

## Natural Products

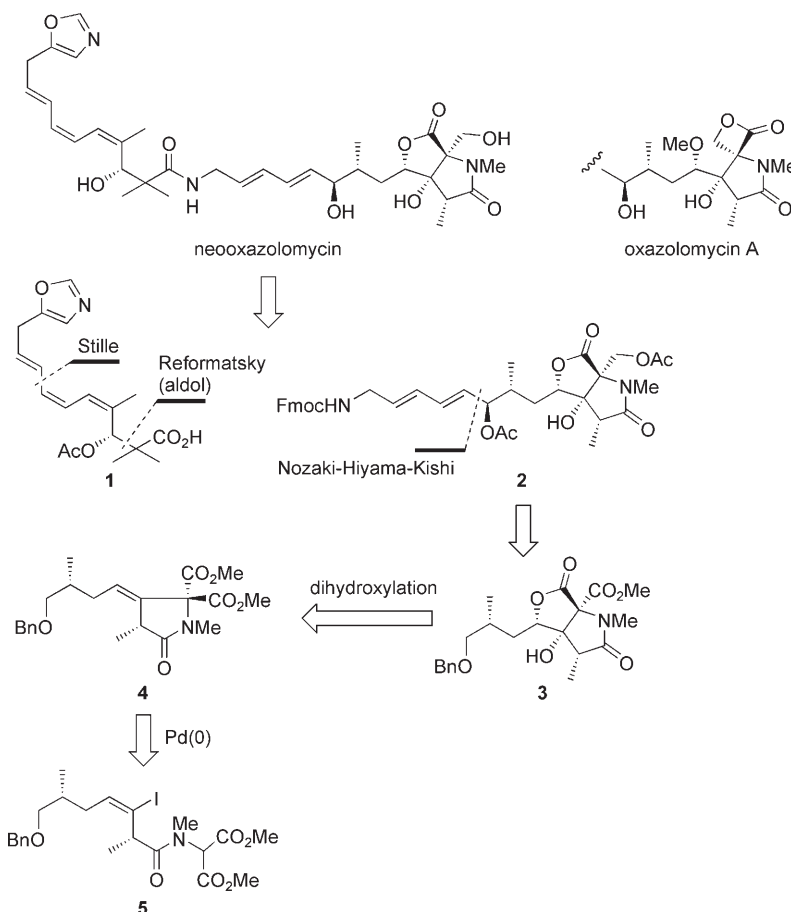
## Total Synthesis of Neooxazolomycin\*\*

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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,<sup>[1]</sup> 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.<sup>[2,3]</sup> In 1990, Kende et al. disclosed the synthesis of neooxazolomycin,<sup>[4]</sup> 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**<sup>[4]</sup> by a Reformatsky-type aldol reaction<sup>[5]</sup> and Stille coupling,<sup>[6]</sup> 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<sup>[7]</sup> and stereoselective dihydroxylation with concomitant lactonization. We postulated



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

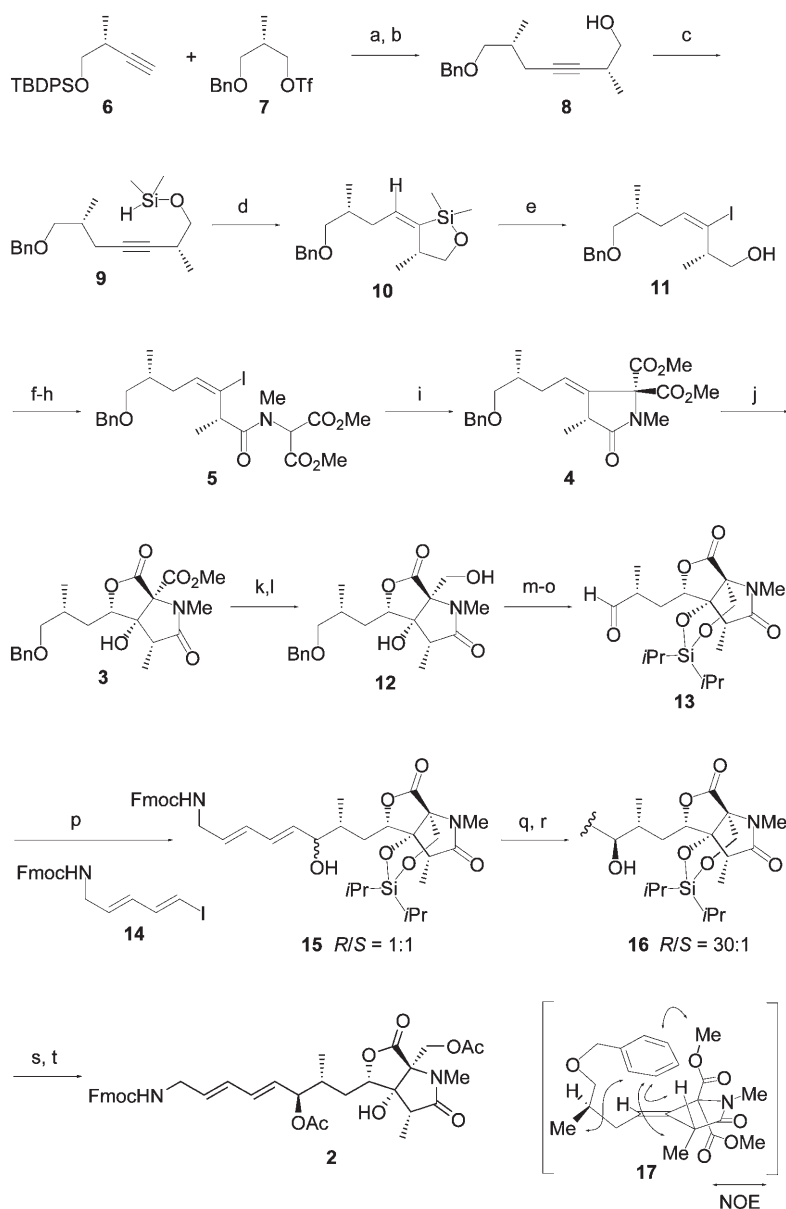
that this precursor could be accessed by a palladium-catalyzed cyclization of amide **5**. This approach is particularly appealing since the three contiguous stereogenic centers including two quaternary centers could be created by one dihydroxylation process.

The required amide **5** was synthesized in a completely stereoselective manner by taking advantage of the intramolecular hydrosilylation<sup>[8]</sup> developed by Tamao et al.<sup>[9]</sup> (Scheme 2). Thus, alkynol **8** was first prepared by the coupling of alkyne **6**<sup>[10]</sup> and triflate **7**,<sup>[11]</sup> 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)]<sup>[12]</sup> 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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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



**Scheme 2.** Synthesis of right-hand segment **2**: a) *n*BuLi, DMPU/THF,  $-78^{\circ}\text{C}$ ; b) TBAF, THF, 81% (2 steps); c)  $\text{H}(\text{Me}_2\text{Si})_2\text{NH}$  (1.1 equiv), neat; d)  $[\text{Pt}(\text{dvds})]$  (0.3 mol %), THF; e)  $\text{I}_2$  (1 equiv), CsF (1.5 equiv), DMF/MeOH (5:1), 82% (3 steps); f)  $\text{H}_2\text{CrO}_4$ , aq acetone,  $-10^{\circ}\text{C}$ ; g)  $\text{SOCl}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; h) 2-(methylamino)malonate, toluene,  $0^{\circ}\text{C}$ , 62% (3 steps); i)  $\text{Pd}(\text{OAc})_2$  (5 mol %),  $\text{Ph}_3\text{P}$  (20 mol %), *n*Bu<sub>4</sub>NBr (1 equiv),  $\text{K}_2\text{CO}_3$  (4 equiv), DMF/H<sub>2</sub>O (9:1),  $70^{\circ}\text{C}$ , 84%; j)  $\text{OsO}_4$  (0.4 equiv), NMO (4 equiv), THF/H<sub>2</sub>O (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),  $0^{\circ}\text{C}$ , then  $\text{NaBH}_4$ , DMF,  $-78^{\circ}\text{C}$  to RT, 57% (3 steps); m) *i*Pr<sub>2</sub>Si(OTf)<sub>2</sub>, 2,6-lutidine,  $\text{ClICH}_2\text{CH}_2\text{Cl}$ , reflux; n) H<sub>2</sub>, Pd/C, MeOH; o) Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , 83% (3 steps); p) **14** (1.7 equiv),  $\text{CrCl}_4$  (4 equiv),  $\text{NiCl}_2$  (0.2 equiv), THF/DMSO (3:1), 73%; q) Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , 87%; r) L-selectride, THF,  $-78^{\circ}\text{C}$ , 96%; s) 46% HF/pyridine/H<sub>2</sub>O/MeCN (1:4:2:20),  $0^{\circ}\text{C}$ ; t)  $\text{Ac}_2\text{O}$ , pyridine, 92% (2 steps). TBDPS = *tert*-butyldiphenylsilyl, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidin-5-oxide, TBAF = tetra-*n*-butylammonium fluoride, dvds = 1,3-divinyl-1,3,3-tetramethyl-disiloxane, NMO = 4-methylmorpholine *N*-oxide, Tf = trifluoromethanesulfonyl.

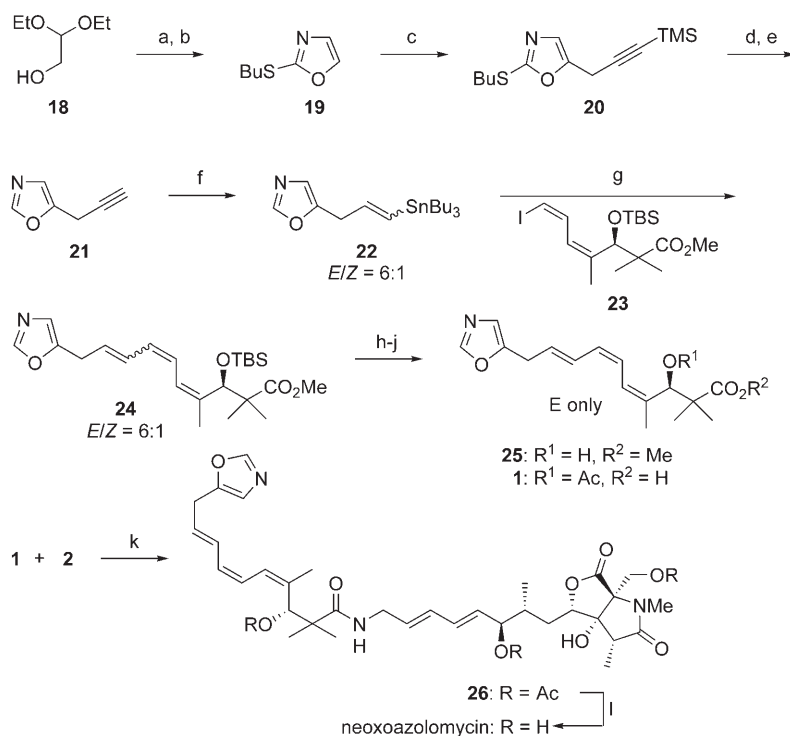
DMF/MeOH furnished (*E*)-iodoalkenol **11** with perfect stereoselectivity in good yield. In the iodination step, the above-mentioned combination of solvent and additive was

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

Treatment of amide **5** with Pd(OAc)<sub>2</sub>/Ph<sub>3</sub>P in the presence of K<sub>2</sub>CO<sub>3</sub> and *n*Bu<sub>4</sub>NBr in aqueous DMF at 70 °C<sup>[15]</sup> 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<sub>4</sub>/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<sub>4</sub> is restricted to the α face. Support for this proposal came from NOE experiments<sup>[16]</sup> and molecular mechanics calculations.<sup>[17]</sup> After hydrolysis of **3**, the resulting carboxylic acid was chemoselectively converted into **12** by a Fujisawa reduction.<sup>[18]</sup> The configuration of **12** was unambiguously confirmed by X-ray analysis of the corresponding mono-*tert*-butyldimethylsilyl (mono-TBS) ether.<sup>[19]</sup> 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**<sup>[20]</sup> was found to be best achieved<sup>[21]</sup> using 4 equivalents of CrCl<sub>2</sub> and 0.2 equivalents of NiCl<sub>2</sub> 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.<sup>[4]</sup> Thus, reaction<sup>[22]</sup> 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<sup>[23]</sup> 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**<sup>[24]</sup>

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 BrCH<sub>2</sub>CCSiMe<sub>3</sub>, −78 °C to RT, 94%; d) Raney Ni, acetone/EtOH (1:1), reflux, 92%; e) AgOTf, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/H<sub>2</sub>O (7:4:1), 73%; f) *n*Bu<sub>3</sub>SnH, AIBN, 70 °C, 88%; g) [PdCl<sub>2</sub>-(MeCN)<sub>2</sub>] (3 mol%), DMF, 79%; h) 47% HF/MeCN, then recrystallization; i) LiOH, THF/MeOH/H<sub>2</sub>O (3:1:1); j) Ac<sub>2</sub>O, pyridine, then sat. NaHCO<sub>3</sub>, aq MeOH, 80% (3 steps); k) **2**, DBU, CH<sub>2</sub>Cl<sub>2</sub>, add to the mixed anhydride (**1**, BOPCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>), 60%; l) LiOH (10 equiv), THF/H<sub>2</sub>O (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,<sup>[4]</sup> 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 (<sup>1</sup>H and <sup>13</sup>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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- [1] a) T. Mori, K. Takahashi, M. Kashiwabara, D. Uemura, *Tetrahedron Lett.* **1985**, 26, 1073–1076; b) K. Takahashi, M. Kawabata, D. Uemura, *Tetrahedron Lett.* **1985**, 26, 1077–1078.
- [2] For a review, see M. G. Moloney, P. C. Trippier, M. Yaqoob, A. Wang, *Curr. Drug Discovery Technol.* **2004**, 1, 181–199.
- [3] a) T. J. Donohoe, J. Y. K. Chiu, R. E. Thomas, *Org. Lett.* **2007**, 9, 421–424; N. J. Bennet, J. C. Prodger, G. Pattenden, *Tetrahedron* **2007**, 63, 6216–6231, and references therein.
- [4] A. S. Kende, K. Kawamura, R. J. DeVita, *J. Am. Chem. Soc.* **1990**, 112, 4070–4072.
- [5] T. Harada, T. Mukaiyama, *Chem. Lett.* **1982**, 161–164.
- [6] J. K. Stille, B. L. Groh, *J. Am. Chem. Soc.* **1987**, 109, 813–817.
- [7] a) H. Jin, J. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, 108, 5644–5646; b) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, 108, 6048–6050.
- [8] For a review, see I. Ojima, Z. Li, J. Zhu in *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Z. Rappoport, Y. Apeloig), Wiley, New York, **1998**, pp. 1687–1792.
- [9] K. Tamao, K. Maeda, T. Tanaka, Y. Ito, *Tetrahedron Lett.* **1988**, 29, 6955–6956.
- [10] B. M. Trost, J. P. N. Papillon, *J. Am. Chem. Soc.* **2004**, 126, 13618–13619.
- [11] A. Abiko, O. Moriya, S. A. Filla, S. Masamune, *Angew. Chem.* **1995**, 107, 869–871; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 793–795.
- [12] S. E. Denmark, W. Pan, *Org. Lett.* **2001**, 3, 61–64.
- [13] When the iodination of **10** was carried out using I<sub>2</sub> (1 equiv) and AgNO<sub>3</sub> (1 equiv) in EtOH at room temperature, the corresponding Z isomer was obtained exclusively in 50% yield.
- [14] R. Heckendorn, *Helv. Chim. Acta* **1990**, 73, 1700–1718.
- [15] X. Liu, J. R. Deschamp, J. M. Cook, *Org. Lett.* **2002**, 4, 3339–3342.
- [16] The NOESY spectrum was recorded in [D<sub>8</sub>]THF/D<sub>2</sub>O (3:1), which was the same solvent system as that employed for the osmylation.
- [17] Conformer **17** was suggested to be the energetically most stable by Molecular mechanics calculations (MMFF, Macro Model 8.5).
- [18] T. Fujisawa, T. Mori, T. Sato, *Chem. Lett.* **1983**, 835–838.
- [19] CCDC-643979 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [20] Prepared by Takai–Utimoto olefination of (*E*)-4-(Fmoc)amino-but-2-enal; see the Supporting Information and also K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, 108, 7408–7410.
- [21] J. S. Panek, P. Liu, *J. Am. Chem. Soc.* **2000**, 122, 11090–11097.
- [22] Y. Watanabe, WO 2003006422.
- [23] a) C. M. Shafer, T. F. Molinsky, *J. Org. Chem.* **1998**, 63, 551–555; b) J. P. Marino, H. N. Nguyen, *Tetrahedron Lett.* **2003**, 44, 7395–7398.
- [24] Prepared by a modified Kende procedure, where the method for the preparation of (*Z*)-2-methyl-5-(trimethylsilyl)pent-2-en-4-ynal, required for the key aldol reaction, was highly improved; see the Supporting Information.