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Double Conjugate Addition of Dithiols to Propargylic Carbonyl Systems To Generate Protected 1,3-Dicarbonyl Compounds

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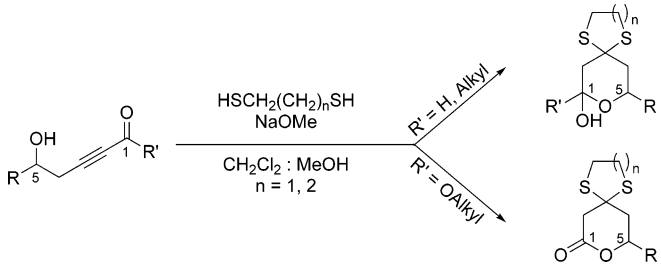

The work describes the efficient double conjugate addition of ethane and propane dithiols in the presence of sodium methoxide to a wide variety of propargylic carbonyl containing compounds. The products of these reactions are differentiated, 1,3-dicarbonyl systems useful for various synthesis programs. By judicious use of hydroxylated substrates tandem cyclization occurs to afford tetrahydropyran lactols or, in the case of hydroxy-substituted propargylic esters, lactones. The corresponding amino-substituted propargylic aldehydes gives piperidine derivatives upon double conjugate addition tandem cyclization.

Introduction

Polyketide-derived natural products have been the subject of synthetic interest for some time, and designing general methods to selectively generate the structural elements embedded in these compounds remains an important goal.[1−3] The most widely used method to obtain a 1,3-polyketide framework is the aldol reaction,[4−6] which has been extensively developed by Evans,[7] Heathcock,[8] Masamune,[9] Mukaiyama,[10] and Paterson[11,12] among others. The cyanohydrin acetonide methodology developed by Rychnovsky also allows a quick and stereoselective preparation of 1,3-polyol chains.[13,14] Other commonly applied approaches to generate 1,3-oxygenation patterns are the use of isoxazolines,[15,16] the rearrangement of epoxyalcohols,[17,18] and the opening of epoxides with dithiane anion,[19] all of which generate latent β-hydroxy carbonyl compounds. During the course of synthetic studies within our laboratory we required a robust and efficient route to orthogonally protected 1,3-dicarbonyl precursors for use in polyketide assembly programs. Our efforts focused on the preparation of β-keto dithiane derivatives, which could act as orthogonally protected 1,3-dicarbonyl precursors.

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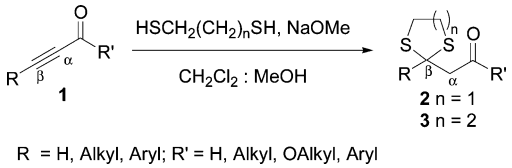
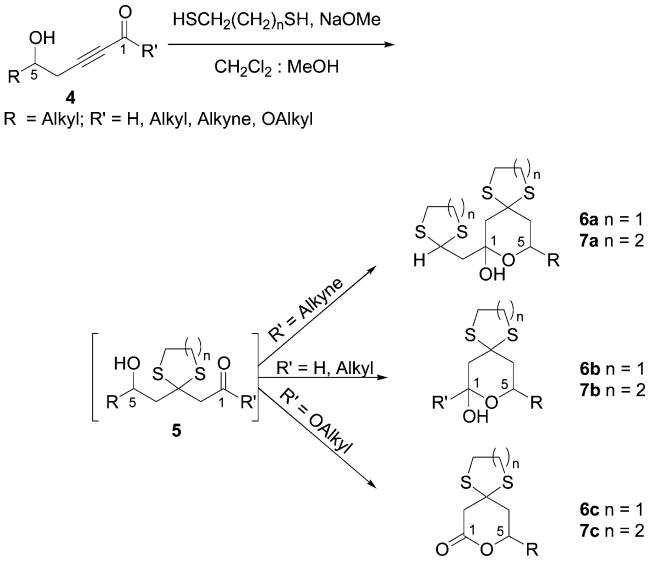
SCHEME 1. Dithiol Conjugate Addition



In earlier communications we have shown that ethane and propane dithiol can be added conjugatively to ynones, ynals, terminal ynoates, and bisynones to give protected 1,3-dicarbonyl systems.[20,21] For example, with ynones of type **1** using ethane or propane dithiol in the presence of methoxide in dichloromethane and methanol, high yields of β-keto dithiolanes **2** and β-keto dithianes **3** are produced, respectively (Scheme 1). The products of these reactions constitute especially useful building blocks for various synthesis programs.[22,23] Other groups, most notably Ranu[24] and Endo,[25] have previously devised alternative conditions to effect these transformations, but we felt that their conditions would not be compatible with the wide range of transformations and protective group sequences we had planned in our studies.

In addition, we have recently shown in the case of other functionalized derivatives such as a 5-hydroxy bisynone **4** that the dithiol addition to form **5** was further followed by tandem in situ cyclization leading to tetrahydropyran derivative **7a** (Scheme 2).[21] Here the versatility of the reaction process was demonstrated using a wide range of both simple and highly functionalized dithiol acceptors such as ynones, ynals, ynoates, and bisynones (Scheme 2).

SCHEME 2. Tandem Dithiol Conjugate Addition Cyclization



Compatibility with many different protecting groups such as silyl ethers, acetals, and ethers in these reactions was also examined. Furthermore the tandem dithiol addition-cyclization method was extended to the preparation of piperidine derivatives by incorporating nitrogen substituents.

Results and Discussion

The work begins by establishing a general and practical method, for a wide range of applications, through the conjugate addition of dithiols. However, it is pertinent to comment first on the possible mechanisms of the process, since intermediate **10** is formed that could lead profitably to the desired product **3** or, alternatively, undergo dimerization to lead to isomers **13**. We believe the addition of a dithiol into the ynone initially involves mono-deprotonation followed by addition to the ynone **1** (Scheme 3). After proton transfer occurs, both *cis* and *trans* isomers **9** of the α,β-unsaturated carbonyl are formed from the allenic-enolate intermediate **8**. The α,β-unsaturated carbonyl thiols **9** are themselves substrates for a second conjugate addition, now an intramolecular reaction, which gives the desired β-keto-1,3-dithianes **3** (path a). However, this second addition competes with the reaction of substrate **10** with another molecule of ynone to give undesired dimeric side products **13** (path b), which are observed in some cases (see later discussion).

The addition of a dithiol, either ethane or propane dithiol, to an ynone in a 1:1 mixture of dichloromethane and methanol at ambient temperature using a stoichiometric quantity of sodium methoxide as the base were our initially chosen conditions. However, conducting the reaction at ambient temperature led to significant formation of a dimeric byproduct **13** (Scheme 3). To minimize dimer formation we found that decreasing the concentration of the reaction helped but did not completely eliminate the problem.

Next, a more effective and practical solution was found by varying the reaction temperature. Addition of dithiol at −10 °C minimized dimer formation during the rapid first reaction of the ynone, and subsequently the slower intramolecular conjugate addition was facilitated by allowing the reaction to warm to ambient temperature. Maintaining the reaction temperature at −10 °C, or lower throughout, resulted in the reaction failing to go to completion within 24 h. The intramolecular process is therefore much slower than the first addition process, typically it takes between 1 and 18 hours at ambient temperature, depending on the degree of steric hindrance of the ynone, and is presumably due to the increased electron density imparted by the first sulfur substituent on the enone acceptor.

Following screening of various bases, sodium methoxide was the most effective, giving good to excellent yields while being compatible with a wide variety of functionalities and protecting groups. Methanol or ethanol was used to aid the solubility of the sodium alkoxide, whereas addition of tetrahydrofuran or dichloromethane as cosolvent improves the solubility of the substrate.

With optimized reaction conditions now available, improved general methods for the synthesis of the ynal and ynone precursors were needed. Two routes were principally investigated (Scheme 4). First, ynals of type **15** were easily prepared by addition of the corresponding terminal alkyne anion to a formylating agent, *N*-formylmorpholine (eq 1). Second, advantage could be taken of the Corey−Fuchs protocol for the

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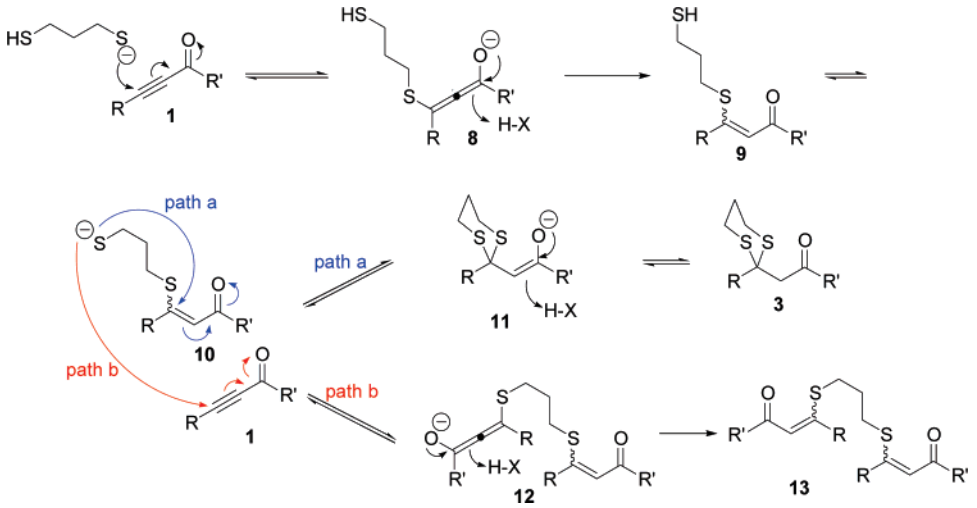
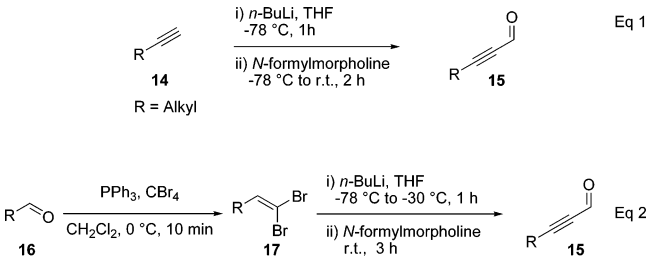
(25) Kuroda, H.; Tomira, I.; Endo, T. *Synth. Commun.* **1996**, *26*, 1539−1543.

SCHEME 3. Proposed Mechanism for the Formation of β-Keto-1,3-dithianes



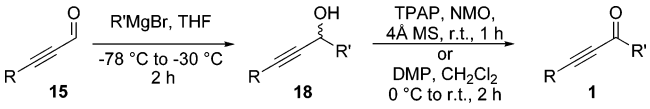
SCHEME 4. General Methods for the Synthesis of Ynals 15



synthesis of alkynes,[21,26] with interception of the resulting acetylide anion with the same formylating agent (eq 2). The intermediate **17** in the Corey−Fuchs reaction was generated, and standard metalation with *n*-BuLi followed by reaction with *N*-formylmorpholine furnished the desired ynals **15** in good yield (70−73%).[21]

The ynones of type **1** were readily available in two steps from the corresponding ynals **15**. Treatment of **15** with Grignard reagents and subsequent oxidation of the ynols **18** with tetrapropylammonium perruthenate[27] (TPAP) or Dess−Martin periodinane[28] (DMP) afforded the ynones **1** in high yields ranging from 75% to 88% (Scheme 5).

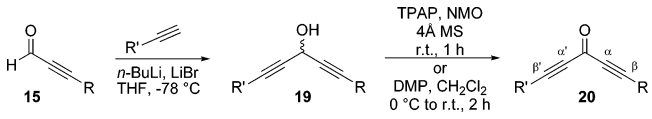
SCHEME 5. General Method for the Synthesis of Ynones 1



With various ynals and ynones now available, the scope of the dithiol addition reaction was then studied in detail. The reaction using sodium methoxide as base and propanedithiol occurred equally successfully with ynones, ynals, and ynoate (Table 1). The addition tolerated substitution of the alkyne (entry 1) or of the carbonyl (entry 2) with an aromatic group. Moderate yields could be obtained even in the case of sterically hindered alkynes (entries 5, 8, and 12). When an α stereogenic center was present in the initial ketone, it was pleasingly retained under the reaction conditions (entries 5 and 6). Both aldehyde **1g** and ketoester **1h** proved to be stable under the applied conditions and were good substrates for this methodology (entries 7 and 8). These more challenging examples amply demonstrated the compatibility of the dithiol addition reaction conditions with a wide range of functional groups and protecting groups. In the case of ynoates, dimerization was responsible for low yields of the desired product. Therefore new reaction conditions were developed where it was shown that by running the reaction in tetrahydrofuran instead of dichloromethane reduced the amount of dimer formed (entries 9−11). Furthermore with 1,2-ethanedithiol as the nucleophilic component the reactions progressed well (entries 8, 11, and 12).

As rapid generation of protected 1,3-polycarbonyl systems is a significant goal in synthesis,[2] the dithiane addition chemistry also constitutes a useful general and versatile method to generate protected 1,3,5-triketone fragments. Consequently double conjugate addition of a dithiol to a bisynone **20** at the β- and β′-alkyne carbon atoms would provide a masked trione of general structure **21** (Table 2). This intermediate could then be used as a highly versatile unit for the synthesis of structural motifs often found in polyketide and 1,3-polyol natural products. Therefore the bisynone substrates must be accessible in a mild and reliable manner, suitable for the convergent coupling of complex fragments. Generation of the ynals **15** according to the procedures previously described (Scheme 3) and addition of a second alkyne anion, followed by oxidation formed the bisynones **20** in 69−92% yield over three steps (Scheme 6).

SCHEME 6. Preparation of Bisynones 20



The bis-addition of dithiols proceeded in high yields for both terminal and internal acetylene moieties. The conjugate addition of 1,3-propanedithiol to a terminal alkyne (entries 4−7) led to a terminal dithiane, a very useful unit since it can be deprotonated and added to other electrophiles and later unmasked as a carbonyl group.[23]

Furthermore we have shown that the products of these reactions can be readily transformed to structurally more complex structures.[21,22] For example, the 1,5-hydroxyketone **22**

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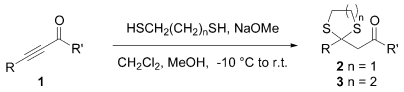
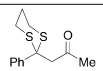
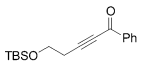
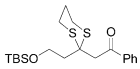
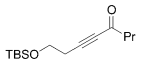
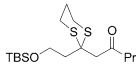
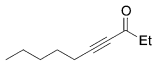
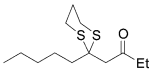
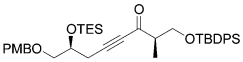
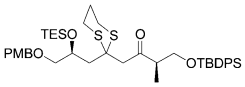
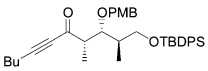
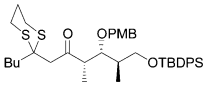
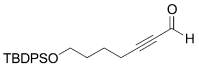
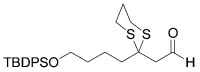
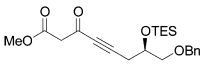
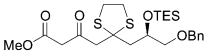
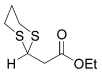
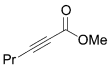
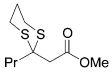
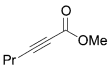
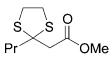
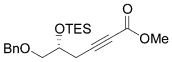
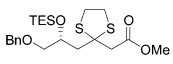
TABLE 1. Addition of 1,3-Propanedithiol into Ynones, Ynals, and Ynoates



Entry	Starting Material		Product		Yield [%]
1		**1a**		**2a**	82
2		**1b**		**2b**	94
3		**1c**		**2c**	88
4		**1d**		**2d**	69
5		**1e**		**2e**	51
6		**1f**		**2f**	80
7		**1g**		**2g**	88
8		**1h**		**3h**	85
9[a,b]		**1i**		**2i**	88
10[b]		**1j**		**2j**	71
11[b]		**1j**		**3j**	90
12		**1k**		**3k**	55

[a] With NaOEt. [b] Reaction run in THF.

upon removal of the protecting group cyclized to the tetrahydropyranyl ring **23** in very high yield (Scheme 7). This latter functional fragment is present in many natural products, and devising methods that allow quick access to these chiral tetrahydropyrans is a useful application of this work.

Therefore to display the generality of this process we prepared a number of precursors that could be subsequently converted to pyran derivatives. As an alternative to employing the Corey–Fuchs methodology described above, we found that opening of an epoxide such as **24** with TMS-acetylide anion gives **25** in excellent yield. This was then progressed via ynal **28** to either an ynone or bisynone **29** using standard methods (Scheme 8).

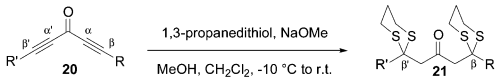
Substrates **29**, after deprotection to **30** are readily transformed by the tandem dithiol conjugate addition followed by cyclization to pyran derivatives **31** and **32**. These reactions were initially conducted with 1,3-propanedithiol (Table 3) and subsequently with 1,2-ethanedithiol as the thiol source (Table 4). Ynones, ynals, and bisynones proved to be good candidates for the tandem process.

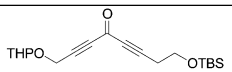
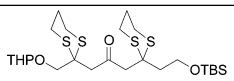
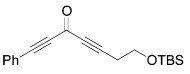
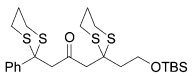
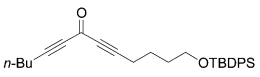
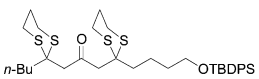
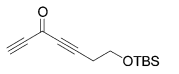
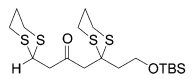
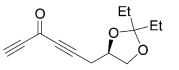
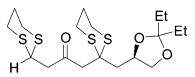
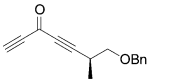
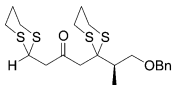
However, further elimination in some cases to the enol was observed using 1,3-propanedithiol (entry 5), and therefore 1,2-ethanedithiol was the preferred nucleophile for the tandem process if the uneliminated hemiketal was the target product (Table 4). The reaction was applicable further to the cyclic system **30c** whenever the hydroxyl internal nucleophile was part of a ring and was transformed correspondingly to more complex tricyclic systems **31c** and **32c** (Table 3, entry 4 and Table 4, entry 4). The ketoester **30g** also readily underwent cyclization to give the desired hemiketal **32g** (entry 6).

The thermodynamically favored α-anomer of the tetrahydropyranyl hemiketal was isolated as the major isomer in most cases as proven by NOE experiments.

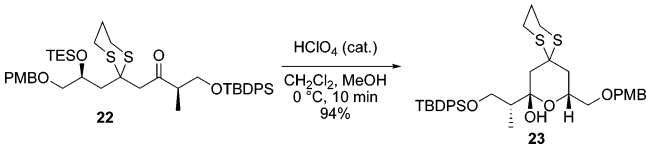
With 5-hydroxy-ynones and ynals the tandem dithiol double addition cyclization readily occurred, leading to tetrahydropyrans **31** and **32**. However, ynoates proved more challenging; indeed the yields were low and mostly uncyclized or dimerized products were isolated using the previously optimized conditions.

TABLE 2. Addition of 1,3-Propanedithiol into Bisynones

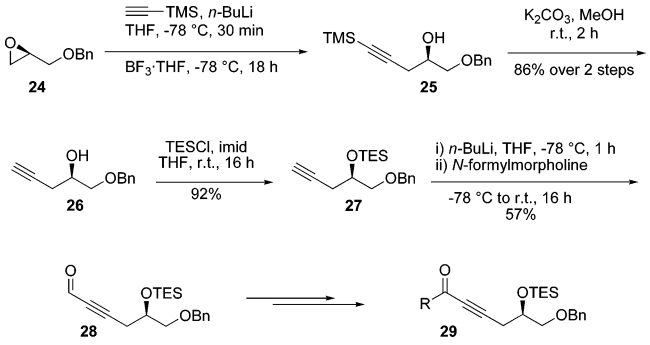


Entry	Starting Material		Product		Yield [%]
1		**20a**		**21a**	89
2		**20b**		**21b**	80
3		**20c**		**21c**	90
4		**20d**		**21d**	94
5		**20e**		**21e**	94
6		**20f**		**21f**	84

SCHEME 7. Cyclization



SCHEME 8. Preparation of 1,5-Hydroxyketone Derivatives



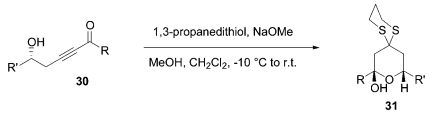
To obtain high yields of the desired lactone, the second intramolecular addition needs to be faster than the intermolecular dimerization process: increasing the dilution and lowering the concentration of methanol was expected to favor this process.

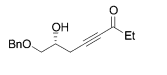
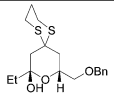
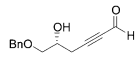
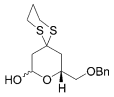
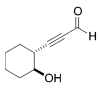
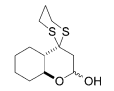
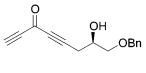
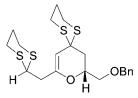
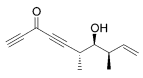
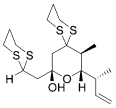
To test this idea, both linear and cyclic ynoates of general structure **35** and **38** were prepared using selective opening of an epoxide **33** or **36** with a propiolate anion in the presence of BF_3·THF (Scheme 9).

Both ethyl- and methyl-ynoates proved to be good substrates for the tandem double addition cyclization process using modified reaction conditions (Table 5). However, the bulkier *tert*-butylynoates afforded mostly the uncyclized product.

Indeed, lowering the concentration of methanol and increasing the dilution resulted in improved yields, but dimerization and mono-addition were still observed to some extent. It was then found that dimerization could be avoided by using tetrahydrofuran as solvent without any added methanol (entries 1 vs 2).

TABLE 3. Tandem 1,3-Propanedithiol Conjugate Addition-Cyclization

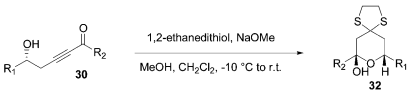


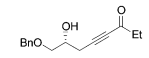
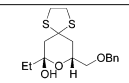
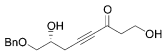
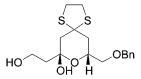
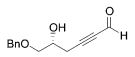
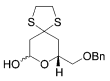
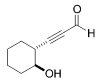
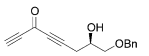
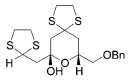
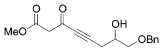
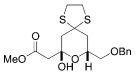
Entry	Starting Material		Product		Yield [%]
1		**30a**		**31a**	58
2		**30b**		**31b**	41
3		**30c**		**31c**	53
5		**30d**		**31d**	91
6		**30e**		**31e**	65

In addition, this method has allowed a quick access to *trans* bicyclic substrates (entries 6 and 7) easily obtained in two steps from the corresponding epoxides. However, in the case of the cyclopentanol derivative **35e** the reaction was performed in dichloromethane at very low concentration and an acidic workup was necessary to induce the cyclization to **39e** (entry 7) as only the uncyclized product was isolated under the usual reaction conditions.

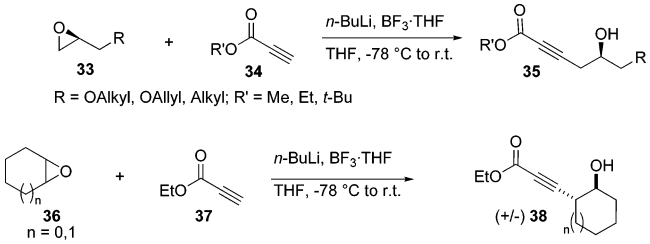
Based on the successful preparation of tetrahydropyran derivatives, the methods were expanded to provide access to

TABLE 4. Tandem 1,2-Ethanedithiol Conjugate Addition-Cyclization



Entry	Starting Material		Product		Yield [%]
1		**30a**		**32a**	63
2		**30f**		**32f**	90
3		**30b**		**32b**	64
4		**30c**		**32c**	58
5		**30d**		**32d**	81
6		**30g**		**32g**	83

SCHEME 9. Preparation of the Ynoates

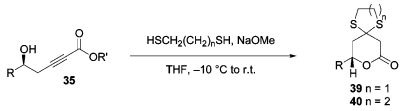


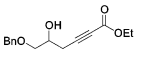
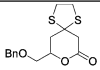
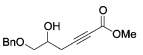
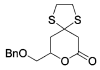
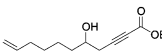
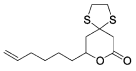
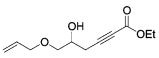
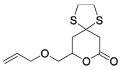
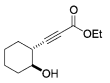
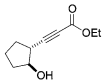
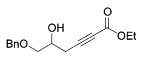
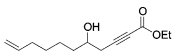
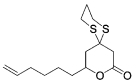
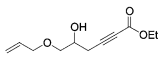
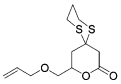
piperidines. The desired 1,5-amino carbonyl precursor was readily prepared from l-leucine via aziridine **41**. The intramolecular attack of an amine into a carbonyl was envisaged to occur after the dithiol addition to the acetylene, causing the ring closure and formation of piperidine.

The aziridine was prepared from l-leucine[29] and the aziridine ring opening was carried out with the anion of tetrahydro-2-(2-propynyloxy)-2H-pyran in 52% (Scheme 10). After acidic hydrolysis of the tetrahydropyranyl moiety of **42**, the primary alcohol was oxidized using Dess−Martin periodinane in excellent yield. The ynone derivative **44** was obtained by ethyl Grignard addition to the aldehyde **43** followed by oxidation.

The 1,5-amino ynal **43** was treated with either 1,2-ethanedithiol or 1,3-propanedithiol, which successfully underwent a conjugate addition followed by a cyclization (Table 6). As in the oxygen series, elimination to the dihydropyridine **45** was observed with the dithiane, but with dithiolane the hemiaminal **46** was stable. In the presence of methanol and pyridinium 4-toluenesulfonate the aminal **48** was formed, and its X-ray crystallographic structural parameters revealed that the β-anomer was formed preferentially with both groups being in the axial position (Scheme 11). On the basis of

TABLE 5. Tandem Conjugate Addition-Cyclization of Ynoates



Entry	Starting Material		Product		Yield [%]
1[a]		**35ae**		**39a**	60
2		**35am**		**39a**	84
3		**35b**		**39b**	79
4		**35c**		**39c**	57
5		**35d**		**39d**	54
6[b]		**35e**		**39e**	50
7		**35a**		**40a**	73
8		**35b**		**40b**	65
9		**35c**		**40c**	58

[a] Reaction run in CH_2Cl_2/MeOH. [b] Reaction run in CH_2Cl_2/MeOH with acid quench.

SCHEME 10. Synthesis of Amino Derivatives 43 and 44

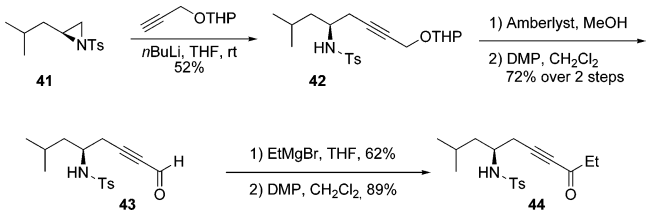
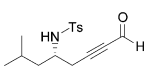
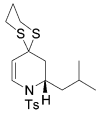
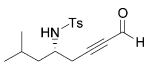
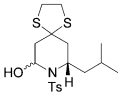
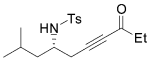
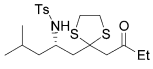


TABLE 6. Nitrogen as Nucleophile for Cyclization

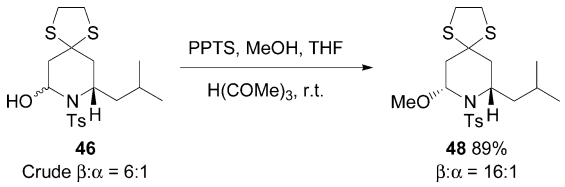
Entry	Starting material		Product		Yields [%]
1		**43**		**45**	78
2		**43**		**46**	89
3		**44**		**47**	74

NOESY experiments we could conclude that the β anomer was the favored anomer for both the hemiaminal **46** and the aminal **48**. The preferential formation of the diaxial com-

(29) Berry, M. B.; Craig, D. *Synlett* **1992**, 41−44.

(30) Piva, O.; U.M.R. U.C.B.L. C.N.R.S., 5622 Domaine Scientifique de la Doua, Bâtiment 305 4eme étage 43 Blvd, 69622 Villeurbanne, Cedex, France.

SCHEME 11. Formation of Aminal 48



pound over the axial−equatorial compound is presumed to be due to the shielding of one face of the piperidine by the tosyl group.

Following this success, the reaction was carried out on the ynone derivative; however, only the uncyclized product **47** was formed. This result could be explained by the steric hindrance caused by the tosyl group on the nitrogen atom clashing with the ethyl group and preventing the cyclization. Nevertheless the method may find further applications for other acyclic amine-substituted arrangements.

The piperidines successfully prepared using these methods potentially could be further functionalized to lead to natural products containing piperidine groups.

Conclusions

This work has developed particularly efficient and high-yielding procedures for the double conjugate addition of ethane and propane dithiols to a wide variety of propargylic carbonyl compounds. The products of the reaction constitute differentiated and protected 1,3-dicarbonyl and 1,3,5-tricarbonyl systems for potential application in organic synthesis. Of particular interest is the tolerance of the procedure to a large range of substituent group protection. Also when further hydroxyl or amino substitution is present, addition and tandem cyclization occurs to give useful lactols, lactones, and aminols as products depending upon the initial substitution patterns. The methods reported are now being employed in various natural product synthesis programs.

Experimental Section

All reactions were performed under an argon atmosphere and carried out using oven-dried glassware. Anhydrous solvents were dried over standard drying agents and freshly distilled prior to use. All other commercially available reagents were used as received. Reactions were monitored by TLC on silica gel and detected by UV fluorescence or by staining with acidic ammonium molybdate(IV) or potassium permanganate(VII). Flash column chromatography was performed on silica gel. Optical rotations were measured with a sodium lamp and are reported as follows: $[\alpha]_D^{25}$ (*c* (g/100 mL), solvent). ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz. Chemical shifts are recorded in ppm (δ) in $CDCl_3$ with the internal reference set to δ 7.26 ppm. ^{13}C NMR spectra were recorded at 100, 125, or 150 MHz. Chemical shifts are recorded in ppm (δ) in $CDCl_3$ with the internal reference set to δ 77.0 ppm. High-resolution mass spectra were obtained using electron impact (EI) or electrospray (+ESI). The general procedures can be found in the Supporting Information.

1-(2-Pentyl-[1,3]dithian-2-yl)-butan-2-one (2d). Compound **2d** was prepared using procedure A in 69% yield. IR (neat) 2953, 1708 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (2 H, s), 2.89−2.79 (4 H, m), 2.54 (2 H, q, J = 7.2 Hz), 2.08−1.89 (4 H, m), 1.37−1.07 (6 H, m), 1.05 (3 H, t, J = 7.2 Hz), 0.86 (3 H, t, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 50.3, 48.6, 38.6, 38.4, 31.8, 26.4 (2 C), 25.0, 23.8, 22.5, 14.1, 7.5. HRMS (+ESI) *m*/*z* 260.1276 [(M)$^+$; calcd for $C_{13}H_{24}OS_2$ 260.1269].

(3*R*,2′*S*)-1-{2-[2′-(Triethylsilanyloxy)-3′-(4-methoxybenzyloxy)-propyl]-[1,3]dithian-2-yl}-4-(*tert*-butyldiphenylsilanyloxy)-3-methyl-butan-2-one (2e). Compound **2e** was prepared using procedure A in 51% yield. $[\alpha]_D^{25}$ −13.0 (*c* 0.53, $CHCl_3$). IR (neat) 2932, 1709, 1512, 1247, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (3 H, m), 7.40 (7 H, m), 7.26 (2 H, d, J = 8.6 Hz), 6.86 (2 H, d), 4.45 (2 H, d, J = 2.4 Hz), 4.25−4.22 (1 H, m), 3.80 (3 H, s), 3.80 (1 H, dd, J = 9.9, 7.4 Hz), 3.63 (1 H, dd, J = 9.9, 5.8 Hz), 3.40 (1 H, dd, J = 12.5, 3.3 Hz), 3.38 (1 H, d, J = 15.7 Hz), 3.37 (1 H, dd, J = 12.5 Hz), 3.09 (1 H, d, J = 15.7 Hz), 2.97 (1 H, sextet, J = 6.8 Hz), 2.88−2.70 (4 H, m), 2.44 (1 H, dd, J = 15.2, 3.2 Hz), 2.33 (1 H, dd, J = 14.4, 7.2 Hz), 1.91 (2 H, m), 1.06 (9 H, s), 1.04 (3 H, d, J = 6.9 Hz), 0.94 (9 H, t, J = 7.9 Hz), 0.62 (6 H, q, J = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 159.1, 135.7, 135.6, 134.7, 133.4, 133.3, 130.5, 129.7, 129.3, 127.7, 113.7, 74.9, 72.9, 69.6, 66.5, 55.2, 51.3, 49.74, 49.67, 42.6, 26.9 (2 C), 26.6 (3 C), 26.4, 24.8, 19.2, 12.8, 7.0 (3 C), 5.4 (3 C). HRMS (+ESI) *m*/*z* 789.3475 [(M + Na)$^+$; calcd for $C_{42}H_{62}O_5S_2Si_2Na$ 789.3475].

(2*R*)-4-[2-(3-Benzyloxy-2-triethylsilanyloxy-propyl)-[1,3]dithiolan-2-yl]-3-oxo-butyric Acid Methyl Ester (3h). Compound **3h** was prepared using procedure A in 85% yield. $[\alpha]_D^{25}$ +12.4 (*c* 0.95, $CHCl_3$). IR (neat) 2953, 2875, 1748, 1718, 1238 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (5 H, m), 4.50 (2 H, m), 4.11 (1 H, dddd, J = 5.4, 5.4, 5.4, 5.4 Hz), 3.72 (3 H, s), 3.53 (1 H, d, J = 17.6 Hz), 3.45 (2 H, m), 3.39 (2 H, d, J = 5.3 Hz), 3.31 (1 H, d, J = 17.6 Hz), 3.25 (4 H, m), 2.39 (2 H, d, J = 6.0 Hz), 0.95 (9 H, t, J = 7.9 Hz), 0.62 (6 H, q, J = 7.9 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.6, 167.3, 138.1, 128.3 (2 C), 127.7 (2 C), 127.5, 75.1, 73.2, 71.0, 64.7, 55.6, 52.3, 49.8, 46.5, 39.4, 38.7, 6.8 (3 C), 5.3 (3 C). HRMS (+ES) *m*/*z* 499.2009 [(M + H)$^+$; calcd for $C_{24}H_{39}O_5S_2Si$ 499.2008].

2-(2-Propyl-[1,3]dithian-2-yl)-acetic Acid Methyl Ester (2j). Compound **2j** was prepared using procedure B in 71% yield. IR (neat) 2960, 1732, 1436, 1194, 1179 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (3 H, s), 3.06 (2 H, s), 3.01 (2 H, m), 2.72 (2 H, m), 2.08 (1 H, m), 2.01 (2 H, m), 1.86 (1 H, m), 1.58 (2 H, m), 0.95 (3 H, t, J = 7.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 51.6, 50.2, 42.7, 41.7, 26.4 (2 C), 25.0, 17.2, 14.2. HRMS (+ESI) *m*/*z* 235.0837 [(M + H)$^+$; calcd for $C_{10}H_{19}O_2S_2$ 235.0826].

2-(2-Propyl-[1,3]dithiolan-2-yl)-acetic Acid Methyl Ester (3j). Compound **3j** was prepared using procedure B in 90% yield. IR (neat) 2957, 1736, 1434, 1343, 1193, 1170 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67 (3 H, s), 3.27 (4 H, m), 3.02 (2 H, m), 2.05 (2 H, m), 1.49 (2 H, m), 0.91 (3 H, t, J = 7.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 66.8, 51.7, 47.7, 44.7, 39.5 (2 C), 20.4, 14.0. HRMS (+ESI) *m*/*z* 243.0485 [(M + Na)$^+$; calcd for $C_9H_{16}O_2S_2Na$ 243.0489].

(5*R*)-6-Benzyloxy-3-(1,2-dithiolan-2-yl)-5-triethylsilanyloxy-hexanoic Acid Methyl Ester (3k). Compound **3k** was prepared using procedure A in 55% yield. $[\alpha]_D^{25}$ +23.4 (*c* 0.795, $CHCl_3$). IR (neat) 2952, 2875, 1739 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (4 H, m), 7.26 (1 H, m), 4.52 (1 H, d, J = 12.0 Hz), 4.49 (1 H, d, J = 12.0 Hz), 4.14 (1 H, m), 3.67 (3 H, s), 3.40 (2 H, m), 3.26 (5 H, m), 3.06 (1 H, d, J = 16.6 Hz), 2.48 (1 H, dd, J = 14.8, 7.5 Hz), 2.44 (1 H, dd, J = 14.8, 3.8 Hz), 0.94 (9 H, t, J = 8.0 Hz), 0.62 (6 H, q, J = 8.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 138.2, 128.3, 127.7, 127.5, 75.1, 73.2, 70.9, 65.3, 51.4, 47.9, 46.3, 39.5, 38.8, 6.9, 5.3. HRMS (+ESI) *m*/*z* 457.1904 [(M + H)$^+$; calcd for $C_{22}H_{37}O_4S_2Si$ 457.1903].

(2′*R*,8*S*,10*R*)-8-[1′-(*tert*-Butyldiphenylsilyloxy)prop-2′-yl]-10-(*p*-methoxybenzyloxymethyl)-9-oxa-1,5-dithia-spiro[5.5]undecan-8-ol (23). To a solution of dithiane **22** (37 mg, 0.048 mmol) in MeOH and CH_2Cl_2 (1:1, 2 mL) at 0 °C was added $HClO_4$ (1 drop, 70% aq soln). After stirring at 0 °C for 20 min, the reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ (2 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extracts

were washed with saturated brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/Et_2O, 90:10) afforded **23** (29 mg, 94%) as a clear, colorless oil. $[\alpha]_D^{25}$ −36 (*c* 0.075, $CHCl_3$). IR (neat) 2929, 1654, 1513, 1248, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (4 H, m), 7.35 (6 H, m), 7.24 (2 H, d, J = 8.9 Hz), 6.87 (2 H, d, J = 8.5 Hz), 4.68 (1 H, s), 4.50 (2 H, AB quartet), 4.23 (1 H, m), 3.80 (3 H, s), 3.70 (1 H, dd, J = 9.6, 5.9 Hz), 3.62−3.55 (3 H, m), 3.03−2.95 (2 H, m), 2.75 (2 H, m), 2.69 (1 H, d, J = 13.8 Hz), 2.60 (1 H, m), 2.37 (1 H, m), 2.03 (3 H, m), 1.84 (1 H, m), 1.09 (3 H, d, J = 7.0 Hz), 1.04 (9 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.7, 135.6, 134.8, 133.94, 133.93, 130.3, 129.5, 129.3, 127.6, 113.8, 99.6, 73.1, 73.0, 71.4, 66.1, 55.3, 45.3, 40.9, 38.6, 30.3, 27.5, 27.2, 26.9 (3 C), 24.6, 19.3, 14.7. HRMS (+ESI) *m*/*z* 635.2684 [(M − OH)$^+$; calcd for $C_{36}H_{47}O_4S_2Si$ 634.9655].

(8*R*,10*R*)-10-Benzyloxymethyl-8-ethyl-9-oxa-1,5-dithia-spiro-[5.5]undecan-8-ol (31a). Compound **31a** was prepared using procedure D in 58% yield. $[\alpha]_D^{25}$ +18.0 (*c* 0.31, $CHCl_3$). IR (neat) 3381, 2906 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (5 H, m), 5.47 (1 H, s), 4.58 (2 H, d, J = 6.2 Hz), 4.28 (1 H, m), 3.58 (1 H, dd, J = 10.2, 4.7 Hz), 3.50 (1 H, dd, J = 10.2, 5.1 Hz), 3.11 (1 H, ddd, J = 14.5, 11.6, 2.8 Hz), 2.99 (1 H, ddd, J = 14.1, 11.5, 2.7 Hz), 2.80 (1 H, m), 2.74 (1 H, m), 2.68 (1 H, dd, J = 14.3, 2.2 Hz), 2.13 (2 H, m), 1.92 (2 H, m), 1.77 (1 H, dd, J = 13.5, 2.2 Hz), 1.65 (2 H, q, J = 7.4 Hz), 0.98 (3 H, t, J = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.3, 127.7, 127.6, 97.6, 73.4, 72.6, 64.7, 46.3, 41.7, 40.2, 35.2, 26.3, 25.9, 25.1, 7.3. HRMS (+ESI) *m*/*z* 377.1205 [(M + Na)$^+$; calcd for $C_{18}H_{26}O_3S_2Na$ 377.1221].

(8*RS*,10*R*)-10-Benzyloxymethyl-9-oxa-1,5-dithia-spiro[5.5]-undecan-8-ol (31b). Compound **31b** was prepared using procedure D. The lactol was obtained as an inseparable mixture of anomers (10:7) in 41% yield. IR (neat) 3411, 2907 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (10 H, m), 5.28 (1 H, m), 5.13 (1 H, ddd, J = 9.3, 6.1, 2.1 Hz), 4.57 (4 H, m), 4.36 (1 H, tdd, J = 9.4, 4.6, 2.5 Hz), (1 H, tdd, J = 7.8, 4.1, 2.1 Hz), 3.51 (4 H, m), 3.19 (1 H, d, J = 6.1 Hz), 3.04 (2 H, m), 2.83 (7 H, m), 2.56 (1 H, app. dt, J = 13.4, 2.1), 2.12 (4 H, m), 1.98 (4 H, m), 1.68 (2 H, m), one OH not observed. ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.9,128.41, 128.38,128.2, 127.8, 127.74, 127.67, 92.49, 92.46, 73.6, 73.5, 72.41, 72.39, 70.6, 63.5, 47.4, 45.4, 43.6, 39.9, 39.4, 39.0, 26.4, 26.0, 25.91, 25.86, 25.5, 25.0. HRMS (+ESI) *m*/*z* 349.0903 [(M + Na)$^+$; calcd for $C_{16}H_{22}O_3S_2Na$ 349.0908].

***trans*-(2′*RS*)-[1,3]-Dithian-2-spiro-4′-octahydro-chromen-2′-ol (31c).** Compound **31c** was prepared using procedure D. The lactol was obtained as an inseparable mixture of anomers (10:3.7) in 53% yield. The structure was confirmed by X-ray crystallography. IR (neat) 3380, 2929, 2856 cm^{-1}. Mp = 133−137 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (1 H, d, J = 11.5 Hz), 5.20 (1 H, ddd, J = 12.5, 3.9, 1.0 Hz), 5.12 (1 H, ddd, J = 11.1, 6.6, 1.9 Hz), 3.82 (1 H, app. dt, J = 10.2, 4.7 Hz), 3.60 (1 H, app. dt, J = 10.4, 4.3 Hz), 3.45 (1 H, d, J = 6.6 Hz), 3.13 (3 H, m), 3.04 (3 H, m), 2.81 (1 H, td, J = 14.4, 3.6 Hz), 2.66 (1 H, td, J = 14.4, 7.8 Hz), 2.15 (5 H, m), 1.97 (2 H, m), 1.80 (7 H, m), 1.60 (1 H, m), 1.32 (9 H, m), one OH not observed. ^{13}C NMR (125 MHz, $CDCl_3$) δ 92.8, 92.3, 73.0, 66.7, 52.7, 51.2, 51.1, 50.7, 44.4, 40.1, 32.92, 32.90, 25.76, 25.73, 25.67, 25.63, 25.58, 25.49, 25.41, 25.34, 25.14, 24.5, 24.3. HRMS (+ESI) *m*/*z* 283.0799 [(M + Na)$^+$; calcd for $C_{12}H_{20}O_2S_2$-Na 283.0802].

(10*R*)-10-Benzyloxymethyl-8-([1,3]dithian-2-yl)methyl-9-oxa-1,5-dithia-spiro[5.5]undec-7-ene (31d). Compound **31d** was prepared using procedure E in 91% yield. $[\alpha]_D^{25}$ +16.3 (*c* 1.035, $CHCl_3$). IR (neat) 3346, 2901, 1421, 1091, 1020 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (4 H, m), 7.28 (1 H, m), 5.63 (1 H, s), 4.81 (2 H, AB quartet), 4.39 (1 H, dd, J = 6.9, 5.4 Hz), 4.33 (1 H, m), 3.60 (1 H, dd, J = 10.3, 4.7 Hz), 3.53 (1 H, dd, J = 10.3, 4.9 Hz), 3.06 (1 H, ddd, J = 13.8, 10.8, 2.5 Hz), 2.98−2.76 (7 H, m), 2.21 (1 H, d, J = 13.8 Hz), 2.12 (1 H, dd, J = 14.7, 7.2 Hz), 2.07 (1 H, m), 2.05 (1 H, dd, J = 14.7, 5.3 Hz), 1.95−1.85 (3 H, m), 1.80 (1 H, t, J = 12.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 128.3 (2 C), 127.6 (2 C), 127.5, 96.8, 73.4, 72.5, 69.0, 65.3, 47.7, 46.3, 40.8, 39.8, 30.4, 30.2, 26.4, 26.0, 25.4, 25.0. HRMS (+ESI) *m*/*z* 463.0870 [(M + Na)$^+$; calcd for $C_{21}H_{28}O_2S_4Na$ 463.0870].

(8*R*,10*S*,11*S*)-8-([1,3]Dithian-2-yl)methyl-11-methyl-10-(1-methyl-allyl)-9-oxa-1,5-dithia-spiro[5.5]undecan-8-ol (31e).[21] Compound **31e** was prepared using procedure E in 65% yield. $[\alpha]_D^{25}$ +3.8 (*c* 1.00, $CHCl_3$). IR (neat) 3350, 2900, 1638, 1413, 1019 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 6.02 (1 H, ddd, J = 17.2, 10.4, 7.5 Hz), 5.95 (1 H, s), 5.04 (1 H, d, J = 17.2 Hz), 4.98 (1 H, d, J = 10.4 Hz), 4.40 (1 H, t, J = 6.2 Hz), 3.77 (1 H, dd, J = 10.4, 2.1 Hz), 3.16 (1 H, dt, J = 14.7, 2.4 Hz), 3.09 (1 H, app. d, J = 14.6 Hz), 2.93 (2 H, dt, J = 11.2, 2.5 Hz), 2.80 (3 H, m), 2.68 (1 H, m), 2.40 (1 H, app. t, J = 7.1 Hz), 2.14 (1 H, m), 2.08 (2 H, m), 2.03 (2 H, app. dq, J = 14.6, 5.8 Hz), 1.84 (3 H, m), 1.18 (3 H, d, J = 6.8 Hz), 0.99 (3 H, d, J = 7.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.5, 113.5, 95.9, 72.1, 53.4, 47.9, 43.5, 42.0, 41.4, 38.6, 30.7, 30.7, 25.8, 25.7, 25.5, 25.1, 11.9, 11.8. HRMS (+ESI) *m*/*z* 429.1026 [(M + Na)$^+$; calcd for $C_{18}H_{30}O_2S_4Na$ 429.1019].

(7*R*,9*R*)-9-Benzyloxymethyl-7-ethyl-8-oxa-1,4-dithia-spiro[4.5]-decan-7-ol (32a). Compound **32a** was prepared using procedure D in 63% yield. $[\alpha]_D^{25}$ +8.5 (*c* 0.42, $CHCl_3$). IR (neat) 3422, 2919 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (5 H, m), 4.57 (2 H, s), 4.24 (1 H, m), 3.53 (1 H, dd, J = 10.3, 5.4), 3.47 (1 H, dd, J = 10.3, 4.5 Hz), 3.31 (4 H, m), 3.21 (1 H, d, J = 0.9 Hz), 2.28 (1 H, dd, J = 14.1, 2.1 Hz), 2.12 (2 H, m), 1.92 (1 H, dd, J = 13.4, 11.5 Hz), 1.65 (2 H, q, J = 7.6 Hz), 0.95 (3 H, t, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 128.3 (2 C), 127.7 (2 C), 127.6, 97.7, 73.4, 72.7, 69.0, 60.3, 46.4, 44.0, 39.4, 37.6, 35.6, 7.4. HRMS (+ESI) *m*/*z* 363.1035 [(M + Na)$^+$; calcd for $C_{17}H_{24}O_3S_2Na$ 363.1065].

(7*R*,9*R*)-9-Benzyloxymethyl-7-(2-hydroxy-ethyl)-8-oxa-1,4-dithia-spiro[4.5]decan-7-ol (32f). Compound **32f** was prepared using procedure D in 90% yield. The β-anomer was formed in trace amounts, therefore only the α-anomer is reported below. $[\alpha]_D^{25}$ −4.3 (*c* 0.65, $CHCl_3$). IR (neat) 3393, 2918, 1091 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36−7.26 (5 H, m). 4.60 (1 H, s), 4.56 (2 H, m), 4.30 (1 H, m), 3.97 (1 H, m), 3.84 (1 H, m), 3.52 (2 H, dd, J = 6.8, 5.4 Hz), 3.33 (4 H, m), 2.64 (1 H, t, J = 4.9 Hz), 2.33 (1 H, dd, J = 13.9, 2.0 Hz), 2.19 (1 H, d, J = 13.9 Hz), 2.14 (1 H, d, J = 13.5 Hz), 1.99 (1 H, m), 1.93 (1 H, ddd, J = 14.5, 8.6, 3.6 Hz, 1 H), 1.83 (1 H, ddd, J = 14.5, 6.2, 3.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 128.4 (2 C), 127.68 (2 C), 127.65, 98.0, 73.4, 72.5, 68.9, 62.8, 58.5, 48.0, 43.7, 42.8, 39.4, 37.6. HRMS (+ESI) *m*/*z* 379.1000 [(M + Na)$^+$; calcd for $C_{17}H_{24}O_4S_2Na$ 379.1014].

(9*R*)-9-Benzyloxymethyl-8-oxa-1,4-dithia-spiro[4.5]decan-7-ol (32b). Compound **32b** was prepared using procedure D. The lactol was obtained as a mixture of anomers (10:6.5) in 64% yield. IR (neat) 3402, 2919, 2862 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (10 H, m), 5.34 (1 H, m), 4.88 (1 H, ddd, J = 9.3, 6.0, 2.0 Hz), 4.57 (4 H, m), 4.32 (1 H, m), 3.88 (1 H, m), 3.50 (4 H, m), 3.32 (8 H, m), 2.99 (1 H, d, J = 6.0 Hz), 2.36 (4 H, m), 2.01 (4 H, m), one OH not observed. ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.9, 128.40, 128.38, 127.83, 127.77, 127.72, 127.67, 95.2, 92.0, 73.8, 73.5, 73.4, 72.5, 72.3, 67.7, 64.0, 61.8, 48.1, 43.9, 43.7, 43.5, 39.6, 39.5, 38.0, 37.8. HRMS (+ESI) *m*/*z* 335.0744 [(M + Na)$^+$; calcd for $C_{15}H_{20}O_3S_2Na$ 335.0752].

***trans*-(2′*RS*)-[1,3]-Dithiolan-2-spiro-4′-octahydro-chromen-2′-ol (32c).** Compound **32c** was prepared using procedure D. The lactol was obtained as a mixture of anomers (10:4) in 58% yield. The structure was confirmed by X-ray crystallography. IR (neat) 3384, 2929, 2857 cm^{-1}. Mp = 109−111 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 5.25 (1 H, m), 4.86 (1 H, m), 4.08 (1 H, m), 3.70 (1 H, app. td J = 10.2, 4.4 Hz), 3.24 (9 H, m), 2.46 (3 H, m), 2.14 (2 H, m), 2.03 (1 H, dd, J = 13.0, 9.3 Hz), 1.96 (2 H, m), 1.92 (1 H, m),

1.75 (4 H, m), 1.65 (1 H, m), 1.53 (1 H, m), 1.32 (8 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 94.6, 92.1, 77.3, 71.5, 69.5, 67.3, 51.9, 51.5 (2 C), 47.7, 40.3 (2 C), 38.8, 38.6, 32.8, 32.7, 26.0, 25.6, 25.5, 25.4, 24.6. HRMS (+ESI) *m*/*z* 269.0650 [(M + Na)$^+$; calcd for $C_{11}H_{18}O_2S_2Na$ 269.0646].

(9*R*)-9-Benzyloxymethyl-7-([1,3]dithiolan-2-yl)methyl-8-oxa-1,4-dithia-spiro[4.5]decan-7-ol (32d). Compound **32d** was prepared using procedure E in 81% yield. $[\alpha]_D^{25}$ −8.0 (*c* 0.24, $CHCl_3$). IR (neat) 3398, 2919, 1423, 1091, 1038 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (4 H, m), 7.28 (1 H, m), 4.81 (1 H, dd, J = 8.7, 5.4 Hz), 4.58 (2 H, d, J = 3.1 Hz), 4.44 (1 H, s), 4.28 (1 H, m), 3.56 (1 H, dd, J = 10.3, 5.1 Hz), 3.51 (1 H, dd, J = 10.3, 4.5 Hz), 3.48 (4 H, m), 3.30 (3 H, m), 3.17 (1 H, m), 2.35 (1 H, dd, J = 11.8, 9.0 Hz), 2.24 (1 H, dd, J = 14.4, 9.0 Hz), 2.14 (2 H, m), 2.13 (1 H, d, J = 14.4 Hz), 1.95 (1 H, dd, J = 13.4, 11.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 128.3 (2 C), 127.6 (2 C), 127.6, 96.4, 73.4, 72.6, 69.0, 62.8, 49.9, 48.3, 47.3, 44.1, 39.5, 38.0, 37.9, 37.6. HRMS (+ESI) *m*/*z* 453.0654 [(M + Na)$^+$; calcd for $C_{19}H_{26}O_3S_4$-Na 453.0663].

(±)-(9-Benzyloxymethyl-7-hydroxy-8-oxa-1,4-dithia-spiro[4.5]-dec-7-yl)-acetic Acid Methyl Ester (32g). Compound **32g** was prepared using procedure D in 83% yield. IR (neat) 3452, 2921, 1717, 1437, 1168, 1092, 1022 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (4 H, m), 7.27 (1 H, m), 5.07 (1 H, d, J = 2.0 Hz), 4.55 (2 H, m), 4.35 (1 H, dddd, J = 11.3, 4.8, 4.8, 1.9 Hz), 3.71 (3 H, s), 3.49 (2 H, m), 3.30 (4 H, m), 2.67 (1 H, d, J = 15.4 Hz), 2.60 (1 H, d, J = 15.4 Hz), 2.42 (1 H, dd, J = 13.7, 1.9 Hz), 2.18 (1 H, dd, J = 13.7, 1.8 Hz), 2.12 (1 H, ddd, J = 13.5, 1.8, 1.8 Hz), 1.91 (1 H, dd, J = 13.5, 11.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 138.4, 128.3 (2 C), 127.6 (2 C), 127.5, 95.4, 73.2, 72.4, 69.1, 62.6, 51.9, 47.6, 44.7 (2 C), 39.8, 37.7. HRMS (+ESI) *m*/*z* 407.0963 [(M + Na)$^+$; calcd for $C_{18}H_{24}O_5S_2Na$ 407.0963].

(±)-9-Benzyloxymethyl-8-oxa-1,4-dithia-spiro[4.5]decan-7-one (39a). Compound **39a** was prepared using procedure A in 60% yield. Compound **39a** was prepared using procedure F in 84% yield. IR (neat) 2922, 1730, 1368, 1231, 1095, 1062 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33 (5 H, m), 4.67 (1 H, m), 4.59 (1 H, d, J = 12.0 Hz), 4.56 (1 H, d, J = 12.1 Hz), 3.69 (1 H, dd, J = 10.5, 4.2 Hz), 3.64 (1 H, dd, J = 10.5, 4.0 Hz), 3.40 (5 H, m), 3.17 (1 H, dd, J = 17.6, 2.3 Hz), 2.98 (1 H, d, J = 17.6 Hz), 2.42 (1 H, dd, J = 13.8, 11.5 Hz), 2.35 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.7, 137.6, 128.5 (2 C), 127.9, 127.7 (2 C), 78.3, 73.7, 71.2, 61.3, 47.0, 40.6, 39.9, 39.7. HRMS (+ESI) *m*/*z* 333.0587 [(M + Na)$^+$; calcd for $C_{15}H_{18}O_3S_2Na$ 333.0595].

(±)-9-Hex-5-enyl-8-oxa-1,4-dithia-spiro[4.5]decan-7-one (39b). Compound **39b** was prepared using procedure F in 79% yield. IR (neat) 2927, 1732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1 H, m), 5.00 (1 H, dd, J = 17.1, 1.5 Hz), 4.95 (1 H, app. d, J = 10.2 Hz), 4.47 (1 H, dddd, J = 11.6, 7.6, 4.8, 3.4 Hz), 3.39 (4 H, m), 3.17 (1 H, dd, J = 17.6, 2.3 Hz), 2.96 (1 H, d, J = 17.6 Hz), 2.34 (1 H, app. ddd, J = 14.1, 2.7, 2.7 Hz), 2.14 (1 H, app. dd, J = 14.0, 11.7 Hz), 2.06 (2 H, app. dd, J = 13.3, 6.6 Hz)), 1.73 (1 H, m), 1.65 (1 H, m), 1.55 (1 H, m), 1.44 (3 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 138.5, 114.7, 79.5, 61.4, 47.3, 44.3, 39.9, 39.7, 35.5, 33.5, 28.6, 24.2. HRMS (+ESI) *m*/*z* 295.0807 [(M + Na)$^+$; calcd for $C_{13}H_{20}O_3S_2Na$ 295.0802].

(±)-9-Allyloxymethyl-8-oxa-1,4-dithia-spiro[4.5]decan-7-one (39c). Compound **39c** was prepared using procedure F in 57% yield. IR (neat) 2927, 1732 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (1 H, m), 5.27 (1 H, dd, J = 17.1, 1.4 Hz), 5.19 (1 H, dd, J = 10.4, 0.8 Hz), 4.64 (1 H, m), 4.03 (2 H, m), 3.65 (1 H, dd, J = 10.6, 4.2 Hz), 3.61 (1 H, dd, J = 10.7, 4.0 Hz), 3.39 (4 H, m), 3.17 (1 H, dd, J = 17.6, 2.3 Hz), 2.98 (1 H, d, J = 17.6 Hz), 2.36 (2 H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 134.1, 117.5, 78.3, 72.6, 71.1, 61.3, 47.0, 40.6, 39.9, 39.7. HRMS (+ESI) *m*/*z* 283.0423 [(M + Na)$^+$; calcd for $C_{11}H_{16}O_3S_2Na$ 283.0439].

(±)-*trans*-[1,3]-Dithiolan-2-spiro-4′-octahydro-chromen-2′-one (39d). Compound **39d** was prepared using procedure F in 54% yield. IR (neat) 2933, 1730, 1231, 1198, 1044 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (1H, ddd, J = 10.6, 10.6, 4.2 Hz), 3.36 (3 H, m), 3.30 (1 H, d, J = 17.5 Hz), 3.20 (1 H, m), 3.02 (1 H, d, J = 17.7 Hz), 2.31 (1 H, m), 2.18 (1 H, m), 1.83 (3 H, m), 1.32 (4 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 82.5, 66.6, 50.3, 49.3, 40.3, 40.2, 32.9, 25.8, 24.9 24.3. HRMS (+ESI) *m*/*z* 267.0478 [(M + Na)$^+$; calcd for $C_{11}H_{16}O_2S_2Na$ 267.0489].

(±)-*trans*-[1,3]-Dithiolan-2-spiro-4′-hexahydro-cyclopenta[*b*]-pyran-2′-one (39e). Compound **39e** was prepared using a modified procedure F. The reaction was quenched with concentrated HCl and allowed to stir for 7 h. The reaction was neutralized with saturated $NaHCO_3$ and then worked up following procedure G. The lactone was obtained in 50% yield. The structure was confirmed by X-ray crystallography. IR (neat) 2977, 2921, 1729, 1219, 1094 cm^{-1}. Mp = 79−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (1 H, ddd, J = 10.1, 9.9, 7.7 Hz), 3.4−3.2 (4 H, m), 3.37 (1 H, d, J = 18.1 Hz), 3.16 (1 H, d, J = 18.3 Hz), 2.27 (1 H, td, J = 10.8, 7.1 Hz), 2.17 (1 H, m), 1.95 (1 H, m), 1.89 (1 H, m), 1.73 (3 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 82.9, 64.7, 52.2, 49.4, 40.7, 39.8, 29.3, 22.3, 18.4. HRMS (+ESI) *m*/*z* 231.0511 [(M + H)$^+$; calcd for $C_{10}H_{15}O_2S_2$ 231.0513].

(±)-10-Benzyloxymethyl-9-oxa-1,5-dithia-spiro[5.5]undecan-8-one (40a). Compound **40a** was prepared using procedure F in 73% yield. IR (neat) 2906, 1731, 1238, 1098, 1060 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (5 H, m), 4.80 (1 H, dddd, J = 11.9, 4.0, 4.0, 4.0 Hz), 4.60 (1 H, d, J = 12 Hz), 4.56 (1 H, d, J = 12 Hz), 3.68 (1 H, dd, J = 10.6, 4.4 Hz), 3.65 (1 H, dd, J = 10.6, 4.2 Hz), 3.21 (1 H, d, J = 17.4 Hz), 3.0−2.8 (4 H, m), 2.86 (1 H, d, J = 17.2 Hz), 2.50 (1 H, ddd, J = 14.4, 2.7, 2.7 Hz), 2.16 (1 H, dd, J = 14.4, 12.0 Hz), 2.00 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 137.6, 128.4 (2 C), 127.8, 127.7 (2 C), 75.7, 73.7, 71.1, 44.8, 43.3, 37.3, 26.6, 26.5, 24.5. HRMS (+ESI) *m*/*z* 325.0947 [(M + H)$^+$; calcd for $C_{16}H_{21}O_3S_2$ 325.0947].

(±)-10-[Hex-5-enyl]-9-oxa-1,5-dithia-spiro[5.5]undecan-8-one (40b). Compound **40b** was prepared using procedure F in 65% yield. IR (neat) 2931, 2858, 1728, 1238, 1052 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1 H, dddd, J = 16.9, 10.1, 6.7, 6.7 Hz), 5.00 (1 H, dd, J = 17.1, 1.6 Hz), 4.95 (1 H, bd, J = 10.2 Hz), 4.61 (1 H, m), 3.21 (1 H, dd, J = 17.2, 1.7 Hz), 3.02−2.80 (4 H, m), 2.92 (1 H, d, J = 17.0 Hz), 2.43 (1 H, ddd, J = 14.5, 2.6, 2.2 Hz), 2.04 (4 H, m), 1.90 (1H, dd, J = 14.4, 11.8 Hz), 1.63 (1 H, m), 1.43 (2 H, m), 1.25 (3 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 138.4, 114.6, 76.4, 44.8, 43.4, 41.3, 35.0, 33.5, 28.5, 26.7, 26.6, 24.5, 24.2. HRMS (+ESI) *m*/*z* 287.1133 [(M + H)$^+$; calcd for $C_{14}H_{23}O_2S_2$ 287.1139].

(±)-10-Allyloxymethyl-9-oxa-1,5-dithia-spiro[5.5]undecan-8-one (40c). Compound **40c** was prepared using procedure F in 58% yield. IR (neat) 2907, 1730, 1422, 1239, 1060 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1 H, dddd, J = 17.0, 10.6, 5.6, 5.3 Hz), 5.25 (1 H, bd, J = 17.2 Hz), 5.17 (1 H, bd, J = 10.3 Hz), 4.76 (1 H, m), 4.02 (2 H, AB quartet), 3.99 (1 H, d, J = 13.4 Hz), 3.61 (2 H, m), 3.17 (1 H, d, J = 17.3 Hz), 2.98−2.78 (5 H, m), 2.49 (1 H, bd, J = 14.4 Hz), 2.12 (1 H, m), 2.00 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 134.1, 117.4, 75.6, 72.5, 71.0, 44.8, 43.3, 37.3, 26.5, 26.4, 24.4. HRMS (+ESI) *m*/*z* 275.0763 [(M + H)$^+$; calcd for $C_{12}H_{19}O_3S_2$ 275.0776].

(*S*)-1-Isobutyl-5-(tetrahydro-pyran-2-yloxy)-*N*-toluensulfonyl-pent-3-ynylamine (42). To a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (2.25 mL, 16 mmol) in THF (9 mL) at −10 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 10 mL, 16 mmol). The resulting solution was stirred at ambient temperature for 30 min. The aziridine **41** (1.0 g, 4 mmol) in THF (4.4 mL) was added dropwise, and the reaction was stirred for 22 h. The mixture was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a yellow oil, which was purified by gradient flash column chromatography (hexanes/AcOEt 86:14 → 75:25) to yield compound **42** as a mixture of diastereomers (0.797 g, 52%). IR (neat) 3269, 2952, 2869, 1598 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (2 H, d, J = 8 Hz), 7.75

(2 H, d, J = 8 Hz), 7.28 (4 H, d, J = 8 Hz), 4.76 (2 H, m), 4.68 (2 H, m), 4.20 (4 H, m), 3.84 (2 H, m), 3.53 (2 H, m), 3.39 (2 H, m), 2.41 (6 H, s), 2.26 (4 H, m), 1.82 (2 H, m), 1.73 (2 H, m), 1.57 (10 H, m), 1.32 (4 H, m), 0.81 (6 H, d, J = 6 Hz), 0.73 (3 H, d, J = 6 Hz), 0.72 (3 H, d, J = 6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3 (2 C), 138.1 (2 C), 129.6 (4 C), 127.0 (4 C), 97.2, 97.0, 81.3 (2 C), 79.4, 79.3, 62.2, 62.1, 54.6, 54.5, 50.0 (2 C), 43.5 (2 C), 30.3 (2 C), 25.5, 25.3, 24.3 (2 C), 22.7 (2 C), 21.9 (2 C), 21.5 (2 C), 19.2 (2 C), 19.1 (2 C). HRMS (ESI) m/z 416.1891 [(M + Na)$^+$; calcd for $C_{21}H_{31}NO_4SNa$ 416.1872].

(5*S*)-5-(*N*-Toluensulfonyl-amino)-7-methyl-oct-2-ynal (43). The protected alcohol **42** (0.571 g, 1.45 mmol) was dissolved in MeOH (2 mL), amberlyst 15 was added (300 mg), and the reaction was stirred overnight at ambient temperature. The mixture was filtered, and the amberlyst was washed with Et_2O. The combined organic layers were concentrated under reduced pressure. Gradient flash column chromatography (hexanes/AcOEt 80:20 → 75:25 → 70:30) yielded starting material **42** (0.133 g, 23%) and the alcohol (0.241 g, 54%). $[\alpha]_D^{25}$ −83.0 (c 1.05, $CHCl_3$). IR (neat) 3272, 3020, 2957, 2870, 1598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2 H, d, J = 8.3 Hz), 7.29 (2 H, d, J = 8.5 Hz), 5.06 (1 H, m), 4.20 (2 H, s), 3.40 (1 H, m), 2.41 (3 H, s), 2.33 (1 H, m), 2.23 (1 H, m), 2.12 (1 H, br s), 1.52 (1 H, m), 1.32 (2 H, m), 0.79 (3 H, d, J = 6.6 Hz), 0.71 (3 H, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.1, 129.6 (2 C), 127.0 (2 C), 81.7, 81.1, 51.1, 50.1, 43.5, 25.5, 24.5, 22.5, 21.8, 21.5. HRMS (ESI) m/z 310.1469 [(M + H)$^+$; calcd for $C_{16}H_{24}NO_3S$ 310.1477].

The alcohol (750 mg, 2.44 mmol) was dissolved in CH_2Cl_2 (1.3 mL), and the solution was cooled to 0 °C. Dess−Martin periodinane (1.56 g, 3.7 mmol) was added, and while warming to ambient temperature the reaction was stirred for 2 h. The reaction was then quenched with saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ (1:1, 10 mL). The organic and aqueous layers were separated, and the aqueous layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a yellow oil. Gradient flash column chromatography (petroleum ether/AcOEt 80:20 → 70:30) yielded the aldehyde **43** as an opaque oil (736 mg, 99%). $[\alpha]_D^{25}$ −96.6 (c 1.1, $CHCl_3$). IR (neat) 3272, 2957, 2870, 2203, 1662, 1598 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (1 H, s), 7.76 (2 H, d, J = 8.3 Hz), 7.30 (2 H, d, J = 8.0 Hz), 4.56 (1 H, d, J = 8.6 Hz), 3.47 (1 H, m), 2.61 (1 H, ddd, J = 17.5, 5.9, 0.4 Hz), 2.53 (1 H, ddd, J = 17.4, 3.8, 0.4 Hz), 2.42 (3 H, s), 1.49 (1 H, m), 1.33 (2 H, m), 0.81 (3 H, d, J = 6.7 Hz), 0.66 (3 H, d, J = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 143.7, 137.5, 129.8 (2 C), 127.1 (2 C), 93.6, 83.5, 49.6, 43.5, 26.4, 24.4, 22.7, 21.57, 21.53. HRMS (ESI) m/z 308.1325 [(M + H)$^+$; calcd for $C_{16}H_{22}NO_3S$: 308.1320].

(7*S*)-7-(*N*-Toluensulfonyl-amino)-9-methyl-dec-4-yn-3-one (44). The aldehyde **43** (231 mg, 0.75 mmol) was dissolved in THF (13 mL) and cooled to −78 °C. To this stirred mixture was added ethylmagnesium bromide (3 M in Et_2O, 0.5 mL, 1.5 mmol), and the reaction mixture was allowed to warm to −30 °C and then stirred for 1 h. The reaction was cooled to −78 °C, EtMgBr (3 M in Et_2O, 0.25 mL, 0.75 mmol) was added, and then the reaction was stirred at −30 °C for 2 h. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a yellow oil. Gradient flash column chromatography (petroleum ether/AcOEt 75:25 → 70:30 → 65:35) yielded the alcohol (156 mg, 62%). IR (neat) 2961, 2253 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2 H, d, J = 8.1 Hz), 7.29 (2 H, d, J = 8.1 Hz), 4.81 (1 H, d, J = 9.1 Hz), 4.28 (1 H, br s), 3.40 (1 H, m), 2.42 (3 H, s), 2.27 (2 H, m), 2.02 (1 H, br s), 1.66 (2 H, m), 1.53 (1 H, m), 1.33 (2 H, m), 0.97 (3 H, t, J = 7.4 Hz), 0.80 (3 H, d, J = 6.6 Hz), 0.71 (3 H, d, J = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 138.1, 129.7 (2 C), 127.0 (2 C), 84.5, 80.1, 63.7, 50.1, 43.5, 31.0, 25.4, 24.3, 22.7, 21.9, 9.5. HRMS (ESI) m/z 360.1617 [(M + Na)$^+$; calcd for $C_{18}H_{27}NO_3SNa$ 360.1609].

The alcohol (119 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. To this solution was added Dess−Martin periodinane (225 mg, 0.53 mmol), and the resulting mixture was stirred for 30 min at 0 °C, then allowed to warm to ambient temperature, and stirred for 90 min. The reaction was quenched with saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ (1:1, 10 mL). The organic and aqueous layers were separated, the aqueous phase was extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography (petroleum ether/AcOEt 80:20) yielded the ketone **44** (104 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ −100.0 (c 0.515, $CHCl_3$). IR (neat) 3281, 2957, 2871, 2212, 1672, 1598 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (2 H, d, J = 8.3 Hz), 7.30 (2 H, d, J = 8.0 Hz), 4.43 (1 H, d, J = 8.8 Hz), 3.46 (1 H, m), 2.52 (4 H, m), 2.42 (3 H, s), 1.49 (1 H, m), 1.34 (2 H, m), 1.12 (3 H, t, J = 7.4 Hz), 0.82 (3 H, d, J = 6.6 Hz), 0.67 (3 H, d, J = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 143.7, 137.7, 129.8 (2 C), 127.0 (2 C), 88.5, 82.9, 49.7, 43.5, 33.8, 26.2, 24.4, 22.7, 21.6, 21.5, 8.0. HRMS (ESI) m/z 358.1446 [(M + Na)$^+$; calcd for $C_{18}H_{25}NO_3SNa$ 358.1453].

(10*S*)-10-Isobutyl-*N*-toluensulfonyl-1,5-dithia-9-aza-spiro[5.5]-undec-7-ene (45). The aldehyde **43** (58 mg, 0.19 mmol) was dissolved in CH_2Cl_2 and MeOH (1:1, 6 mL) and stirred at −10 °C for 30 min. Then 1,3-propanedithiol (29 μL, 0.28 mmol) followed by NaOMe (15 mg, 0.28 mmol) were added, and the reaction was allowed to warm to ambient temperature and was stirred for 12 h. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (1% MeOH in CH_2Cl_2) yielded piperidine **45** (59 mg, 78%). $[\alpha]_D^{25}$ +272.8 (c 1.85, $CHCl_3$). IR (neat) 2954, 2868, 1632, 1596 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (2 H, d, J = 8.3 Hz), 7.28 (2 H, d, J = 8.0 Hz), 6.62 (1 H, dd, J = 8.2, 1.0 Hz), 5.45 (1 H, dd, J = 8.2, 1.6 Hz), 3.92 (1 H, m), 2.92 (2 H, m), 2.77 (2 H, m), 2.40 (3 H, s), 2.36 (1 H, ddd, J = 14.7, 2.0, 2.0 Hz), 1.92 (2 H, m), 1.79 (1 H, m), 1.70 (1 H, m), 1.54 (1 H, ddd, J = 13.5, 6.7, 1.5 Hz), 1.52 (1 H, dd, J = 14.8, 5.4 Hz), 0.90 (3 H, d, J = 6.5 Hz), 0.89 (3 H, d, J = 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 136.0, 129.8 (2 C), 126.9 (2 C), 122.7, 110.5, 51.6, 42.0, 41.8, 37.3, 27.8, 26.5, 24.8, 24.5, 22.7, 21.6. HRMS (ESI) m/z 398.1277 [(M + H)$^+$; calcd for $C_{19}H_{28}NO_2S_3$ 398.1282].

(9*S*)-9-Isobutyl-*N*-toluensulfonyl-1,4-dithia-8-aza-spiro[4.5]-decan-7-ol (46). The aldehyde **43** (19 mg, 0.07 mmol) was dissolved in CH_2Cl_2 and MeOH (1:1, 1 mL) and stirred at −10 °C for 30 min. Then 1,2-ethanedithiol (9.2 μL, 0.11 mmol) followed by NaOMe (6 mg, 0.11 mmol) were added, and the reaction was allowed to warm to ambient temperature and was stirred for 12 h. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (0.5% MeOH in CH_2Cl_2) yielded a diastereomeric 6:1 mixture of piperidine **46** (19 mg, 71%). Only the major β-anomer is reported. IR (neat) 3486, 2954, 2921, 1325, 1160 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (2 H, d, J = 8.3 Hz), 7.29 (2 H, d, J = 8.0 Hz), 5.54 (1 H, ddd, J = 7.8, 4.9, 4.5 Hz), 4.15 (1 H, m), 3.52 (1 H, d, J = 5.0 Hz), 3.34 (2 H, td, J = 6.0, 2.0 Hz), 3.21 (2 H, t, J = 6.0 Hz), 2.46 (1 H, ddd, J = 14.3, 2.0, 2.0 Hz), 2.41 (3 H, s), 2.33 (1 H, ddd, J = 14.3, 3.1, 1.6 Hz), 2.18 (2 H, m), 1.60 (3 H, m), 0.89 (3 H, d, J = 6.3 Hz), 0.88 (3 H, d, J = 6.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.7, 129.6 (2 C), 127.3 (2 C), 76.7, 60.1, 51.7, 45.7, 44.6, 41.0, 40.2, 38.7, 25.5, 23.5, 21.5, 21.0. HRMS (ESI) m/z 402.1223 [(M + H)$^+$; calcd for $C_{18}H_{28}NO_3S_3$ 402.1231].

(2*S*)-1-[2-(2-(*N*-Toluensulfonyl-amino)-4-methyl-pentyl)-[1,3]-dithiolan-2-yl]-butan-2-one (47). The ketone **44** (52 mg, 0.155 mmol) was dissolved in CH_2Cl_2 and MeOH (1:1, 2 mL) and stirred at −10 °C for 20 min. Then 1,2-ethanedithiol (19 μL, 0.22 mmol) followed by NaOMe (12 mg, 0.22 mmol) were added ,and the reaction was allowed to warm to ambient temperature and was

stirred for 12 h. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (petroleum ether/AcOEt 80:20) yielded ketone **47** (48 mg, 74%). $[\alpha]_D^{25}$ +22.9 (*c* 0.535, $CHCl_3$). IR (neat) 3265, 2955, 2161, 2022, 1706, 1598 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (2 H, d, J = 8.2 Hz), 7.30 (2 H, d, J = 8.0 Hz), 4.73 (1 H, m), 3.50 (1 H, d, J = 18.1 Hz), 3.41 (1 H, m), 3.25 (2 H, m), 3.19 (2 H, m), 3.09 (1 H, d, J = 18.1 Hz), 2.46 (2 H, m), 2.43 (3 H, s), 2.29 (2 H, m), 1.42 (1 H, m), 1.13 (1 H, ddd, J = 13.5, 10.1, 4.2 Hz), 1.05 (3 H, t, J = 7.3 Hz), 0.92 (1 H, ddd, J = 16.9, 9.9, 3.5 Hz), 0.74 (3 H, d, J = 6.5 Hz), 0.69 (3 H, d, J = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.5, 143.3, 138.5, 129.6 (2 C), 127.3 (2 C), 64.8, 53.4, 52.1, 46.3, 45.7, 39.5, 38.0, 36.3, 24.6, 23.6, 21.5, 21.4, 7.5. HRMS (ESI) *m*/*z* 430.1552 $[(M + H)^+$; calcd for $C_{20}H_{32}NO_3S_3$: 430.1544].

(7*S*,9*R*)-7-Isobutyl-9-methoxy-*N*-toluensulfonyl-1,4-dithia-8-aza-spiro[4.5]decane (48). The crude hemiaminal **46** (900 mg) was dissolved in MeOH (60 mL), and then trimethylorthoformate (6 mL), THF (6 mL) and PPTS (621 mg, 2.47 mmol) were added. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched with saturated NH_4Cl and saturated $NaHCO_3$ (1:1), extracted with Et_2O, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield a yellow-white solid. Flash column chromatography (petroleum ether:AcOEt 90:10) yielded eliminated product in 2% yield and a diastereomeric 16:1 mixture of the piperidine **48** (759 mg, 89% over 2 steps). The structure was confirmed by X-ray crystallography. $[\alpha]_D^{25}$ +52.3 (*c* 1.2, $CHCl_3$). IR (neat) 2949, 1597 cm^{-1}. Mp = 91−98 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (2 H, d, J = 8.3 Hz), 7.30 (2 H, d, J = 8.0 Hz), 5.23 (1 H, dd, J = 3, 1 Hz), 3.93 (1 H, m), 3.39 (3 H, s), 3.33 (1 H, m), 3.23 (1 H, m), 3.15 (2 H, m), 2.49 (1 H, ddd, J = 14.5, 1.8, 1.8 Hz), 2.42 (3 H, s), 2.17 (1 H, ddd, J = 14.3,2.2, 2.1 Hz), 2.02 (2 H, m), 1.76 (2 H, m), 1.68 (1 H, m), 0.92 (3 H, t, J = 6.5 Hz), 0.88 (3 H, d, J = 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.7, 129.8 (2 C), 126.9 (2 C), 84.5, 60.2, 55.2, 51.9, 44.8, 43.1, 41.5, 40.9, 37.8, 25.1, 23.1, 21.5, 21.3. HRMS (ESI) *m*/*z* 438.1217 $[(M + Na)^+$; calcd for $C_{19}H_{29}NO_3S_3Na$ 438.1231].

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Supporting Information Available: Characterization data for the previously published compounds **2a**−**c**, **2f**−**g**, **2i**, **21a**−**c**, and **21e**−**g**; experimental data for compounds **25**−**28**; ^1H NMR and ^{13}C NMR spectra for unknown compounds; X-ray crystallographic data file in CIF format for **31c**, **32c**, **39e**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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