ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Asymmetric Synthesis of the Fully Elaborated Pyrrolidinone Core of Oxazolomycin A

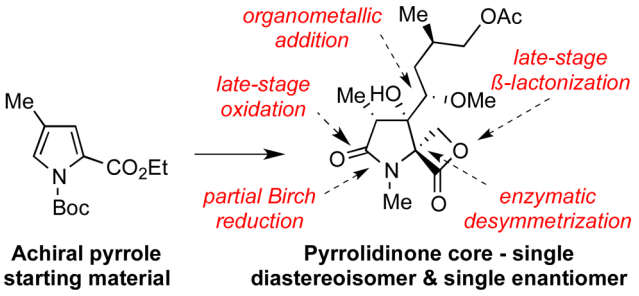
Timothy J. Donohoe,*,† Timothy J. C. O'Riordan,†,§ Manuel Peifer,† Christopher R. Jones,† and Timothy J. Miles‡

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K., and Medicines Research Centre, GlaxoSmithKline, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

timothy.donohoe@chem.ox.ac.uk

Received September 14, 2012

ABSTRACT



The asymmetric synthesis of the key pyrrolidinone core, including a highly elaborated exocyclic carbon chain, of the γ-lactam β-lactone antibiotic oxazolomycin A is described. Principal features include the Birch reduction of an aromatic pyrrole nucleus, a late stage RuO_4 catalyzed pyrrolidine oxidation, and a highly diastereoselective organocerium addition to an aldehyde.

First isolated in 1985 by Uemura et al.[1] from *Streptomyces species*, oxazolomycin A **1** is the parent compound of a class of spiro γ-lactam β-lactone ring containing antibiotics[2] that have been shown to exhibit wide ranging antibacterial and antiviral activities.[3] Due to its structural complexity and potent biological activity, oxazolomycin A has attracted considerable attention from the chemistry community. Syntheses of the diene and triene fragments, in addition to a large number of studies focusing on models of the pyrrolidinone core, void of the exocyclic carbon chain, have been described.[4] The sole total synthesis of oxazolomycin A was reported in 2011 by Hatakeyama et al. in 34 linear steps, utilizing a Conia-ene type cyclization to construct the central γ-lactam ring.[5] Elsewhere, the groups of Kende in 1990 and Hatakeyama in 2007 have

† University of Oxford.
‡ GlaxoSmithKline.
§ Author to whom correspondence regarding X-ray crystallography should be addressed.

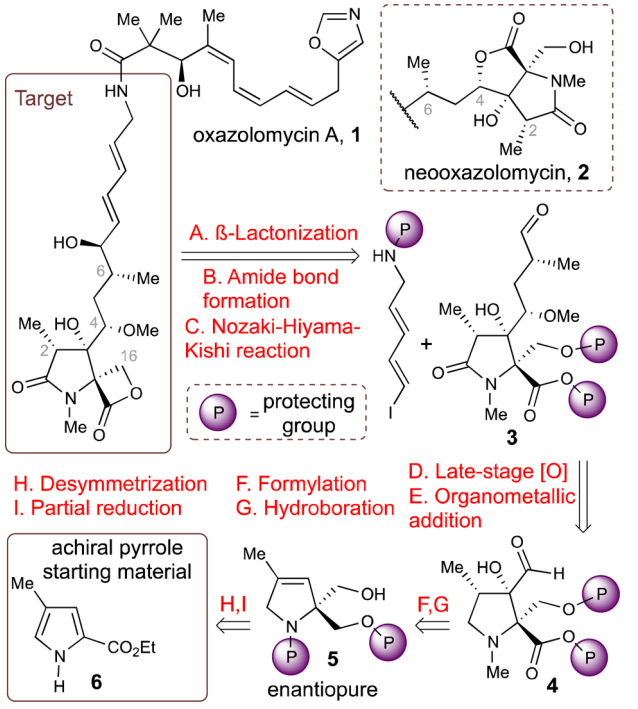
(1) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073.
(2) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181.
(3) (a) Kawai, S.; Kawabata, G.; Kobayashi, A.; Kawazu, K. *Agric. Biol. Chem.* **1989**, *53*, 1127. (b) Tonew, E.; Tonew, M.; Gräfe, U.; Zoepel, P. *Acta Virol.* **1992**, *36*, 166.
(4) (a) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, 612. (b) Henaff, N.; Whiting, A. *Org. Lett.* **1999**, *1*, 1137. (c) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1987. (d) Wang, Z.; Moloney, M. G. *Tetrahedron Lett.* **2002**, *43*, 9629. (e) Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003**, *1*, 3726. (f) Moloney, M. G.; Yaqoob, M. *Synlett* **2004**, 1631. (g) Mohaptra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031. (h) Bennett, N. J.; Prodger, J. C.; Pattenden, G. *Tetrahedron* **2007**, *63*, 6216. (i) Yamada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2008**, *19*, 2789. (j) Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero, M.; Donald, C.; Taylor, R. J. K. *Tetrahedron* **2008**, *64*, 4778. (k) Mondal, D.; Bera, S. *Synthesis* **2010**, 3301. (l) Bastin, R.; Dale, J. W.; Edwards, M. G.; Papillon, J. P. N.; Webb, M. R.; Taylor, R. J. K. *Tetrahedron* **2011**, *67*, 10026.
(5) Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, *13*, 5398.
(6) (a) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070. (b) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6703.

10.1021/ol302541j

presented syntheses of neooxazolomycin **2**, the γ-lactone congener of **1**.[6]

We have previously reported applications of the partial Birch reduction of substituted aromatic pyrroles[7] to the synthesis of complex natural products.[8] With a view to extending the utility of this methodology, we targeted an asymmetric synthesis of the γ-lactam β-lactone core of oxazolomycin A, including an elaborated exocyclic carbon chain primed for a future total synthesis.

Scheme 1. Retrosynthetic Analysis



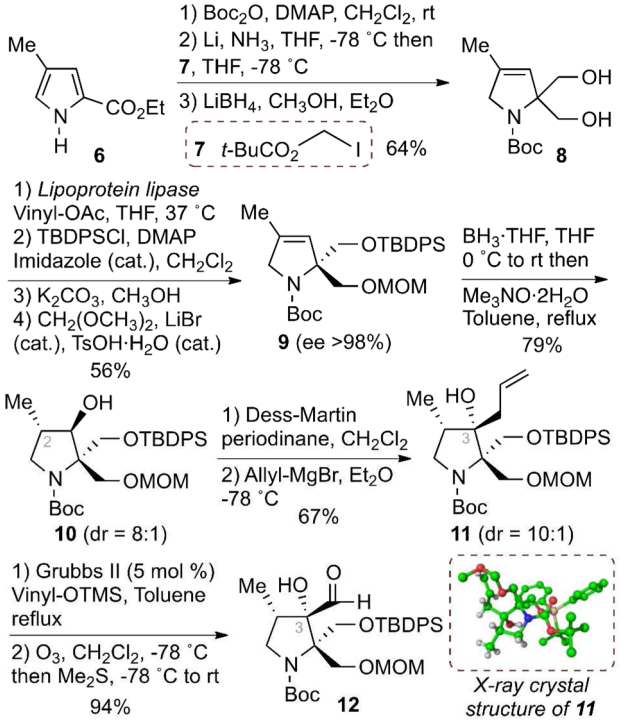
Given that the labile β-lactone ring would need to be constructed in the final step of any subsequent synthesis of **1**, a protected hydroxy acid would be taken through the sequence (Scheme 1). Similar to Hatakeyama,[5,6b] the central diene fragment would be introduced *via* a Nozaki–Hiyama–Kishi reaction with aldehyde **3**. A unique late-stage introduction of the lactam carbonyl group onto **4** would avoid complications from potential epimerization at the C-2 methyl stereocenter,[4a] while chelation-controlled addition to aldehyde **4** would install the exocyclic side chain. Finally, pyrroline **5** could be accessed *via* desymmetrization of the achiral diol arising from partial Birch reduction of pyrrole **6**.

The synthesis began by *N*-Boc protecting commercially available pyrrole **6** and subjecting this to a partial Birch reduction, quenched with iodomethyl pivalate **7** (Scheme 2).[9]

The resulting diester was reduced to furnish diol **8** with the required all-carbon quaternary center, and subsequent enzymatic desymmetrization[10] produced the monoacetate in good yield and excellent ee (>98% ee).[11]

In order to control facial selectivity in the key olefin hydroboration, the remaining alcohol was protected as a bulky *tert*-butyldiphenyl silyl ether. The acetate group, however, proved to be labile under the hydroboration conditions and was thus exchanged for a MOM group to afford pyrroline **9** in 79% yield over two steps. Treatment of the olefin in **9** with $BH_3 \cdot THF$, followed by an oxidative workup with trimethylamine *N*-oxide,[12] gave the desired hydroxy pyrrolidine **10** with excellent regioselectivity and good diastereoselectivity (8:1), resulting from addition to the less hindered face to set the C-2 methyl stereocenter.

Scheme 2. Synthesis of Pyrrolidine Core **12**



Oxidation of alcohol **10** was effected using Dess-Martin periodinane to give the corresponding ketone. Unfortunately the opportunity to install the complete side chain at this stage, via the addition to the ketone of an α-oxyanion, proved unsuccessful.[13] As a result, we pursued an alternative strategy to generate an α-hydroxy-aldehyde that

(7) Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 667.

(8) (a) Donohoe, T. J.; Sisangia, L.; Sintim, H. O.; Harding, J. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2293. (b) Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. *Org. Lett.* **2007**, *9*, 421.

(9) Schieweck, F.; Altenbach, H.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3409.

(10) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298.

(11) The enantiomeric excess of this reaction was determined by HPLC analysis of a derivative of **9**; see the Supporting Information for details, and the absolute configuration by analogy with ref 10.

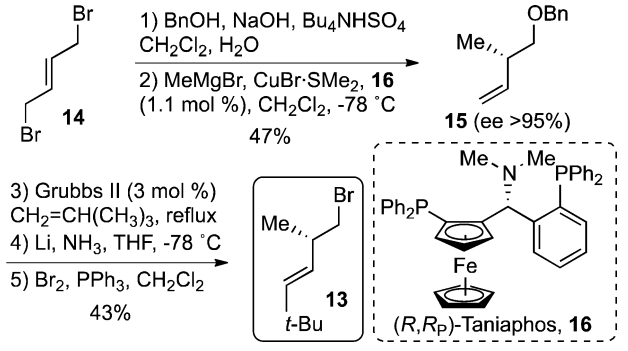
(12) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.

(13) Including metallated allylic ethers: (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. $LiCH_2O$-CH_2OCH_3: (b) Johnson, C. R.; Medich, J. R.; Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K. *Org. Synth.* **1993**, *71*, 133.

could then be used to introduce the carbon chain. To this end, addition of allylmagnesium bromide to the less hindered face of the ketone afforded homoallylic alcohol **11** in 70% yield to set the C-3 stereocenter with very good diastereocontrol (10:1 dr). X-ray crystallographic analysis confirmed the relative configuration of the major diastereoisomer (see Scheme 2).[14] Isomerization of the terminal olefin employing a [Ru]−H species generated *in situ* from Grubbs' second generation catalyst[15] gave the allylic alcohol, and ozonolysis of this internal olefin provided the desired α-hydroxy-aldehyde **12** in excellent yield.

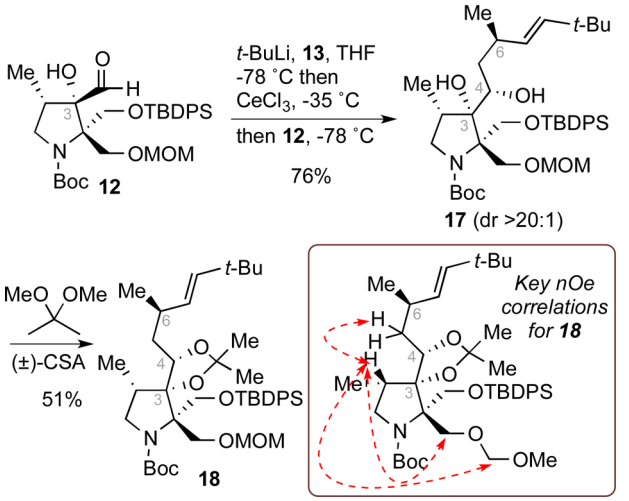
Next we prepared a nucleophile that would enable the carbon skeleton of the side chain to be installed onto aldehyde **12**. Hence we embarked on the synthesis of bromide **13** that possesses the C-6 methyl stereocenter and an alkene unit acting as a masked carbonyl group (Scheme 3). Phase transfer conditions[16] with benzyl alcohol enabled monosubstitution of dibromide **14**, which was then subjected to the asymmetric allylic alkylation protocol developed by Feringa et al. to produce olefin **15** as a single enantiomer.[17] Cross metathesis of **15** with 3,3-dimethyl-1-butene afforded exclusively the *E*-isomer of the disubstituted olefin. Finally, bromination of the primary alcohol resulting from benzyl ether deprotection gave the desired bromide **13** in 82% yield over two steps.

Scheme 3. Synthesis of Bromide **13**



With enantiopure bromide **13** in hand, attention turned to the union of the exocyclic carbon chain and aldehyde **12**. At length it was found that chelation-controlled addition of an organocerium species derived from bromide **13** provided the desired diol **17** in the best yield and as a single diastereoisomer (Scheme 4). To confirm that the addition had occurred from the required *Si*-face of **12** acetonide **18** was prepared and subsequent NOE analysis confirmed the correct configuration at C-4.

Scheme 4. Chelation Control for the Synthesis of Diol **17**



Conversion of the newly formed secondary alcohol **17** into its corresponding methyl ether was accomplished in 78% yield using Meerwein's reagent and proton sponge (Scheme 5). Ozonolysis of the pendant olefin, followed by reduction of the ozonide and protection of the resulting primary alcohol furnished acetate **19**. Oxidation and *N*-functionalization was smoothly effected using catalytic RuO_4 followed by dilute TFA in the presence of a cation scavenger (to selectively remove the *N*-Boc over *O*-MOM protecting group) and then *N*-methylation to afford **20**. Next, a higher concentration of TFA cleaved the *O*-MOM group, and a two-step oxidation protocol then yielded carboxylic acid **21** in 99% yield over two steps. A derivative of **21** lacking the pyrrolidinone *N*-methyl group **22** proved suitable for X-ray crystallographic analysis,[18] providing confirmation of the desired stereochemistry at all five stereogenic centers as well as the site of *O*-methylation (see Scheme 5). Considering a future total synthesis of oxazolomycin A, we decided to test the viability of a late-stage β-lactonization. To this end, deprotection of the silyl ether in **21** followed by lactonization of the resulting hydroxy-acid furnished the γ-lactam β-lactone core **23** in 64% yield over two steps. As suspected, this β-lactone proved to be extremely labile; hence carboxylic acid **21** required a suitable protecting group for the remainder of the sequence.

At length, it was found that the bulky di-*tert*-butylmethylsilyl ester of **21**, prepared in 91% yield from DTBMS triflate,[19] was stable to the proceeding *O*-acetate

(14) CCDC 894648 contains the supplementary crystallographic data for compound **11**; see the Supporting Information for further details.

(15) (a) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255. For a recent review, see: (b) Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014.

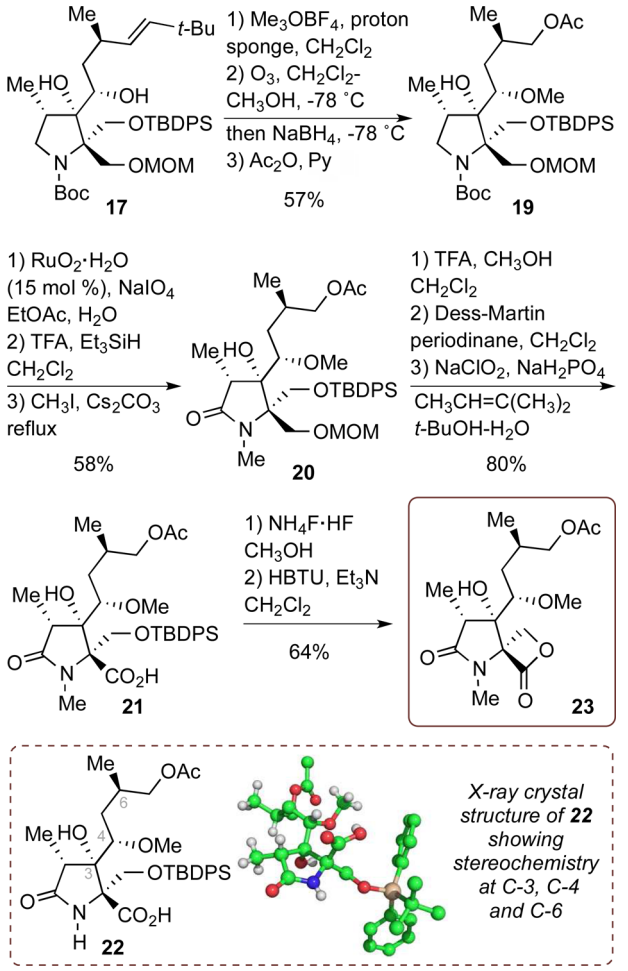
(16) Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. *J. Med. Chem.* **2002**, *45*, 2289.

(17) (a) van Zijl, A. W.; López, F.; Minnaard, A. L.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558. (b) van Zijl, A. W.; Szymanski, W.; López, F.; Minnaard, A. L.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 6994. The enantiomeric excess of this reaction was determined by HPLC analysis of a derivative of **15** (see the Supporting Information for details), and the absolute configuration has been determined previously by Feringa and co-workers; see ref 17a.

(18) CCDC 894647 contains the supplementary crystallographic data for compound **22**; see the Supporting Information for all of the details.

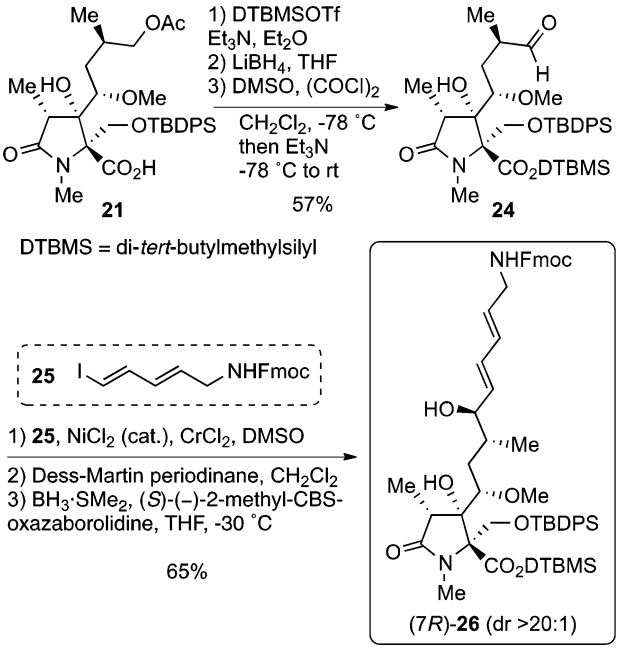
(19) Bhide, R. S.; Levison, B. S.; Sharma, R. B.; Ghosh, S.; Salomon, R. G. *Tetrahedron Lett.* **1986**, *27*, 671.

Scheme 5. Synthesis of the γ-Lactam β-Lactone Core **23**



cleavage (Scheme 6). It is also worth noting that this silyl group was compatible with our β-lactonization protocol. Next, a Swern oxidation of the resulting primary alcohol afforded aldehyde **24** in 72% yield. The central diene component was successfully installed using a Nozaki–Hiyama–Kishi reaction,[5,6b] with vinyl iodide **25**,[5] to produce vinyl alcohol **26** as a 1:1 mixture of epimers. Finally, oxidation to the C-7 ketone using Dess-Martin periodinane, followed by diastereoselective reduction employing $BH_3·SMe_2$ in the presence of (*S*)-(−)-2-methyl-CBS-oxazaborolidine at −30 °C, afforded the target vinyl alcohol (7*R*)-**26** in 96% yield and with excellent diastereoselectivity (> 20:1 dr).[20] This Fmoc protected amine **26** is primed for conjunction with inthomycin, the triene-oxazole portion of oxazolomycin A. Subsequent global protecting group removal and β-lactonization would complete a synthesis of the natural product.

Scheme 6. Elaborating the Side Chain in the Synthesis of (*R*)-**26**



The pyrrolidinone core **26** of oxazolomycin A, including a fully elaborated exocyclic carbon chain, has been synthesized in 28 linear steps from commercially available pyrrole **6**. This advanced oxazolomycin A intermediate has been created as a single diastereoisomer and a single enantiomer. Work is currently underway in our laboratories to establish a concise preparation of inthomycin; its application to the total synthesis of oxazolomycin A **1** will then follow.

Acknowledgment. We are grateful to GlaxoSmithKline (T.J.C.), SNF (M.P.), and St. John's College Oxford (C.R.J.) for providing financial support and Matthew Tatton (University of Oxford) for help with X-ray crystallographic analysis.

Supporting Information Available. Experimental procedures and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Absolute configuration of the C-7 alcohol after CBS reduction could not be unequivocally proven by analytical means; however, the desired diastereomeric outcome is supported by literature precedent for CBS reduction of alkyl-vinyl ketones. See: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986 and references cited therein.

The authors declare no competing financial interest.