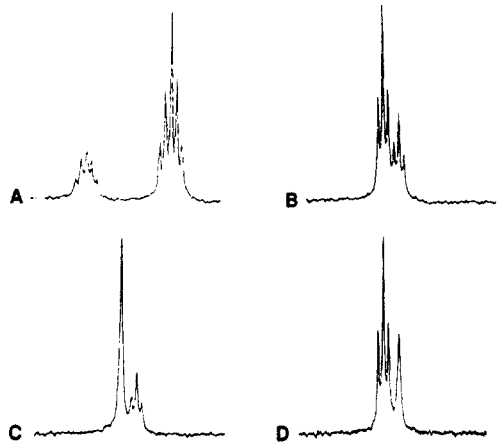
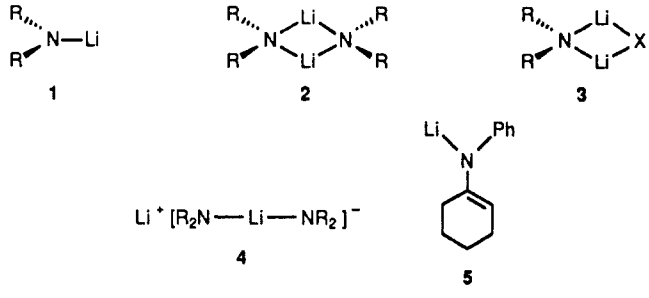
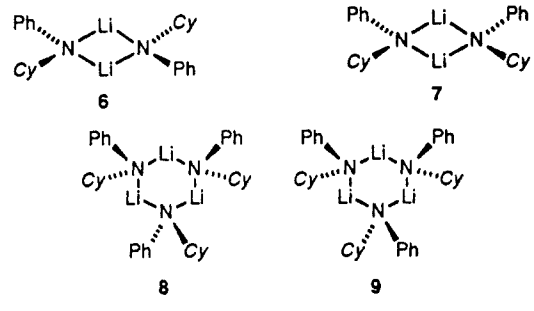


Figure 1. NMR spectra recorded at −93 °C of a 0.3 M solution of lithiated imine **5** in toluene-d_8 containing 2.0 equiv of THF/lithium: (A) ^{15}N NMR spectrum (30.42 MHz); (B) ^{6}Li NMR spectrum (44.19 MHz) observed via the ^{2}H lock channel as described in the text; (C) ^{6}Li NMR spectrum observed via the ^{2}H lock channel with concomitant irradiation of the upfield (major) ^{15}N resonance in spectrum A; (D) ^{6}Li NMR spectrum observed via the ^{2}H 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 ^{2}H lock circuitry. This allows the ^{2}H lock channel to function as a ^{6}Li observe (or decoupling) channel operating at 44.19 MHz.[5] A proton filter in the ^{2}H 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 ^{6}Li 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 134.6 ppm causes clean collapse of the major ^{6}Li resonance to a singlet. Similarly, irradiation of the minor ^{15}N quintet causes the minor ^{6}Li 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 ^{6}Li triplets to collapse to a doublet and singlet, respectively. Similarly, irradiation of the minor ^{15}N resonance would have caused collapse of the major ^{6}Li triplet to a doublet without change in the minor ^{6}Li triplet. Thus, the results of the single-frequency decouplings are consistent with stereoisomeric dimers **6** and **7** *and* inconsistent with a trimer structure.

^{6}Li 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 ^{6}Li–^{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; ^{6}Li, 14258-72-1.

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

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

(11) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

Enantioselective Total Synthesis of Neooxazolomycin

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Received January 10, 1990

Neooxazolomycin (**1**) is a structurally novel $C_{34}H_{47}N_3O_9$ 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**, R_1 = 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 known[3] (*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 coupling[4] 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.

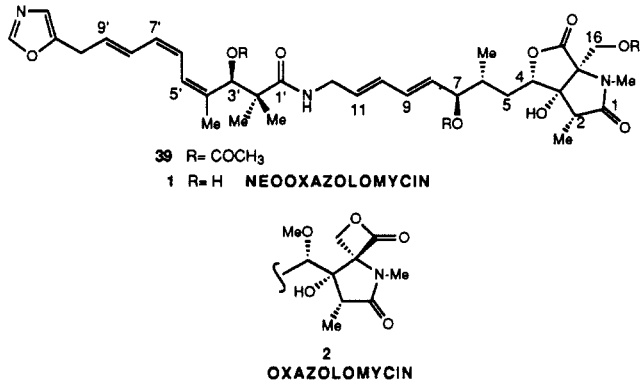
(2) All new compounds showed NMR, IR, and C,H or mass spectrometric analyses consistent with the assigned structures.

(3) Fischetti, W.; Mak, K. T.; Stakem, F. G.; Kim, J.-I.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.

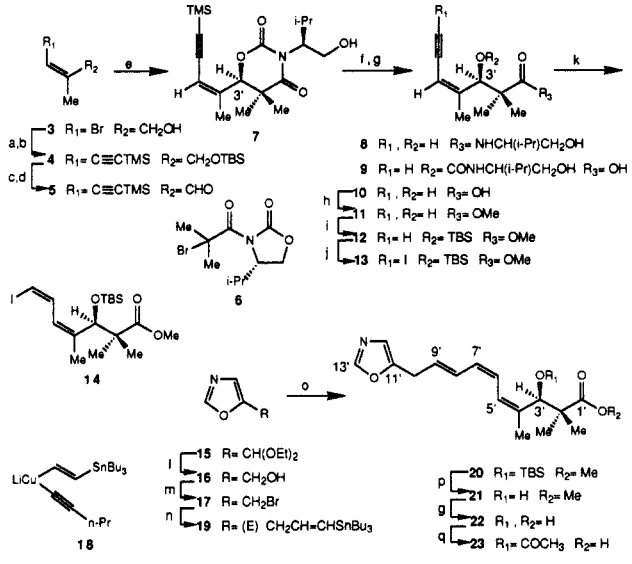
(4) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

0002-7863/90/1512-4070$02.50/0

Chart I



Scheme I[a]

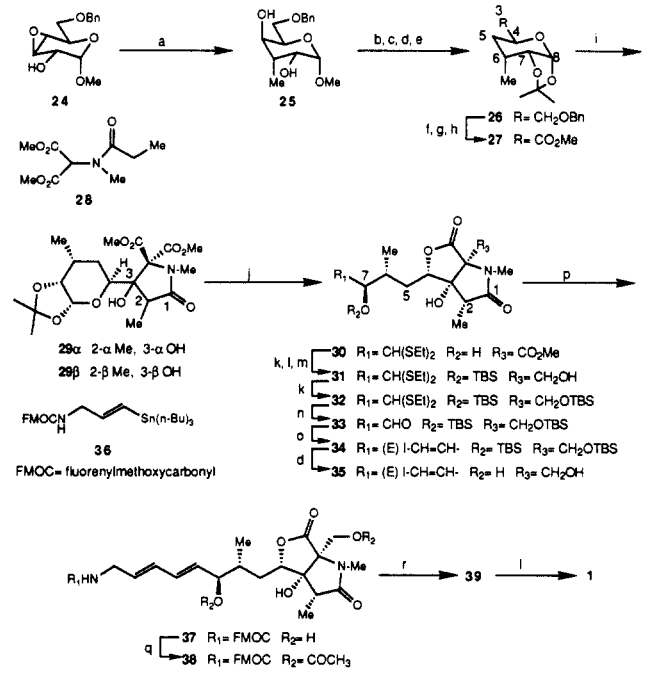


[a] Reagents: (a) TBSCl, imidazole, DMF, 0 °C, 5 min; (b) $TMSC{\equiv}CH$, $Pd(Ph_3P)_4$, CuI, *n*-$BuNH_2$, PhH, 23 °C, 18 h; (c) AcOH/THF/H_2O, 23 °C, 18 h; (d) basic MnO_2, hexane/CH_2Cl_2, 23 °C, 2 h; (e) $SnCl_2$, $LiAlH_4$, THF, 20 °C, 20 min, then **6** in THF, 20 °C, 45 min, then **5** in THF, 20 °C, 16 h; (f) 30% H_2O_2, LiOH, THF/H_2O, 20 °C, 24 h; (g) LiOH (3 equiv), THF/MeOH/H_2O, 23 °C, 24 h; (h) CH_2N_2, Et_2O, 0 °C; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 0.5 h; (j) *n*-BuLi, THF, −78 °C, 1 h, then I_2 in THF, 1 h; (k) NH_2NH_2 (5 equiv), $CuSO_4{\cdot}5H_2O$ (0.1 equiv), 95% EtOH, 23 °C, air (bubbled), 16 h; (l) THF/H_2O/concentrated HCl (cat.), 23 °C, 17 h, then saturated $NaHCO_3$, 10 min; $NaBH_4$, 0 °C; (m) NBS, Ph_3P, THF, 23 °C, 1 h; (n) (*E*)-$Bu_3SnCH{=}CHSnBu_3$, *n*-BuLi, THF, −78 °C → −40 °C, 0.5 h; then addition to $CuC{\equiv}CPr$, THF, −40 °C, 0.5 h; addition to **17**, THF, −78 °C → −10 °C; (o) **14**, 3 mol % $PdCl_2(MeCN)_2$, DMF, 23 °C, 91 h; (p) 50% HF/MeCN, 23 °C 4 h; (q) Ac_2O, pyr, 23 °C, 20 h; saturated $NaHCO_3$, MeOH/H_2O, 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 $SnCl_2$ (2 equiv) and $LiAlH_4$ (1 equiv) in THF[5] proceeded in 95% yield to give the anticipated[6] 1,3-oxazine-2,4-dione **7** [mp 95–96 °C, $[\alpha]_D$ +8.1° (*c* 0.6, CH_2Cl_2)] 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% H_2O_2 (6 equiv) and LiOH (2 equiv)[8] produced 13% of the 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** [$[\alpha]_D$ −26.6° (*c* 0.94, CH_2Cl_2), 81%], shown to be enantiomerically homogeneous (>99%) by use of $Eu(hfc)_3$ employing racemic **11** as standard.

Scheme II[a]



[a] Reagents: (a) MeLi, MeMgCl, THF/Et_2O, 23 °C, 16 h; (b) *i*-Pr_3SiOTf, 2,6-lutidine, THF, −78 °C → 23 °C, 16 h; (c) $S{=}C(Im)_2$, $(CH_2Cl)_2$, Δ; *n*-Bu_3SnH, xylene, Δ, 6 h; (d) *n*-Bu_4NF, THF, 23 °C; (e) $FeCl_3$, acetone, 23 °C, 4 h; (f) H_2, $Pd(OH)_2$, MeOH, 23 °C, 4 h; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min, then 0 °C, 1 h; $KMnO_4$, *t*-BuOH/5%NaH_2PO_4, 23 °C, 0.5 h; (h) CH_2N_2, Et_2O, 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, CH_2Cl_2, 23 °C; (l) LiOH, THF/H_2O, 23 °C, 1 h, then 1 N HCl; (m) $[Me_2N{=}CHCl]^+Cl^-$, MeCN/THF, 0 °C, 1 h; $NaBH_4$, DMF, −78 °C → 23 °C, 16 h; (n) $HgCl_2$, $CaCO_3$, MeCN/H_2O, 23 °C, 1 h; (o) CHI_3, $CrCl_2$, THF, 23 °C, 1.5 h; (p) **36**, 5 mol % $PdCl_2(MeCN)_2$, DMF, 23 °C, 24 h; (q) Ac_2O, pyr, 23 °C, 24 h; (r) DBU, CH_2Cl_2, 23 °C, 0.5 h; addition to the mixed anhydride [**23**, *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride, Et_3N, CH_2Cl_2, 23 °C, 3 h], then 23 °C, 0.5 h.

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 I_2 quenching, and (3) diimide reduction[9] 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 $NaBH_4$ reduction gave the oxazole methanol **16**, mp 27–28 °C, in 68% yield. NBS/Ph_3P transformed **16** to the unstable bromide **17** (44%), which was immediately reacted with the cuprate **18**[11] (1.2 equiv) to produce the (*E*)-vinyl stannane **19** in 49% yield. The critical Stille coupling[12] of **19** with

(5) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 161.
(6) Kende, A. S.; Kawamura, K.; Orwat, M. J. *Tetrahedron Lett.* **1989**, *30*, 5821.
(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.
(8) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
(9) Ohno, M.; Okamoto, M. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 281.
(10) Schöllkopf, U.; Schröder, R. *Angew Chem., Int. Ed. Engl.* **1971**, *10*, 333.
(11) For a similar coupling reaction, see: Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630 and references therein.

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° (*c* 1.0, CH_2Cl_2), 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 Me_2Mg,[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*-Bu_4NF desilylation, and (4) condensation with acetone/$FeCl_3$.[18] Hydrogenolytic debenzylation of **26** and then Swern oxidation followed by buffered $KMnO_4$ and diazomethane gave ester **27** [mp 47–49 °C, $[\alpha]_D$ −25.4° (*c* 1.6, CH_2Cl_2)] in 70% yield over four steps from **26**.

With the six carbons of **27** corresponding to neooxazolomycin C-3 through C-8 as marked, we used the ester group of **27** as the electrophile in a cyclocondensation[19] 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 reduction[21] 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 $CHI_3/CrCl_2$ gave a 70% yield of the (*E*)-vinyl iodide **34** (mp 134–136 °C).[23] Quantitative desilylation[24] 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 Et_3N (2.2 equiv) to give the activated anhydride,[26] to which was added a CH_2Cl_2 solution of the free amine prepared by DBU (2 equiv) deprotection[25] of the FMOC diacetate **38** (1 equiv). Reaction for 1 h produced neooxazolomycin 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 neooxazolomycin (**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.

(12) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(13) Deprotection using other conventional reagents (Bu_4NF, Py·HF, CsF, KF) failed.
(14) Hydrolysis of ester **21** requires assistance from the β-hydroxyl group via hydrogen bonding; silyl-protected ester **20** could not be hydrolyzed.
(15) Buchanan, J. G.; Fletcher, R. *J. Chem. Soc.* **1965**, 6316.
(16) Parker, K. A.; Babine, R. E. *Tetrahedron Lett.* **1982**, *23*, 1763. No product from Payne rearrangement was observed. Treatment of the TBS ether of **24** with excess Me_2CuLi gave an 8:1 mixture of the undesired regioisomer. Reaction of **24** with excess Me_2CuLi gave a 1:1 mixture of regioisomers.
(17) For this modified Barton deoxygenation, see: Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.
(18) Dasgupta, F.; Singh, P. P.; Srivastava, H. C. *Indian J. Chem.* **1980**, *19B*, 1056.
(19) Kende, A. S.; DeVita, R. J. *Tetrahedron Lett.* **1988**, *29*, 2521.
(20) This is contrary to the stereochemical outcome in the chiral acyclic model ester (*S*)-MOM lactate, suggesting that the use of a more conformationally flexible acyclic ester synthon could preferentially give the desired α-isomer **29α** (see ref 19); however, direct formation of the acyclic dithioacetal ester from **27** failed.
(21) Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* **1983**, 835.
(22) To confirm the structure, intermediate **31** was converted to the known triacetate which had been prepared from **39** by Uemura et al.; see ref 1a.
(23) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(24) Deprotection at this stage was necessary, because removal of TBS groups from the synthetic disilyl ether of **37** or trisilyl ether of **1** under all conventional methods proceeded poorly.
(25) The vinylstannane **36** was prepared from propargylamine by the sequence following: (1) FMOCCl/Py/CH_2Cl_2; (2) Bu_3SnH/AIBN (Kende, A. S.; DeVita, R. J. *Tetrahedron Lett.* **1990**, *31*, 307).
(26) Cabré, J.; Palomo, A. L. *Synthesis* **1984**, 413.

(27) We are grateful to Dr. D. Uemura of Shizuoka University, Japan, for samples of neooxazolomycin 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 Procedure[1]

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We report the preparation and applications of new organosulfur reagents, allenyl chloromethyl sulfones (**1**), $RR'C{=}C{=}CHSO_2CH_2Cl$, 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**), $H_2C{=}C{=}CHSO_2CH_2Cl$, chloromethyl tetradeca-1,2-dienyl sulfone (**3**), $CH_3(CH_2)_{10}CH{=}C{=}CHSO_2CH_2Cl$, and chloromethyl 3-methylbuta-1,2-dienyl sulfone (**4**), $Me_2C{=}C{=}CHSO_2CH_2Cl$. 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 sulfonylallenes 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, $ClCH_2SCl$,[4] with propargylic alcohols ($RR'C(OH)C{\equiv}CH$) giving *S*-chloromethyl propargyl sulfenates, $ClCH_2SOCRR'C{\equiv}CH$ (**5**), [2,3]-sigmatropic rearrangement[5] of **5** to chloromethyl 1,2-alkadienyl sulfoxides, $RR'C{=}C{=}CHS(O)CH_2Cl$ (**6**), and oxidation

(1) Presented at the 199th National Meeting of the American Chemical Society, April 24, 1990, Boston, MA.
(2) (a) Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.-A.; Wall, A. *J. Am. Chem. Soc.* **1986**, *108*, 4568. (b) Block, E.; Aslam, M. *Org. Synth.* **1987**, *65*, 90.
(3) (a) Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 512. (b) Barbarella, G.; Cinquini, M.; Colonna, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1646. (c) Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532. (d) Lindermann, R. J.; Suhr, Y. *J. Org. Chem.* **1988**, *53*, 1569.
(4) Douglass, I. B.; Norton, R. V.; Weichman, R. L.; Clarkson, R. B. *J. Org. Chem.* **1969**, *34*, 1803.
(5) Braverman, S.; Stabinsky, Y. *Isr. J. Chem.* **1967**, *5*, 125.

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