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Asymmetric Total Synthesis of (+)-Neooxazolomycin Using a Chirality Transfer Strategy

Jae Hyun Kim, Illan Kim, Yeonghun Song, Min Jung Kim and Sanghee Kim*

Abstract: The total synthesis of (+)-neooxazolomycin was achieved from the amino acid D-serine. The efficiency of our approach is derived from the use of principles of memory of chirality and dynamic kinetic resolution in the intramolecular aldol reaction of a serine derivative to build the densely functionalized lactam framework and to install three contiguous stereocenters. The key intermediate was readily elaborated to the target natural product.

Oxazolomycins are structurally unique natural products that are characterized by fused or spiro bicyclic lactam-lactone systems as well as a polyene subunit. Since the isolation of neooxazolomycin (1, Scheme 1) in 1985,^[1] a number of members of this family have been identified, including oxazolomycins A-C,^[2] oxazolomycin A2, bisoxazolomycin A,^[3] 16-methyloxazolomycin,^[4] curromycins A–B,^[5] KSM-2690 B–C,^[6] and lajollamycins A–D.^[7] These oxazolomycins exhibit a wide range of potent antibacterial and antiviral activities as well as in vivo antitumor activity.^[8] Because of their structural complexity and potent biological activities, considerable attention has been paid to their synthesis.^[9] However, there are only a few reports on the successful total syntheses of oxazolomycins.^[10]

Structurally, neooxzolomycin (1) is comprised of a left-hand fragment 2 containing oxazole triene and right-hand fragment 3 containing a densely functionalized fused lactam-lactone ring system. A major challenge in the synthesis of this complex natural product is the stereocontrolled installation of six stereocenters in the right-hand fragment 3. Kende et al. achieved the total synthesis by employing а cyclocondensation of an amidomalonate dianion with a functionalized galactoside derivative, albeit with the undesired diastereoselectivity.^[10a] Hatakeyama et al. reported an elegant total synthesis using a stereoconvergent approach by connecting chiral building blocks and a substrate controlled installation of the remaining stereocenters.[10b,c]

Given our interest in the asymmetric total synthesis with chirality conservation,^[11] we sought a retrosynthetic scheme that would lead to simple D-serine as the only chiral source in the preparation of stereochemically enriched right-hand fragment **3**. Herein we report the asymmetric total synthesis of (+)-neooxazolomycin (**1**) from D-serine through a strategy that features a number of novel chirality transfer processes.

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Scheme 1. Retrosynthetic analysis of (+)-neooxazolomycin (1).

Our retrosynthetic analysis is shown in Scheme 1. An obvious disconnection of the amide linkage of 1 gave two fragments, 2 and 3. The amide form of left-hand fragment 2 is a naturally occurring compound named inthomycin A.^[12] We envisaged that the (Z,Z,E)-configured triene unit of 2 could be constructed from (*Z*)-unsaturated aldehyde 4. The *Z* configuration of the trisubstituted double bond in 4 was expected to be installed by a 1,4-addition of methyl cuprate to alkynoic ester 5. In turn, alkynoic ester 5 could be accessible from hydroxypivalic acid.

We envisioned that the exocyclic stereocenters and the dienyl amine moiety of right-hand fragment **3** would be installed from the hydroxyl methyl group in **6** in a substrate-controlled manner utilizing the stereochemical features of the fused bicyclic lactam system. We planned to conduct an intramolecular aldol reaction of oxaproline derivative **7** to construct the lactam ring of **6** and to install the three contiguous stereocenters. This type of aldol reaction has been proposed as a plausible step in the biosynthetic pathway towards oxazolomycins.^[13] In turn, it was envisioned that **7** could be traced back to known β -keto acid **8**^[9c] and D-serine. If the principles of "memory of chirality" (MOC) and "dynamic kinetic

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resolution" (DKR) were applied to the aldol reaction of serine derived oxaproline amide **7**,^[14] as in our previous total synthesis of (–)-penibruguieramine starting from L-proline,^[11a] the asymmetric synthesis of right-hand fragment **3** could be achieved from D-serine without the aid of external chiral influences. If successful, this approach would complete the total synthesis of the natural product with high chiral economy and might also have implications in the biosynthesis of the oxazolomycin family of natural products.

Our synthesis commenced with the preparation of aldol substrate **7**, which could be obtained by coupling serine derivative **9** with β -keto acid **8** (Scheme 2). Starting from D-serine, Cbz-protected oxaproline *t*-butyl ester **10** was obtained in two steps.^[15] Under hydrogenolysis conditions, the Cbz moiety was removed to provide oxaproline **9**. Meanwhile, the reaction of ethyl 4-chloroacetoacetate (**11**) with sodium benzyloxide, and subsequent monomethylation afforded **12**. The hydrolysis of **12** afforded **8**. Because both coupling partners (**8** and **9**) are unstable, the amide coupling was conducted immediately after the preparation of these species, and aldol reaction substrate **7** was obtained in a good overall yield as an inseparable 1.4:1 mixture of C2 diastereomers (neooxazolomycin numbering).



For the intramolecular aldol reaction, **7** was treated with NaOEt at room temperature. Desired aldol product **13** was obtained as a single diastereomer in 61% yield with perfect enantioselectivity (>99% e.e.). The only noticeable side product was the C2,C3 dehydrated product (20%). Dehydration of **13** was suppressed at lower temperatures. For example, the reaction at -20 °C provided the essentially enantiomerically pure aldol product **13** in 76% yield without the formation of the dehydrated side product, but two minor diastereomers were formed in a 10:1:1 ratio. The configuration of the three contiguous stereocenters of **13** was unambiguously confirmed by XRD analysis.^[16] The preservation

of the chirality of serine and the stereochemical outcome at C2 indicated that MOC and DKR were active during the reaction. Notably, in the previous reports by Moloney,^[9c] similar aldol reactions of Seebach's oxazolidine substrates **14** (Scheme 2) proceeded with low stereoselectivity, which highlights the efficiency of our MOC aldol ring closure of oxaproline substrate **7**.



Scheme 3. Construction of the exocyclic carbon chain. Reagents and conditions: a) Pd/C, H₂, MeOH/AcOH (2:1), RT, 16 h, 97%; b) TEMPO, TCCA, CH₂Cl₂, 0 °C, 1 h, 84%; c) i. **16**, In, TBAI, water, RT, 5 h; ii. EtOAc, 50 °C, 4 h, 79%, 12:1 d.r.; d) Pd/C, H₂, MeOH/AcOH (2:1), RT, 16 h, 99%; e) *N*,O-dimethylhydroxylamine hydrochloride, *I*PrMgCI, THF, -78 °C to RT, 30 min, 92%; f) NMO, TPAP, CH₂Cl₂, 0 °C to RT, 2 h, 90%; g) CeCl₃-7H₂O, NaBH₄, MeOH, 0 °C, 1 h, 85%, 15:1 d.r.; h) HMDS, TMSCl, pyridine, RT, 16 h, 94%. TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy; TCCA: trichloroisocyanuric acid; TBAI: tetrabutylamnonium iodide; NMO: *N*-methylmorpholine *N*-oxide; TPAP: tetrapropylamnonium perruthenate; HMDS: hexamethyldisilazane; TMSCI: chlorotimethylsilane.

To introduce the exocyclic carbon chain, the benzyl protecting group of 13 was removed, and the resulting hydroxyl group was oxidized (Scheme 3). With aldehyde 15 in hand, various nucleophilic addition reactions, such as a Grignard reaction, an NHK reaction, and a Barbier-type addition, were examined. Among them, only the Barbier-type addition with allyl bromide 16^[17] was successful. The best result was obtained when the Barbier reaction was conducted in water using indium and TBAI to give 17 in 12:1 d.r. and 79% yield after spontaneous lactonization in EtOAc (see the Supporting Information for optimizations).^[18] The newly generated stereocenter at the C4 position is epimeric to that of target natural product 1. However, this stereochemistry was useful in the induction of the desired C6 stereocenter by hydrogenation.^[19] The stereochemistry of **18**, obtained from 17 under hydrogen atmosphere with Pd/C as the catalyst, was confirmed by XRD analysis.^[16] The lactone ring of 18 was opened to Weinreb amide 19, and the resulting C4 secondary hydroxyl group was then inverted by a sequential oxidation and stereoselective reduction (15:1 d.r.) to give 20. Protection of the secondary hydroxy group of 20 required careful selection of the reaction conditions because of the facile lactonization with the nearby carbonyl groups. TMS protection

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using HMDS and TMSCI in pyridine gave **21** without undesired lactonization.



Scheme 4. Preparation of right-hand fragment. Reagents and conditions: a) dimethyl methylphosphonate, *n*BuLi, THF, –78 °C to 0 °C, 30 min, 82%; b) TBAF, THF, –10 °C, 2 h, 80%; c) FeCl₃, Et₃SiH, CH₂Cl₂, RT, 3 h, 51% (60% brsm); d) Si(*i*Pr)₂(OTf)₂, 2,6-lutidine, 0 °C, 20 min, 99%; e) Ba(OH)₂, **26**, THF/H₂O (40:1), –30 °C, 16 h, 75%; f) L-selectride, THF, –95 °C, 20 min; g) Ac₂O, pyridine, RT, 3 h, 75% for 2 steps, 4:1 d.r. TBAF: tetrabutylammonium fluoride.

We employed a Horner–Wadsworth–Emmons (HWE) reaction to install the dienyl amine moiety. In this regard, lithiomethylphosphonate was added to Weinreb amide **21** to give β -keto phosphonate **22**. Prior to the HWE reaction, construction of the *N*-methylated fused lactam-lactone system of the natural product was accomplished as follows. Desilylation of **22** proceeded with concomitant lactonization to give **23**. The reductive ring opening of the oxaproline moiety of **23** with Et₃SiH/FeCl₃^[21] provided *N*-methylated product **24**.^[16] The hydroxyl groups in **24** were protected as dioxasilinane to give **25**.^[10b,22]

After extensive experiments,^[23] we found that the HWE reaction of **25** with aldehyde **26** proceeded in good yield when substoichiometric amounts of Ba(OH)₂ were employed at -30 °C (see the Supporting Information for optimizations). During the HWE reaction, the dioxasilinane group was partially hydrolyzed to give **27** in 75% yield. Under these reaction conditions, no isomerization at C6 was observed. Ketone **27** was reduced with L-selectride and immediately acetylated to produce **28** in a ratio of 4:1. Notably, no diastereoselectivity was observed in the formation of C7 stereocenter when the primary hydroxy group was not protected.





Scheme 5. Preparation of the left-hand fragment. Reagents and conditions: a) (COCI)₂, pyridine, DMF, CH₂Cl₂, RT, 2 h; b) Cul, DIPEA, methyl propiolate, CH2Cl2, RT, 16 h, 86% for 2 steps; c) (+)-DIPCl, RT, 16 h, 72%, 93% e.e.; d) BzCl, Et₃N, DMAP, CH₂Cl₂, 0 °C to RT, 20 min, 98%; e) Cul, MeLi, THF, -78 °C, 30 min, 89%; f) DIBAL-H, THF, -78 to -20 °C, 1 h, 83%; g) NMO, TPAP, CH_2Cl_2, RT, 30 min, 98%; h) CBr4, PPh3, Et3N, CH2Cl2, 0 °C to RT, 16 h, 99%; i) Pd(PPh₃)₄, Bu₃SnH, toluene, RT, 16 h, 99%; j) 36, PEPPSI-*i*Pr, DMF, 55 °C, 36 h, 70%; k) HF-pyridine, THF/pyridine (5:3), 0 °C to RT, 20 h, 90%; I) (COCI)2, DMSO, Et₃N, -78 °C to RT, 1 h, 96%; m) NaClO₂, NaH₂PO₄·H₂O, 2-methyl-2butene, tBuOH/water (1:1), 0 °C to RT, 30 min, 84%. DMF: N.Ndimethylformamide; DIPEA: N,N-diisopropylethylamine; DIPCI: DIBAL-H: diisobutylaluminum chlorodiisopinocampheylborane; hydride. PEPPSI-*i*Pr: [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3chloropyridyl)palladium(II) dichloride.

The synthesis of the left-hand fragment commenced with known TBS-protected hydroxypivalic acid $29^{[24]}$ (Scheme 5). The copper acetylide of propiolate was reacted with the acyl chloride of **29** to afford **30**.^[25] To install the required (*R*)-configuration at C3', (+)-DIP-chloride^[26] was used for the asymmetric reduction of prochiral ketone to give **31** in 93% e.e. and 72% yield. The resulting hydroxyl group was protected with BzCl to provide **32**. With careful selection of the copper salt and methyl anion, the *Z*-selective 1,4-addition of methyl cuprate to alkynoic ester **32** was achieved to afford **33** with complete stereoselectivity.^[27] The methyl ester of **33** was selectively reduced to the hydroxyl group without affecting the benzoate protecting group,^[28] and this species was then oxidized to aldehyde **34**.

Attempts to construct the (*Z*,*Z*,*E*)-configured triene unit from (*Z*)configured unsaturated aldehyde **34** by a Wittig-type condensation were not successful mainly because of poor *Z*/*E* selectivity. Attempts towards the preparation of geometrically pure *Z*,*Z*-1-halodienes or *Z*,*Z*-1-boryldienes in a single step from **34** also failed. However, *Z*,*Z*-1-bromodiene **35** was selectively obtained in two steps using Uenishi's protocol^[29] which involves a Corey–Fuchs dibromoolefination and Pd-catalyzed hydrogenolysis. The stille coupling of **35** with known vinyl stannane **36**^[30] successfully provided oxazole triene **37** without significant isomerization of any of the double bonds.^[31] The TBS

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protecting group was removed, and the resulting alcohol was oxidized to the acid by a Swern oxidation followed by a Pinnick oxidation to provide **38**.



Scheme 6. Completion of the total synthesis of (+)-neooxazolomycin (1). Reagents and conditions: a) i. 38, BOPCI, Et₃N, CH₂Cl₂, RT, 2 h; ii. 28, DBU, CH₂Cl₂, RT, 30 min; iii. The reaction mixture of ii. was added to the reaction mixture of i., RT, 2 h, 51%; b) i. K₂CO₃, MeOH, RT, 16 h; ii. Amberlyst IRC-86, MeOH, RT, 16 h, 90%. BOPCI: bis(2-oxo-3-oxazolidinyl)phosphinic chloride; DBU: 1,8-diazabicyclo(5.4.0)undec-7-ene.

With left-hand fragment **38** and right-hand fragment **28** in hand, we connected these parts to complete the total synthesis (Scheme 6). The BOP-mediated coupling between acid **38** and the free amine generated in situ from **28** furnished amide **39**. The silyl protecting group was also removed during the reaction. Obtained coupling product **39** was treated with K₂CO₃ in MeOH to cleave the benzoate and acetate protective groups. The required reaction conditions led to partial lactone ring opening. However, relactonization was achieved simply by treatment with acidic resin to give neooxazolomycin (1). The spectral data and optical rotation of synthetic **1** were in good agreement with those previously reported.

In summary, we have accomplished the asymmetric total synthesis of (+)-neooxazolomycin (1) using a minimum number of chiral sources. The right-hand fragment with six stereocenters was synthesized from D-serine as the only chiral source. Several chirality propagation processes were employed, including MOC, DKR and substrate-controlled asymmetric inductions. The only chirality present in the left-hand fragment was installed by the asymmetric reduction of a ketone. The (*Z*,*Z*,*E*)-configured triene unit was stereoselectively constructed using metal-assisted reactions such as a cuprate addition, a Pd-catalyzed hydrogenolysis of a dibromoalkene, and a Stille reaction. This synthesis is an exceptionally attractive strategy for the synthesis of other oxazolomycins is currently under investigation.

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