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Synthesis of the middle fragment of oxazolomycin

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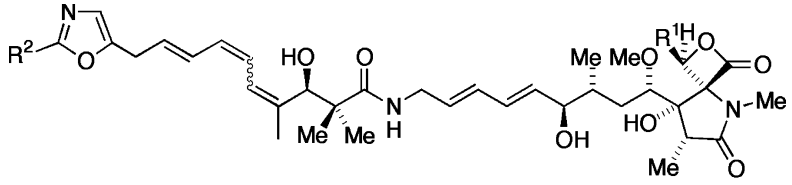
Abstract—A stereoselective and direct synthesis of an (*E*,*E*)-diene suitable for application to the synthesis of oxazolomycin and its analogues is reported.

Oxazolomycin A **1a** is the parent member of a class of antibiotics,[1] other members being oxazolomycin B **1b** and C **1c**,[2] the 16-methylisomer **1d**, and the curromycins **1e**,**f**.[3] The oxazolomycins exhibit wide ranging and potent antibiotic activity, including inhibitory activity against Gram-positive bacteria, antiviral activity against vaccinia, herpes simplex type I and influenza A, as well as in vivo antitumour activity, but with low toxicity (LD_{50} of 10.6 mg/kg for intraperitoneal injection in mice). A recent report has described the potent antibacterial and cytotoxicity of 16-methyloxazolomycin **1d** (MIC against *Bacillus subtilis* 5 μg/ml and IC_{50} against P388 leukaemia cells, 0.23 μg/ml).[4] Some of the details of the biosynthesis of this structurally novel class of compounds have been established.[5]

The broad-spectrum activity of the oxazolomycins has been attributed to their protonophoric (i.e. proton carrying) properties,[6,7] and the pharmacological interest in these compounds comes not only from their antibiotic activity but also their unusual mode of action. The significance of this mode of action is apparent from a consideration of the life-cycle of influenza A, for which the membrane fusions essential for the ingestion of a virion by endocytosis, its release into the host cell and the expulsion of new infectious particles have been studied in detail.[8,9] The intrinsically acidic pH of the endosome is of primary importance for the dispersal of the viral RNA replication machinery into the cytosol. Under these acidic conditions, a significant conformational change (triggered by the protonation of six Asp side chain carboxylates in a 19 residue spacing segment, reducing charge–charge repulsions between them) translocates a membrane-bound fusion peptide by some 100 Å in such a way that it can bridge both the viral and cellular membranes, thereby facilitating fusion.[10] Significantly, it has been shown that lipid soluble bases (such as NH_3 and Me_3N) can inhibit viral infection, by raising the pH of the normally acidic endosomes, and preventing these protonations. This also forms the basis of the action of the well-known anti-influenza drugs, amantidine and rimantidine, and it is our hypothesis that oxazolomycin acts similarly. However, the low toxicity of oxazolomycin (vide supra) is surprising, and this suggests that its protonophoric activity might be selective for the endosomal membrane over the mito-



1a Oxazolomycin A: R^1 = H, R^2 = H; 4'*Z*,6'*Z*,8'*E*
1b Oxazolomycin B: R^1 = H, R^2 = H; 4'*E*,6'*E*,8'*E*
1c Oxazolomycin C: R^1 = H, R^2 = H; 4'*Z*,6'*E*,8'*E*
1d 16-Methyloxazolomycin: R^1 = Me, R^2 = H; 4'*Z*,6'*Z*,8'*E*
1e Curromycin A: R^1 = CH_3OCH_2, R^2 = Me; 4'*Z*,6'*Z*,8'*E*
1f Curromycin B: R^1 = Me, R^2 = Me; 4'*Z*,6'*Z*,8'*E*

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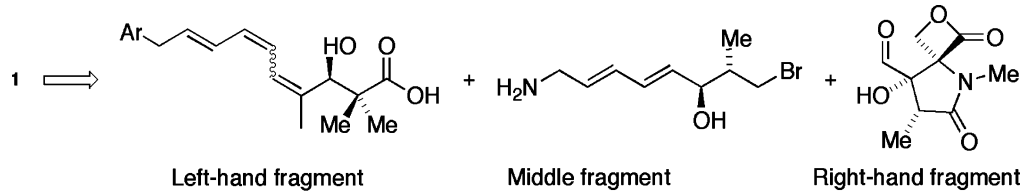
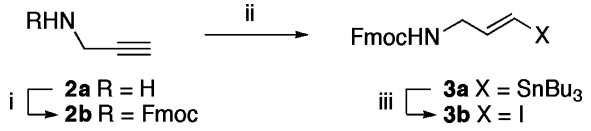


Figure 1.



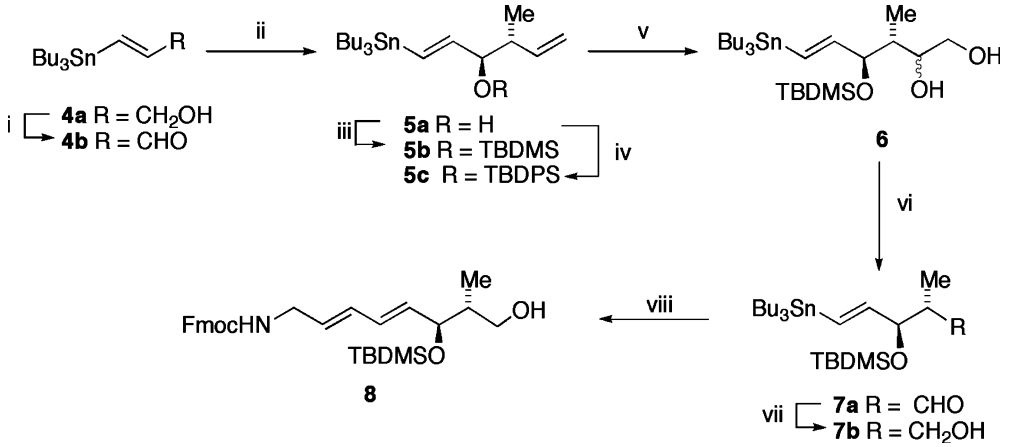
Scheme 1. *Reagents and conditions*: (i) FmocCl, py, DCM (83%); (ii) *n*-Bu_3SnH, AlBN (73%); (iii) I_2, DCM (79%).

chondrial membrane and therefore does not disrupt general mitochondrial ATP synthesis, for which the generation of a proton gradient is also required. Furthermore, the action of the oxazolomycins is made even more unusual and potentially valuable by its disruption of membrane fusion *early* in the viral life-cycle. We hypothesise that the antibacterial and cytotoxic nature of these compounds results from a similar disruption of essential membrane fusion activity.

In order to probe in more detail the molecular basis of action of the oxazolomycins, we require access to both the natural products and to analogues. The only extant total synthesis of any of these compounds, namely neooxazolomycin, is very lengthy,[11] and relies on an efficient Stille coupling approach for the diene fragment.[12] Using a simple retrosynthetic strategy based upon amide and 1,2-diol disconnections, the three fragments indicated in Fig. 1 were identified as pivotal intermediate targets, and synthetic strategies for the left and right hand fragments have been developed.[13,14] Key questions worthy of examination include the effect of double bond geometry and of the length of the spacer group between the left and right hand fragments on biological activity. We report here a direct and versatile route to the middle fragment of the oxazolomycins which makes use of the elegant work of Andrus for the selective dihydroxylation of terminal alkenes over more substituted ones.[15–17]

We planned to use a similar approach to that of Kende,[12] by applying a Stille coupling for the diene fragment. To this end, vinylstannane **3a** was prepared from propargylamine **2a** by initial protection as the Fmoc derivative **2b** and subsequent hydrostannylation using the literature procedure[12] and this was converted to vinyl iodide **3b** using standard methodology (Scheme 1).

For the other component, Hiyama methodology involving Cr(II)-mediated addition of an allyl bromide to an aldehyde,[18] was used for the construction of the required *anti* stereochemistry (Scheme 2). Reaction of stannane **4b**, prepared from **4a**[19] by Swern or PCC oxidation, with crotyl bromide in the presence of chromium(III) chloride/lithium aluminium hydride gave allylic alcohol **5a**, whose *anti*-stereochemistry was established using a combination of NOESY and molecular modelling analysis (Fig. 2), consistent with the literature precedent. Chem 3D analysis indicated a single preferred minimum energy conformation in which the C-1/C-6 backbone is such that the two double bonds are approximately coplanar and parallel; strong



Scheme 2. *Reagents and conditions*: (i) PCC/DCM or $(ClCO)_2$/DMSO (70%); (ii) crotyl bromide, $CrCl_3$/LaH (73%); (iii) TBDMSCl, imidazole, DCM (90%); (iv) TBDPSCl, imidazole, DCM (90%); (v) AD-mix-α, *t*-BuOH, H_2O (72%); (vi) $NaIO_4$, THF, H_2O (89%); (vii) $NaBH_4$, EtOH (85%); (viii) **3b**, $Pd(CH_3CN)_2Cl_2$/THF (65%).

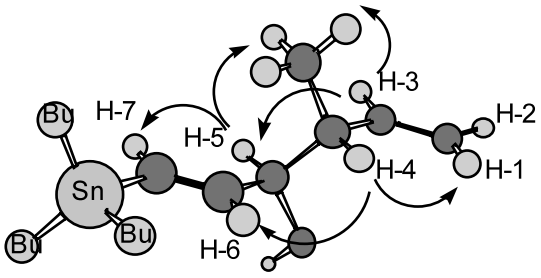


Figure 2. NOESY enhancements for **5a** (butyl residues on Sn simplified for clarity).

enhancement sequences from H-1→H-4→H-6 and H-3→H-5→H-7 and H-5→CH_3 are most consistent with an *anti*- C3(Me)–C4(OH) arrangement. Protection as the TBDMS or TBDPS ether gave **5b**,**c** in excellent yield (90%). At this point, the sequence diverged, and each protected derivative was used to investigate different routes. TBDMS ether **5b** was treated with AD-mix-α according to the Andrus protocol[15] to afford diol **6** in 72% yield as a 1:1 mixture of diastereomers, which was immediately converted to aldehyde **7a** ($NaIO_4$, THF, H_2O) and thence to alcohol **7b** ($NaBH_4$, EtOH) in 85% yield over the two steps. Coupling of this compound with iodide **3b** under standard Stille conditions gave diene **8** in 65% yield.[20]

In order to investigate an alternative coupling strategy to generate intermediates which might prove to be crystalline and therefore permit independent stereochemical assignment, the silyl ether **5c** was converted to vinyl iodide **9** (I_2, DCM, 93% yield) (Scheme 3) and thence to diol **10** in 65% yield as a 1:1 mixture of diastereomers by application of the Andrus protocol.[15] This product was converted to aldehyde **11a** (92% yield) and then to alcohol **11b** (91% yield) via the same strategy outlined above. These products however, proved to be colourless oils. Stille coupling of this compound with **3a** gave the diene product **12a** in 65% yield. Alternatively, alcohol **11b** was converted to bromide **11c** which was in turn coupled to vinyl stannane **3a** to give diene **12b** in 65% yield.[21]

This route represents a direct and versatile approach to a key intermediate for the synthesis of oxazolomycin and its analogues, suitable for the elucidation of its biological action, and details of this work will be published in due course.

Acknowledgements

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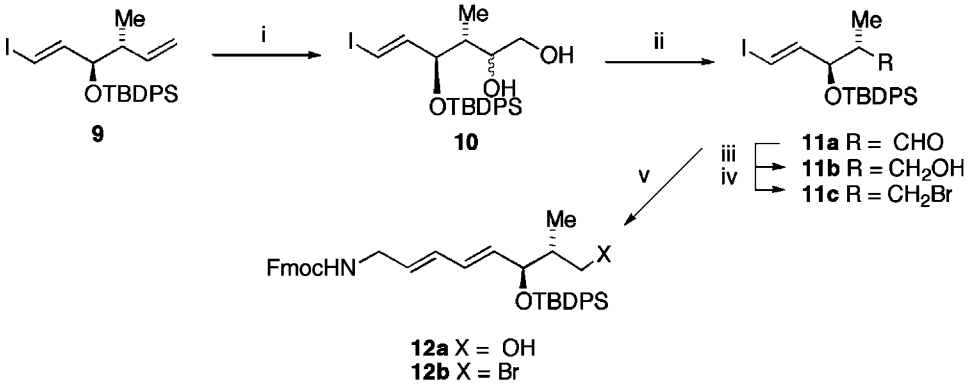
References

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*, 1073–1076.
2. Kanzaki, H.; Wada, K.; Nitoda, T.; Kawazu, K. *Biosci. Biotechnol. Biochem*. **1998**, *62*, 438–442.
3. Kanzaki, H.; Ichioka, T.; Kobayashi, A.; Kawazu, K. *Biosci. Biotechnol. Biochem*. **1996**, *60*, 1535–1537.
4. Ryu, G.; Kim, S.-K. *J. Antibiot*. **1999**, *52*, 193–197.
5. Grafe, U.; Kluge, H.; Thiericke, R. *Liebigs. Ann. Chem*. **1992**, 429–432.
6. Grigorjev, P. A.; Schlegel, R.; Grafe, U. *Pharmazie* **1992**, *47*, 707–709.
7. Tonew, E.; Tonew, M.; Grafe, U.; Zopel, P. *Acta Virol*. **1992**, *36*, 166–172.
8. Bullough, P. A.; Hughson, F. M.; Skehel, J. J.; Wiley, D. C. *Nature* **1994**, *371*, 37–43.
9. Carr, C. M.; Kim, P. S. *Cell* **1994**, *73*, 823–832.
10. Doms, R. W. *Methods Enzymol*. **1993**, *221*, 61–72.
11. Kende, A. S.; Kawamura, K.; deVita, R. J. *J. Am. Chem. Soc*. **1990**, *112*, 4070–4072.
12. Kende, A. S.; deVita, R. J. *Tetrahedron Lett*. **1990**, *31*, 307–310.
13. Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Synlett* **2002**, 1871.
14. Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, 612–614.



Scheme 3. *Reagents and conditions*: (i) AD-mix-α, *t*-BuOH, H_2O (65%); (ii) $NaIO_4$, THF, H_2O (92%); (iii) $NaBH_4$, EtOH (91%); (iv) CBr_4, PPh_3, THF (85%); (v) **3a**, $Pd(CH_3CN)_2Cl_2$/THF (65%).

15. Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159–12169.
16. Andrus, M. B.; Lepore, S. D.; Sclafani, J. A. *Tetrahedron Lett.* **1997**, *38*, 4043–4046.
17. Andrus, M. B.; Turner, T. M.; Asgari, D.; Li, W. *J. Org. Chem.* **1999**, *64*, 2978–2979.
18. Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037–1040.
19. Jung, M.; Light, L. *Tetrahedron Lett.* **1982**, *23*, 3851.
20. Data for *N*-Fmoc-8-amino-3-(*tert*-butyldimethylsilanyloxy)-1-hydroxy-2-methyl-octa-4,6-diene **8**: R_f: 0.40 (Petrol/EA = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.08 (s, 3H, CH_3), 0.10 (s, 3H, CH_3), 0.92 (m, 12H, CH_3 and C(CH_3)$_3$), 1.74 (m, 1H, H-2), 2.67 (br, 1H, OH), 3.58 (m, 1H, H-1), 3.72 (m, 1H, H-1′), 3.88 (br, 2H, H-8), 4.11 (t, 1H, H-3), 4.23 (t, 1H, CHCH$_2$), 4.44 (d, J = 6.8 Hz, 2H, CHCH_2), 4.82 (br, 1H, NH), 5.67 (m, 2H, H-4 and H-7), 6.15 (m, 2H, H-5 and H-6), 7.33 (t, J = 7.4 Hz, 2H, ArH), 7.42 (t, J = 7.4 Hz, 2H, ArH), 7.61 (d, J = 7.4 Hz, 2H, ArH), 7.78 (d, J = 7.5 Hz, 2H, ArH); ^{13}C NMR (125.73 MHz) δ_C: −4.11 (*C*H$_3$), 13.89 (*C*H$_3$), 17.92 (*C*H$_3$), 25.70 (C(*C*H$_3$)$_3$), 41.03 (C-2), 42.57 (C-8), 47.12 (*C*HCH$_2$), 65.87 (C-1), 66.58 (CH*C*H$_2$), 78.44 (C-3), 119.87, 124.88, 126.91, 127.57, 129.33, 129.76, 130.97, 135.38, 141.21, 143.80, 156.09 (C=O). HRMS: 530.2703 (M+Na$^+$), calcd for $C_{30}H_{41}NO_4SiNa$: 530.2703.
21. Data for *N*-Fmoc-8-amino-1-bromo-3-(*tert*-butyldimethylsilanyloxy)-2-methyl-octa-4,6-diene **12b**: R_f: 0.50(Petrol/EA = 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.96 (d, 3H, CH_3, J = 6.8 Hz), 1.07 (s, 9H, C(CH_3)$_3$), 2.00 (m, 1H, H-2), 3.33 and 3.39 (m, 2H, H-1 and H-1′), 3.80 (br, 2H, H-8), 4.23 (m, 2H, H-3 and CHCH$_2$), 4.45 (d, J = 6.8 Hz, 2H, CHCH_2), 4.75 (br, 1H, NH), 5.46 (m, 2H, H-4 and H-7), 5.68 (q, 1H, H-5), 5.92 (m, 1H, H-6), 7.37 (m, 10H), 7.64 (m, 6H), 7.79 (d, 2H, J = 7.5 Hz); ^{13}C NMR (100.6) MHz) δ_C: 14.21 (*C*H$_3$), 19.29, 26.94, 37.13 (C-1), 41.76 (C-2), 42.49 (C-8), 47.13 (*C*HCH$_2$), 66.55 (CH*C*H$_2$), 75.93 (C-3), 119.88, 124.88, 126.92, 127.24, 127.42, 127.58, 129.35, 129.56, 130.88, 131.53, 132.29, 133.62, 133.94, 135.83, 135.87, 141.21, 143.90, 156.04 (C=O). MS(ES): 711.26 (M+NH$_4$), 684.20 (M+1), 610.19, 550.50, 536.17, 440.11. HRMS: 711.2604 (M+NH$_4$), calcd for ($C_{40}H_{45}NO_4Si$+NH$_4$): 711.2618.
22. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.