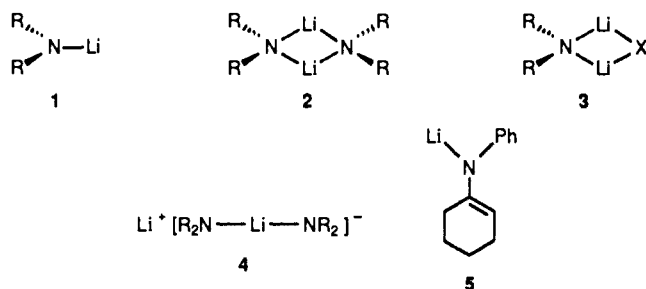
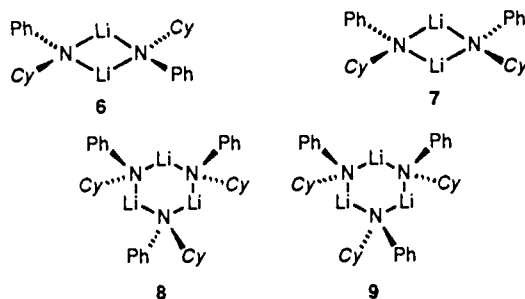


Figure 1. NMR spectra recorded at $-93\text{ }^{\circ}\text{C}$ of a 0.3 M solution of lithiated imine **5** in toluene- d_6 containing 2.0 equiv of THF/lithium: (A) ^{15}N NMR spectrum (30.42 MHz); (B) ^6Li NMR spectrum (44.19 MHz) observed via the ^2H lock channel as described in the text; (C) ^6Li NMR spectrum observed via the ^2H lock channel with concomitant irradiation of the upfield (major) ^{15}N resonance in spectrum A; (D) ^6Li NMR spectrum observed via the ^2H lock channel with concomitant irradiation of the downfield (minor) ^{15}N resonance in spectrum A.

Chart I



we were unable to unequivocally exclude trimer **8**. The inability to distinguish dimers from higher oligomers has haunted subsequent structural and mechanistic studies of N-lithiated species.^{4,9}



The hardware modifications needed to achieve single-frequency decoupling of ^{15}N are straightforward. The ^{109}Ag - ^{31}P broadband probe of a Bruker AC300 NMR spectrometer equipped with an X-nucleus decoupler is modified by the addition of a variable capacitor in the ^2H lock circuitry. This allows the ^2H lock channel to function as a ^6Li observe (or decoupling) channel operating at 44.19 MHz.⁵ A proton filter in the ^2H lock circuitry was removed to improve sensitivity. Substantial noise introduced by the X-nucleus decoupler necessitates inclusion of quarter wavelength coaxial cable filters at the frequency ranges of ^6Li and ^{15}N . A decoupling power of 30–50 μW proved sufficient to achieve decoupling without perturbing resonances ≥ 50 Hz away.

The results of single-frequency irradiations are illustrated in Figure 1C,D. Irradiation of the major ^{15}N quintet centered at

(9) In several other instances wherein N-lithiated species display a concentration-independent pair of ^6Li resonances,^{2,3} ratios closer to 1:1 further argue against cyclic trimers.

134.6 ppm causes clean collapse of the major ^6Li resonance to a singlet. Similarly, irradiation of the minor ^{15}N quintet causes the minor ^6Li triplet to collapse to a singlet. The decouplings are consistent with two chemically distinct isomeric dimers **6** and **7**.¹⁰ Furthermore, if cis,trans trimer **8** had been the predominant aggregate in solution, irradiation of the major ^{15}N resonance would have caused the major and minor ^6Li triplets to collapse to a doublet and singlet, respectively. Similarly, irradiation of the minor ^{15}N resonance would have caused collapse of the major ^6Li triplet to a doublet without change in the minor ^6Li triplet. Thus, the results of the single-frequency decouplings are consistent with stereoisomeric dimers **6** and **7** and inconsistent with a trimer structure.

^6Li and ^{15}N resonance correlations, when placed in the context of the stereochemical consequences of aggregation, provide a direct probe of aggregate structure. The exclusion of cyclic trimers in this specific case strengthens the dimer assignments for other solvated lithium amide species as well. As we continue to uncover lithium amide aggregates and mixed aggregates of increasing complexities,¹¹ such ^6Li - ^{15}N resonance correlations will become essential components of solution structure determinations.

Acknowledgment. We thank Jim Simms of MIT and Brian Andrew of Bruker for several very helpful discussions. We acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility. D.B.C. and J.H.G. thank the National Institutes of Health for support of this work.

Registry No. **5**, 101773-95-9; ^6Li , 14258-72-1.

(10) In contrast to the irradiations of the ^{15}N multiplets separated by 55 Hz, irradiation of each of the narrowly spaced (11 Hz) ^6Li triplets failed to afford fully selective decoupling.

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Enantioselective Total Synthesis of Neooxazolomycin

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Neooxazolomycin (**1**) is a structurally novel $\text{C}_{34}\text{H}_{47}\text{N}_3\text{O}_9$ oxazole polyene lactam-lactone antitumor antibiotic isolated from several *Streptomyces* strains.^{1a,b} The structures and absolute configurations of this compound^{1a} and its β -lactone congener, oxazolomycin (**2**),^{1c} were described in 1985. Neooxazolomycin (**1**) is an acid-, base- and light-sensitive molecule that may be regarded as an amide formed between a *Z,Z,E* oxazole triene acid left half (**22**) and a highly functionalized lactam-lactone amino diene (**37**, $\text{R}_1 = \text{H}$) right half (Chart I). We now report the first enantioselective total synthesis of neooxazolomycin.²

The oxazole triene acid left half of the antibiotic was synthesized from the known³ (*Z*)-3-bromo-2-methyl-2-propenol (**3**), converted to the *Z* aldehyde **5** in 84% yield by a four-step sequence (Scheme I): (1) O-silylation, (2) Pd-catalyzed coupling⁴ with (trimethylsilyl)acetylene to produce the enyne **4**, (3) selective O-

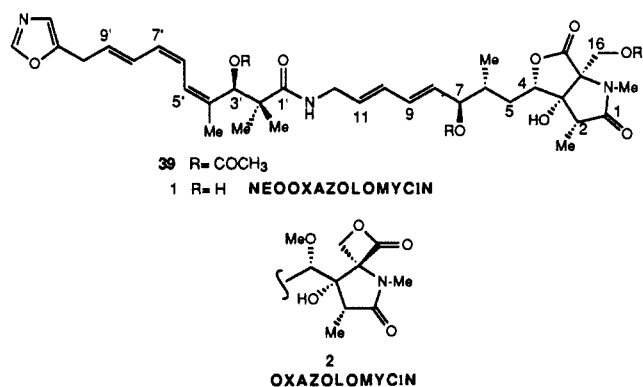
(1) (a) Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1077. (b) Kawai, S.; Kawabata, G.; Kobayashi, A.; Kawazu, K. *Agric. Biol. Chem.* **1989**, *53*, 1127. (c) Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073.

(2) All new compounds showed NMR, IR, and C,H or mass spectrometric analyses consistent with the assigned structures.

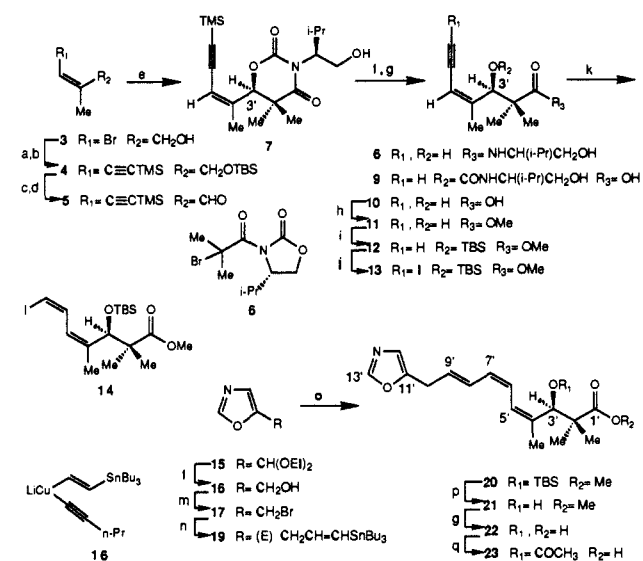
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Chart I



Scheme I^a

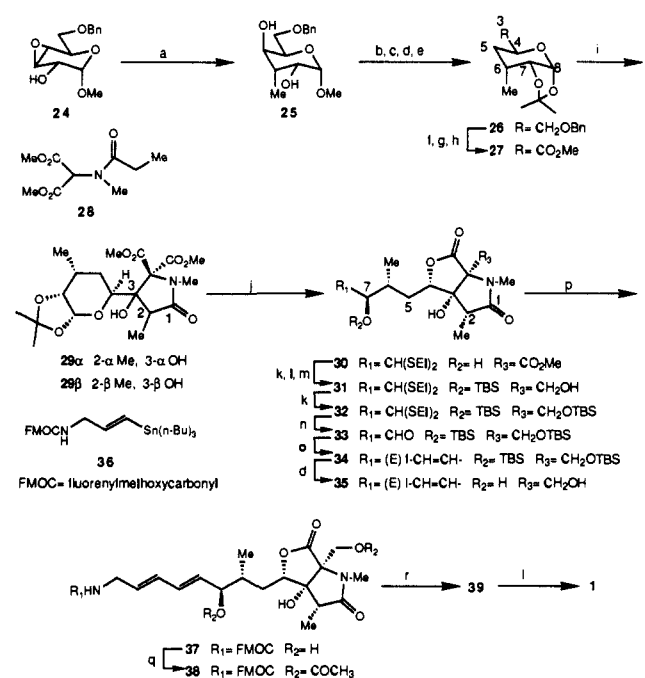


^a Reagents: (a) TBSCl, imidazole, DMF, 0 °C, 5 min; (b) TMS-C≡CH, Pd(Ph₃P)₄, CuI, *n*-BuNH₂, PhH, 23 °C, 18 h; (c) AcOH/THF/H₂O, 23 °C, 18 h; (d) basic MnO₂, hexane/CH₂Cl₂, 23 °C, 2 h; (e) SnCl₂, LiAlH₄, THF, 20 °C, 20 min, then 6 in THF, 20 °C, 45 min, then 5 in THF, 20 °C, 16 h; (f) 30% H₂O₂, LiOH, THF/H₂O, 20 °C, 24 h; (g) LiOH (3 equiv), THF/MeOH/H₂O, 23 °C, 24 h; (h) CH₂N₂, Et₂O, 0 °C; (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 23 °C, 0.5 h; (j) *n*-BuLi, THF, -78 °C, 1 h, then I₂ in THF, 1 h; (k) NH₂NH₂ (5 equiv), CuSO₄·5H₂O (0.1 equiv), 95% EtOH, 23 °C, air (bubbled), 16 h; (l) THF/H₂O/concentrated HCl (cat.), 23 °C, 17 h, then saturated NaHCO₃, 10 min; NaBH₄, 0 °C; (m) NBS, Ph₃P, THF, 23 °C, 1 h; (n) (*E*)-Bu₃SnCH=CNSnBu₃, *n*-BuLi, THF, -78 °C → -40 °C, 0.5 h; then addition to CuC≡CPr, THF, -40 °C, 0.5 h; addition to 17, THF, -78 °C → -10 °C; (o) 14, 3 mol % PdCl₂(MeCN)₂, DMF, 23 °C, 91 h; (p) 50% HF/MeCN, 23 °C, 4 h; (q) Ac₂O, pyr, 23 °C, 20 h; saturated NaHCO₃, MeOH/H₂O, 23 °C, 1 h.

desilylation, and (4) oxidation to the aldehyde 5.

Diastereoselective Reformatsky-type condensation of 5 with the tin(II) enolate derived from chiral acyloxazolidinone 6 (1.2 equiv) by use of SnCl₂ (2 equiv) and LiAlH₄ (1 equiv) in THF⁵ proceeded in 95% yield to give the anticipated⁶ 1,3-oxazine-2,4-dione 7 [mp 95–96 °C, [α]_D²⁵ +8.1° (c 0.6, CH₂Cl₂)] having the desired 3'*R* configuration (neooxazolomycin numbering) in >99% de and complete retention of the alkene *Z* geometry.⁷ Mild removal of the chiral auxiliary and C-silyl group had to be performed via the following two-step procedure. Reaction of 7 with 30% H₂O₂ (6 equiv) and LiOH (2 equiv)⁸ produced 13% of the

Scheme II^a



^a Reagents: (a) MeLi, MeMgCl, THF/Et₂O, 23 °C, 16 h; (b) *i*-Pr₃SiOTf, 2,6-lutidine, THF, -78 °C → 23 °C, 16 h; (c) S=C(Im)₂, (CH₂Cl)₂, Δ; *n*-Bu₃SnH, xylene, Δ, 6 h; (d) *n*-Bu₄NF, THF, 23 °C; (e) FeCl₃, acetone, 23 °C, 4 h; (f) H₂, Pd(OH)₂, MeOH, 23 °C, 4 h; (g) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 20 min, then 0 °C, 1 h; KMnO₄, *t*-BuOH/5% NaH₂PO₄, 23 °C, 0.5 h; (h) CH₂N₂, Et₂O, 0 °C; (i) 28 (1.06 equiv), *t*-BuLi (2.12 equiv), TMEDA (2.12 equiv), THF, -78 °C, then addition to 27 in THF, -78 °C; (j) EtSH, concentrated HCl (cat.); (k) TBSOTf, 2,6-lutidine, CH₂Cl₂, 23 °C; (l) LiOH, THF/H₂O, 23 °C, 1 h, then 1 N HCl; (m) [Me₂N=CHCl]⁺Cl⁻, MeCN/THF, 0 °C, 1 h; NaBH₄, DMF, -78 °C → 23 °C, 16 h; (n) HgCl₂, CaCO₃, MeCN/H₂O, 23 °C, 1 h; (o) CHI₃, CrCl₂, THF, 23 °C, 1.5 h; (p) 36, 5 mol % PdCl₂(MeCN)₂, DMF, 23 °C, 24 h; (q) Ac₂O, pyr, 23 °C, 24 h; (r) DBU, CH₂Cl₂, 23 °C, 0.5 h; addition to the mixed anhydride [23, *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride, Et₃N, CH₂Cl₂, 23 °C, 3 h], then 23 °C, 0.5 h.

diol amide 8 and 87% of the desired carboxylic acids 9 and 10 in a 24:1 ratio. The acid mixture was then hydrolyzed with LiOH to give 85% of 10, along with 69% of the recovered homochiral Evans oxazolidinone. Diazomethane on 10 gave the ester 11 [[α]_D²⁵ -26.6° (c 0.94, CH₂Cl₂), 81%], shown to be enantiomerically homogeneous (>99%) by use of Eu(hfc)₃ employing racemic 11 as standard.

To construct the (*Z,Z,E*)-triene system, the acetylenic terminus of 11 was stereoselectively converted to the (*Z*)-vinyl iodide 14 by the following sequence: (1) O-silylation, (2) iodination of the silyl ether 12 by metalation followed by I₂ quenching, and (3) diimide reduction⁹ of the iodoacetylene 13, to give, on silica gel TLC, a 72% overall yield of 14, along with 10% of recovered alkyne 12. The oxazole stannane 19 required to complete the left-hand chain was synthesized in five steps as follows. The oxazole acetal 15 was prepared in 86% yield from ethyl diethoxyacetate and lithiated MeNC by Schöllkopf condensation.¹⁰ Hydrolysis of 15 and then NaBH₄ reduction gave the oxazole methanol 16, mp 27–28 °C, in 68% yield. NBS/Ph₃P transformed 16 to the unstable bromide 17 (44%), which was immediately reacted with the cuprate 18¹¹ (1.2 equiv) to produce the (*E*)-vinyl stannane 19 in 49% yield. The critical Stille coupling¹² of 19 with

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(7) Observation of the positive NOE (22.5%) between vinylic and methyl protons strongly indicated the retention of the *Z* geometry of 7 under the strongly acidic conditions; see ref 6.

the polyfunctional vinyl iodide **14** gave the desired triene ester **20** in 79% yield with complete retention of all alkene stereochemistries. Deprotection of **20** with HF gave the free alcohol **21** [mp 100–102 °C, $[\alpha]_D +102.1^\circ$ (*c* 1.0, CH₂Cl₂), 92%] without any isomerization of the triene.¹³ Hydrolysis of **21** gave 94% of the hydroxy acid **22**;¹⁴ acetylation of **22** followed by hydrolysis of the resulting mixed anhydride gave the acetoxy acid **23** (99%), presenting the left half of the target in suitably protected form.

To construct a chiral synthon corresponding to C-3 through C-8 of the right-half amino diene, we employed the readily available anhydrogalactoside **24**¹⁵ as a chiral source (Scheme II). The stereogenic center at C-6 was generated by trans-diaxial epoxide opening of **24** using 10 equiv of Me₂Mg,¹⁶ to yield 95% of the diol **25**. This was converted to deoxy acetonide **26** in 64% overall yield by the following sequence: (1) selective silylation of equatorial hydroxyl group, (2) conversion of the axial hydroxyl group to the imidazole thiocarbamate followed by radical deoxygenation,¹⁷ (3) *n*-Bu₄NF desilylation, and (4) condensation with acetone/FeCl₃.¹⁸ Hydrogenolytic debenzoylation of **26** and then Swern oxidation followed by buffered KMnO₄ and diazomethane gave ester **27** [mp 47–49 °C, $[\alpha]_D -25.4^\circ$ (*c* 1.6, CH₂Cl₂)] in 70% yield over four steps from **26**.

With the six carbons of **27** corresponding to neoxazolomycin C-3 through C-8 as marked, we used the ester group of **27** as the electrophile in a cyclocondensation¹⁹ with the dianion of amidomalonate **28**. Formation of the dianion of **28** and reverse addition at –78 °C to **27** in THF gave a mixture of **29α** and **29β** (1:1.4 ratio) in 82% yield based on recovered ester (49%).²⁰ After chromatographic separation, the desired lactam **29α** was rearranged to the thioacetal ester **30** in nearly quantitative yield. This was converted by O-silylation at C-7, saponification, Fujisawa reduction²¹ to the carbinol **31**,²² and silylation of the new hydroxyl group to the fully elaborated thioacetal **32**, mp 118–120 °C, in 59% overall yield from **30**.

Hydrolysis of **32** to the aldehyde **33** (99%), mp 138–139 °C, paved the way for completion of the right half. Treatment of **33** with CHI₃/CrCl₂ gave a 70% yield of the (*E*)-vinyl iodide **34** (mp 134–136 °C).²³ Quantitative desilylation²⁴ gave the triol **35**, which was condensed with our Fmoc-amino propenylstannane reagent **36** (1.1 equiv)²⁵ under Stille conditions,¹² to afford cleanly the (*E,E*)-dienylamide **37** (mp 95–98 °C, 84%). Double O-acetylation gave 96% of the diacetate **38**.

Our synthesis culminated in the reaction of the protected acid **23**, *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (1.1 equiv), and Et₃N (2.2 equiv) to give the activated anhydride,²⁶

to which was added a CH₂Cl₂ solution of the free amine prepared by DBU (2 equiv) deprotection²⁵ of the Fmoc diacetate **38** (1 equiv). Reaction for 1 h produced neoxazolomycin triacetate (**39**) in 60% yield. The spectroscopic properties of our synthetic triacetate were in full agreement with those reported for naturally derived **39**.^{1a} Finally, careful hydrolysis of **39** with LiOH (10 equiv) followed by acidification gave a 67% yield of pure neoxazolomycin (**1**), identical with an authentic sample by 300-MHz ¹H NMR, IR, TLC (silica gel and reverse phase) in several solvent systems, HPLC, and FAB mass spectrometric comparisons.²⁷

Supplementary Material Available: Spectral data and physical properties for compounds **4–17**, **19–23**, **25–27**, and **29–39** (10 pages). Ordering information is given on any current masthead page.

(27) We are grateful to Dr. D. Uemura of Shizuoka University, Japan, for samples of neoxazolomycin and the degradation product triacetate and to Dr. Joseph Wright, Eastman Kodak Co., for determination of mass spectra. Partial support of this research by Grant CA 18846, awarded by the National Cancer Institute, NIH-USPHS, is gratefully acknowledged. R. J. DeVita thanks the Smith Kline and French Co. for an American Chemical Society, Organic Division, predoctoral fellowship.

Allenyl Chloromethyl Sulfones: New Dienophile–Diene Synthons. A Simple Iterative Ring-Growing Procedure¹

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We report the preparation and applications of new organosulfur reagents, allenyl chloromethyl sulfones (**1**), RR'C=C=CHSO₂CH₂Cl, functioning as potent dienophiles whose Diels–Alder adducts give 1,3-dienes with base, thus allowing two-step “cyclohomologation” of dienes. Examples of this class of reagents include the parent compound, chloromethyl 1,2-propadienyl sulfone (**2**), H₂C=C=CHSO₂CH₂Cl, chloromethyl tetradeca-1,2-dienyl sulfone (**3**), CH₃(CH₂)₁₀CH=C=CHSO₂CH₂Cl, and chloromethyl 3-methylbuta-1,2-dienyl sulfone (**4**), Me₂C=C=CHSO₂CH₂Cl. Reagents **1** were developed in the course of seeking new applications of the Ramberg–Bäcklund reaction in which the necessary reaction components, sulfonyl group and α-halogen, are already present in the same reagent.² We describe herein the use of **1** in a novel iterative ring-growing procedure for construction of linear fused carbocycles.

The choice of **1** was suggested by the known high reactivity of sulfonyllallenes as dienophiles due to their low LUMO,³ the anticipated susceptibility of the allylic sulfone Diels–Alder adduct toward base-induced elimination, and a simple projected synthesis of **1** via coupling of chloromethylsulfenyl chloride, ClCH₂SOCl,⁴ with propargylic alcohols (RR'(C)(OH)C≡CH) giving *S*-chloromethyl propargyl sulfenates, ClCH₂SOCR'R''C≡CH (**5**), [2,3]-sigmatropic rearrangement⁵ of **5** to chloromethyl 1,2-alkadienyl sulfoxides, RR'C=C=CHS(O)CH₂Cl (**6**), and oxidation

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