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Bis(alkylthio)carbenes as Novel Reagents for Organic Synthesis

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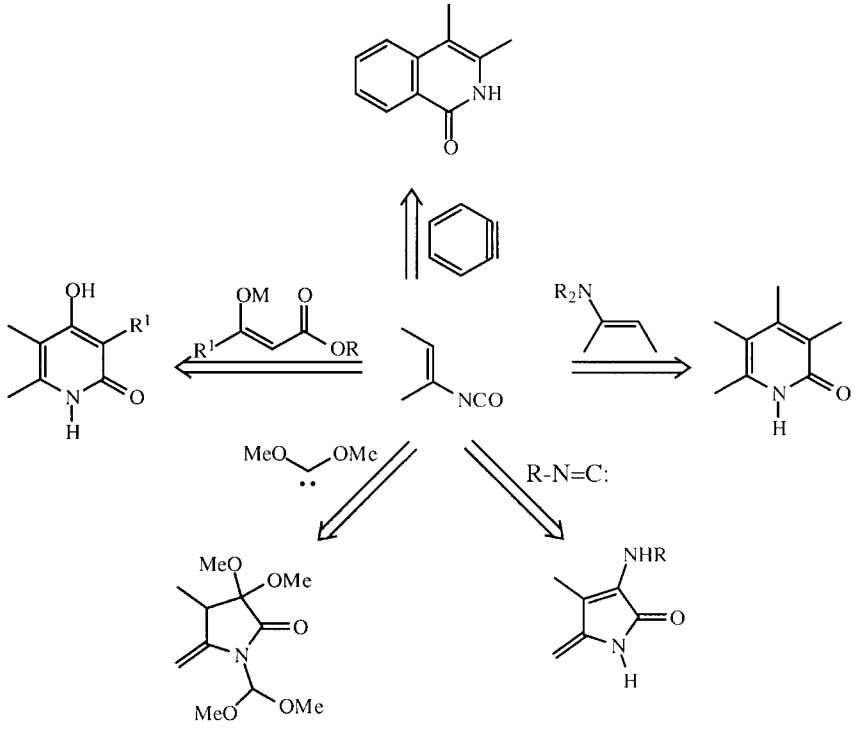
Abstract—Bis(alkylthio)carbenes have been shown to be a useful class of reactive intermediates for applications to organic synthesis. Substituted hydroindolones, isatins and hydroquinolones can be prepared by the addition of these carbenes to vinyl isocyanates.

Vinyl isocyanates are versatile functions that can undergo efficient reaction with a wide variety of nucleophilic addends to deliver a range of product structures.[1] Pyridones of various types can be assembled using enamines,[2a] benzynes[2b] and ester enolates as reaction partners with isocyanates. Furthermore, pyrrolidone structures can be accessed by reaction with various 1,1-dipolar equivalents such as alkyl isocyanides[3a] and dimethoxycarbene[3b] (Scheme 1).

The products of these novel transformations are rich in functionality and, consequently, are well-suited to various synthetically useful post-cycloaddition manipulations. Approaches into the basic ring systems of a number of alkaloid targets have been achieved in this fashion, as have several total synthetic efforts. Entries into the erythrina,[4a] galanthan,[4a] camptothecin[4b] and stemona[4c] systems and total syntheses of several amaryllidaceae[5a,b] and narciclasine[5c] alkaloids have been accomplished



Scheme 1.

Keywords: carbenes; cycloadditions; isocyanates.

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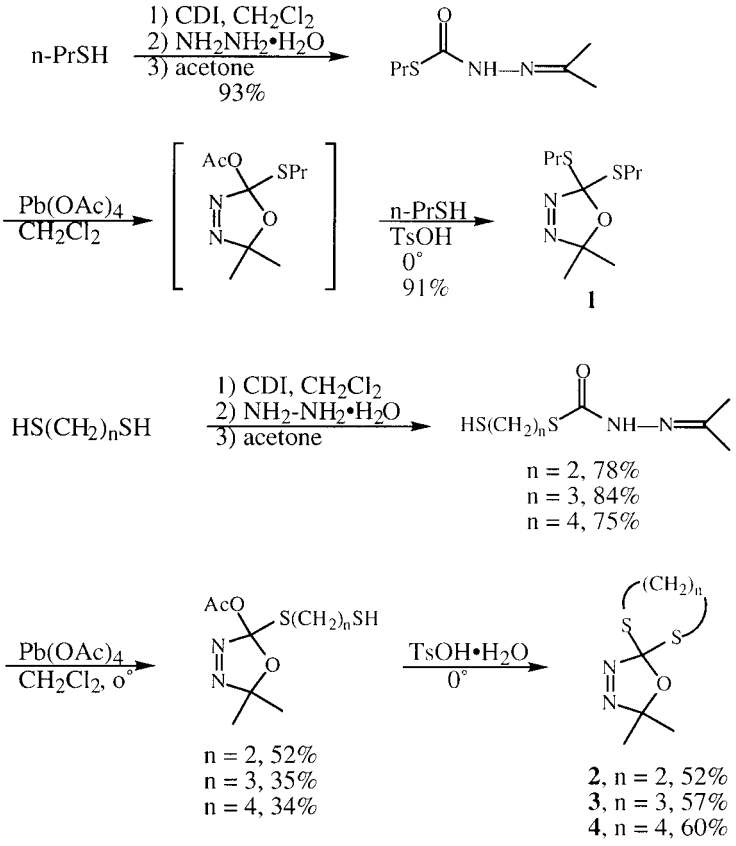
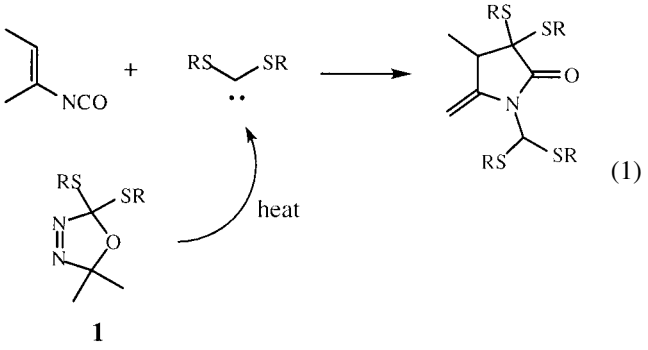


Scheme 2.

employing vinyl isocyanate cyclization technology as the key strategy-level transformation.



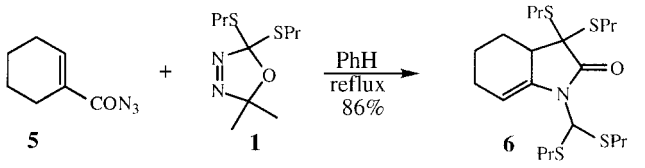
(1)

Recently, bis(alkylthio)carbenes have been added to the list of nucleophilic carbenes that are useful 1,1-dipole equivalents in reactions with vinyl isocyanates, often displaying reactivity that is somewhat different than other carbenes studied to date.[6] An extensive examination of these interesting reactive intermediates has been conducted in our laboratory, and a generalized reaction scheme is shown in Eq. (1).

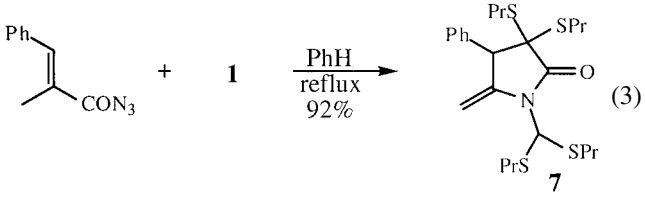
Key to the success of this endeavor was the accessibility of the requisite dithiooxadiazoline (**1**) as the precursor to the carbene. While the corresponding dialkoxy-substituted heterocycles were readily available using the procedures of Warkentin,[7,8] the dithio species initially proved to be somewhat elusive. After considerable experimentation, the sequences outlined in Scheme 2 were found to provide suitable quantities of various dithiocarbene precursors. Thus, *N′*-isopropylidenehydrazinecarbothioic acid *S*-propyl ester was prepared by sequential treatment of excess 1-propanethiol with CDI, hydrazine and acetone. Exposure of this material to $Pb(OAc)_4$ afforded the corresponding mixed *O*,*S*-oxadiazoline, paralleling previous work.[7a] Exchange of the acetoxy substituent for a second propylthio group was achieved only under precisely controlled conditions employing 5 equiv. of PrSH in the presence of a catalytic amount of $TsOH{\cdot}H_2O$ at 0°C. This provided the crucial, thermally labile carbene precursor **1** in excellent yield. A closely related process was developed to make various cyclic species (**2**–**4**) as well (Scheme 2).

With a number of carbene precursors in hand, attention turned to exploring the reactions of these species with vinyl isocyanates. In most instances in situ conversion of the corresponding acyl azide into the reactive isocyanate followed by addition of **1** was the most convenient procedure. Thus, heating precursor **1** (2.5 equiv.) in the presence of the isocyanate derived from acyl azide **5** in refluxing benzene afforded the expected 2:1 adduct **6** in excellent yield. This result closely parallels our previous observations in the corresponding dimethoxy carbene series.[3b] The insertion of the second equivalent of carbene at the enamide nitrogen is interesting and probably involves initial deprotonation of the relatively acidic amide proton followed by re-addition of the resultant dithioxonium ion, a

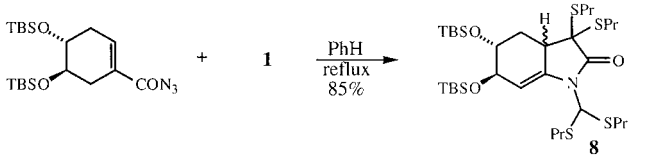
process not without relevant precedent.[9] Additional examples of typical reactions in this series are shown in Eqs. (3)–(5).



5 1 6 (2)



7 (3)



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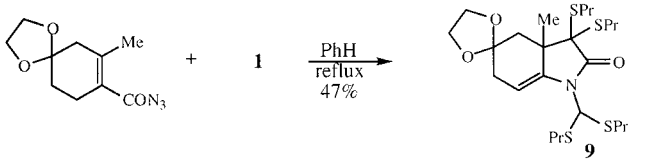


9 (5)

Cyclic dithiocarbenes were also reacted with various vinyl isocyanates to give, in most cases, products paralleling those shown above. The exception was when oxadiazoline **2** was heated with the isocyanate derived from acyl azide **5**. In this instance no adducts of any kind could be isolated, a result which was fully anticipated based on the well-known fragmentation of five-membered cyclic carbenes of this general type (Fig. 1).[10] Based on these observations, our attention was refocused on the six- and seven-membered cyclic dithiocarbenes.

The corresponding six- and seven-membered dithiocarbenes behaved well and provided the expected 2:1 adducts in good yields (Eqs. (6)–(11)).

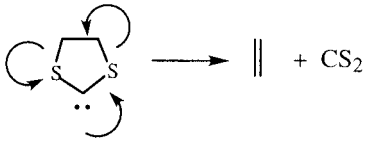
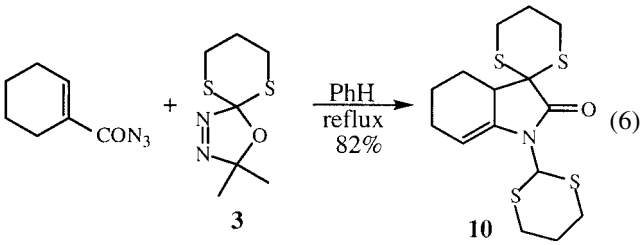
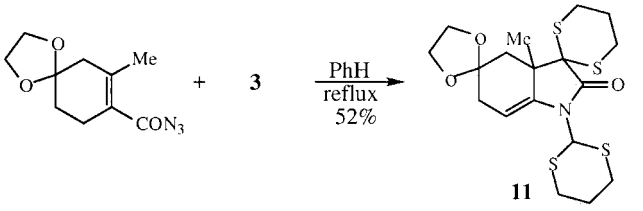


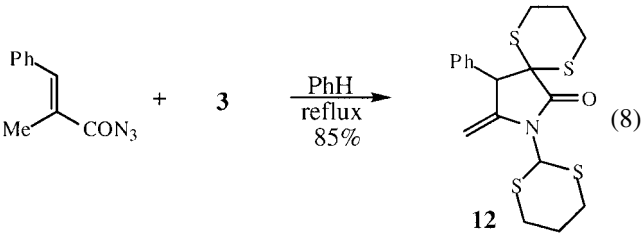
Figure 1. Fragmentation of dithiolane carbenes.



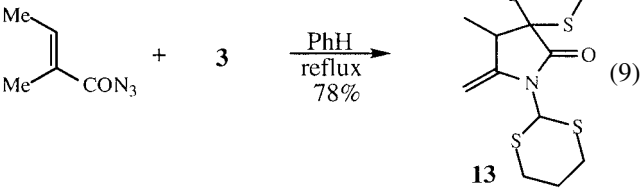
3 10 (6)



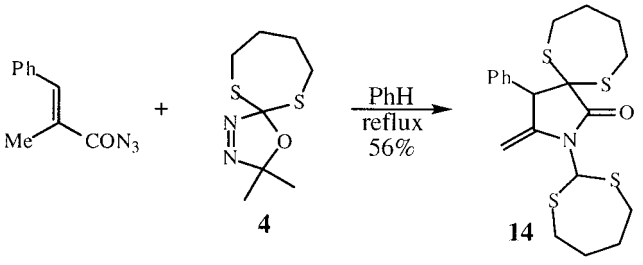
11 (7)



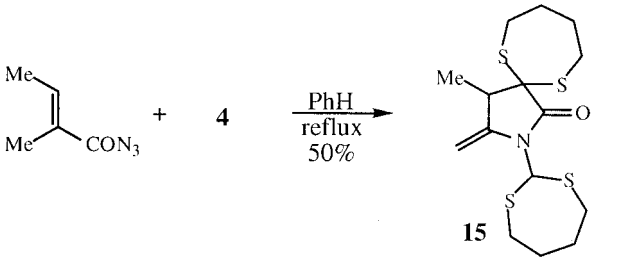
12 (8)



13 (9)



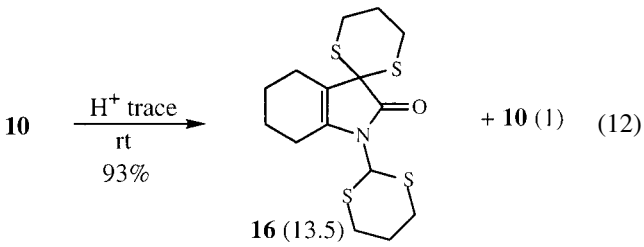
4 14 (10)



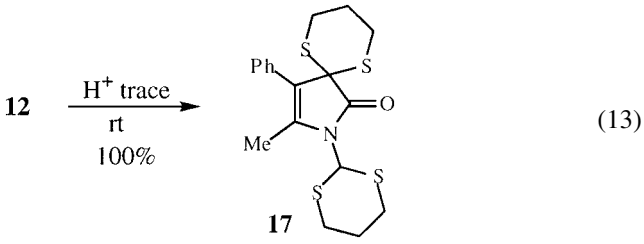
15 (11)

A noteworthy feature of several of the adducts described above came to light when it was observed that rapid equilibration of the enamide double bond to

the ring-fusion position occurred while obtaining ^1H NMR spectra in $CDCl_3$ that was not pre-treated with basic alumina. Interestingly, a similar bond migration was not observed in the dioxo-series, even under more forcing conditions. This difference in behavior may stem from slight conformational dissimilarities in the two series. Examples of this process are shown in the following equations.



(12)

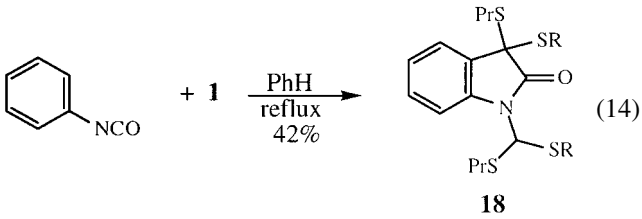


(13)

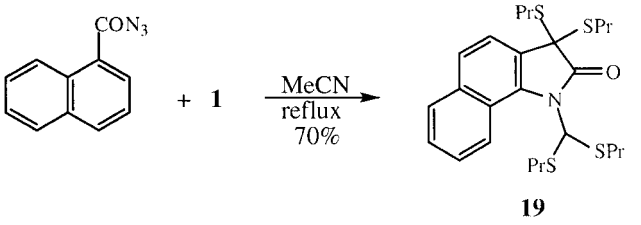
In addition to exhibiting a reaction profile that, by and large, parallels that of the dioxycarbenes, bis(alkylthio)carbenes also undergo several transformations that the oxygen species do not. Notable among these reactions is a [4+1] addition to aryl isocyanates to produce highly substituted isatins, a pathway that is in dramatic contrast to the course of reaction between dimethoxycarbene and phenyl isocyanate, which is known to give hydantoin products via an alternative 2:1 route.[11] This contrasting behavior is summarized in Scheme 3.

To the best of our knowledge only one other example of a [4+1] cycloaddition between an aryl isocyanate and a nucleophilic carbene has been observed.[8b] In the present case, heating phenyl isocyanate with excess bis(*n*-propylthio)oxadiazoline (**1**) in refluxing benzene afforded the 2:1 adduct **18** in serviceable yields.

The reaction is, for the most part, general in scope, and in most instances the reaction can be carried out directly on the corresponding acyl azide precursor. Naphthalene and electron-rich aryl isocyanates provide adducts in reasonable yields, particularly when performed in MeCN as solvent (Eqs. (15)–(17)). However, electron deficient systems are much less effective substrates as evidenced by the inferior yield of the reaction with 4-trifluoromethylphenyl isocyanate (Eq. (18)).



(14)



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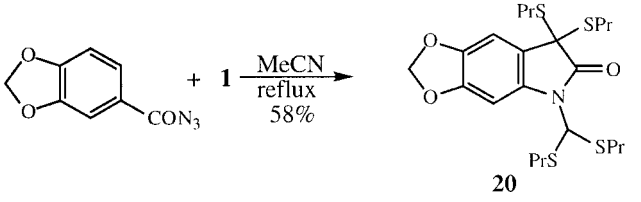
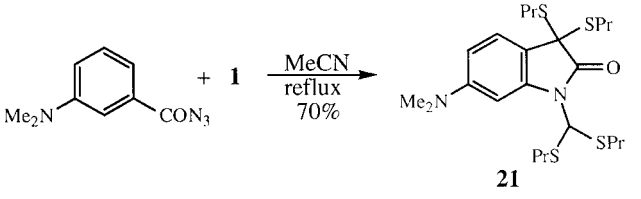
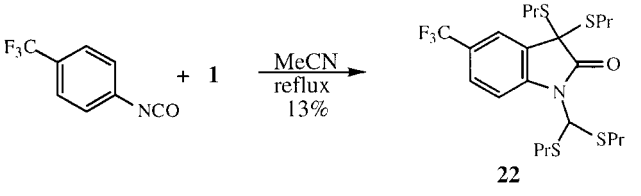


(16)

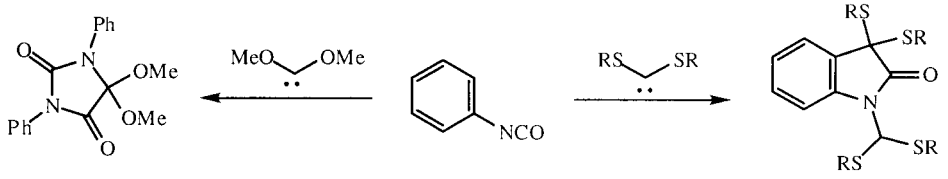


(17)

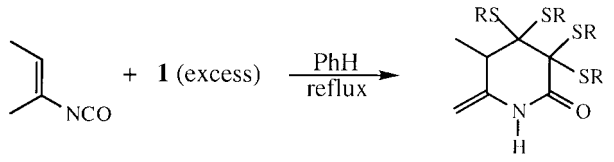


(18)

Yet another remarkable reaction of bis(alkylthio)carbenes with vinyl isocyanates that finds no equivalent in the dioxo series is the novel 2:1 addition process depicted in Scheme 4. In this case, a substituted hydropyridone is produced when a very large excess of oxadiazoline is rapidly decomposed in the presence of an isocyanate partner.

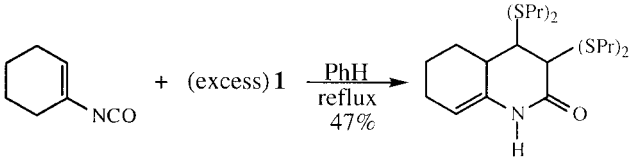


Scheme 3.

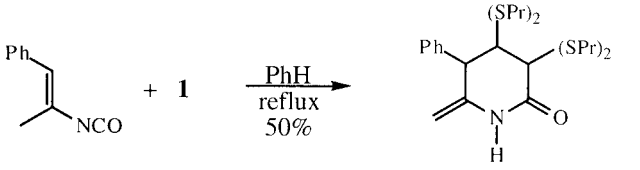


Scheme 4.

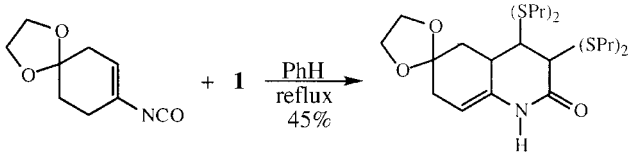
Thus, heating a large excess of **1** with cyclohexenyl isocyanate yields the 2:1 adduct **23** in good yield. It is noteworthy that no insertion of the carbene into the enamide NH bond has occurred. Furthermore, the reaction appears to be as general in scope as the 'normal' addition process described above. Typical examples of these transformations are given in Eqs. (19)–(21).



23 (19)

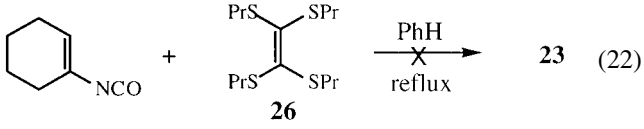


24 (20)



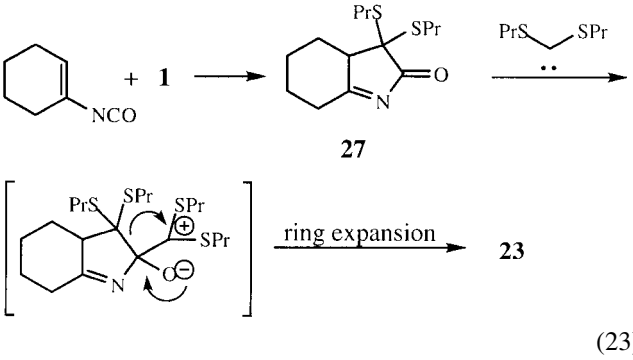
25 (21)

Mechanistically, this is a very intriguing reaction and three plausible pathways can be envisioned. It is possible that with the high concentration of carbene that prevails in these reactions an addition of two carbene units occur to produce dimer **26** which then undergoes a [4+2] cycloaddition across the vinyl isocyanate to give the observed products. This pathway is consistent with the absence of NH insertion and each step is well-presented in other contexts.[12,13] This pathway was tested by intentionally dimerizing the dithiocarbene to give **26** and then heating this species with the isocyanate under standard conditions in an attempt to produce **23**. However, none of this product was obtained, thus discounting this pathway.



26 (22)

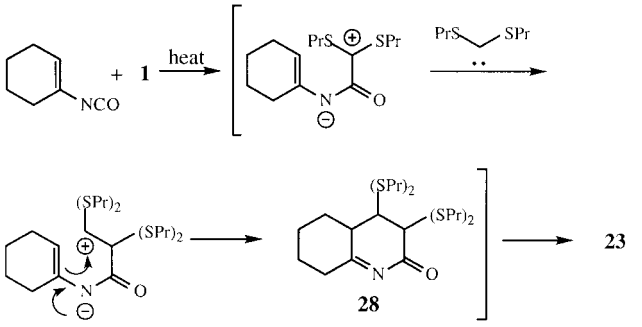
A second possibility involves the addition of carbene to the carbonyl group of the initially formed acylimine **27** followed by ring expansion in a pinacol-like process. Efforts to test this hypothesis experimentally have not been successful, so it cannot be excluded as a viable alternative at this point in time.



27

23 (23)

Finally, a simple double addition pathway can be considered. The keys to the workability of this route would be that the rate for the second carbene addition must be competitive with ring closure of the initially formed 1:1 adduct, and that the acylimine **28** has a longer lifetime than the unreacted carbene.[14] Again no experimental evidence in support of this pathway has been identified, although further work in this direction is currently underway in our laboratory.



28 **23** (24)

In summary, the reactions of bis(alkylthio)carbenes offer numerous synthetic opportunities that are often unique and afford considerable opportunities for application to organic synthesis. Utilization of this methodology in several natural product syntheses is currently being pursued in our laboratory.

Experimental[15]

N′-Isopropylidene-hydrazinecarbothioic acid *S*-propyl ester

To a solution of 1,1′-carbonyldiimidazole (6 g, 37.0 mmol) in CH_2Cl_2 (60 mL) was added 1-propanethiol (6.2 g, 81.4 mmol) at room temperature, the reaction mixture was stirred for 24 h. Hydrazine monohydrate (2.8 g, 55.5 mmol) was then added and stirring was continued for an additional 48 h at room temperature. At this time, acetone (30 mL) was

added and the reaction mixture was stirred for 20 min. The solvent was removed in vacuo and water (30 mL) was added to the residue. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was chromatographed (4:1 Hexanes/EtOAc) to give product (6 g, 93%) as a white solid: mp=74–75°C (Hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.20 (br s, 1H, 2.83 (t, J=7.2 Hz, 2H), 2.02 (s, 3H), 1.88 (s, 3H), 1.63 (m, 2H), 0.98 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 150.7, 30.7, 25.4, 23.3, 16.6, 13.4; IR ($CDCl_3$) ν 3182, 1632 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 174 (M^+, 86.8), 99 (93.9), 43 (100); HRMS calcd for $C_7H_{14}N_2OS$ 174.08267, found 174.0825; Anal. calcd for $C_7H_{14}N_2OS$: C, 48.25; H, 8.10; N, 16.09; Found: C, 48.34; H, 7.99; N, 16.21.

2,2-Bis(propylthio)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (1). To a stirred solution of *N′*-isopropylidene-hydrazine-carbothioic acid *S*-propyl ester (3 g, 17.2 mmol) in CH_2Cl_2 (80 mL) at 0°C, was added dropwise a solution of $Pb(OAc)_4$ (9.2 g, 20.7 mmol, Aldrich) in CH_2Cl_2 (20 mL). When the addition was complete, the yellow solution was stirred 3 h at 0°C. The lead precipitate was filtered through Celite 521 and the filter cake was washed with CH_2Cl_2 (3×20 mL). The organic layer was washed with cold aqueous $NaHCO_3$ solution (5% in weight, 100 mL), cold brine (50 mL) and dried over anhydrous $MgSO_4$. The yellow organic layer was filtered through Celite 521 and the solvent was removed in vacuo to afford the nearly pure 2-acetoxy-5,5-dimethyl-2-propylthio-Δ^3-1,3,4-oxadiazoline (quantitative) as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.93 (m, 2H), 2.13 (s, 3H), 1.73 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 1.01 (t, J=7.5 Hz, 3H). The oxadiazoline was used directly in the next step without further purification.

To a cold solution (0°C) of 2-acetoxy-5,5-dimethyl-2-propylthio-Δ^3-1,3,4-oxadiazoline (4 g, 17.2 mmol) in CH_2Cl_2 (30 mL) was added 1-propanethiol (6.56 g, 86.2 mmol) and $TsOH{\cdot}H_2O$ (33 mg, 0.17 mmol). The yellow solution was stirred at 0°C until the starting material was gone (approximately 2 h). When the reaction was complete, the solvent was removed in vacuo at 0°C, and the residue was chromatographed (20:1 Hexanes/EtOAc) using a jacketed column cooled to 0°C. The desired product eluted first and was collected in a 500 mL round bottom flask kept at 0°C. The solvent was removed in vacuo at 0°C and the residue was dried under high vacuum (1 h, 0.3 mmHg, 0°C) to give 2,2-bis(propylthio)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline **1** (3.9 g, 91%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (dt, J=8.4 Hz, J=1.8 Hz, 4H), 1.61 (m, 4H), 1.57 (s, 6H), 0.94 (t, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8.8, 123.4, 33.4, 24.2, 22.9, 13.5. IR (neat) ν 2957, 1449, 1365, 1224, 1048, 822 cm^{-1}. *Note:* The compound is not stable at room temperature, it was stored for weeks as a 1 M solution in hexanes in the freezer (−5°C).

***N*-(1-Aza-2-methylprop-1-enyl)(2′-sulfanylethylthio)-carboxamide**

To a solution of 1,1′-carbonyldiimidazole (6.00 g, 37.0 mmol) in CH_2Cl_2 (60 mL) was added 1,2-ethanedithiol (3.82 mL, 90%, 41.0 mmol) at 0°C under N_2, the reaction was stirred for 24 h at ambient temperature. Hydrazine monohydrate (2.80 g, 55.5 mmol) was then added and stirring was continued for an additional 72 h at room temperature. Then, acetone (30 mL) was added and the reaction mixture was stirred overnight. The solvent was removed in vacuo and the oily residue was chromatographed (3:1 Hexanes/EtOAc) to give the desired product (5.54 g, 78%) as a white solid: mp=111–113°C (Hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (br s 1H), 3.07 (t, J=7.4 Hz, 2H), 2.79–2.70 (m, 2H), 2.03 (s, 3H), 1.90 (s, 3H), 1.63 (t, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 151.1, 32.9, 25.2, 25.1, 16.6; IR (neat) ν 3180, 3063, 1672, 1328, 1218 cm^{-1}; mass spectrum (EI) (rel. int.) 192 (M^+, 4.1 (133 (32.2), 99 (100); HRMS calcd for $C_6H_{12}N_2OS_2$ 192.0391, found 192.0392.

***N*-(1-Aza-2-methylprop-1-enyl)(3′-sulfanylpropylthio)-carboxamide**

To a solution of 1,1′-carbonyldiimidazole (6.00 g, 37.0 mmol) in CH_2Cl_2 (60 mL) was added 1,3-propanedithiol (4.64 mL, 46.4 mmol) at 0°C under N_2, and the reaction was stirred for 24 h at ambient temperature. Hydrazine monohydrate (2.80 g, 55.5 mmol) was then added and stirring was continued for an additional 72 h at room temperature. Acetone (30 mL) was then added and the reaction mixture was stirred overnight. The solvent was removed in vacuo and the oily reside was chromatographed (3:1 hexanes/EtOAc) to give the desired product (6.35 g, 84%) as a white solid: mp=56–58°C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (br s, 1H), 2.98 (t, J=6.8 Hz, 2H), 2.68–2.58 (m, 2H), 2.03 (s, 3H), 1.94 (quin, J=6.8 Hz, 2H), 1.88 (s, 2H), 1.39 (t, J=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 151.1, 34.0, 27.1, 25.4, 23.4, 16.7; IR (neat) ν 3180, 3050, 2910, 1660, 1320, 1210 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 99 (100); mass spectrum (CI) *m/e* (rel. int.) 207 (M^++1, 68), 99 (100); HRMS calcd for $C_7H_{14}N_2OS_2$ 206.0548, found 206.0507.

***N*-(1-Aza-2-methylprop-1-enyl)(4′-sulfanylbutylthio)-carboxamide**

To a solution of 1,1′-carbonyldiimidazole (6.00 g, 37.0 mmol) in CH_2Cl_2 (60 mL) was added 1,4-butanedithiol (5.34 mL, 90%, 40.7 mmol) at 0°C under N_2, the reaction was stirred for 24 h at ambient temperature. Hydrazine monohydrate (2.80 g, 55.5 mmol) was then added and stirring was continued for an additional 72 h at room temperature. Acetone (30 mL) was then added and the reaction mixture was stirred overnight. The solvent was removed in vacuo and the oily residue was chromatographed (3:1 hexanes/EtOAc) to give the desired product (6.10 g, 75%) as a white solid. Mp=61.5–63°C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (br s, 1H), 2.90–2.81 (m, 2H), 2.52 (q, J=6.8 Hz, 2H), 2.02 (s, 3H), 1.88 (s, 3H), 1.77–1.65 (m, 4H), 1.34 (t, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 151.0, 32.9, 28.7, 28.0, 25.4, 24.1, 16.7; IR (neat) 3180, 3063, 2931, 1663, 1312, 1235 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 187 (M^+−SH, 2.4), 132 (10.8), 99 (100), 72 (54.3); HRMS calcd for $C_8H_{15}N_2OS$ (M−SH) 187.0805, found 187.0905.

8,9-Diaza-7,7-dimethyl-6-oxa-1,4-dithiaspiro[4,4]non-8-ene (2). To a stirred solution of $Pb(OAc)_4$ (5.97 g, 95%, 12.7 mmol) in CH_2Cl_2 (35 mL) at 0°C under N_2, was added dropwise a solution of *N*-(1-aza-2-methylprop-1-enyl) (2-sulfanylethylthio)carboxamide (2.22 g, 11.6 mmol) in CH_2Cl_2 (35 mL). When the addition was completed, the yellow solution was stirred 1 h at 0°C, then another 545 mg (1.16 mmol) of $Pb(OAc)_4$ was added. After 30 min, the lead precipitate was filtered by vacuum filtration and the filter cake was washed with CH_2Cl_2 (3×20 mL). The organic layer was washed with cold sat. $NaHCO_3$, cold brine and dried over Na_2SO_4. The yellow solution was filtered through a cotton plug and the solvent was removed in vacuo. The residue was chromatographed (4:1 hexanes/EtOAc to 3:1 hexanes/EtOAc) to give 1.5 g (52%) of 5,5-dimethyl-2-(2′-sulfanylethylthio)-1,3,4-oxadiazolin-2-yl acetate as a yellow oil (>95% purity by ^1H NMR): ^1H NMR ($CDCl_3$, 400 MHz) δ 3.32–3.23 (m, 1H), 3.22–3.13 (m, 1H), 3.11–3.01 (m, 1H), 2.99–2.98 (m, 1H), 2.11 (s, 3H), 1.62 (s, 3H), 1.59 (s, 1H), 1.51 (s, 3H); IR (neat) 2989, 2930, 1780, 1368, 1202 cm^{-1}.

To a cold solution (0°C) of 5,5-dimethyl-2-(2′-sulfanylethylthio)-1,3,4-oxadiazolin-2-yl acetate (1.5 g 6.0 mmol) in CH_2Cl_2 (30 mL) was added $TsOH{\cdot}H_2O$ (115 mg, 0.60 mmol). The yellow solution was stirred at 0°C until the starting material was gone (approximately 2 h). When the reaction was complete, the solvent was removed in vacuo at 0°C, and the residue was chromatographed (20:1 hexanes/EtOAc) using a jacketed column cooled at 0°C. The fraction with the desired product was collected and the solvent was removed in vacuo at 0°C. The residue was dried under high vacuum (4 h, 0.3 mmHg, 0°C) to give 8,9-diaza-7,7-dimethyl-6-oxa-1,4-dithiaspiro[4.4]non-8-ene (593 mg, 52%) as a white solid with a trace of $TsOH{\cdot}H_2O$ inside. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.62–3.52 (m, 4H), 1.49 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 122.3, 40.7, 23.7; IR (neat) 2982, 2931, 1369, 1058, 824 cm^{-1}. *Note:* This compound is not stable at room temperature, but it could be stored in the freezer for months.

3,4-Diaza-2,2-dimethyl-1-oxz-6,10-dithiaspiro[4.5]dec-3-ene (3). To a stirred solution of $Pb(OAc)_4$ (16.40 g, 95%, 34.9 mmol) in CH_2Cl_2 (100 mL) at 0°C under N_2, was added dropwise a solution of *N*-(1-aza-2-methylprop-1-enyl)(3-sulfanylpropylthio)carboxamide (6.54 g, 31.7 mmol) in CH_2Cl_2 (100 mL). When the addition was completed, the yellow solution was stirred 1 h at 0°C, then another 1.49 g (3.17 mmol) of $Pb(OAc)_4$ was added. After 30 min, the lead precipitate was filtered out by vacuum filtration and the filter cake was washed with CH_2Cl_2 (3×20 mL). The organic layer was washed with cold sat. $NaHCO_3$, cold brine and dried over Na_2SO_4. The yellow solution was filtered through a cotton plug and the solvent was removed in vacuo. The residue was chromatographed (3:1 hexanes/EtOAc) to give 2.95 g (35%) of 5,5-dimethyl-2-(3′-sulfanylpropylthio)-1,3,4-oxadiazolin-2-yl acetate as a yellow oil (>95% purity by ^1H NMR): ^1H NMR ($CDCl_3$, 400 MHz) δ 3.13–2.98 (m, 2H), 2.80–2.74 (m, 2H), 2.13 (s, 3H), 2.19–2.06 (m, 2H), 1.65 (s, 3H), 1.62 (s, 1H), 1.54 (s, 3H): IR (neat) 2988, 2940, 1779, 1367, 1212 cm^{-1}.

To a cold solution (0°C) of 5,5-dimethyl-1-(3′-sulfanylpropylthio)-1,3,4-oxadiazolin-2-yl acetate (2.8 g, 10.6 mmol) in CH_2Cl_2 (80 mL) was added $TsOH{\cdot}H_2O$ (280 mg, 1.06 mmol). The yellow solution was stirred at 0°C until the starting material was gone (approximately 2 h). When the reaction was complete, the solvent was removed in vacuo at 0°C, and the residue was chromatographed (20:1 hexanes/EtOAc) using a jacketed column cooled at 0°C. The fraction with the desired product was collected and the solvent was removed in vacuo at 0°C. The residue was dried under high vacuum (4 h, 0.3 mmHg, 0°C) to give 3,4-diaza-2,2-dimethyl-1-oxa-6,10-dithiaspiro[4.5]dec-3-ene (1.23 g, 57%) as a pale yellow solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 3.60–3.50 (m, 2H), 2.98–288 (m, 2H), 2.25–2.15 (m, 1H), 2.05–1.93 (m, 1H), 1.52 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 124.4, 120.1, 30.8, 2437, 23.6; IR (neat) 2960, 2921, 1421, 1366, 1228, 1082 cm^{-1}. *Note:* This compound is not stable at room temperature, it could be stored in the freezer for months.

3,4-Diaza-2,2-dimethyl-1-oxa-6,11-dithiaspiro[4.6]undec-3-ene (4). To a stirred solution of $Pb(OAc)_4$ (10.3 g, 95%, 22.0 mmol) in CH_2Cl_2 (60 mL) at 0°C under N_2, was added dropwise a solution of *N*-(1-aza-2-methylprop-1-enyl)(4-sulfanylbutylthio)carboxamide (4.40 g, 20.0 mmol) in CH_2Cl_2 (60 mL). When the addition was completed, the yellow solution was stirred 1 h at 0°C, then another 940 mg (2.00 mmol) of $Pb(OAc)_4$ was added. After 30 min, the lead precipitate was filtered out by vacuum filtration and the filter cake was washed with CH_2Cl_2 (3×20 mL). The organic layer was washed with cold saturated $NaHCO_3$ solution, cold brine and dried over anhydrous Na_2SO_4. The yellow solution was filtered through a cotton plug and the solvent was removed in vacuo. The residue was chromatographed (4:1 hexanes/EtOAc to 3:1 hexanes/EtOAc) to give 1.87 g (34%) of 5,5-dimethyl-2-(4′-sulfanylbutylthio)-1,3,4-oxadiazolin-2-yl acetate as a yellow oil (>95% purity by ^1H NMR). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.07–2.98 (m, 1H), 2.97–2.88 (m, 1H), 2.74–2.65 (m, 2H), 2.13 (s, 3H), 1.86–1.76 (m, 4H), 1.66 (s, 3H), 1.63 (s, 1H), 1.55 (s, 3H): IR (neat) 2988, 2938, 1779, 1367, 1212 cm^{-1}.

To a cold solution (0°C) of 5,5-dimethyl-2-(4′-sulfanylbutylthio)-1,3,4-oxadiazolin-2yl acetate (3.0 g, 10.8 mmol) in CH_2Cl_2 (100 mL) was added $TsOH{\cdot}H_2O$ (280 mg, 1.06 mmol). The yellow solution was stirred at 0°C until the starting material was gone (approximately 2 h). When the reaction was complete, the solvent was removed in vacuo at 0°C, and the residue was chromatographed (20:1 hexanes/EtOAc) using a jacketed column cooled at 0°C. The fraction with the desired product was collected and the solvent was removed in vacuo at 0°C. The residue was dried under high vacuum (4 h, 0.3 mmHg, 0°C) to give 3,4-diaza-2,2,-dimethlo-1-oxa-6,11-dithiaspiro[4.6]undec-3-ene (1.49 g, 60%) as a colorless oil. Due to the coexistence of several conformers of the 7-membered ring at room temperature, the peaks of each conformer could be observed by both ^1H NMR and ^{13}C NMR. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.21–2.61 (br m, 5H), 2.13 (s, small peak for $-CH_3$), 2.05 (br s, for $-CH_3$), 1.97–1.62 (br m, 3H), 1.56 (s, for $-CH_3$), 1.50 (s, for $-CH_3$), 1.26 (s, small peak for $-CH_3$), 1.24 (s, small peak for $-CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.9, 129.1, 124.3, 123.6, 38.6, 31.9, 31.5 (small), 30.8, 30.6 (medium), 30.3 (small), 27.3, 27.0,

24.6, 24.3, 21.7; IR (neat 2918, 1667, 1229, 1048 cm^{-1}. *Note:* This compound is not stable at room temperature, but it could be stored in the freezer for months.

General procedure for the preparation of acyl azides

To a solution of the α,β-unsaturated carboxylic acid, the preparations of which have been described elsewhere,[2a] in benzene (0.2 M) is added Et_3N (1.0 equiv.) and after 10 min of stirring, diphenylphosphorzaeidate DPPA (1.0 equiv.) is slowly added. The resulting reaction mixture is stirred for an additional 40 min at which time the solvent is removed in vacuo. The crude mixture is purified by flash chromatography (10:1 hexanes/Et_2O) to afford the pure acyl azide.

General procedure for the [4+1] cycloaddition of vinyl isocyanates with bis-(alkylthio)carbenes

The appropriate acyl azide (1 equiv.) was dissolved in dry benzene (concentration=0.2 M) and refluxed for 45 min to afford the corresponding isocyanate. To the refluxing mixture was added the oxadiazoline **1** (about 2.5 equiv., 1 M solution in hexanes kept at −78°C prior to addition) over a period of 45 min via syringe. After the addition was complete, the reaction mixture was refluxed for another 30 min at which point the pale yellow solution was allowed to cool to room temperature. The solvent was removed in vacuo and the residue was chromatographed (hexanes/EtOAc+2% Et_3N) to give the pure products. $CDCl_3$ was passed through basic alumina (ICN Biomedicals) before obtaining NMR of all compounds described below.

1-Bis(propylthio)methyl-3,3-bis(propylthio)-1,3,3a,4,5,6-hexahydro-indol-2-one (6). From the acyl azide **5** (72 mg, 0.48 mmol) and the oxadiazoline **1** (1.20 mL, 1.20 mmol) was obtained, after flash chromatography (30:1 hexanes/EtOAc+2% Et_3N), indolone **6** (186 mg, 86%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.42 (s, 1H), 5.72 (s, 1H), 3.06 (m, 1H), 2.90 (m, 1H), 2.64–2.47 (m, 7H), 2.23 (m, 2H), 1.96 (m, 2H), 1.76–1.53 (m, 10H), 1.01–0.94 (m, 12H): ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 133.5, 106.6, 62.6, 58.6, 48.2, 36.1, 35.5, 32.9, 32.6, 24.2, 23.4, 23.4, 23.3, 23.1, 23.0, 22.4, 14.5, 14.5, 14.1, 14.1; IR (neat) ν 2914, 1710, 1675, 1449, 1365 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 372 ($M-C_3H_7S$, 100), 297 (21); HRMS calcd for $C_{21}H_{37}NOS_4$ ($M-C_3H_7S$) 372.14895, found 372.1487; Anal. calcd for $C_{21}H_{37}NOS_4$: C, 56.35; H, 8.34; N, 3.13; found: C, 56.58; H, 8.22; N, 2.94.

1-Bis(propylthio)methyl-3,3-bis(propylthio)-5-methylene-4-phenyl-pyrrolidin-2-one (7). From the acyl azide (88 mg, 0.47 mmol) and the oxadiazoline **1** (1.20 mL, 1.20 mmol) was obtained, after flash chromatography (40:1 hexanes/EtOAc+2% Et_3N), pyrrolidinone **7** (210 mg, 92%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.34 (m, 5H), 6.61 (s, 1H), 5.33 (s, 1H), 4.48 (s, 1H), 4.28 (s, 1H), 2.75–2.55 (m, 6H), 2.43 (t, *J*=7.5 Hz, 2H), 1.74–1.61 (m, 6H), 1.36 (1, *J*=7.5 Hz, 2H), 1.01 (m, 9H), 0.82 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 140.8, 135.1, 130.7, 128.1, 127.8, 95.2, 62.8, 58.4, 56.4, 35.2, 35.1, 32.9, 32.0, 22.7, 22.6, 22.1, 22.0, 13.8, 13.4, 13.4; IR (neat) ν 2957, 1710, 1639, 1315 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 483 (M^+, 1.9), 408 (100), 333 (28.2); HRMS calcd for $C_{24}H_{37}NOS_4$ (M^+) 483.17579, found 483.1757.

5,6-Bis-(tert-butyl-dimethyl-silanyloxy)-1-bis(propylthio)methyl-3,3-bis(propylthio-1,3,3a,4,5,6-hexahydro-indol-2-one (8). From the acyl azide (155 mg, 0.38 mmol) and the oxadiazoline **1** (830 μL, 0.83 mmol) was obtained after flash chromatography (40:1 hexanes/EtOAc+2% Et_3N) indolone **8** (226 mg, 85%) as a colorless oil. The product consisted of a 1:1 mixture of inseparable diastereomers. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.46 (s, 1H), 6.37 (s, 1H), 5.71 (s, 2H), 4.37 (m, 1H), 4.05 (m, 1H), 3.93 (m, 1H), 3.77 (m, 1H), 3.37 (m, 1H), 3.25 (m, 1H0, 3.00–2.30 (m, 16H), 2.12 (t, *J*=11.0 Hz, 1H), 1.96 (m, 2H), 1.82 (m, 1H), 1.68–1.50 (m, 16H), 1.11–0.82 (m, 60H), 0.14–0.08 (m, 24H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 170.8, 135.3, 133.8, 108.4, 105.4, 74.6, 74.4, 70.7, 68.8, 61.2, 60.70, 57.9, 57.6, 46.9, 41.3, 35.2, 35.0, 34.8, 34.5, 34.4, 32.3, 32.0, 31.9, 31.9, 31.4, 26.0, 25.9, 25.9, 25.7, 25.6, 25.1, 22.6, 22.5, 22.4, 22.3, 22.2, 22.1, 22.0, 17.9, 17.8, 13.7, 13.6, 13.5, 13.3, 13.2, −3.9, −4.1, −4.2, −4.5, −4.6, −4.7, −4.8, −4.9; IR (neat) ν 2950, 1717, 1675, 1245, 1083, 829 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 632 ($M-C_3H_7S$, 51.5), 556 (49.6), 469 (20.2), 163 (100); HRMS calcd for $C_{33}H_{65}NO_3S_4Si_2$ ($M-C_3H_7S$) 632.31173, found 632.3120.

1-Bis(propylthio)methyl-3,3-bis(propylthio)-5,5-ethylenedioxy-3a-methyl-1,3,3a,4,5,6-hexahydro-indol-2-one (9). From the acyl azide (269 mg, 1.20 mmol) and the oxadiazoline **1** (3 mL, 3.00 mmol) was obtained after flash chromatography (20:1 hexanes/EtOAc) indolone **9** (293 mg, 47%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.39 (s, 1H), 5.68 (t, *J*=4 Hz, 1H), 4.03 (m, 2H), 3.96 (m, 1H), 3.90 (m, 1H), 2.87 (m, 1H), 2.69 (m, 2H), 2.60–2.45 (m, 7H), 2.41 (d, *J*=13 Hz, 1H), 1.70–1.55 (m, 9H), 1.48 (s, 3H), 1.03 (t, *J*=7.5 Hz, 3H), 0.97 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 137.4, 107.6, 102.5, 71.7, 64.6, 63.7, 58.1, 49.0, 38.1, 35.1, 34.7, 34.6, 32.7, 31.0, 25.8, 22.5, 22.5, 22.3, 21.8, 13.8, 13.8, 13.7, 13.3; IR (neat) 2957, 1710, 1675 cm^{-1}, mass spectrum (EI) *m/e* (rel. int.) 519 (M^+, 1.1), 444 (100), 369 (21.7), 163 (70.4); HRMS calcd for $C_{24}H_{41}NO_3S_4$ (M^+) 519.19692, found 519.1974.

7-(1,3-Dithian-2-yl)spiro[1,3-dithiane-2,3′-3,4′,5′,6′,3a′-pentahydroindole]-8-one (10). From the acyl azide (30 mg, 0.2 mmol) in 4.0 mL of benzene and oxadiazoline **3** (1.0 mL, 0.5 mmol) was obtained 59 mg (82%) of the desired product as a colorless oil after flash chromatography (5:1 hexanes/EtOAc+2% NEt_3). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.48 (s, 1H), 5.81–5.75 (m, 1H), 4.11 (dt, J_1=13.2 Hz, J_2=2.8 Hz, 1H), 3.44–3.33 (m, 1H), 3.17–3.03 (m, 2H), 3.02–2.92 (m, 2H), 2.69–2.53 (m, 3H), 2.28–2.06 (m, 4H), 1.98–1.64 (m, 5H), 1.61–1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 133.4, 104.8, 56.9, 50.4, 45.7, 32.5, 32.4, 27.2, 26.4, 25.2, 24.8, 23.2, 22.2, 21.5; IR (neat) ν 2917, 1718, 1682, 1377, 1311 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 359 (M^+, 4.3) 240 (76.4), 119 (100); HRMS calcd for $C_{15}H_{21}NOS_4$ 359.0506, found 359.0506.

6-(1,3-Dithian-2-yl)-3a-methyldispiro[1,3-dioxolane-2,5′,3′,4′,5,6′,3a′-pentahydroinole-3′,2″-1,3-dithiane]-7-

one (11). From the acyl azide (46 mg, 0.2 mmol) in 4.0 mL of benzene and **3** (1.0 mL, 0.5 mmol) was obtained 45 mg (52%) of the desired produce as a colorless oil after flash chromatography (3.5:1 hexanes/EtOAc+2% NEt_3): ^1H NMR ($CDCl_3$, 400 MHz) δ 6.48 (s, 1H), 5.70 (t, J=4.0 Hz, 1H), 4.07–3.86 (m, 5H), 3.28–3.18 (m, 1H), 3.15–2.92 (m, 4H), 2.74–2.43 (m, 4H), 2.34 (d, J=5.6 Hz, 1H), 2.18–2.07 (m, 2H), 1.86–1.72 (m, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 137.6, 107.5, 102.1, 64.4, 63.7, 58.1, 56.8, 46.5, 35.7, 34.8, 32.3, 32.1, 27.2, 26.6, 25.1, 24.6, 22.9; IR (neat) ν 2964, 2929, 2896, 1723, 1687 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 431 (M^+, 7.2), 312 (47.4), 119 (100); HRMS calcd for $C_{18}H_{25}NO_3S_4$ 431.0717, found 431.0712.

2-Aza-2-(1,3-dithian-2-yl)-3-methyl-4-phenyl-6,10-dithiaspiro[4.5]decan-1-one (12). From the acyl azide (38 mg, 0.2 mmol) in 4.0 mL of benzene and **3** (1.0 mL, 0.5 mmol) was obtained 67 mg (85%) of the desired product as a colorless oil after flash chromatography (5:1 hexanes/EtOAc+2% NEt_3). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.29 (m, 5H), 6.67 (s, 1H), 5.47 (t, J=2.2 Hz, 1H), 4.42 (t, J=2.2 Hz, 1H), 3.97 (t, J=1.8 Hz, 1H), 3.82 (dt, J_1=13.4 Hz, J_2=2.4 Hz, 1H), 3.66 (dt, J_1=13.4 Hz, J_2=2.4 Hz, 1), 3.23–3.10 (m, 2H), 3.08–2.96 (m, 2H), 2.60 (td, J_1=14.0 Hz, J_2=3.4 Hz, 1H), 2.51 (td, J_1=14.0 Hz, J_2=3.4 Hz, 1H), 2.21–2.06 (m, 2H), 1.91–1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 141.9, 134.6, 130.1, 128.4, 128.0, 94.1, 57.1, 55.6, 50.7, 32.5, 32.4, 27.9, 27.1, 25.1, 24.0; IR (neat) ν 2918, 1710, 1645, 1354, 1210 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 395 (M^+, 7.7) 276 (86.6), 119 (100); HRMS calcd for $C_{18}H_{21}NOS_4$ 395.0506, found 395.0505.

2-Aza-2-(1,3-dithian-2-yl)-4-methyl-3-methylene-6,10-dithiaspiro[4.5]decan-1-one (13). From the acyl azide (25 mg, 0.2 mmol) in 4.0 mL of benzene and **3** (1.0 mL, 0.5 mmol) was obtained 52 mg (78%) of the desired product as a colorless oil after flash chromatography (7:1 hexanes/EtOAc+2% NEt_3). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.53 (s, 1H), 5.30 (t, J=2.4 Hz, 1H), 4.46 (t, J=2.4 Hz, 1H), 3.99 (dt, J_1=13.4 Hz, J_2=2.4 Hz, 1H), 3.54–3.43 (m, 1H), 3.17–3.04 (m, 2H), 3.04–2.92 (m, 2H), 2.82–2.73 (m, 1H), 2.69–2.54 (m, 2H), 2.28–2.06 (m, 2H), 1.92–1.74 (m, 2H), 1.31 (d, J=7.2 Hz, 3H): ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 143.7, 91.2, 56.9, 50.9, 43.7, 32.5, 32.4, 27.3, 26.3, 25.1, 24.6, 11.6; IR (neat) ν 2910, 1710, 1680, 1340, 1300 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 333 (M^+, 5.7), 214 (99.5), 119 (100); HRMS calcd for $C_{13}H_{19}NOS_4$ 333.0350, found 333.0350.

2-Aza-2-(1,3-diethiepan-2-yl)-3-methylene-4-phenyl-6,11-dithiaspiro[4.6]undecan-1-one (14). From the acyl azide (38 mg, 0.2 mmol) in 4.0 mL of benzene and oxadiazoline **4** (1.0 mL, 0.5 mmol) was obtained 47 mg (56%) of the desired product as a colorless oil after flash chromatography (10:1 hexanes/EtOAc+2% NEt_3). Due to the coexistence of several conformers of the two 7-membered rings at room temperature, the peaks of each conformer could be observed by both ^1H NMR and ^{13}C NMR: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48–7.30 (m, 5H), 6.58 (br s, 1H), 5.19 (s, 1H), 5.15 (br s, 0.5H), 4.47 (t, J=2.0 Hz, 1H), 4.42 (m, 0.5H), 4.17 (t, J=2.0 Hz, 1H), 3.35–3.26 (m, 1H), 2.93–2.65 (m, 8H), 2.30–1.68 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5, 140.9, 134.5, 130.9, 130.0, 128.1, 128.0, 127.8, 94.8, 62.6, 59.1, 57.0, 39.2, 39.1, 33.3, 33.1, 31.7, 31.1, 29.9, 28.9, 28.2, 28.0, 27.7, 27.4; IR (neat) ν 2918, 1712, 1650, 1326 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 423 (M^+, 17.8), 289 (21.0), 132 (100), 120 (84.7), 87 (51.7); HRMS calcd for $C_{20}H_{24}NOS_4$ 423.0819, found 423.0817.

2-Aza-2-(1,3-dithiepan-2-yl)-4-methyl-3-methylene-6,11-dithiaspiro[4.6]undecan-1-one (15). From the acyl azide (31 mg, 0.25 mmol) in 5.0 mL of benzene and **4** (1.0 mL, 0.5 mmol) was obtained 41 mg (50%) of the desired product as a colorless oil after flash chromatography (15:1 hexanes/EtOAc+2% NEt_3). Due to the coexistence of several conformers of the two 7-membered rings at room temperature, the peaks of each conformer could be observed by both ^1H NMR and ^{13}C NMR: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.47 (s, 1H), 5.20 (s, 0.5H), 5.06 (t, J=2.2 Hz, 1H), 4.91 (d, 0.5H, J=2.8 Hz), 4.52 (t, J=2.2 Hz, 1H), 3.34–3.07 (m, 1H), 3.01–2.58 (m, 8H), 2.22–1.71 (m, 8H), 1.34 (d, J=6.8 Hz, 3H), 1.29 (d, 0.5H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 143.1, 91.9, 61.7, 58.8, 45.6, 39.3, 39.1, 33.1 32.9, 31.8, 31.6, 31.5, 30.4, 30.0, 29.7, 28.9, 28.2, 27.7, 27.4, 27.3, 27.2; IR (neat) 2923, 2850, 1713, 1649, 1326, 1213 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 361 (M^+, 55.6) 228 (53.3), 133 (100), 87 (50.2); HRMS calcd for $C_{15}H_{23}NOS_4$ 361.0663, found 361.0661.

7-(1,3-Dithian-2-yl)spiro[1,3-dithiane-2,3′-3,4′,5′,6′,7′-pentahydroindole]-8-one (16). At room temperature, a total of 54 mg (0.15 mmol) of **10** was dissolved into 0.5 mL of $CDCl_3$ (obtained from Cambridge Isotope Laboratories, Inc.; directly used without passing through basic alumina) in a NMR tube. The reaction turned out to be a slow process and monitored by ^1H NMR. After 2 d at room temperature, the ratio between the desired product and the starting material was 13.5:1. This ratio had been the same even after 7 d: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.45 (s, 1H), 3.90 (dt, J_1=13.6 Hz, J_2=2.4 Hz, 2H), 3.08 (dt, J_1=13.6 Hz, J_2=2.4 Hz, 2H), 2.96 (td, J_1=13.6 Hz, J_2=3.6 Hz, 2H), 2.76–2.68 (m, 2H), 2.54 (td, J_1=13.6 Hz, J_2=3.6 Hz, 2H), 2.25–2.05 (m, 4H), 1.98–1.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.8, 138.2, 114.4, 55.7, 49.1, 32.8, 24.9, 24.2, 230, 22.2, 21.9, 19.8. After the solvent was removed, a total of 54 mg (93% of the desired product based on the ratio) of an inseparable mixture was obtained as a pale yellow oil. IR (neat) ν 2933, 1705, 1668, 1315 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 359 (M^+, 8.0), 240 (50.6), 119 (100); HRMS calcd for $C_{15}H_{21}NOS_4$ 359.0506, found 359.0506.

2-Aza-2-(1,3-dithian-2-yl)-3-methyl-4-phenyl-6,10-dithiaspiro[4.5]dec-3-en-1-one (17). At room temperature, 60 mg (0.15 mmol) of **12** was dissolved in 0.5 mL of $CDCl_3$ (obtained from Cambridge Isotope Laboratories, Inc.; directly used without passing through basic alumina) in a NMR tube: ^1H NMR demonstrated that the reaction was complete. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.30 (m, 5H), 6.59 (s, 1H), 3.95 (dt, J_1=13.6 Hz, J2=2.4 Hz, 2H), 3.17–3.08 (m, 2H), 3.00 (td, J_1=14.0 Hz, J2=3.8 Hz, 2H), 2.51 (td, J_1=14.0 Hz, J_2=3.8 Hz, 2H), 2.33 (s, 3H), 2.18–2.10 (m, 2H), 1.91–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 174.9, 138.3, 131.7, 130.5, 128.0, 127.8, 117.4, 56.0, 50.6, 32.8, 25.0, 24.8, 23.8, 12.9. After the solvent was removed, a total of 60 mg (100%) of the desired product was obtained as a pale yellow oil. IR (neat) 2939, 2889, 1701, 1344 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 395 (M^+, 9.1), 276 (19.9), 119 (100); HRMS calcd for $C_{18}H_{21}NOS_4$ 395.0506, found 395.0511.

General procedure for the [4+1] cycloaddition between aryl isocyanates and bis(alkylthio)carbenes

To a two-necked round bottom flask equipped with a reflux condenser, is added the pure acyl azide in a CH_3CN solution (0.1 M) and refluxed for 0.5–1.0 h until the corresponding isocyanate is formed (monitored by IR). To this solution is added oxadiazoline **1** in a THF solution (1.0 M) in 0.200 mL portions every 10 min. The resulting solution is refluxed for 16 h at which time the solvent is removed under vacuum. Flash chromatography (hexanes/Et_2O) of the mixture affords the pure adduct.

1-[Bis(propylthio)methyl]-3,3-bis(propylthio)indolin-2-one (18). Phenyl isocyanate (0.1 g, 0.87 mol) in acetonitrile (8 mL) afforded 0.156 g (42%) of product: ^1H NMR (500 MHz, $CDCl_3$) δ 0.97–1.00 (m, 12H), 1.58–1.62 (m, 4H), 1.65–1.67 (m, 4H), 2.54 (m, 2H), 2.68–2.71 (m, 2H), 2.81–2.86 (m, 2H), 7.11–7.34 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 14.7, 21.7, 22.8, 23.3, 32.2, 35.4, 58.8, 115.4, 124.0, 129.2, 129.7, 130.1, 139.9, 165.4; IR (NaCl) ν 2960, 2871, 1728, 1639, 1463, 1273 cm^{-1}; mass spectrum *m/e* (rel. int.) 368 (20), 293 (9), 194 (14), 163 (63), 119 (100), 91 (40), 43 (58); HRMS for $C_{18}H_{26}NOS_3$ ($M^+-C_3H_7S$) calcd 368.1171, found 368.1182.

1-[Bis(propylthio)methyl]-3,3-bis(propylthio)benz[g]indolin-2-one (19). 1-Naphthyloylazide (0.11 g, 0.56 mmol) in CH_3CN (6 mL) yielded 0.193 g (70%) of product: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87–0.96 (m, 12H), 1.43–1.56 (m, 4H), 1.61–1.71 (m, 4H), 2.54–2.75 (m, 8H), 7.13 (s, 1H), 7.48–7.60 (m, 2H), 7.62–7.64 (m, 2H), 7.72–7.75 (d, 1H), 7.83–7.86 (d, 1H), 8.89–8.92 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.8, 22.5, 23.1, 32.4, 63.1, 56.3, 59.6, 120.9, 121.4, 125.5, 125.7, 125.9, 126.6, 127.6, 129.1, 135.6, 136.0, 176.1; IR (NaCl) ν 2930, 1709, 1393, 1298, 1039 cm^{-1}; mass spectrum *m/e* (rel. int.) 493 (2), 330 (26), 256 (8), 163 (100), 121 (10), 43 (19); HRMS for $C_{25}H_{35}NOS_4$ calcd 493.1602, found 493.1601; Anal. for $C_{25}H_{35}NOS_4$ calcd C, 61.83; H, 7.15; N, 2.85; found C, 61.57; H, 7.14; N, 2.94.

5-[Bis(propylthio)methyl]-7,7-bis(propylthio)-5H-1,3-dioxolano[4,5-f]indolin-2-one (20). Piperonyloylazide (0.19 g, 1 mmol) in acetonitrile (10 mL) gave 0.281 g (58%) of product: ^1H NMR (500 MHz, $CDCl_3$) δ 0.92–0.95 (m, 12H), 1.50–1.55 (m, 4H), 1.58–1.66 (m, 4H), 2.42–2.46 (m, 2H), 2.54–2.58 (m, 2H), 2.61–2.66 (m, 4H), 5.99 (s, 2H), 6.62 (s, 1H), 6.96 (s, 1H), 7.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.3, 23.0, 23.3, 32.9, 35.5, 58.1, 97.9, 102.2, 105.9, 121.5, 132.8, 144.8, 148.8, 174.9; IR (NaCl) ν 2962, 1712, 1471, 1156, 1038 cm^{-1}; mass spectrum *m/e* (rel. int.) 412 (25), 337 (15), 224 (13), 163 (100), 121 (12), 79 (6); HRMS for $C_{22}H_{33}NO_3S_4$ calcd 487.1343, found 487.1340.

6-Dimethylamino-1-[bis(propylthio)methyl]-3,3-bis-(propylthio)indolin-2-one (21). 3-Dimethylaminobenzoylazide (0.12 g, 0.63 mmol) in CH_3CN (6 mL) gave 0.233 g (70%) of product: ^1H NMR (500 MHz, $CDCl_3$) δ 0.89–0.94 (m, 12H), 1.48–1.53 (m, 4H), 1.58–1.66 (m, 4H), 2.41–2.47 (m, 2H), 2.55–2.66 (m, 6H), 3.02 (s, 6H), 6.43–6.44 (d, 1H, J=8.5 Hz), 6.64 (s, 1H), 6.98 (s, 1H), 7.25–7.27 (d, 1H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 13.8, 22.6, 22.9, 32.6, 35.1, 40.8, 56.7, 57.5, 98.5, 107.0, 115.3, 124.9, 139.1, 151.4, 174.9; IR (NaCl) ν 2961, 1713, 1619, 1511, 1376, 1116 cm^{-1}; mass spectrum *m/e* (rel. int.) 411 (49), 293 (20), 249 (100), 223 (14), 163 (15), 121 (6), 76 (3); HRMS for $C_{20}H_{31}N_2OS_3$ ($M-C_3H_7S$) calcd 411.1599, found 411.1499; Anal. for $C_{23}H_{38}N_2OS_4$ calcd C 56.77; H, 7.88; N, 5.76; found C, 56.95; H, 7.75; N 5.68.

1-[Bis(propylthio)methyl]-3,3-bis(propylthio)-5-(trifluoromethyl)indolin-2-one (22). 4-Trifluoromethylbenzene-1-isocyanate (0.15 g, 0.8 mmol) in acetonitrile (8 mL) gave 0.054 (13%) of product: ^1H NMR (500 MHz, $CDCl_3$) δ 0.92–1.02 (m, 12H), 1.51–1.57 (m, 4H), 1.59–1.67 (m, 4H), 2.43–2.47 (m, 2H), 2.54–2.60 (m, 2H), 2.63–2.72 (m, 4H), 6.64 (s, 1H), 7.61–7.63 (d, 1H, J=10 Hz), 7.69–7.71 (d, 1H, J=10 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 14.5, 22.5, 22.9, 23.3, 30.4, 33.4, 34.3, 35.6, 58.3, 114.6, 119.7, 122.1, 127.3; IR (NaCl) 2963, 2873, 1721, 1620, 1327, 1165; mass spectrum *m/e* (relative intensity) 436 (47), 350 (30), 232 (17), 163 (54), 57 (21), 43 (100); HRMS for $C_{19}H_{24}F_3NOS_3$ ($M-C_3H_7S$) calcd 436.1051, found 436.1053.

General procedure for the double cycloaddition of bis(propylthio)carbenes with vinyl isocyanates

A round bottom flask (100 mL) was fitted with a long condenser. The appropriate acyl azide (1 equiv.) was dissolved in dry benzene (concentration=0.5 M) and refluxed for 45 min (oil bath temperature 95°C) to give the corresponding isocyanate. The oxadiazoline (10 equiv.) was dissolved in hexanes (concentration =6.0 M) at room temperature and added as fast as possible to the refluxing solution of isocyanate via syringe through the condenser (CAUTION: VERY EXOTHERMIC REACTION). The reaction was refluxed for 30 min after which time a light orange solution was obtained. The reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was chromatographed (hexanes/EtOAc+2% Et_3N) to give the pure products.

1-Bis(propylthio)methyl-3,3,4,4-tetrakis(propylthio)-3,4,4a,5,6,7-hexahydro-1*H*-quinolin-2-one (23). From the acyl azide (210 mg, 1.39 mmol) and the oxadiazoline **1** (3.40 g, 13.9 mmol) was obtained after flash chromatography (20:1 hexanes/EtOAc+2% Et_3N) quinolinone **23** (290 mg, 47%) as a pale yellow solid: mp=87–89°C (hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70 (s, 1H, exchangeable with D_2O), 4.88 (d, J=3.0 Hz, 1H), 3.75 (m, 1H), 2.92 (m, 6H), 2.76 (m, 1H), 2.62 (m, 1H), 2.35 (m, 1H), 2.14 (m, 2H), 1.90 (m, 2H), 1.72–1.50 (m, 9H), 1.00 (t,

J=7.5 Hz, 9H), 0.95 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 136.4, 98.6, 79.1, 68.9, 46.1, 35.4, 35.4, 35.4, 34.6, 25.9, 23.2, 22.3, 22.2, 22.1, 22.1, 22.1, 14.0, 14.0, 14.0, 13.7; IR ($CDCl_3$) ν 3224, 2943, 1689, 1449 cm^{-1}; mass spectrum (EI) *m/e* (rel. int.) 372 (M−C_3H_7S, 10) 236 (100); HRMS calcd for $C_{21}H_{37}NOS_4$ (M−C_3H_7S) 372.14895, found 372.1493; Anal. calcd for $C_{21}H_{37}NOS_4$: C, 56.35; H, 8.34; N, 3.13; found: C, 56.12; H, 8.24; N, 3.21.

6-Methylene-5-phenyl-3,3,4,4-tetrakis(propylthio)-piperidin-2-one (24). From the acyl azide (190 mg, 1.01 mmol) and the oxadiazoline **1** (2.52 g, 10.10 mmol) was obtained after flash chromatography (20:1 hexanes/EtOAc+2% Et_3N) piperidinone **24** (244 mg, 50%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (s, 1H, exchangeable with D_2O), 7.64 (m, 2H), 7.27 (m, 3H), 5.28 (t, J=2.5 Hz, 1H), 4.50 (t, J=2.5 Hz, 1H), 3.91 (t, J=2.5 Hz, 1H), 2.87 (m, 3H), 2.71 (m, 4H), 2.40 (m, 1H), 1.58 (m, 6H), 1.35 (m, 1H), 1.25 (m, 1H), 0.98 (t, J=7.0 Hz, 9H), 0.83 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 146.2, 138.4, 127.1, 126.9, 126.9, 87.8, 80.4, 71.8, 55.5, 35.5, 35.5, 35.5, 35.3, 22.2, 22.2, 22.1, 22.1, 14.0, 14.0, 14.0, 13.6; IR (film) ν 3232, 2922, 1689, 1450, 1337, 1273, 1224 cm^{-1}; mass spectrum (CI) *m/e* (rel. int.) 408 (M−C_3H_7S, 28.4), 334 (18.7), 248 (14), 237 (100); HRMS calcd for $C_{24}H_{37}NOS_4$ (M−C_3H_7S) 408.14895, found 408.1488.

6,6-Ethylenedioxy-3,3,4,4-tetrakis(propylthio)-3,4,4a,5,6,7-hexahydro-1*H*-quinolin-2-one (25). From the acyl azide (300 mg, 1.43 mmol) and the oxadiazoline **1** (3.56 g, 14.30 mmol) was obtained after flash chromatography (4:1 hexanes/EtOAc+2% Et_3N) quinolinone **25** (326 mg, 45%) as a pale yellow solid: mp=128–129°C (CH_3CN); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H, exchangeable with D_2O), 4.83 (m, 1H), 4.12–3.93 (m, 5H), 2.89 (t, J=7.0 Hz, 6H), 2.73 (m, 1H), 2.58 (m, 1H), 2.51–2.43 (m, 2H), 2.30 (m, 1H), 2.09 (t, J=12.0 Hz, 1H), 1.63–1.55 (m, 6H), 1.52–1.47 (m, 2H), 0.98 (t, J=7.5 Hz, 9H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 136.1, 108.5, 95.3, 78.7, 69.0, 64.4, 64.3, 44.5, 35.3, 35.3, 35.3, 34.6, 34.5, 34.3, 22.2, 22.1, 22.1, 22.1, 13.6, 13.9, 13.9, 13.7; IR ($CDCl_3$) 3251, 2948, 1694, 1454, 1088 cm^{-1}; mass spectrum (FAB) *m/e* (rel. int.) 538 (M+H, 1), 430 (100), 354 (27.6); HRMS calcd for $C_{23}H_{39}NO_3S_4$ (M−C_3H_7S) 430.15443, found 430.1542; Anal. calcd for $C_{23}H_{39}NO_3S_4$: C, 54.63; H, 7.78; N, 2.77; found: C, 54.90; H, 7.78; N, 2.80.

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