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Total Synthesis of Oxazolomycin A

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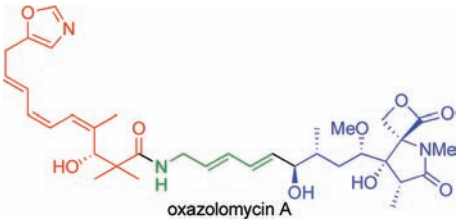
ABSTRACT



The first total synthesis of oxazolomycin A, a structurally novel oxazole polyene γ-lactam/β-lactone antibiotic, is described. Key features include the stereocontrolled construction of the right-hand heterocyclic core by taking advantage of an In(III)-catalyzed Conia-ene type cyclization and the asymmetric synthesis of the left-hand segment starting with a *Cinchona* alkaloid-catalyzed cyclocondensation of an aldehyde with an acid chloride.

Oxazolomycin A (**1**), first isolated from a strain of *Streptomyces* together with neooxazolomycin in 1985 by Uemura et al.,[1] is the parent member of a family of structurally novel polyene lactone-lactam antibiotics.[2] Other members identified to date include oxazolomycins B and C,[3] 16-methyloxazolomycin,[4] curromycins A and B,[5] KSM-2690 B and C,[6] and lajollamycin.[7]

These oxazolomycins exhibit wide ranging and potent antibacterial and antiviral activities as well as in vivo antitumor activity.[2] The characteristic β-lactone-γ-lactam motif draws much attention due to the structural similarity with the pharmacophores of omuralide and salinosporamide A, representative 20S proteasome inhibitors.[8] The intriguing biological properties and structural challenges have made oxazolomycins and their analogs[9] attractive targets for synthesis. Although a number of methodologies for the construction of each left-hand polyene part[10] and right-hand heterocyclic core[11] have been developed, the

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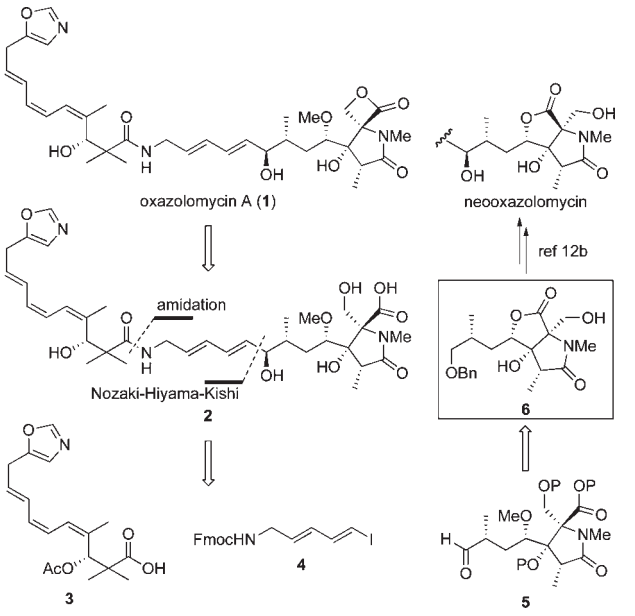
total synthesis of any other members except neooxazolomycin[12] has yet to be accomplished. Herein we report the first total synthesis of oxazolomycin A (**1**).

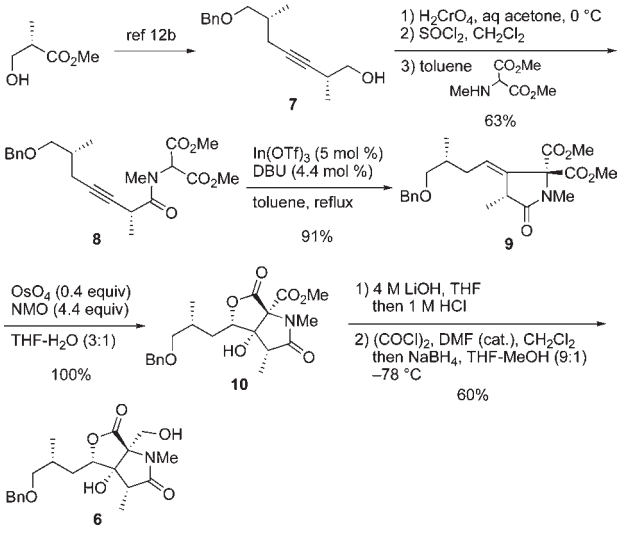
Scheme 1. Retrosynthesis of Oxazolomycin A



Taking into account the labile nature of **1** under various deprotection conditions, we focused on a challenging strategy wherein the final step is the selective construction of the β-lactone ring from unprotected tetrahydroxy acid **2** (Scheme 1). Based on the methodology developed in our synthesis of neooxazolomycin,[12b] we envisioned the assembly of **2** from the left-hand segment **3**, the middle segment **4**, and the right-hand segment **5**. For the right-hand segment **5**, we considered an approach from γ-lactam **6**, neooxazolomycin's right-hand core,[12b] via cleavage of the γ-lactone, methylation of the secondary alcohol, and appropriate protection. Compound **6** can be expected to serve as a common synthetic precursor of most members of this family of antibiotics. For the left-hand segment **3**, we sought to address the preparation by a method potentially applicable to other geometrical isomers.

The opening phase of our effort was the development of an efficient second-generation synthesis of **6**[13] by taking advantage of an In(III)-catalyzed Conia-ene type cyclization[14] which we have recently developed (Scheme 2). Thus, alkynol **7**,[12b] readily available from methyl (*S*)-3-hydroxy-2-methylpropionate, was converted to amide **8** by Jones oxidation followed by condensation with dimethyl 2-(methylamino)malonate[15] via the corresponding acid chloride. Upon treatment of **8** with a catalytic amount of $In(OTf)_3$ in the presence of DBU in boiling toluene, regio- and stereoselective cyclization took place to afford lactam **9** as the sole product in good yield. It should be stressed that the reaction occurred with complete *E*-selectivity and without epimerization. As previously reported,[12b] exposure of **9** to OsO_4–NMO conditions allowed the installation of three contiguous asymmetric centers including two quaternary centers in a single operation to give lactone **10**, quantitatively. The ester group of **10** was then chemoselectively reduced via an acid chloride to give alcohol **6**.

Scheme 2. Synthesis of the Key γ-Lactone[16]



After several shorter approaches proved inefficient,[17] the key right-hand segment **17** was elaborated as follows (Scheme 3). Thus, compound **6** was converted to TBS ether **11** in good yield by sequential methoxymethylation, $NaBH_4$ reduction of the lactone ring, and selective silylation. The subsequent methylation of **11** was cleanly achieved using Meerwein reagent and a proton sponge[18] to provide **12** in 95% yield. After desilylation of **12**, Jones oxidation followed by Pinnick oxidation and $ZrCl_4$-mediated cleavage[19] of the MOM protecting group afforded hydroxy acid **14**. After many discouraging results, we eventually found that treatment of **14** with triisopropylsilyloxymethyl(dodecyl)sulfane[20] in the presence of $CuBr_2$, tetrabutylammonium bromide, and triethylamine allowed the selective esterification without affecting the primary hydroxy group to give ester **15** in

(13) The early stages of the work were presented at the 17th International Conference on Organic Synthesis (ICOS-17) (Daejeon, Korea, June 22–27, 2008). Hatakeyama, S. *Pure Appl. Chem.* **2009**, *81*, 217.

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(15) Heckendorn, R. *Helv. Chim. Acta* **1990**, *73*, 1700.

(16) Highly improved in total yield and number of steps compared with the previous route[12b] (24% in 14 steps versus 15% in 17 steps).

(17) For example, the compound obtained from **6** by a four-step sequence (i. i-$Pr_2Si(OTf)_2$; ii. DIBAH; iii. $NaBH_4$; iv. Ac_2O) did not undergo methylation.

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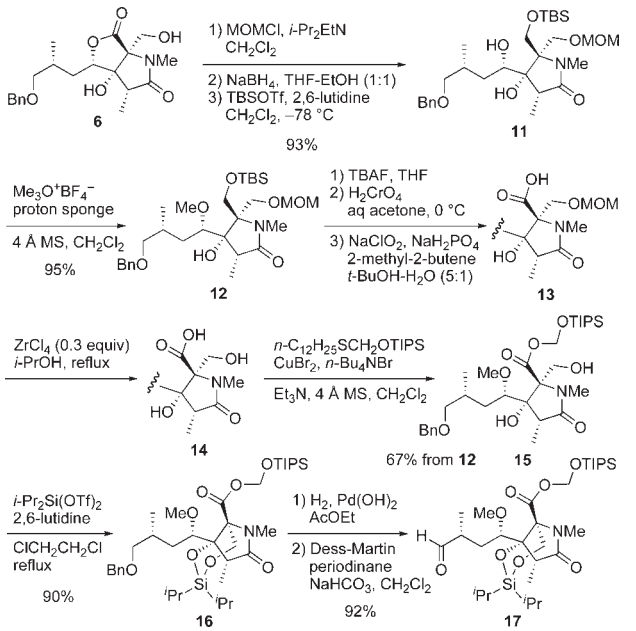
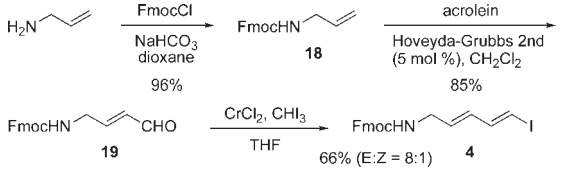
67% overall yield from **12**. It turned out that this esterification did not proceed selectively in the absence of triethylamine to afford the compound in which both the carboxylic acid and the primary alcohol were protected. The envisaged right-hand segment **5** was successfully prepared as aldehyde **17** from **15** by a three-step sequence involving protection as the dioxasilinane, debenzylation, and Dess-Martin oxidation.

Scheme 3. Synthesis of the Right-Hand Segment



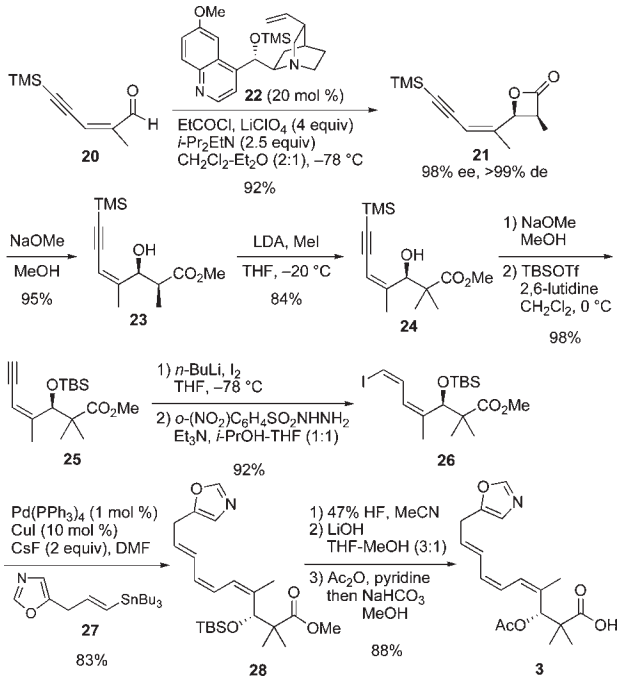
The middle segment **4** was prepared from allylamine in three steps in good overall yield (Scheme 4).[21] Allylamine was first converted to **18**, which was then subjected to a cross-metathesis reaction[22] with acrolein using a second generation Hoveyda–Grubbs catalyst followed by Takai's iodoalkenylation[23] to provide **4** as a 8:1 *E*/*Z*-mixture. Geometrically pure **4** was obtained by recrystallization from AcOEt.

Scheme 4. Synthesis of the Middle Segment



The left-hand segment **3** was prepared by the method outlined in Scheme 5 which features a remarkable improvement of the procedure[12b] we previously reported. The synthesis began with a *Cinchona* alkaloid-catalyzed asymmetric cyclocondensation[24] of an aldehyde and an acid chloride. Thus, according to Nelson's protocol,[24c] aldehyde **20**, readily available from propargyl alcohol,[12b] was reacted with propionyl chloride using 0.2 equiv of **22** and 4 equiv of $LiClO_4$ at −78 °C to give *β*-lactone **21** in excellent enantioselectivity (98% ee) and diastereoselectivity (>99% de).[25,26] After methanolysis of **21**, methylation[27] of the lithium enolate generated from **23** afforded **24** in good yield. Desilylation of **24** followed by TBS protection gave known intermediate **25** which was converted to **26** following the previously established procedure.[12b] Iodoalkene **26** was then subjected to Stille coupling with stannane **27**[10h] using $Pd(PPh_3)_4$, CuI, and CsF[28] in DMF at room temperature to give *Z*,*Z*,*E*-triene **28** in geometrically pure form. When this coupling was carried out using a Pd(0) catalyst alone, isomerization of the triene system to some extent was always observed. Upon successive desilylation, saponification, and acetylation of the resulting hydroxy acid, **28** furnished the left-hand segment **3**.

Scheme 5. Synthesis of the Left-Hand Segment[29]



(21) Previously, compound **4** was prepared from propargyl alcohol in 18% yield (9 steps). See the Supporting Information of ref 12b.

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(25) Isobutyryl chloride was not effective for the cyclocondensation reaction with **20**, and the desired *β*-lactone was not obtained at all.

(26) The cyclocondensation reaction with the *E*-isomer of **20** gave the corresponding *β*-lactone in excellent enantio- and diastereoselectivity (97% ee, >99% de) in 82% yield. The geometrically isomeric left-hand segments of oxazolomycins B and C were stereoselectively synthesized from this *β*-lactone. These syntheses will be reported in due course.

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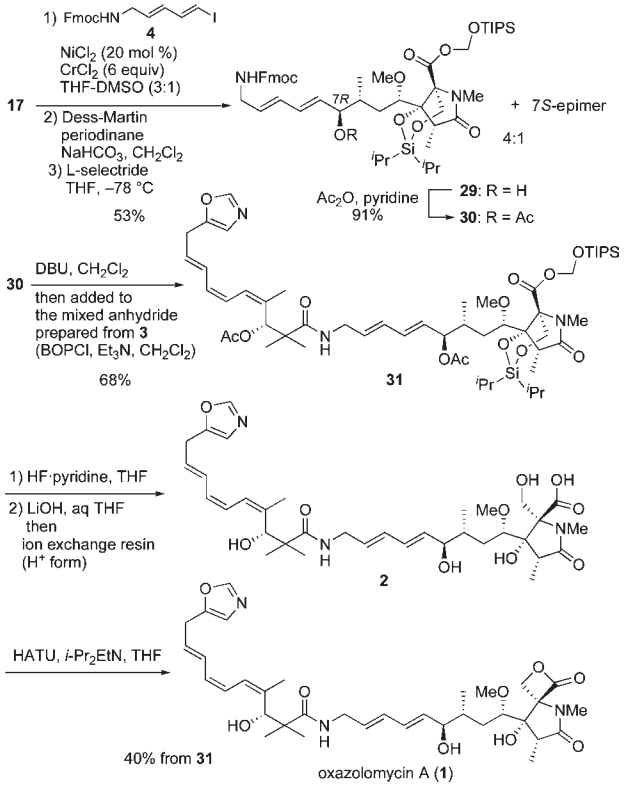
Scheme 6. Synthesis of Oxazolomycin A



With the three segments in hand, we addressed the total synthesis of oxazolomycin A (**1**) through their union, complete deprotection, and the selective formation of the β-lactone ring (Scheme 6). The right-hand segment **17** was first united with the middle segment **4** under Nozaki–Hiyama–Kishi reaction conditions[30,31] using 6 equiv of $CrCl_2$ and 0.2 equiv of $NiCl_2$ in THF–DMSO at room temperature to give a 3:2 mixture of **29** with a 7*R* configuration and its *S*-epimer in 81% yield. Dess-Martin oxidation followed by L-selectride reduction afforded **29** and the 7*S*-epimer in a ratio of 4:1. After separation, the latter was recycled by the above-mentioned oxidation–reduction procedure. As a result of this sequence, **29** was obtained in ca. 50% yield from **17**. After acetylation, treatment of **30** with DBU provided the corresponding free amine which was directly condensed with the left-hand segment **3** using BOPCl to give amide **31** in acceptable yield. Exposure of **31** to HF-pyridine followed by saponification allowed us to obtain the desired tetrahydroxy acid **2** after acidification with ion-exchange resin. Finally, treatment of **2** with HATU[32] in the presence of Hünig's base in THF at room temperature furnished oxazolomycin A (**1**) in 40% yield from **31**. The spectroscopic data were identical with those[1a,3,33] reported for natural oxazolomycin A. The structure of synthetic **1** was further confirmed by the comparison of the spectral data of its diacetate with those reported.[1a,33]

In conclusion, we have achieved the first total synthesis of oxazolomycin A (**1**) in 34 steps of the longest linear sequence in 1.4% overall yield from methyl (*S*)-3-hydroxy-2-methylpropionate. The convergent methodology is of general value in approaches to other oxazolomycins, the synthesis of which is currently under investigation.

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

(29) Highly improved in total yield and number of steps compared with the previous route[12b] (29% in 14 steps versus 12% in 17 steps).

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