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

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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.

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 analogs[7] and the modification of the acetamidomethyl group present at C-4 of the oxazolidinone ring.[8]

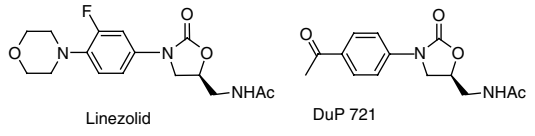

Figure 1.

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)aminomethyl susbstituent 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 reaction[9] 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,

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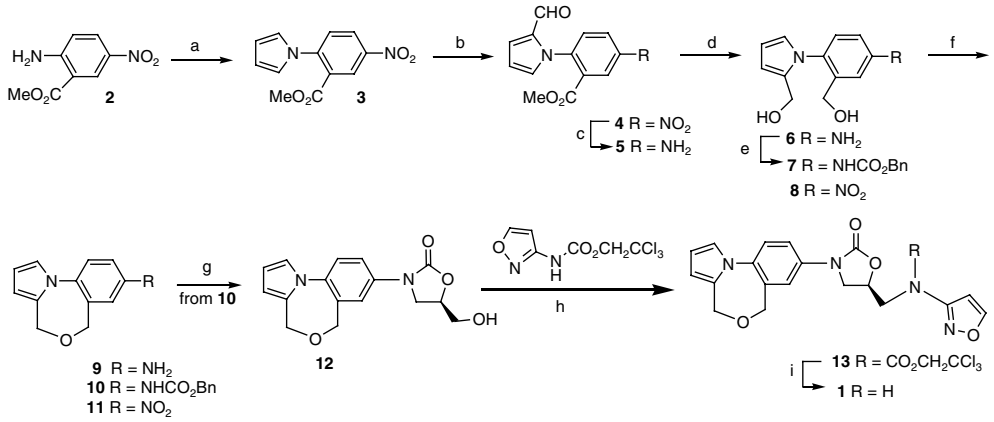


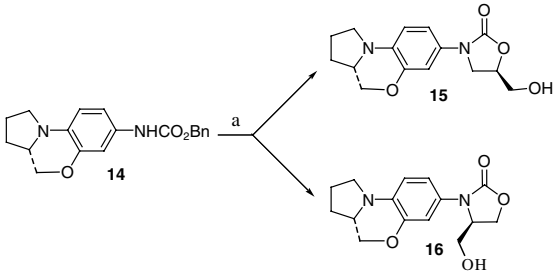
Scheme 1. Reagents and conditions: (a) 2,5-dimethoxytetrahydrofuran, AcOH, reflux; (b) $POCl_3$, DMF, reflux; (c) H_2, PtO_2, MeOH, rt; (d) $LiAlH_4$, THF, rt; (e) $ClCO_2Bn$, Na_2CO_3, acetone, 0 °C to rt; (f) P_2O_5, toluene, 60 °C; (g) (*R*)-glycidyl butyrate, *n*-BuLi, THF, −78 °C to rt, then MeOH, K_2CO_3, rt; (h) PPh_3, DIAD, THF, rt; (i) Zn, AcOH, THF/H_2O, rt.

the nitro group of **4** was chemoselectively reduced by catalytic hydrogenation over PtO_2 to give aniline **5** in 90% yield. A subsequent $LiAlH_4$ 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 P_2O_5-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 $LiAlH_4$ or Red-Al, followed by cyclodehydration of the resulting diol **8** with P_2O_5 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 reported[12] 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 ^{13}C NMR from



Scheme 2. Reagents and conditions: (a) (*R*)-glycidyl butyrate, *n*-BuLi, THF, −78 °C to rt, then MeOH, K_2CO_3, 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]

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References and notes

1. (a) Service, R. F. *Science* **1995**, *270*, 724; (b) Linden, P. K. *Drugs* **2002**, *62*, 425.
2. (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) Ammazzalorso, 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.; Jeganathan, 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.; Goggiamani, 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**: ^{1}H 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 K_2CO_3/MeOH is necessary to complete the hydrolysis of the butyrate esters resulting from the cyclization.
17. Spectroscopic data for **1**: ^{1}H 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).