Intramolecular Addition of a Dioxolanyl Radical to the Indole Nucleus: Preparation of Enantiomerically Pure, Oxygenated Perhydro-3*H*-pyrrolo[1,2-*a*]indoles

Frederick E. Ziegler* and Patrick G. Harran

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511

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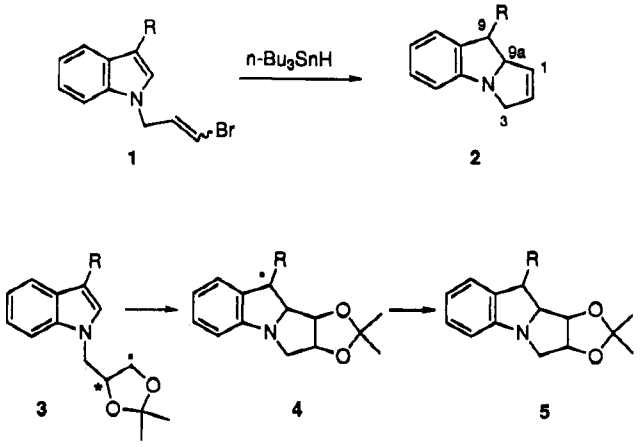
The cyclization of dioxolanyl radicals, which were generated by the Barton tartrate-derived thiohydroxamate ester (mixed anhydride) procedure, with an indole nucleus has been explored. The products derived from these reactions have been identified and their chemistry investigated with the goal of uncovering new entries into enantiomerically pure, mitomycin-like structures. Thus, the photolysis of 1-hydroxy-2-thiopyridone ester **8c** and 1-hydroxy-4-methylthiazole-2(3*H*)-thione ester **8d** has been conducted with UV and visible light. The photochemistry of the products, namely, dimer **9**, dihydroindole **12a**, indole **11**, and thiazole **13c**, derived from the thiohydroxamate esters and putative intermediates **18a** and **18b**, was also explored.

Introduction

A previous report from this laboratory described the radical cyclization **1** → **2** as a route to 9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles, which are substructures related to mitomycins.[1,2] This approach suffered in two respects: the olefin would have required functionalization and the products would have been racemic. To circumvent these difficulties, the sequence **3** → **4** → **5** was considered as a



useful study. The dioxolanyl radical **3** could undergo cyclization to form the benzylic radical **4**, which would be reduced by an appropriate hydrogen atom source to afford **5**. The starred stereogenic, enantiomerically pure center of **3** could serve as a stereocontrol element in the cyclization.

Barton has demonstrated that thiohydroxamate esters (mixed carboxylic acid/thiohydroxamic acid anhydrides) can serve as a convenient source of carbon radicals[3] that can engage in intramolecular additions to olefins[4] in both chain and nonchain reactions.[5] In addition, tartrate-derived thiohydroxamate esters can be used to generate dioxolanyl radicals that participate in intermolecular additions to electron deficient olefins.[6] We chose to explore the tartrate-derived radicals to achieve the transformation described in the reaction **3** → **4** → **5**.

Results and Discussion

Methyl 2,3-*O*-isopropylidene-L-threonate (**7a**) was prepared from dimethyl L-tartrate as described by Rapoport.[7] Neither the derived mesylate **7b**[7] nor the iodide **7c**[8] served as effective electrophiles for the alkylation of 3-cyanoindole (**6**). However, when the triflate **7d**, which was prepared in situ, was treated with the potassium salt of 3-cyanoindole, the ester **8a** was isolated in 86% yield. Acid **8b**, which was readily prepared by saponification with aqueous LiOH, was converted to the thiohydroxamate esters **8c** and **8d** by a variation of the mixed anhydride method.[9] When isobutyl chloroformate and *N*-methylmorpholine were added to the carboxylic acid to form the mixed anhydride prior to the addition of 1-hydroxy-2-thiopyridone or 1-hydroxy-4-methylthiazole-2(3*H*)-thione, substantial amounts of the carboxylic acid were eventually reisolated. This order of addition was suspect because it allows excess carboxylic acid to exist in the presence of mixed anhydride, which could lead to symmetrical anhydride, a source of acid upon acylation of the *N*-hydroxy species. The yields of the thiohydroxamates were improved by adding slowly the amine and carboxylic acid to a solution of the chloroformate. Because the thiohydroxamates proved somewhat labile, **8c** more so than **8d**, they were not subjected to chromatographic purification. The

(1) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479.
(2) For reviews on the synthesis of mitomycins, see: (a) Kametani, T.; Takahashi, K. *Heterocycles* **1978**, *9*, 293. (b) Takahashi, K.; Kametani, T.; *Heterocycles* **1979**, *13*, 411. (c) Franck, R. W. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 1. (d) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549. (e) Kasai, M.; Kono, M. *Synth. Lett.* **1992**, 778. For more recent, notable contributions to the field, see: (f) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891. (g) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7880. (h) Benbow, J. W.; Schulte, G. K.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 915.
(3) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(4) a) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkins Trans. I* **1986**, *39*. b) Barton, D. H. R.; Guilhem, J.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron Lett.* **1987**, *28*, 1413.
(5) a) Barton, D. H. R.; Crich, D.; Potier, P. *Tetrahedron Lett.* **1985**, *26*, 5943. b) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733.
(6) Barton, D. H. R.; Gateau-Olesker, A.; Gero, S. D.; Lacher, B.; Tachdjian, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1987**, 1790.
(7) Musich, J. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 4865.
(8) Tanaka, A.; Yamashita, K. *Chem. Lett.* **1981**, 319.
(9) a) Barton, D. H. R.; Bridon, D.; Hervé, Y.; Potier, P.; Thierry, J.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 4983. b) Barton, D. H. R.; Crich, C.; Hervé, Y.; Potier, P.; Thierry, J. *Ibid.* **1985**, *41*, 4347.

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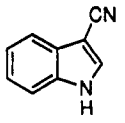

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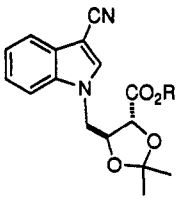
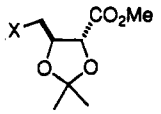


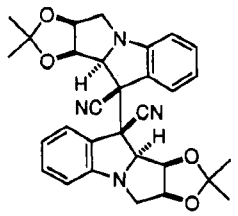
8 a, R = Me
b, R = H
c, R =
d, R =



7 a, X = OH
b, X = OMs
c, X = I
d, X = OTf

decomposition of the thiohydroxamate esters was initiated photochemically in degassed ~0.05 M THF solution under N_2 in a Pyrex vessel; the yields of products are based upon acid **8b**. Photolyses of the products isolated from these reactions were conducted at 0.01 M in THF.

Irradiation of the *N*-hydroxypyridine-2-thione ester **8c** with a 500-W tungsten lamp (visible light) at room temperature led to the formation of a single, cyclized dimer **9** in 37% yield along with the formation of dipyridyl disulfide **10** (36%), smaller amounts of cyclized indole **11**, and uncyclized thiopyridines **13a** and **13b**. The formation



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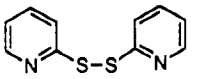

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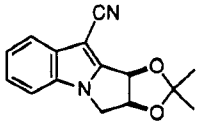

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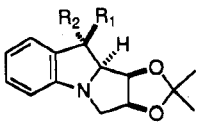
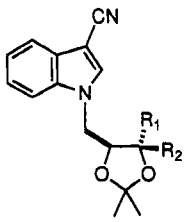
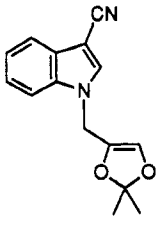


12 a, R_1 = CN, R_2 = H
b, R_1 = H, R_2 = CN



13 a, R_1 = S-2-pyr, R_2 = H
b, R_1 = H, R_2 = S-2-pyr
c, R_1 = S-2-thiazole, R_2 = H
d, R_1 = H, R_2 = S-2-thiazole
e, R_1 = R_2 = H



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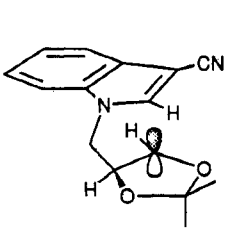
of the dimer requires homolysis of the N–O bond of **8c**, decarboxylation, radical inversion, stereoselective formation of the C_{1-9a} bond,[10] and stereoselective dimerization. The well-resolved ^1H NMR spectrum of the dimer displayed an odd number of protons (nine) and the high-resolution mass spectrum indicated a molecular formula of $C_{30}H_{30}N_4O_4$. The unanticipated stereochemistry of the dimer was revealed by a single crystal X-ray analysis.[11] The initial expectation was that cyclization would occur through the less-congested transition state with the geometry of **15** to avoid any interaction between the *gem*-dimethyl group and the aromatic ring. It is clear that the more-congested transition state **16** is involved in the cyclization. Transition state **16** may be governed by an electronic effect, perhaps electron transfer, that leads to the stabilized radical **17**, which is compelled to undergo dimerization on the convex face. Alternatively, the odd electron may be transferred to the electron-deficient aromatic system via **15** to give a charge-transfer species that cyclizes through the geometry of **16**.



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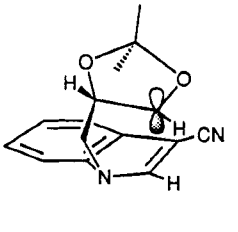

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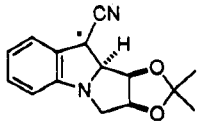

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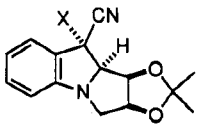
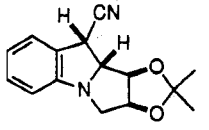


18 a, X = S-2-pyr
b, X = S-2-thiazole



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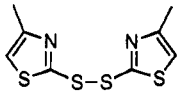

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The presence of thiopyridine **18a**, or its C_9 stereoisomer, could not be detected in the reaction mixture. However, epimeric dihydroindoles **12a** and **12b** formed a yellow anion with n-BuLi in THF, which, upon treatment with dipyridyl disulfide **10**, led to the formation of thiopyridine **18a**, whose stereochemistry at C_9 was assumed to arise, as had the dimer, by convex face bond formation. Thiopyridine **18a** was stable to irradiation with visible light in THF over a period of 30 min at room temperature, which demonstrated that **18a** was not an intermediate in the formation of dimer **9**. However, exposure of **18a** to UV irradiation (Hanovia, 450 W) produced indole **11** and 2-mercaptopyridine within 5 min. Moreover, an NMR sample of **18a** in $CDCl_3$ decomposed to the same two products after 4 h, a reaction that was presumably catalyzed by a trace of acid in the solvent. The small amount of indole **11** that was formed along with dimer in the original photolysis could have arisen by hydrogen atom abstraction from radical **17** by pyridinethiyl radical.

Photolysis of thiohydroxamate ester **8c** at −78 °C for 75 min gave principally uncyclized products. A mixture

(10) Mitomycin numbering is used. See structure 2.

(11) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(43%) of *trans*- and *cis*-thiopyridines **13a** and **13b** (~3:1 by ^{1}H NMR) were isolated as the major products. The methine hydrogen at the sulfur-bearing carbon of the major isomer showed J = 6.7 Hz (δ 6.01) while the minor isomer displayed J = 4.6 Hz (δ 5.50). These chemical shifts and coupling constants were correlated with the values obtained for the thiazole congeners **13c** and **13d**, whose stereochemical assignments were supported by NOE studies (vide infra). The appearance of 11% of dioxolene **14** suggests that the uncyclized dioxolanyl radical may either capture pyridinethiyl radical or the dioxolanyl radical may lose a hydrogen atom to form **14** in a solvent cage. The small amount of dimer **9** detected in the crude ^{1}H NMR spectrum would also be consistent with a cage mechanism. Irradiation of thiohydroxamate ester **8c** with UV light (Hanovia, 450 W) for 8 min at room temperature produced dimer **9** (40%), uncyclized thiopyridines **13a** and **13b** (20%, 2.8:1), cyclized indole **11** (20%), and dihydroindole **12a** (~2%). The stereochemistry of **12a**, a compound that can be prepared more efficiently by other means (vide infra), was corroborated by the appearance of strong NOEs between the C_9-H and C_{9a}-H (9%) and the C_{9a}-H and C_1-H (10%), an observation that, taken in the context of the magnitude of the NOEs of the other two isomers, suggested a cis arrangement of the three vicinal hydrogens.

In an effort to form monomeric dihydroindoles from the dimer, it was heated at reflux in thiophenol[12] to form indole **11**, dihydroindole **12a**, and fragmentation product **13e**. A more effective process was to submit dimer **9** to UV irradiation in degassed THF over 3 h, which gave near equal amounts of indole **11** and dihydroindole **12a**. The facial selectivity in the hydrogen atom abstraction is the same as that observed in the dimerization. This disproportionation is reminiscent of the decomposition of AIBN.[13] The reaction can be conducted under conditions that give either of the two monomers. Thus, UV irradiation of dimer **9** in the presence of 4 equiv of n-Bu_3SnH under the same conditions gave a 7:1 ratio of **12a** and its C_9 epimer **12b**. The epimeric nature of the two compounds was confirmed as described above, namely, by the formation of **18b** from both compounds. Not surprisingly, *exo*-nitrile **12b** reacted more slowly than **12a** upon deprotonation with n-BuLi. Moreover, NOE studies on **12b** revealed a 9% enhancement between the C_{9a}-H and C_1-H (cis) and 3% enhancement between the C_9-H and C_{9a}-H (trans). Both dihydroindoles arise from reduction of radical **17**. However, the minor isomer **12b** was not detected in the photolytic reduction of indole **11** (vide infra) in the presence of n-Bu_3SnH; only dihydroindole **12a** as the major product and dihydroindole **19** as the minor product were found. To the degree that dihydroindole **19** is not detected in the reduction of the dimer, indole **11** is not an intermediate in the reduction of the dimer but rather the radical **17** abstracts a hydrogen atom from n-Bu_3SnH prior to disproportionation.

When the dimer was photolyzed with UV light in the presence of disulfide **20** at room temperature to 50% conversion, indole **11** predominated over dihydroindole **12a** in a 9:1 ratio. Ultimately, the oxidation occurs by hydrogen atom abstraction from radical **17**. The generation of these species may be viewed as arising by attack of radical **17** on the disulfide to form thiazole **18b** followed by its photolysis. This pathway (S_H2) has been shown by Barton to be operationally ineffective upon thermal decarboxylation of palmitoyl thiohydroxamate in excess (30 equiv, 74% yield) molten diphenyl disulfide whereas photolytic conditions are efficient (0 °C, 2 equiv of disulfide).[5b] Alternatively, both the dimer and dipyridyl disulfide are susceptible to photodissociation, a process that would generate both the carbon and thiyl radicals and permit hydrogen atom abstraction from radical **17** by the thiyl radical. Moreover, disulfide **20** is reduced faster than the dimer by n-Bu_3SnH under photolytic conditions.

Owing to the relative instability of the *N*-hydroxypyridine-2-thione ester **8c**, the photochemistry of the *N*-hydroxy-4-methylthiazole-2-thione ester **8d** was investigated.[4a] Irradiation of ester **8d** with UV light afforded cyclized indole **11** (48%), an ~3:1 mixture of uncyclized thiazoles **13c** and **13d** (22%), dioxolene **14** (6%), and <5% (^{1}H NMR) of dimer **9**. The methine hydrogen at the sulfur-bearing carbon of **13c** displayed J = 6.5 Hz (δ 5.50) while the minor isomer revealed J = 4.6 Hz (δ 6.23). A 3% NOE was observed for the vicinal hydrogen of trans isomer **13c** and a 13% NOE for cis isomer **13d** upon irradiation of the hydrogen at the sulfur-bearing carbon. The formation of uncyclized thiazole **13c** did not prove to be a dead-end product. UV irradiation of **13c** (~0.01 M) in the presence of 4 equiv of n-Bu_3SnH for 7 h slowly gave rise to dihydroindoles **12a** (61%) and **12b** (11%) and indole **11** (14%).

The lack of appreciable dimer (<5%, ^{1}H NMR) in the photolysis of ester **8d** may be viewed as a chain process for the formation of indole **11**. Thiazole **18b**, which was prepared by the procedure described for **18a**, led to the formation of indole **11** upon UV irradiation, a result consistent with a chain mechanism. The photolysis of **18b** generates stabilized radical **17**, which undergoes hydrogen atom abstraction by the thiazolethiyl radical. However, this result only demonstrates that thiazole **18b**, if formed, can afford indole **11** upon UV photolysis. For a chain mechanism to be operable, radical **17**, once having added to the C=S bond of **8d**, would have to favor N–O bond cleavage relative to the same reaction with **8c**. An alternative view holds that radical **17** is formed in a nonchain process upon irradiation of thiohydroxamate ester **8d** and that the formation of indole **11** reflects a greater propensity for the thiazolethiyl radical to hydrogen atom abstract from radical **17** compared with the pyridinethiyl radical.

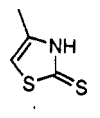
The diphenylmethyl radical has been shown to add reversibly to the carbon–sulfur double bond of thiohydroxamate esters in refluxing benzene during the process of forming tetraphenylethane.[5b] When ester **8d** was heated in refluxing THF, the product distribution was similar to that for the photolysis. Indole **11** (21%) and uncyclized thiazoles **13a** and **13b** (31%) were formed in addition to the dioxolene **14** (10%).

Several experiments were designed to illustrate that thiazolethiyl radicals can be scavenged by n-Bu_3SnH. First, thiazolyl disulfide **20** undergoes reduction by n-Bu_3SnH upon UV irradiation. Secondly, UV photolysis of thiazole **18b** (0.03 M/THF) in the presence of 4 equiv of n-Bu_3SnH for 5 min gave a 3:1 ratio of indole **11** to dimer **9**. The high ratio indicates that the abstraction of a hydrogen atom by thiazolethiyl radical from radical **17** is faster than abstraction from n-Bu_3SnH. Finally, the course of the

(12) Peterson, L. I. *J. Am. Chem. Soc.* **1967**, *89*, 2677.
(13) Jaffe, A. B.; Skinner, K. J.; J. M. McBride *J. Am. Chem. Soc.* **1972**, *94*, 8510 and references cited therein.

photolysis of thiohydroxamate ester **8d** can be changed to produce dimer **9** as the major product. During the period of the photolysis, 2 equiv of n-Bu_3SnH were added slowly to the reaction mixture. Examination of the mixture by ^1H NMR revealed that dimer **9** was the major product along with lesser amounts of indole **11** and thiazoles **13a** and **13b**. Because these four indolic species can be channeled on to dihydroindoles, the irradiation was continued for 6.5 h in the presence of an additional quantity of n-Bu_3SnH (4 equiv) to give dihydroindoles **12a** (41%) and **12b** (20%), indole **11** (17%), and dioxolane **13e** (3%).

Indole **11**, as noted earlier, is itself susceptible to photoreduction. Irradiation of indole **11** in the presence of 4 equiv of n-Bu_3SnH afforded the expected dihydroindole **12a** with no detectable amount of its epimer **12b**. A third dihydroindole, namely **19**, was isolated in 17% yield. It displayed an 11% NOE between the C_9-H and C_{9a}-H (cis) and a 2% NOE between the C_1-H and C_{9a}-H (trans). This dihydroindole arises by the addition of hydrogen at C_{9a} cis to the dioxolane ring to give the diastereomeric radical of **17** that suffers subsequent reduction. In addition, two products of over-reduction were isolated and assigned structures **22a** (6%) and **23** (11%). These substances had virtually identical mass spectra while **22a**



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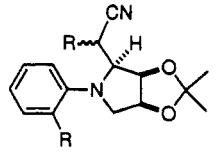
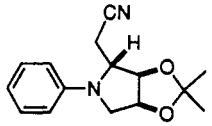


22 a, R = H
b, R = D



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displayed a first-order ^1H NMR spectrum whose contiguity of aliphatic protons was readily determined by 2D COSY experiments. The stereochemistries of these compounds were determined when prolonged irradiation (10 h) of dihydroindole **12a** in the presence of 4 equiv of n-Bu_3SnH led to **22a** in 87% yield. When the experiment was repeated with n-Bu_3SnD, deuterium was incorporated at two sites: one at an ortho position of the aromatic ring and the other adjacent to the nitrile group. This process is viewed as the addition of a hydrogen atom at C_{8a} of an excited state followed by ring fragmentation.

These studies have provided a new entry into the construction of functionalized, enantiomerically pure, dihydroindoles. We are currently studying the manipulation of their functionality and the extension of carbon-centered heterocyclic radicals to the synthesis of other functional groups.

Experimental Section

All reactions were performed in dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. *N*-Hydroxy-2-thiopyridone was precipitated from an aqueous solution of its sodium salt hydrate (Aldrich) with 6 M HCl, filtered, dissolved in Et_2O, and dried over $MgSO_4$ prior to use. All photolyses were conducted in Pyrex vessels and were degassed (freeze-pump-thaw) prior to irradiation. Visible light photolyses were degassed in the dark and were irradiated with a Sylvania 500-W tungsten lamp; UV irradiations employed a 450-W medium pressure Hanovia Hg lamp. ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ unless noted otherwise; chemical shifts (δ) are reported relative to the residual chloroform signal (δ 7.27). ^{13}C NMR spectra were recorded at 75.6 MHz and are reported in ppm unless stated otherwise. Melting points are uncorrected. Chromatography on silica gel was conducted as described by Still.[14]

Methyl 2,2-Dimethyl-5(*S*)-[[*N*-(3-cyanoindolyl)]methyl]-1,3-dioxolane-4(*R*)-carboxylate (8a). To a stirred, cooled (−23 °C) solution of methyl 2,3-*O*-isopropylidene-L-threonate (2.27 g, 11.92 mmol) and dry pyridine (1.06 mL, 13.11 mmol) in CH_2Cl_2 (53 mL) is added $(F_3CSO_2)_2O$ (2.18 mL, 13.11 mmol) dropwise over several minutes. The suspension is stirred vigorously for 5 min, followed by the addition over 5 min of a precooled (−23 °C) solution of 3-cyanoindole (3.39 g, 23.84 mmol) and t-BuOK (3.08 g, 27.42 mmol) in THF (220 mL) via a cannulating needle. The temperature is maintained for 30 min, brought to room temperature, and quenched with 5 mL of saturated NH_4Cl. The solids are filtered, washed with EtOAc, and the filtrate concentrated to ca. $^1/_3$ its volume in vacuo. The remaining solution is diluted with 500 mL of EtOAc, washed with H_2O, brine, dried (Na_2SO_4), and concentrated to afford a red-orange paste. The residue is preabsorbed on a minimal amount of silica gel. Chromatography (2.5 → 4% $CH_3CN/CHCl_3$) affords **8a** (3.22 g, 86%) and excess 3-cyanoindole (1.82 g). **8a**: ^1H NMR (benzene-d_6) 7.62 (1 H, d, J = 7.8 Hz), 7.15 (1 H, d, J = 8.2 Hz), 6.96–7.08 (2 H, m), 6.93 (1 H, s, NCH=), 3.95 (1 H, ddd, J = 3.0, 5.5, 7.9 Hz, $CH_2CH(OR)$), 3.74 (1 H, d, J = 7.9 Hz, $CH(OR)CO_2CH_3$), 3.67 (1 H, dd, J = 3.0, 15.1 Hz, NCH_AH_B), 3.54 (1 H, dd, J = 5.5, 15.1 Hz, NCH_AH_B), 3.15 (3 H, s, CO_2Me), 1.11 (3 H, s), 1.01 (3 H, s); ^{13}C NMR 170.0, 136.0, 135.7, 127.3, 123.9, 122.1, 119.6, 115.5, 111.8, 110.4, 86.3, 77.2, 75.2, 52.6, 47.6, 26.4, 25.5; IR ($CHCl_3$) 2224, 1731 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{18}N_2O_4$: 314.1267, found 314.1271.

2,2-Dimethyl-5(*S*)-[[*N*-(3-cyanoindolyl)]methyl]-1,3-dioxolane-4(*R*)-carboxylic Acid (8b). To a solution of ester **8a** (2.35 g, 7.46 mmol) in THF (230 mL) at 10 °C is added 71 mL of 0.21 M LiOH (14.9 mmol) over several minutes and the resulting mixture is stirred at 10 °C for 4 h. The solution is concentrated to $^1/_2$ its original volume in vacuo, diluted with H_2O, and washed with Et_2O. The aqueous layer is acidified to pH 5 with 1.0 M HCl, saturated with NaCl, and extracted with EtOAc. The combined extracts are washed with brine, dried (Na_2SO_4), and concentrated to afford **8b** (2.08 g, 93%) as a pale yellow solid: mp 132–133 °C (EtOAc/hexanes); ^1H NMR (benzene-d_6) 10.28 (1 H, bs, CO_2H), 7.59 (1 H, d, J = 7.6 Hz), 7.24 (1 H, d, J = 8.2 Hz), 6.93–7.09 (3 H, m), 3.98 (1 H, ddd, J = 2.5, 5.4, 8.2 Hz, $CH_2CH(OR)$), 3.78 (1 H, d, J = 8.2 Hz, $CH(OR)CO_2H$), 3.77 (1 H, dd, J = 2.5, 15.2 Hz, overlaps signal at 3.78, NCH_AH_B), 3.61 (1 H, dd, J = 5.4, 15.2 Hz, NCH_AH_B), 1.09 (3 H, s), 0.99 (3 H, s); ^{13}C NMR 173.6, 136.2, 135.8, 127.3, 124.1, 122.3, 119.7, 115.5, 112.3, 110.5, 86.2, 77.3, 74.7, 47.5, 26.5, 25.4; IR ($CHCl_3$) 2994, 2223, 1737 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}N_2O_4$: 300.1111, found 300.1109. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.06; H, 5.41; N, 9.28.

General Procedure: UV Irradiation of Thiohydroxamate Ester 8c. To a cooled (−15 °C) solution of isobutyl chloroformate (0.016 mL, 0.123 mmol) in THF (0.47 mL) is added dropwise a mixture of carboxylic acid **8b** (33.5 mg, 0.112 mmol) and 4-methylmorpholine (0.014 mL, 0.123 mmol) in THF (1.15 mL). After 5 min, *N*-hydroxy-2-thiopyridone (15.2 mg, 0.12 mmol) and dry pyridine (0.01 mL, 0.12 mmol) in THF (0.65 mL) is introduced via syringe and the resulting yellow solution is stirred in the dark for 20 min, brought to room temperature, degassed, and irradiated for 8 min. The crude reaction mixture is diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), and concentrated. Flash chromatography (30 → 50% EtOAc/hexanes) affords *cis*-thiopyridine **13b** (2.1 mg, 5%), a mixture (11.4 mg) of dipyridyl disulfide **10** (5.8 mg) and *trans*-thiopyridine **13a** (5.6 mg, 14%), and indole **11** (5.8 mg, 20%) and dimer **9** (13 mg) contaminated with small amounts of dihydroindole **12a**.

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Additional chromatography (5% $CH_3CN/CHCl_3$) affords pure **9** (11.7 mg, 40%). **13b**: ^1H NMR 8.51 (1 H, d, J = 5.3 Hz), 7.78 (1 H, s, NCH=), 7.77 (1 H, d, J = 7.8 Hz), 7.58 (1 H, m), 7.49 (1 H, d, J = 7.8 Hz), 7.26–7.39 (3 H, m), 7.11 (1 H, dd, J = 5.3, 7.2 Hz), 6.59 (1 H, d, J = 4.6 Hz, CH(OR)Spyr), 4.69–4.75 (2 H, m), 4.42 (1 H, dd, J = 8.9, 15.2 Hz, NCH_2), 1.62 (3 H, s), 1.35 (3 H, s); HRMS (EI) calcd for $C_{20}H_{19}N_3O_2S$: 365.1198, found: 365.1196. **13a**: ^1H NMR 8.45 (1 H, m), 7.78 (1 H, s, NCH=), 7.77 (1 H, m), 7.56 (1 H, td, J = 1.4, 7.6 Hz), 7.46 (1 H, m), 7.24–7.31 (3 H, m), 7.10 (1 H, m), 6.01 (1 H, d, J = 6.7 Hz, CH(OR)Spyr), 4.67 (1 H, dd, J = 2.6, 14.6 Hz, NCH_2), 4.54 (1 H, ddd, J = 2.6, 6.3, 6.7 Hz, $CH_2CH(OR)$), 4.42 (1 H, dd, 6.3, 14.6 Hz, NCH_2), 1.47 (3 H, s), 1.43 (3 H, s); ^{13}C NMR 156.4, 149.5, 136.5, 135.8, 135.6, 127.5, 123.7, 123.1, 122.0, 120.6, 119.7, 115.6, 112.2, 110.5, 86.3, 81.7, 80.3, 47.8, 27.0, 25.4; IR ($CDCl_3$) 2223 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{19}N_3O_2S$: 365.1198, found 365.1200. **11**: mp 163–164 °C (Et_2O/pentane); ^1H NMR 7.74 (1 H, m), 7.28–7.33 (3 H, m), 5.80 (1 H, d, J = 5.9 Hz, (OR)CHC(=C)N), 5.44 (1 H, m), 4.34 (2 H, m), 1.48 (3 H, s), 1.28 (3 H, s); ^{13}C NMR (62.9 MHz) 148.6, 132.5, 131.9, 124.1, 122.7, 120.7, 115.2, 114.1, 111.2, 82.2, 80.4, 76.0, 51.3, 27.2, 26.0; IR ($CHCl_3$) 2222 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$: 254.1056, found 254.1056. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.91; H, 5.56; N, 10.97. **9**: mp 190–191 °C (Et_2O/pentane); ^1H NMR 7.83 (2 H, d, J = 7.4 Hz), 7.25 (2 H, app t, J = 7.3 Hz), 6.91 (2 H, dd, J = 7.3, 8.0 Hz), 6.65 (2 H, d, J = 80 Hz), 4.65 (2 H, app t, J = 4.9 Hz, $CH_2CH(OR)$), 4.46 (2 H, dd, 4.2, 5.0 Hz, $CH(OR)CHN$), 3.73 (2 H, d, J = 13.8 Hz, NCH_2), 3.63 (2 H, d, J = 4.2 Hz, NCH), 3.11 (2 H, dd, J = 4.5, 13.8 Hz, NCH_2), 1.10 (6 H, s), 0.64 (6 H, s); ^{13}C NMR (62.9 MHz) 153.7, 130.9, 125.9, 125.2, 120.3, 118.0, 112.7, 109.1, 81.6, 81.3, 72.6, 54.8, 54.3, 25.1, 24.1; IR 2251 cm^{-1}; HRMS (CI) calcd for $C_{30}H_{30}N_4O_4$: (M + H) 511.2347, found 511.2348. Anal. Calcd for $C_{30}H_{30}N_4O_4$: C, 70.57; H, 5.92; N, 10.97. Found: C, 70.34; H, 5.96; N, 10.89.

Visible Light Photolyses of Thiohydroxamate Ester 8c. A. Irradiation at −78 °C. According to the general procedure, acid **8b** (36.1 mg, 0.12 mmol) is converted to the mixed thiohydroxamic acid anhydride **8c** and irradiated with visible light for 75 min at −78 °C. Workup provides a crude mixture which is chromatographed (30% EtOAc/hexanes) to afford dioxolene **14** (3.3 mg, 11%), *cis*-thiopyridine **13b** (3.8 mg, 9%), and a mixture (22.5 mg) of *trans*-thiopyridine **13a** and 2-mercaptopyridine. Further chromatography (2% $CH_3CN/CHCl_3$) provides pure **13a** (14.8 mg, 34%) and 2-mercaptopyridine (6.9 mg). Small quantities (ca. 5–7%) of cyclized materials are detected in the crude ^1H NMR spectrum but are not isolated in this experiment. **14**: ^1H NMR 7.77 (1 H, d, J = 8.6 Hz), 7.70 (1 H, s, NCH=), 7.47 (1 H, d, 8.7 Hz), 7.29–7.38 (2 H, m), 6.30 (1 H, s, =CHOR), 4.83 (2 H, s, NCH_2), 1.47 (6 H, s); ^{13}C NMR (14 of 15 carbons) 135.1, 134.3, 132.6, 127.7, 125.3, 123.7, 122.1, 119.8, 115.8, 115.7, 110.2, 41.1, 24.9 (2×); HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$: 254.1056, found 254.1067.

B. Irradiation at Room Temperature. When acid **8b** (95.2 mg, 0.317 mmol) is activated to form **8c** and irradiated for 1.5 h at room temperature, workup and chromatography (50% EtOAc/hexanes) affords dipyridyl sulfide **10** (12.4 mg, 36%, slightly impure) and dimer **9** (29.9 mg, 37%). On the basis of isolated **9**, integration of the crude ^1H NMR spectrum shows that the following compounds were formed: indole **11** (8.5%), **13a** (7.0%), **13b** (~2.5%), and **14** (~2%).

Decomposition of Thiohydroxamate Ester 8d. These transformations are carried out according to the general procedure. 3-Hydroxy-4-methylthiazole-2(3*H*)-thione[4a] is substituted for *N*-hydroxy-2-thiopyridone. Protection of **8d** from room light is not necessary.

A. UV Photolysis. Carboxylic acid **8b** (306 mg, 1.02 mmol) is converted to thiohydroxamate ester **8d**, irradiated for 45 min at room temperature, worked up, and chromatographed (30 → 50% EtOAc/hexanes) to afford dioxolene **14** (16.4 mg, 6%), *cis*-thiazole **13d** (21.8 mg, impure), *trans*-thiazole **13c** (68 mg, 17%), and a mixture (214 mg) of indole **11** and 4-methylthiazole-2(3*H*)-thione (**21**). Subsequent chromatography of impure **13d** and mixed fractions (2% and 3% $CH_3CN/CHCl_3$, respectively) provides pure **13d** (19.5 mg, 5%), **11** (125 mg, 48%), and 4-methylthiazole-2(3*H*)-thione (66 mg, 90% based on isolated **11** and **14**). **13d**: ^1H NMR 7.80 (1 H, s, -NCH=), 7.79 (1 H, d, J = 6.9 Hz), 7.52 (1 H, d, J = 7.8 Hz), 7.30–7.40 (2 H, m), 6.88 (1 H, s, thiazole vinyl), 6.23 (1 H, d, J = 4.6 Hz, CH(OR)S-thiazole), 4.87 (1 H, dd, J = 2.4, 14.8 Hz, NCH_2), 4.66 (1 H, ddd, J = 2.4, 4.6, 8.4 Hz, $CH_2CH(OR)$), 4.46 (1 H, dd, J = 8.4, 14.8 Hz, NCH_2), 2.49 (3 H, s), 1.62 (3 H, s), 1.33 (3 H, s); HRMS (EI) calcd for $C_{19}H_{19}N_3O_2S_2$: 385.0921, found 385.0945. **13c**: ^1H NMR 7.77 (1 H, d, J = 8.1 Hz), 7.76 (1 H, s, NCH=), 7.51 (1 H, d, J = 7.2 Hz), 7.27–7.36 (2 H, m), 6.91 (1 H, s, thiazole vinyl), 5.50 (1 H, d, J = 6.5 Hz, CH(OR)S-thiazole), 4.66 (1 H, dd, J = 2.5, 14.7 Hz, NCH_2), 4.55 (1 H, ddd, J = 2.5, 6.0, 6.5 Hz, $CH_2CH(OR)$), 4.42 (1 H, dd, J = 6.0, 14.7 Hz, NCH_2), 2.47 (3 H, s), 1.42 (3 H, s), 1.40 (3 H, s); ^{13}C-NMR 158.1, 153.7, 135.8, 135.7, 127.4, 123.8, 122.1, 119.8, 116.2, 115.6, 112.6, 110.4, 86.4, 84.7, 80.6, 47.5, 26.9, 25.4, 17.0; IR ($CHCl_3$) 2223 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{19}N_3O_2S_2$: 385.0921, found 385.0913.

B. Thermolysis. Acid **8b** (48.4 mg, 0.161 mmol) is converted to **8d** (vide supra), which is heated at 70 °C for 3 h. Workup and chromatography (30% EtOAc/hexanes) gives dioxolene **14** (4.1 mg, 10%), **13d** (4.3 mg, 7%), a mixture (22.5 mg) of thiazole **13c** and 4-methylthiazole-2(3*H*)-thione **21**, and indole **11** (8.5 mg, 21%). Mixed fractions are rechromatographed (5% $CH_3CN/CHCl_3$) to afford pure **13c** (14.6 mg, 24%) and **21** (6.0 mg).

C. UV Photolysis in the Presence of n-Bu_3SnH. Acid **8b** (217.2 mg, 0.723 mmol) is converted to **8d** and irradiation is begun as n-Bu_3SnH (0.390 mL, 1.45 mmol) in THF (8.5 mL) is added slowly over 25 min via syringe pump. After the addition, 4 equiv of n-Bu_3SnH (0.78 mL) is added and the photolysis is continued for 6 h at room temperature. Workup proceeds as described except that the organic layer is also washed with cold 1.0 M NaOH. The basic extracts are acidified with 2.0 M HCl and extracted with EtOAc, and the combined organics are washed with brine, dried (Na_2SO_4), and concentrated to afford 41 mg of a mixture containing 27.5 mg (from ^1H NMR integration) acid **8b** and 13.5 mg of 4-methylthiazole-2(3*H*)-thione (**21**). The original neutral layer is chromatographed (30 → 50% EtOAc/hexanes) to provide dihydroindole **12a** (67 mg, 41%) and a mixture (77 mg) of diastereomer **12b**, indole **11**, and uncyclized dioxolane **13e**. Additional chromatography (3% $CH_3CN/CHCl_3$) gives **12b** (32 mg, 20%) and a mixture (33.4 mg) containing **11** (28 mg, 17%) and **13e** (5.4 mg, 3%). **12a**: ^1H NMR 7.22 (1 H, d, J = 7.5 Hz), 7.14 (1 H, app t, J = 7.7 Hz), 6.81 (1 H, app t, J = 7.4 Hz), 6.68 (1 H, d, J = 7.9 Hz), 4.77–4.82 (2 H, m), 4.49 (1 H, d, J = 8.5 Hz, ArCHCN), 3.93 (1 H, dd, J = 3.7, 8.5 Hz, NCH), 3.87 (1 H, d, J = 14.0 Hz, NCH_2), 3.15 (1 H, dd, J = 3.4, 14.0 Hz, NCH_2), 1.17 (3 H, s), 0.57 (3 H, s); ^{13}C NMR 151.9, 128.1, 125.0, 122.7, 119.6, 117.6, 112.3, 109.5, 81.4, 80.8, 70.4, 54.9, 32.1, 24.4, 23.6; IR ($CDCl_3$) 2251 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}N_2O_2$: 256.1212, found 256.1206. **12b**: mp 164 °C (Et_2O/pentane); ^1H NMR 7.17 (2 H, m), 6.79 (1 H, t, J = 7.4 Hz), 6.67 (1 H, d, J = 7.9 Hz), 4.79 (1 H, dd, J = 3.8, 5.5 Hz, $CH_2CH(OR)$), 4.67 (1 H, app, t, J = 5.3 Hz, $CH(OR)CHN$), 4.60 (1 H, app s, ArCHCN), 4.05 (1 H, dd, 1.8, 5.0 Hz, NCH), 3.85 (1 H, d, J = 14.1 Hz, NCH_2), 3.18 (1 H, dd, J = 3.8, 14.1 Hz, NCH_2), 1.18 (3 H, s), 0.61 (3 H, s); ^{13}C NMR 152.8, 129.4, 124.2, 123.8, 120.2, 119.7, 112.0, 109.9, 81.3, 80.1, 71.7, 54.1, 31.2, 24.7, 23.8; IR ($CDCl_3$) 2245 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}N_2O_2$: 256.1212, found: 256.1213. **13e**: ^1H NMR 7.78 (1 H, d, J = 7.4 Hz), 7.72 (1 H, s, NCH=), 7.28–7.43 (3 H, m), 4.46 (1 H, m, $CH_2CH(OR)$), 4.32 (1 H, dd, J = 4.1, 14.6 Hz, NCH_2), 4.22 (1 H, dd, J = 6.5, 14.6 Hz, NCH_2), 4.11 (1 H, dd, J = 6.2, 8.7 Hz, CH_2OR), 3.69 (1 H, dd, 5.9, 8.7 Hz, CH_2OR), 1.41 (3 H, s), 1.34 (3 H, s); ^{13}C-NMR (125 MHz) 136.0, 135.8, 128.0, 124.2, 122.5, 120.3, 115.9, 110.6, 110.5, 86.7, 74.4, 66.8, 49.5, 27.0, 25.5; IR ($CHCl_3$) 2222 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}N_2O_2$: 256.1212, found 256.1206.

Disproportionation of Dimer 9. A solution of dimer **9** (36.5 mg, 0.072 mmol) in THF (7.2 mL) is irradiated (UV) for 3 h at room temperature. The solvent is removed under vacuum and the crude material chromatographed (30 → 50% EtOAc/hexanes) to afford indole **11** (16.4 mg, 45%) and dihydroindole **12a** (16.3 mg, 44%).

Reductive Cleavage of Dimer 9. A solution of dimer **9** (36.2 mg, 0.071 mmol) and n-Bu_3SnH (0.076 mL, 0.284 mmol) in THF (7.1 mL) is irradiated (UV) for 3 h at room temperature. The solvent is removed in vacuo and the crude material is chromatographed (50% EtOAc/hexanes) to afford dihydroindoles **12a** (29.5 mg, 81%) and **12b** (3.9 mg, 11%).

Photolysis of *trans*-Thiazole 13c. A THF solution (6.5 mL) of **13c** (24.9 mg, 0.065 mmol) and n-Bu_3SnH (0.052 mL, 0.195 mmol) is irradiated (UV) for 7 h at room temperature. The black precipitate is filtered, the solution concentrated, and the crude product chromatographed (EtOAc/hexanes) to give dihydroindole **12a** (10.2 mg, 61%) and a mixture (8.7 mg) containing (amounts assigned by comparison with internal DMSO standard) indole **11** (14%), dihydroindole **12b** (11%), and dioxolane **13e** (3%).

Pyrrolidine 22a. A solution of **12a** (30.0 mg, 0.117 mmol) and n-Bu_3SnH (0.126 mL, 0.47 mmol) in THF (3.0 mL) is irradiated (UV) for 10 h at room temperature. Solvent evaporation and chromatography (30% EtOAc/hexanes) gives pyrrolidine **22a** (26.1 mg, 87%) as a white solid: mp 118 °C (Et_2O/pentane); ^1H NMR 7.29 (2 H, app t, J = 8.1 Hz), 6.88 (1 H, t, J = 7.3 Hz), 6.73 (2 H, d, J = 8.1 Hz), 4.89–4.99 (2 H, m), 4.09 (1 H, ddd, J = 3.5, 6.7, 9.3 Hz, NCH), 3.61 (1 H, dd, J = 2.2, 10.9 Hz, NCH_2), 3.47 (1 H, dd, J = 6.0, 10.9 Hz, NCH_2), 2.73 (1 H, dd, J = 3.5, 16.5 Hz, CH_2CN), 2.63 (1 H, dd, J = 9.3, 16.5 Hz, CH_2CN), 1.62 (3 H, s), 1.43 (3 H, s); ^{13}C NMR 145.6, 129.4, 119.4, 117.9, 115.0, 113.1, 79.2, 77.9, 57.9, 54.7, 25.8, 24.7, 16.2; IR ($CDCl_3$) 2254 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}N_2O_2$: 258.1368, found 256.1358.

Photolytic Reduction of Indole 11. A solution of **11** (59.0 mg, 0.232 mmol) and n-Bu_3SnH (0.25 mL, 0.93 mmol) in THF (23.2 mL) is irradiated for 2.25 h at room temperature. Solvent removal and chromatography (30 → 50% EtOAc/hexanes) affords dihydroindole **12a** (34.1 mg, 57%), dihydroindole **19** (5.3 mg), pyrrolidine **23** (6.8 mg, 11%), and a mixture (8.1 mg) containing **19** (4.7 mg, total yield 17%) and 4-methylthiazole-2(3*H*)-thione (**21**) (3.4 mg). **19**: ^1H NMR 7.31 (1 H, d, J = 7.6 Hz), 7.23 (1 H, app t, J = 7.6 Hz), 6.90 (1 H, app t, J = 7.4 Hz), 6.65 (1 H, d, J = 8.0 Hz), 4.75 (2 H, m), 4.43 (1 H, d, J = 9.2 Hz, ArCHCN), 4.08 (1 H, dd, J = 4.8, 9.2 Hz NCH), 3.81 (1 H, dd, J = 6.1, 13.0 Hz, NCH_2), 3.50 (1 H, dd, J = 3.1, 13.0 Hz, NCH_2), 1.60 (3 H, s), 1.36 (3 H, s); HRMS (EI) calcd for $C_{15}H_{16}N_2O_2$: 256.1212, found 256.1220. **23**: ^1H NMR 7.26 (2 H, m), 6.81 (1 H, app t, 7.3 Hz), 6.62 (2 H, d, J = 7.9 Hz), 5.07 (1 H, m, $CH_2CH(OR)$), 4.86 (1 H, d, J = 6.2 Hz, $CH(OR)CHN$), 4.37 (1 H, dd, J = 3.9, 6.7 Hz, NCH), 3.62 (2 H, d, J = 3.3 Hz, NCH_2), 2.61 (1 H, dd, J = 3.9, 16.9 Hz, CH_2CN), 2.53 (1 H, dd, J = 6.7, 16.9 Hz, CH_2CN), 1.45 (3 H, s), 1.39 (3 H, s); HRMS (EI) calcd for $C_{15}H_{18}N_2O_2$: 256.1368, found 256.1361.

Thiopyridine 18a. A THF solution (2.1 mL) of **12a** (22.8 mg, 0.089 mmol) is cooled to −78 °C and n-BuLi (0.063 mL, 0.089 mmol, 1.41 M in hexanes) added dropwise. After waiting 5 min, **10** (19.6 mg, 0.089 mmol) in THF (0.7 mL) is added dropwise and the mixture warmed to room temperature. After 2 h, the reaction is quenched with several drops of saturated NH_4Cl, diluted with EtOAc (30 mL), washed with H_2O and brine, dried (Na_2SO_4), and concentrated to produce a crude mixture (41 mg) of **18a** and 2-mercaptopyridine. **18a**: ^1H NMR (partial) 4.97 (1 H, dd, J = 4.4, 5.4 Hz, $CH_2CH(OR)$), 4.84 (1 H, dd, J = 4.1, 5.4 Hz, $CH(OR)$-CHN), 4.58 (1 H, d, J = 4.4 Hz, NCH), 3.85 (1 H, d, J = 14.0 Hz, NCH_2), 3.19 (1 H, dd, J = 4.1, 14.0 Hz, NCH_2), 1.19 (3 H, s), 0.64 (3 H, s); HRMS (CI) calcd for $C_{20}H_{19}N_3O_2S$: (M + H) 366.1276, found 366.1293.

Thiazole 18b. In the manner described above, **12a** (22.7 mg, 0.089 mmol) and 2,2′-dithiobis(4-methylthiazole) (23.2 mg, 0.089 mmol) give a crude mixture (44 mg) of **18b** and 4-methylthiazole-2(3*H*)-thione (**21**): ^1H NMR 7.20–7.26 (2 H, m), 7.09 (1 H, s), 6.82 (1 H, app *t*, J = 7.5 Hz), 6.75 (1 H, d, J = 8.2 Hz), 4.84 (1 H, dd, J = 4.0, 5.3 Hz, $CH_2CH(OR)$), 4.74 (1 H, dd, J = 4.4, 5.3 Hz, $CH(OR)CHN$), 4.51 (1 H, d, J = 4.4 Hz, NCH), 3.87 (1 H, d, J = 14.0 Hz, NCH_2), 3.27 (1 H, dd, J = 4.0, 14.0 Hz, NCH_2), 2.52 (3 H, s), 1.13 (3 H, s), 0.58 (3 H, s), HRMS (CI) calcd for $C_{19}H_{19}N_3O_2S_2$: (M + H) 386.0999, found 386.1012.

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