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Regioselective and Stereospecific Synthesis of Enantiopure 1,3-Oxazolidin-2-ones by Intramolecular Ring Opening of 2-(Boc-aminomethyl)aziridines. Preparation of the Antibiotic Linezolid†

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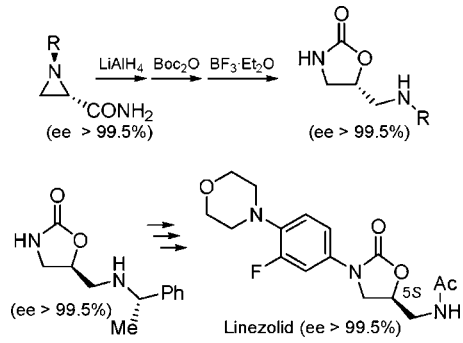
ABSTRACT



The amide moiety of several enantiopure unactivated 1-aryl- or 1-alkylaziridine-2-carboxamides were reduced and then *N*-Boc-protected to afford enantiopure 2-(Boc-aminomethyl)aziridines, which were further converted into enantiopure 5-(aminomethyl)-1,3-oxazolidin-2-ones by means of a stereospecific and fully regioselective BF_3·Et_2O-promoted intramolecular nucleophilic ring opening. One of these oxazolidinones was transformed into the antibiotic linezolid through a CuI-catalyzed N-arylation reaction at its carbamate moiety.

Optically active 1,3-oxazolidin-2-ones have been widely used as chiral synthons and auxiliaries in asymmetric synthesis, including polymer-supported synthesis[1] and the employment of their Fischer carbene complexes,[2] as reported in review articles[3] and in the introduction sections of many full papers dealing with these compounds.[4] Their use as protecting groups for β-amino alcohols in organic synthesis is well established, as is also their ability to act as building blocks for the construction of pseudopeptide foldamers.[5] The discovery that (*S*)-5-(acetamidomethyl)-3-aryl-1,3-oxazolidin-2-ones display good antibacterial activity against Gram-positive bacteria exhibiting resistance to conventional antibiotics was of special significance[6] and led to the development of the new antibiotic linezolid (Zyvox), **1**.[7]

† In memory of the late Professor Lorenzo Pueyo.

(1) Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387–399.

(2) Wulff, W. D. *Organometallics* **1998**, *17*, 3116–34.

(3) (a) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **2005**, *61*, 8173–8194. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.

(4) See, for instance: Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Yun, H.; Dong, Y.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 104–108.

(5) (a) Angelici, G.; Luppi, G.; Kaptein, B.; Broxterman, Q. B.; Hofmann, H.-J.; Tomasini, C. *Eur. J. Org. Chem.* **2007**, 2713–2721. (b) Tomasini, C.; Luppi, G.; Monari, M. *J. Am. Chem. Soc.* **2006**, *128*, 2410–2420, and their own references therein. .

(6) Gregory, W. A.; Brittelli, D. R.; Wang, C. L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Slee, A. M.; Forbes, M.; Bartholomew, P. T. *J. Med. Chem.* **1989**, *32*, 1673–1681.

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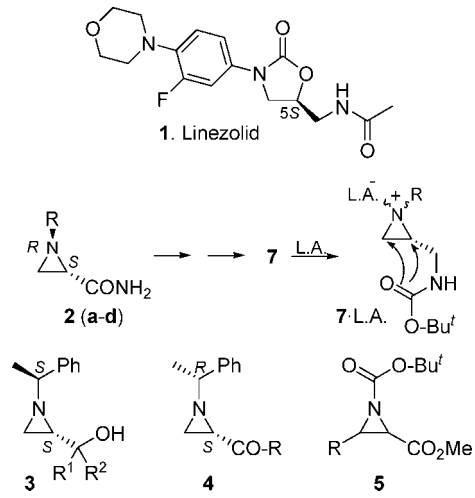


The importance of optically active 1,3-oxazolidin-2-ones and our own interest in the reactivity of enantiopure unactivated aziridines such as **2**[8] converge in the possibility of obtaining the former from the latter. In fact, ring expansions of optically active aziridines have been employed to prepare optically active 1,3-oxazolidin-2-ones. For instance, Korean researchers have used processes of this type in two main stereoselective ways: (a) cyclization at the N and O atoms of aziridines **3** using either iodotrimethylsilane and 1,1′-carbonyldiimidazole[9] or sodium hydride and phosgene[10] and (b) activation of the nitrogen atom of aziridines **4** as a carbamate by reaction with methyl chloroformate, with subsequent ring opening by the chloride anion and ring closure through the carbamate carbonyl.[4] The latter option is close to the ring expansion of activated *N*-Boc aziridines **5** to 1,3-oxazolidin-2-ones, which has been reported to occur stereoselectively with lithium halides in the presence of Amberlyst 15[11] and also with the aid of Lewis acids. However, the results of these Lewis acid promoted ring expansions are known to depend strongly on the aziridine's substituents and stereochemistry.[12] Lewis acid mediated ring expansions of activated *N*-acylaziridines do not lead to 1,3-oxazolidin-2-ones but to 4,5-dihydro-1,3-oxazoles (oxazolines).[13]

In view of the above findings, we envisaged that the reduction of the amide moiety of our aziridines **2** and the subsequent *N*-Boc protection at the resulting exocyclic amine group would lead to aziridines **7**, whose carbonyl group would be able to attack either the C-2 or the C-3 aziridinic positions in a related, though different, way to that already described for compounds **5**. The resulting intramolecular ring opening, which is known for several 2-(Boc-aminomethyl) oxiranes,[14] though to the best of our knowledge not for their aziridine analogues,[15] would pose interesting questions as to its regio- and stereoselectivity. We disclose in this paper our first findings regarding these intramolecular ring openings and, moreover, exploit the presence of an aminomethyl substituent in the resulting 1,3-oxazolidin-2-ones to report a new synthetic approach to the antibiotic linezolid, **1**.

The starting enantiopure 1-substituted aziridine-2-carboxamides **2** were prepared via bacterial kinetic resolution of their racemates as recently reported[8] [(1*R*,2*S*)-**2a**−**d**], or by Gabriel−Cromwell aziridination[16] between ethyl (±)-2,3-dibromopropanoate and (*S*)-α-methylbenzylamine, followed by chromatographic separation of the resulting diastereomers and subsequent ammonolyses [(1*S*,1′*S*,2*S*)-**2e**, (1*R*,1′*S*,2*R*)-**2f**].[17] The trans relationship between the carbamoyl group and the aryl or alkyl substituent at the nitrogen atom in all six aziridines **2** was elucidated by NOESY experiments: the ortho protons of **2a**−**c**, the exocyclic methylene protons of **2d** and the exocyclic methine proton of **2e**,**f** correlate with two protons of the aziridine ring, that of the C-2 position, and the proton cis to the latter at the C-3 atom.

All of the starting materials **2** were transformed into the corresponding enantiopure 5-(aminomethyl)-1,3-oxazolidin-2-ones **8** with a yield of 40−55% (Table 1) over the three sequential steps shown in Scheme 1.[18]

Table 1. Preparation of Oxazolidinones **8** from Aziridines **2**[a]

aziridine	*N*-substituent	time[b] (h)	product	yield[c](%)
(1*R*,2*S*)-**2a**	Ph	6.25	(*R*)-**8a**	45
(1*R*,2*S*)-**2b**	4-Me-C_6H_4	5	(*R*)-**8b**	42
(1*R*,2*S*)-**2c**	4-MeO-C_6H_4	5.25	(*R*)-**8c**	40
(1*R*,2*S*)-**2d**	Ph-CH_2	4.5	(*R*)-**8d**	49
(1*S*,1′*S*,2*S*)-**2e**	(*S*)-PhCHMe	1.5	(3′S,5*R*)-**8e**	55
(1*R*,1′*S*,2*R*)-**2f**	(*S*)-PhCHMe	2	(3′S,5*S*)-**8f**	44

[a] See Scheme 1. [b] Third step, THF reflux time. [c] Overall yield (after three steps); isolated yield (after column chromatography).

A number of side reactions were observed during the overall process: for instance, LAH-reduction processes of 1-arylaziridine-2-carboxamides **2a**−**c** were accompanied by some hydride ring opening at the C-3 position; *N*-Boc protection of 2-(aminomethyl)-1-arylaziridines **6a**−**c** also affords *N*,*N*′-diBoc 2-(arylaminomethyl)aziridines,[19] whose similar polarities to those of intermediates **7a**−**c** resulted in inefficient chromatographic purifications. Other side-products observed in the NMR spectra of the intermediate and final crude materials could not be identified, despite which we were able to characterize several intermediates **6** and **7** as essentially pure compounds. Nevertheless, all these problems were overcome by performing only one chromatographic

(7) (a) Renslo, A. R.; Luehr, G. W.; Gordeev, M. F. *Bioorg. Med. Chem.* **2006**, *14*, 4227–4240. (b) Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529–542. (c) Barbachyn, M. R.; Ford, C. W. *Angew. Chem. Int. Ed* **2003**, *42*, 2010–2023.

(8) Morán-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2007**, *9*, 521–524.

(9) Pyun, D. K.; Lee, C. H.; Ha, H.-J.; Park, C. S.; Chang, J.-W.; Lee, W. K. *Org. Lett.* **2001**, *3*, 4197–4199.

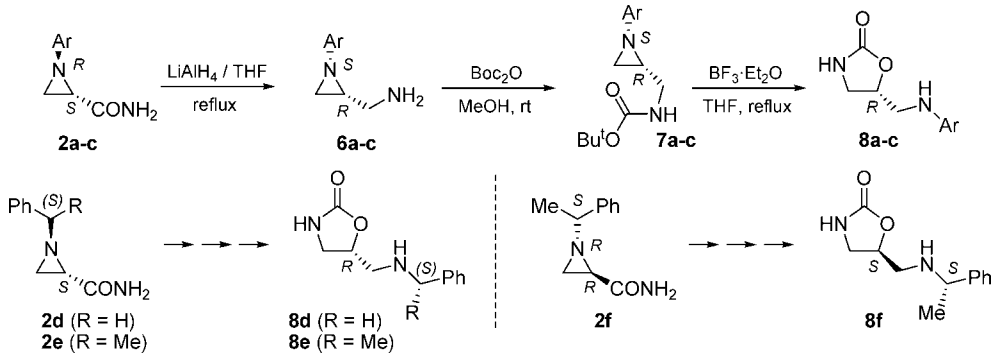
(10) Park, C. S.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Choi, D.; Lee, W. K.; Chang, J.-W.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 43–49. In this case, (1′*R*,2*R*)-**3** was used as the starting material.

(11) Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* **2002**, *43*, 5867–5869.

(12) (a) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185–7194. (b) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synlett* **2000**, 1309–1311. (c) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153–2156.

(13) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39–50.

Scheme 1. Three-Step Preparation of Enantiopure 1,3-Oxazolidin-2-ones **8** from Enantiopure Aziridine-2-carboxamides **2**



purification at the end of the last step, exploiting the very high polarities of the obtained 1,3-oxazolidin-2-ones **8**.

Although the trans relationship between both substituents of all six aziridines **2** remains in the *N*-alkyl intermediates **6d**−**f** and **7d**−**f**, it should be noted that the relationship changes to cis in the *N*-aryl intermediates **6a**−**c** and **7a**−**c**, as deduced from NOESY experiments and from analysis of the ^{1}H NMR chemical shifts observed for the C-3 aziridinic protons (see the Supporting Information).

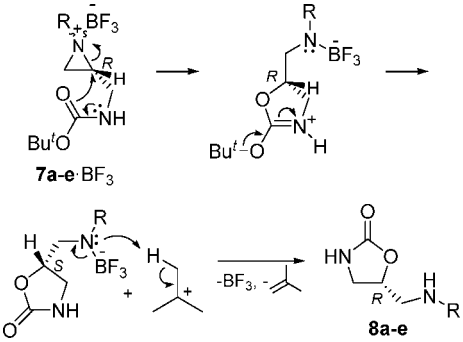
The key step in the overall process is the last one, i.e., the Lewis acid promoted intramolecular ring opening. For this reason, although the reaction conditions shown in Scheme 1 are the best we have found (together with the reaction times in Table 1), we also assayed several other methodologies, always using anhydrous solvents and pure carbamate **7d** as a reference substrate. Interestingly, no competitive nucleophilic ring opening was observed by refluxing **7d** with methanol[8] in the presence of BF_3·Et_2O; however, the results were slightly worse with regard to the yield and purity of the resulting oxazolidinone **8d**. The use of refluxing acetonitrile as solvent resulted in the obtaining of more impure **8d**. Catalytic amounts of copper(II) triflate, on the other hand, have been reported to efficiently promote ring expansions of *N*-Boc aziridines **5**;[12c] in our case, the use of $Cu(OTf)_2$ (10 mol %) as Lewis acid led to a very complex mixture of unidentifiable products both in refluxing THF or dichloromethane. Finally, microwave activation was found to be superior to normal heating in the BF_3·Et_2O-promoted ring expansions of several *N*-Boc aziridines;[12b] however, this is not the case for **7d**,[20] due to a substantial decrease in yield.

Only five-membered, but not six-membered, heterocycles were obtained after the intramolecular ring opening, as deduced from the analysis of the ^{1}H NMR spectra of the corresponding crude materials.[21] Therefore, this step happens with full regioselectivity at the C-2 ring position of intermediates **7**. Moreover, products **8** were shown to be enantiopure, which implies that the opening of the aziridine ring takes place stereoselectively. Finally, jointly considering the transformations of **7e** and **7f**, it can be concluded that this third step is also stereospecific.

Assignment of the absolute configurations for the 1,3-oxazolidin-2-ones **8** relies on three facts: (1) the comparison of the sign of the specific rotation of (*R*)-(+)-**8a** with that reported for (*S*)-(−)-5-(phenylaminomethyl)-1,3-oxazolidin-2-one;[22] (2) the chemical correlation between **8f** and linezolid **1**, since no alteration in the oxazolidinone C-5 chiral center is made during the conversion of the former into the latter (see below); and (3) the enantiopure character of all the products **8a**−**f**.

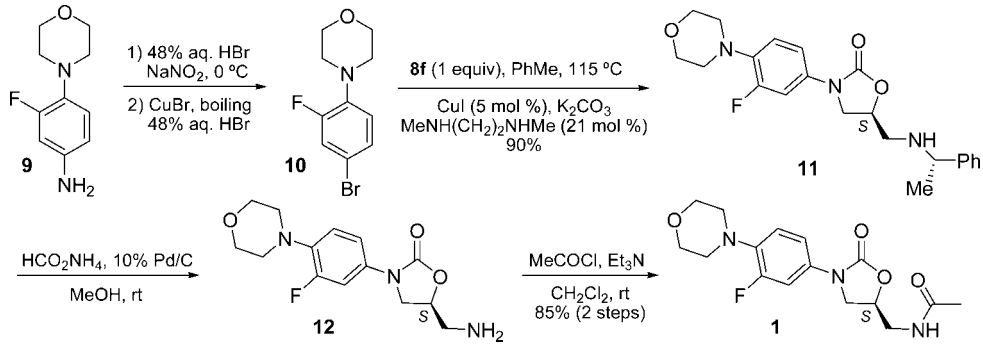
The above facts can be seen as indirect evidence for the probable mechanism proposed in Scheme 2 for the intramolecular ring opening step of the *N*-Boc intermediates **7**. Within this context, it should be noted that only in the first step of this mechanism is there an actual inversion of configuration, although it does not involve any change in the *R* stereodescriptor due to changes in CIP priorities. This same reason accounts for the *R*/*S* variations in the second and third mechanistic steps, which nevertheless have to occur with retention of configuration.

Scheme 2. Probable Mechanism for the Intramolecular Ring-Opening Step



The key question in the previously reported syntheses of linezolid, **1**, is the access to the oxazolidin-2-one ring with the appropriate *S*-configuration at its C-5 position, a goal which has been achieved in different ways. A recent method entails an L-proline-catalyzed asymmetric α-aminooxylation of an aldehyde derivative of 3-fluoro-4-morpholinoaniline, **9**.[23] The methods employed by pharmaceutical companies

Scheme 3. Synthesis of Enantiopure Linezolid, **1**, from the 1,3-Oxazolidin-2-one (3′*S*,5*S*)-**8f**



are chiral pool approaches starting from appropriate derivatives of **9**: for instance, from 3-fluoro-4-morpholinophenyl isocyanate and (*R*)-glycidyl butyrate[6] or from benzyl *N*-(3-fluoro-4-morpholinophenyl)carbamate and (*S*)-3-chloropropane-1,2-diol[7c,24] [or (*S*)-epichlorohydrin[25]].

The structural core of linezolid **1** is its (5*S*)-(aminomethyl)-1,3-oxazolidin-2-one unit, which is also present in our 1,3-oxazolidin-2-one **8f**; we therefore started from **8f** in the subsequent synthetic approach to **1**. An additional feature of **8f** is that the outer substituent at its exocyclic nitrogen atom is benzylic in nature, which will facilitate its replacement by the acetyl group present in **1**, one out of the two structural modifications required in **8f**. The other transformation to be made in this precursor is the coupling of a 3-fluoro-4-morpholinophenyl group into its N-3 ring atom; this N-arylation reaction has been previously used for the synthesis of several antibacterial agents[26] and for the racemic form of linezolide itself.[27]

The synthesis of linezolid from **8f** with an overall yield of 77% is outlined in Scheme 3. First, we prepared 3-fluoro-4-morpholinophenyl bromide, **10**, by diazotization and further Sandmeyer reaction of 3-fluoro-4-morpholinoaniline, **9**.[28] The carbamate nature of the N-3 ring atom and the presence of an amine moiety in **8f** require the CuI-catalyzed Goldberg−Buchwald protocol[29,25] rather than the Pd-catalyzed method[30,24] for its coupling with the aryl bromide **10**. We thereby easily prepared the coupled intermediate **11**, which was finally converted into linezolid **1** after hydrogenolysis and further acetylation. This reaction sequence proves the *S*-configuration at the C-5 position of **8f**.

In conclusion, a stereospecific and fully regioselective conversion of easily accessible enantiopure aziridine-2-carboxamides into enantiopure 5-(aminomethyl)-1,3-oxazolidin-2-ones has been described. Oxazolidinone **8f** was conveniently transformed into the antibiotic linezolid.

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Supporting Information Available: Experimental procedures, characterization data, an NMR study of the cis−trans stereochemistry of compounds **2**, **6**, and **7**, and copies of the corresponding ^{1}H and ^{13}C NMR and NOESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701–2724.

(15) However, it has been reported that two *N*-Boc 2-substituted aziridines led to the same γ-(Boc-aminomethyl)-γ-lactone through a fully stereoselective Lewis acid catalyzed intramolecular ring-opening process quite close to that intended here on our aziridines **6**: Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513–6516.

(16) (a) Weller, R. L.; Rajski, S. R. *Tetrahedron Lett.* **2004**, *45*, 5807–5810. and references therein. (b) Lim, Y.; Lee, W. K. *Tetrahedron Lett.* **1995**, *36*, 8431–8134.

(17) The absolute configurations of **2e** and **2f** were assigned by comparison of the sign of the specific rotation of **2e** with that of an authentic sample of its enantiomer (compound 570559 in 2007−08 Aldrich catalog, in which the configuration at the N chiral center is not specified).

(18) The range of yields of each step, estimated from the weights and the ^{1}H NMR spectra of the corresponding crude materials, is 75−85%.

(19) See the Supporting Information for preliminary details on this subject.

(20) Microwave irradiations were carried out with a Discover CEM microwave reactor (240 W, 65 °C). **6d** was dissolved in THF, and 1.1 equiv of BF_3•Et_2O was added.

(21) Especially those proceeding from pure intermediates **7**.

(22) Ikeda, H.; Takeyama, T.; Hidaka, M.; Arai, K. PCT WO 2001016118, 2001 (CAN 134:193425).

(23) Narina, S. V.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 6799–6802.

(24) Pearlman, B. A.; Perrault, W. R.; Barbachyn, M. R.; Manninen, P. R.; Toops, D. S.; Houser, D. J.; Fleck, T. J. US 5837870, 1998 (CAN 130:25061).

(25) Imbordino, R. J.; Perrault, W. R.; Reeder, M. R. PCT WO 2007116284, 2007 (CAN 147:469356).

(26) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681–3684.

(27) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963–965.

(28) 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*, 673–679.

(29) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

(30) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539–2541.