = –27.3 (c = 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.06 (s, 3 H, Ac), 3.13 (t, J = 4.8 Hz, 4 H, morph$H_{3,5}$), 3.83–3.94 (m, 6 H, CH_2N, morph$H_{2,6}$), 5.05 (t, J = 5.4 Hz, 1 H, CH_2CH), 5.93 (br. t, 1 H, AcNH), 7.01 (t, J = 8.8 Hz, 1 H, ArH_2), 7.15–7.19 (m, 2 H, $ArH_{6,5}$) ppm. ^{13}C NMR (DMSO): δ = 23.0, 39.4, 51.0, 66.8, 79.1, 115.2, 115.5, 119.7, 124.0, 125.4, 125.5, 140.8, 153.5, 154.9, 171.1, 171.2 ppm. MS (ESI) calcd. 352.1 $[M + H]^+$; found 352.1. $C_{16}H_{18}FN_3O_5$ (351.33): calcd. C 54.70, H 5.16, F 5.41, N 11.96; found C 55.02, H 5.19, F 5.45, N 12.04.

5-Acetamidomethyl-4-hydroxyoxazolidin-2-one (5): Fresh $NaBH_4$ (0.057 g, 1.5 mmol) was added at 0 °C under inert atmosphere to a stirred solution of **4b** (0.35 g, 1.0 mmol) in MeOH/THF (1:1, 5 mL). The reaction was quenched after 24 h by addition of acetone. The mixture was concentrated at reduced pressure, and the residue was diluted with water (5 mL). The mixture was extracted twice with CH_2Cl_2 and once with EtOAc. The organic layers were collected and dried with Na_2SO_4. The solution was filtered, and solvent was evaporated at reduced pressure. The oily **5** was isolated (0.33 g, 95%) by flash chromatography over silica gel (eluent: cyclohexane/EtOAc 50:50). $[\alpha]_D^{20}$ = +1.8 (c = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.98 (s, 3 H, Ac), 3.07 (dd, J = 3.0, 5.8 Hz, 4 H, morph$H_{3,5}$), 3.55 (ddd, J = 5.0, 9.0, 14.4 Hz, 1 H, CH_2N), 3.73 (ddd, J = 5.0, 9.0, 14.4 Hz, 1 H, CH_2N), 3.87 (dd, J = 3.0, 5.8 Hz, 4 H, morph$H_{2,6}$), 4.47 (br. t, 1 H, CH_2CH), 5.02 (br. s, 1 H, OH), 5.60 (s, 1 H, $CHOH$), 6.36 (t, J = 6.0 Hz, 1 H, AcNH), 6.93 (t, J = 9.2 Hz, 1 H, ArH_1), 7.22 (dd, J = 2.0, 10.4 Hz, 1 H, ArH_6), 7.31 (dd, J = 2.2, 13.8 Hz, 1 H, ArH_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.9, 40.7, 50.9, 66.8, 80.9, 83.1, 111.0, 111.3, 118.3, 119.0, 125.5, 154.0, 154.8, 156.5, 171.9 ppm. MS (ESI) calcd. 354.1 $[M + H]^+$; found 354.0. $C_{16}H_{20}FN_3O_5$ (353.35): calcd. C 54.39, H 5.71, F 5.38, N 11.89; found C 54.67, H 5.75, F 5.36, N 11.99.

5-(Aminomethyl)oxazolidin-2-ones 1 and 7: Dry molecular sieves (4 Å, 100% w/w) were added under inert atmosphere to a solution of the appropriate compound **4** (1.0 mmol) in freshly distilled THF (10 mL). BH_3·DMS (2.0 mmol) was added to the suspension under inert atmosphere at 0 °C. After having been stirred for 7 h, the reaction mixture was quenched with HCl (0.1 M, 10 mL). The mixture was concentrated at reduced pressure to half of the initial volume, and extracted three times with EtOAc (3× 15 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated at reduced pressure. The products, **1** or **7** (yields: see Table 3), were purified by flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 75:25).

LZD (1):[3,11a] $[\alpha]_D^{20}$ = –9.0 (c = 0.5, $CHCl_3$), ref.[11a] $[\alpha]_D^{23}$ = –9.8 (c = 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.04 (s, 3 H, Ac), 3.11 (t, J = 4.2 Hz, 4 H, morph$H_{3,5}$), 3.62 (ddd, J = 3.2, 6.0, 14.8 Hz, 1 H, CH_2N), 3.71 (ddd, J = 3.2, 6.0, 14.8 Hz, 1 H, CH_2N), 3.76 (dd, J = 7.2, 9.0 Hz, 1 H, OxdH_4), 3.91 (t, J = 4.4 Hz, 4 H, morph$H_{2,6}$), 4.04 (dd, J = 7.2, 9.0 Hz, 1 H, OxdH_4), 4.78 (m, 1 H, OxdH_5), 5.99 (br. t, J = 6.0 Hz, 1 H, AcNH), 7.05–7.10 (m, 2 H, $ArH_{1,6}$), 7.49 (dd, J = 2.8, 15.2 Hz, 1 H, ArH_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1, 42.1, 47.7, 51.3, 66.5, 71.9, 107.5, 107.8, 113.9, 119.8, 132.8, 133.0, 136.4, 136.5, 154.2, 154.4, 156.8, 171.1 ppm. MS (ESI) calcd. 338.2 $[M + H]^+$; found 338.2. $C_{16}H_{20}FN_3O_4$ (337.35): calcd. C 56.97, H 5.98, F 5.63, N 12.46; found C 57.23, H 6.05, F 5.61, N 12.68.

Compound 7:[29] $[\alpha]_D^{20}$ = –34.4 (c = 0.3, CH_3CN), ref. $[\alpha]_D^{25}$ = –36 (c = 0.71, CH_3CN). ^1H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, tBu), 3.06 (t, J = 4.8 Hz, 4 H, morph$H_{3,5}$), 3.46–3.54 (m, 2 H, CH_2N), 3.81 (dd, J = 6.6, 9.0 Hz, 1 H, OxdH_4), 3.87 (t, J = 4.8 Hz, 4 H, morph$H_{2,6}$), 4.00 (dd, J = 6.6, 9.0 Hz, 1 H, OxdH_4), 4.74 (m, 1 H, OxdH_5), 5.02 (br. t, 1 H, BocNH), 6.94 (t, J = 9.0 Hz, 1 H, ArH_1), 7.09 (ddd, J = 1.2, 2.8, 8.8 Hz, 1 H, ArH_6), 7.44 (dd, J = 2.8, 14.2 Hz, 1 H, ArH_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2, 47.5, 51.0, 66.9, 72.0, 80.3, 107.4, 107.6, 113.9, 118.9, 119.0, 133.2, 133.3, 136.4, 154.3, 156.2, 156.7 ppm. MS (ESI) calcd. 396.2 $[M + H]^+$; found 396.2. $C_{19}H_{26}FN_3O_5$ (395.43): calcd. C 57.71, H 6.63, F 4.80, N 10.63; found C 57.98, H 6.62, F 4.91, N 10.89.

Synthesis of 1 via 7: Compound **7** (0.40 g, 1.0 mmol) was treated with TFA/CH_2Cl_2 (1:3, 5 mL) with stirring at room temp. After 15 min, the solution was evaporated at reduced pressure, and the residue was subjected to the same treatment. The crude residue was suspended in Et_2O (20 mL), and the precipitate was collected by centrifuge. A stirred suspension of the crude TFA salt was suspended in EtOAc (5 mL) and treated with Ac_2O (0.14 mL, 1.5 mmol) and TEA (0.28 mL, 2.0 mmol) at room temp. After 3 h, the mixture was diluted with EtOAc (40 mL), and washed with HCl (0.1 M, 5 mL) and brine (5 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated at reduced pressure. The product **1** was isolated (0.33 g, 97%) by flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 75:25).

Supporting Information (see footnote on the first page of this article): Synthesis of **2**, **3a**; chiral HPLC analyses; ^1H and ^{13}C NMR spectra.

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