Natural Products

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Total Synthesis of Neooxazolomycin**

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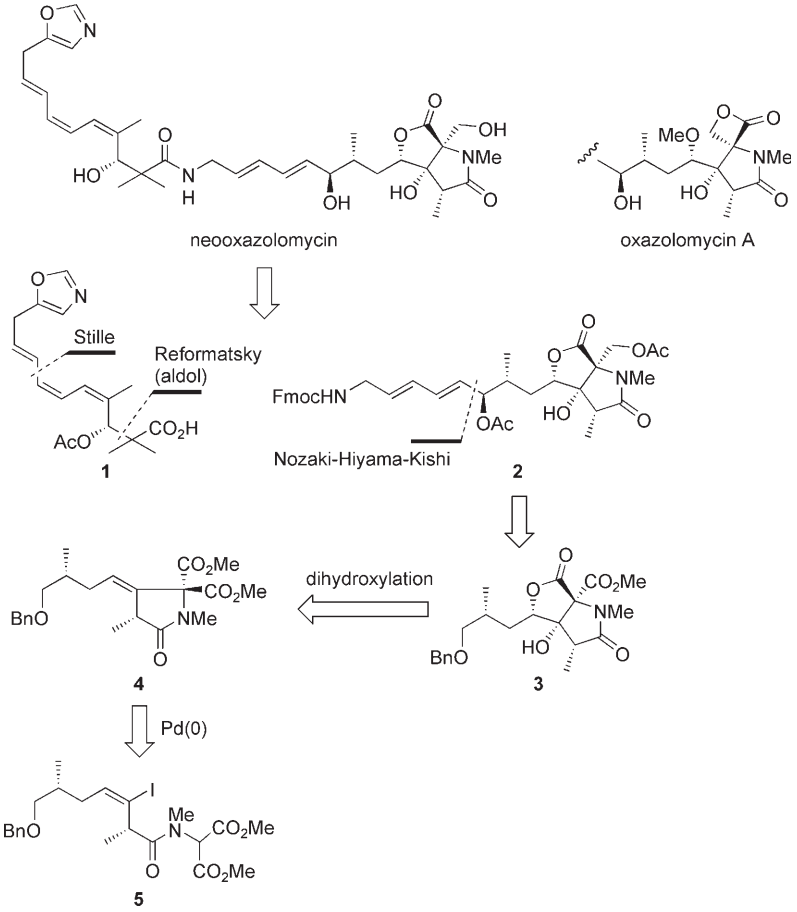
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

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 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.



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

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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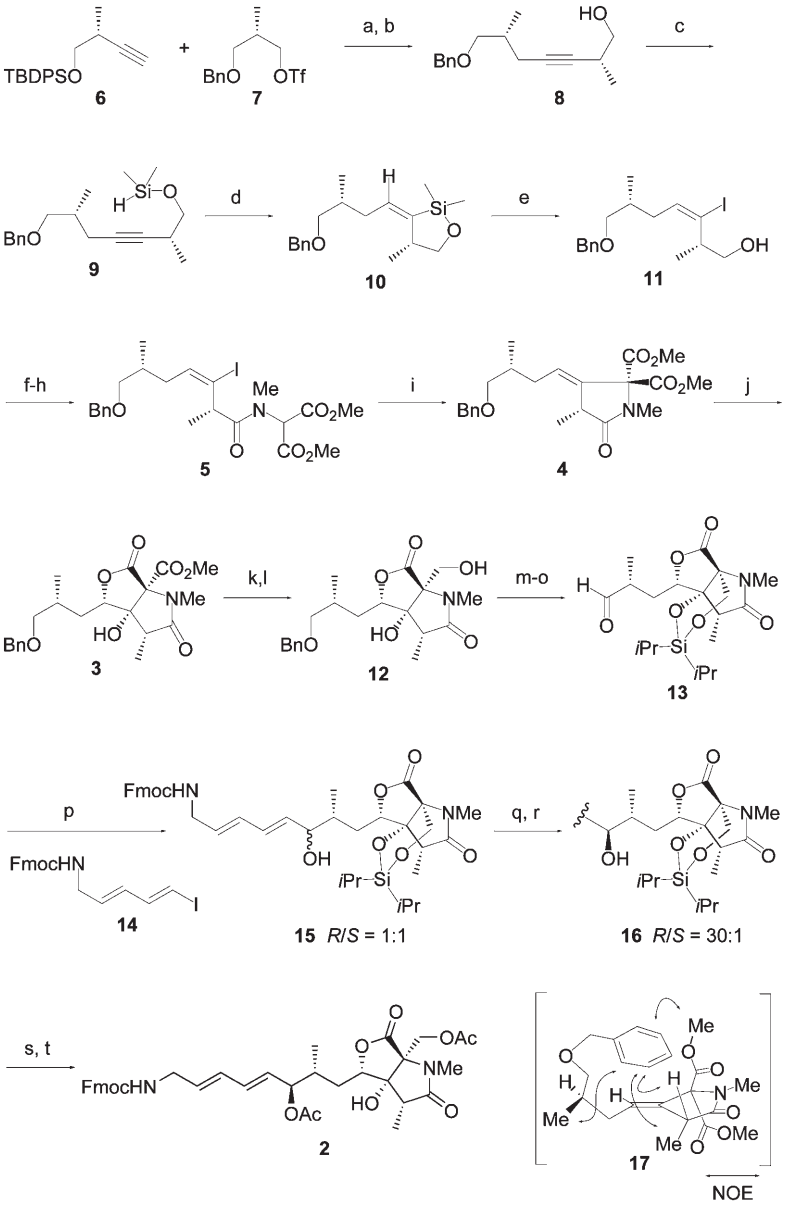
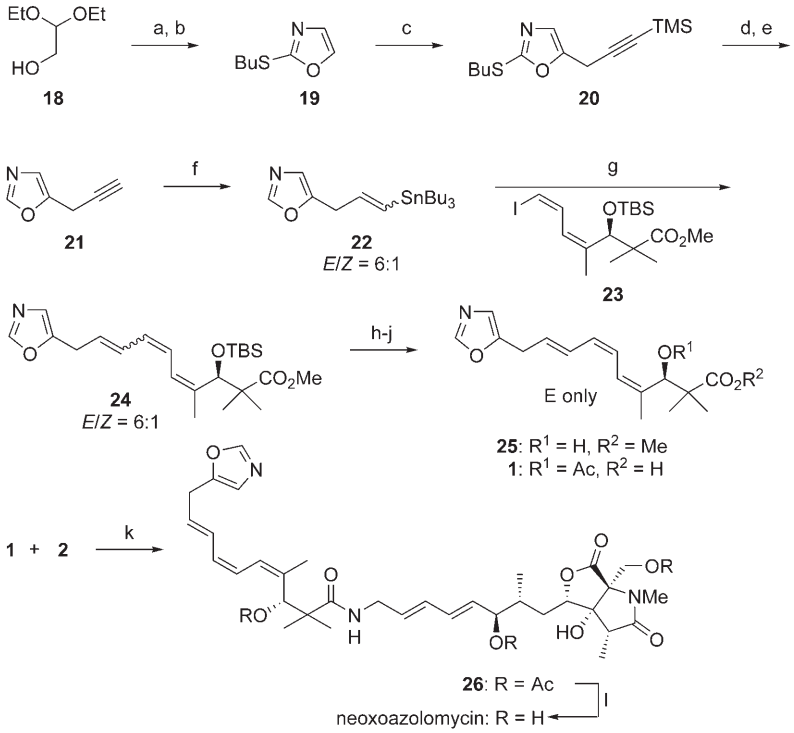


Scheme 2. Synthesis of right-hand segment **2**: a) *n*BuLi, DMPU/THF, −78 °C; b) TBAF, THF, 81% (2 steps); c) $(HMe_2Si)_2NH$ (1.1 equiv), neat; d) [Pt(dvds)] (0.3 mol%), THF; e) I_2 (1 equiv), CsF (1.5 equiv), DMF/MeOH (5:1), 82% (3 steps); f) H_2CrO_4, aq acetone, −10 °C; g) $SOCl_2$, CH_2Cl_2; h) 2-(methylamino)malonate, toluene, 0 °C, 62% (3 steps); i) $Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%), nBu_4NBr (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) $[Me_2N{=}CHCl]^+Cl^-$, MeCN/THF (1:4), 0 °C, then $NaBH_4$, DMF, −78 °C to RT, 57% (3 steps); m) $iPr_2Si(OTf)_2$, 2,6-lutidine, $ClCH_2CH_2Cl$, 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). TBDPS = *tert*-butyldiphenylsilyl, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-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 $Pd(OAc)_2/Ph_3P$ in the presence of K_2CO_3 and nBu_4NBr 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 dioxasilinane, debenzylation 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*BuI, THF, 79% (2 steps); c) *t*BuLi, CuCN·2 LiCl, THF, −78°C, then $BrCH_2CCSiMe_3$, −78°C to RT, 94%; d) Raney Ni, acetone/EtOH (1:1), reflux, 92%; e) AgOTf, CH_2Cl_2/MeOH/H_2O (7:4:1), 73%; f) nBu_3SnH, AIBN, 70°C, 88%; g) $[PdCl_2(MeCN)_2]$ (3 mol%), DMF, 79%; h) 47% HF/MeCN, then recrystallization; i) LiOH, THF/MeOH/H_2O (3:1:1); j) Ac_2O, pyridine, then sat. $NaHCO_3$, aq MeOH, 80% (3 steps); k) **2**, DBU, CH_2Cl_2, add to the mixed anhydride (**1**, BOPCl, Et_3N, CH_2Cl_2), 60%; l) LiOH (10 equiv), THF/H_2O (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)-phosphinic 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 ^{13}C 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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