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# Asymmetric Synthesis of the Fully Elaborated Pyrrolidinone Core of Oxazolomycin A

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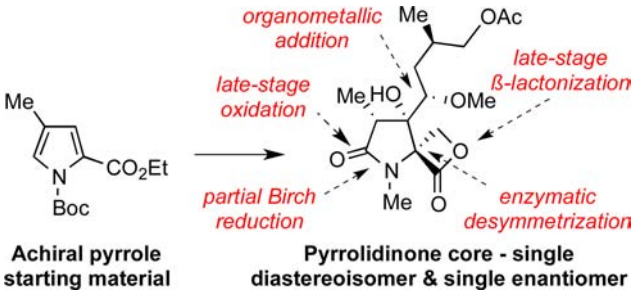
## ABSTRACT




**The asymmetric synthesis of the key pyrrolidinone core, including a highly elaborated exocyclic carbon chain, of the $\gamma$-lactam $\beta$-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 $\gamma$-lactam $\beta$-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 $\gamma$-lactam ring.[5] Elsewhere, the groups of Kende in 1990 and Hatakeyama in 2007 have

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(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.

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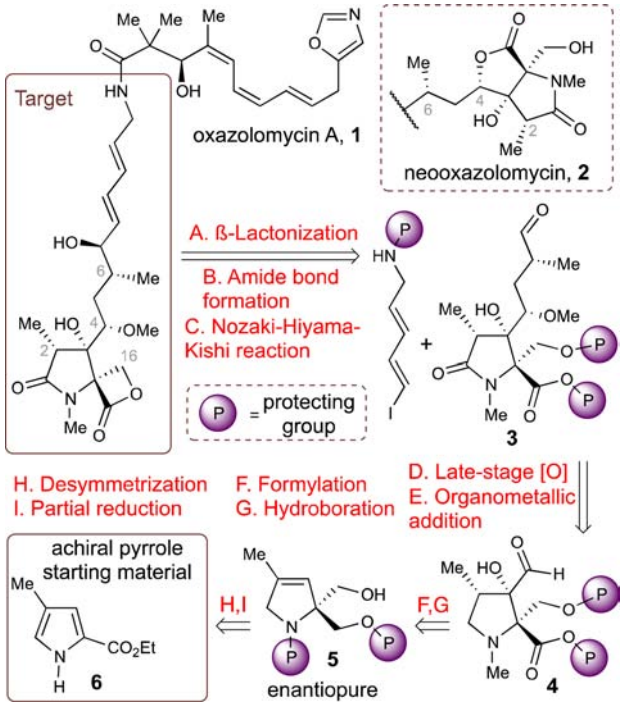
presented syntheses of neooxazolomycin **2**, the $\gamma$-lactone congener of **1**.[6]

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 $\gamma$-lactam $\beta$-lactone core of oxazolomycin A, including an elaborated exocyclic carbon chain primed for a future total synthesis.

**Scheme 1.** Retrosynthetic Analysis



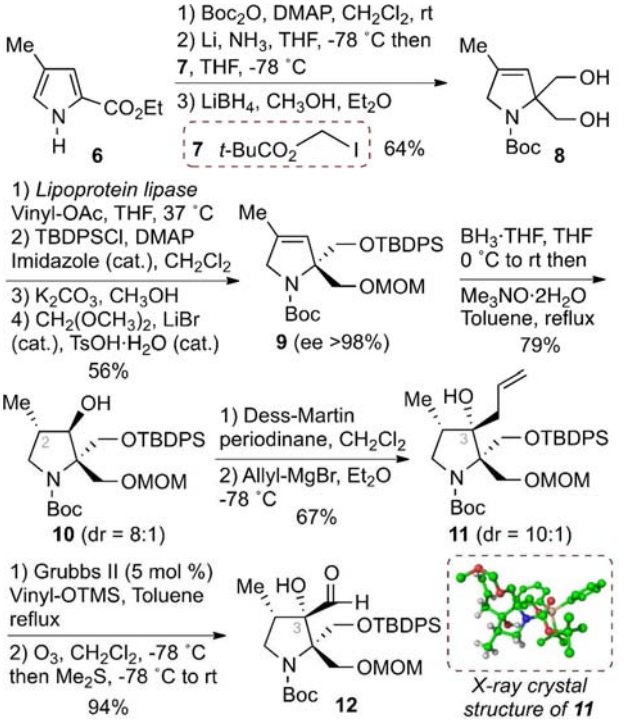

Given that the labile $\beta$-lactone ring would need to be constructed in the final step of any subsequent synthesis of **1**, a protected hydroxy acid would be taken through the sequence (Scheme 1). Similar to Hatakeyama,[5,6b] the central diene fragment would be introduced *via* a Nozaki–Hiyama–Kishi 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.

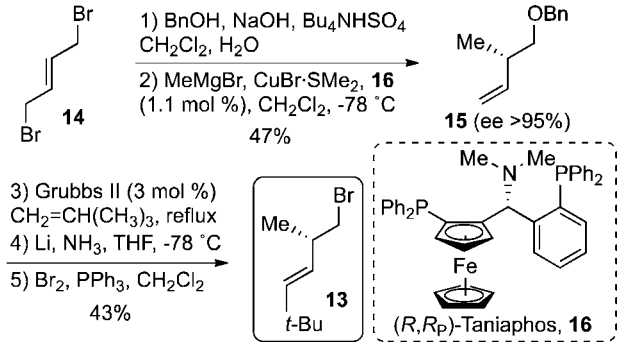
(12) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.

(13) Including metallated allylic ethers: (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. $LiCH_2OCH_2OCH_3$: (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.

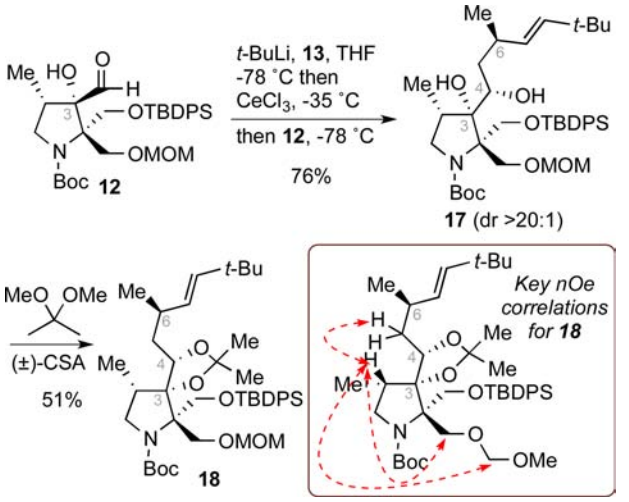
Next we prepared a nucleophile that would enable the carbon skeleton of the side chain to be installed onto aldehyde **12**. Hence we embarked on the synthesis of bromide **13** that possesses the C-6 methyl stereocenter and an alkene unit acting as a masked carbonyl group (Scheme 3). Phase transfer 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.

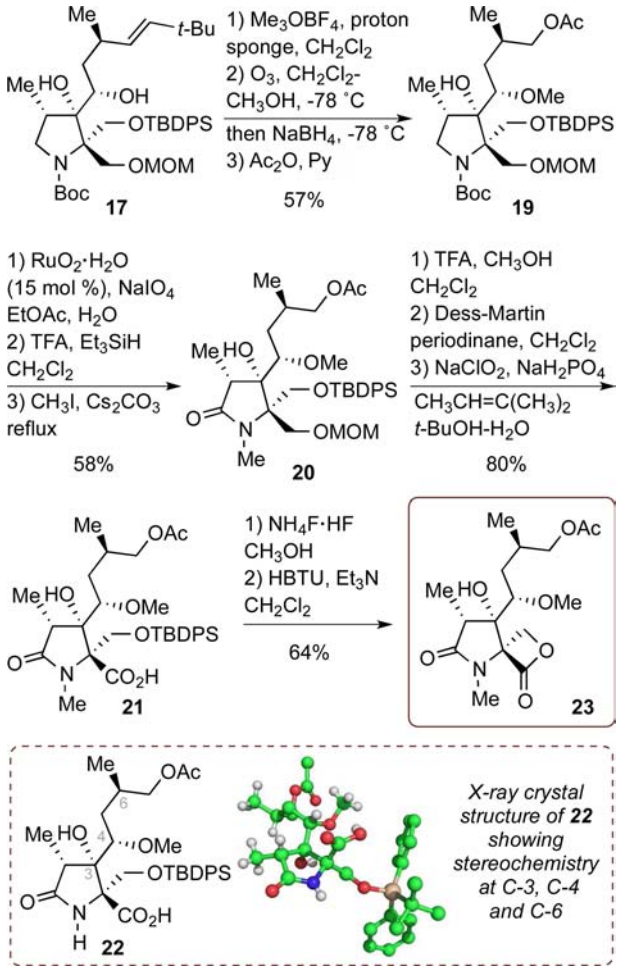
(16) Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. *J. Med. Chem.* **2002**, *45*, 2289.

(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.

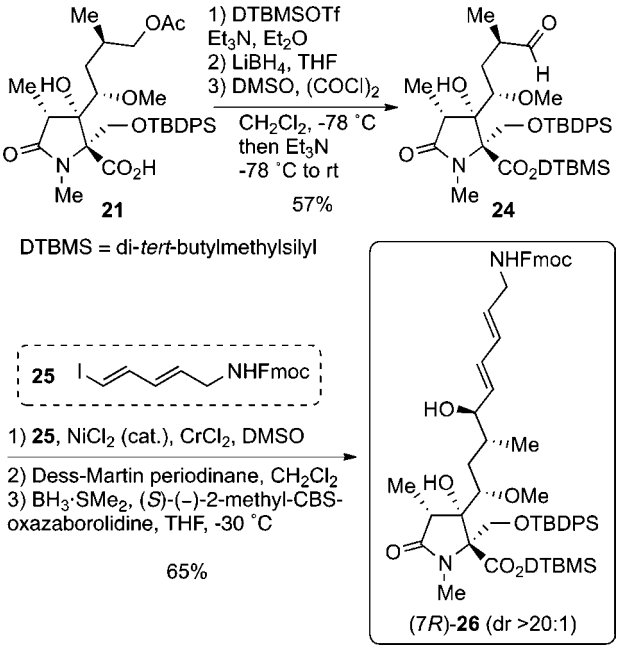
(19) Bhide, R. S.; Levison, B. S.; Sharma, R. B.; Ghosh, S.; Salomon, R. G. *Tetrahedron Lett.* **1986**, *27*, 671.

**Scheme 5.** Synthesis of the $\gamma$-Lactam $\beta$-Lactone Core **23**




cleavage (Scheme 6). It is also worth noting that this silyl group was compatible with our $\beta$-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 $\beta$-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.

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**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.