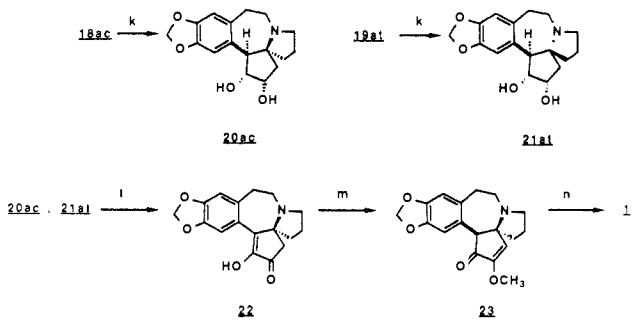
Scheme III[a]



[a](k) 1 N HCl:THF (1:1), room temperature; (l) DMSO, TFAA, Et_3N, CH_2Cl_2, -78 °C; (m) dimethoxypropane, dioxane, *p*-TsOH, reflux; (n) $NaBH_4$, MeOH, -78 °C → room temperature.

alcohols can be separated.[15] It is more expedient to simply carry the mixture through the three steps of NO bond cleavage, mesylation, and intramolecular nitrogen alkylation of the resultant lactam-mesylate. This procedure affords 46% of **14ac** and 23% of **15at** which are easily separable by plug filtration on silica. The major product from this sequence is assigned the expected anti-cis stereochemistry **14ac**.[15] The minor product was proposed to be the anti-trans adduct **15at**.[15] The formation of **13at** is *formally* the result of an intramolecular Diels-Alder reaction which requires the acyl nitroso moiety to approach the diene moiety from the opposite face of the tethering arene group. Although several examples of unusual regiochemical arrangements have been observed in the macrocyclic version of the IDA reaction[16] and other examples of simultaneous formation of fused 7/6 ring systems are known,[17] this observation is unprecedented in the intramolecular Diels-Alder literature.[18,19] This finding would seem to necessitate critical evaluation of the implicit assumption of "syn-tether specificity" in all intramolecular reactions where a ring size of seven or greater is being formed.

Both adduct **14ac** and **15at** have been converted to *dl*-cephalotaxine (**1**). Hydrogenation of the $C_{6,7}$ double bond followed by lactam reduction with BH_3-THF[20] provided the saturated pentacyclic amines **18ac** (81%) and **19at** (87%), respectively. At this stage it was possible to verify by X-ray crystallography[21,22] that **19** (and by implication **13**, **15**, and **17**) bore the assigned anti-trans stereochemistry (see Supplementary Material).

Culmination of the synthesis involved individual deprotection of the acetonide moieties of **18ac** and **19at** and to afford amino diols **20ac** (91%) and **21at** (99%), respectively. Swern oxidation[23] of both of these diols afforded demethylcephalotaxinone **22** (75-88%)[24,25] which was converted to cephalotaxinone **23** (70-84%) followed by borohydride reduction to afford *dl*-cephalotaxine (**1**) (97%).[25,26] The overall yield of **1** from **4** is 14-17% considering that both isomers **12ac** and **13at** were utilized.

Acknowledgment. We thank the National Institute of Health (GM 32693) for their generous support of this work. We also thank the Purdue University Biological Magnetic Resonance Laboratory (NIH RR01077) for access to the 470 MHz high field proton spectrophotometer, Mark Anderson and Dr. C. R. Jones for their assistance with the 2D NMR work, and Arlene Rothwell for providing mass spectral data. Professors Ken Shea of the University of California, Irvine, and Bob Boeckman of the University of Rochester are acknowledged for their helpful discussions concerning the IDA reaction.

Supplementary Material Available: Experimental data for the preparation of OBO ester **5** from piperonyl alcohol, structures, carbon, proton, spectral data for ABD allylic alcohols and acetates, 2D NMR and spectral data for **14ac** and **15at**, stereoscopic and ORTEP drawings of **19at**, and tables of crystal data, bond angles and distances, torsion angles, and positional parameters (32 pages). Ordering information is given on any current masthead page.

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(19) Speculations on the relative importance of various conformational and electronic effects (including the possibility of nonsynchronous bond formation) pertaining to the generation of **13** will have to await future computational modeling. These results will be subsequentially published in a full paper.

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(22) Tables of bond angles and distances can be found in the Supplementary Material.

(23) For references on the 1,2-diol to α-diketone oxidations, see: Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 0000 and references cited therein.

(24) As can be seen in Scheme III, the oxidation of **20ac** and **21at** afford the same racemic enolized α-diketone **22**. It should be noted that an alternative structure (**13sc**, see Supplementary Material) for the minor Diels-Alder adduct would also have given **22** after the oxidation step, underscoring the need for the X-ray determination for **19at**.

(25) We wish to thank Professor Steve Weinreb of Penn State for an authentic sample of **22** and R. G. Powell of the USDA, Peoria, IL, for an authentic sample of **1**.

(26) Conversion of **22** to **23** was carried out by a Merck modification of the original Weinreb procedure (literature yields: 99×86%).[3b] We thank Professor Weinreb for this information.

Poly(*n*-hexylsilyne): Synthesis and Properties of the First Alkyl Silicon $[RSi]_n$ Network Polymer

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Linear silicon-silicon bonded polymers $[R_1R_2Si]_n$ are presently the focus of intense investigation[1] and have already found applications as SiC precursors,[2] photoresists,[3] and photoinitiators.[4] However, little progress has been made toward the synthesis of

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Table I. Characteristic ^{29}Si Chemical Shifts for Materials with Various Degrees of Silyl Substitution

no. of silyl substituents	compound	$\delta^{29}Si^a$	ref
2	poly(di-*n*-hexylsilane)	−24.8	1h
	poly(methylhexylsilane)	−32.0	1h
3	1 (solution)	−57	this
	1 (solid state)	−60	work
	(hexyl)Si($SiMe_3$)$_3$	−74.8	10
	(phenyl)Si($SiMe_3$)$_3$	−74.2	10
4	Si($SiMe_3$)$_4$	−135.5	11
sp^2	(Mes)$_2$Si=Si(Mes)$_2$	+63.6	12
	(*t*-Bu)$_2$Si=Si(*t*-Bu)$_2$	+64.06	13

[a] In ppm versus tetramethylsilane.

polymers of monoalkylsilyne units,[5] $[RSi]_n$, the "polyalkylsilynes". Such polymers could adopt a variety of microstructures beyond those exhibited by their carbon analogues, the polyacetylenes, and may therefore possess novel physical properties. We describe here the synthesis and properties of the first such material, "poly(*n*-hexylsilyne)".

Our attempts to apply conventional heterogeneous reductive condensation approaches used for polysilane syntheses (eq 1)[1a-c]

$$R^1R^2SiCl_2 + 2Na \xrightarrow[\text{toluene}]{\text{reflux}} \left[\begin{array}{c} R^1 \\ | \\ -Si- \\ | \\ R^2 \end{array}\right]_n + 2NaCl \qquad (1)$$

R^1, R^2 = alkyl or aryl

to $RSiCl_3$ monomers were complicated by incomplete reduction and rearrangements to complex product mixtures. These difficulties were overcome by promoting an essentially homogeneous, near ambient temperature reaction between $RSiCl_3$ and liquid Na/K alloy emulsions by using high-intensity ultrasound.[6]

The synthesis was conducted inside an inert atmosphere glovebox equipped with a high intensity (375 W, 20 KHz) ultrasonic immersion horn.[7] Na/K alloy (50:50 mol %, 4.43 g, 142.5 mequiv) was added dropwise directly beneath the tip of the activated horn immersed into a solution of *n*-hexyl$SiCl_3$ (11.0 g, 50 mmol) in pentane (100 mL). When the addition was complete and the reaction subsided, 100 mL of THF was added, and sonication continued for an additional 5 min, after which the reaction mixture was allowed to cool to room temperature with stirring. A solution of hexyl magnesium bromide in ethyl ether (approximately 7.5 mmol) was added until a hydrolyzed aliquot of the solution tested at neutral pH.[8] The reaction mixture was then removed from the glovebox and poured into cold water under a stream of inert gas. The resulting yellow precipitate was quickly removed by filtration, redissolved in THF, and reprecipitated sequentially from methanol and 2-propanol to give 1.85 g (33%) of poly(*n*-hexylsilyne) (**1**) as a yellow, hexane-soluble powder. IR spectra of material so obtained revealed the absence of Si–H and Si–O–Si bands, and chemical analysis was consistent with the empirical formula $[C_6H_{13}Si]$.[9] Gel permeation chromatography

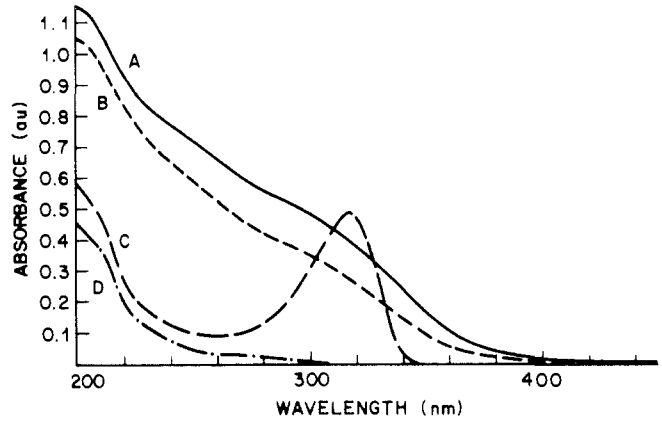

Figure 1. Comparison of UV photosensitivity of poly(*n*-hexylsilyne) and poly(dihexylsilane) as 4×10^{-5} M solutions in cyclohexane: (A) poly(*n*-hexylsilyne) before irradiation, (B) poly(*n*-hexylsilyne) after 80 mJ/cm^2 broad band UV exposure, (C) poly(dihexylsilane) before irradiation, and (D) poly(dihexylsilane) after 80 mJ/cm^2 broad band UV exposure.

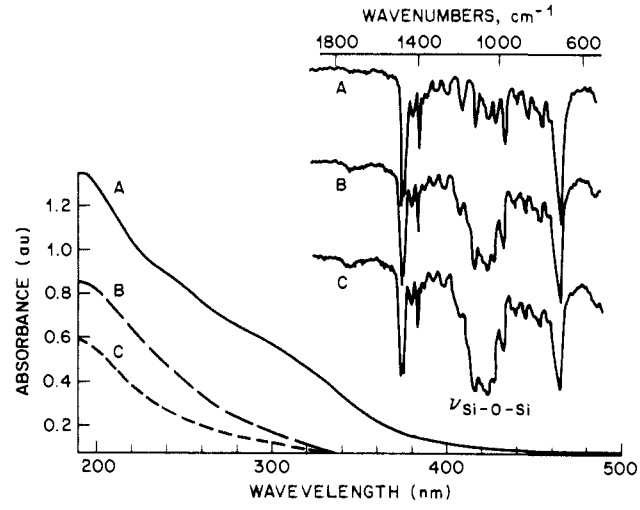

Figure 2. UV–vis and IR spectral changes upon 254-nm irradiation of poly(*n*-hexylsilyne) films in the presence of oxygen: (A) before exposure, (B) after 1-min irradiation, and (C) after 2-min irradiation.

of **1** indicated a $\bar{M}_w = 2.4 \times 10^4$ versus polystyrene, in a single envelope with a polydispersity of 2.1. Differential scanning calorimetry and X-ray powder pattern studies on **1** revealed the absence of crystallinity or structural regularity.

The solution ^{29}Si NMR spectrum of **1** exhibits one very broad resonance ($\delta\nu_{1/2} \approx 245$ Hz) centered at −57 ppm versus tetramethylsilane. As illustrated in Table I, this chemical shift is most characteristic of tetrahedral silicons which have three silyl substituents and eliminates silicon–silicon double bonds as a primary structural feature of **1**. The broadness of the ^{29}Si resonance (in contrast to the narrow resonances observed for linear polysilanes[1h]) and the progressive increase of the line widths of the ^{13}C NMR resonances moving inward along the hexyl chain[9] indicate both backbone rigidity and diversity of silicon chemical environments in **1**. These data are consistent with a randomly constructed rigid network of monoalkyl sp^3-hybridized silicon units, the stoichiometric and structural intermediate between linear polysilanes and

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(9) **1**: ^1H NMR (360 MHz, C_6D_6) δ = 0.95 (br), 1.49 (br); $^{13}C\{^1H\}$ NMR (90.6 MHz, C_6D_6) δ = 14.39 (CH_3, $\delta\nu_{1/2}$ = 14 Hz), 23.15 (C5, $\delta\nu_{1/2}$ = 43 Hz), 30.77 (C2, $\delta\nu_{1/2}$ = 56 Hz), 32.22 (C4, $\delta\nu_{1/2}$ = 56 Hz), 34.84 (C3, $\delta\nu_{1/2}$ = 112 Hz), C1 broad and resolved; $^{29}Si\{^1H\}$ NMR (71.5 MHz, C_6D_6) δ = −57; IR (neat film on KBr, cm^{-1}) 2957 (vs), 2919 (vs), 2874 (vs), 2852 (vs), 1466 (s), 1458 (s), 1419 (w), 1379 (m), 1340 (w), 1293 (w), 1249 (w), 1165 (m), 1098 (s), 1042 (m), 1032 (m), 997 (m), 950 (s), 889 (w), 839 (w), 760 (w), 669 (vs). UV–vis (hexane, 4.0 mM in Si) $\lambda \leq$ 200–450 nm, ϵ at 200 nm = 29 000 per Si. Anal. Calcd for $C_6H_{13}Si$: C, 63.63; H, 11.57; Si, 24.8. Found: C, 63.38; H, 11.25; Si, 24.9.

elemental silicon. Steric considerations, the polymer's high solubility, and the propensity of related reactions to give cyclic and polycyclic compounds[5a,5b,10] suggest a sheetlike or open cage arrangement of fused rings.

While linear polysilanes exhibit strong $\sigma-\sigma^*$ transitions (λ_{max} = 300–350 nm)[1] in the near UV, **1** exhibits a broad and more intense absorption band edge tailing into the visible (Figure 1), associated with extension of Si–Si σ-"conjugation" into three dimensions. Poly(*n*-hexylsilyne) is far more stable to photodegradation in an inert atmosphere than are linear polysilanes (Figure 1), possibly due to the more delocalized nature of excitations or to the greater propensity of a network structure to enforce recombination of photogenerated radicals. Both polydialkylsilanes and **1** photooxidize upon irradiation in air, but while polysilanes fragment to give cyclic oligomers, **1** crosslinks to form polymeric siloxane networks (Figure 2). Also in contrast to linear polysilanes,[1a] **1** converts directly (without pretreatment) upon pyrolysis to mixtures of Si/SiC without loss of volatile silicon fragments.[10] Further studies on the synthesis and properties of other members of this new class of silicon polymers are in progress.

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Registry No. Na/K, 12056-29-0; hexylSiCl$_3$ (homopolymer), 113219-09-3.

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New Tetrodotoxin Analogues from the Newt *Cynops ensicauda*

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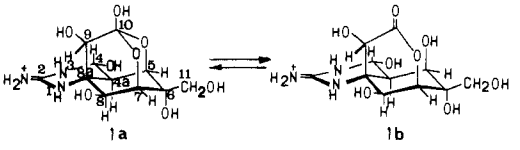
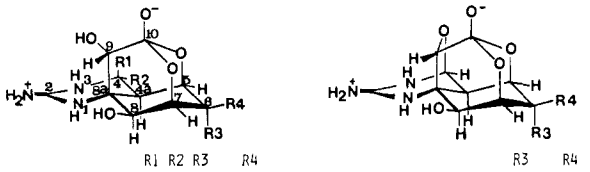
Tetrodotoxin (TTX, **1**), a potent neurotoxin first isolated from puffers[1] and then from California newts,[2] has recently been reported from various biota.[3] Its use as a sodium channel blocker is also expanding. Yet we know little of its biosynthesis or natural analogues.[3a] Major obstacles are the lack of a detection method for TTX analogues and the poor resolution of ^{1}H and ^{13}C NMR spectra of TTX due to the hemilactal–lactone tautomerism (Figure 1). We previously isolated 4-*epi*TTX (**2**) and 4,9-anhydroTTX (**3**) from puffers.[4] Both compounds are derivable from TTX with acids and thus provide little information about metabolic pathways. Significantly, we have now isolated from the newt *Cynops ensicauda* 6-*epi*TTX, 11-deoxyTTX, and their conversion products.



1a **1b**

Figure 1. Hemilactal (**1a**) and lactone (**1b**) forms of TTX.

The newts (3.5 kg) collected in Okinawa, Japan, were extracted with hot 0.1% HOAc, and the extracts were chromatographed successively on columns of charcoal, BioGel P-2, BioRex 70, and Hitachi 3011C ion exchange gel.[4] Separation of TTX analogues was monitored by a TTX analyzer[5] and TLC. The following compounds were isolated: TTX (**1**, 120 mg), 4-*epi*TTX (**2**, 15 mg), 4,9-anhydroTTX (**3**, 20 mg), 6-*epi*TTX (**4**, 18 mg), 4,9-anhydro-6-*epi*TTX (**5**, 3 mg), 11-deoxyTTX (**6**, 30 mg), 11-deoxy-4-*epi*TTX (**7**, 2 mg), and 4,9-anhydro-11-deoxyTTX (**8**, 1 mg). The structural determination of the analogues was



		R1	R2	R3	R4
1	TTX	H	OH	OH	CH_2OH
2	4-epiTTX	OH	H	OH	CH_2OH
4	6-epiTTX	H	OH	CH_2OH	OH
6	11-deoxyTTX	H	OH	OH	CH_3
7	11-deoxy-4-epiTTX	OH	H	OH	CH_3

		R3	R4
3	4,9-anhydroTTX	OH	CH_2OH
5	4,9-anhydro-6-epiTTX	CH_2OH	OH
8	4,9-anhydro-11-deoxyTTX	OH	CH_3

achieved mainly through NMR measurements. Addition of CF_3COOD to the solvent markedly improved the resolution of signals in the NMR spectra of TTX and thus allowed us to assign for the first time all ^{1}H and ^{13}C signals by ^{1}H–^{1}H and ^{13}C–^{1}H COSY measurements (Table I).

6-*epi*TTX (**4**); $[\alpha]^{25}_D$ −4.8° (*c* 0.33, 0.05 N HOAc). The molecular formula by high resolution FABMS[6] was identical with that of TTX, $C_{11}H_{17}N_3O_8$ (MH^+, *m/z* 320.1094, found 320.1106). The LD_{50} of **4** to mice was 60 μg/kg (ip). ^{13}C and ^{1}H NMR spectra revealed double sets of signals, thereby indicating that **4** exists as hemilactal–lactone tautomers, as does TTX. The tautomerism was evidenced by negative crosspeaks due to saturation transfer between corresponding protons in a phase sensitive NOESY spectrum. The ratio of hemilactal–lactone tautomers was 6:4. Comparison of ^{13}C and ^{1}H NMR signals of TTX and 6-*epi*TTX is shown in Table I. Assignments of the signals were derived from ^{1}H–^{1}H and ^{13}C–^{1}H COSY measurements. Signals in **4** due to H-4a, H-8, H-11, C-4a, C-5, C-6, and C-7 were significantly shifted from the corresponding signals of TTX, supporting the 6-epi assignment. Proton COSY of **4**, showed couplings between H-4/H-4a, H-4a/H-5, H-5/H-7 (W-type), and H-7/H-8, analogous with TTX. The coupling patterns also agreed with those of TTX. Thus structure changes at C-4a, C-5, C-7, and C-8 were ruled out. Because 4,9-anhydro-6-*epi*TTX (**5**)[7] isolated from the same newts was convertible in acid in **4**, as is 4,9-anhydroTTX to TTX, C-8a and C-9 of **4** must have the same stereochemistry as in TTX. NOE measurements and difference spectra confirmed the axial substitution of C-11; irradiation at

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(6) The HRFABMS was measured on a JEOL JMS-DX303HF mass spectrometer by K. Nojima of JEOL Co.
(7) 4,9-anhydro-6-*epi*TTX (**5**); $[\alpha]^{25}_D$ +10.0° (*c* 0.08, 0.05 N HOAc); HRFABMS, MH^+ *m/z* 302.0999 (calcd for $C_{11}H_{16}N_3O_7$ 302.0988); ^{1}H NMR of a hemilactal form δ 5.54 (H-4, s), 2.87 (H-4a, d, J_{4a-5} = 2.3 Hz), 4.33 (H-5, dd, J_{5-4a} = 2.3, J_{5-7} = 2.0 Hz), 4.20 (H-7, t, J_{7-5}, J_{7-8} = 2.0 Hz), 4.41 (H-8, d, J_{8-7} = 2.0 Hz), 4.61 (H-9, s), 3.65, 3.67 (CH_2-11, d, J_{gem} = 12.7 Hz). When irradiated at δ 3.65 (CH_2-11), 12.4% and 13.4% of NOE were observed on H-4a and H-8, respectively.

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