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Synthesis of oxazolidinones from *N*-aryl-carbamate and epichlorohydrin under mild conditions

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Dedicated to Prof. Girolamo Cirrincione on the occasion of his retirement

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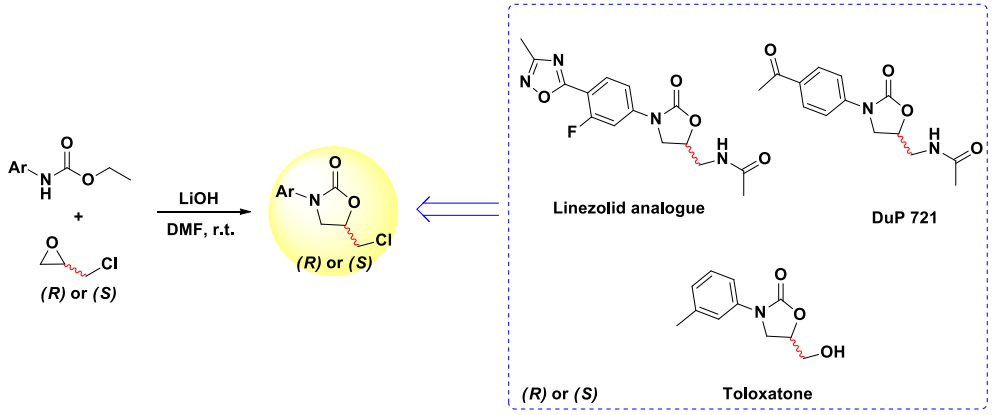
Abstract

The reaction conditions for an enantiospecific synthesis of various *N*-aryl-oxazolidinones from *N*-aryl-carbamates and *(R) or (S)* epichlorohydrin were optimized. The *N*-aryl-oxazolidinones were applied to the synthesis of compounds of biological interest such as DuP 721, toloxatone and a linezolid analogue.



Keywords: Oxazolidinone, carbamate, epichlorohydrin, linezolid, toloxatone

Introduction

Oxazolidinones are a class of five-membered heterocycles containing nitrogen and oxygen with a broad range of applications. They are used as chiral auxiliaries in asymmetric synthesis[1,2] and are present in several biologically active compounds (Figure 1).[3,4]

Particularly, *N*-aryl oxazolidinones have been extensively studied as antibacterial agents.[5,6] In 1987, the pharmaceutical company DuPont identified the first oxazolidin-2-one, named DuP 721, that showed in vitro activity against Gram-positive pathogens[7] and *M. tuberculosis.*[8] It shows liver toxicity in mice and, for this reason, there are no published results about clinical studies. Subsequent SAR studies, starting from DuP 721, led to the production of linezolid (ZYVOX ®), the first example of oxazolidinone approved for clinical use in 2000 by the FDA.[6] This drug, binding the 50S ribosomal subunit, inhibits protein synthesis.[9] It exerts antibacterial activity against Gram-positive multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus (MRSA*) and vancomycin-resistant enterococci (VRE).[10] Since 2001, the antibiotic resistance of pathogens to linezolid directed research activities to the identification of novel oxazolidinones and numerous structure-activity relationships (SAR) studies have been reported.[11–13] For example, the replacement of the morpholine ring with a 1,2,4-oxadiazole ring, and the replacement of the carbonyl group with a thionyl in the side chain, gave new linezolid-like compounds with antibacterial activity against resistant *S. aureus* (linezolid analogue in Figure 1).[14]

The *N*-aryl-oxazolidinone ring is also the central core of several MAO inhibitors that are potential candidates for the treatment of several neurological diseases.[15,16] To date, the oxazolidinone toloxatone (HUMORYL®) is in clinical use as a potent antidepressant drug.[17,18]

In terms of another example, the oxazolidinone rivaroxaban (XARELTO ®) is a direct inhibitor of the pro-coagulant factor Xa. It was approved in many countries for the prevention of several thromboembolic disorders.[19]

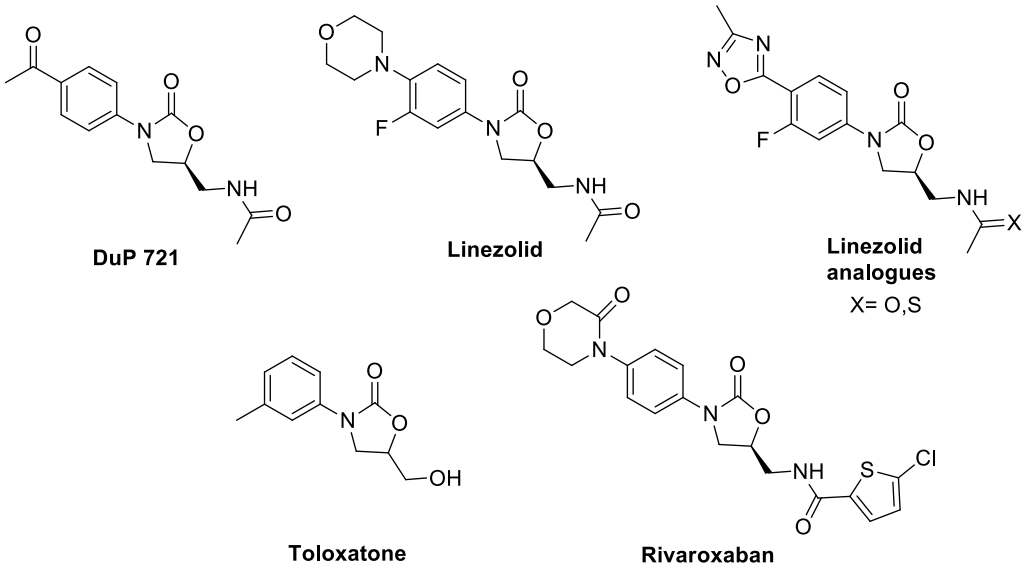


Figure 1. Bioactive *N*-aryl-oxazolidinones.

Organic chemists have reported several pathways for the building of the oxazolidinone frame. The most widely used substrates are 1,2-aminoalcohols[20] which can easily be obtained from alpha-aminoacids.[20-22] In the

presence of these compounds, the oxazolidinone ring closure is mediated by reactants such as phosgene, disphogene, urea and carbodiimidazole, acting as the source of the carbonyl group.[20] Particularly, the Pd-catalyzed oxidative carbonylation of aminoalcohols to give oxazolidinone compounds is an efficient synthetic approach known in the literature.[23] Synthesis of enantiopure 5-substituted oxazolidin-2-ones from β-aminoalcohols could also be performed through an initial carboxylation with CO_2, followed by intramolecular Mitsunobu reaction.[24]

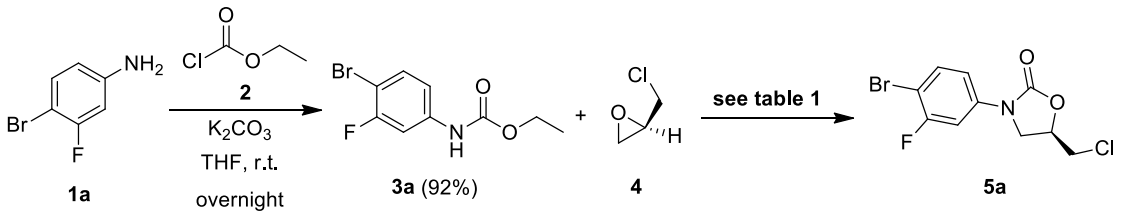
The opening of the epoxy ring in presence of isocyanate is an alternative way used to obtain the oxazolidinone core. This [3+2] coupling reaction is arguably the most useful approach for the synthesis of *N*-aryl-oxazolidinones. This reaction has been carried out in presence of several catalytic systems.[25–33] Some of these methods involve the use of high temperatures or heavy metals and the use of isocyanate could be limited by polymerization.[30] Researchers have tried to overcome these limits by introducing new, safer and more economical organo-catalyst systems. Recently, hydrogen-bond donor (HBD) catalytic systems have been used as a platform to synthetize enantiopure *N*-aryl-oxazolidinones under solvent and metal free conditions.[34–36]

Chiral oxazolidinone compounds in high enantiomeric excess can be obtained by reaction of commercially available *(R)*-glycidyl butyrate and readily available aryl carbamates. This strategy produces good yields, but requires low temperature (-78 °C) and the use of *n*-butyllithium as deprotonation agent.[37] Also, solid phase synthesis on solid support have been reported, this time by using Solketal as building block.[38] It should be noted that the synthesis of oxazolidinones was very recently reviewed.[39]

Considering the important role of the *N*-aryl-oxazolidinones moiety in pharmaceutical chemistry and some limitations of literature synthetic methods, in particular, the use of high-cost chiral building blocks or organic bases and the use of low/high temperatures, we decided to develop a new efficient and stereoselective synthetic strategy involving mild conditions as well as available and cheap reagents. In this context, DuP 721, toloxatone, a linezolid analogue and other *N*-aryl-oxazolidinones have been synthetized from readly available *N*-aryl-carbamates and enantiopure epichlorohydrin, a very cheap chiral building block, using lithium hydroxide as base at room temperature.

Results and Discussion

Ethyl 4-bromo-3-fluorophenylcarbamate **3a** and *(R)*-epichlorohydrin **4** were used as substrates for the optimization of the reaction conditions related to the formation of the oxazolidinone core. The aryl-carbamate **3a** was obtained by the reaction of 4-bromo-3-fluoroaniline **1a** with ethyl chloroformate **2** (Scheme 1).



Scheme 1. Synthesis of oxazolidinone **5a** from ethyl 4-bromo-3-fluorophenylcarbamate **3a** and *(R)*-epichlorohydrin **4**.

Table 1. Optimization of oxazolidinone **5a** synthesis from ethyl 4-bromo-3-fluorophenylcarbamate **3a** and (*R)*-epichlorohydrin **4**[a]

Entry	conditions				5a
	Base	Solvent	Temperature	Time (h)	Yield %[b] (% rec. 3a)[b]
1	*t*-BuOK	THF	Reflux	5	12 (61)
2	*t*-BuOK	Acetonitrile	Reflux	1	26 (43)
3	*t*-BuOK	Acetonitrile	r.t	24	29 (58)
4	K_2CO_3	Acetonitrile	Reflux	3	13 (37)
5	K_2CO_3	Acetonitrile	r.t.	24	5 (81)
6	Et_3N	Acetonitrile	Reflux	5	5 (69)
7	DIPEA	Acetonitrile	Reflux	5	NR[c] (76)
8	DMAP	Acetonitrile	Reflux	3	37 (26)
9	DMAP	Acetonitrile	r.t.	24	15 (63)
10	LiOH	Acetonitrile	r.t.	24	NR[c] (91)
11	*t*-BuOK	DMSO	r.t.	96	23 (36)
12	NaOH	DMSO	r.t.	24	56 (28)
13	KOH	DMSO	r.t.	24	48 (27)
14	DIMAP	DMSO	r.t.	24	42 (31)
15	LiOH	DMSO	r.t.	24	62 (22)
16	Cs_2CO_3	DMSO	r.t.	24	59 (24)
17	DABCO	DMSO	r.t.	24	40 (48)
18	DBU	DMSO	r.t.	24	8 (71)
19	LiOH	DMF	r.t.	24	65 (23)
20[d]	LiOH	DMF	r.t.	24	36 (47)
21[e]	LiOH	DMF	r.t.	24	28 (31)
22[f]	LiOH	DMF	r.t.	24	51 (23)

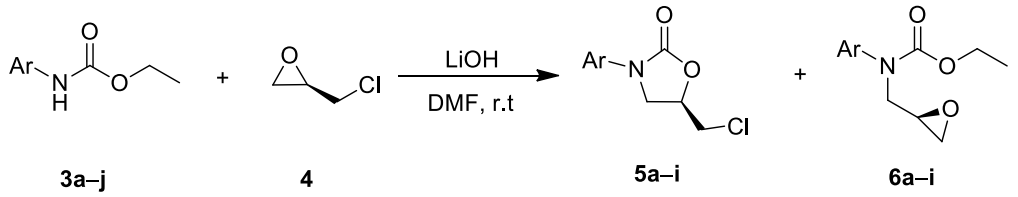
[a] The reactions were performed using 1 equiv. of ethyl 4-bromo-3-fluorophenylcarbamate **3a**, 3 equiv. of *(R)*-epichlorohydrin **4** and 1.5 equiv. of the respective base; [b] Yields of purified products; [c] no reaction. [d]The reaction was performed using 1 equiv. of **3a**, 3 equiv. of *(R)*-epichlorohydrin **4** and 1 equiv. of LiOH; [e]The reaction was performed using 1 equiv. of **3a**, 1 equiv. of *(R)*-epichlorohydrin **4** and 1.5 equiv. of LiOH. [f]The reaction was performed using 1 equiv. of **3a**, 3 equiv. of *(R)*-epichlorohydrin **4** and 3 equiv. of LiOH.

The next key step involved the reaction of ethyl 4-bromo-3-fluorophenylcarbamate **3a** and (*R*)-epichlorohydrin **4** under a variety of conditions to give oxazolidinone **5a**. As shown in Table 1, when acetonitrile or THF were used as solvent the product **5a** was obtained in low yields when potassium *tert*-butoxide (*t*-BuOK) was used as base (Entries 1-3). Trying different bases in acetonitrile (Entries 3-10), we observed moderate yields just with 4-dimethylaminopyridine (DMAP) under reflux (Entry 8). When we moved to dimethyl sulfoxide (DMSO) at ambient temperature and using different bases (Entries 11–18), the formation of the corresponding oxazolidinone **5a** in reasonable yields (40-62%) was observed, except when *t*-BuOK (Entry 11) or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (Entry 18) were used. In the end, lithium hydroxide proved to be the best base (Entry 15). Moreover, in the presence of LiOH the solvent substitution of DMSO

with dimethylformamide (DMF) resulted in a further increase in the isolated product (Entry 19). Considering LiOH as a good compromise between good yield and low cost, we decided to further explore the stoichiometry of the reaction (Entries 20-22). By using a stoichiometric amount of base we observed a lower yield, as well as conversion (Entry 20). With a stoichiometric amount of epoxide **4** (Entry 21), **5a** was obtained in low yield, but a considerable conversion was observed, while an excess of 3 equiv. for LiOH and 4 (Entry 22), gave a moderate yield (51%), but with a similar conversion compared to Entry 19. Of particular interest, was that chiral HPLC revealed that the obtained oxazolidinone **5a** was substantially obtained as single enantiomer (ee> 96%).

The optimized method, involving LiOH as base and DMF as solvent, was applied to the reaction of variously substituted *N*-aryl-carbamates **3a-i** with enantiopure epichlorohydrin **4**. Interestingly, in some cases, in addition to the desired **6a-i**, epoxides **6a-i** were also isolated in low yields. Table 2 explains how the *N*-aryl-oxazolidin-2-ones **5a-i** and the corresponding epoxy derivatives **6a-i** were obtained.

Table 2. Synthesis of oxazolidinone and epoxy derivatives[a]



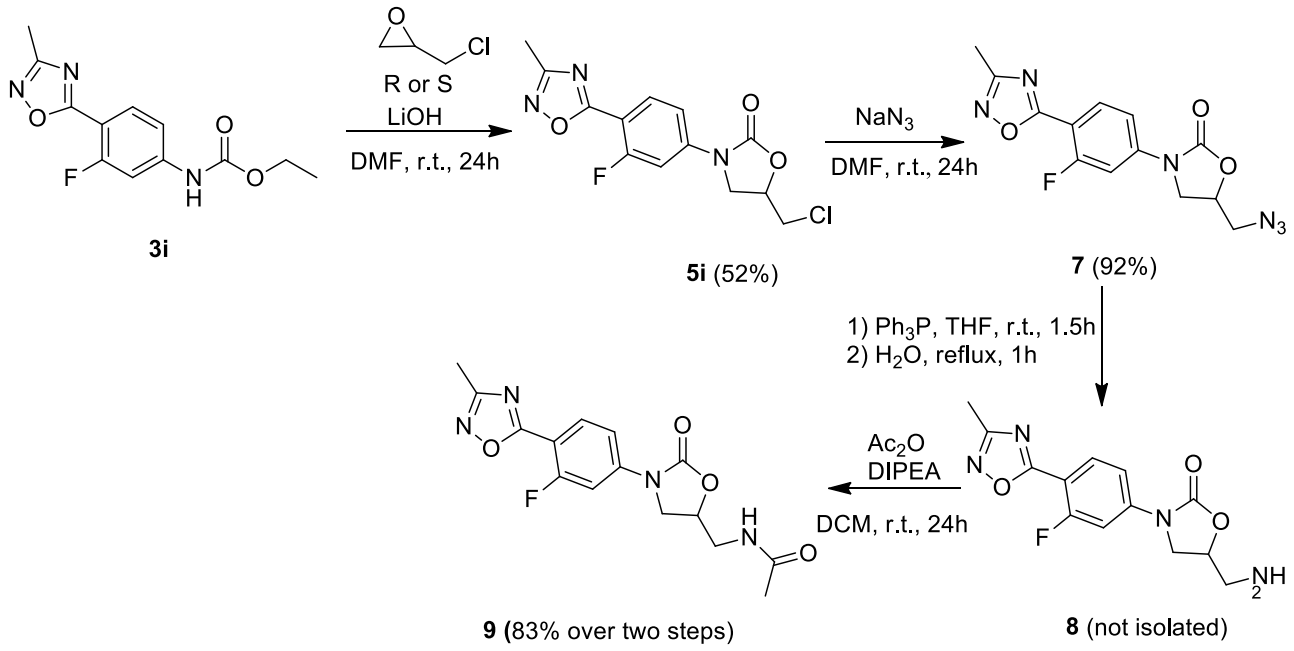
3a–j **4** **5a–i** **6a–i**

Derivate	Ar	Yield (%)[b]	
		5	**6**
3a	3-F-4-BrC_6H_3	65	10
3b	4-$CH_3COC_6H_4$	65	trace
3c	3,4-$F_2C_6H_3$	34	13
3d	4-ClC_6H_4	20	11
3e	3-Cl-4-FC_6H_3	43	14
3f	3-$CH_3C_6H_4$	8	18
3g	3-BrC_6H_4	22	trace
3h	3-F-4-morpholine-C_6H_3	18	29
3i	3-F-4-[5(3-methyl-1,2,4-oxadiazole)]-C_6H_3	52	trace
3j	2-$CH_3OC(O)C_6H_4$	-[c]	-[c]

[a] The reactions were performed using 1 equiv. of ethyl 4-bromo-3-fluorophenylcarbamate **3a**, 3 equiv. of *(R)*-epichlorohydrin **4** and 1.5 equiv. of the respective base; [b] Yields of purified products; [c] Quantitative formation of 2-aminobenzoic acid

All compounds were synthetized using enantiopure *(R)*-epichlorohydrin **4**, while for the derivatives **3a**,**b**,**i** the same reaction was also conducted with (*S)*-epichlorohydrin with similar results. In some cases, the epoxy derivatives **6** were observed by TLC, but their reactivity made their isolation and characterization impossible. In the case of ester group of **3j**, the limitation was due to concurrent saponification of the starting compound. Moreover, the presence of different electron-withdrawing substituents and their different positions on the aryl moiety gave different reaction time and product yields. Generally, the *N*-aryloxazolidin-2-ones **5(a-i)** were obtained in greater quantities than the epoxy derivatives **6(a-i)**, except for **5f** and **5h**, which contained electron-donating groups (EDG).

The development of enantioselective synthesis is often a challenge for medicinal chemists. Particularly, in the synthesis of linezolid and its derivatives it is important to obtain the *(S)*-enantiomer that has higher antibacterial activity than the racemic mixture.[40] In order to assess the enantiospecificity of the proposed method, we employed oxazolidinone **5i**, obtained from the *N*-aryl-carbamate **3i** and *(R)*-epichlorohydrin or *(S)*-epichlorohydrin, as key intermediate in the synthesis of the already known active derivative **9**.[14] As shown in Scheme 2, **5i** was treated with sodium azide in dimethylformamide to synthesize **7**. The reduction of **7** to its amino-derivative **8**, with triphenylphosphine, and the acetylation performed with acetic anhydride gave the derivative **9**.[14]



Scheme 2. Synthesis of the linezolid analogue derivative **9.**

The determination of the which enantiomer had been obtained from epichlorohydrin was achieved by means of chiral HPLC with a Daicel Chiralpak IA column and hexane/*i*PrOH (80:20) as mobile phase. Literature data concerning the enantioselective HPLC analysis of racemic linezolid and oxadiazole-containing analogues showed that under these conditions the (*S)*-enantiomer elutes before the *(R)*-enantiomer.[40] The HPLC traces of compound **9**, obtained using *(R)*- or *(S)*-epichlorohydrin, were compared with that of the racemic mixture (Figure 2). From the results obtained, all reactions are thus assumed to be perfectly enantiospecific and in general the proposed method allows us to obtain oxazolidinones as single enantiomer. In addition, the desired active *(S)*-enantiomer was obtained using *(R)*-epichlorohydrin.

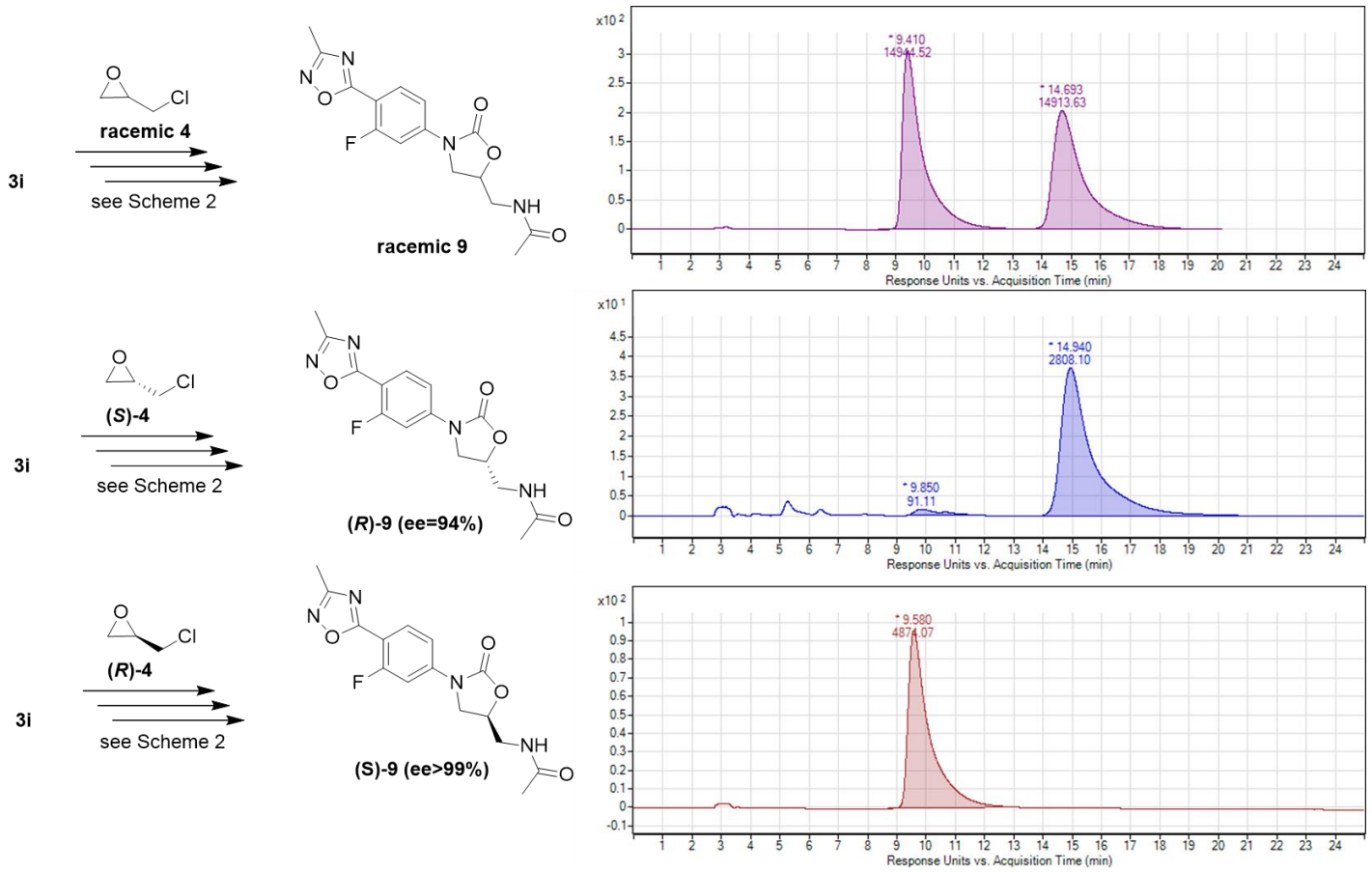
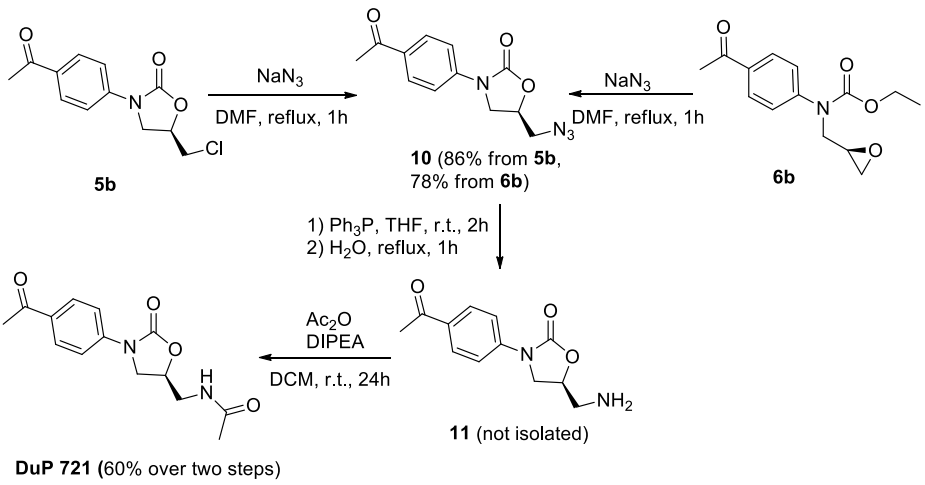


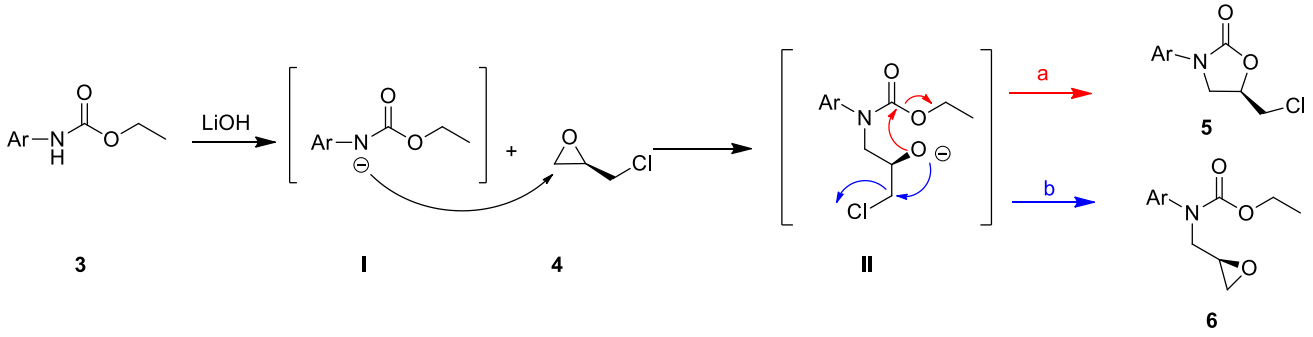
Figure 2. HPLC traces of oxazolidinone **9** obtained as for scheme 2 starting from: racemic epichlorohydrin (upper), *(S)*-epichlorohydrin (middle) and *(R)*-epichlorohydrin (bottom).

Secondly, the bioactive enantiopure oxazolidinone DuP 721 was synthetized from **5b**, following the same synthetic pathway of the linezolid-like compound. The reaction of the aryl-carbamate **3b** with *(R)*-epichlorohydrin yielded **R-5b**, which could readily be converted into the active *(S)*-enantiomer of DuP 721 as shown (Scheme 3). Moreover, nucleophilic ring-opening of epoxide **6b** with sodium azide, give the azido-derivative **10**, thus demonstrating that epoxides **6** are not just reaction by-product, but could be used for obtaining biologically relevant oxazolidinones (Scheme 3). Similarly, oxazolidinone ***(R)*-5h** could be envisaged as intermediate in the synthesis of *(S)*-linezolid.

Considering the enantiospecific acquirement of compounds **5** and **6**, we speculate that they originate from two concurrent cyclization pathway (a or b) involving intermediate **II**, in turn obtained from the nucleophilic ring opening of epichlorohydrin by anion **I** (Scheme 4). This pathway is also in agreement with the lower yields for derivatives **3f,h** containing EDGs, thus reducing the electrophilic character of the carbamate and favoring path b.

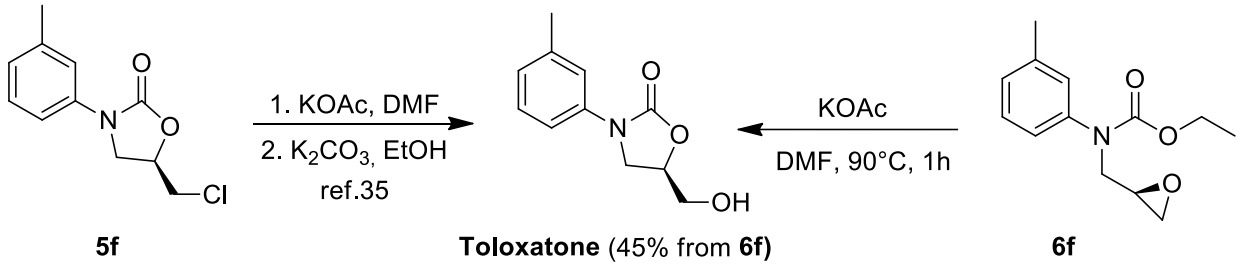


Scheme 3. Enantiospecific synthesis of DuP 721.



Scheme 4. Proposed mechanism underlying the formation of the oxazolidinone **5** and epoxy derivative **6**.

Finally, the synthesis of the antidepressant toloxatone was successful achieved by using two different strategies: the reaction of the oxazolidinone **5f** with potassium acetate (KOAc), followed by selective saponification;[35] or in a single reaction step from the epoxy derivative **6f** after treatment with KOAc (Scheme 5).



Scheme 5. Synthesis of toloxatone.

Conclusions

A new synthetic procedure was developed for the preparation of chiral oxazolidinones **5a-i** from *N*-aryl-carbamates **3a-i** with enantiopure epichlorohydrin **4**. We have succeeded in finding appropriate conditions for this reaction by varying the temperature, solvent and base. The use of stirring at room temperature, LiOH as base and DMF as solvent gave the best yields. Epoxy derivative **6** were obtained as secondary product, except for substates bearing EDGs such as **6f** and **6h**. *N*-aryl-oxazolidinones **5b,f,i** were used as precursors for the synthesis of the linezolid analogue **9**, DuP 721 and toloxatone, respectively. Additionally, HPLC analysis of the linezolid-like derivative **9** allowed us to demonstrate that this synthetic strategy is enantiospecific. The correct relative configuration of biologically active oxazolidinone, such as (*S*)-Linezolid, was obtained using *(R*)-epichlorohydrin.

Experimental Section

General. All solvent and reagents were obtained from commercial sources and were used without purification. Hygroscopic solvents were purchased as anhydrous in sealed bottles with septa and over molecular sieves. The reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates. The synthesized compounds were purified by silica flash chromatography, using Merck silica gel (particle size 0.040-0.063 mm) and mixtures of ethyl acetate and petroleum ether (fraction boiling in the range of 40-60 °C) in various ratios. Melting points were determined on a Reichart-Thermovar hot-stage apparatus. ^{1}H NMR, ^{13}C NMR and HPLC/MS are utilized to verify the structure and purity of synthesized compounds. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Advance (^{1}H: 300 MHz, ^{13}C: 75.5 MHz); DMSO-d_6 or $CDCl_3$ were used as solvent and TMS as an internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants as *J* values in Hertz. HRMS spectra were recorded in positive mode with HPLC/MS (6540 UHD Accurate Mass Q-TOF LC/MS – Agilent Technologies) and Dual AJS ESI source. Chiral HPLC (HPLC/UV 1260 infinity – Agilent Technologies, Inc., Santa Clara, CA, USA) with a Daicel Chiralpak IA column and hexane/*i*PrOH (80:20) as mobile phase, as previously reported.[40]

The compounds **3c** and **3d** were purchased from Sigma Aldrich (Sigma Aldrich, St. Louis, MO, USA).

The derivatives **3i,7-9**[14] and toloxatone[35] were synthetized as previously reported. ^{1}H NMR spectroscopic data of the known compounds **3b,**[41] **3e**,[42] **3f**,[43] **3g,**[44] **3h**,[45] **5a**,[46] **5b**,[37] **5d**,[46] **5f**,[35] **5h**,[47] **6h**,[44] **9,**[14] **10**,[37] and DuP 721[37] are consistent with literature.

General procedure for the synthesis of compounds 3a, b, e, f, g, h.

In a round bottom flask, with a magnetic stir bar and a stopper, a mixture of the appropriate aniline **1** (1 mmol), ethyl chloroformate **2** (105 µL, 1.1 mmol) and K_2CO_3 (152 mg, 1.1 mmol) in THF (10 mL) was stirred at room temperature overnight. The solvent was evaporated under vacuum and 50 mL of water was added, then the mixture was neutralized with HCl (10%). The residue was extracted with ethyl acetate (50 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by column chromatography eluting with petroleum ether/ethyl acetate (5:1).

Ethyl-4-bromo-3-fluorophenylcarbamate (3a). White solid; mp: 61-62°C; yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, *J* 7.2Hz, 3H, CH_3), 4.25 (q, *J* 7.2 Hz, 2H, CH_2), 6.72 (s, 1H, NH), 6.95-6.98 (m, 1H, arom.), 7.41-7.47 (m, 2H, arom.). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.60, 61.80, 102.16 (d, *J* 21.3 Hz), 107.17 (d, *J* 21.3 Hz), 115.18,

133.46, 139.13 (d, *J* 10.0 Hz), 153.32, 159.35 (d, *J* 245.50 Hz); HRMS (ESI) $[M+H]^+$ calcd for $(C_9H_{10}BrNO_2)^+$: 261.9873, found: 261.9873.

Ethyl-4-acetylphenylcarbamate (3b). Brown oil; yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, *J* 7.1 Hz, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.27 (q, *J* 7.1 Hz, 2H, CH_2), 6.87 (s, 1H, NH), 7.53 (d, *J* 8.7 Hz, 2H, arom.), 7.95 (d, *J* 8.7 Hz, 2H, arom.). Consistent with literature.[41]

Ethyl 3-chloro-4-fluorophenylcarbamate (3e). Brown oil; yield 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, *J* 6.9 Hz, 3H, CH_3), 4.25 (q, *J* 6.9 Hz, 2H, CH_2), 6.58 (s, 1H, NH), 7.06-7.22 (m, 2H, arom.), 7.57-5.58 (m, 1H, arom.). Consistent with literature.[42]

Ethyl *m*-tolylcarbamate (3f). Brown oil; yield 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, *J* 7.2 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.25 (q, *J* 7.2 Hz, 2H, CH_2), 6.58 (s, 1H, NH), 6.95 (d, *J* 6.6 Hz, 1H, arom.), 7.18-7.28 (m, 3H, arom.). Consistent with literature.[43]

Ethyl 3-bromophenylcarbamate (3g). Brown oil; yield 26%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, *J* 6.6 Hz, 3H, CH_3), 4.25 (q, *J* 6.6 Hz, 2H, CH_2), 6.60 (s, 1H, NH), 7.17-7.18 (m, 3H, arom.), 7.68 (s, 1H, arom.). Consistent with literature.[44]

Ethyl 3-fluoro-4-morpholinophenylcarbamate (3h). White solid; mp: 121-123°C; yield 25%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, *J* 7.2 Hz, 3H, CH_3), 3.04 (t, *J* 4.5 Hz, 4H, CH_2), 3.87 (t, *J* 4.5 Hz, 4H, CH_2), 4.23 (q, *J* 7.2 Hz, 2H, CH_2), 6.57 (s, 1H, NH), 6.85-6.91 (m, 1H, arom.), 6.96-7.00 (m, 1H, arom.), 7.27-7.31 (m, 1H, arom.). Consistent with literature.[45]

Procedure for the synthesis of oxazolidinones 5 and epoxy derivatives 6.

In a round bottom flask, with a magnetic stir bar and a stopper, the appropriate *N*-aryl carbamate **3a–j** (1 mmol) was dissolved in DMF (2 mL) and then *(R)*- or *(S)*- epichlorohydrin (165 µL, 3 mmol) and LiOH (36 mg, 1.5 mmol) were added. The mixture was stirred at room temperature for different reaction times (24 hours for **3e,i**, 48 hours for **3 c,d**, 72 hours for **3a,b,f,g** and 96 hours for **3h**). The mixture was lyophilized and 50 mL of water were added, after which the mixture was extracted with ethyl acetate (50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The products were purified by column chromatography using a mixture of petroleum ether and ethyl acetate (2:1) as eluent.

***(R)*-3-(4-Bromo-3-fluorophenyl)-5-(chloromethyl)oxazolidin-2-one (5a).** Brown oil; yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.75-3.86 (m, 2H), 3.95 (dd, *J* 9.3, 5.7 Hz, 1H), 4.16 (t, *J* 8.9 Hz, 1H), 4.87-4.97 (m, 1H), 7.17-7.21 (m, 1H, arom.), 7.52-7.58 (m, 2H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 44.5, 47.9, 70.9, 103.7 (d, *J* 21.3 Hz), 106.9 (d, *J* 27.9 Hz), 114.4 (d, *J* 3.5 Hz), 133.6, 138.6 (d, *J* 9.7 Hz), 153.5, 159.3 (d, *J* 246.5 Hz). Consistent with literature.[41]

***(R)*-3-(4-Acetylphenyl)-5-(chloromethyl)oxazolidin-2-one (5b).** Brown oil; yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.61 (s, 3H, CH_3), 3.80-3.83 (m, 2H), 4.03 (dd, *J* 9.3, 5.7 Hz, 1H), 4.24 (t, *J* 9.3 Hz, 1H), 4.90-4.99 (m, 1H), 7.68 (d, *J* 8.7 Hz, 2H, arom.), 8.01 (d, *J* 8.7 Hz, 2H, arom.); Consistent with literature.[37]

***(R)*-5-(Chloromethyl)-3-(3,4-difluorophenyl)oxazolidin-2-one (5c).** White solid; mp 71-73 °C (from EtOAc); yield 34%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.75-3.86 (m, 2H), 3.93-3.98 (dd, *J* 9.0 , 5.7 Hz, 1H), 4.16 (t, *J* 9.0 Hz, 1H), 4.88-4.96 (m, 1H), 7.13-7.24 (m, 2H, arom.), 7.58-7.66 (m, 1H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 44.9, 47.9, 70.9, 108.1 (d, *J* 22.4 Hz), 113.7 (dd, *J* 5.9, 3.6 Hz), 117.3 (d, *J* 18.2 Hz), 134.4 (dd, *J* 7.25, 2.5 Hz), 146.9 (dd, *J* 244.1, 12.6 Hz), 150,095 (dd, *J* 245.6, 13.2 Hz), 153.9. HRMS (ESI) $[M+H]^+$ calcd for $(C_{10}H_9ClF_2NO_2)^+$: 248.0284, found: 248.0287.

***(R)*-5-(Chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one (5d).** White solid; mp 132-134 °C (from EtOAc); yield 20%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.74-3.85 (m, 2H), 3.94-3.99 (dd, *J* 9.3, 5.7 Hz, 1H), 4.17 (t, *J* 9.0 Hz, 1H), 4.86-4.95 (m, 1H), 7.37 (d, *J* 9.0 Hz, 2H, arom.), 7.52 (d, *J* 9.0 Hz, 2H, arom.). Consistent with literature.[46]

***(R)*-3-(3-Chloro-4-fluorophenyl)-5-(chloromethyl)oxazolidin-2-one (5e).** White solid; mp 120-123 °C (from EtOAc); yield 43%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.75-3.86 (m, 2H), 3.93-3.99 (dd, *J* 9.0, 5.7 Hz, 1H), 4.17 (t, *J* 9.0 Hz, 1H), 4.88-4.96 (m, 1H), 7.15-7.21 (m, 1H, arom.), 7.43-7.48 (m, 1H, arom.), 7.65-7.68 (dd, *J* 6.3, 2.7 Hz, 1H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 44.6, 48.2, 70.8, 116.8 (d, *J* 21.9 Hz), 117.9 (d, *J* 7.05 Hz), 120.5, 121.5 (d, *J* 18.5 Hz), 134.5 (d, *J* 2.6 Hz), 153.5 (d, *J* 41 Hz), 156.5. HRMS (ESI) $[M+H]^+$ calcd for $(C_{10}H_9Cl_2FNO_2)^+$: 263.9989, found: 263.9992.

***(R)*-5-(Chloromethyl)-3-*m*-tolyl-oxazolidin-2-one (5f).** White solid; mp 78-81 °C (from EtOAc); yield 8%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 3.73-3.85 (m, 2H), 3.97 (dd, *J* 9.0, 5.7 Hz, 1H), 4.19 (t, *J* 9.0 Hz, 1H), 4.84-4.91 (m, 1H), 6.99-7.13 (m, 1H, arom.), 7.26-7.42 (m, 3H, arom.); Consistent with literature.[35]

***(R)*-3-(3-Bromophenyl)-5-(chloromethyl)oxazolidin-2-one (5g).** White solid; mp 76-80 °C (from EtOAc); yield 22%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.74-3.95 (m, 2H), 3.95-4.00 (m, 1H), 4.18 (t, *J* 8.7 Hz, 1H), 4.87-4.96 (m, 1H), 7.24-7.34 (m, 2H, arom.), 7.54-7.58 (m, 1H, arom.), 7.73-7.74 (m, 1H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 44.7, 47.9, 70.9, 116.6, 121.1, 122.9, 127.2, 130.4, 139.1, 153.7; HRMS (ESI) $[M+H]^+$ calcd for $(C_{10}H_{10}BrClNO_2)^+$: 289.9578, found: 289.9593.

***(R)*-5-(Chloromethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (5h).** Brown oil; yield 18%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.07-3.10 (m, 4H), 3.73-3.96 (m, 7H), 4.18 (t, *J* 9.0 Hz, 1H), 4.85-4.93 (m, 1H), 6.96-7.02 (m, 1H, arom.), 7.13-7.17 (m, 1H, arom.), 7.48 (dd, *J* 12.6, 3.9 Hz, 1H, arom.). Consistent with literature.[47]

***(R)*-5-(Chloromethyl)-3-(3-fluoro-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)oxazolidin-2-one (5i).** White solid; mp 139-142 °C (from EtOAc); yield 52%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.51 (s, 3H, CH_3), 3.83 (d, *J* 4.5 Hz, 2H), 4.02 (dd, *J* 9.0, 5.7 Hz, 1H), 4.23 (t, *J* 9.0 Hz, 1H), 4.94-5.02 (m, 1H), 7.43-7.46 (m, 1H, arom.), 7.66-7.70 (dd, *J* 12.9, 2.1 Hz, 1H, arom.), 8.09-8.14 (m, 1H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 11.7, 44.4, 47.8, 70.9, 106.3 (d, *J* 27.3 Hz), 108.1 (d, *J* 11.9 Hz), 113.3 (d, *J* 3.3 Hz), 131.3 (d, *J* 2.7 Hz), 143.0 (d, *J* = 11.0 Hz), 153.2, 159.4, 162.8, 167.6, 171.7 (d, *J* = 5.1 Hz). HRMS (ESI) $[M+H]^+$ calcd for $(C_{13}H_{12}ClFN_3O_3)^+$: 312.0546, found: 312.0568.

Ethyl-4-bromo-3-fluorophenyl(*(R)*-oxiran-2-yl)methylcarbamate (6a). Brown oil; yield 10%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, *J* 7.0 Hz, 3H, CH_3), 2.56-2.57 (dd, *J* 4.8, 2.7 Hz, 1H), 2.85 (t, *J* 4.5 Hz, 1H), 3.25-3.30 (m, 1H), 3.45-3.52 (dd, *J* 15.0, 6.3 Hz, 1H), 4.06-4.12 (dd, *J* 15.0, 3.3 Hz, 1H), 4.22 (q, *J* 7.0 Hz, 2H, CH_2), 7.03-7.06 (m, 1H, arom.), 7.15-7.18 (dd, *J* 10.0, 2 Hz, 1H, arom.), 7.50-7.58 (m, 1H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.5, 45.8, 50.2, 52.9, 62.5, 115.4 (d, *J* 24.2 Hz), 123.6, 128.3, 133.8, 142.9 (d, *J* 8.9 Hz), 155.0, 158.8 (d, *J* 246.2 Hz). HRMS (ESI) $[M+H]^+$ calcd for $(C_{12}H_{14}BrFNO_3)^+$: 318.0136, found: 318.0153.

Ethyl-3,4-difluorophenyl(*(S)*-oxiran-2-yl)methylcarbamate (6c). Brown oil; yield 13%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, *J* 7.0 Hz, 3H, CH_3), 2.57 (dd, *J* 4.8, 2.7 Hz, 1H), 2.85 (t, *J* 4.5 Hz, 1H), 3.24-3.30 (m, 1H), 3.48 (dd, *J* 15.0, 6.3 Hz, 1H), 4.05 (dd, *J* 15.0, 3.3 Hz, 1H), 4.21 (q, *J* 7.0 Hz, 2H, CH_2), 7,05-7.25 (m, 3H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.5, 45.7, 50.2, 53.0, 62.3, 116.2 (dd, *J* 6.3, 3.8 Hz), 116.6 (d, *J* 18.4 Hz), 117.1 (d, *J* 18.9 Hz), 138.7 (dd, *J* 7.7, 3.5 Hz), 148.9 (dd, *J* 248.2, 12.6 Hz), 149.8 (dd, *J* 249.1, 13.6 Hz), 155.2. HRMS (ESI) $[M+H]^+$ calcd for $(C_{12}H_{15}F_2NO_3)^+$: 258.0936, found: 258.0929.

Ethyl-4-chlorophenyl((S)-oxiran-2-yl)methylcarbamate (6d). Brown oil; yield 11%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* 7.2 Hz, 3H, CH_3), 2.52-2.55 (dd, *J* 4.8, 2.7 Hz, 1H), 2.83 (t, *J* 4.5 Hz, 1H), 3.23-3.29 (m, 1H), 3.51-3.58 (dd, *J* 14.7, 6.0 Hz, 1H), 3.97-4.03 (dd, *J* 15.0, 4.0 Hz, 1H), 4.20 (q, *J* 7.2 Hz, 2H), 7.24 (d, *J* 9.0 Hz, 2H, arom.), 7.33 (d, *J* 9.0 Hz, 2H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.5, 45.8, 50.2, 53.0, 62.1, 128.3, 129.1, 132.2, 140.8, 155.3; HRMS (ESI) $[M+H]^+$ calcd for $(C_{12}H_{15}ClNO_3)^+$: 256.0735, found: 256.0742.

Ethyl-3-chloro-4-fluorophenyl(*(S)*-oxiran-2-yl)methylcarbamate (6e). Brown oil; yield 14%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, *J* 6.6 Hz, 3H, CH_3), 2.52 (dd, *J* 3.6, 2.7 Hz, 1H), 2.81 (t, *J* 4.2 Hz, 1H), 3.23 (dd, *J* 6.0, 3.0 Hz, 1H), 3.46 (dd, *J* 14.7, 6.0 Hz, 1H), 4.01 (dd, *J* 14.7, 6.0 Hz, 1H), 4.18 (q, *J* 6.6 Hz, 2H, CH_2), 7.07-7.20 (m, 2H, arom.), 7.37 (d, *J* 5.4 Hz, 1H, arom.); ^{13}C NMR 75.5 MHz, $CDCl_3$) δ: 14.5, 45.7, 50.1, 53.0, 62.3, 116.6 (d, *J* 22.0 Hz),

120.9 (d, *J* 19.0 Hz), 127.0 (d, *J* 7.1 Hz), 129.4, 138.8 (d, *J* 3.3 Hz), 155.2, 156.5 (d, *J* 247.3 Hz). HRMS (ESI) $[M+H]^+$ calcd for $(C_{12}H_{14}ClFNO_3)^+$: 274.0641, found: 274.0658.

Ethyl(*(S)*-oxiran-2-yl)methyl-tolylcarbamate (6f). Orange oil; yield 18%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* 7.0 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.52-2.54 (dd, *J* 4.8, 2.7 Hz, 1H), 2.80 (t, *J* 4.8 Hz, 1H), 3.22-3.27 (m, 1H), 3.62-3.69 (dd, *J* 14.7, 5.7 Hz, 1H), 3.87-3.93 (dd, *J* 14.7, 4.2 Hz, 1H), 4.20 (q, *J* 7.0 Hz, 2H, CH_2), 7.08 (d, *J* 8.1 Hz, 2H, arom.), 7.26 (t, *J* 7.5 Hz, 1H, arom.); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.6, 21.3, 46.0, 50.2, 53.0, 61.9, 124.1, 127.6, 127.7, 128.8, 138.9, 142.1, 155.7. HRMS (ESI) $[M+H]^+$ calcd for $(C_{13}H_{18}NO_3)^+$: 236.1281, found: 236.1287.

Ethyl-3-fluoro-4-morpholinophenyl(*(S)*-oxiran-2-yl)methylcarbamate (6h). Brown oil; yield 29%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* 6.6 Hz, 3H, CH_3), 2.54 (dd, *J* 4.8, 2.7 Hz, 1H), 2.81-2.83 (m, 1H), 3.10 (t, *J* 4.8 Hz, 4H), 3.22-3.27 (m, 1H), 3.52-3.59 (dd, *J* 14.7, 5.7 Hz, 1H), 3.89 (t, *J* 4.5 Hz, 4H), 3.91-3.98 (dd, *J* 15.0, 3.6 Hz, 1H), 4.20 (q, *J* 6.9 Hz, 2H, CH_2), 6.90 (t, *J* 9.0 Hz, 1H, arom.), 7.01 (d, *J* 9.6 Hz, 2H, arom.). Consistent with literature.[45]

Procedure for the synthesis of Linezolid derivative 9.

Oxazolidinone **5i** was reacted with NaN_3 in DMF to obtain compound **7** as previously reported,[14] giving **7** as a white solid; mp 126–128 °C (from EtOAc, lit. 126-128 °C)[14]; yield 92%. In the second step, compound **7** was reacted with Ph_3P in THF yielding amine **8** as previously reported[14] and employed without further purification. In a round bottom flask, with a magnetic stir bar and a stopper, amine **8** (88 mg, 0.3 mmol) was treated with acetic anhydride (56 µL, 0.6 mmol) in CH_2Cl_2 containing also DIPEA (107 µL, 0.6 mmol). The solution was stirred at room temperature for 24 hours, after which the solvent was removed *in vacuo* and the residue treated with water (50 mL) and then HCl 1 M until pH 6. The mixture was extracted with ethyl acetate (50 mL), the organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Compound **9** was purified by column chromatography using ethyl acetate as eluent.

3-(3'-Fluoro-4'-(3''-methyl-1,2,4-oxadiazol-5-yl)-phenyl)-5-(*N*-acetylaminomethyl)-oxazolidin-2-one (9). White solid; mp 185-186 °C (from EtOAc); yield 83%; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 2.05 (s, 3H); 2.52 (s, 3H); 3.68-3.75 (m, 2H); 3.88 (dd, *J* 9.2, 6.8 Hz, 1H); 4.14 (t, *J* 9.0 Hz, 1H); 4.82–4.90 (m, 1H); 5.93-5.98 (m, 1H, NH); 7.37-7.41 (m, 1H); 7.70 (dd, *J* 12.8, 2.2 Hz, 1H); 8.05–8.15 (m, 1H). Consistent with literature.[14]

Procedure for the synthesis of DuP 721.

In a round bottom flask, with a magnetic stir bar and a stopper, to a solution in DMF (1 mL) of the oxazolidinone **5b** (160 mg, 0.63 mmol), or epoxide **6b** (166 mg, 0.63 mmol), NaN_3 (164 mg, 2.52 mmol) was added. The reaction mixture was heated, in a heating mantel, to reflux for 1 hour and after cooling, lyophilized. The residue was treated with 50 mL of water and then the mixture was extracted with ethyl acetate (50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Compound **10** was isolated by column chromatography eluting with petroleum ether/ethyl acetate (1:1).

***(R)*-3-(4-Acetylphenyl)-5-(azidomethyl)oxazolidin-2-one (10).** White solid; mp 75-77 °C (from EtOAc); yield 86% from **5b**, 78% from **6b**; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.62 (s, 3H, CH_3), 3.64 (dd, *J* 13.0, 4.2 Hz, 1H), 3,77 (dd, *J* 13.0, 4.2 Hz, 1H), 3.95 (dd, *J* 8.7, 6.5 Hz, 1H), 4.17 (t, *J* 9.0 Hz, 1H), 4.82-4.88 (m, 1H), 7.68 (d, *J* 8.0 Hz, 2H, arom), 8.02 (d, *J* 8.0 Hz, 2H. arom.). Consistent with literature.[38]

In a round bottom flask, with a magnetic stir bar and a stopper, compound **10** (100 mg, 0.384 mmol) was reacted with Ph_3P (131 mg, 0.499 mmol) in THF (5 mL). The solution was stirred at room temperature for about 2 hours after which 1 mL of distilled water was added and the resulting mixture was refluxed for 1 hour in a heating mantle. After cooling to room temperature, THF was removed under reduced pressure, the resulting residue was treated with water (50 mL) and then HCl 1 M was added until pH 4 was achieved, after which the mixture was extracted with ethyl acetate (50 mL). The aqueous phase, containing the product, was

treated with NaOH 1 M until pH 10 and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure, yielding crude compound **11** (Yield: 78%).

In a round bottom flask, with a magnetic stir bar and a stopper, to a solution of **11** (70 mg, 0.3 mmol) in CH_2Cl_2 containing also DIPEA (107 µL, 0.6 mmol), acetic anhydride (56 µL, 0.6 mmol) was added. The solution was stirred at room temperature for 24 hours after which the solvent was removed under reduced pressure and was treated with water (50 mL) and then HCl 1 M until pH 4, and extracted with ethyl acetate (50 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to give DuP 721 after recrystallization with EtOAc.

***N*-[*(S)*-3-(4-acetylphenyl)-2-oxo-oxazolidin-5-yl)methyl]acetamide (DuP 721).** White solid; mp 163-165 °C (from EtOAc); yield 60%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.04 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.61-3.78 (m, 2H), 3.87 (t, *J* 7.2 Hz, 1H), 4.14 (t, *J* 9.0 Hz, 1H), 4.78-4.88 (m, 1H), 5.99 (s, 1H, NH), 7.65 (d, *J* 8.7 Hz, 2H, arom.), 8.00 (d, *J* 8.7 Hz, 2H, arom.). Consistent with literature.[37]

Procedure for the synthesis of toloxatone from 6f.

In a round bottom flask, with a magnetic stir bar and a stopper, to a solution of oxirane **6f** (141 mg, 0.6 mmol) in DMF (1.5 mL), potassium acetate (293.4 mg, 3 mmol) was added. The reaction mixture was stirred in an oil bath at 90 °C. The reaction progress was monitored by TLC. After 1 hour, the mixture was cooled and lyophilized. The residue was treated with water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Toloxatone was isolated by column chromatography using a mixture of petroleum ether and ethyl acetate (1:1) as eluent.

***(S)*-5-(Hydroxymethyl)-3-*m*-tolyloxazolidin-2-one (toloxatone).** White solid; mp 78-80 °C (from EtOAc); yield 45%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 2.70 (s, 1H), 3.72-3.78 (dd, *J* 12.6, 3.9 Hz, 1H), 3.94-4.03 (m, 3H), 4.69-4.77 (m, 1H), 6.97 (d, *J* 7.2 Hz, 1H, arom.), 7.22-7.33 (m, 2H, arom.), 7.38 (s, 1H, arom.). Consistent with literature.[35]

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Supplementary Material

Copies of ^{1}H NMR, ^{13}C NMR and HRMS spectra for new compounds and for known compounds obtained with the proposed method are given in the Supplementary Material file associated with the manuscript.

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