

Natural Products

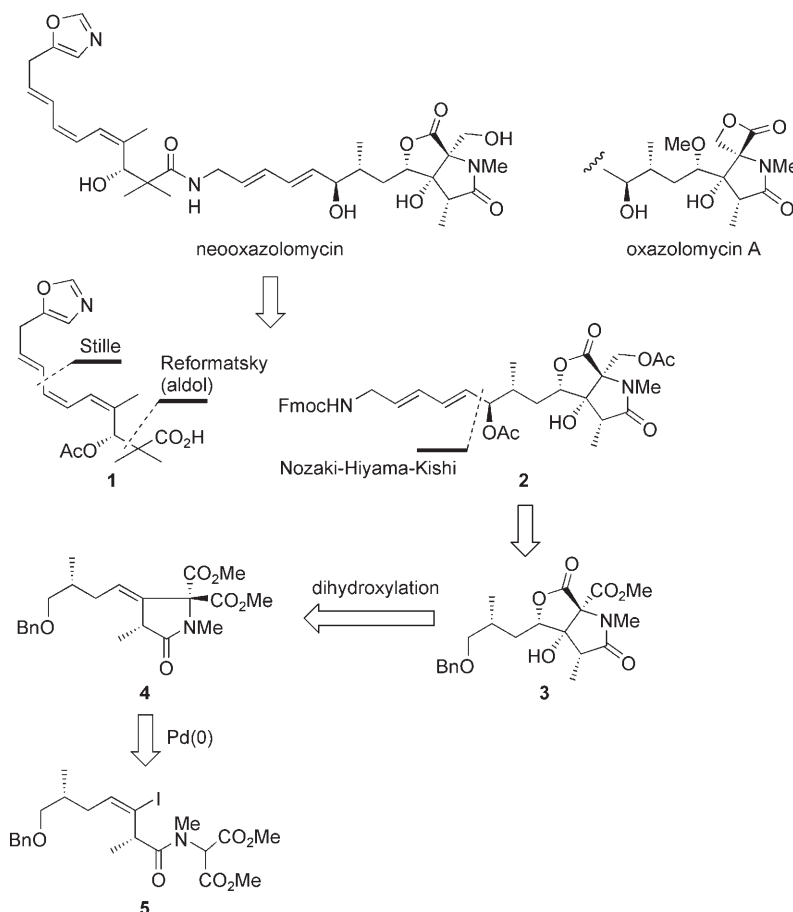
Total Synthesis of Neooxazolomycin**

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Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Neooxazolomycin and oxazolomycin A, originally isolated from a strain of *Streptomyces* by Uemura and co-workers in 1985,^[1] together with the seven other congeners identified to date constitute a family of structurally unique oxazole polyene lactam-lactone antibiotics. These oxazolomycins were found to exhibit wide-ranging and potent antibacterial and antiviral activities as well as in vivo antitumor activity. Their intriguing molecular architectures and biological activities make these compounds attractive targets for synthesis.^[2,3] In 1990, Kende et al. disclosed the synthesis of neooxazolomycin,^[4] and this superb achievement is the first and only total synthesis of any member of this family; however the stereocontrolled construction of the right-hand core has remained an unanswered challenge.

Our synthetic plan for neooxazolomycin makes a disconnection at the amide linkage to give the left-hand segment **1** and right-hand segment **2** (Scheme 1). Since Kende et al. had already demonstrated an effective method for the synthesis of **1**^[4] by a Reformatsky-type aldol reaction^[5] and Stille coupling,^[6] the major challenge in the synthesis resided in the stereoselective construction of **2**. From the retrosynthetic perspective, we envisioned pyrrolidinone **4** as a precursor of **2** with considerably less structural complexity which would lead to **2** through a Nozaki–Hiyama–Kishi reaction^[7] and stereoselective dihydroxylation with concomitant lactonization. We postulated



Scheme 1. Retrosynthetic analysis of neooxazolomycin. Bn = benzyl, Fmoc = 9-fluorenylmethoxycarbonyl.

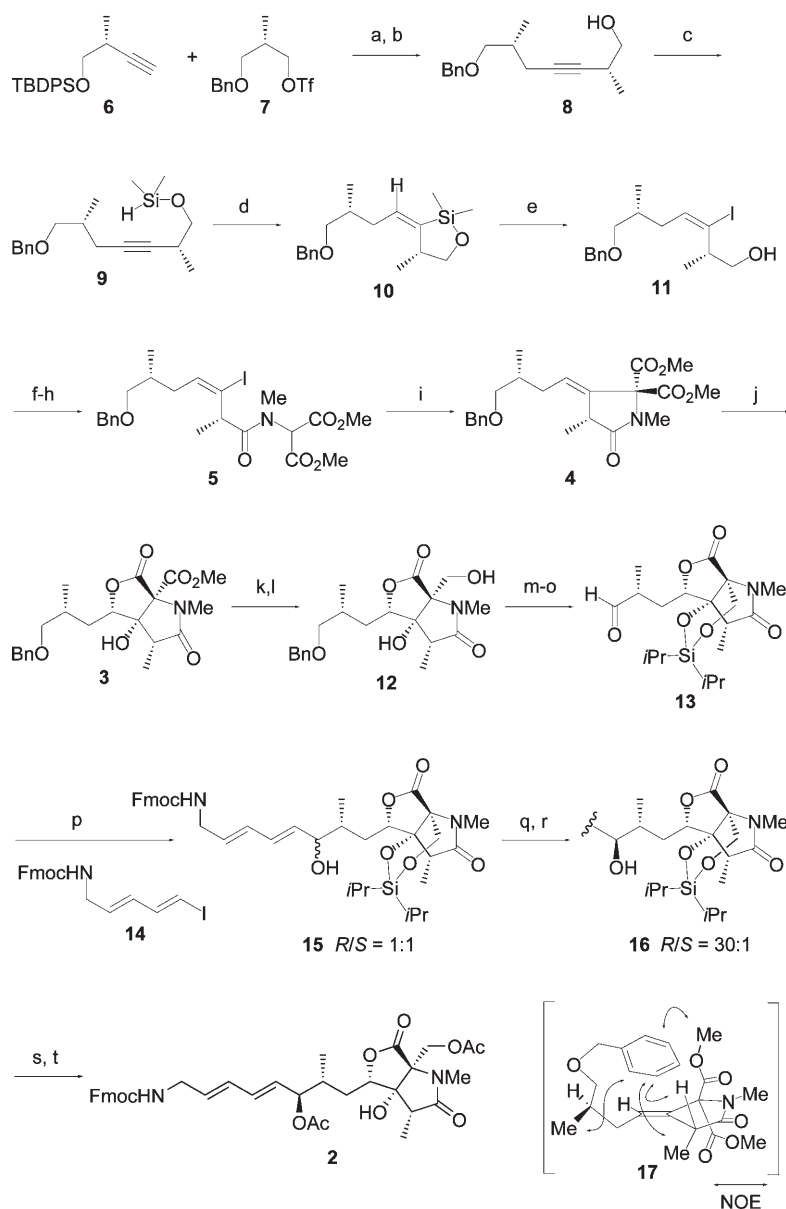
that this precursor could be accessed by a palladium-catalyzed cyclization of amide **5**. This approach is particularly appealing since the three contiguous stereogenic centers including two quaternary centers could be created by one dihydroxylation process.

The required amide **5** was synthesized in a completely stereoselective manner by taking advantage of the intramolecular hydrosilylation^[8] developed by Tamao et al.^[9] (Scheme 2). Thus, alkynol **8** was first prepared by the coupling of alkyne **6**^[10] and triflate **7**,^[11] both readily available from (*S*)-hydroxy-2-methylpropanoate, followed by desilylation. Reaction of **8** with tetramethyldisilazane provided hydrodimethylsilyl ether **9**, which upon hydrosilylation with [Pt(dvds)]^[12] as a catalyst in THF at room temperature followed by exposure of the resulting siloxane **10** to iodine in the presence of CsF in

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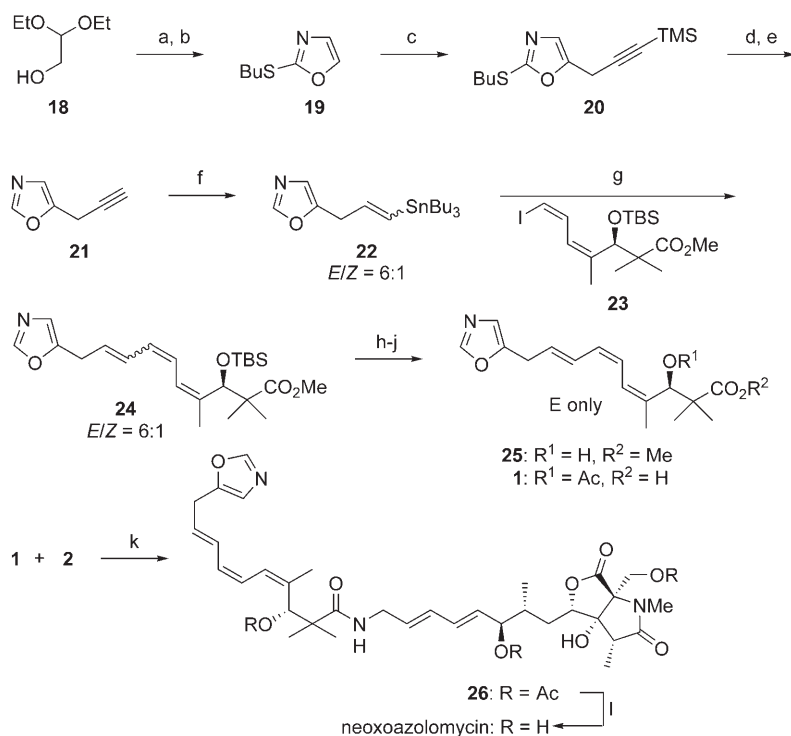
Scheme 2. Synthesis of right-hand segment **2**: a) $n\text{BuLi}$, DMPU/THF, -78°C ; b) TBAF, THF, 81% (2 steps); c) $(\text{HMe}_2\text{Si})_2\text{NH}$ (1.1 equiv), neat; d) $[\text{Pt}(\text{dvds})]$ (0.3 mol%), THF; e) I_2 (1 equiv), CsF (1.5 equiv), DMF/MeOH (5:1), 82% (3 steps); f) H_2CrO_4 , aq acetone, -10°C ; g) SOCl_2 , CH_2Cl_2 ; h) 2-(methylamino)malonate, toluene, 0°C , 62% (3 steps); i) $\text{Pd}(\text{OAc})_2$ (5 mol%), Ph_3P (20 mol%), $n\text{Bu}_4\text{NBr}$ (1 equiv), K_2CO_3 (4 equiv), DMF/ H_2O (9:1), 70°C , 84%; j) OsO_4 (0.4 equiv), NMO (4 equiv), THF/ H_2O (3:1), 88%; k) 4 M LiOH , THF, then 1 M HCl ; l) $[\text{Me}_2\text{N}=\text{CHCl}]^+\text{Cl}^-$, MeCN/THF (1:4), 0°C , then NaBH_4 , DMF, -78°C to RT, 57% (3 steps); m) $i\text{Pr}_2\text{Si}(\text{OTf})_2$, 2,6-lutidine, $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux; n) H_2 , Pd/C , MeOH; o) Dess–Martin periodinane, CH_2Cl_2 , 83% (3 steps); p) **14** (1.7 equiv), CrCl_2 (4 equiv), NiCl_2 (0.2 equiv), THF/DMSO (3:1), 73%; q) Dess–Martin periodinane, CH_2Cl_2 , 87%; r) L -selectride, THF, -78°C , 96%; s) 46% HF/pyridine/ H_2O /MeCN (1:4:2:20), 0°C ; t) Ac_2O , pyridine, 92% (2 steps). TBDSO = *tert*-butyldiphenylsilyl, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, TBAF = tetra-*n*-butylammonium fluoride, dvds = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane, NMO = 4-methylmorpholine *N*-oxide, Tf = trifluoromethanesulfonyl.

DMF/MeOH furnished (*E*)-iodoalkenol **11** with perfect stereoselectivity in good yield. In the iodination step, the above-mentioned combination of solvent and additive was

found to be crucial for the predominant production of the *E* isomer.^[13] After Jones oxidation of **11**, the resulting carboxylic acid was condensed with dimethyl 2-(methylamino)malonate^[14] via the corresponding acid chloride to give amide **5**.

Treatment of amide **5** with $\text{Pd}(\text{OAc})_2/\text{Ph}_3\text{P}$ in the presence of K_2CO_3 and $n\text{Bu}_4\text{NBr}$ in aqueous DMF at 70°C ^[15] resulted in a clean stereoselective cyclization to produce pyrrolidinone **4** in good yield. In the subsequent crucial dihydroxylation of **4**, we gratifyingly found that OsO_4/NMO conditions promoted a highly α -face-selective dihydroxylation accompanied by concomitant lactonization to yield lactone **3** as the sole product; the other stereoisomer was not detected in this transformation. The observed high diastereoselectivity can be explained by assuming that **17** is the preferred conformer, where the approach of OsO_4 is restricted to the α face. Support for this proposal came from NOE experiments^[16] and molecular mechanics calculations.^[17] After hydrolysis of **3**, the resulting carboxylic acid was chemoselectively converted into **12** by a Fujisawa reduction.^[18] The configuration of **12** was unambiguously confirmed by X-ray analysis of the corresponding mono-*tert*-butyldimethylsilyl (mono-TBS) ether.^[19] After protection of **12** as its dioxasilanane, debenzoylation and Dess–Martin oxidation afforded aldehyde **13**. After considerable experimentation with various conditions, a Nozaki–Hiyama–Kishi reaction of **13** with **14**^[20] was found to be best achieved^[21] using 4 equivalents of CrCl_2 and 0.2 equivalents of NiCl_2 in THF/DMSO at room temperature to give **15** in satisfying yield. Although no diastereoselectivity was observed in this reaction, Dess–Martin oxidation followed by reduction with L -selectride allowed the highly stereoselective production of **16** with the desired *R* configuration. Exposure of **16** to HF/pyridine followed by acetylation of the resulting triol furnished the right-hand segment **2**, almost quantitatively.

The left-hand segment **1** was constructed by the method outlined in Scheme 3, which gave a remarkable improvement in the overall yield compared with the procedure used by Kende et al.^[4] Thus, reaction^[22] of 2,2-diethoxyethanol (**18**) with KSCN under acidic conditions followed by butylation of the resulting oxazole-2-thiol afforded **19** in good yield. Copper-catalyzed propargylation^[23] of **19** cleanly produced **20** which, upon desulfurization, desilylation, and hydrostannylation, gave stannane **22** as a 6:1 mixture of *E* and *Z* isomers. It should be noted that although Stille coupling of **22** with **23**^[24] afforded **24** as an inseparable mixture of *E* and *Z* isomers, the left-hand segment **1** could be obtained in geometrically pure form through recrystallization of **25**. Finally, following the



Scheme 3. Completion of the total synthesis of neooxazolomycin: a) KSCN, conc. HCl, MeCN, reflux; b) KH, *n*BuLi, THF, 79% (2 steps); c) *t*BuLi, CuCN·2 LiCl, THF, −78 °C, then BrCH₂CCSiMe₃, −78 °C to RT, 94%; d) Raney Ni, acetone/EtOH (1:1), reflux, 92%; e) AgOTf, CH₂Cl₂/MeOH/H₂O (7:4:1), 73%; f) *n*Bu₃SnH, AIBN, 70 °C, 88%; g) [PdCl₂-(MeCN)₂] (3 mol%), DMF, 79%; h) 47% HF/MeCN, then recrystallization; i) LiOH, THF/MeOH/H₂O (3:1:1); j) Ac₂O, pyridine, then sat. NaHCO₃, aq MeOH, 80% (3 steps); k) **2**, DBU, CH₂Cl₂, add to the mixed anhydride (**1**, BOPCl, Et₃N, CH₂Cl₂), 60%; l) LiOH (10 equiv), THF/H₂O (3:1), then 1 M HCl, 59%. AIBN = 2,2'-azobisisobutyronitrile, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, BOPCl = bis(2-oxo-3-oxazolidinyl)-phosphonic chloride.

previous synthetic route,^[4] condensation of **1** with the free amine generated in situ from **2** followed by deacetylation of **26** furnished neooxazolomycin, which was identical with a natural specimen by spectroscopic (¹H and ¹³C NMR) and chromatographic (TLC and HPLC) comparisons.

In conclusion, neooxazolomycin has been synthesized by a convergent strategy that features a highly stereoselective approach involving Tamao hydrosilylation, palladium-catalyzed enolate alkenylation, dihydroxylation accompanied by lactonization, and a Nozaki–Hiyama–Kishi reaction to construct the right-hand segment **2** and an improved assembly of the left-hand segment **1**. Application of this methodology to the synthesis of other oxazolomycins is currently under investigation.

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