δ 59.1, 39.0, 31.3, 20.6, 14.3. MS: *m/z* (relative intensity) 155 (M^+, 0.79), 154 (M – H, 1.9), 112 (M – C_3H_7, 100), 69 (M – $2C_3H_7$, 20).

***cis*-2-Heptyl-5-butylpyrrolidine (16c)** was prepared from tosylate **1c**, using the method described for **15a**. The spectral characteristics were identical with those of a known sample of **16c**.[7a] ^{1}H NMR: δ 2.93 (m, unresolved, 2 H, methine), 1.82 (m, 2 H, methylene protons from ring), 1.65–1.15 (m, 21 H), 0.88 (q, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 59.41, 59.39, 36.7, 36.4, 31.8, 31.3 (two carbons), 29.8, 29.7, 29.3, 27.5, 22.9, 22.7, 14.1 (2 C). MS: *m/z* (relative intensity) 224 (M – H, 1), 168 (M – C_4H_9, 60), 126 (M – C_7H_{15}, 100).

Acknowledgment. We thank the Swedish Natural Science Research Council and the Swedish Board of Technical Development for financial support.

Registry No. **1a**, 123994-00-3; **1b**, 81330-01-0; (±)-**1c**, 123994-01-4; **1d**, 123994-02-5; (±)-**2a**, 123993-96-4; (±)-**2b**, 123993-97-5; (±)-**2c**, 123993-98-6; (±)-**2e**, 123993-99-7; **3** (R = *n*-C_3H_7), 627-19-0; **3** (R = *n*-C_7H_{15}), 3452-09-3; **5a**, 53721-79-2; **5c**, 123993-59-9; **5d**, 30651-68-4; **5e**, 123993-60-2; (±)-**6a**, 123993-61-3; (±)-**6b**, 124095-79-0; (±)-**6c**, 123993-62-4; (±)-**6c** (R = *n*-C_7H_{15}, R′ = *n*-C_4H_9), 123994-05-8; (±)-**6d**, 123993-63-5; (±)-**6e**, 123993-64-6; (±)-**6e** (R = *n*-C_4H_9, R′ = *n*-C_3H_7), 123994-06-9; (±)-**7a**, 123993-65-7; (±)-**7b**, 123993-66-8; (±)-**7c**, 123993-67-9; (±)-**7c** regioisomer, 124561-41-7; (±)-**7d**, 123993-68-0; (±)-**8a**, 124020-50-4; (±)-**8b**, 123993-77-1; (±)-**8c**, 123993-78-2; (±)-**8c** regioisomer, 124561-42-8; (±)-**8d**, 123993-79-3; (±)-**9a**, 123993-84-0; (±)-**9b**, 123993-85-1; (±)-**9c**, 123993-86-2; (±)-**9c** regioisomer, 124561-43-9; (±)-**9d**, 123993-87-3; (±)-**10a**, 123993-92-0; (±)-**10b**, 123993-93-1; (±)-**10c**, 123993-94-2; (±)-**10c** regioisomer, 124561-44-0; (±)-**10d**, 123993-95-3; (±)-**11a**, 123993-69-1; (±)-**11b**, 123993-70-4; (±)-**11c**, 123993-71-5; (±)-**11c** regioisomer, 124561-45-1; (±)-**11e**, 123993-72-6; (±)-**11e** regioisomer, 124581-01-7; (±)-**12a**, 123993-73-7; (±)-**12b**, 123993-74-8; (±)-**12c**, 123993-75-9; (±)-**12c** regioisomer, 124561-46-2; (±)-**12e**, 123993-76-0; (±)-**12e** regioisomer, 124561-47-3; (±)-**13a**, 123993-80-6; (±)-**13b**, 123993-81-7; (±)-**13c**, 123993-82-8; (±)-**13c** regioisomer, 124561-48-4; (±)-**13e**, 123993-83-9; (±)-**13e** regioisomer, 124561-49-5; (±)-**14a**, 123993-88-4; (±)-**14b**, 123993-89-5; (±)-**14c**, 123993-90-8; (±)-**14c** regioisomer, 124561-50-8; (±)-**14e**, 123993-91-9; (±)-**14e** regioisomer, 124561-51-9; (±)-**15a**, 123994-03-6; (±)-**15c**, 116558-84-0; **16a**, 123994-04-7; (±)-**16c**, 116558-83-9; (*E*)-*n*-C_4H_9CH=CHI, 16644-98-7; NaNHTs, 18522-92-4; (*E*)-(*R**,*S**)-(±)-$CH_3CHClCH$=CHCHCOAc)CH_3, 124095-80-3.

New Routes to Functionalized Benzazepine Substructures: A Novel Transformation of an α-Diketone Thioamide Induced by Trimethyl Phosphite

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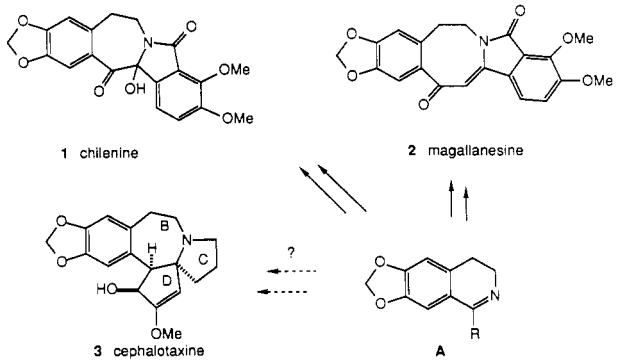
General protocols for the transformation of substituted dihydroisoquinolines into functionalized benzazepine products are described. An important element involves initial hydrolytic succinoylation of a dihydroisoquinoline to afford a ring-opened intermediate. Subsequent closure to the homologous benzazepine ring is accomplished by condensation of several carbenoid-type equivalents with monothioimide and thioamide carbonyl groups. Application of this methodology to a formal synthesis of cephalotaxine (**3**) is described.

Introduction

Recently, we have described novel protocols for the transformation of readily available dihydroisoquinolines (cf. A) to isoindolobenzazepine and isoindolobenzazocine ring systems in the context of the total syntheses of chilenine (**1**) and magallanesine (**2**).[2,3] In an effort to expand the scope of these methods to include pyrrolobenzazepine structures relevant to a total synthesis of cephalotaxine (**3**),[4,5] we undertook an investigation into the hydrolytic succinoylation and subsequent reductive ring closure of several substituted dihydroisoquinolines (cf. eq i).



The successful implementation of this process for the case R = H would constitute a formal synthesis of **3**.[6] A potentially more useful application of this strategy would be one in which the three-carbon chain necessary for construction of the D ring of **3** was incorporated into the

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(2) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2747.

(3) Fang, F. G.; Feigelson, G. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2743.

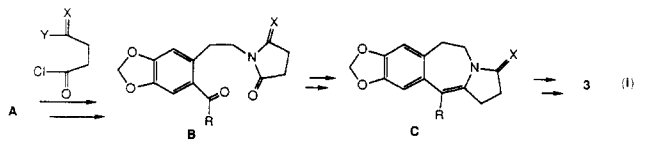
(4) Cephalotaxine isolation and structure determination: (a) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194. (b) Powell, R. G.; Weisleder, D.; Smith, C. R.; Wolff, I. A. *Tetrahedron Lett.* **1969**, 4081. (c) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Lett.* **1969**, 4085. (d) Arora, S. K.; Bates, R. B.; Grady, R. A. *J. Org. Chem.* **1974**, *39*, 1269. (e) Arora, S. K.; Bates, R. B.; Grady, R. A.; Germain, G.; DeClerc, J. P.; Powell, R. G. *J. Org. Chem.* **1976**, *41*, 551.

(5) For previous synthesis of cephalotaxine (**3**) see: (a) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172. (b) Semmelhack, M. F.; Chong, B. C.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629. (c) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158. (d) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, 2023. (e) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439. (f) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341.

(6) Compound C (R = H, X = H_2) served as a key intermediate in Weinreb's total synthesis of cephalotaxine (**3**) (see ref 5a) and has also been prepared by several other groups: (a) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691. (b) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875. (c) Tse, I.; Snieckus, V. *Chem. Commun.* **1976**, 505.

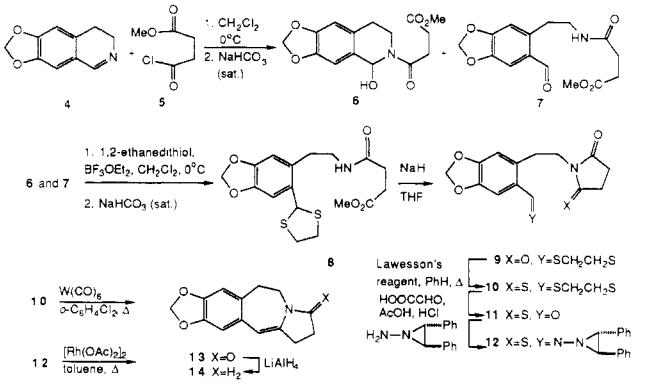
0022-3263/90/1955-0831$02.50/0

cyclization precursor. In this paper we report the realization of this process for achieving the first goal (eq. i, R = H). In addition, it was possible to include a one-carbon chain (R = CO_2Me) in the cyclization process. An attempt to maintain a three-carbon chain (R = propionyl) through the cyclization reaction led to ring closure with concomitant C → S propionyl migration.

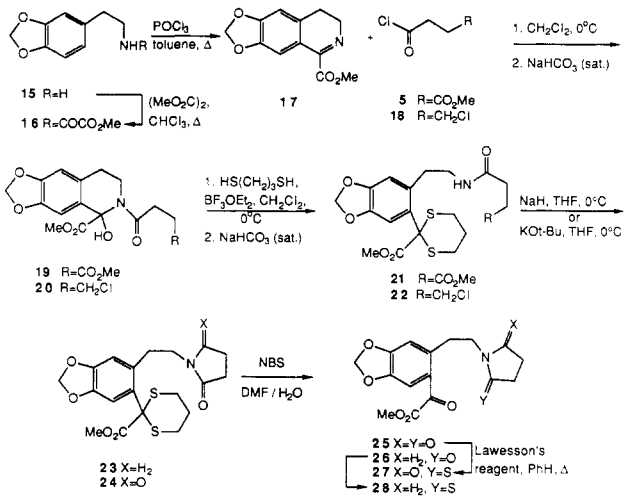


Discussion of Results

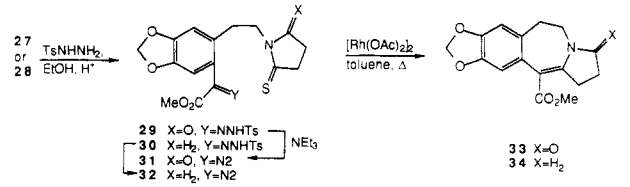
Treatment of norhydrastinine (**4**)[7] with 3-carbomethoxypropionyl chloride (**5**) in methylene chloride at 0 °C followed by addition of saturated aqueous sodium bicarbonate yielded acylated products **6** and **7** in 86% yield. This mixture was treated directly with 1,2-ethanedithiol and boron trifluoride etherate at 0 °C to afford a single dithiolane (**8**) in 86% yield. Base-catalyzed cyclization of **8** provided imide dithiolane **9** in 90% yield. Reaction of **9** with Lawesson's reagent[8] afforded monothioimide **10** in 81% yield. Tungsten hexacarbonyl mediated cyclization of dithiolane **10** proceeded to give enamide **13** in 55% yield.[9,10] Presumably this process had occurred by generation of an intermediate tungsten carbene species which subsequently added across the carbon–sulfur double bond and extruded sulfur.[11] An alternative method for achieving this transformation made use of aldehyde **11**, readily available from **10** by transthioacetalization with glyoxylic acid in acetic acid (78%).[12] Treatment of **11** with 1-amino-*trans*-2,3-diphenylaziridine[13] provided hydrazone **12** in 82% yield. Addition of **12** to a refluxing suspension of rhodium(II) acetate dimer in toluene afforded a 76% yield of enamide **13**. Reduction of **13** with lithium aluminum hydride in ether gave enamine **14**, the key intermediate in Weinreb's total synthesis of cephalotaxine (**3**).



The success realized in these studies encouraged us to explore a process wherein a one-carbon chain necessary for further elaboration to the final 5-membered ring of cephalotaxine (**3**) was incorporated. Readily available[7] 3,4-(methylenedioxy)-β-phenethylamine (**15**) was allowed to condense with dimethyl oxalate in refluxing chloroform to afford oxalamide **16** in 68% yield.[14] Bischler–Napieralski cyclization of **16** with phosphorous oxytrichloride in refluxing toluene afforded dihydroisoquinoline **17** in 50% yield. Treatment of **17** with acid chlorides **5** or **18** in methylene chloride at 0 °C followed by addition of saturated aqueous sodium bicarbonate afforded carbinolamides **19** and **20** (74 and 78% yield, respectively). Treatment of **19** or **20** with 1,3-propanedithiol and boron trifluoride etherate in methylene chloride at 0 °C provided ring-opened dithianes **21** (37%) or **22** (55%). Both **21** and **22** could be converted to **23** (89%) and **24** (95%) by treatment with sodium hydride or potassium *tert*-butoxide, respectively, in THF at 0 °C. Oxidative removal of the dithiane moiety (*N*-bromosuccinimide (NBS) in THF/H_2O) in **23** and **24** gave α-keto esters **25** (91%) and **26** (90%). Lawesson's reaction[8] of **25** or **26** proceeded regioselectively at the amide carbonyl groups to give **27** or **28** in 80 and 91% yields, respectively. Compounds **27** and



28 were transformed in two steps ((i) tosylhydrazide, ethanol, HCl (cat.), Δ; (ii) NEt_3, CH_2Cl_2) to diazo esters **31** (73%) and **32** (77%) respectively. Either **31** or **32** could be cyclized upon treatment with rhodium(II) acetate dimer in refluxing toluene to give carbomethoxy-substituted benzazepines **33** and **34** in 77 and 79% yields, respectively.



At this point, the possibility that all the carbons necessary for elaboration of the D ring of cephalotaxine (**3**) could be included in the cyclization substrate was considered. The synthesis of the required acylated dihydroisoquinolines relied on the recent findings by Livinghouse that isonitriles can serve as precursors for the generation of acylnitrylium electrophiles under mild conditions.[15] Formamide **35**[7] was dehydrated by treatment with phos-

(7) Slemon, C. E.; Hellwig, L. C.; Ruder, J.-P.; Hoskins, E. W.; McLean, D. B. *Can. J. Chem.* **1981**, *59*, 3055.

(8) For a review on the use of Lawesson's reagent for the generation for the generation of thiocarbonyl compounds, see: Cava, M.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

(9) For a previous example of this type of cyclization see ref 2.

(10) Tungsten hexacarbonyl has previously been utilized to reductively dimerize aryl dithiolanes: Yeung, L. L.; Luh, T.-Y. *J. Chem. Soc., Chem. Commun.* **1987**, 981.

(11) For examples of aryl-substituted tungsten carbonyl carbene complexes, see: (a) Casey, C. P.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 5833. (b) Casey, C. P.; Burkhardt, T. J. Bunnell, C. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 2127.

(12) Muxfeldt, H.; Unterweger, W.-D.; Helmchen, G. *Synthesis* **1976**, 694.

(13) Muller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 114.

(14) Lambert, J. B.; Huseland, D. E.; Wang, G.-T. *Synthesis* **1986**, 657.

(15) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51* (8), 1159.

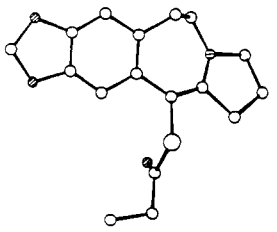
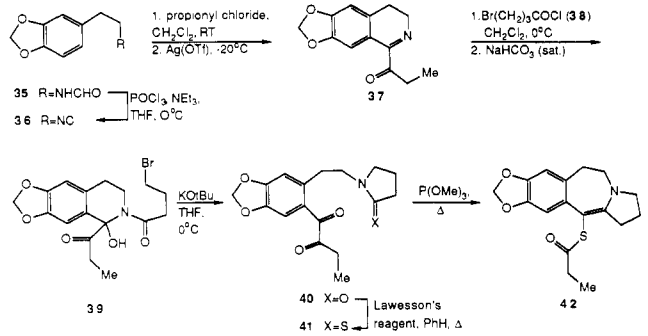


Figure 1. X-ray structure of **42**.

phorous oxytrichloride and triethylamine in THF at 0 °C to afford isonitrile **36** in 72% yield. Treatment of **36** with propionyl chloride in methylene chloride at room temperature followed by addition of silver triflate at −20 °C generated dihydroisoquinoline **37** in 68% yield. Addition of **37** to 4-bromobutyroyl chloride (**38**) in methylene chloride at 0 °C followed by the addition of saturated aqueous sodium bicarbonate produced carbinolamide **39** in 81% yield. Base-mediated (potassium *tert*-butoxide, THF, 0 °C) ring-opening of **39** was accompanied by δ-lactam formation to provide α-diketone **40** (52%). Treatment of **40** with Lawesson's reagent in THF at room temperature afforded thiolactam **41** in 96% yield.



It seemed unlikely that the benzylic carbonyl of the α-diketone in **41** could be regioselectively converted to a tosylhydrazone.[16] A more promising outcome was projected via reaction of **41** with trimethyl phosphite.[17] The premise was that a phosphorous enediolate would initially form. The regioselectivity of the subsequent reaction of this unsymmetrical enediolate was expected to be governed by a preference for generating a seven-membered rather than eight-membered ring. In that event, reaction of **41** with excess refluxing trimethyl phosphite produced a single identifiable compound. Mass spectroscopy indicated that **41** had lost 16 mass units but still contained sulfur. Proton NMR was suggestive of a cyclized compound.[18] Finally the structure of this material was determined by single-crystal X-ray crystallography and shown to be that of the rearranged enethiol ester **42** (Figure 1).

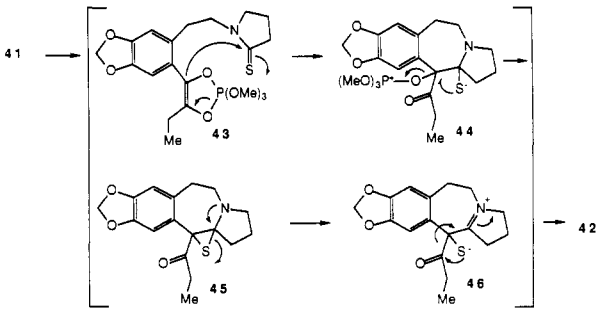
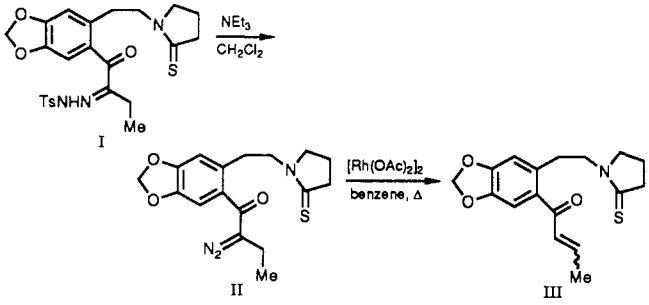


Figure 2. Mechanism for trimethyl phosphite induced rearrangement of **41** to **42**.

Although the desired seven-membered ring had been formed, an unexpected carbon to sulfur acyl migration had taken place as well. A possible mechanism for this process is shown in Figure 2. The first step is reduction of the α-diketone by trimethyl phosphite giving enediolate **43**. This product could be characterized by proton NMR. In addition, indirect evidence for this reduction was obtained by isolation of a mixture of α-ketols upon attempted chromatography of **43**. The second step involves enolate addition to the thiolactam in **43** to give **44** followed by episulfide formation to give **45**.[19] The putative episulfide **45** is analogous to intermediates obtained in Eschenmoser-type sulfide contractions of thiolactams.[20] Indeed a similar intermediate was presumably involved in the cyclizations of diazo esters **31** and **32** to **33** and **34**. Apparently, in the case of these diazo esters, elemental sulfur was extruded spontaneously from the intermediate episulfides. In the case of compound **45**, however, a carbon to sulfur propionyl shift via thiolate–iminium **46** takes place to give rearranged **42**. That a different pathway is followed by **45** is perhaps due to the greater electrophilicity of the propionyl over the methoxycarbonyl group to attack by sulfur.

In summary, a novel strategy for the synthesis of functionalized pyrrolobenzazepines has been realized. Using this approach, a formal total synthesis of cephalotaxine was achieved. These studies serve to illustrate the utility of carbenoid species for condensation with thioamide and monothioimide carbonyl groups. Future efforts will be concerned with controlling the fate of intermediate epi-

(16) Reaction of **41** with tosylhydrazide in ethanol in the presence of a catalytic amount of HCl produced a single tosylhydrazine (^{1}H NMR (250 MHz, $CDCl_3$) δ 8.64 (broad s), 7.67 and 7.31 (AB_q, J_{AB} = 8.2 Hz, $\Delta\nu$ = 92.1 Hz, 4 H, SO_2ArH), 6.87 (s, 1 H, ArH), 6.56 (s, 1 H, ArH), 6.07 (s, 2 H, OCH_2O), 3.85 (t, J = 7.8 Hz, 2 H, NCH_2CH_2Ar), 3.53 (t, J = 7.8 Hz, 2 H, $NCH_2CH_2CH_2$), 3.00 (t, J = 7.5 Hz, 2 H, $CSCH_2$), 2.88 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 2.55 (q, J = 8.2 Hz, 2 H, CH_2CH_3), 2.46 (s, 3 H, $ArCH_3$), 1.98 (apparent p, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 1.07 (t, J = 8.2 Hz, 3 H, CH_2CH_3)). Indirectly, this was shown to be the undesired regioisomer by its conversion to diazo ketone (II) (^{1}H NMR (250 MHz, $CDCl_3$) δ 6.87 (s, 1 H, ArH), 6.78 (s, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 3.93 (t, J = 7.8 Hz, 2 H, NCH_2CH_2Ar), 3.57 (t, J = 7.8 Hz, 2 H, $NCH_2CH_2CH_2$), 3.02 (t, J = 7.7 Hz, 2 H, $CSCH_2$), 2.96 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 2.52 (broad q, J = 7.8 Hz, 2 H, CH_2CH_3), 2.00 (apparent p, J = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 1.20 (t, J = 7.8 Hz, 3 H, CH_2CH_3)) and subsequent rhodium(II) acetate dimer catalyzed decomposition to give enone III as a 2.5:1 mixture of olefin isomers (major isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.12 (s, 1 H, ArH), 6.90 (s, 1 H, ArH), 6.58–6.30 (m, 2 H, HC=CH), 6.02 (s, 2 H, OCH_2O), 4.00 (t, J = 7.9 Hz, 2 H, NCH_2CH_2Ar), 3.73 (t, J = 7.7 Hz, 2 H, $ArCH_2$), 3.04 (t, J = 7.5 Hz, 2 H, $CSCH_2$), 2.08 (dd, J = 6.4 Hz and 1 Hz, 3 H, CH_3), 2.00 (hidden p, 2 H, $CH_2CH_2CH_2$)).



(17) For the use of trimethyl phosphite to effect reductive-aldol reactions of α-dicarbonyl compounds see: (a) Ramirez, F.; Ramanathan, N.; Desai, N. B. *J. Am. Chem. Soc* **1962**, *84*, 1317. (b) Ramirez, F. *Synthesis* **1974**, 90.

(18) The ^{1}H NMR spectrum of this product (**42**) as well as those of the related benzazepine structures **13** and **34** all show a distinctive broadening of the ethylene protons between nitrogen and the aromatic ring relative to the corresponding acyclic precursors.

(19) An alternative possibility is that the benzylic carbon–oxygen bond in enediolate **43** undergoes heterolysis to give a carbenoid intermediate which adds to the thiolactam to give episulfide **45** directly.

(20) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54* (2), 710.

sulfides (cf. **45**) with respect to subsequent rearrangement processes.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 250 MHz. Column chromatography was performed on Merck silica gel 60 (230–400 mesh).

Methyl 1-Hydroxy-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline-2-(α-oxo)butyrate (6) and Aldehyde (7). To a solution of 6,7-(methylenedioxy)-3,4-dihydroisoquinoline (norhydrastinine) (**4**) (2.33 g, 13.29 mmol)[7] in 100 mL of methylene chloride at 0 °C was added 3-carbomethoxypropionyl chloride (**5**) (2.29 mL, 2.80 g, 18.6 mmol) via syringe. After the resultant yellow solution was stirred for 10 min at 0 °C, 150 mL of saturated $NaHCO_3$ was added all at once. The ensuing clear, colorless biphasic mixture was vigorously stirred for 30 min. The layers were separated, and the aqueous portion was extracted twice with 100 mL of CH_2Cl_2. The combined organics were dried (Na_2SO_4) and evaporated to give 4.96 g of a yellow oil. This was chromatographed (4.5 × 10 cm, 5:4 EtOAc–CH_2Cl_2) to give 3.528 g (86%) of a mixture of aldehyde (**7**) and aminal (**6**). This mixture was taken on to the next reaction without further purification. Aldehyde **7** was characterized: IR ν_{max} (CH_2Cl_2) 3425, 3050, 2950, 2900, 1735, 1675, 1605, 1505, 1485, 1440, 1375, 1250, 1175, 1040, 940 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.03 (s, 1 H, CHO), 7.26 (s, 1 H, ArH), 6.76 (s, 1 H, ArH), 6.05 (s, 2 H, OCH_2O), 3.70 (s, 3 H, OCH_3), 3.46 (apparent q, J = 6.7 Hz, 2 H, NCH_2), 3.16 (br t, J = 6.9 Hz, $ArCH_2$), 2.65 (t, J = 6.7 Hz, $O_2CCH_2CH_2CON$), 2.43 (t, J = 6.7 Hz, $O_2CCH_2CH_2CON$); MS m/e (relative intensity) 308 (2.1), (M^+) 307 (11.6), 192 (11.0), 177 (21.1), 176 (100), 175 (106), 164 (33.9), 163 (12.1), 148 (50.1), 115 (43.9); HRMS m/e calcd (M^+) 307.1056, obsd 307.1074.

Dithiolane 8. To the mixture of **6** and **7** (3.528 g, 11.48 mmol) dissolved in 50 mL of CH_2Cl_2 at 0 °C was added 1,2-ethanedithiol (1.38 mL, 1.44 g, 13.7 mmol) followed by boron trifluoride etherate (1.97 mL, 2.28 g, 16 mmol). The reaction was allowed to stir for 10 h at which point TLC analysis indicated a single new compound. The reaction was quenched with 100 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous portion was extracted twice with 100 mL of CH_2Cl_2. The combined organics were dried (Na_2SO_4), concentrated, and chromatographed (4.5 × 10 cm, 3:1 EtOAc–CH_2Cl_2) to give 3.94 g (86%) of dithiolane **8** as a white solid (mp 136–137 °C): IR ν_{max} (CH_2Cl_2) 3430, 3040, 2940, 2920, 1730, 1675, 1515, 1500, 1480, 1250, 1220, 1170, 1040, 940 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (s, 1 H, ArH), 6.58 (s, 1 H, ArH), 5.94 (s, 2 H, OCH_2O), 5.89 (s, 1 H, SCHArS), 5.77 (br s, 1 H, NH), 3.71 (s, 3 H, OCH_3), 3.56–3.36 (m, 6 H, NCH_2 and SCH_2CH_2S), 2.85 (t, J = 7.0 Hz, 2 H, $ArCH_2$), 2.68 (t, J = 6.6 Hz, 2 H, $O_2CCH_2CH_2CON$), 2.48 (t, J = 6.6 Hz, 2 H, $O_2CCH_2CH_2CON$); MS m/e (relative intensity) 385 (2.7), 384 (4.4), (M^+) 383 (23.7), 227 (p.1), 226 (15.6), 225 (100), 193 (5.1), 192 (12.3), 191 (44.7), 179 (15.9), 176 (10.1); HRMS m/e calcd (M^+) 383.0862, obsd 383.0865.

1-[2-[6-(1,3-Dithiolan-2-yl)-1,3-benzodioxol-5-yl]ethyl]-2,5-pyrrolidinedione (9). To a solution of amide **8** (1.115 g, 2.80 mmol) in 80 mL of THF at 0 °C was added sodium hydride (80 mg, 3.2 mmol) in one portion. After 5 min the reaction mixture had turned slightly brown and gas was evolved. The reaction was complete by TLC analysis. Water (10 mL) was added, followed by sufficient 1 N HCl to neutralize the medium. Methylene chloride (15 mL) was added, and the layers were separated. The upper aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed once with 10 mL of water, dried over Na_2SO_4, and concentrated to give a brown oil. This was chromatographed (3 × 6 cm, 8:1 CH_2Cl_2–EtOAc) to give 929 mg (90%) of imide **9** as a white powder (mp 122–123 °C): IR ν_{max} (CH_2Cl_2) 3050, 2915, 1770, 1505, 1485, 1405, 1170, 1045 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 (s, 1 H, ArH), 6.63 (s, 1 H, ArH), 5.99 (s, 1 H, SCHArS), 5.93 (s, 2 H, OCH_2O), 3.71 (br t, J = 7.8 Hz, 2 H, NCH_2), 3.59–3.34 (s, 4 H, SCH_2CH_2S), 2.88 (br t, J = 7.9 Hz, 2 H, $ArCH_2$), 2.72 (s, 4 H, $COCH_2CH_2CO$); MS m/e (relative intensity) (M + 2) 353 (1.7), (M + 1) 352 (2.9), (M^+) 351 (12.7), 227 (7.5), 226 (11.0), 225 (100), 199 (1.6), 198 (2.9), 197 (13.3), 191 (28.1), 179 (10.2); HRMS m/e calcd (M^+) 351.0600, obsd 351.0554. Anal. Calcd for $C_{16}H_{17}NO_4S_2$: C, 54.68; H, 4.88; N, 3.99; S, 18.25. Found: C, 54.76; H, 4.76; N, 3.75; S, 18.32.

1-[2-[6-(1,3-Dithiolan-2-yl)-1,3-benzodioxol-5-yl]ethyl]-5-thioxo-2-pyrrolidinone (10). To a solution of imide **9** (0.88 g, 2.5 mmol) in 10 mL of benzene was added 505 mg (1.25 mmol) of Lawesson's reagent. The reaction mixture was heated to reflux for 4 h. The solution was cooled to room temperature, concentrated, and chromatographed (2.5 × 10 cm, 10:1 CH_2Cl_2–EtOAc) to give 743 mg (81%) of monothioimide **10** as a white solid (mp 125–126 °C): IR ν_{max} (CH_2Cl_2) 3040, 2915, 1750, 1505, 1485, 1440, 1345, 1270, 1180, 1135, 1040 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (s, 1 H, ArH), 6.68 (s, 1 H, ArH), 6.10 (s, 1 H, ArH), 5.94 (s, 2 H, OCH_2O), 4.06 (br t, J = 8.1 Hz, 2 H, NCH_2), 3.59–3.36 (m, 4 H, SCH_2CH_2S), 3.18 (br t, J = 6.8 Hz, 2 H, $CSCH_2CH_2CO$), 2.92 (br t, J = 8.1 Hz, 2 H, $ArCH_2$), 2.74 (br t, J = 6.8 Hz, 2 H, $CSCH_2CH_2CO$); MS m/e (relative intensity) (M + 2) 369 (2.1), (M + 1) 368 (2.4), (M^+) 367 (12.7), 243 (29.2), 226 (14.5), 225 (100), 224 (20.0), 191 (29.1); HRMS m/e calcd (M^+) 367.0372, obsd 367.0367. Anal. Calcd for $C_{16}H_{17}NO_3S_3$: C, 52.29; H, 4.66; N, 3.81; S, 26.18. Found: C, 52.33; H, 4.70; N, 3.74; S, 26.09.

1-[2-(6-Formyl-1,3-benzodioxol-5-yl)ethyl]-5-thioxo-2-pyrrolidinone (11). To a suspension of dithiolane **10** (1.097 g, 2.99 mmol) and glyoxylic acid in glacial acetic acid was added 1 mL of concentrated HCl. The mixture was warmed to 50 °C for 30 min by which time a clear red solution had formed. The solution was cooled to room temperature and added to 200 mL of H_2O. This was extracted with 3 × 50 mL of CH_2Cl_2. The combined organics were extracted with saturated $NaHCO_3$ (2 × 100 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to give 679 mg (78%) of aldehyde **11** as a pale yellow solid (mp 159–161 °C): IR ν_{max} (CH_2Cl_2) 1750, 1690, 1675, 1615, 1500, 1480, 1430, 1395, 1340 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.21 (s, 1 H, ArCHO), 7.32 (s, 1 H, ArH), 6.77 (s, 1 H, ArH), 6.05 (s, 2 H, OCH_2O), 4.13 (br t, J = 7.8 Hz, 2 H, NCH_2), 3.28 (br t, J = 7.8 Hz, 2 H, $ArCH_2$), 3.13 (br t, J = 6.8 Hz, 2 H, $CSCH_2CH_2CO$), 2.70 (br t, J = 6.8 Hz, $CSCH_2CH_2CO$); MS m/e (relative intensity) (M^+) 291 (5.0), 259 (13.4), 258 (93.2), 176 (59.0), 175 (12.0), 149 (11.2), 148 (100), 147 (39.3); HRMS m/e calcd (M^+) 291.0566, obsd 291.0564.

5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-8-one (13). Method A (from dithiolane **10**). A mixture of **10** (367 mg, 1.0 mmol) and tungsten hexacarbonyl (1.056 g, 3.0 mmol) in 30 mL of *o*-dichlorobenzene was heated at reflux for 6 h. The resultant black reaction mixture was cooled, filtered through Celite, and concentrated to give a bright yellow residue. Column chromatography (2:1 hexanes–EtOAc) afforded 135 mg (55%) of enamide **13**.

Method B (from aldehyde **11**). To a solution of aldehyde (291 mg, 1.0 mmol) in CH_2Cl_2 at 0 °C was added 1-amino-*trans*-2,3-diphenylaziridine (210 mg, 1.0 mmol). The reaction mixture was allowed to stir for 2 h at 0 °C. The solvent was removed in vacuo, and 30 mL of toluene was added. This solution was added to a refluxing suspension of rhodium(II) acetate dimer (22 mg, 0.05 mmol) in 100 mL of toluene over 1 h. The reaction mixture was cooled, concentrated, and chromatographed to afford 185 mg (76%) of enamide **13**: IR ν_{max} (CH_2Cl_2) 3050, 2900, 1715, 1660, 1505, 1490, 1380, 1320, 1290, 1235, 1195, 1165, 1045 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.60 (br s, 2 H, 2(ArH)), 5.93 (s, 2 H, OCH2O), 5.48 (br s, 1 H, C=CH), 4.0–3.6 (m, 2 H, NCH_2), 2.94–2.80 (m, 4 H, $ArCH_2$ and $COCH_2CH_2$), 2.58 (br t, J = 6.9 Hz, 2 H, $COCH_2CH_2$); MS m/e (relative intensity) (M + 2) 245 (3.0), (M + 1) 244 (19.4), (M^+) 243 (100), 228 (34.9), 129 (22.7); HRMS m/e calcd (M^+) 243.0896, obsd 243.0912.

5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine (14). A solution of 243 mg (1.0 mmol) of enamide **13** in 10 mL of THF was treated with 152 mg (4.0 mmol) of lithium aluminum hydride. The mixture was heated at reflux for 1.25 h, cooled, and diluted with ether. A solution of 1.5 mL of water in 10 mL of THF was slowly added, followed by 1.5 mL of 15% sodium hydroxide. The granular precipitate was removed by filtration, and the filtrate was concentrated to afford 232 mg (100%) of **14** as a tan solid (mp 81–83 °C, lit. 82–83 °C) which had spectral properties identical with those reported for this compound by Weinreb.[5a]

Oxalamide 16. To a refluxing solution of dimethyl oxalate (16.84 g, 102 mmol) in 70 mL of chloroform was added a solution of 3,4-(methylenedioxy)-β-phenethylamine in 20 mL of chloroform

dropwise over 30 min. After 10 h at reflux the hot reaction mixture was filtered through a medium-porosity frit and concentrated to give 17.6 g (68%) of oxalamide **16** as a light yellow powder (mp 95–97 °C): IR ν_{max} (CH_2Cl_2) 3400, 3050, 2980, 2950, 2890, 1765, 1735, 1705, 1525, 1505, 1495, 1440, 1300, 1250, 1220, 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.13 (br m, 1 H, NH), 6.76 and 6.65 (AB_q, J_{AB} = 7.8 Hz, $\Delta\nu$ = 27.5 Hz, 2 H, ArH), 6.69 (d, J = 1 Hz, 1 H, ArH), 5.95 (s, 2 H, OCH_2O), 3.89 (s, 3 H, OCH_3), 3.57 (apparent q, J = 6.6 Hz, 2 H, NCH_2), 2.79 (t, J = 6.9 Hz, 2 H, 2 H, $ArCH_2$); MS m/e (relative intensity) (M^+) 251 (10.5), 192 (5.5), 149 (16.3), 148 (100), 147 (7.7), 135 (39.0); HRMS m/e calcd (M^+) 251.0794, obsd 251.0794.

Methyl 6,7-(Methylenedioxy)-3,4-dihydroisoquinoline-1-carboxylate (17). To a solution of oxalamide **16** (6.56 g, 26.12 mmol) in 200 mL of acetonitrile was added phosphorous oxytrichloride (21 mL, 34.2 g, 22.3 mmol). The reaction mixture was allowed to reflux for 9 h. Water (60 mL) was added to the reaction mixture under ice-bath cooling. The resultant mixture was poured onto ice (150 g) and extracted twice with benzene. The benzene extracts were washed with 0.1 N HCl (50 mL). The combined aqueous extracts were brought to pH 8 with 30% NH_4OH. The aqueous extracts were then washed with benzene (5 × 120 mL). These organic extracts were dried (K_2CO_3), concentrated, and chromatographed (6:1 CH_2Cl_2–EtOAc) to give 3.0 g (50%) of **17** as an off-white solid (mp 63–64 °C): IR ν_{max} (CH_2Cl_2) 2950, 2820, 1725, 1625, 1615, 1590, 1485, 1435, 1380, 1320, 1240, 1205, 1095, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (s, 1 H, ArH), 6.69 (s, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 3.95 (s, 3 H, OCH_3), 3.83 (br t, J = 7.7 Hz, 2 H, NCH_2), 2.68 (br t, J = 7.7 Hz, $ArCH_2$); MS m/e (relative intensity) (M + 1) 234.1 (6.4), (M^+) 233 (47.9), 218 (14.1), 188 (23.4), 176 (13.0), 175 (100), 174 (57.7), 173 (11.7), 172 (13.5), 160 (17.1), 148 (18.2), 116 (12.1); HRMS m/e calcd (M^+) 233.0688, obsd 233.0689. Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.82; H, 4.70; N, 5.93.

Methyl 1-Hydroxy-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline-2-(α-oxo)butyrate (19). To a solution of **17** (3.395 g, 14.55 mmol) in 30 mL of CH_2Cl_2 at 0 °C was added 2.5 mL (3.06 g, 20 mmol) of 3-carbomethoxylpropionyl chloride (**5**). After 10 min, 30 mL of saturated $NaHCO_3$ solution was added, and the mixture was stirred for 1.5 h. The layers were separated, and the aqueous phase was extracted twice with 30 mL of CH_2Cl_2. The combined organics were dried (Na_2SO_4), concentrated, and chromatographed (4.5 × 14 cm, 4:1 CH_2Cl_2–EtOAc) to give 3.95 g (74%) of **19** as a white solid (mp 110–112 °C): IR ν_{max} (CH_2Cl_2) 3450, 3025, 2950, 2920, 2900, 1740, 1640, 1505, 1490, 1370, 1250, 1170, 1100, 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.13 (s, 1 H, ArH), 6.62 (s, 1 H, ArH), 5.95 and 5.94 (AB_q, J_{AB} = 1.3 Hz, $\Delta\nu$ = 1.7 Hz, 2 H, OCH_2O), 5.40 (s, 1 H, OH), 4.06–3.98 (m, 1 H, NCH), 3.70 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.44 (td, J_t = 12.1 Hz, J_d = 3 Hz, 1 H, NCH), 3.04 (br t, J = 13.9 Hz, 1 H, COCH), 2.85–2.65 (m, 5 H, $ArCH_2$ and $COCH_2CH_2CO_2Me$); MS m/e (relative intensity) (M^+) 365 (1.1), 306 (15.6), 234 (12.0), 192 (100), 175 (37.5), 163 (15.0), 115 (36.3); HRMS m/e calcd (M^+) 365.1111, obsd 365.1094.

Methyl 1-Hydroxy-2-(4-chlorobutyryl)-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (20). To a solution of **17** (2.75 g, 11.8 mmol) in 25 mL of CH_2Cl at 0 °C was added 2.0 mL (2.5 g, 17.7 mmol) of 4-chlorobutyroyl chloride (**18**). After 10 min, 30 mL of saturated $NaHCO_3$ solution was added, and the mixture was stirred for 1.5 h. The layers were separated, and the aqueous phase was extracted twice with 30 mL of CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated to afford a light brown powder. Recrystallization from CH_2Cl_2/ether/hexanes gave 3.26 g (78%) of **20** as an off-white powder: IR ν_{max} (CH_2Cl_2) 3490, 3050, 2940, 2900, 1745, 1640, 1505, 1485, 1435, 1250, 1155, 1095, 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.13 (s, 1 H, ArH), 6.62 (s, 1 H, ArH), 5.96 (s, 2 H, OCH_2O), 5.44 (s, 1 H, OH), 4.03 (br d, J = 12 Hz, 1 H, NCH), 3.80 (partially hidden t, J = 6.1 Hz, 2 H, $ClCH_2$), 3.66 (s, 3 H, OCH_3), 3.43 (td, J_t = 12 Hz, J_d = 2.8 Hz, NCH), 3.04 (br t, J = 13.1 Hz, 1 H, COCH), 2.78–2.55 (m, 3 H, COCH and $ArCH_2$), 2.15 (apparent p, J = 6.2 Hz, 2 H, $CH_2CH_2CH_2$); MS m/e (relative intensity) (M^+) 355 (0.4), 298 (14.0), 296 (45.7), 193 (10.8), 192 (100); HRMS m/e calcd (M^+) 355.0823, obsd 355.0800.

Dithiane Amide 21. To a solution of **19** (3.95 g, 10.81 mmol) in 40 mL of CH_2Cl_2 was added 1,3-propanedithiol (1.6 mL, 1.64 g, 15.2 mmol) followed by BF_3OEt_2 (2 mL, 2.3 g, 16.2 mmol) at 0 °C. The resultant orange mixture was stirred for 10 h. The solution was poured onto 100 mL of ice cold saturated $NaHCO_3$ and shaken. The layers were separated, and the aqueous phase was extracted with 2 × 40 mL of CH_2Cl_2. The combined organics were dried ($MgSO_4$), concentrated, and chromatographed (18 × 4.5 cm, 5:1 CH_2Cl_2–EtOAc) to give 1.83 g (37%) of dithiane **21** (mp 118–120 °C): IR ν_{max} (CH_2Cl_2) 3420, 3050, 2990, 2950, 1735, 1675, 1505, 1490, 1440, 1430, 1360, 1245, 1170, 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (s, 1 H, ArH), 6.82 (s, 1 H, ArH), 5.98 (s, 2 H, OCH_2O), 5.83 (br m, 1 H, NH), 3.74 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.70–3.47 (m, 4 H, NCH_2 and 2(SCH)), 2.79–2.70 (m, 4 H, $ArCH_2$ and 2(SCH)), 2.65 (t, J = 6.8 Hz, 2 H, $O_2CCH_2CH_2CON$), 2.44 (t, J = 6.8 Hz, $O_2CCH_2CH_2CON$); MS m/e (relative intensity) (M^+) 455 (4.3), 381 (14.5), 250 (12.1), 249 (71.1), 219 (12.4), 218 (111), 205 (12.0), 174 (28.7), 115 (16.1); HRMS m/e calcd (M^+) 455.1074, obsd 455.1083.

Dithiane Amide 22. To a solution of **20** (3.26 g, 9.16 mmol) in 40 mL of CH_2Cl_2 was added 1,3-propanedithiol (1.3 mL, 1.39 g, 12.8 mmol) followed by BF_3OEt_2 (1.7 mL, 1.95 g, 13.7 mmol) at 0 °C. The resultant orange mixture was stirred for 10 h. The solution was poured onto 100 mL of ice-cold saturated $NaHCO_3$ and shaken. The layers were separated, and the aqueous phase was extracted with 2 × 40 mL of CH_2Cl_2. The combined organics were dried ($MgSO_4$), concentrated, and chromatographed (16 × 4.5 cm, 6:1 CH_2Cl_2–EtOAc) to afford 2.27 g (55%) of dithiane amide **22**: IR ν_{max} (CH_2Cl_2) 3420, 3040, 2945, 2900, 1720, 1670, 1510, 1490, 1430, 1245, 1220, 1040, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (s, 1 H, ArH), 6.81 (s, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 5.78 (br s, 1 H, NH), 3.74 (s, 3 H, OCH_3), 3.58–3.47 (m, 6 H, NCH_2, $ClCH_2$, and 2(SCH)), 2.81–2.73 (m, 4 H, $ArCH_2$ and 2(SCH)), 2.30 (t, J = 7.0 Hz, 2 H, $COCCH_2$), 2.24–1.89 (m, 2 H, $SCH_2CH_2CH_2S$), 2.07 (apparent p, J = 6.8 Hz, $ClCH_2CH_2CH_2$); MS m/e (relative intensity) (M + 2) 447 (3.3), (M + 1) 446 (1.4), (M^+) 445 (8.5), 265 (14.6), 250 (16.1), 249 (74.4), 244 (23.6), 237 (14.2), 234 (12.7), 233 (17.2), 232 (96.5), 219 (15.1), 218 (100), 205 (14.3), 174 (28.2); HRMS m/e calcd (M^+) 445.0786, obsd 445.0775.

1-[2-[6-[2-(Methoxycarbonyl)-1,3-dithiolan-2-yl]-1,3-benzodioxol-5-yl]ethyl]-2,5-pyrrolidinedione (23). To a solution of amide **19** (1.83 g, 4.017 mmol) in 30 mL of THF at 0 °C was added 145 mg (6 mmol) of sodium hydride. The reaction mixture was stirred for 5 h at room temperature by which time a change in its color to burgundy signalled the completion of the reaction. Methanol was carefully added to the reaction with ice cooling. EtOAc (100 mL) was added, and the solution was washed with ammonium chloride (30 mL). The aqueous layer was extracted once with 50 mL of CH_2Cl_2, and the combined organics were dried ($MgSO_4$), concentrated, and chromatographed (2.2 × 12 cm, 8:1 CH_2Cl_2–EtOAc) to give 1.53 g (89%) of imide **23** as a slightly yellow powder (mp 214–216 °C): IR ν_{max} (CH_2Cl_2) 2900, 1705, 1505, 1485, 1405, 1355, 1240, 1170, 1150, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (s, 1 H, ArH), 6.93 (s, 1 H, ArH), 5.98 (s, 2 H, OCH_2O), 3.88 (s, 3 H, OCH_3), 3.71 (br t, J = 8.1 Hz, 2 H, NCH_2), 3.53 (br t, J = ~13 Hz, 2 H, 2(SCH)), 2.84 (br t, J = 8.1 Hz, 2 H, $ArCH_2$), 2.78–2.70 (m, 2 H, 2(SCH)), 2.72 (s, 4 H, $COCH_2CH_2CO$), 2.23–1.85 (m, 2 H, $CH_2CH_2CH_2$); MS m/e (relative intensity) (M + 2) 425 (3.7), (M + 1) 424 (6.6), (M^+) 423 (29.1), 366 (9.8), 365 (19.3), 364 (100), 348 (26.8), 256 (20.7), 249 (55.3), 237 (10.2), 219 (11.3), 218 (81.2), 205 (49.2); HRMS m/e calcd (M^+) 423.0811, obsd 423.0829.

1-[2-[6-[2-(Methoxycarbonyl)-1,3-dithiolan-2-yl]-1,3-benzodioxol-5-yl]ethyl]-2-pyrrolidinone (24). To a solution of potassium *tert*-butoxide (760 mg, 6.8 mmol) in 25 mL of THF at 0 °C was added a solution of amide **23** (2.06 g, 4.46 mmol) in 25 mL of THF. After being stirred for 15 min at 0 °C the reaction mixture was poured onto 50 mL of ice-cold saturated NH_4Cl solution and shaken. The layers were separated, and the organics were extracted with water, dried ($MgSO_4$), and concentrated to give 1.8 g (95%) of crude lactam **24** (mp 188–190 °C): IR ν_{max} (CH_2Cl_2) 2980, 2900, 1720, 1680, 1505, 1485, 1465, 1440, 1290, 1265, 1245, 1220, 1040, 1015, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (s, 1 H, ArH), 6.85 (s, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 3.76 (s, 3 H, OCH_3), 3.73–3.34 (m, 4 H, NCH_2CH_2Ar and 2(SCH)), 3.41 (t, J = 7.1 Hz, 2 H, $NCH_2CH_2CH_2$), 2.81–2.71 (m, 4 H, $ArCH_2$ and 2(SCH)), 2.39 (t, J = 8.1 Hz, 2 H, $COCH_2$), 2.21–1.88 (m, 4 H, $SCH_2CH_2CH_2$ and $NCH_2CH_2CH_2$); MS m/e (relative intensity)

(M + 2) 411 (1.1), (M + 1) 410 (2.2), (M^+) 409 (9.2), 334 (12.2), 250 (13.6), 249 (63.3), 243 (100), 242 (23.1), 237 (15.4), 210 (12.7), 218 (100), 205 (14.2), 98 (18.6); HRMS *m/e* calcd (M^+) 409.1019, obsd 409.1040.

Methyl [6-[2-(2,5-Dioxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl](α-oxo)acetate (25). To a slurry of the dithiane **23** (1.53 g, 3.612 mmol) in 40 mL of 95% acetone at −5 °C (ice/methanol) was added a solution of *N*-bromosuccinimide (5.14 g, 29 mmol) in 40 mL of 95% acetone also at −5 °C. After 5 min the orange reaction mixture was quenched with 3 M Na_2SO_3, giving a yellow solution. This was concentrated to about 10 mL and partitioned between chloroform (50 mL) and water (50 mL). The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (4.5 × 16 cm, 5:1 CH_2Cl_2–EtOAc) to give 1.104 g (91%) of keto ester **25** as a white solid (mp 138–140 °C): IR ν_{max} (CH_2Cl_2) 2940, 2900, 1700, 1600, 1500, 1485, 1395, 1375, 1160, 1080, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.10 (s, 1 H, ArH), 6.74 (s, 1 H, ArH), 6.05 (s, 2 H, OCH_2O), 3.94 (s, 3 H, OCH_3), 3.81 (t, *J* = 6.7 Hz, 2 H, NCH_2), 3.16 (t, *J* = 6.7 Hz, 2 H, $ArCH_2$), 2.64 (s, 4 H, $COCH_2CH_2CO$); MS *m/e* (relative intensity) (M + 2) 335 (3.5), (M + 1) (334 (18.9), (M^+) 333 (67.8), 302 (11.1), 301 (47.1), 275 (21.6), 273 (100), 256 (10.5), 247 (25.1), 246 (93.0), 204 (10.5), 192 (37.2), 175 (27.0), 174 (10.0); HRMS *m/e* calcd (M^+) 333.0849, obsd 333.0861.

Methyl [6-[2-(2-Oxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl](α-oxo)acetate (26). To a slurry of the dithiane **24** (1.718 g, 4.20 mmol) in 40 mL of 95% acetone at −5 °C (ice/methanol) was added a solution of *N*-bromosuccinimide (5.98 g, 33.6 mmol) in 45 mL of 95% acetone also at −5 °C. After 8 min the yellow-orange reaction mixture was quenched with 3 M Na_2SO_3, giving a pale yellow solution. This was concentrated to about 10 mL and partitioned between chloroform (50 mL) and water (50 mL). The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (4.5 × 16 cm, 4:1 CH_2Cl_2–EtOAc) to give 1.2 g (90%) of keto ester **26** (mp 92–94 °C): IR ν_{max} (CH_2Cl_2) 2945, 2900, 1735, 1675, 1605, 1505, 1485, 1375, 1285, 1205, 1160, 1080, 1040, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.16 (s, 1 H, ArH), 6.89 (s, 1 H, ArH), 6.08 (s, 2 H, OCH_2O), 3.97 (s, 3 H, OCH_3), 3.51–3.43 (m, 4 H, 2(NCH_2)), 3.13 (br t, *J* = 7.1 Hz, 2 H, $ArCH_2$). 2.38 (t, *J* = 7.6 Hz, 2 H, $COCH_2$), 2.00 (apparent pentet, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_2$); MS *m/e* (relative intensity) (M^+) 319 (5.4), 260 (15.2), 234 (29.6), 176 (11.4), 175 (67.4), 98 (100), 70 (13.5); HRMS *m/e* calcd (M^+) 319.1056, obsd 319.1055.

Methyl [6-[2-(5-Thioxo-2-oxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl](α-oxo)acetate (27). To a solution of imide **25** (1.195 g, 3.58 mmol) in 15 mL of benzene was added 728 mg (1.8 mmol) of Lawesson's reagent. The reaction mixture was heated to reflux for 4.5 h. The solution was cooled to room temperature, concentrated, and chromatographed (3.2 × 16 cm, 50:1 CH_2Cl_2–Et_2O) to give 1.067 g (80%) of monothioimide **27** as a light yellow solid (mp 124–125 °C): IR ν_{max} (CH_2Cl_2) 2950, 2900, 1750, 1680, 1605, 1505, 1480, 1395, 1380, 1345, 1260, 1170, 1135, 1080, 1040, 990, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.12 (s, 1 H, ArH), 6.77 (s, 1 H, ArH), 6.06 (s, 2 H, OCH_2O), 4.21 (t, *J* = 6.8 Hz, 2 H, NCH_2), 3.96 (s, 3 H, OCH_3), 3.26 (t, *J* = 6.8 Hz, 2 H, $ArCH_2$), 3.10 (t, *J* = 6.8 Hz, 2 H, $CSCH_2$), 2.67 (t, *J* = 6.8 Hz, 2 H, $COCH_2$); MS *m/e* (relative intensity) (M + 2) 351 (8.4), (M + 1) 350 (28.8), (M^+) 349 (100), 290 (18.9), 289 (13.4), 262 (19.8), 234 (40.0), 230 (39.3), 176 (10.1), 175 (84.4); HRMS *m/e* calcd (M^+) 349.0621, obsd 349.0622.

Methyl [6-[2-(2-Thioxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl](α-oxo)acetate (28). To a solution of lactam **27** (638 mg, 2.0 mmol) in 30 mL of THF was added 404 mg (1.0 mmol) of Lawesson's reagent. The reaction mixture was stirred at room temperature for 30 min at which point TLC analysis indicated complete consumption of the starting material. The yellow solution was concentrated and chromatographed (2.5 × 16 cm, 2:1 hexanes–EtOAc) to give 702 mg (91%) of thiolactam **28** as a crystalline light yellow solid (mp 115–117 °C): IR ν_{max} (CH_2Cl_2) 3040, 2950, 2900, 1740, 1680, 1605, 1510, 1490, 1380, 1290, 1160, 1080, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.17 (s, 1 H, ArH), 6.97 (s, 1 H, ArH), 6.08 (s, 2 H, OCH_2O), 3.97 (s, 3 H, OCH_3), 3.92 (br t, *J* = 8 Hz, 2 H, NCH_2CH_2Ar), 3.78 (t, *J* = 7.3 Hz, 2 H, NCH_2 (lactam)), 3.27 (br t, *J* = 8.0 Hz, 2 H, $ArCH_2$), 3.04 (t, *J* = 7.9 Hz, 2 H, $COCH_2$), 2.04 (apparent p, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_2$); MS *m/e* (relative intensity) (M + 2) 337 (3.6), (M + 1) 336 (11.0), 335 (55.0), 276 (15.1), 275 (28.0), 234 (15.6), 176 (12.5), 175 (100), 147 (10.1); HRMS *m/e* calcd (M^+) 335.0828, obsd 335.0829.

Hydrazone 29. To a mixture of **27** (1.06 g, 3.034 mmol) and tosyl hydrazide (620 mg, 3.3 mmol) in 10 mL of ethanol was added 80 μL of concentrated HCl. The reaction mixture was allowed to reflux for 4 h, giving a yellow slurry. The reaction mixture was cooled in an ice/methanol bath, and the solid was collected by filtration. The solid was washed with cold ethanol and dried under vacuum to give 1.294 g (83%) of tosylhydrazone **29** as a light yellow powder: ^1H NMR (250 MHz, $CDCl_3$) δ 7.82 and 7.37 (AB_q, J_{AB} = 8.3 Hz, Δν = 125 Hz, 4 H, SO_2ArH), 6.76 (s, 1 H, ArH), 6.53 (s, 1 H, ArH), 5.98 (s, 2 H, OCH_2O), 4.15–4.02 (m, 2 H, NCH_2), 3.79 (s, 3 H, OCH_3), 3.07 (br t, *J* = 4.7 Hz, 2 H, $CSCH_2$), 4.75–4.62 (m, 4 H, $COCH_2$ and $ArCH_2$), 2.41 (s, 3 H, $ArCH_3$).

Hydrazone 30. To a mixture of **28** (367 mg, 1.0 mmol) and tosyl hydrazide (208 mg, 1.1 mmol) in 4 mL of ethanol was added 25 μL of concentrated HCl. The reaction mixture was allowed to reflux for 4 h, giving a yellow slurry. The reaction mixture was cooled in an ice/methanol bath, and the solid was collected by filtration. The solid was washed with cold ethanol and dried under vacuum to give 428 mg (85%) of tosylhydrazone **30** as a light yellow powder: ^1H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1 H, NH), 7.84 and 7.34 (AB_q, J_{AB} = 8.2 Hz, Δν = 126 Hz, 4 H, SO_2ArH), 6.80 (s, 1 H, ArH), 6.40 (s, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 3.83 (s, 3 H, OCH_3), 3.79–3.67 (m, 2 H, NCH_2CH_2Ar), 3.49 (t, *J* = 7.0 Hz, 2 H, $NCH_2CH_2CH_2$), 2.97 (t, *J* = 8.2 Hz, 2 H, $CSCH_2$), 2.64–2.39 (m, 2 H, $ArCH_2$), 2.46 (s, 3 H, $ArCH_3$), 2.00 (apparent p, *J* = 7.8 Hz, $CH_2CH_2CH_2$).

Methyl [6-[2-(5-Thioxo-2-oxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl](α-diazo)acetate (31). To a solution of **2** (1.294 g, 2.54 mmol) in 10 mL of CH_2Cl_2 was added 700 μL (5 mmol) of triethylamine. The solution was stirred for 10 h at room temperature. The solution was extracted with 10 mL of water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (3.5 × 16 cm, hexane–EtOAc, 3:2) to give 805 mg (88%) of diazo ester **31**: IR ν_{max} (CH_2Cl_2) 2920, 2090, 1750, 1695, 1505, 1485, 1435, 1400, 1345, 1270, 1180, 1040, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.87 (s, 1 H, ArH), 6.82 (s, 1 H, ArH), 5.99 (s, 2 H, OCH_2O), 4.05 (t, *J* = 7.8 Hz, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 3.12 (t, *J* = 6.9 Hz, 2 H, $CSCH_2$), 2.87 (t, *J* = 7.8 Hz, 2 H, $ArCH_2$), 2.70 (t, *J* = 6.9 Hz, 2 H, $COCH_2$); MS *m/e* (relative intensity) (M^+) (−N_2, −S) 301 (9.0).

Methyl [6-[2-(2-Thioxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl](α-diazo)acetate (32). To a solution of **30** (428 mg, 0.85 mmol) in 5 mL of CH_2Cl_2 was added 235 μL (1.7 mmol) of triethylamine. The solution was stirred for 10 h at room temperature. The solution was extracted with 5 mL of water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (2.5 × 12 cm, hexanes–EtOAc, 3:2) to give 263 mg (90%) of diazo ester **32**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.87 (s, 1 H, ArH), 6.82 (s, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 3.90 (t, *J* = 6.8 Hz, 2 H, NCH_2CH_2Ar), 3.82 (s, 3 H, OCH_3), 3.56 (t, *J* = 7.2 Hz,-$NCH_2CH_2CH_2$), 3.02 (t, *J* = 7.6 Hz, 2 H, $CSCH_2$), 2.93 (t, *J* = 6.8 Hz, 2 H, $ArCH_2$), 2.01 (apparent p, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_2$).

Methyl 5,8,9,10-Tetrahydro-8-oxo-6*H*-1,3-dioxolo[4,5-*h*]-pyrrolo[2,1-*b*][3]benzazepine-11-carboxylate (33). To a suspension of rhodium(II) acetate dimer (75 mg, 0.28 mmol) in refluxing benzene (180 mL) was added a solution of diazo compound **31** (1 g, 2.79 mmol) in 15 mL of benzene over 5 h. The reaction mixture was cooled, concentrated, and chromatographed (3.2 × 16 cm, 18:1 CH_2Cl_2–EtOAc) to give 640 mg (77%) of cyclized compound **33** as a light yellow powder (mp 147–148 °C): IR ν_{max} (CH_2Cl_2) 3040, 1720, 1640, 1610, 1505, 1490, 1370, 1190, 1155, 1100, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.60 (s, 1 H, ArH), 6.59 (s, 1 H, ArH), 5.95 (s, 2 H, OCH_2O), 3.95–3.65 (br m, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 3.13 (br t, *J* = 7.2 Hz, 2 H, CH_2CH_2CO), 2.90 (br t, *J* = 4.4 Hz, 2 H, $ArCH_2$), 2.57 (t, *J* = 7.5 Hz, 2 H, CH_2CH_2CO); MS *m/e* (relative intensity) 303 (2.5), 302 (17.4), (M^+) 301 (100), 286 (17.7), 270 (11.5), 242 (27.9), 241 (9.2); HRMS *m/e* calcd (M^+) 301.0951, obsd 301.0954. Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.75; H, 4.95; N, 4.45.

Methyl 5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]-pyrrolo[2,1-*b*][3]benzazepine-11-carboxylate (34). To a suspension of rhodium(II) acetate dimer (15 mg, 0.06 mmol) in refluxing benzene (40 mL) was added a solution of diazo compound **32** (210 mg, 0.61 mmol) in 4 mL of benzene over 5 h. The reaction mixture was cooled, concentrated, and chromatographed (2.5 × 10 cm, 18:1 CH_2Cl_2–EtOAc) to give 136 mg (79%) of cyclized compound **34** as a light yellow powder: ^1H NMR (250 MHz, $CDCl_3$) δ 6.82 (s, 1 H, ArH), 6.52 (s, 1 H, ArH), 5.91 (s, 2 H, OCH_2O), 3.67 (s, 3 H, OCH_3), 3.58 (br t, J = 5.0 Hz, 2 H, NCH_2CH_2Ar), 3.33 (t (partially hidden), J = 7.6 Hz, 2 H, $NCH_2CH_2CH_2$), 3.31 (t (partially hidden), J = 7.6 Hz, 2 H, $NCH_2CH_2CH_2$), 2.90 (br t, J = 5.0 Hz, 2 H, $ArCH_2$), 1.93 (apparent p, J = 7.2 Hz, 2 H, $CH_2CH_2CH_2$).

2-(1,3-Benzodioxol-5-yl)ethyl Isocyanide (36). An oven-dried, three-necked flask equipped with a thermometer, addition funnel, nitrogen inlet adapter, and magnetic stirring bar was charged with 135 mL of THF, 13.12 g (68 mmol) of β-[3,4-(methylenedioxy)phenyl]ethyl formamide (**35**) and 47.6 mL (342 mmol) of triethylamine. The reaction mixture was cooled to 10 °C, and 11.5 g (75 mmol) of phosphorous oxychloride in 7 mL of THF was added at a rate so that the reaction temperature remained below 16 °C. After the addition was complete, the mixture was quenched with 340 mL of ice water and stirring was continued for an additional 2 h. The resultant mixture was extracted with 3 × 150 mL of ether, washed with brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by chromatography on 100 g of silica gel (25% ether–pentane) to yield 9.64 g (81%) of isocyanide **36** as a colorless oil: IR ν_{max} (CH_2Cl_2) 3020, 2980, 2890, 2150, 1500, 1490, 1445, 1250, 1195, 1100, 1040, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.78 and 6.69 (AB_q, J_{AB} = 8.1 Hz, $\Delta\nu$ = 21.4 Hz, 2 H, 2(ArH)), 6.71 (s, 1 H, ArH), 5.96 (s, 2 H, OCH_2O), 3.57 (br t, J = 7.0 Hz, 2 H, NCH_2), 2.91 (br t, J = 7.0 Hz, 2 H, $ArCH_2$).

1-Propionyl-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (37). To a solution of 2-[3,4-(methylenedioxy)phenyl]ethyl isocyanide (**36**) (4.025 g, 23 mmol) in 60 mL of CH_2Cl_2 was added propionyl chloride (2.12 g, 23 mmol). The reaction mixture was stirred for 7 h at 25 °C, cooled to −20 °C, and treated with 6.2 g of silver triflate (24 mmol). The suspension was then stirred in the dark at −20 °C for a further 3 h. The reaction mixture was treated with 4.0 mL of triethylamine (28 mmol) at −20 °C followed by 6 mL of 10% aqueous $KHCO_3$. The mixture was stirred for 0.5 h at 25 °C and filtered through a bed of Celite using 500 mL of CH_2Cl_2. The filtrate was then extracted with 30 mL of H_2O, and the organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were removed, and the residue was submitted to chromatography (30% EtOAc/hexanes) to afford 4.71 g (89%) of dihydroisoquinoline **37** as a white crystalline solid (mp 64–65 °C); IR ν_{max} (CH_2Cl_2) 2970, 2920, 2900, 2820, 1705, 1620, 1585, 1505, 1485, 1380, 1320, 1270, 1245, 1095, 1050, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.24 (s, 1 H, ArH), 6.68 (s, 1 H, ArH), 5.98 (s, 2 H, OCH_2O), 3.78 (br t, J = 7.7 Hz, 2 H, NCH_2), 3.00 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.63 (br t, J = 7.7 Hz, 2 H, ArH), 1.16 (t, J = 7.3 Hz, 3 H, CH_2CH_3); MS m/e (relative intensity) 232 (12.1) (M^+) 231 (66.8), 230 (49.1), 203 (10.6), 202 (55.4), 201 (100), 176 (13.9), 175 (94.5), 174 (90.0), 148 (19.4), 116 (12.0); HRMS m/e calcd (M^+) 231.0896, obsd 231.0906. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.02; N, 4.65. Found: C, 67.75; H, 4.95; N, 4.45.

Amide 39. To a solution of **37** (2.310 g, 10 mmol) in 25 mL of CH_2Cl_2 at 0 °C was added 1.73 mL (2.77 g, 15 mmol) of 4-bromobutyroyl chloride (**38**). After 10 min, 30 mL of saturated $NaHCO_3$ solution was added and the mixture stirred 1.5 h. The layers were separated, and the aqueous phase was extracted twice with 30 mL of CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated to afford a bright yellow crystalline residue. This was triturated with 50 mL of cold EtOAc and then recrystallized (EtOAc) to afford 3.36 g (84%) of amide **39** as a white crystalline solid (mp 130–131 °C): IR ν_{max} (CH_2Cl_2) 3450, 3045, 2965, 2925, 2885, 1715, 1650, 1500, 1485, 1436, 1415, 1245, 1090, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.79 (s, 1 H, ArH), 6.63 (s, 1 H, ArH), 5.95 (s, 2 H, OCH_2O), 5.77 (s, 1 H, OH), 4.08 (br d, J = 12.3 Hz, 1 H, NCH), 3.55–3.40 (m, 3 H, $BrCH_2$ and NCH), 3.03 (triplet of d, J_t = 13.7 Hz, J_d = 3.6 Hz, 1 H, COCH), 2.83–2.55 (m, 3 H, CH_2CH_3 and COCH), 2.42–2.06 (m, 4 H, $ArCH_2$ and $CH_2CH_2CH_2$), 0.94 (t, J = 7.2 Hz, 3 H, CH_2CH_3); MS m/e (relative intensity) (M^+) 398 (0.3), 342 (11.8), 340 (13.3), 260 (8.0), 193 (12.6), 192 (100), 174 (6.4), 149 (6.3); HRMS m/e calcd (M^+) 397.0525, obsd 397.0510.

Keto Lactam 40. To a solution of **39** (1.592 g, 4.0 mmol) in 100 mL of THF at 0 °C was added potassium *tert*-butoxide (452 mg, 4.0 mmol) in one portion. After the solution was stirred for 30 min at 0 °C, the reaction was quenched with 50 mL of saturated NH_4Cl. The mixture was concentrated to about 50 mL and then partitioned between chloroform (100 mL) and water (100 mL). The organics were dried (Na_2SO_4), filtered, and concentrated. Chromatography (EtOAc) of the residue afforded 694 mg (52%) of **40**: IR ν_{max} (CH_2Cl_2) 2970, 2930, 1710, 1675, 1600, 1505, 1485, 1675, 1245, 1040, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.06 (s, 1 H, ArH), 6.87 (s, 1 H, ArH), 6.06 (s, 2 H, OCH_2O), 3.48 (t, J = 7 Hz, 2 H, NCH_2CH_2Ar), 3.42 (t, J = 7 Hz, 2 H, $NCH_2CH_2CH_2$), 3.10 (t, J = 7 Hz, 2 H, $ArCH_2$), 2.90 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.38 (t, J = 7.8 Hz, 2 H, $NCOCH_2$), 2.00 (apparent p, J = 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 1.20 (t, J = 7.3 Hz, 3 H, CH_3); MS m/e (relative intensity) (M + 2) 317 (1.7), (M + 1) 316 (2.5), (M^+) 315 (7.4), 299 (23.2), 260 (28.8), 242 (11.3), 232 (15.8), 230 (10.1), 215 (15.1), 214 (100), 192 (20.7), 175 (20.6), 98 (16.6); HRMS m/e calcd (M^+) 317.1264, obsd 317.1270.

Thiolactam 41. To a solution of **40** (630 mg, 2.0 mmol) in 30 mL of THF was added 404 mg (1 mmol) of Lawesson's reagent at room temperature. After 30 min, the solution was concentrated and chromatographed (4:1 hexanes–EtOAc) to give 639 mg (96%) of **41** as a pale yellow powder: IR ν_{max} (CH_2Cl_2) 3030, 2965, 2930, 2900, 1710, 1665, 1510, 1490, 1380, 1300, 1240, 1040, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.06 (s, 1 H, ArH), 6.94 (s, 1 H, ArH), 6.06 (s, 2 H, OCH_2O), 3.93 (t, J = 7.7 Hz, 2 H, NCH_2CH_2Ar), 3.74 (t, J = 7.3 Hz, 2 H, $NCH_2CH_2CH_2$), 3.24 (t, J = 7.7 Hz, 2 H, $ArCH_2$), 3.03 (t, J = 7.9 Hz, 2 H, $CSCH_2$), 2.89 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.03 (apparent p, J = 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 1.20 (t, J = 7.2 Hz, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) d 203.85, 200.41, 193.37, 151.62, 145.92, 138.10, 123.64, 111.87, 111.32, 101.91, 55.00, 48.17, 44.34, 31.42, 30.09, 19.19, 6.35; MS m/e (relative intensity) 335 (1.7), 334 (4.6), (M^+) 333 (24.6), 276 (17.2), 258 (10.1), 232 (39.4), 176 (15.5), 175 (100); HRMS m/e calcd (M^+) 333.0879, obsd 333.1029.

11-(Propionylthio)-5,8,9,10-tetrahydro-6*H*-1,3-dioxolo-[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine (42). A solution of **41** (333 mg, 1.0 mmol) in 20 mL of trimethyl phosphite was heated at reflux for 24 h. The excess trimethyl phosphite was distilled off, and the resultant residue was subjected to chromatography (4:1 hexanes–EtOAc) to give 77 mg (24%) of **42**: IR ν_{max} (CH_2Cl_2) 2990, 2880, 1690, 1575, 1505, 1480, 1250, 1220, 1150, 1040, 930 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.94 (s, 1 H, ArH), 6.47 (s, 1 H, ArH), 5.89 (s, 2 H, OCH_2O), 3.61 (t, J = 4.2 Hz, 2 H, NCH_2CH_2Ar), 3.44 (t, J = 7.3 Hz, 2 H, $NCH_2CH_2CH_2$), 3.06–2.75 (broad m, 4 H, $ArCH_2$ and $C{=}CCH_2$), 2.61 (q, J = 7.7 Hz, 2 H, CH_2CH_3), 1.90 (apparent p, J = 7.3 Hz, 2 H, $CH_2CH_2CH_2$), 1.21 (t, J = 7.7 Hz, 3 H, CH_2CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.56 (C=O), 154.56, 146.08, 144.28, 133.93, 132.03, 107.95, 107.57, 100.47, 83.88, 57.92, 54.89, 36.35, 35.57, 35.10, 21.05, 9.49; MS m/e (relative intensity) (M + 2) 319 (1.8), (M + 1) 318 (5.6), (M^+) 317 (28.3), 262 (7.5), 261 (25.4), 260 (100), 228 (103), 216 (47.4).

4-[6-[2-(2-Thioxopyrrolidin-1-yl)ethyl]-1,3-benzodioxol-5-yl]-2,2-dihydro-2,2,2-trimethoxy-5-methyl-1,3,2-dioxaphosphole (43). To a solution of **41** (33 mg 0.1 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube was added 3 equiv of trimethyl phosphite. The tube was placed in a water bath at 50 °C. Within 40 min, monitoring of the reaction by ^1H NMR indicated complete conversion to enediolate **43**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.85 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 3.92 (br t, J = 7.7 Hz, 2 H, NCH_2CH_2Ar), 3.65 (d, J = 13.1 Hz, 9 H, $P(OCH_3)_3$), 3.60 (hidden m, 2 H, $NCH_2CH_2CH_2$), 3.03 (br t, J = 7.9 Hz, 2 H, $COCH_2CH_2$), 2.96 (br t, J = 7.6 Hz, 2 H, $ArCH_2$), 2.27 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 2.00 (apparent p, J = 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 1.15 (t, J = 7.5 Hz, 3 H, CH_2CH_3).

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Registry No. (±)-**3**, 38848-21-4; **4**, 6882-28-6; **5**, 1490-25-1; (±)-**6**, 124021-68-7; **7**, 124021-69-8; **8**, 124021-70-1; **9**, 124021-71-2; **10**, 124021-72-3; **11**, 124021-73-4; (±)-**12**, 124021-74-5; **13**, 124021-75-6; **14**, 35667-11-9; **15**, 1484-85-1; **16**, 124021-76-7; **17**, 124021-77-8; **18**, 4635-59-0; (±)-**19**, 124021-78-9; (±)-**20**, 124021-79-0; **21**, 124021-80-3; **22**, 124021-81-4; **23**, 124021-82-5; **24**, 124021-83-6; **25**, 124021-84-7; **26**, 124021-85-8; **27**, 124021-86-9; **28**, 124021-87-0; **29**, 124021-88-1; **30**, 124021-89-2; **31**, 124021-90-5; **32**, 124021-91-6; **33**, 124021-92-7; **34**, 124021-93-8; **35**, 33542-98-2; **36**, 65239-07-8; **37**, 124021-94-9; **38**, 927-58-2; (±)-**39**, 124021-95-0; **40**, 124021-96-1; **41**, 124021-97-2; **42**, 124021-98-3; **43**, 124021-99-4; I, 124021-66-5; II, 124021-67-6; (*E*)-III, 124022-00-0; (*Z*)-III, 124022-01-1; $(MeO_2C)_2$, 553-90-2.

Supplementary Material Available: Single-crystal X-ray analysis of compound **42**, including positional parameters, intramolecular distances, bond angles, torsional angles, and *U* values, and ^1H NMR spectra of compounds **7–11**, **13**, **16**, **17**, **19–22**, **24–28**, **33**, **36**, **37**, and **39–43** (32 pages). Ordering information is given on any current masthead page.

Glycosylcarborane Derivatives and the Determination of the Absolute Configuration of a Diastereomeric Triol from X-ray Diffraction

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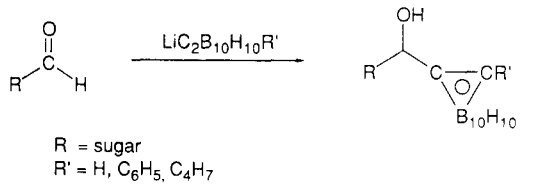
Lithiated 1,2-dicarba-*closo*-dodecaboranes (carboranes)[1] react with aldehydic sugars to give the corresponding hydroxyalkylated carboranes in good yields. In tetrahydrofuran solutions, high diastereoselectivity is observed. A single-crystal X-ray structure of a typical reaction product (**1e**) confirmed that the erythro isomer was the major diastereomer formed. Epimeric inversion was accomplished by a simple oxidation–reduction sequence, which can introduce a tritium label into the glycosylcarborane. A representative 1-(hydroxyalkyl)-2-phenyl-1,2-dicarba-*closo*-dodecaborane was converted to a *m*-diazonium ion and coupled to β-naphthol.

Introduction

The application of the cytotoxic ^{10}B neutron-capture reaction [$^{10}B(n,\alpha)^7Li$] to the treatment of human tumors coupled with the use of antitumor antibodies as a vehicle for depositing boron-10 selectively in tumors has been discussed for many years.[2] The slow progress in this approach has been principally due to the difficulty in labeling antibodies with large quantities of boron while retaining immunoreactivity of the immunoglobulins and also to the lack of a truly specific tumor-localizing antibody for human studies. Mizusawa et al. have shown that it is possible to attach as many as 14 molecules of suitably functionalized carborane units to a single antibody molecule.[3] However, they also found that protein precipitation and loss of immunoreactivity are significant when as few as six carborane units are attached to each antibody.[3] The extremely hydrophobic nature of the carboranes used in these studies led us to conclude that the addition of polar, hydrophilic functional groups had the potential of drastically reducing antibody conjugate precipitation.

Attempts to increase the water solubility of carborane–antibody complexes have met with some success in the past. Soloway and co-workers examined the inclusion of a gluconamide moiety in a polyhedral borane prior to IgG coupling.[4] This resulted in placement of the water-soluble group between the polyhedral borane and the protein backbone. Gabel et al. have reported the preparation of dextran molecules boronated with decachlorocarboranes and subsequent conjugation of these hydrophilic compounds to antibodies.[5] We propose that the hydrophobic character of the carborane cage could be more effectively minimized if this unit were placed between the protein and the hydrophilic carbohydrate group. Our initial work in this area[6] focused on the extension of Ferrier-type chemistry[7] to include the addition of carboranyl alcohols to unsaturated sugars. Upon examining the reactivity of

Scheme I



(1) Throughout this paper, the terms carborane or 1,2-dicarba-*closo*-dodecaborane refer to an icosahedron with carbons at two adjacent vertices and boron at the remaining ten. Unsubstituted carborane has the formula $C_2B_{10}H_{12}$, with one hydrogen attached to each of the heavier atoms.

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