SYNTHESIS AND NEMATOCIDAL ACTIVITIES OF JIETACIN A AND ITS ANALOGS

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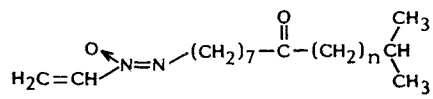
Simple, efficient syntheses of jietacin A, a nematocidal antibiotic, and its analogs have been developed in order to study structure-activity relationships. A series of α,β-unsaturated azoxy compounds was prepared from phenylselenomethyl azoxy compounds as key intermediates and its nematocidal activity was determined.

As reported in the previous papers,[1,2] jietacins A (**1**) and B (**2**) produced by *Streptomyces* sp. KP-197 contain an unique vinylazoxy structure and show a potent activity against the pine wood nematode *Bursaphelenchus lignicolus*. We became interested in the participation of the characteristic vinylazoxy moiety of **1** in its prominent activity. In this paper we will describe the first total synthesis of **1** and the synthesis of azoxy analogs as well as their activities against *B. lignicolus*.

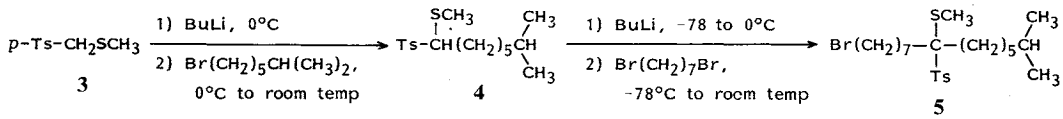


1 n=5
2 n=6

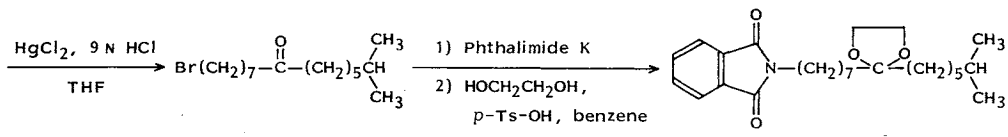
Chemistry

Our synthetic approach to **1** is outlined in Schemes 1 and 2. Aminoacetal **9**, which corresponds

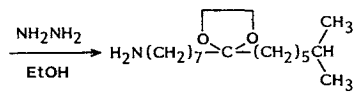
Scheme 1.



3 **4** **5**



6 **7**



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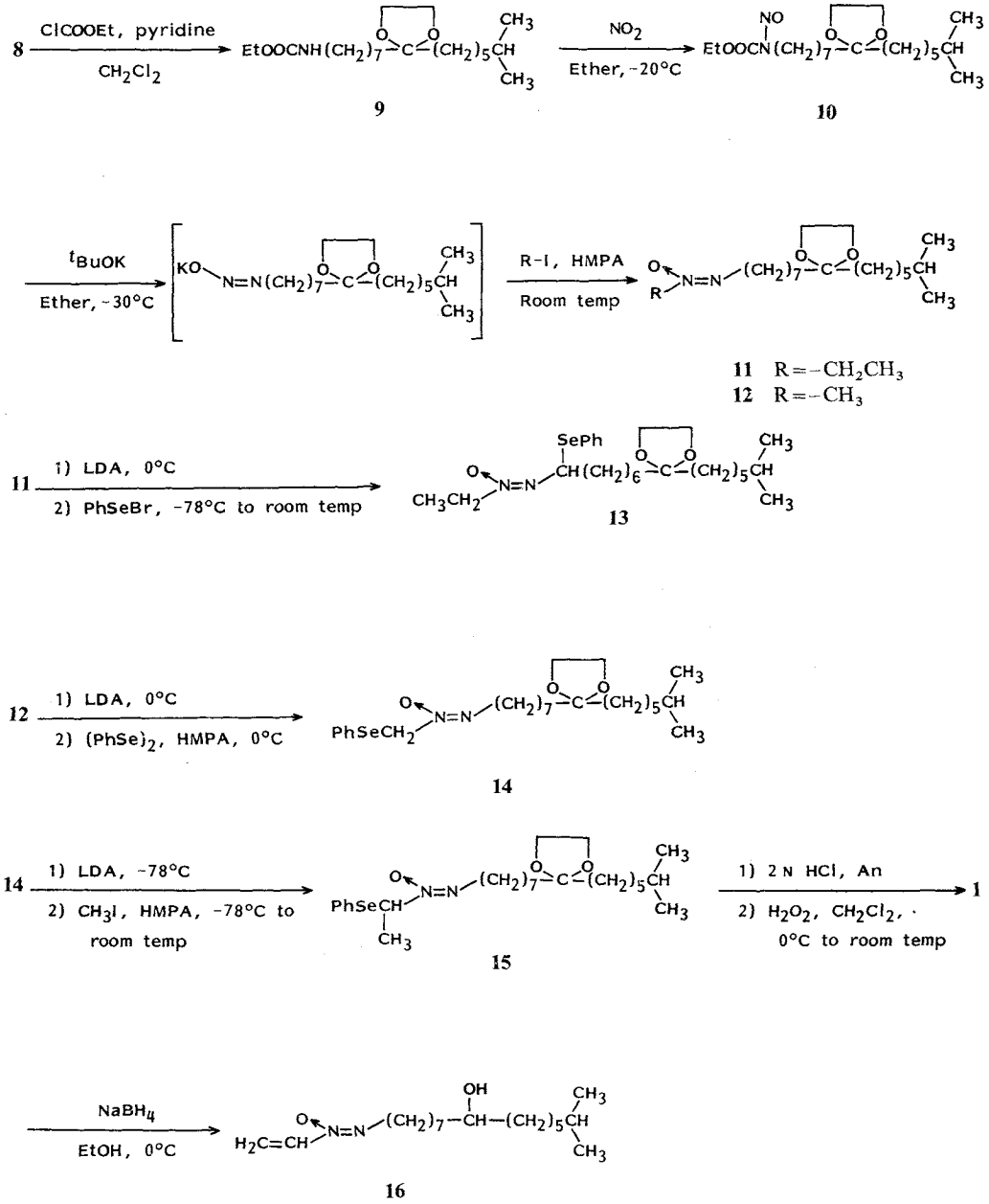
Scheme 2.



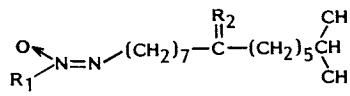
to an alkyl side chain of the azoxy group, was chosen for the most suitable intermediate by considering the structural feature of **1**. Metalation of (methylthio)methyl *p*-tolyl sulfone (**3**) using *n*-butyllithium in tetrahydrofuran (THF) at 0°C, followed by alkylation with 1-bromo-6-methylheptane,[3] gave **4** in 80% yield. Addition of *n*-butyllithium to a THF solution of **4** at 0°C in a similar manner as the first alkylation step resulted in decomposition of the substrate. A successful formation of carbanion of **4** was accomplished by the procedures that involved the careful addition of *n*-butyllithium to a well stirred THF solution of **4** at −78°C and then warming the solution at 0°C to complete the deprotonation. The resulting anion

was quenched by 1,7-dibromoheptane at −78°C to give **5**, which was directly hydrolyzed without purification using mercuric chloride and 9 N HCl in THF at 0°C to give **6** in 68% overall yield from **4** since the attempted isolation of **5** by column chromatography on silica gel resulted in contamination with **6**. The conversion of **6** into primary amine **8** was performed by adopting the Gabriel synthesis, namely, succesive treatments including reaction with potassium phthalimide at 100°C in *N*,*N*-dimethylformamide, protection of a carbonyl group as an ethylene acetal and hydrazinolysis furnished **8** in 73% overall yield.

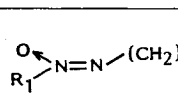
The preparation of the azoxy moiety was performed by a regioselective alkylation of a diazoate generalized by the treatment of the *N*-nitrosourethane with potassium *tert*-butoxide, according to the Moss's procedure.[4] Urethane **9**, which was obtained by reaction of **8** with ethyl chloroformate in dichloromethane (CH_2Cl_2) in 90% yield, was treated with dinitrogen tetraoxide at −20°C in ether to give *N*-nitrosourethane **10**. The cleavage of **10** with *tert*-butoxide in ether at −30°C, followed by trapping of the resulting diazoate anion with ethyl iodide and methyl iodide in hexamethylphosphoric triamide (HMPA) at room temperature gave **11** and **12**, respectively, in 38% and 40% yield. Direct conversion of **11** into the vinylazoxy compound was attempted without success. Treatment of **11** with lithium diisopropylamide (LDA) in THF at 0°C and quenching of the generated anion with benzeneselenenyl bromide gave unfavorable α′-phenylseleno derivative **13**. On the other hand, similar deprotonation of **12** with LDA[5] and subsequent selenenylation with diphenyl diselenide in the presence of HMPA gave α-phenylseleno derivative **14** regioselectively in 53% yield. Finally, **14** was employed in a straightforward construction of the characteristic vinylazoxy moiety of **1**. Selective deprotonation of **14** using LDA in THF at −78°C and subsequent methylation of the generated anion with methyl iodide in the presence of HMPA gave **15** in 51% yield. Hydrolysis of the acetal function with 2 N HCl in acetone, followed by oxidative elimination of the phenylseleno group by a two phase method (aqueous hydrogen peroxide-CH_2Cl_2),[6] furnished jietacin A (**1**) in 82% overall yield from **15**, spectral data (^1H and ^{23}C NMR, IR, UV, MS) of which were identical in all respects with those of an authentic sample. Reduction of **1** with $NaBH_4$ in ethanol at 0°C gave the alcohol **16** quantitatively.

Following these procedures, several jietacin analogs were synthesized. Alkylation of **14** with reactive alkyl halides such as ethyl iodide, allyl bromide, benzyl bromide and propargyl bromide gave the corresponding azoxy derivatives in 18～36% yield, which were converted to α,β-unsaturated azoxyalkene **21**, **22**, **23** and **24**, respectively, in 80～82% overall yield. Starting from 6-methylheptylamine, **18** was obtained according to our established method.

Table 1. Nematocidal activities (IC_{50} values) of jietacin A (**1**) and its analogs against *Bursaphelenchus lignicolus*.



	R_1	R_2	IC_{50} (μg/ml)
Jietacin A (**1**)	$-CH=CH_2$	=O	0.038
16	$-CH=CH_2$	-OH, -H	0.08
17	$-CH=CH_2$		0.08
18[a]	$-CH=CH_2$	—	0.06
19	$-CH_3$	=O	600
20	$-C_2H_5$	=O	4
21	(*E*)-CH=CH-CH_3	=O	20
22	(*E*)-CH=CH-CH=CH_2	=O	35
23	(*E*)- 	=O	600
24	(*E*)-CH=CH-C≡CH	=O	0.3

[a] 

Results and Discussion

Nematocidal activities (IC_{50} values) of the syn-

thesized azoxy compounds are summarized in Table 1. Modification of the vinyl group of **1** greatly diminished a nematocidal activity, while chemical change of the carbonyl function did not affect the activity. Moreover, the fact that **18** retained the activity comparable to that of jietacin may suggest that the alkyl side chain of **1** is not important for manifestation of nematocidal activity. It is noteworthy that **19** exhibited a considerably decreased activity compared with **20**. The length of carbon chain may be another possible factor affecting the activity apart from unsaturated character. To summarize the results of the present study, we could establish a convergent synthetic method of jietacin A and its analogs. And their nematocidal activities clearly indicate that the vinylazoxy moiety is a responsible site for the potent activity of **1**.

Experimental

MP's were determined on a micro melting point apparatus (Yanaco MP-3). They were uncorrected. NMR spectra were run in $CDCl_3$ on a 90 MHz spectrometer (Jeol FX-90Q). IR spectra were taken on a Jasco A-102 spectrometer. Elemental analysis for carbon, hydrogen and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer. Column chromatography was performed on Silica gel 60 (Art. No. 7734, Merck) and preparative TLC was performed on silica gel (Art. No. 13895, Merck).

7-Methyl-1-methylthiooctyl *p*-Tolyl Sulfone (**4**)

To a stirred solution of methylthiomethyl *p*-tolyl sulfone **3** (10 g, 46.2 mmol) in dry THF (100 ml) at $-78°C$ under nitrogen was added dropwise 33 ml (50.5 mmol) of 1.53 M *n*-butyllithium in hexane. After the addition was complete, the solution was stirred at $-78°C$ for further 10 minutes and then warmed to 0°C for 30 minutes, a solution of 6-methyl-1-bromoheptane (11 g, 57.0 mmol) in THF (10 ml) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature gradually. After 12 hours, the mixture was diluted with CH_2Cl_2, washed with 2 N HCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane - ethyl acetate (20 : 1) to afford 12 g (79%) of **4** as a colorless oil: IR (neat) cm^{-1} 3025, 2950, 2925, 2860, 1598; ^1H NMR ($CDCl_3$) δ 0.85 (6H, d, $J=6.1$ Hz), 2.22 (3H, s), 2.45 (3H, s), 3.65 (1H, dd, $J=10.3$ and 2.9 Hz), 7.35 (2H, d, $J=8.2$ Hz), 7.83 (2H, d, $J=8.2$ Hz); MS *m/z* 328 (M^+).

Anal Calcd for $C_{17}H_{28}O_2S_2$: C 62.15, H 8.59.
Found: C 62.20, H 8.71.

1-Bromo-14-methyl-8-pentadecanone (**6**)

To a stirred solution of **4** (5 g, 15.2 mmol) in THF (50 ml) at $-78°C$ under nitrogen was added dropwise over 30 minutes 11 ml (16.8 mmol) of 1.53 M *n*-butyllithium in hexane. After the addition was complete, the solution was stirred at $-78°C$ for 5 minutes and then warmed to 0°C. After the stirring was continued for 20 minutes at 0°C, the solution was cooled at $-78°C$ again. A solution of 1,7-dibromoheptane (4.7 g, 18.2 mmol) in THF (5 ml) was added and the resulting mixture was allowed to warm to room temperature gradually. After 12 hours, the mixture was diluted with CH_2Cl_2, washed with 2 N HCl, dried (Na_2SO_4), and concentrated *in vacuo* to leave 1-bromo-14-methyl-8-methylthio-8-pentadecanyl *p*-tolyl sulfone (**5**) as a slightly yellow oil. To a stirred solution of $HgCl_2$ (1.6 g, 58.9 mmol) in 9 N HCl (6 ml) and THF (24 ml) at 0°C was added a solution of the crude **5** in THF (3 ml). After stirring at 0°C for 1.5 hours, the mixture was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatograhy on silica gel, eluting with hexane - ethyl acetate (20 : 1) to afford 3.3 g (68%) of **6** as a colorless oil: IR (neat) cm^{-1} 2940, 2860, 1715; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, $J=6.1$ Hz), 2.39 (4H, t, $J=7.1$ Hz), 3.40 (2H, t, $J=6.7$ Hz); MS *m/z* 239 ($M^+ - Br$).

Anal Calcd for $C_{16}H_{31}BrO$: C 60.18, H 9.78.
Found: C 60.04, H 9.78.

N-(8,8-Ethylenedioxy-14-methylpentadecanyl)phthalimide (**7**)

A solution of **6** (6 g, 18.8 mmol) and potassium phthalimide (5.2 g, 28.1 mmol) in DMF (100 ml) was heated to 100°C for 15 hours. The mixture was concentrated *in vacuo* and the residue was diluted in

CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. A solution of the resulting crude *N*-(14-methyl-8-pentadecanonyl)phthalimide, ethylene glycol (3.5 g, 56.4 mmol) and *p*-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol) in benzene (100 ml) was heated at reflux under a Dean-Stark trap for 20 hours. The mixture was washed with saturated $NaHCO_3$ aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 6.2 g (77%) of **7** as a colorless oil: IR (neat) cm^{-1} 2930, 2860, 1770, 1710, 1607; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 3.68 (2H, t, J=7.0 Hz), 3.92 (4H, s), 7.77 (4H, m); MS *m/z* 386 ($M^+-C_3H_7$).

Anal Calcd for $C_{26}H_{39}NO_4$: C 72.69, H 9.15, N 3.26.
Found: C 72.51, H 9.09, N 3.09.

Ethyl 8,8-Ethylenedioxy-14-methylpentadecanyl Carbamate (**9**)

A solution of **7** (2 g, 4.66 mmol) and 80% hydrazine monohydrate (0.3 ml, 4.84 mmol) in EtOH (15 ml) was heated at reflux for 1.5 hours. The reaction mixture began to solidify within 15 minutes from the start of refluxing. The mixture was cooled to room temperature and CH_2Cl_2 (15 ml) and 3 N KOH (8 ml) were added with stirring. The suspension began to be separated into two clear layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford 8,8-ethylenedioxy-14-methylpentadecanamine (**8**) as a colorless oil. **8**: IR (neat) cm^{-1} 3320, 2930, 2850, 1570; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 2.26 (2H, m), 2.67 (2H, m), 3.92 (4H, s); MS *m/z* 186 ($M^+-C_8H_{17}$), 185 ($M^+-C_7H_{16}N$).

The crude product was dissolved in $CHCl_3$ (10 ml). To the stirred solution at 0°C were added pyridine (0.57 ml, 7.05 mmol) and ethyl chloroformate (0.54 ml, 5.65 mmol). Stirring was continued for 1 hour and then the mixture was poured into ice-saturated $NaHCO_3$ aqueous solution. The product was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 1.6 g (93%) of **9** as a colorless oil. IR (neat) cm^{-1}, 3340, 2930, 2860, 1700; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 1.23 (3H, t, J=7.1 Hz), 3.14 (2H, br q, J=6.4 Hz), 3.92 (4H, s), 4.10 (2H, q, J=7.1 Hz), 4.77 (1H, br t); MS *m/z* 328 ($M^+-C_3H_7$).

Anal Calcd for $C_{21}H_{41}NO_4$: C 67.88, H 11.12, N 3.77.
Found: C 67.97, H 11.02, N 3.87.

8,8-Ethylenedioxy-14-methyl-1-(methyl-*O*,*N*,*N*-azoxy)pentadecane (**12**)

To a vigorously stirred suspension of **9** (3 g, 8.07 mmol) and $NaHCO_3$ (6 g, 71.4 mmol) in dry ethyl ether (15 ml) at −40°C under nitrogen was added dropwise a solution of N_2O_4 (5.5 g, 59.8 mmol) in ethyl ether (4 ml). After the addition was complete, the reaction mixture was stirred at −20°C for 30 minutes and then poured into ice-saturated $NaHCO_3$ aqueous solution. The ethereal layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* under 30°C to afford the *N*-nitroso product (**10**) as yellow oil, which was stored at −80°C and was used for the next reaction without further purification. To a suspension of potassium *tert*-butoxide (1.36 g, 12.1 mmol) in ethyl ether (20 ml) at −40°C under nitrogen was added dropwise a solution of the *N*-nitroso product in ethyl ether (6 ml). After the mixture was stirred at −25°C for 1 hour, the solvent was removed under 0°C *in vacuo*. To the residue were added HMPA (20 ml) and methyl iodide (5 ml, 80.3 mmol) and then the resulting mixture was stirred at room temperature for 20 hours. The solvents were removed *in vacuo* and the residue was diluted with CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 1.1 g (40%) of **12** as a slightly yellow oil: IR (neat) cm^{-1} 2910, 2850, 1510; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 3.39 (2H, br t, J=6.9 Hz), 3.92 (4H, s), 4.06 (3H, t, J=1.5 Hz); MS *m/z* 325 (M^+-OH).

Anal Calcd for $C_{19}H_{38}N_2O_3$: C 66.63, H 11.18, N 8.18.
Found: C 66.56, H 11.11, N 8.10.

8,8-Ethylenedioxy-14-methyl-1-(phenylselenomethyl-*O*,*N*,*N*-azoxy)pentadecane (**14**)

A solution of LDA was prepared by adding 2 ml (3.28 mmol) of 1.64 M *n*-butyllithium in hexane to diisopropylamine (0.45 ml, 3.21 mmol) in THF (4 ml). The solution was stirred and cooled to 0°C, and a

solution of **12** (1 g, 2.92 mmol) in THF (2 ml) was added. After 30 minutes, a solution of diphenyl diselenide (1.37 g, 4.39 mmol) and HMPA (1 ml, 5.75 mmol) in THF (1 ml) was added to the resulting solution of the carbanion. Stirring was continued for 90 minutes at 0°C. The reaction mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 772 mg (53%) of **14** as a slightly yellow oil: IR (neat) cm^{-1} 3070, 2950, 2880, 1580, 1502; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.4 Hz), 3.36 (2H, t, J=6.7 Hz), 3.92 (4H, s), 5.40 (2H, s), 7.3 (3H, m), 7.6 (2H, m); MS m/z 385 ($M^+ - C_8H_{17}$).

Anal Calcd for $C_{25}H_{42}N_2O_3Se$: C 60.35, H 8.51, N 5.63.
Found: C 60.28, H 8.47, N 5.72.

8,8-Ethylenedioxy-14-methyl-1-(1-phenylselenoethyl-*O*,*N*,*N*-azoxy)pentadecane (**15**)

A solution of LDA prepared from 1.25 ml (1.91 mmol) of 1.53 M *n*-butyllithium in hexane and diisopropylamine (0.27 ml, 1.93 mmol) in THF (2.5 ml) was cooled to −78°C and a solution of **14** (860 mg, 1.73 mmol) in THF (1 ml) was added dropwise. After 1 hour, HMPA (0.3 ml, 1.72 mmol) and methyl iodide (0.32 ml, 5.14 mmol) were added. After stirring at −78°C for 1 hour, the mixture was allowed to warm up to room temperature. After 20 hours the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 450 mg (51%) of **15** as a slightly yellow oil: IR (neat) cm^{-1} 3050, 2910, 2850, 1575, 1498; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 1.84 (3H, d, J=7.1 Hz), 3.30 (2H, t, J=6.9 Hz), 3.92 (4H, s), 5.64 (1H, q, J=7.1 Hz), 7.3 (3H, m), 7.6 (2H, m); MS m/z 399 ($M^+ - C_8H_{17}$).

Anal Calcd for $C_{26}H_{44}N_2O_3Se$: C 61.04, H 8.67, N 5.48.
Found: C 60.84, H 8.70, N 5.59.

Jietacin A (**1**)

To a solution of **15** (670 mg, 1.31 mmol) in acetone (5 ml) was added 2 N HCl (0.5 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated $NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (5 ml) and cooled to 0°C. To the stirred solution was added 35% H_2O_2 (0.5 ml). The resulting mixture was stirred for 30 minutes at 0°C, warmed to room temperature, and stirred for 2 hours. After addition of water, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 3.35 mg (82%) of jietacin A (**1**), mp 39°C as white crystals: Spectral data (^1H and ^{13}C NMR, IR, UV, mass spectral) were identical in all respects with those of an authentic sample.[1,2]

8,8-Ethylenedioxy-14-methyl-1-(1-phenylselenopropyl-*O*,*N*,*N*-azoxy)pentadecane (**25**)

A solution of LDA prepared from 0.265 ml (0.42 mmol) of 1.64 M *n*-butyllithium in hexane and diisopropylamine (0.061 ml, 0.44 mmol) in THF (0.5 ml) was cooled to −78°C and a solution of **14** (195 mg, 0.39 mmol) in THF (0.4 ml) was added dropwise. After 1 hour, HMPA (0.137 ml, 0.79 mmol) and ethyl bromide (0.09 ml, 1.21 mmol) were added. After stirring at −78°C for 1 hour, the mixture was allowed to warm up to room temperature. After 20 hours the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 36 mg of **14** and 75 mg (36%) of **25** as a slightly yellow oil: IR (neat) cm^{-1} 3075, 2940, 2870, 1580, 1502; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 0.98 (3H, t, J=7.4 Hz), 2.11 (2H, m), 3.32 (2H, t, J=6.6 Hz), 3.92 (4H, s), 5.41 (1H, dd, J=8.8 and 6.1 Hz), 7.3 (3H, m), 7.6 (2H, m); MS m/z 526 (M^+).

Anal Calcd for $C_{27}H_{46}N_2O_3Se$: C 61.70, H 8.82, N 5.33.
Found: C 61.74, H 8.88, N 5.45.

14-Methyl-1-(1-propenyl-*O*,*N*,*N*-azoxy)-8-pentadecanone (**21**)

To a solution of **25** (74 mg, 0.14 mmol) in acetone (2 ml) was added 2 N HCl (0.5 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated

$NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (2 ml) and cooled to 0°C. To the stirred solution was added 35% H_2O_2 (0.3 ml). The resulting mixture was stirred for 30 minutes at 0°C, warmed to room temperature, and stirred for 2 hours. After addition of water, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 37 mg (81%) of **21**, mp 50~51°C as white crystals: IR (neat) cm^{-1} 3100, 2930, 2870, 1705, 1465; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 1.87 (3H, d, J=5.2 Hz), 2.39 (4H, t, J=7.0 Hz), 3.51 (2H, t, J=6.7 Hz), 7.0 (2H, m); MS m/z 307 (M^+-17).

Anal Calcd for $C_{19}H_{36}N_2O_2$: C 70.33, H 11.18, N 8.63.
Found: C 70.17, H 11.15, N 8.68.

8,8-Ethylenedioxy-14-methyl-1-(1-phenylseleno-3-butenyl-*O*,*N*,*N*-azoxy)pentadecane (**26**)

A solution of LDA prepared from 0.24 ml (0.39 mmol) of 1.64 M *n*-butyllithium in hexane and diisopropylamine (0.056 ml, 0.40 mmol) in THF (1 ml) was cooled to −78°C and a solution of **14** (181 mg, 0.36 mmol) in THF (0.8 ml) was added dropwise. After 1 hour, HMPA (0.127 ml, 0.73 mmol) and allyl bromide (0.1 ml, 1.16 mmol) were added. After stirring at −78°C for 1 hour, the mixture was allowed to warm up to room temperature. After 3 hours, the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 27 mg of **14** and 67 mg (34%) of **26** as a slightly yellow oil: IR (neat) cm^{-1} 3070, 2940, 2870, 1642, 1580, 1500; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 2.8 (2H, m), 3.30 (2H, t, J=6.6 Hz), 3.92 (4H, s), 5.51 (1H, dd, J=8.8 and 6.1 Hz), 5.7 (3H, m), 7.3 (3H, m), 7.6 (2H, m); MS m/z 538 (M^+).

Anal Calcd for $C_{28}H_{46}N_2O_3Se$: C 62.55, H 8.62, N 5.21.
Found: C 62.45, H 8.62, N 5.36.

14-Methyl-1-(1,3-butadienyl-*O*,*N*,*N*-azoxy)-8-pentadecanone (**22**)

To a solution of **26** (86 mg, 0.16 mmol) in acetone (2 ml) was added 2 N HCl (0.2 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated $NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (2 ml) and cooled to 0°C. To the stirred solution was added 35% H_2O_2 (0.3 ml). The resulting mixture was stirred for 30 minutes at 0°C, warmed to room temperature, and stirred for 2 hours. After addition of water, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 44 mg (82%) of **22**, mp 53~54°C as white crystals: IR (neat) cm^{-1} 3080, 2930, 2850, 1702, 1600, 1460; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 2.39 (4H, t, J=7.0 Hz), 3.54 (2H, t, J=6.7 Hz), 5.52 (1H, d, J=10.2 Hz), 5.66 (1H, dd, J=16.9 Hz), 6.46 (1H, dt, J=16.9 and 10.2 Hz), 7.08 (1H, d, J=13.3 Hz), 7.40 (1H, dd, J=13.3 and 10.2 Hz); MS m/z 319 (M^+-OH).

Anal Calcd for $C_{20}H_{36}N_2O_2$: C 71.38, H 10.78, N 8.32.
Found: C 71.42, H 70.80, N 8.11.

8,8-Ethylenedioxy-14-methyl-1-(1-phenylseleno-3-butynyl-*O*,*N*,*N*-azoxy)pentadecane (**27**)

A solution of LDA prepared from 0.25 ml (0.41 mmol) of 1.64 M *n*-butyllithium in hexane and diisopropylamine (0.058 ml, 0.41 mmol) in THF (0.5 ml) was cooled to −78°C and a solution of **14** (186 mg, 0.37 mmol) in THF (0.4 ml) was added dropwise. After 1 hour, HMPA (0.13 ml, 0.75 mmol) and propargyl bromide (0.1 ml, 1.12 mmol) were added. After stirring at −78°C for 1 hour, the mixture was allowed to warm up to room temperature. After 3 hours, the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 64 mg of **14** and 52 mg (26%) of **27** as a slightly yellow oil: IR (neat) cm^{-1} 3275, 2925, 2850, 1575, 1500; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 2.10 (1H, t, J=2.6 Hz), 3.0 (2H, m), 3.36 (2H, t, J=6.6 Hz), 3.92 (4H, s), 5.56 (1H, dd, J=8.5 and 6.5 Hz), 7.3 (3H, m), 7.6 (2H, m); MS m/z 536 (M^+).

Anal Calcd for $C_{28}H_{44}N_2O_3Se$: C 62.79, H 8.28, N 5.23.
Found: C 62.80, H 8.30, N 5.13.

14-Methyl-1-(1-buten-3-ynyl-*O*,*N*,*N*-azoxy)-8-pentadecanone (**24**)

To a solution of **27** (50 mg, 0.093 mmol) in acetone (2 ml) was added 2 N HCl (0.2 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated $NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (2 ml) and cooled to 0°C. To the stirred solution was added 35% H_2O_2 (0.3 ml). The resulting mixture was stirred for 30 minutes at 0°C, warmed to room temperature, and stirred for 2 hours. After addition of water, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 25 mg (80%) of **24**, mp 58~59°C as white crystals: IR (neat) cm^{-1} 3300, 3120, 2930, 2860, 1705, 1462; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 2.39 (4H, t, J=7.1 Hz), 3.34 (1H, d, J=2.5 Hz), 3.54 (2H, t, J=6.7 Hz), 6.88 (1H, dd, J=14.0 and 2.5 Hz), 7.36 (1H, d, J=14.0 Hz); MS m/z 317 (M^+-OH).

Anal Calcd for $C_{20}H_{34}N_2O_2$: C 71.81, H 10.24, N 8.37.
Found: C 71.66, H 10.07, N 8.51.

8,8-Ethylenedioxy-14-methyl-1-(2-phenyl-1-phenylselenoethyl-*O*,*N*,*N*-azoxy)pentadecane (**28**)

A solution of LDA prepared from 0.31 ml (0.51 mmol) of 1.64 M *n*-butyllithium in hexane and diisopropylamine (0.071 ml, 0.51 mmol) in THF (0.5 ml) was cooled to −78°C and a solution of **14** (230 mg, 0.46 mmol) in THF (0.6 ml) was added dropwise. After 1 hour, HMPA (0.16 ml, 0.92 mmol) and benzyl bromide (0.17 ml, 1.43 mmol) were added. After stirring at −78°C for 1 hour, the mixture was allowed to warm up to room temperature. After 20 hours, the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 45 mg of **14** and 48 mg (18%) of **28** as a slightly yellow oil: IR (neat) cm^{-1} 3060, 3030, 2930, 2860, 1578, 1490; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 3.17 (2H, t, J=6.6 Hz), 3.42 (2H, ABX, J_{AB}=14.3 Hz, J_{AX}=5.9 Hz, J_{BX}=9.6 Hz), 3.92 (4H, s), 5.68 (1H, dd, J=9.6 and 5.9 Hz), 7.21 (5H, s), 7.3 (3H, m), 7.6 (2H, m); MS m/z 588 (M^+).

Anal Calcd for $C_{32}H_{48}N_2O_3Se$: C 65.40, H 8.23, N 4.77.
Found: C 65.14, H 8.30, N 5.05.

14-Methyl-1-(styryl-*O*,*N*,*N*-azoxy)-8-pentadecanone (**23**)

To a solution of **28** (47 mg, 0.08 mmol) in acetone (2 ml) was added 2 N HCl (0.2 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated $NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (2 ml) and cooled to 0°C. To the stirred solution was added 35% H_2O_2 (0.3 ml). The resulting mixture was stirred for 30 minutes at 0°C, warmed to room temperature, and stirred for 2 hours. After addition of water, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, developing with hexane-ethyl acetate (10:1) to afford 25 mg (81%) of **23**, mp 63~65°C as white crystals: IR (neat) cm^{-1} 2930, 2860, 1702, 1640, 1460; ^1H NMR ($CDCl_3$) δ 0.85 (6H, d, J=6.1 Hz), 2.39 (4H, t, J=7.1 Hz), 3.60 (2H, t, J=6.9 Hz), 7.46 (5H, m), 7.54 (1H, d, J=14.0 Hz), 7.82 (1H, d, J=14.0 Hz); MS m/z 386 (M^+).

Anal Calcd for $C_{24}H_{38}N_2O_2$: C 74.57, H 9.91, N 7.25.
Found: C 74.57, H 9.83, N 7.00.

14-Methyl-1-(methyl-*O*,*N*,*N*-azoxy)-8-pentadecanone (**19**)

To a solution of **12** (65 mg, 0.19 mmol) in acetone (2 ml) was added 2 N HCl (0.2 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated $NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 49 mg (87%) of **19** as a colorless oil: IR (neat), cm^{-1} 2920, 2850,

1705, 1508; ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 2.39 (4H, t, J=7.0 Hz), 3.39 (2H, br t, J=6.9 Hz), 4.05 (3H, br s); MS m/z 281 ($M^+ - OH$).

Anal Calcd for $C_{17}H_{34}N_2O_2$: C 68.41, H 11.48, N 9.39.
Found: C 68.35, H 11.45, N 9.13.

8,8-Ethylenedioxy-14-methyl-1-(ethyl-*O*,*N*,*N*-azoxy)pentadecane (**11**)

To a vigorously stirred suspension of **9** (3 g, 8.07 mmol) and $NaHCO_3$ (6 g, 71.4 mmol) in dry ethyl ether (15 ml) at −40°C under nitrogen was added dropwise a solution of N_2O_4 (5.5 g, 59.8 mmol) in ethyl ether (4 ml). After the addition was complete, the reaction mixture was stirred at −20°C for 30 minutes and then poured into ice-saturated $NaHCO_3$ aqueous solution. The ethereal layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* under 30°C to afford the *N*-nitroso product (**10**) as yellow oil, which was used for the next reaction without further purification. To a suspension of potassium *tert*-butoxide (1.36 g, 12.1 mmol) in ethyl ether (20 ml) at −40°C under nitrogen was added dropwise a solution of the *N*-nitroso product in ethyl ether (6 ml). After the mixture was stirred at −25°C for 1 hour, the solvent was removed under 0°C *in vacuo*. To the residue were added HMPA (20 ml) and ethyl iodide (5 ml, 62.5 mmol) and then the resulting mixture was stirred at room temperature for 20 hours. The solvents were removed *in vacuo* and the residue was diluted with CH_2Cl_2. The solution was washed with water, dried (Na_2SO_2) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 1.1 g (38%) of **11** as a slightly yellow oil: IR (neat) cm^{-1} 2930, 2860, 1510; ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 1.51 (3H, t, J=7.4 Hz), 3.39 (2H, t, J=6.9 Hz), 3.92 (4H, s), 4.19 (2H, q, J=7.4 Hz); MS m/z 339 ($M^+ - OH$).

Anal Calcd for $C_{20}H_{40}N_2O_3$: C 67.37, H 11.31, N 7.86.
Found: C 67.40, H 11.22, N 8.12.

14-Methyl-1-(ethyl-*O*,*N*,*N*-azoxy)-8-pentadecanone (**20**)

To a solution of **11** (55 mg, 0.15 mmol) in acetone (2 ml) was added 2 N HCl (0.2 ml) and the resulting mixture was stirred for 30 minutes at room temperature. After the mixture was neutralized with saturated $NaHCO_3$ aqueous solution, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afford 41 mg (85%) of **20** as a colorless oil: IR (neat) cm^{-1} 2930, 2860, 1705, 1502; ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 1.51 (3H, t, J=7.4 Hz), 2.39 (4H, t, J=7.1 Hz), 3.39 (2H, br t, J=6.9 Hz), 4.19 (2H, br q, J=7.4 Hz); MS m/z 295 ($M^+ - OH$).

Anal Calcd for $C_{18}H_{36}N_2O_2$: C 69.18, H 11.61, N 8.96.
Found: C 69.24, H 11.66, N 8.82.

8-Hydroxy-14-methyl-1-(vinyl-*O*,*N*,*N*-azoxy)pentadecane (**16**)

To a solution of jietacin A (**1**) (46 mg, 0.15 mmol) in ethanol (2 ml) at 0°C was added $NaBH_4$ (5 mg, 0.13 mmol) and the resulting mixture was stirred for 2 hours. After the reaction was quenched by addition of acetic acid, water was added to the mixture and the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (5:1) to afford 38 mg (82%) of **16** as a colorless oil: IR (neat) cm^{-1} 3400, 2940, 2860, 1470; ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.1 Hz), 3.55 (2H, t, J=7.1 Hz), 5.50 (1H, d, J=7.7 Hz), 6.41 (1H, d, J=15.3 Hz), 7.11 (1H, dd, J=15.3 and 7.7 Hz); MS m/z 295 ($M^+ - OH$).

Anal Calcd for $C_{18}H_{36}N_2O_2$: C 69.18, H 11.61, N 8.96.
Found: C 69.32, H 11.71, N 9.00.

Ethyl 6-Methylheptyl Carbamate (**29**)

To a stirred solution of 6-methylheptylamine (895 ml, 6.92 mmol) in $CHCl_3$ (10 ml) at 0°C were added pyridine (1.5 ml, 18.5 mmol) and ethyl chloroformate (1.21 ml, 12.7 mmol). Stirring was continued for 1 hour and then the mixture was poured into ice-saturated $NaHCO_3$ aqueous solution. The product was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (1:1) to afford 1.2 g (86%) of **29** as a colorless oil: IR (neat) cm^{-1} 3340, 2960, 2930, 2870, 1700, 1535; ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, d,

J=6.1 Hz), 1.24 (3H, t, J=7.1 Hz), 3.16 (2H, q, J=6.1 Hz), 4.11 (2H, q, J=7.1 Hz); MS m/z 201 (M^+).

Anal Calcd for $C_{11}H_{23}NO_2$: C 65.63, H 11.52, N 6.96.
Found: C 65.74, H 11.64, N 6.89.

6-Methyl-1-(methyl-*O*,*N*,*N*-azoxy)heptane (**30**)

To a vigorously stirred suspension of **29** (3 g, 14.9 mmol) and $NaHCO_3$ (6 g, 71.4 mmol) in dry ethyl ether (15 ml) at −40°C under nitrogen was added dropwise a solution of N_2O_4 (5.9 g, 64.1 mmol) in ethyl ether (4 ml). After the addition was complete, the reaction mixture was stirred at −20°C for 30 minutes and then poured into ice-saturated $NaHCO_3$ aqueous solution. The ethereal layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* under 30°C to afford the *N*-nitroso product as yellow oil, which was used for the next reaction without further purification. To a suspension of potassium *tert*-butoxide (3.43 g, 30.6 mmol) in ethyl ether (12 ml) at −40°C under nitrogen was added dropwise a solution of the *N*-nitroso product in ethyl ether (5 ml). After the mixture was stirred at −25°C for 1 hour, the solvent was removed under 0°C *in vacuo*. To the residue were added HMPA (25 ml) and methyl iodide (6 ml, 96.4 mmol) and then the resulting mixture was stirred at room temperature for 20 hours. The solvents were removed *in vacuo* and the residue was diluted with CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane - ethyl acetate (10 : 1) to afford 975 mg (38%) of **30** as a slightly yellow oil: IR (neat) cm^{-1} 2950, 2920, 2850, 1512; ^1H NMR ($CDCl_3$) δ 0.87 (6H, d, J=6.1 Hz), 3.39 (2H, dt, J=6.9 and 1.5 Hz), 4.06 (3H, t, J=1.5 Hz); MS m/z 155 ($M^+ - OH$).

Anal Calcd for $C_9H_{20}N_2O$: C 62.75, H 11.70, N 16.26.
Found: C 62.84, H 11.93, N 15.97.

6-Methyl-1-(phenylselenomethyl-*O*,*N*,*N*-azoxy)heptane (**31**)

A solution of LDA was prepared by adding 2.13 ml (3.49 mmol) of 1.64 M *n*-butyllithium in hexane to diisopropylamine (0.49 ml, 3.50 mmol) in THF (4 ml). The solution was stirred and cooled to 0°C, and a solution of **30** (550 mg, 3.19 mmol) in THF (4 ml) was added. After 30 minutes, a solution of diphenyl diselenide (1.49 g, 4.77 mmol) and HMPA (0.61 ml, 3.51 mmol) in THF (0.6 ml) was added to the resulting solution of the carbanion. Stirring was continued for 90 minutes at 0°C. The reaction mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane - ethyl acetate (10 : 1) to afford 570 mg (55%) of **31** as a slightly yellow oil: IR (neat) cm^{-1} 3050, 2940, 2920, 2850, 1575, 1495; ^1H NMR ($CDCl_3$) δ 0.87 (6H, d, J=6.8 Hz), 3.36 (2H, t, J=7.3 Hz), 5.39 (2H, s), 7.3 (3H, m), 7.6 (2H, m); MS m/z 171 ($M^+ - SePh$).

Anal Calcd for $C_{15}H_{24}N_2OSe$: C 55.04, H 7.39, N 8.56.
Found: C 55.14, H 7.32, N 8.46.

6-Methyl-1-(1-phenylselenoethyl-*O*,*N*,*N*-azoxy)heptane (**32**)

A solution of LDA prepared from 1.04 ml (1.71 mmol) of 1.64 M *n*-butyllithium in hexane and diisopropylamine (0.24 ml, 1.71 mmol) in THF (2 ml) was cooled to −78°C and a solution of **31** (510 mg, 1.56 mmol) in THF (2 ml) was added dropwise. After 1 hour, HMPA (0.41 ml, 2.36 mmol) and methyl iodide (0.31 ml, 4.98 mmol) were added. After stirring at −78°C for 1 hour, the mixture was allowed to warm up to room temperature. After 2 hours, the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl aqueous solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane - ethyl acetate (10 : 1) to afford 390 mg (73%) of **32** as a slightly yellow oil: IR (neat) cm^{-1} 3040, 2930, 2900, 2840, 1570, 1492; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J=6.4 Hz), 1.84 (3H, d, J=6.9 Hz), 3.30 (2H, t, J=6.7 Hz), 5.64 (1H, q, J=6.9 Hz), 7.3 (3H, m), 7.6 (2H, m); MS m/z 341 (M^+).

Anal Calcd for $C_{16}H_{26}N_2OSe$: C 56.30, H 7.68, N 8.21.
Found: C 56.42, H 7.38, N 7.92.

6-Methyl-1-(vinyl-*O*,*N*,*N*-azoxy)heptane (**18**)

To a stirred solution of **32** (360 mg, 1.05 mmol) in CH_2Cl_2 (5 ml) at 0°C was added 35% H_2O_2 (0.5 ml). The resulting mixture was stirred for 30 minutes at 0°C, warmed to room temperature, and stirred for 2

hours. After addition of water, the product was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (20:1) to afford 170 mg (87%) of **18** as a colorless oil: IR (neat) cm^{-1} 3080, 2930, 2900, 2850, 1635, 1465; ^1H NMR ($CDCl_3$) δ 0.87 (6H, d, J=6.1 Hz), 3.55 (2H, t, J=6.9 Hz), 5.49 (1H, t, J=7.6 Hz), 6.41 (1H, d, J=15.0 Hz), 7.12 (1H, dd, J=15.0 and 7.6 Hz); MS m/z 167 ($M^+ - OH$).

Anal Calcd for $C_{10}H_{20}N_2O$: C 65.18, H 10.94, N 15.20.
Found: C 65.18, H 10.97, N 15.19.

Nematocidal Activity

The nematocidal activity against the pine wood nematode *B. lignicolus* was assayed as described previously.[7]

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