A Tandem Horner−Emmons Olefination−Conjugate Addition Approach to the Synthesis of 1,5-Disubstituted-6-azabicyclo[3.2.1]octanes Based on the AE Ring Structure of the Norditerpenoid Alkaloid Methyllycaconitine

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A novel Horner−Emmons olefination conjugate addition reaction of *N*-acetylamides to form 1,5-disubstituted-6-azabicyclo[3.2.1]octanes with two bridgehead quarternary carbon centers is reported. This reaction is a key step in an approach to the synthesis of small ring analogues based on the AE ring structure of the *Delphinium* norditerpenoid, methyllycaconitine (MLA) (**1**). Initially, 3-(hydroxymethyl)cyclohex-2-en-1-one (**10**) was selected as the starting material to these structures, but its generation proved inefficient. In contrast, the synthesis of 3-[(phenylthio)methyl]cyclohex-2-en-1-one (**6**) and 3-(1,3-dithian-2-yl)cyclohex-2-en-1-one (**11**) proceeded in good yield. Subsequent hydrocyanation, ketalization, reduction, acetylation, deprotection of the acetal, and Horner−Emmons olefination−conjugate addition reaction to form 1-[(phenylthio)methyl]-5-[(ethoxycarbonyl)methyl]-6-acetamido-6-azabicyclo[3.2.1]octane (**28**), 1-(1,3-dithian-2-yl)-5-[(ethoxycarbonyl)methyl]-6-acetyl-6-azabicyclo[3.2.1]octane (**29**), respectively, are reported, as well as for readily available 3-methylcyclohex-2-en-1-one (**12**). Studies on the Pummerer rearrangement of **28** and subsequent desulfurization and reduction to form an hydroxymethyl-substituted azabicyclo[3.2.1.]octane (**40**) and then selective protection to form a protected hydroxyethyl *N*-ethyl (hydroxymethyl)azabicyclo-[3.2.1]octane (**3**) are also described.

Introduction

Azabicyclo[3.2.1]octanes are invaluable intermediates in natural product synthesis.[1] For example, Speckamp *et al.*[2] reported the formation of a 6-azabicyclo[3.2.1]-octanone by silicon-assisted *N*-acyliminium ion cyclization as a key step in the synthesis of the *Aristotelia* alkaloid peduncularine. Holmes *et al.*[3] reported a stereoselective synthesis of (±)-actinbolamine, the main degradation product of the antitumour compound, actinobolin, via a 6-azabicyclo[3.2.1]octane. Carroll *et al.*[4] have described a concise synthesis of (+)-6-methyl-6-azabicyclo[3.2.1]octan-3-ol, a key intermediate for the preparation of azaprophen (a novel conformationally restricted, highly potent antimuscarinic analogue of atropine). Shibanuma *et al.*[5] have published a synthetic approach to kobusine, a diterpene alkaloid whose BD ring system is a 6-azabicyclo[3.2.1]octane. Notwithstanding these achievements, stereocontrolled generation of 1,5 disubstituted 6-azabicyclo[3.2.1]octanes containing two bridgehead quaternary carbon centers, a structural feature not present in the azabicyclooctanes described above, is not well documented.[6] The formation of these heterocycles would be of value in the course of our synthetic studies in the structure−activity relationships of the *Delphinium* norditerpenoid methyllycaconitine (MLA) (**1**). Previously, construction of the AE ring system of this potent nicotinic acetylcholine receptor[7] antagonist used a double Mannich reaction on a keto ester to form the required azabicyclo[3.3.1]nonanes.[8] This bicyclic structure forms a crucial part of the rigid homocholine motif of the proposed MLA pharmacophore. Its relationship to acetylcholine[9] (**2**) is shown in Figure 1. However, in order to synthesize the related azabicyclo[3.2.1]octane system of our target (**3**) (Figure 2), to explore the effect of ring contraction upon antagonist activity, a different strategy was required. Our synthetic strategy is illustrated by the retrosynthetic analysis shown below (Scheme 1).

Discussion

Initially, attention was focused on the synthesis of 3-hydroxymethyl-substituted cyclohex-2-en-1-ones. The synthesis of 3-substituted cyclohex-2-en-1-ones has been comprehensively examined by Heathcock *et al.*[10] during synthetic investigations directed at the antitumor lactone, vernolepin. Recently, multistep syntheses of 3-substituted cyclohex-2-en-1-ones have been reported sepa-

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(4) Phillip, A.; Pitner, J. B.; Joo, Y. J.; Triggle, D. J.; Carroll, F. I. *J. Chem. Soc., Chem. Commun.* **1990**, 984.

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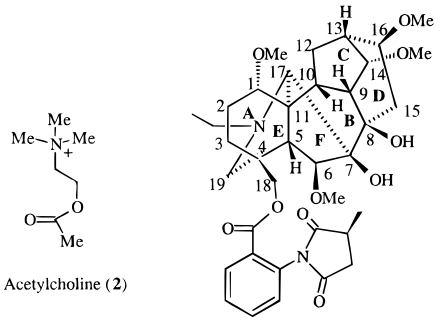


Figure 1.

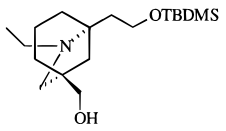
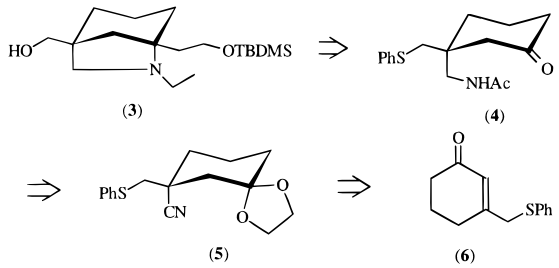


Figure 2.

Scheme 1



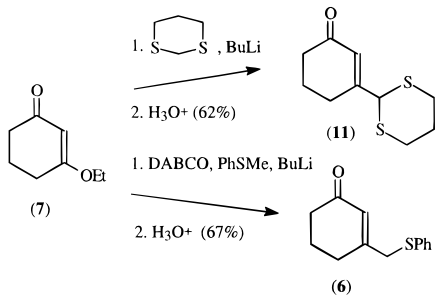
rately by Knochel *et al.*[11a] and Gleiter *et al.*[11b] The one-pot "reductive cyclization" (i.e. Birch reduction/hydrolysis) of 2,6-disubstituted pyridines to produce C-3 alkyl-substituted cyclohexenones as described by Danishefsky *et al.*[12] looked attractive, but attempts to apply this chemistry to the problem were not successful.[13] We therefore decided to utilize **11** and **6**, which incorporate dithianyl and (phenylthio)methyl groups, respectively, capable of later modification (Scheme 2).

Model reactions for our synthetic route were carried out on the readily available 3-methylcyclohex-2-en-1-one (**12**). Treatment of **12** with KCN, NH_4Cl, and DMF/15% H_2O[14] gave rise to the conjugate addition product **13** in 55% yield. Ketalization (ethylene glycol, PTSA) and lithium aluminum hydride reduction in diglyme at 85 °C[15] proceeded smoothly in yields of 90% and 75%, respectively. The key intermediate, keto acetamide **17**, was prepared from **16** by treatment with Et_3N and acetyl chloride in 91% yield, followed by deketalization in 90% yield (Scheme 3 and Table 1).

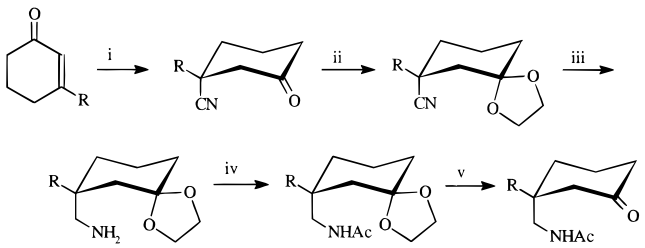
For the synthesis of key intermediates **6** and **11**, the commercially available 3-ethoxycyclohex-2-en-1-one (**7**) was used as a convenient starting material. Treatment of **7** with dithiane anion[10] in THF followed by acidic hydrolysis gave rise to dithianyl enone **11**[16] in 62% overall yield (Scheme 2). The corresponding β-cyano ketone **18** was prepared in yields ranging from 32−40% by reaction of **11** with KCN, DMF/15% H_2O and NH_4Cl at 105 °C for 6 h. The moderate yields of this reaction compared to that of **12** are attributed to the steric influence of the dithianyl substituent on the β-carbon of the cyclohexenone ring. The use of alternative reagents such as diethylaluminum cyanide[17] and trimethylsilyl cyanide[18] produced only unchanged starting material. Formation of acetal **21** from β-cyano ketone **18** was unproblematic (Scheme 3 and Table 1).

Interestingly, deprotection of ketal **21** gave rise to azabicyclooctanol (**22**)[19] and the ketoacetamide **23** in 87% combined yield in an approximate ratio of 1:1 by NMR. The NMR spectrum of the mixture of **22** and **23** showed

Scheme 2



Scheme 3[a]



[a] Reagents and Conditions: (i) KCN, NH_4Cl, DMF; (ii) PTSA, ethylene glycol; (iii) $LiAlH_4$, diglyme; (iv) AcCl, Et_3N; (v) H_2SO_4, H_2O, H_2O/THF.

Table 1

	yield (%) and compound no.				
	i	ii	iii	iv	v
R = Me (**12**)	55 (**13**)	90 (**14**)	75 (**15**)	91 (**16**)	90 (**17**)
R = 1,3-dithian-2-yl (**11**)	40 (**18**)	92 (**19**)	79 (**20**)	93 (**21**)	87 (1:1(**22**)/(**23**))
R = CH_2SPh (**6**)	46 (**24**)	95 (**5**)	78 (**25**)	88 (**26**)	91 (**4**)

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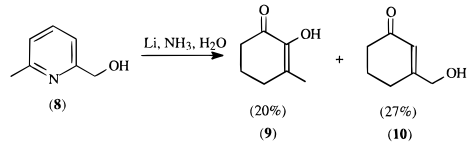
(13) At a concentration of 16 mmol, Birch reduction of pyridine **8** with lithium and water, formed the required trisubstituted cyclohex-2-en-1-one **10** and the unrequired tetrasubstituted cyclohex-2-en-1-one (**9**) in 27% and 20% yields, respectively. With higher concentrations, diminished yields of **9** and **10** were obtained.



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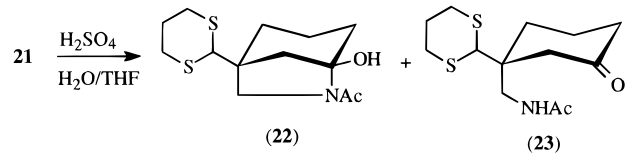
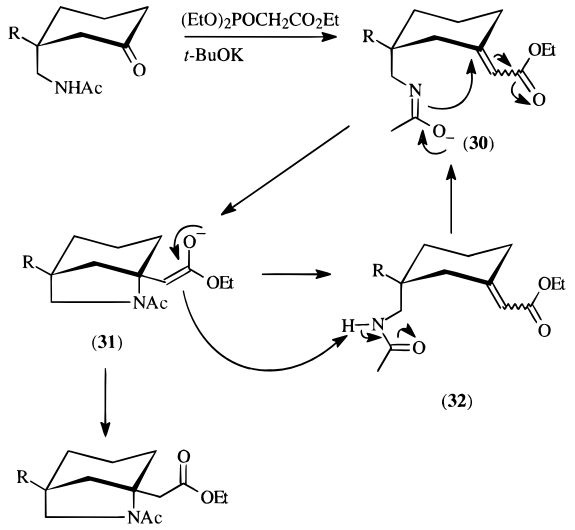
Scheme 4



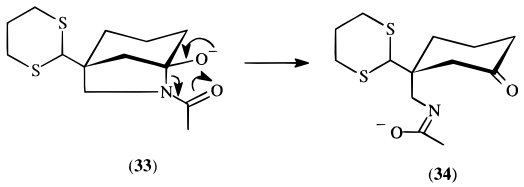
(**22**) (**23**)

Scheme 5

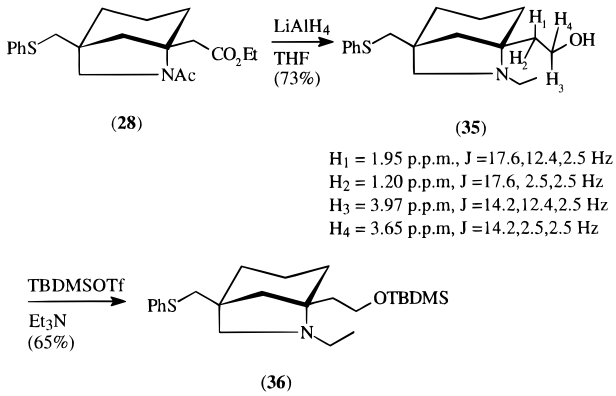


R = Me (50%) (**27**)
CH_2SPh (65%) (**28**)
1,3-dithian-2-yl (55%) (**29**)

Scheme 6



Scheme 7



a sharp singlet at δ 5.8 which disappears on deuteriation. The ^{13}C spectrum shows a peak at δ 93 indicating a quaternary carbon, the C-5 bridgehead chiral center. These data are consistent with the structure **22** (Scheme 4).

The preparation of acetamide **4** closely parallels that of **17** and **23** (Scheme 3 and Table 1). Ketone **6**[20] was prepared in 67% yield by treatment of **7** with thioanisole,[21] DABCO, BuLi, and THF, followed by acid hydrolysis[10] (Scheme 2). Interestingly, during the transformation of **16** to **17** and **26** to **4**, the (phenythio)methyl or methyl analogues of **22** were not observed. We assume that during the acid hydrolysis of the ketal the acetamide group is held closer to the ketone in **23** than in **17** or **4** as a consequence of the greater steric bulk of the dithianyl substituent favoring ring closure under acidic conditions to azabicyclo[3.2.1]octanol (**22**) (Scheme 4).

Optimum conditions for the ring closure of ketones **4**, **17**, and a mixture of **22** and **23** to esters **27**, **28**, and **29**, respectively, were found to be potassium *tert*-butoxide (1.1 equiv) and triethyl phosphonoacetate (1.1 equiv) in DMF or THF (Scheme 5). Clearly, 1 equiv of the base and the phosphonoacetate is consumed in the formation of the protonated form of **30**, which was not isolated. The residual 0.1 equiv of base effects deprotonation and hence the conjugate addition. The enolate **31** formed during ring closure is responsible for the deprotonation of more of the acetamide NH in **32**, *en route* to the bicyclic materials **27**, **28**, and **29**, respectively (formed in yields of 50%, 65%, and 55%, respectively). For the formation of **29** we assume the deprotonated alcohol **33** is first converted to ketone (**34**) (Scheme 6) which can then take part in the reaction cycle (Scheme 5).

The intramolecular Michael reaction has been the subject of a recent and detailed review.[22] Our Horner–Emmons olefination conjugate addition approach to azabicycles from amides appears to have little precedent, although a few related examples not involving amides are known in the carbohydrate field.[23]

In order to find appropriate conditions for the differential protection of the diol **40**, reduction of both the amide and ester groups of **28** was achieved by heating with $LiAlH_4$ in THF for 0.5 h to produce amino-alcohol **35**. Discrete chemical shifts and coupling constants for the protons H_1, H_2, H_3, and H_4 reveals a conformationally restricted hydroxyethyl side chain, the probable result of intramolecular H-bonding. Surprisingly, we were unable to *O*-alkylate amino alcohol **35** with benzyl bromide or methyl iodide and sodium hydride under standard conditions.[24] In stark contrast, the conversion of **35** to the corresponding silyl ether **36** was accomplished by utilizing the strong silylating agent TBDMSOTf and Et_3N in CH_2Cl_2[25] (Scheme 7).

A Pummerer rearrangement/desulfurization strategy[26] was proposed as a means of unmasking the (phenylthio)-methyl group to an hydroxymethyl group present in the target molecule **3**. Treatment of **28** with sodium periodate in MeOH at reflux produced a diastereoisomeric mixture of sulfoxides **37** in 76% yield. The rearrange-

(19) 5-Exo-trigonal ring closure of an amide NH group onto a ketone culminating in the formation of 6-methoxy-7-azabicyclo[4.2.1]nona-8-one has been reported, see: Newman, H.; Fields, T. L. *Tetrahedron* **1972**, *28*, 4051.

(20) For previous syntheses of (**6**) see: (a) Cohen, T.; Yu, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 2811. (b) Luzzio, F. A.; Moore, W. J. *J. Org. Chem.* **1993**, *58*, 2966.

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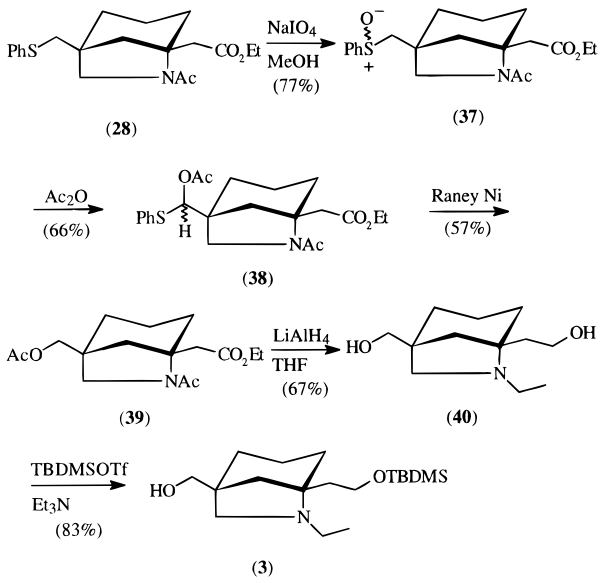
(23) Olefination conjugate additions with phosphonate sulfones to optically active tetrahydropyrans have been described: (a) Davidson, A. H.; Hughes, L. R.; Qureshi, S. S.; Wright, B. *Tetrahedron Lett.* **1988**, *29*, 693. (b) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317. (c) Bloch, R.; Seck, M. *Tetrahedron* **1989**, *45*, 3731. (d) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447. (e) Georges, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 5754.

(24) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

(25) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(26) (a) Delucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157. (b) Parham, W. E.; Edwards, L. D. *J. Org. Chem.* **1968**, *33*, 4150.

Scheme 8



ment product **38** was obtained as a mixture of diastereoisomers in 66% yield by treatment of **37** with acetic anhydride at reflux for 24 h. The downfield shift in the NMR spectrum for the PhSC*H*OAc proton (δ 6.20) confirmed that **38** had been formed.[26b] Raney nickel desulfurization produced **39** in 57% yield after chromatography, together surprisingly with **27** in a yield of 13%. Reduction of diester **39** produced diol **40**, which reacted under the same conditions as alcohol **35** to form silyl ether **3** in 83% yield (Scheme 8). The addition of the C-18 anthranoyl succinimide side chain of our intended analogues of MLA can be achieved on silyl ether (**3**) by established methodology.[8]

Conclusions

We have demonstrated that the tactical combination of intermolecular Horner−Emmons olefination and intramolecular conjugate addition is an effective method for the generation of the bridgehead substituted 6-azabicyclo[3.2.1]octane skeleton. This versatile and general methodology described above has produced a range of heterocycles. One of these heterocycles **28** has been shown to be capable of further elaboration to precursors for small ring analogues of the *Delphinium* alkaloid MLA, and the (phenylthio)methyl moiety has been shown to be a suitable masked hydroxymethyl group for the preparation of the C-18 ester side chain based on MLA (**1**).

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded either neat or in Nujol as indicated. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent and are reported in ppm downfield from TMS. Elemental analyses were performed at the University of Bath. Mass spectra were recorded at an ionizing voltage of 70 eV. THF was distilled from sodium benzophenone ketyl; toluene was distilled from P_2O_5 under nitrogen. All chiral compounds in this study were racemic mixtures unless indicated otherwise, and the names of structures describe only the relative stereochemistry of substituents.

2-Hydroxy-3-methylcyclohex-2-en-1-one (9) and 3-(Hydroxymethyl)cyclohex-2-en-1-one (10). To a vigorously stirred solution of 2-(hydroxymethyl)-6-methylpyridine (**8**) (2 g, 16 mmol) in H_2O (1.7 mL, 94 mmol) and NH_3 (20 mL) at −78 °C was added lithium (0.33 g, 48 mmol) in small pieces producing a dark blue solution. After approximately 20 min the dark blue coloration disappeared and the NH_3 was evaporated off under a stream of nitrogen. H_2O (20 mL) was added dropwise (cautiously!), and the resulting aqueous mixture were extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to produce a dark red oil. The crude product was purified by flash column chromatography (EtOAc) to yield **9** as a light brown solid (0.41 g, 20% R_f 0.71, mp 58−60 °C: lit. mp 60−61 °C[27]) and **10** as an orange oil (0.55 g, 27%, R_f 0.40).

For **9**: ^{1}H NMR ($CDCl_3$), δ 1.92 (3 H, s), 1.96 (2 H, quint, J = 6.4 Hz), 2.36 (2 H, tq, J = 6.4 and 1.1 Hz), 2.49 (2 H, t, J = 6.4 Hz), 6.08 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 16.8, 22.2, 30.4, 35.7, 130.7, 143.7, 194.1; IR ν 3450, 1670 cm^{-1}; mass spectrum *m*/*z*(%) 126(100), 111(10), 97(20), 84(20), 70(30), 55(24), 43(33), 27(20); HRMS: calcd for $C_7H_{10}O_2$ *m*/*z* 126.0680, found 126.0678. Anal. Calcd for $C_7H_{10}O_2$: C, 66.65, H, 7.99. Found: C, 66.80, H, 8.10.

For **10**: ^{1}H NMR ($CDCl_3$), δ 2.18−1.98 (2 H, m), 2.26 (2 H, q, J = 6.0 Hz), 2.31 (1 H, s(br)), 2.42 (2 H, t, J = 7.0 Hz), 4.26 (2 H, d, J = 1.6 Hz), 6.15 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 22.4, 26.1, 37.7, 64.7, 122.9, 167.4, 200.2; IR ν 3300−3400, 1710, 1646 cm^{-1}; mass spectrum *m*/*z*(%) 127(M + H)$^+$(100), 107(10), 91(10), 81(20). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.40; H, 8.29.

3-Cyano-3-methylcyclohexan-1-one (13). 3-Methylcyclohex-2-en-1-one (**12**) (10 g, 90 mmol) was dissolved in 15% H_2O/DMF (100 mL). KCN (11.84 g, 180 mmol) and NH_4Cl (17.29 g, 135 mmol) were added, and the mixture was heated at 100 °C for 1 h. The solution was cooled to room temperature and evaporated *in vacuo*, and H_2O (100 mL) was added. The aqueous phase was extracted with $CHCl_3$ (3 × 75 mL), and the combined extracts were washed with H_2O (2 × 70 mL), dried ($MgSO_4$), and evaporated *in vacuo* to form a dark brown oil. Column chromatography (50% EtOAc/hexane) produced **13** (6.85 g, 55%) as an orange oil: ^{1}H NMR ($CDCl_3$), δ 1.50 (3 H, s), 1.80−2.30 (5 H, m), 2.35 (1 H, dd, J = 14.5, 1.1 Hz), 2.46 (d(br), J = 14.5 Hz), 2.70 (1 H, ddd, J = 14.5, 2.0, 16.0 Hz); ^{13}C NMR ($CDCl_3$) δ 22.1, 26.1, 35.3, 36.6, 39.9, 50.8, 122.5, 205.8; IR ν 2250, 1725 cm^{-1}; mass spectrum *m*/*z*(%) 137(25), 94(25), 55(100); HRMS: calcd for $C_8H_{11}NO$ *m*/*z* 137.0841, found 137.0834. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.10; H, 8.05; N, 10.45.

7-Cyano-7-methyl-1,4-dioxaspiro[4.5]decane (14). Ketone **13** (6 g, 33 mmol) was dissolved in toluene (125 mL). Ethylene glycol (12.2 mL, 218 mmol) and PTSA (0.83 g, 4.3 mmol) were added. The mixture was heated at reflux in a Dean−Stark trap for 15 h. The solution was cooled to 25 °C and evaporated *in vacuo*, and H_2O (100 mL) was added. The mixture was neutralized with 2 M Na_2CO_3 solution, extracted with $CHCl_3$ (3 × 70 mL), dried ($MgSO_4$), and evaporated *in vacuo* to provide a dark red oil. Column chromatography (50% EtOAc/hexane) produced acetal **14** (7.13 g, 90%) as a red oil: ^{1}H NMR ($CDCl_3$) δ 1.20−2.10 (8 H, m), 1.40 (3 H, s), 3.80−4.00 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 20.7, 27.8, 33.7, 34.3, 36.4, 43.8, 64.3, 64.6, 107.0, 124.3; IR ν 2215, 1725 cm^{-1}; mass spectrum *m*/*z*(%) 181(30), 113(75), 99(100); HRMS: calcd for $C_{10}H_{15}NO_2$ *m*/*z* 181.1103, found 181.1097. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27, N, 7.73, H, 8.34. Found: C, 66.40; N, 7.60; H, 8.49.

7-(Aminomethyl)-7-methyl-1,4-dioxaspiro[4.5]decane (15). To a suspension of $LiAlH_4$ (3.14 g, 83 mmol) in diglyme (50 mL) was added dropwise acetal (**14**) (6 g, 33 mmol) in diglyme (150 mL) at 25 °C under nitrogen. The solution was heated to 85 °C for 5 min and cooled to 0 °C. H_2O (100 mL) was added very cautiously over a period of 0.75 h. The reaction mixture was extracted with Et_2O (3 × 70 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield the amine **15** (4.59 g, 75%) as a green oil, which was used in the next stage without further purification: ^{1}H NMR ($CDCl_3$) 0.90 (3 H, s), 1.20−1.70 (10 H, m) 2.44 (1 H, d, J = 13.0 Hz), 2.60 (1 H, d, J = 13.0 Hz), 3.90 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 19.5, 24.3, 34.4, 34.76, 36.2, 42.4, 52.3, 64.0, 71.8,

(27) Ohashi, M.; Takashashi, T.; Inoue, S.; Sato, K. *Bull. Chem. Soc. Jpn.* **1975,** *48,* 1892.

109.3; IR ν 3300, 1450 cm^{-1}; mass spectrum *m*/*z*(%) 185(15), 155(60), 141(50), 113(40), 99(100).

7-(Acetamidomethyl)-7-methyl-1,4-dioxaspiro[4.5]decane (16). Crude amine **15** (5.55 g, 19 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (2.11 g, 20 mmol) and acetyl chloride (1.64 g, 20 mmol) were added dropwise over a period of 0.5 h. The reaction mixture was warmed to 25 °C and stirred for 3 h. H_2O (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 60 mL). The combined extracts were washed with H_2O (4 × 50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to yield **16** (5.76 g, 91%) as a green oil after flash chromatography (10% MeOH/$CHCl_3$): ^1H NMR ($CDCl_3$) δ 1.30−1.90 (10 H, m), 2.10 (3 H, s), 3.10 (1 H, dd, J = 14.3, 4.8 Hz), 3.73 (1 H, dd, J = 14.3, 8.2 Hz), 4.77 (1 H, s), 6.20 (1 H, s(br)); ^{13}C NMR ($CDCl_3$) δ 19.4, 23.1, 24.8, 34.2, 34.3, 35.9, 43.0, 48.5, 63.8, 63.9, 108.9, 170.1; IR ν 3250, 1720, 1650, 1550 cm^{-1}; mass spectrum *m*/*z*(%) 227(5), 155(30), 99(50), 43(100); HRMS: calcd for $C_{12}H_{21}NO_3$ *m*/*z* 227.1521, found 227.1529. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; N, 6.16; H, 9.31. Found: C, 63.10; N, 6.22; H, 9.30.

3-(Acetamidomethyl)-3-methylcyclohexan-1-one (17). The acetamide **16** (4.33 g, 19 mmol) was dissolved in 10% H_2O/THF to which had been added concd H_2SO_4 (5 drops). The solution was refluxed for 3 h and then cooled to room temperature followed by evaporation *in vacuo*. H_2O (100 mL) was added, and the solution was neutralized with aqueous saturated $NaHCO_3$ solution followed by extraction with $CHCl_3$ (3 × 70 mL). The $CHCl_3$ extracts were combined and dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Flash chromatography (10% MeOH/$CHCl_3$) provided the ketone **17** (3.14 g, 90%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.50−1.90 (8 H, m), 2.00 (3 H, s), 3.10 (2 H, dd, J = 14.3, 6.4 Hz), 3.22 (2 H, dd, J = 14.3, 6.4 Hz), 5.68 (1 H, s(br)); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.7, 22.9, 33.5, 40.0, 40.7, 48.9, 50.9, 170.5, 211.4; mass spectrum *m*/*z*(%) 184(M + H)$^+$(100), 166(69), 124(28), 111(46); HRMS: calcd for $C_{10}H_{17}NO_2$ *m*/*z* 183.1259, found 183.1260. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; N, 7.64; H, 9.35. Found: C, 65.50; N, 7.50; H, 9.70.

1-Methyl-5-[(ethoxycarbonyl)methyl]-6-acetyl-6-azabicyclo[3.2.1]octane (28). Triethyl phosphonoacetate (1.35 g, 6 mmol) was dissolved in THF (20 mL) under nitrogen. Potassium *tert*-butoxide (1 M, 6 mmol) was added dropwise at 25 °C. The mixture was stirred at 25 °C for 1 h. Ketone **17** (1 g, 5 mmol) in THF (30 mL) was added dropwise at 25 °C. The solution was heated at reflux for 13 h, cooled to 25 °C, and evaporated *in vacuo*. H_2O (70 mL) was added, and the mixture was extracted with EtOAc (3 × 60 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to from a clear gum. Column chromatography (EtOAc) provided **28** (0.68 g, 50%) as a clear gum: ^1H NMR ($CDCl_3$) δ 1.05 (3 H, s), 1.21 (3 H, t, J = 7.1 Hz), 1.40−1.80 (8 H, m), 2.01 (3 H, s), 3.10 (2 H, d, J = 15.3 Hz), 3.25 (2 H, d, J = 15.3 Hz), 4.06 (2 H, q, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.1, 23.4, 24.0, 32.0, 37.0, 37.2, 41.1, 48.9, 59.7, 60.5, 64.4, 169.0, 171.0; IR ν 1750, 1725, 1650 cm^{-1}; mass spectrum *m*/*z*(%) 253(16), 210(32), 168(100), 122(10), 94(35), 43(15); HRMS: calcd for $C_{14}H_{23}NO_3$ *m*/*z* 253.1678, found 253.1681. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; N, 5.53; H, 9.15. Found: C, 66.20; N, 5.49; H, 9.35.

3-(1,3-Dithian-2-yl)cyclohex-2-en-1-one (11). To a solution of 1,3-dithiane (8.57 g, 71 mmol) in THF (125 mL) at −78 °C was added dropwise BuLi (2.5 M, 28.5 mL, 71 mmol), and the mixture was stirred at −78 °C for 2 h. 3-Ethoxycyclohex-2-en-1-one (**7**) (10 g, 71 mmol) in THF (25 mL) was added dropwise at −78 °C and the mixture stirred for 30 min. The mixture was warmed to −5 °C and stored overnight. The mixture was warmed to 25 °C and concentrated *in vacuo*, and H_2O (100 mL) was added. The resulting mixture was acidified (pH 3) with concd HCl and stirred at 25 °C for 1 h. The mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3 × 80 mL). The combined extracts were washed with H_2O (2 × 70 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a dark red oil. Column chromatography (50% EtOAc/hexane) produced **11** as a light green solid (9.5 g, 62%): mp 107−108 °C; ^1H NMR ($CDCl_3$) δ 1.80−2.20 (4 H, m), 2.40 (2 H, t, J = 6.4 Hz) 2.54 (2 H, t, J = 5.9 Hz), 2.95 (4 H, ddd, J = 2.9, 2.9, 2.9 Hz), 4.64 (1H, s), 6.10 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.9, 28.0, 30.3, 37.1, 51.6, 127.3, 160.3, 199.0; IR ν (Nujol) 1650, 1440 cm^{-1}; mass spectrum *m*/*z*(%) 214(100), 106(20), 73(52); HRMS: calcd for $C_{10}H_{14}OS_2$ *m*/*z* 214.0486, found 214.0492. Anal. Calcd for $C_{10}H_{14}OS_2$: C, 56.04; H, 6.58. Found: C, 56.00; H, 6.69.

3-Cyano-3-(1,3-dithian-2-yl)cyclohexan-1-one (18). The ketone **11** (9 g, 42 mmol), KCN (5.47 g, 84 mmol), and NH_4Cl (3.37 g, 63 mmol) were heated in 15% H_2O/DMF (100 mL) for 6 h at 105 °C. The solvent was evaporated *in vacuo*, and the resulting residue partitioned between H_2O and $CHCl_3$ as for **12**, evaporated *in vacuo*, and dried ($MgSO_4$). Pure product was obtained by flash chromatography (5% EtOAc/$CHCl_3$) to yield compound **18** (4.05 g, 40%) as a light brown solid: mp 112−113 °C; ^1H NMR ($CDCl_3$) δ 1.80−2.50 (8 H, m), 2.66 (1 H, d, J = 14.8 Hz) 2.85 (2 H, ddd, J = 14.5, 8.2, 2.9 Hz), 3.04 (2 H, ddd, J = 14.3, 3.6, 3.6 Hz), 4.10 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 17.2, 21.8, 24.9, 29.8, 31.8, 40.0, 46.7, 47.6, 52.7, 119.6, 205.2; IR ν (Nujol) 2250, 1650 cm^{-1}; mass spectrum *m*/*z*(%) 242(M + H)$^+$(100), 119(97), 85(26), 69(55); HRMS: calcd for $C_{11}H_{15}NOS_2$ *m*/*z* 241.0595, found 241.0594. Anal. Calcd for $C_{11}H_{15}NOS_2$: C, 54.74; H, 6.26; N, 5.80. Found: C, 54.80; H, 6.30; N, 6.18.

7-Cyano-(1,3-dithian-2-yl)-1,4-dioxaspiro[4.5]decane (19). Ketone **18** (6.6 g, 27 mmol) was dissolved in toluene (125 mL). Ethylene glycol (7.6 mL, 136 mmol) and PTSA (0.52 g, 2.7 mmol) were added. The mixture was heated at reflux with a Dean−Stark trap for 15 h. The solution was cooled to 25 °C and evaporated *in vacuo*, and H_2O (100 mL) was added. The aqueous mixture was neutralized with 2 M Na_2CO_3 solution and extracted with $CHCl_3$ (3 × 70 mL), dried ($MgSO_4$), and evaporated to yield **19** (7.19 g, 92%) as a dark red oil: ^1H NMR ($CDCl_3$), δ 1.50−2.20 (5 H, m), 2.22 (2 H, d, J = 14.4 Hz) 2.86 (2 H, ddd, J = 11.3, 4.6, 4.6 Hz), 3.08 (2 H, ddd, J = 14.3, 5.4, 5.4 Hz), 3.90 (2 H, m), 4.00 (2 H, m), 4.20 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 20.0, 24.9, 29.3, 29.4, 32.9, 34.4, 39.9, 43.6, 52.8, 64.3, 64.5, 106.8, 121.3; IR ν 2250 cm^{-1}; mass spectrum *m*/*z*(%) 286(M + H)$^+$(100), 268(10), 242(10); HRMS: calcd for $C_{13}H_{19}NO_2S_2$ *m*/*z* 285.0857, found 285.0888. Anal. Calcd for $C_{13}H_{19}NO_2S_2$: C, 54.71; H, 6.71; N, 4.91. Found: C, 54.60; H, 6.90; N, 4.85.

7-(Aminomethyl)-7-(1,3-dithian-2-yl)-1,4-dioxaspiro-[4.5]decane (20). The ketal **19** (6.93 g, 24.3 mmol) was treated with $LiAlH_4$ (2.50 g, 65.9 mmol) in diglyme as for compound **14**. Partitioning between Et_2O and H_2O and evaporation *in vacuo* in the previously described manner gave rise to amine **20** (5.53 g, 79%) as an orange oil, which was used in the next stage without further purification: ^1H NMR ($CDCl_3$) δ 1.25−2.20 (14 H, m), 2.90 (2 H, dd, J = 18.0, 14.0 Hz), 2.92 (4 H, dd, J = 7.6, 4.9 Hz), 4.00 (4 H, m), 4.50 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.3, 30.0, 31.6, 31.8, 34.9, 37.5, 43.7, 46.6, 57.6, 63.9, 64.1, 108.8; IR ν 3,200−3,500 cm^{-1}; mass spectrum *m*/*z*(%) 290(M + H)$^+$(50), 272(10), 230(5), 99(15).

7-(Acetamidomethyl)-7-(1,3-dithan-2-yl)-1,4-dioxaspiro-[4.5]decane (21). Crude amine **20** (5.33 g, 18 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (2.05 g, 20 mmol) and acetyl chloride (1.59 g, 20 mmol) were added dropwise over a period of 0.5 h. The reaction was warmed to 25 °C and stirred for 3 h. H_2O (100 mL) was added and extracted with $CHCl_3$ (3 × 80 mL). The combined extracts were washed with H_2O (4 × 60 mL), dried ($MgSO_4$), and evaporated *in vacuo* to form an orange oil. Column chromatography (10% MeOH/$CHCl_3$) produced **21** (5.67 g, 93%) as an orange gum: ^1H NMR ($CDCl_3$) δ 1.30−1.90 (10 H, m), 2.10 (3 H, s), 2.90 (4 H, m), 3.10 (1 H, dd, J = 14.3, 4.8 Hz), 3.73 (1 H, dd, J = 14.3, 8.2 Hz), 4.77 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.9, 26.2, 30.5, 31.3, 32.0, 35.0, 38.7, 43.5, 45.2, 56.4, 63.8, 64.2, 109.0, 169.8; mass spectrum *m*/*z*(%) 332(M + H)$^+$(50), 272(40), 259(27), 212(100), 119(45), 99(90). Anal. Calcd for $C_{15}H_{25}NO_3S_2$: C, 54.35; N, 4.23; H, 7.60. Found: C, 54.0; N, 3.95; H, 7.87.

1-(1,3-Dithian-2-yl)-5-hydroxy-6-acetyl-6-azabicyclo-[3.2.1]octane (22) and 3-(Acetamidomethyl)-3-(1,3-dithian-2-yl)cyclohexanone (23). Acetamide **21** (5.82 g, 17 mmol) was dissolved in 10% H_2O/THF (60 mL). Five drops of concentrated H_2SO_4 were added and the solution refluxed for 3 h. The mixture was cooled to 25 °C and evaporated *in vacuo*. H_2O (100 mL) was added and the solution neutralized with aqueous saturated $NaHCO_3$ solution and extracted with $CHCl_3$

(3 × 70 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to form an orange gum. Column chromatography (10% MeOH/$CHCl_3$) produced an approximate 1:1 mixture of **22** and **23** (4.37 g, 87%) as an orange solid. This mixture was used in the next stage without further purification: ^{1}H NMR ($CDCl_3$) δ 1.40−1.90 (16 H, m), 1.95 (3 H, s), 2.00 (3 H, s), 2.05−2.10 (4 H, m), 2.30−2.40 (4 H, m), 3.00 (8 H, m), 3.25 (1 H, d, J = 5.5 Hz), 3.30 (1 H, d, J = 5.3 Hz), 3.40 (1 H, m), 3.55 (1 H, d, J = 7.9 Hz), 4.10 (1 H, s), 4.20 (1 H, s), 5.95 (1 H, s), 6.25 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 20.2, 20.9, 22.4, 23.1, 25.7, 30.7, 30.9, 31.2, 31.3, 31.5, 35.5, 40.5, 43.9, 44.9, 46.8, 46.8, 47.3, 56.1, 56.7, 92.8, 170.0, 170.7, 209.6; IR ν (Nujol) 1705, 1650 cm^{-1}; mass spectrum *m*/*z*(%) 287(5), 271(45), 119(100), 110(60), 99(45), 83(84).

1-(1,3-Dithian-2-yl)-5-[(ethoxycarbonyl)methyl]-6-acetyl-6-azabicylo[3.2.1]octane (29). Triethylphosphonoacetate (13.01 g, 14 mmol) was dissolved in DMF (20 mL) under nitrogen. Potassium *tert*-butoxide (1 M, 14 mL, 14 mmol) was added dropwise at 25 °C. The mixture was stirred at 25 °C for 1 h. The mixture of keto amide **22** and alcohol **23** (3.74 g, 13 mmol) in DMF (70 mL) was added dropwise at 25 °C. The solution was heated at 60 °C for 13 h, cooled to 25 °C, and evaporated *in vacuo*. H_2O (80 mL) was added and the aqueous layer extracted with EtOAc (3 × 70 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to form an orange gum. Column chromatography (EtOAc) produced **29** (2.56 g, 55%) as a white solid: mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, t, J = 7.2 Hz), 1.40−1.90 (6 H, m), 2.00 (3 H, s), 2.90 (4 H, m), 3.00 (1 H, d, J = 15.9 Hz), 3 27 (1 H, d, J = 15.9 Hz), 3.45 (1 H, d, J = 9.9 Hz), 3.52 (1 H, d, J = 9.9 Hz), 4.10 (2 H, q, J = 7.2 H), 4.20 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.6, 23.4, 25.7, 30.9, 31.1, 31.4, 32.6, 40.7, 44.9, 46.4, 57.5, 58.5, 59.7, 64.2, 169.1, 170.7; IR ν (Nujol) 1740, 1640 cm^{-1}; mass spectrum *m*/*z*(%) 357(17), 312(15), 238(48), 196(100), 118(43), 69(47), HRMS: calcd for $C_{17}H_{27}NO_3S_2$ *m*/*z* 357.1432, found 357.1479. Anal. Calcd for $C_{17}H_{27}NO_3S_2$: C, 57.11; N, 3.92; H, 7.61. Found: C, 56.80; N, 3.80; H, 7.76.

3-[(Phenylthio)methyl]cyclohex-2-en-1-one (6). To a solution of thioanisole (17.72 g, 143 mmol) and DABCO (16.00 g, 143 mmol) in THF (100 mL) at 0 °C was added dropwise BuLi (2.5 M, 57 mL, 143 mmol), and the mixture was stirred at 0 °C for 0.75 h. 3-Ethoxycyclohex-2-enone (**7**) (20 g, 143 mmol) in THF (50 mL) was added dropwise at 0 °C, the mixture stirred at room temperature for 15 h and concentrated *in vacuo*, and H_2O (150 mL) was added. The resulting mixture was acidified (pH 3) with concd HCl and stirred at 25 °C for 1 h. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 125 mL). The combined extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a dark red oil. Column chromatography (25% EtOAc/hexane) produced ketone **6** (20.84 g, 67%) as a light green oil: ^{1}H NMR ($CDCl_3$) δ 2.00 (2 H, dd, J = 6.0, 6.2), 2.30 (2 H, t, J = 6.1 Hz), 2.45 (2 H, t, J = 6.2 Hz), 3.60 (1 H, s), 5.80 (1 H, s), 7.20−7.40 (5 H, m); IR ν 1675 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 22.6, 28.2, 37.3, 41.9, 127.4, 127.5, 129.0, 131.2, 134.4, 159.9; mass spectrum *m*/*z*(%) 218(100), 203(20), 124(25), 110(22), 51(33), 39(62), 27(25); HRMS: calcd for $C_{13}H_{14}OS$ *m*/*z* 218.0721, found 218.0729. Anal. Calcd for $C_{13}H_{14}OS$: C, 71.52; H, 6.46. Found: C, 71.60; H, 6.60.

3-Cyano-3-[(phenylthio)methyl]-1-cyclohexan-1-one (24). Ketone **6** (10 g, 46 mmol) was dissolved in 15% H_2O/DMF (100 mL). KCN (5.97 g, 92 mmol) and NH_4Cl (3.68 g, 68 mmol) were added, and the mixture was heated at 100 °C for 3 h. The solution was cooled to room temperature and evaporated *in vacuo* and H_2O (100 mL) added. The mixture was extracted with $CHCl_3$ (3 × 90 mL), and the combined extracts were washed with H_2O (80 mL), dried ($MgSO_4$), and evaporated *in vacuo* to form a dark brown oil. Column chromatography (5% EtOAc/$CHCl_3$) produced cyano ketone **24** (5.17 g, 46%) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 1.80−2.40 (5 H, m), 2.50 (2 H, d(br), J = 18.0 Hz), 2.70 (1 H, d(br), J = 14.5 Hz), 3.23 (2 H, dd, J = 13.7 Hz), 7.20−7.43 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 22.0, 32.9, 40.1, 43.0, 43.9, 48.6, 120.7, 127.6, 129.3, 131.1, 134.9, 205.1; IR ν (Nujol) 2250, 1725 cm^{-1}; mass spectrum *m*/*z*(%) 245(5), 123(23), 43(100); HRMS: calcd for $C_{14}H_{15}NOS$ *m*/*z* 245.0874, found 245.0956. Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.60; H, 6.14; N, 5.79.

7-Cyano-7-[(phenylthio)methyl]-1,4-dioxaspiro[4.5]-decane (5). The ketone **24** (9.20 g, 37.6 mmol) in toluene was reacted with ethylene glycol (10.5 mL, 188.3 mmol) and PTSA (0.71 g, 3.7 mmol) as described for compound **19**. Ketal **5** was isolated by flash chromatography (50% EtOAc/hexane) (10.33 g, 95%) as a green oil: ^{1}H NMR ($CDCl_3$) δ 1.40−2.00 (7 H, m), 2.10 (1 H, d, J = 13.7 Hz), 3.20 (2 H, s), 4.00 (4 H, m), 7.18−7.42 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 20.2, 34.0, 34.4, 40.0, 41.3, 44.6, 64.4, 64.6, 106.9, 122.4, 127.3, 129.1, 130.9, 135.0; IR ν 2250 cm^{-1}; mass spectrum *m*/*z*(%) 289(100), 180(42), 99(64); HRMS: calcd for $C_{16}H_{19}NO_2S$ *m*/*z* 289.1136, found 289.1130. Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; N, 4.84; H, 6.62. Found: C, 66.30; N, 4.86; H, 6.67.

7-(Aminomethyl)-7-[(phenylthio)methyl]-1,4-dioxo-aspiro[4.5]decane (25). To a suspension of $LiAlH_4$ (3.1 g, 81 mmol) in diglyme (50 mL) was added dropwise acetal **5** (9.45 g, 32 mmol) in diglyme (150 mL) at 25 °C under nitrogen. The solution was heated to 85 °C for 5 min and cooled to 0 °C. H_2O (100 mL) was added very cautiously over a period of 0.75 h. The resulting aqueous was extracted with Et_2O (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to form crude amine **25** (7.47 g, 78%) as a red oil: ^{1}H NMR ($CDCl_3$) δ 1.20−1.80 (8 H, m), 2.70 (2 H, dd, J = 13.4, 13.4 Hz), 3.15 (2 H, dd, J = 12.3, 12.3 Hz), 3.90 (4 H, m), 7.20−7.42 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 18.2, 33.6, 35.7, 40.2, 40.7, 49.1, 63.8, 70.8, 71.7, 109.3, 126.8, 129.1, 130.1, 138.4; IR ν 3,200−3,400 cm^{-1}; mass spectrum *m*/*z*(%) 294(100), 184(27), 155(28), 99(20).

7-(Acetamidomethyl)-7-[(phenylthio)methyl]-1,4-dioxoaspiro[4.5]decane (26). Crude amine **25** (7.40 g, 25.2 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (2.80 g, 27.7 mmol) and acetyl chloride (2.17 g, 27.7 mmol) were added dropwise over a period of 0.5 h. The reaction was warmed to 25 °C and stirred for 3 h. H_2O (100 mL) was added and the resulting aqueous extracted with $CHCl_3$ (3 × 70 mL). The combined extracts were washed with H_2O (4 × 60 mL), dried ($MgSO_4$), and evaporated *in vacuo* to form a yellow oil. Column chromatography (10% MeOH/$CHCl_3$) produced amide **26** (7.42 g, 88%) as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 1.20−1.80 (6 H, m), 1.90 (3 H, s), 2.10 (2 H, m), 3.00−3.20 (2 H, m), 3.40 (2 H, m), 3.90 (4H, m), 5.40 (1 H, s), 7.20−7.40 (5 H, m); ^{13}C NMR δ 19.1, 23.1, 32.0, 33.9, 34.5, 40.2, 40.5, 41.9, 45.9, 63.9, 108.6, 125.9, 128.8, 129.5, 137.4, 170.2; IR ν, 3300, 1740 cm^{-1}; mass spectrum *m*/*z*(%) 335(5), 212(10), 99(30), 43(100); HRMS: calcd for $C_{18}H_{25}NO_3S$ *m*/*z* 335.1555, found 335.1557. Anal. Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; N, 4.18; H, 7.51. Found: C, 64.20; N, 4.13; H, 7.51.

3-(Acetamidomethyl)-3-[(phenylthio)methyl]cyclohexanone (4). The ketal **26** (5.08 g, 15.2 mmol) was treated with 10% H_2O/THF (100 mL) and concd H_2SO_4 (cat.) in the manner described for compound **16**. Ketone **4** was isolated by flash chromatography (10% MeOH/$CHCl_3$) as a yellow oil (4.05 g, 91%): ^{1}H NMR ($CDCl_3$) δ 1.60−2.00 (8 H, m), 2.30 (3 H, s), 2.90 (2 H, s), 3.21 (dd, J = 14.3, 6.4 Hz), 3.35 (1 H, dd, J = 14.3, 7.2 Hz), 5.41 (1 H, s(br)), 7.20−7.40 (5 H, m); ^{13}C NMR δ 13.8, 21.0, 22.6, 30.3, 40.3, 43.9, 44.8, 48.7, 126.1, 128.7, 129.4, 136.2, 170.5, 210.4; IR ν 3400−3200, 1700, 1660 cm^{-1}; mass spectrum *m*/*z*(%) 291(20), 219(45), 182(42), 123(64), 59(44), 30(100). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; N, 4.81; H, 7.26. Found: C, 65.70; N, 4.70; H, 7.40.

5-[(Ethoxycarbonyl)methyl]-1-[(phenylthio)methyl]-6-acetamido-6-azabicyclo[3.2.1]octane (28). Triethyl phosphonoacetate (1.33 g, 6 mmol) was dissolved in THF (20 mL) under nitrogen. Potassium *tert*-butoxide (1 M, 6 mL, 6 mmol) was added dropwise at 25 °C for 1 h. Ketone **4** (1.57 g, 5 mmol) in THF (30 mL) was added dropwise at 25 °C. The solution was heated at reflux for 13 h, cooled to 25 °C, and evaporated *in vacuo*. H_2O (70 mL) was added and the mixture extracted with EtOAc (3 × 60 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to form a yellow gum. Column chromatography (EtOAc) produced a yellow gum **28** (1.26 g, 65%): ^{1}H NMR ($CDCl_3$) 1.20 (3 H, t, J = 7.2 Hz), 1.40−1.80 (6 H, m), 2.00 (3 H, s), 3.00 (2 H, s), 3.06 (1 H, d, J = 15.6 Hz), 3.20 (1 H, d, J = 15.6 Hz), 3.30 (1 H, d, J = 9.9 Hz), 3.40 (1 H, d, J = 9.9 Hz), 4.10 (2 H, quart, J = 15.6 Hz), 7.08−7.40

(5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.9, 23.4, 32.4, 34.6, 41.0, 41.9, 43.0, 47.2, 58.3, 59.8, 64.1, 126.1, 128.8, 129.4, 136.8, 169.1, 170.9; IR ν 1745, 1650 cm^{-1}; mass spectrum *m/z*(%) 362(M + H)$^+$(100), 316(10), 196(10); HRMS: calcd for $C_{20}H_{27}NO_3S$ *m/z* 361.1712, found 361.1710. Anal. Calcd for $C_{20}H_{27}NO_3S$: C, 66.45; N, 3.87; H, 7.53. Found: C, 66.20; N, 3.90; H, 7.64.

1-[(Phenylthio)methyl]-5-(hydroxyethyl)-6-ethyl-6-azabicyclo[3.2.1]octane (35). To a suspension of $LiAlH_4$ (0.38 g, 10 mmol) in THF (10 mL) was added dropwise ester **28** (1.43 g, 4 mmol) in THF (30 mL) at 25 °C under nitrogen. The solution was heated at reflux for 0.5 h and cooled to 0 °C. H_2O (50 mL) was added very cautiously over a period of 0.5 h. The aqueous was extracted with Et_2O (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to form ester **35** (0.88 g, 73%) as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.20 (1 H, ddd, J = 17.6, 2.5, 2.5 Hz), 1.40−1.70 (7 H, m), 1.95 (1 H, ddd, J = 17.6, 12.4, 2.5 Hz), 2.18 (1 H, dd, J = 17.6, 2.5, 2.5 Hz), 2.45 (1 H, d, J = 8.9 Hz), 2.80 (1 H, dd, J = 7.5, 7.5 Hz), 3.10 (2 H, s), 3.15 (1 H, d, J = 8.9 Hz), 3.65 (1 H, ddd, J = 14.2, 2.5, 2.5 Hz), 3.97 (1 H, ddd, J = 14.2, 12.4, 2.5 Hz), 6.00 (1 H, s(br)), 7.20−7.40 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.3, 20.0, 32.1, 35.7, 36.5, 40.2, 41.1, 43.7, 44.0, 49.9, 50.7, 64.1, 126.4, 130.1, 130.7, 147.3; IR ν 3,100−3,500 cm^{-1}; mass spectrum *m/z*(%) 306(M + H)$^+$(100), 182(73); HRMS: calcd for $C_{18}H_{27}NOS$ *m/z* 305.1813, found 305.1820. Anal. Calcd for $C_{18}H_{27}NOS$: C, 70.77; N, 4.59; H, 8.91. Found: C, 70.50; N, 4.35; H, 8.78.

1-[(Phenylthio)methyl]-5-[(*tert*-butyldimethylsiloxy)ethyl]-6-ethyl-6-azabicyclo[3.2.1]octane (36). Alcohol (**35**) (0.20 g, 0.66 mmol) was dissolved in CH_2Cl_2 (8 mL). The reaction was cooled to 0 °C (ice/salt) and triethylamine (0.07 g, 0.72 mmol) was added. The resulting solution was stirred for approximately 30 min, and then TBDMSOTf (0.19 g, 0.72 mmol) was added. Stirring was continued for 30 min, and the solvent was evaporated *in vacuo*. H_2O (10 mL) was added and the resulting solution extracted with EtOAc (3 × 10 mL). The combined extracts were washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated *in vacuo* to form silyl ether **36** (0.18 g, 65%) as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 0.04 (6 H, s), 0.86 (9H, s), 1.22 (3 H, m), 1.50−1.70 (5 H, m), 1.80 (3 H, m), 1.90−2.10 (2 H, m), 2.30 (1 H, d, J = 11.9 Hz), 2.80 (2 H, m), 3.20 (2 H, s), 3.60 (1 H, d, J = 11.5 Hz), 3.70 (1 H, m), 4.0 (1 H, m), 7.20−7.40 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −3.7, 11.9, 19.1, 25.6, 32.3, 33.2, 34.1, 42.4, 42.8, 43.5, 43.9, 57.6, 59.5, 71.6, 126.5, 129.8 132.6 136.1; IR ν 1450, 1050, 850 cm^{-1}; mass spectrum *m/z*(%) 420(M + H)$^+$(100), 296(50), 164(50). Anal. Calcd for $C_{24}H_{41}NOSSi$: C, 68.68; N, 3.34; H, 9.85. Found: C, 68.40; N, 3.21; H, 9.69.

1-[(Phenylsulfinyl)methyl]-5-[(ethoxycarbonyl)methyl]-6-acetyl-6-azabicyclo[3.2.1]octane (37). Ester **28** (0.5 g, 1.4 mmol) was dissolved in MeOH (10 mL). Sodium periodate (0.62 g, 2.9 mmol) was added and the mixture heated at reflux for 1 h. The solution was cooled to 25 °C and evaporated *in vacuo*. The mixture was diluted with CH_2Cl_2 (30 mL), washed with brine (20 mL), dried ($MgSO_4$), and evaporated *in vacuo* to form an approximate 1:1 diastereoisomeric mixture of sulfoxides (**37**) (0.40 g, 77%) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 1.20 (6 H, t, J = 7.1 Hz), 1.40−1.85 (12 H, m), 2.00 (6 H, s), 2.65 (2 H, d, J = 13.7 Hz), 2.86 (2 H, d, J = 13.7 Hz), 3.20 (2 H, d, J = 10.4 Hz), 3.54 (2 H, d, J = 10.4 Hz), 3.68 (4 H, d, J = 5.1 Hz), 4.20 (4 H, q, J = 7.1 Hz), 7.20−7.50 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.8, 23.5, 32.1, 34.3, 35.4, 40.2, 40.4, 40.7, 40.8, 48.5, 58.1, 58.3, 59.9, 62.7, 67.1, 68.0, 123.5, 127.4, 129.3, 131.7, 169.4, 170.8, 170.9; IR ν 1750, 1650, 1050 cm^{-1}; mass spectrum *m/z*(%) 378(M + H)$^+$(100), 362(20); HRMS: calcd for $C_{20}H_{27}NO_4S$ *m/z* 360.1633 (M − OH$^+$), found 360.1640. Anal. Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; N, 3.71; H, 7.21. Found: C, 63.50; N, 3.65; H, 7.22.

1-Acetoxy-1-[(phenythio)methyl]-5-[(ethoxycarbonyl)methyl]-6-acetyl-6-azabicyclo[3.2.1]octane (38). Sulfoxides (**37**) (0.40 g, 1 mmol) were heated at reflux for 24 h in Ac_2O (8 mL). The solution was cooled to 25 °C, diluted with H_2O (15 mL), and extracted with EtOAc (3 × 30 mL). The combined extracts were evaporated *in vacuo*, washed with saturated $NaHCO_3$ solution (20 mL) and H_2O (20 mL), dried ($MgSO_4$), and evaporated *in vacuo* to produce an orange gum. Column chromatography (Et_2O) produced an approximate 1;1 diastereoisomeric mixture of diesters **38** (0.29 g, 66%) as an orange gum: ^{1}H NMR ($CDCl_3$) δ 1.20 (6 H, t, J = 7.8 Hz), 1.40−1.80 (16 H, m), 1.95 (3 H, s), 2.00 (3 H, s), 3.15 (2 H, d, J = 14.1 Hz), 3.40 (1 H, d, J = 10.9 Hz), 3.45−3.50 (4 H, m), 4.10 (4 H, q, J = 7.9 Hz), 6.20 (2 H, s), 7.20−7.70 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.5, 20.7, 23.5, 31.1, 32.3, 32.5, 40.9, 45.2, 46.1, 46.2, 55.9, 56.7, 59.9, 63.9, 64.3, 85.6, 86.4, 128.4, 129.0, 133.6, 169.3, 170.8; IR ν 1750, 1650 cm^{-1}; mass spectrum *m/z*(%) 420(M + H)$^+$(100), 360(25), 268(20), 222(15); HRMS: calcd for $C_{22}H_{29}NO_5S$ *m/z* 419.1766, found 419.1762. Anal. Calcd for $C_{22}H_{29}NO_5S$: C, 62.98; N, 3.34; H, 6.97. Found: C, 62.70; N, 3.30; H, 7.01.

1-(Acetoxymethyl)-5-[(ethoxycarbonyl)methyl]-6-acetyl-6-azabicyclo[3.2.1]octane (39). Phenylthio diester **38** (0.19 g, 0.4 mmol) was dissolved in EtOH (10 mL). Raney nickel (3.71 g, 63 mmol) was added and the solution heated at reflux for 0.5 h and cooled to 25 °C. The mixture was filtered and evaporated *in vacuo* to form an orange gum. Column chromatography (40% hexane/acetone) produced diester **39** (0.08 g, 57%) and ester **27** (0.015 g, 13%).

For **39**: ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, s), 1.40−1.80 (6 H, m), 2.03 (3 H, s), 2.05 (3 H, s), 3.10 (1 H, d, J = 15.6 Hz), 3.20 (1 H, d, J = 15.6 Hz), 3.30 (1 H, d, J = 9.7 Hz), 3.45 (1 H, d, J = 9.7 Hz), 3.95 (1 H, d, J = 11.2 Hz), 4.00 (1 H, d, J = 11.2 Hz), 4.10 (2 H, q, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.8, 20.9, 23.8, 29.8, 32.6, 32.8, 41.2, 41.4, 44.6, 57.0, 60.2, 64.2, 68.9, 169.6, 171.1,171.3; IR ν 1745, 1650 cm^{-1}; mass spectrum *m/z*(%) 311(15), 238(55), 196(100), 168(72), 122(50), 105(40); HRMS: calcd for $C_{16}H_{25}NO_5$ *m/z* 311.1733, found 311.1695. Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; N, 4.50; H, 8.09. Found: C, 61.60; N, 4.50; H, 8.30.

1-(Hydroxymethyl)-5-(hydroxyethyl)-6-ethyl-6-azabicyclo[3.2.1]octane (40). To a suspension of $LiAlH_4$ (1.05 g, 27.7 mmol) in THF (10 mL) was added dropwise diester **39** (3.32 g, 10.7 mmol) in THF (30 mL) at 25 °C under nitrogen. The solution was heated and worked up as described for amide **28** to form diol **40** (1.53 g, 67%) as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, t, J = 6.8 Hz), 1.10−1.40 (4 H, m), 1.50−1.70 (2 H, m), 1.75 (1 H, m), 1.95 (1 H, m), 2.00 (1 H, d, J = 10.7 Hz), 2.40 (1 H, d, J = 9.8 Hz), 2.50 (2 H, s), 2.95 (1 H, m), 3.20 (1 H, m), 3.50 (2 H, s), 3.60 (1 H, m,), 4.00 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.27, 19.82, 32.88, 33.01, 35.00, 40.45, 41.84, 46.63, 57.92, 60.42, 65.47, 69.09; IR (neat) ν 3200−3400, 1470, 1000 cm^{-1}; mass spectrum *m/z*(%) 213(25), 182(100), 154 (15). Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; N, 6.57; H, 10.87. Found: C, 67.30; N, 6.37; H, 10.77.

1-(Hydroxymethyl)-5-[(*tert*-butyldimethylsiloxy)ethyl]-6-ethyl-6-azabicyclo[3.2.1]octane (3). Diol **40** (1.10 g, 5.2 mmol) was reacted in CH_2Cl_2 (10 mL) with Et_3N (0.55 g, 5.7 mmol) and TBDMSOTf (1.43 g, 5.7 mmol) as described for alcohol **35** to form silyl ether **3** (1.40 g, 83%, R_f 0.19) as a clear gum: ^{1}H NMR ($CDCl_3$) δ 0.05 (6 H, s), 0.90 (9H, s), 1.25 (3 H, t, J = 7.0 Hz), 1.30−2.00 (10 H, m), 2.80 (2 H, m), 2.90 (2 H, m), 3.60 (2 H, s), 3.70 (1 H, m), 3.75 (1 H, m); ^{13}C NMR ($CDCl_3$) δ −5.51, 12.29, 18.16, 19.00, 25.61, 31.40, 32.09, 38.19, 38.76, 42.21, 44.66, 59.57, 66.86, 70.24; IR (neat) ν 3,300−3,400 (br),1450, 1250, 1100, 820, 780 cm^{-1}; mass spectrum *m/z*(%) 327(15), 296(100), 182 (15), 164 (67). Anal. Calcd for $C_{18}H_{37}NO_2Si$: C, 66.00; H, 11.38; N, 4.28. Found: C, 65.70; H, 11.30; N, 4.03.

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