α,β-Unsaturated Nitriles: Stereoselective Conjugate Addition Reactions

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Dithiane anions undergo intramolecular conjugate additions with α,β-unsaturated nitriles when a dithiane anion is tethered to N-1 of the 3-cyano-1,4,5,6-tetrahydropyridine nucleus. 3-Cyano-1-[2-(1,3-dithianyl-2-yl)ethyl]-1,4,5,6-tetrahydropyridine (**1a**) and the one-carbon homologue **1b** cyclize in the presence of 12-crown-4 to generate indolizidine **3** and quinolizidine **9**, in which the nitrile group exhibits a strong, thermodynamic preference for the axial orientation. Oxidation of **1b** provides dithiane *S*-oxide **10** that undergoes a highly stereoselective conjugate addition to provide crystalline quinolizidine **13**. The X-ray structure of **13** is reported and corroborates our "peg-in-a-pocket" principle for stereoselective conjugate additions with α,β-unsaturated nitriles.

Introduction

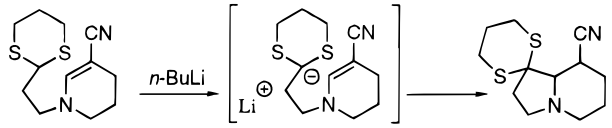
Conjugate addition reactions are of central importance for carbon−carbon bond formation.[2] Numerous anionic nucleophiles react conjugately with unsaturated carbonyl derivatives, but many analogous reactions involving unsaturated nitriles are problematic. Several organocopper[3] and phenolic[4] nucleophiles simply do not react with many α,β-unsaturated nitriles. Other, more reactive, organocopper reagents[5] and alkaline peroxide[6] afford products resulting from both 1,2- and 1,4-addition.

The sparse number of conjugate additions to unsaturated nitriles stimulated us to examine the key requirements for this reaction. From these initial studies[7] we developed highly efficient conjugate additions of sulfur and selenium nucleophiles to various substituted α,β-unsaturated nitriles. Our intention is to extend the conjugate additions of unsaturated nitriles to carbon-based nucleophiles, specifically with dithiane anions.

The reactions of dithiane anions are well established[8] and include one report[9] in which 2-lithio-1,3-dithiane reacts conjugately with α,β-unsaturated nitriles. The reaction is efficient provided that the α-carbon is conjugated to an aromatic substituent, but the yield is significantly reduced with aliphatic substituents. This report attracted us to dithiane anions, particularly since recent advances in the formation[10] and reactions of chiral dithiane equivalents (dithiane *S*-oxides[11] and dithiane *S*,*S*-dioxides)[12] indicated potential for a stereoselective conjugate addition reaction.

Our strategy was to promote the conjugate addition

Scheme 1



1a **2** **3**

by tethering a dithiane anion to an α,β-unsaturated nitrile (Scheme 1). This strategy benefits from the entropic advantage associated with constraining the two reacting partners in close proximity but requires generating a dithiane anion with a base that will neither react with the nitrile group nor cause deprotonation at other sites in the molecule. These constraints have restricted intramolecular cyclizations of dithiane anions to simple alkyl halides and tosylates[13] in all but a few[14] cases.

Enamino nitrile **1a** appeared to be an ideal substrate for probing the intramolecular conjugate addition reaction. Potential γ-deprotonation is avoided in **1a**, and we believed that the nitrile group would only slowly react with *n*-butyllithium. The reaction of alkyllithiums and Grignard reagents with nitriles is often sluggish[15] and would be further retarded since the nitrile is conjugated. Enamino nitrile **1a** had additional appeal since the successful cyclization assembles indolizidine skeleton **3**, common to a number of natural products.[16] In this paper

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(2) (a) Perlmutter, P. *Conjugate addition reactions in organic synthesis*; Pergamon: New York, 1992. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(3) (a) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893. (b) Totleben, M. J.; Curran, D. P.; Wipf, P. *J. Org. Chem.* **1992**, *57*, 1740, footnote 17. (c) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

(4) Kawamine, K.; Takeuchi, R.; Miyashita, M.; Irie, H.; Shimamoto, Ohfune, Y. *Chem. Pharm. Bull.* **1991**, *39*, 3170.

(5) (a) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.

(6) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Robert, A; Fouchaud, A. *Bull. Chim. Soc. Fr.* **1969**, 4528.

(7) Fleming, F. F.; Pak, J. J. *J. Org. Chem.* **1995**, *60*, 4299.

(8) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

(9) Basha, F. Z.; DeBernardis, J. F.; Spanton, S. *J. Org. Chem.* **1985**, *50*, 4160.

(10) (a) Bulman Page, P. C.; Wilkes, R. D.; Namwindwa, E. S.; Witty, M. J. *Tetrahedron* **1996**, *52*, 2125. (b) Bulman Page, P. C.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2911. (c) Colonna, S.; Gaggero, N.; Bertinotti, A.; Carrea, G.; Pasta, P.; Bernardi, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1123. (d) Aggarwal, V. K.; Evans, G.; Moya, E.; Dowden, J. *J. Org. Chem.* **1992**, *57*, 6390. (e) Aggarwal, V. K.; Davies, I. W.; Franklin, R. J.; Maddock, J.; Mahon, M.F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. I* **1991**, 662. (f) Bortolini, O.; Di Furia, F.; Licini, G.; Modena, G.; Rossi, M. *Tetrahedron Lett.* **1986**, *27*, 6257.

(11) (a) Bulman Page, P. C.; Shuttleworth, S. J.; Schilling, M. B.; Tapolczay, D. J. *Tetrahedron Lett.* **1993**, *34*, 6947. (b) Bulman Page, P. C.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902.

(12) Aggarwal, V. K.; Franklin, R.; Maddock, J.; Evans, G. R.; Thomas, A.; Mahon, M. F.; Molloy, K. C.; Rice, M. J. *J. Org. Chem.* **1995**, *60*, 2174.

(13) (a) Krohn, K.; Börner, G. *J. Org. Chem.* **1994**, *59*, 6063. (b) Sih, J. C. *J. Org. Chem.* **1982**, *47*, 4311. (c) Seebach, D.; Jones, N. R.; Corey, E. J. *J. Org. Chem.* **1968**, *33*, 300.

(14) (a) Grotjahn, D. B.; Andersen, N. H. *J. Chem. Soc., Chem. Commun.* **1981**, 306. (b) Davey, A. E.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 25.

(15) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.

(16) Michael, J. P. *Nat. Prod. Rep.* **1994**, *11*, 639.

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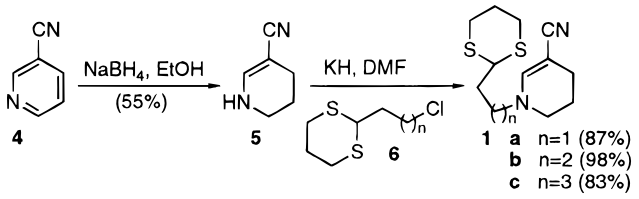
Scheme 2



we provide a full account of the first intramolecular conjugate addition between a dithiane anion and an α,β-unsaturated nitrile.

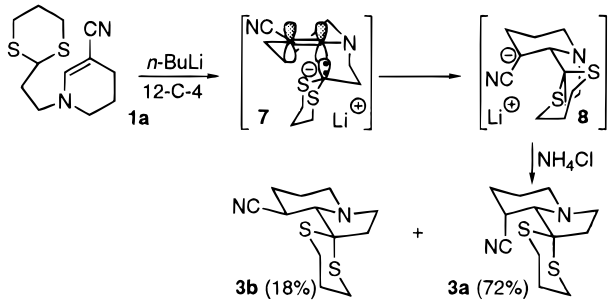
Results and Discussion

Enamino nitrile **1a** was readily prepared by coupling the two requisite dithiane and nitrile fragments, **6** and **5**. The latter is readily prepared by reduction of nicotinonitrile (**4**),[17] providing a fast, inexpensive method for preparing large quantities of tetrahydropyridine **5**. Initial attempts to alkylate **5** with the known[13c] dithianes **6a**−**c** were based on similar alkylations with the corresponding ester[18] (**5**, CN═CO_2Me). Typically the yields of alkylated tetrahydropyridines **1a**−**c** ranged between 50 and 60%, being comparable to alkylations with the corresponding esters. We ultimately found that the moderate yields resulted from hydroxide-promoted elimination and displacement reactions that were easily avoided by scrupulously drying the rather hygroscopic tetrahydropyridine **5**. This simple precaution provided the alkylated tetrahydropyridines **1a**−**c** in 83−98% yield (Scheme 2).

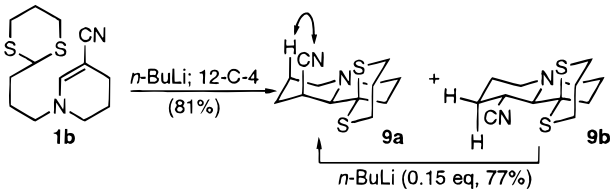
The rapid synthesis of **1a**−**c** expediently provided suitable precursors for examining the intramolecular conjugate addition reaction. We were surprised to find that the addition of butyllithium to a THF solution of **1a** afforded mainly unreacted material and only a trace of the desired indolizidine, particularly since these conditions were successful for the intermolecular reaction with α-aryl unsaturated nitriles.[9] A survey of different solvents (Et_2O, HMPA, TMEDA), additives (BF_3·OEt_2, Et_2-AlCl, Ti(*i*-PrO)$_4$, HMPA), and metal salts (LiCl, $ZnBr_2$) afforded varying amounts of the desired indolizidine where the amount of indolizidine roughly correlated with the solvation of the dithiane anion.

Solvent-separated ion pairs are known to promote conjugate addition reactions,[19] suggesting that sequestering the counterion would facilitate the cyclization. The cyclization did indeed proceed favorably when catalytic 12-crown-4 was added to the preformed anion, to provide a 4:1 ratio[20] of indolizidines **3a** and **3b** in 90% yield (Scheme 3). The requirement for 12-crown-4 may reflect the need for a free carbanion with an orbital that can overlap with the π-system of the unsaturated nitrile, as depicted in **7**. The high yield of this reaction precludes significant addition of butyllithium to the nitrile group, and this was further confirmed by GCMS analysis[21] of the crude reaction mixture.

Scheme 3



Scheme 4



Stereochemical assignment of the indolizidine epimers was achieved by X-ray crystallography. Surprisingly, the major isomer **3a** was found[22] to have the nitrile group in the axial orientation. The origin for this stereochemical preference is unclear, but we note that a thermodynamic preference for the axial isomer is conceivable given the small *A*-value (0.2 kcal mol^{-1})[23] for a nitrile group (vide infra).

Having optimized the conjugate addition reaction for indolizidine formation, we turned to the cyclization of homologue **1b** (Scheme 4). Deprotonation of **1b** and subsequent addition of 12-crown-4 smoothly afforded a mixture of quinolizidines **9a** and **9b** (3:1 ratio,[20] respectively; 81% combined yield). Separation of the individual epimers was more difficult than that for the indolizidines, requiring a combination of chromatography and crystallization, but these efforts were rewarded with a highly crystalline sample of the major epimer. X-ray analysis again demonstrated that the nitrile group was axial in the major isomer[24] and equatorial in the minor isomer.[25]

The unusual stereochemical preference for an axially oriented nitrile prompted us to examine the origin of this effect. Since both cyclizations occurred without significant interference from butyllithium, we used catalytic butyllithium to equilibrate a mixture of **9a** and **9b** to underscore the low reactivity of the nitrile group toward this nucleophilic base. Equilibration resulted in the exclusive formation of **9a** (Scheme 4). This equilibration is in stark contrast to analogous reactions of quinolizidine esters that result in the ester adopting an equatorial orientation.[26] We interpret the preference for an axial nitrile substituent as arising from a very small nitrile−proton syn−axial interaction rather than a less favorable gauche interaction with the adjacent methylene in **9b**.[27]

(17) Kikugawa, Y.; Kuramoto, M.; Saito, I.; Yamada, S.-I. *Chem. Pharm. Bull.* **1973**, *21*, 1914.
(18) Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269.
(19) (a) Cohen, T.; Abraham, W. D.; Meyers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923. (b) Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869.
(20) Based on isolated yields.
(21) Only trace amounts of a material with a molecular weight corresponding to the addition of butyllithum to the nitrile group was detected by GCMS.
(22) Fleming, F. F.; Hussain, Z.; Mullaney, M.; Norman, R. E.; Chang, S.-C. *Acta Crystallogr.* **1996**, *C52*, 2849.
(23) Eliel, E. L.; Wilen, S. H. Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 697.
(24) Hussain, Z.; Fleming, F. F.; Norman, R. E.; Chang, S.-C. *Acta Crystallogr.* **1996**, *C52*, 1296.
(25) Fleming, F. F.; Hussain, Z.; Norman, R. E.; Chang, S.-C. *Acta Crystallogr.* submitted.
(26) (a) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. I* **1994**, 2903. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 2219. (c) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037. (d) Goldberg, S. I.; Lipkin, A. H. *J. Org. Chem.* **1970**, *35*, 242.

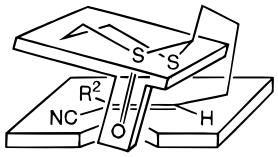
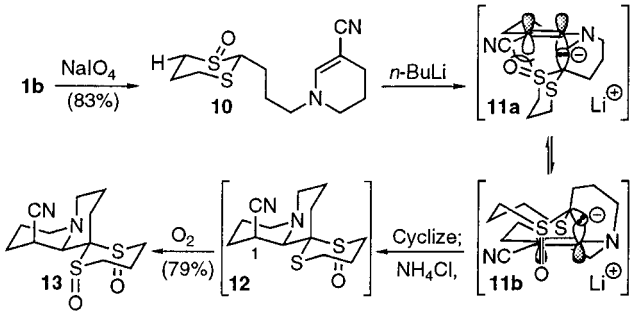


Figure 1.

Scheme 5



All attempts to extend this cyclization to formation of a 7-membered ring, with **1c**, have been unsuccessful.

Asymmetric carbon−carbon bond formation is very rare for nitrile-based methodology, mainly because of the difficulty of associating a chiral auxiliary with the CN unit. We reasoned that high stereoselectivity might be achieved by exploiting the unique topology of α,β-unsaturated nitriles. α,β-Unsaturated nitriles with one *trans* β-substituent contain a pocket between the small nitrile group and the proton that can act as a template in reactions with chiral nucleophiles (Figure 1). We envisaged that a dithiane *S*-oxide could provide a "peg" capable of locating in the nitrile pocket with only one matched "peg-in-a-pocket" conformation being accessible for a dithiane *S*-oxide tethered to the β-carbon of an α,β-unsaturated nitrile.

We employed dithiane *S*-oxide **10** to test this "peg-in-a-pocket" principle of stereocontrol. Periodate oxidation of dithianes is known[28] to generate *trans*-dithiane *S*-oxides, and in this case treatment with sodium metaperiodate furnished *trans*-*S*-oxide **10** (Scheme 5). ^{1}H NMR is particularly effective for assigning[29] the stereochemistry of the resultant *S*-oxide since the adjacent equatorial proton appears between δ 3.2 and 3.6 for the *trans* isomer and at higher fields for the *cis* isomer. The stereochemical assignment of **10** is confirmed by the diagnostic signal at δ 3.44, while the ^{13}C NMR clearly shows 13 distinct signals indicative of an unsymmetrical dithiane ring.

The cyclization of **10** to **12** was remarkably stereoselective (Scheme 5). Deprotonation of **10** caused formation of a precipitate with no cyclization occurring until the presumed anion was dissolved by the addition of HMPA.[30] Purification of the crude, cyclic, quinolizidine again required both chromatography and crystallization,

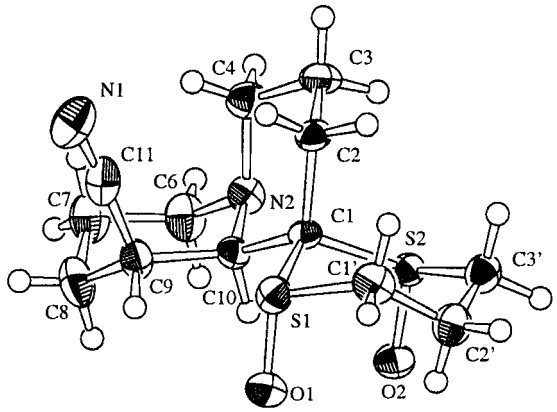


Figure 2. ORTEP drawing of the cyclic dithiane di-*S*-oxide **13**.

providing a single diastereomer in 79% yield. This diastereomer was highly crystalline and subjected to X-ray analysis to facilitate an otherwise difficult stereochemical assignment. We were initially surprised to find that the X-ray structure[31] (Figure 2) contained an additional *S*-oxide moiety. Di-*S*-oxide **13** contains a *cis*-fused quinolizidine, unlike **3** and **9**, which presumably reflects the strong steric interactions that would otherwise arise with the diaxial oxygen atoms. The quinolizidine ring is twisted slightly such that the axial nitrile is positioned further away from the ring methylene protons, effectively minimizing these 1,3-diaxial interactions.

We have previously noted[25] that dithiane-substituted quinolizidines are easily oxidized, and on one occasion oxidation occurred during crystallization from oxygen-containing solvents. The cyclic dithiane *S*-oxide **12** seems particularly susceptible to oxidation during purification, and we have observed that the ^{1}H NMR spectrum of the crude cyclization product differs from that of **13**, obtained after chromatography. The *cis* relationship between the *S*-oxide and the angular proton is established during C−C bond formation, and severe steric interactions are only avoided by positioning the *S*-oxide in the nitrile pocket (**11b**). This cyclization leads directly to **12** with the same conformation as that observed in the crystal structure. A subsequent ring-flip to the *trans*-fused quinolizidine is not expected since this would position the oxygen atom close to the methine proton at C-1. Oxidation of **12** from the *cis* conformer is likely directed[29] by the neighboring sulfoxide group leading to the observed di-*S*-oxide **13**.

Conclusion

Functionalized indolizidine and quinolizidines are rapidly assembled by an intramolecular conjugate addition between a dithiane-type anion and an α,β-unsaturated nitrile. This cyclization is one of the few known intramolecular conjugate additions involving an α,β-

(27) Molecular mechanics calculations (Chem-3D) indicate that the equatorially oriented nitrile **9b** is 0.2 kcal/mol more stable than **9a**. The X-ray structure[24] of **9a** shows that the quinolizidine ring is twisted so that the nitrile and the syn-axial proton are splayed further away from each other than in a true syn-axial relationship. In the X-ray structure[25] of the *S*-oxide derived from **9b**, the nitrile group is bent away from the dithiane ring and closer to the adjacent methylene unit, thereby exacerbating the gauche interaction between the nitrile and methylene groups.

(28) Cook, M. J.; Tonge, A. P. *J. Chem. Soc., Perkin Trans. II* **1974**, 767.

(29) Carey, F. A.; Dailey, O. D., Jr.; Hernandez, O.; Tucker, J. R. *J. Org. Chem.* **1976**, *41*, 3975.

(30) The use of catalytic 12-crown-4 did not homogenize the colloidal solution, and no cyclization was observed.

(31) Crystal data for $C_{13}H_{20}N_2O_2S_2$, **13**: M = 300.43, orthorhombic space group $Pca2_1$ (No. 29), a = 11.103(2) Å, b = 10.517(2) Å, c = 12.244(2) Å, V = 1429.8(8) Å, D_c = 1.40 g cm^{-3}, Z = 4, μ(Mo Kα) = 3.7 cm^{-1}, l (Mo Kα) = 0.710 69 Å, R = 0.032, R_w = 0.027 for 1379 observed reflections ($I > 3\sigma(I)$). The authors have deposited atomic coordinates for **13** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21EZ, U.K.

unsaturated nitrile and demonstrates the advantage of using the nitrile group in dithiane-based cyclizations. The method is unique in affording alkaloids with the nitrile group in an axial orientation and opens numerous possibilities for preparing axially-substituted indolizidines and quinolizidines. We have demonstrated excellent stereoselectivity in the first intramolecular conjugate addition of a dithiane *S*-oxide and envisage several chiral extensions using our "peg-in-a-pocket" principle.

Experimental Section

General experimental details can be found in ref 7. ^{1}H NMR spectra are recorded at 300 MHz while ^{13}C NMR spectra are recorded at 75 MHz. 3-Cyano-1,4,5,6-tetrahydropyridine was prepared as previously described[17] and dried by heating (75−85 °C) under vacuum for 10 min. The (chloroalkyl)dithianes **6b** and **6c** were prepared by known methods[13c] while **6a** was prepared as described but using *p*-toluenesulfonic acid in place of gaseous HCl.

N-Alkylation of 3-Cyano-1,4,5,6-tetrahydropyridine. Freshly distilled DMF (5 mL) was added to dry, THF-washed (3 × 1 mL), potassium hydride (35 wt %, 3 equiv) at room temperature. Molten 3-cyano-1,4,5,6-tetrahydropyridine (1 equiv) was added in one portion, and then 2 mL of DMF was used to wash the remaining material into the reaction flask. The resultant solution was stirred for 30 min, and then neat 2-(ω-chloroalkyl)-1,3-dithiane (1 equiv) was added. After 2 h, saturated aqueous NH_4Cl was added, and the aqueous phase was separated and then extracted with ether (3 × 20 mL). The extracts were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

3-Cyano-1-[2-(1,3-dithian-2-yl)ethyl]-1,4,5,6-tetrahydropyridine (1a). The general procedure was employed with potassium hydride (187.6 mg, 1.64 mmol), 3-cyano-1,4,5,6-tetrahydropyridine (59.0 mg, 0.55 mmol), and 2-(2-chloroethyl)-1,3-dithiane (99.7 mg, 0.55 mmol). The crude material was purified by radial chromatography (3:7 EtOAc:hexanes) to afford 120.1 mg (87%) of **1a** as a viscous, light yellow liquid: IR (film) 2931, 2181, 1623, 912 cm^{-1}; ^{1}H NMR δ 1.72−1.79 (m, 3H), 1.84 (br q, *J* = 7 Hz, 2H), 2.02−2.06 (m, 1H), 2.10 (br t, *J* = 6 Hz, 2H), 2.72−2.85 (m, 4 H), 3.00 (br t, *J* = 5 Hz, 2H), 3.19 (t, *J* = 6.6 Hz, 2H), 3.87 (t, *J* = 7.0 Hz, 1 H), 6.73 (s, 1 H); ^{13}C NMR δ 20.0 (t), 20.9 (t), 24.9 (t), 29.1 (t), 33.0 (t), 42.9 (d), 44.1 (t), 51.3 (t), 71.4 (s), 122.4 (s), 146.3 (d); MS *m*/*e* 254 (M^+).

3-Cyano-1-[3-(1,3-dithian-2-yl)propyl]-1,4,5,6-tetrahydropyridine (1b). The general procedure was employed with potassium hydride (767.0 mg, 6.71 mmol), 3-cyano-1,4,5,6-tetrahydropyridine (241.7 mg, 2.24 mmol), and 2-(3-chloropropyl)-1,3-dithiane (439.8 mg, 2.24 mmol). The crude material was purified by radial chromatography (4 mm plate, 3:7 EtOAc:hexane) to afford 589.7 mg (98%) of **1b** as a viscous, yellow liquid: IR (film) 2931, 2178, 1621 cm^{-1}; ^{1}H NMR δ 1.63−1.87 (m, 7H), 2.04−2.10 (m, 1H), 2.14 (t, *J* = 6.0 Hz, 2H), 2.74−2.89 (m, 4H), 3.01−3.05 (m, 4H), 3.99 (br t, *J* = 6 Hz, 1H), 6.69 (s, 1H); ^{13}C NMR δ 20.7 (t), 21.6 (t), 25.1 (t), 25.6 (t), 30.1 (t), 32.0 (t), 44.8 (t), 46.7 (d), 55.0 (t), 71.9 (s), 123.4 (s), 146.9 (d); MS *m*/*e* 269 (MH^+).

3-Cyano-1-[4-(1,3-dithian-2-yl)butyl]-1,4,5,6-tetrahydropyridine (1c). The general procedure was used with potassium hydride (1.63 g, 14.2 mmol), 3-cyano-1,4,5,6-tetrahydropyridine (512.4 mg, 4.74 mmol), and 2-(4-chlorobutyl)-1,3-dithiane (998.9 mg, 4.74 mmol). The crude material was purified by radial chromatography (4 mm plate, 3:7 EtOAc:hexane) to afford 1.11 g (83%) of **1c** as a white solid. A portion was recrystallized from hot hexane to provide **1c** as white needles (mp 73−75 °C); IR (KBr) 2930, 2167, 1619 cm^{-1}; ^{1}H NMR δ 1.43−1.58 (m, 4H), 1.71−1.92 (m, 5H), 2.05−2.08 (m, 1H), 2.09 (br t, *J* = 3 Hz, 2H), 2.78−2.93 (m, 4 H), 3.02−3.07 (m, 4H), 4.03 (t, *J* = 6.8 Hz, 1H), 6.73 (s, 1H); ^{13}C NMR δ 20.7 (t), 21.6 (t), 23.4 (t), 25.7 (t), 27.8 (t), 30.2 (t), 34.8 (t), 45.0 (t), 47.0 (d), 55.3 (t), 71.6 (s), 123.5 (s), 147.0 (d); MS *m*/*e* 283 (MH^+).

General Procedure for the Cyclization of 3-Cyano-1-[ω-(1,3-dithian-2-yl)alkyl]-1,4,5,6-tetrahydropyridines. A hexane solution of *n*-butyllithium (1.36 M, 1.4 equiv) was added by syringe to a THF solution (1 mL) of the 3-cyano-1-[ω-(1, 3-dithian-2-yl)alkyl]-1,4,5,6-tetrahydropyridine (1 equiv) at room temperature. The solution was stirred for 30 min and then neat 12-crown-4 (0.1 equiv) was added. After 18 h saturated, aqueous NH_4Cl was added, and the aqueous phase was separated and was then extracted with EtOAc (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude material that was purified by radial chromatography.

(±)-(8*R*,8a*S*)-Indolizidine-1-spiro-2′-(1′,3′-dithiane)-8-carbonitrile (3a). The general procedure was used with *n*-butyllithium (0.18 mL, 0.24 mmol), 3-cyano-1-[2-(1,3-dithian-2-yl)ethyl]-1,4,5,6-tetrahydropyridine (44.9 mg, 0.18 mmol), and 12-crown-4 (3.1 mg, 17.6 μmol). The crude product was purified by radial chromatography (1 mm plate, 1:1 EtOAc:hexane) to provide 32.5 mg (72%) of one diastereomer and 8.1 mg of another diastereomer (18%), both as white solids. The major diastereomer was recrystallized (EtOAc/hexane) to afford colorless crystals (mp 103−105 °C) of **3a**: IR (KBr) 2934, 2806, 2250, 1041 cm^{-1}; ^{1}H NMR δ 1.54−1.71 (m, 3H), 2.02−2.17 (m, 4H), 2.25−2.29 (m, 1H), 2.39 (br q, *J* = 9 Hz, 1H), 2.54−2.73 (m, 2H), 2.81−3.18 (m, 7H); ^{13}C NMR δ 23.8, 25.5, 26.9, 28.8, 29.5, 29.6, 43.1, 52.3, 52.5, 56.4, 74.9, 120.4; MS 254 (M^+). The minor diastereomer was recrystallized from hot hexane to give white crystalline (mp 96−99 °C) **3b**: IR (KBr) 2943, 2252, 1039 cm^{-1}; ^{1}H NMR δ 1.55−1.66 (m, 2H), 1.87−2.23 (m, 6H), 2.36−2.61 (m, 3H), 2.77 (br dt, *J* = 15, 4 Hz, 1H), 2.88 (br dt, *J* = 15, 4 Hz, 1H), 2.97 (br ddd, *J* = 14, 10.5, 3.2 Hz, 1H), 3.08−3.26 (m, 4H); ^{13}C NMR δ 21.3, 25.2, 27.6, 29.1, 29.9, 30.0, 42.0, 52.3, 53.2, 56.0, 77.3, 120.9; MS *m*/*e* 255 (MH^+).

(±)-(9*S*,9a*R*)-1,3,4,6,7,8,9,9a-Octahydro-2*H*-quinolizine-1-spiro-2′-(1′,3′-dithiane)-9-carbonitrile (9a). The general procedure was employed with *n*-butyllithium (70 uL, 99.1 μmol), 3-cyano-1-[3-(1,3-dithian-2-yl)propyl]-1,4,5,6-tetrahydropyridine (19.0 mg, 70.9 μmol) and 12-crown-4 (1.2 mg, 6.8 μmol). The crude reaction mixture was concentrated until all but 0.5 mL of the solvent was removed, and the remaining solvent was allowed to slowly evaporate. This procedure afforded a solid that was recrystallized from hexane to afford 9.0 mg (47%) of **9a** as a white, crystalline solid (mp 176−178 °C): IR (KBr) 2953, 2824, 2767, 2229, 1114, 913 cm^{-1}; ^{1}H NMR δ 1.49−1.55 (m, 1H), 1.70−1.94 (m, 4H), 2.04−2.25 (m, 5H), 2.43 (d, *J* = 6.1 Hz, 1H), 2.63 (dt, *J* = 14.4, 3.8 Hz, 1H), 2.72−2.94 (m, 5H), 3.03 (ddd, *J* = 14.3, 11.2, 3.1 Hz, 2H), 3.55 (br q, *J* = 6 Hz, 1H); ^{13}C NMR δ 20.2, 21.7, 25.3, 25.6, 26.4, 28.6, 30.3, 35.6, 53.9, 54.5, 57.5, 70.1, 122.1; MS *m*/*e* 269 (MH^+). The remaining oil was purified by radial chromatography (1 mm plate, 3:7 EtOAc:hexane) to afford 4.0 mg (21%) of **9b** as a light brown solid (mp 175−177 °C): IR (KBr) 2942, 2809, 2761, 2234, 1143 cm^{-1}; ^{1}H NMR δ 1.53−1.78 (m, 4H), 1.88−2.23 (m, 8H), 2.31 (br s, 1H), 2.63−2.91 (m, 5H), 3.00−3.18 (m, 3H), 3.55 (br s, 1H); ^{13}C NMR δ 21.0, 22.2, 25.3, 25.6, 26.1, 26.4, 28.5, 37.0, 53.1, 56.2, 56.5, 71.3, 122.9; MS *m*/*e* 269 (MH^+). Several mixed fractions, containing predominantly **9a**, were obtained providing 2.5 mg (13%) of a mixture of quinolizine isomers **9a** and **9b**.

Equilibration. A hexane solution of *n*-butyllithium (5 μL, 7 μmol) was added to a THF solution (1 mL) of a mixture of quinolizidine epimers **9a** and **9b** (11.8 mg, 44.0 μmol), causing the solution to become a light brown color. After 12 h saturated, aqueous NH_4Cl was added and the aqueous phase was separated and was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude material that was purified by radial chromatography (1mm plate, 3:7 EtOAc:hexane) to give 9.2 mg (78%) of **9a**, identical in all respects to the material previously isolated.

3-Cyano-1-[3-(*trans*-1-oxo-1,3-dithian-2-yl)propyl]-1,4,5,6-tetrahydropyridine (10). An aqueous solution (1 mL) of sodium metaperiodate (20.2 mg, 0.09 mmol) was added, dropwise, to a methanolic solution (2 mL) of **1b** (23.1 mg, 0.09 mmol) at room temperature. After 1 h the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the extracts were

combined and then dried over anhydrous sodium sulfate. The crude material was concentrated under reduced pressure and purified by radial chromatography (1 mm plate, 1:6 EtOH:EtOAc) to afford 20.3 mg (83%) of **10** as a light yellow oil: IR (film) 2933, 2854, 2178, 1621, 1018 cm^{-1}; ^1H NMR δ 1.62−1.91 (m, 5H), 2.17 (br t, J = 6 Hz, 2H), 2.21−2.33 (m, 2H), 2.43−2.48 (m, 1H), 2.56−2.75 (m, 3H), 3.04−3.12 (m, 4H), 3.44 (br d, J = 13 Hz, 1H), 3.56−3.60 (m, 1H), 6.72 (s, 1H); ^{13}C NMR δ 20.7 (t), 21.7 (t), 24.6 (t), 25.9 (t), 29.3 (t), 29.9 (t), 45.0 (t), 53.8 (t), 55.1 (t), 65.3 (d), 72.4 (s), 123.4 (s), 146.9 (d).

(±)-(1′*S*,3′*R*,9*S*,9a*R*)-1,3,4,6,7,8,9,9a-Octahydro-2*H*-quinolizine-1-spiro-2′-(1′,3′-dioxo-1′,3′-dithiane)-9-carbonitrile (13).[31] A hexane solution of *n*-butyllithium (149.3 μL, 0.21 mmol) was added by syringe to a THF solution (1 mL) of **10** (19.8 mg, 69.7 μmol) at room temperature. After 30 min, neat HMPA (120 μL) was added and the resultant solution was allowed to stir for a further 6 h. Saturated, aqueous NH_4Cl was then added the aqueous phase was separated and then extracted with EtOAc (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a light yellow liquid. The crude product was purified by radial chromatography (2 mm plate, 1:20 EtOH:CH_2Cl_2) and recrystallized from a mixture of EtOAc and EtOH to afford 15.6 mg (79%) of **13** as a white, crystalline solid (mp 194−196 °C): IR (film) 2996, 2916, 2250, 1047 cm^{-1}; ^1H NMR δ 1.25 (br s, 1H), 1.40−1.53 (m, 2H), 1.76−2.38 (m, 6H), 2.53 (br td, J = 14, 5.7 Hz, 1H), 2.63 (dd, J = 12.1, 4.2 Hz, 1H), 2.92−3.41 (m, 6H), 3.60 (br s, 1H), 3.84 (td, J = 12.1, 3.7 Hz, 1H), 4.16 (d, J = 3.3 Hz, 1H); ^{13}C NMR δ 3.9, 15.8, 20.4, 21.1, 22.1, 29.9, 41.9, 42.1, 44.0, 54.4, 55.0, 67.2, 123.6.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all new compounds and a table of fractional atomic coordinates (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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