

A synthetic route to a novel type of conformationally constrained *N*-aryloxazolidinones

Rosa Griera,^a Carme Cantos-Llopart,^a Mercedes Amat,^a Joan Bosch,^{a,*}
Juan-C. del Castillo^b and Joan Huguet^b

^aLaboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 0802-Barcelona, Spain

^bLaboratorios Lesvi S.L., 08970-Sant Joan Despí, Barcelona, Spain

Received 19 November 2004; revised 17 March 2005; accepted 17 March 2005

Available online 12 April 2005

Abstract—The synthesis of *N*-aryloxazolidinone **1**, a conformationally constrained analog of linezolid embodying a tricyclic pyrrolo[1,2-*a*][4,1]benzoxazepine moiety as the *N*-aryl substituent, is reported. The synthetic route involves the successive construction of the pyrrole, oxazepine, and oxazolidinone rings, with incorporation of the isoxazolylamino moiety in the last synthetic steps. © 2005 Elsevier Ltd. All rights reserved.

The emergence of bacterial resistance to antibiotics is a problem of ever increasing significance.¹ *N*-aryl oxazolidinones have recently attracted a great deal of attention as a new class of orally active, synthetic antibacterial agents with activity against Gram-positive and anaerobic bacteria.² DuP 721 was the first drug candidate of this family of totally synthetic antibiotics,³ whereas linezolid was the first member of this series introduced in the market (Fig. 1).⁴ The novel mechanism of action of linezolid, involving the inhibition of bacterial protein synthesis at a very early stage,⁵ combined with its biological activity against resistant organisms has stimulated further synthetic work in the area.⁶ Among the many different approaches to modify the chemical structure of linezolid, two different strategies have received particular attention: the synthesis of conformationally constrained analogs⁷ and the modification

of the acetamidomethyl group present at C-4 of the oxazolidinone ring.⁸

We present here the synthesis of *N*-aryl oxazolidinone **1** as the first example of a new class of conformationally constrained analogs of linezolid, bearing a tricyclic pyrrolo[1,2-*a*][4,1]benzoxazepine moiety as the aryl substituent on the nitrogen of the core oxazolidinone ring. Additionally, **1** incorporates an *N*-(isoxazol-3-yl)amino-methyl substituent at the C-4 position of the oxazolidinone ring instead of the acetamidomethyl group present in linezolid. The synthetic route is depicted in Scheme 1 and involves, as the key steps, the successive construction of the pyrrole, oxazepine, and C-4 substituted oxazolidinone rings, with incorporation of the isoxazolylamino moiety in the last synthetic steps from the key intermediate **12**.

The pyrrole ring was constructed via Clauson–Kaas reaction⁹ by refluxing a solution of methyl 2-amino-5-nitrobenzoate (**2**)¹⁰ and 2,5-dimethoxytetrahydrofuran in glacial acetic acid. *N*-arylpyrrole **3** was obtained in 82% yield.

The closure of the oxazepine ring was accomplished by intramolecular dehydration of a diol, as previously reported for the construction of the basic pyrrolo[1,2-*a*][4,1]benzoxazepine ring system.¹¹ Thus, formylation of **3** under Vilsmeier–Haack conditions occurred regioselectively on the 2-position of the pyrrole ring to give 2-formylpyrrole **4** (65%) as the major product. Then,

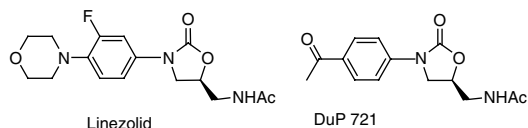
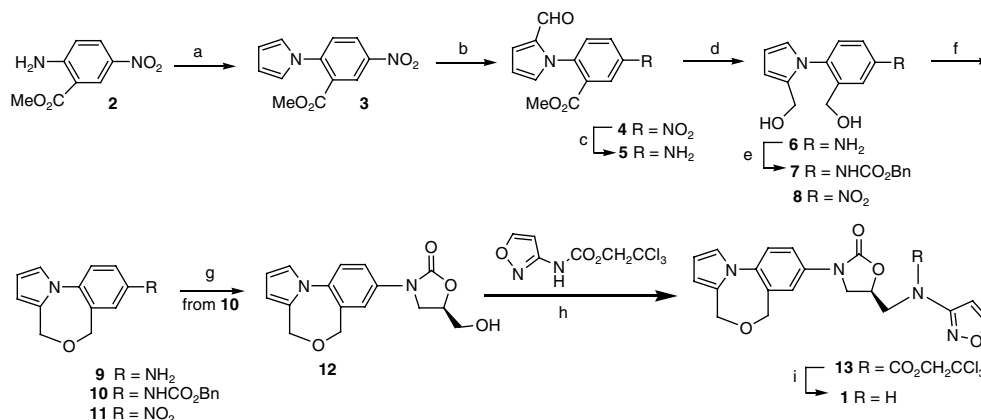


Figure 1.

Keywords: *N*-Aryloxazolidinones; Antibiotics; Linezolid; Constrained analogs; Pyrrolo[1,2-*a*][4,1]benzoxazepine.

* Corresponding author. Tel.: +34 93 402 45 38; fax: +34 93 402 45 39; e-mail: joanbosch@ub.edu



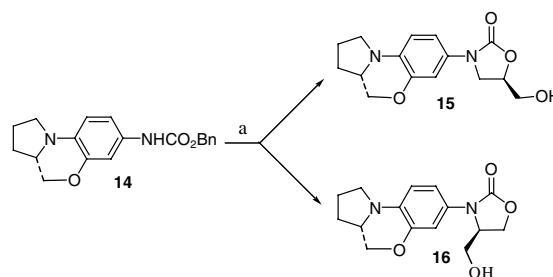
Scheme 1. Reagents and conditions: (a) 2,5-dimethoxytetrahydrofuran, AcOH, reflux; (b) POCl₃, DMF, reflux; (c) H₂, PtO₂, MeOH, rt; (d) LiAlH₄, THF, rt; (e) ClCO₂Bn, Na₂CO₃, acetone, 0 °C to rt; (f) P₂O₅, toluene, 60 °C; (g) (*R*)-glycidyl butyrate, *n*-BuLi, THF, –78 °C to rt, then MeOH, K₂CO₃, rt; (h) PPh₃, DIAD, THF, rt; (i) Zn, AcOH, THF/H₂O, rt.

the nitro group of **4** was chemoselectively reduced by catalytic hydrogenation over PtO₂ to give aniline **5** in 90% yield. A subsequent LiAlH₄ reduction of **5** brought about the reduction of both the formyl and ester groups to give the required aminodiol **6** in 80% yield. Although direct P₂O₅-promoted cyclodehydration of **6** gave tricyclic aniline **9** in poor yield (17%), the closure of the oxazepine ring was satisfactorily accomplished from carbamate **7**, which was easily accessible by treatment of **6** with benzyl chloroformate. The tricyclic carbamate **10** was obtained in 60% overall yield from **6**. An alternative sequence involving the initial reduction of **4** with either LiAlH₄ or Red-Al, followed by cyclodehydration of the resulting diol **8** with P₂O₅ to give **11** took place in poor yields.

For the construction of the 5-substituted oxazolidinone ring we took advantage of the carbamate function present in **10** and used the previously reported regiospecific lithium-ion dependent alkylation–cyclization of aryl *N*-lithiocarbamates with (*R*)-glycidyl butyrate.^{4,12–14} Thus, the tricyclic aryl carbamate **10** was treated with *n*-BuLi, and the resulting lithiated intermediate was allowed to react with (*R*)-glycidyl butyrate to furnish, after in situ hydrolysis of the ester function, 5(*R*)-(hydroxymethyl)oxazolidinone **12**¹⁵ in 51% overall yield. Variable amounts (<10%) of the corresponding regioisomeric 4-substituted oxazolidinone were also formed. The formation of mixtures of 4- and 5-(hydroxymethyl)oxazolidinones from (*R*)-glycidyl butyrate have been reported¹² when using *N*-potassium or sodium (but not lithium) carbamate salts. An initial nucleophilic attack of the carbamate anion on the substituted C-1, rather than C-2, position of the oxirane ring accounts for the formation of the unexpected 4-substituted isomer.

It is worth mentioning that we also isolated a similar C-4 substituted oxazolidinone **16** as a by-product (5% yield), in addition to the previously reported 5-substituted isomer **15**^{7c} (45%), from the reaction of tricyclic carbamate **14** with (*R*)-glycidyl butyrate (Scheme 2).¹⁶

The 4- and 5-substituted regioisomeric oxazolidinones were easily distinguished by ¹H and ¹³C NMR from



Scheme 2. Reagents and conditions: (a) (*R*)-glycidyl butyrate, *n*-BuLi, THF, –78 °C to rt, then MeOH, K₂CO₃, rt.

the chemical shift of the oxazolidinone methine and methylene groups.

Finally, the 3-aminoisoxazole moiety was incorporated by Mitsunobu reaction of alcohol **12** with 3-(2,2,2-trichloroethoxycarbonylamino)isoxazole, followed by deprotection of the resulting trichloroethyl carbamate **13** with zinc in acetic acid. The target oxazolidinone **1**¹⁷ was obtained in 52% overall yield from **12**.

The efficient route reported above for the preparation of **1** can provide facile and practical access to structurally diverse new tricyclic oxazolidinones, since the hydroxymethyl substituent of the key intermediate **12** can be further elaborated into a variety of methylene *O* and *N* linked substituents at the C-5 position of the oxazolidinone ring.⁸

Acknowledgements

Financial support from the DURSI, Generalitat de Catalunya (Grant No. 2001SGR-0084) is gratefully acknowledged.

References and notes

- (a) Service, R. F. *Science* **1995**, 270, 724; (b) Linden, P. K. *Drugs* **2002**, 62, 425.
- (a) Brickner, S. J. *Curr. Pharm. Des.* **1996**, 2, 175; (b) Ford, C. W.; Zurenko, G. E.; Barbachyn, M. R. *Curr.*

- Drug Targets* **2001**, *1*, 181; (c) Halle, E.; Majcher-Peszynska, J.; Drewelow, B. *Chemother. J.* **2002**, *11*, 1.
3. Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.
4. 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.
5. (a) 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; (b) Bobkova, E. V.; Yan, Y. P.; Jordan, D. B.; Kurilla, M. G.; Pompliano, D. L. *J. Biol. Chem.* **2003**, *278*, 9802.
6. For recent work, see: (a) Lee, C. S.; Allwine, D. A.; Barbachyn, M. R.; Grega, K. C.; Dolak, L. A.; Ford, C. W.; Jensen, R. M.; Seest, E. P.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Zurenko, G. E.; Genin, M. J. *Bioorg. Med. Chem.* **2001**, *9*, 3243; (b) Yu, D.; Huiyuan, G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 857; (c) Thomasco, L. M.; Gadwood, R. C.; Weaver, E. A.; Ochoada, J. M.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Schaadt, R. D.; Yagi, B. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4193; (d) Ciske, F. L.; Barbachyn, M. R.; Genin, M. J.; Grega, K. C.; Lee, C. S.; Dolak, L. A.; Seest, E. P.; Watt, W.; Adams, W. J.; Friss, J. M.; Ford, C. W.; Zurenko, G. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4235; (e) Ammazalorso, A.; Amoroso, R.; Bettoni, G.; Fantacuzzi, M.; De Filippis, B.; Giampietro, L.; Maccallini, C.; Paludi, D.; Tricca, M. L. *Il farmaco* **2004**, *59*, 685; (f) Arora, V.; Salunkhe, M. M.; Sinha, N.; Sinha, R. K.; Jain, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4647.
7. (a) Gleave, D. M.; Brickner, S. J. *J. Org. Chem.* **1996**, *61*, 6470; (b) Gleave, D. M.; Brickner, S. J.; Manninen, P. R.; Allwine, D. A.; Lovasz, K. D.; Rohrer, D. C.; Tucker, J. A.; Zurenko, G. E.; Ford, C. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1231; (c) Selvakumar, N.; Srinivas, D.; Khera, M. K.; Kumar, M. S.; Mamidi, R. N. V. S.; Sarnaik, H.; Charavaryamath, C.; Rao, B. S.; Raheem, M. A.; Das, J.; Iqbal, J.; Rajagopalan, R. *J. Med. Chem.* **2002**, *45*, 3953.
8. (a) Gravestock, M. B.; Acton, D. G.; Betts, M. J.; Dennis, M.; Hatter, G.; McGregor, A.; Swain, M. L.; Wilson, R. G.; Woods, L.; Wookey, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4179; (b) Jang, S.-Y.; Ha, Y. H.; Ko, S. W.; Lee, W.; Lee, J.; Kim, S.; Kim, Y. W.; Lee, W. K.; Ha, H.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3881.
9. Boyer, S.; Blazier, E.; Barabi, M.; Long, G.; Zaunius, G. *J. Heterocycl. Chem.* **1988**, *25*, 1003.
10. Kerrigan, J. E.; Vagnoni, L. M. *Tetrahedron* **2001**, *57*, 8227.
11. (a) Massa, S.; Corelli, F.; Stefancich, G. *J. Heterocycl. Chem.* **1981**, *18*, 829; (b) Cheeseman, G. W. H.; Eccleshall, S. A.; Thornton, T. *J. Heterocycl. Chem.* **1985**, *22*, 809.
12. 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.
13. For related approaches from aryl carbamates, see: Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jegannathan, A.; Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrinton, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Greene, M. L.; Barbachyn, M. R. *Org. Process Res. Dev.* **2003**, *7*, 533.
14. For the synthesis of *N*-aryloxazolidinones by Pd-catalyzed arylation, see: (a) Cacchi, S.; Fabrizi, G.; Goggiani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539; (b) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedemann, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681; (c) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207; See also: (d) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963.
15. Spectroscopic data for **12**: ^1H NMR (300 MHz, CD_3OD) δ 3.88 (dd, $J = 12.4$, 4.0 Hz, 1H), 4.03 (dd, $J = 12.4$, 3.4 Hz, 1H), 4.14 (dd, $J = 6.4$, 2.6 Hz, 1H), 4.32 (app t, $J = 8.9$ Hz, 1H), 4.56 (s, 2H), 4.58 (s, 2H), 4.94–5.03 (m, 1H), 6.42–6.46 (m, 2H), 7.27–7.29 (m, 1H), 7.63 (d, $J = 8.6$ Hz, 1H), 7.84 (d, $J = 2.6$ Hz, 1H), 7.90 (dd, $J = 8.6$, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 46.7 (CH_2), 60.0 (CH_2), 62.2 (CH_2), 66.7 (CH_2), 74.0 (CH), 109.4 (2CH), 119.9 (CH), 120.5 (CH), 120.6 (CH), 121.4 (CH), 130.0 (C), 130.2 (C), 136.6 (C), 136.9 (C), 156.0 (C).
16. The final treatment with $\text{K}_2\text{CO}_3/\text{MeOH}$ is necessary to complete the hydrolysis of the butyrate esters resulting from the cyclization.
17. Spectroscopic data for **1**: ^1H NMR (300 MHz, CDCl_3) δ 3.61–3.68 (m, 1H), 3.73–3.81 (m, 1H), 3.94 (dd, $J = 6.7$, 2.0 Hz, 1H), 4.15 (app t, $J = 8.8$ Hz, 1H), 4.45 (s, 2H), 4.48 (s, 2H), 4.56 (app t, $J = 6.4$ Hz, 1H), 4.95–5.02 (m, 1H), 5.89 (d, $J = 1.7$ Hz, 1H), 6.32–6.33 (m, 2H), 7.04 (dd, $J = 2.6$, 1.7 Hz, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 7.57 (d, $J = 2.6$ Hz, 1H), 7.68 (dd, $J = 8.8$, 2.6 Hz, 1H), 8.07 (d, $J = 1.7$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 46.9 (CH_2), 48.1 (CH_2), 60.8 (CH_2), 67.3 (CH_2), 71.8 (CH), 96.8 (CH), 110.0 (2CH), 120.1 (CH), 120.8 (2CH), 121.9 (CH), 130.5 (C), 130.9 (C), 136.6 (C), 137.0 (C), 154.8 (C), 158.7 (CH), 163.9 (C).