(d, J = 6 Hz), 30.97 (d, J = 143 Hz), 24.14. ^{31}P-NMR δ: 40.44. FAB HRMS: calcd for $C_{14}H_{22}O_5P$ (MH^+) 301.1203, found 301.1205.

Methyl 2-[[[1-[*N*-(Benzyloxycarbonyl)amino]methyl]-hydroxyphosphoryl]oxy]acetate (3h). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 8.68 (s, 1 H), 7.35 (m, 5 H), 5.95 (s, 1 H), 5.11 (s, 2 H), 4.61 (d, J = 10 Hz, 2 H), 3.75 (s, 3 H), 3.68 (m, 2 H). ^{13}C-NMR ($CDCl_3$) δ: 169.34 (d, J = 3 Hz), 156.32, 136.31, 128.22, 127.78, 127.70, 66.69, 61.79 (d, J = 4 Hz), 52.09, 37.38 (d, J = 156 Hz). ^{31}P-NMR δ: 22.64. FAB HRMS: calcd for $C_{12}H_{17}NO_7P$ (MH^+) 318.0741, found 318.0743.

Methyl D-2-[[[1-[*N*-(Benzyloxycarbonyl)amino]methyl]-hydroxyphosphoryl]oxy]-3-phenylpropionate (3i). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.64 (s, 1 H), 7.29 (m, 10 H), 5.57 (s, 1 H), 5.10 (m, 3 H), 3.71 (s, 3 H), 3.50 (m, 2 H), 3.16 (m, 2 H). ^{13}C-NMR (CD_3OD) δ: 172.10, 158.51 (d, J = 5 Hz), 138.12, 136.95, 130.78, 130.72, 129.49, 129.07, 128.95, 128.13, 76.20 (d, J = Hz), 67.92, 52.87, 40.29 (d, J = 5 Hz), 38.32 (d, J = 159 Hz). ^{31}P-NMR δ: 21.24. FAB HRMS: calcd for $C_{19}H_{23}NO_7P$ (MH^+) 408.1210, found 408.1212.

Methyl D-2-[[[1-[*N*-(Benzyloxycarbonyl)amino]methyl]-hydroxyphosphoryl]oxy]-3-methylbutyrate (3j). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 8.66 (s, 1 H), 7.33 (m, 5 H), 5.97 (s, 1 H), 5.11 (s, 2 H), 4.73 (m, 1 H), 3.74 (s, 3 H), 3.66 (m, 2 H), 2.12 (m, 1 H), 1.03 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H). ^{13}C-NMR (CD_3OD) δ: 172.43, 158.51, 138.13, 129.45, 129.04, 128.92, 79.90 (d, J = 7 Hz), 67.88, 52.79, 38.45 (d, J = 59 Hz), 32.76 (d, J = 6 Hz), 18.83, 16.96. ^{31}P-NMR δ: 22.01. FAB HRMS: calcd for $C_{15}H_{23}NO_7P$ (MH^+) 360.1210, found 360.1212.

Methyl 2-[[[(*R*,*S*)-1-[*N*-(Benzyloxycarbonyl)amino]-2-methylpropyl]hydroxyphosphoryl]oxy]acetate (3k). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.36 (m, 5 H), 5.82 (d, 1 H), 5.12 (s, 2 H), 4.58 (m, 2 H), 4.03 (m, 1 H), 3.74 (s, 3 H), 2.28 (m, 1 H), 1.03 (t, J = 6.5 Hz). ^{13}C-NMR (CD_3OD) δ: 170.67 (d, J = 6 Hz), 158.96 (d, J = 5 Hz), 138.26, 129.46, 129.01, 128.82, 67.86, 63.01 (d, J = 6 Hz), 55.04 (d, J = 154 Hz), 52.76, 30.26 (d, J = 4 Hz), 21.00 (d, J = 10 Hz), 18.71 (d, J = 6 Hz). ^{31}P-NMR δ: 23.95. FAB HRMS: calcd for $C_{15}H_{23}NO_7P$ (MH^+) 360.1210, found 360.1212.

Methyl D-2-[[[(*R*,*S*)-1-[*N*-(Benzyloxycarbonyl)amino]-2-methylpropyl]hydroxyphosphoryl]oxy]-3-phenylpropionate (3l). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.96 (s, 1 H), 7.33 (m, 5 H), 7.20 (m, 5 H), 5.76 (m, 0.5 H), 5.43 (m, 0.5 H), 5.10 (m, 3 H), 4.03 (m, 1 H), 3.65 (s, 3 H), 3.12 (m, 2 H), 2.14 (m, 1 H), 0.94 (m, 6 H). ^{13}C-NMR ($CDCl_3$) δ: 170.27 (d, J = 16 Hz), 156.32 (d, J = 6 Hz), 136.24 (d, J = 7 Hz), 135.12 (d, J = 5 Hz), 129.27 (d, J = 4 Hz), 128.02, 127.93, 127.86, 127.60, 127.53, 127.48, 127.37, 126.50, 73.97 (d, J = 6 Hz), 73.82 (d, J = 7 Hz), 66.45, 66.33, 53.34 (d, J = 152 Hz), 53.19 (d, J = 152 Hz), 51.76, 51.71, 39.03 (d, J = 8 Hz), 38.94 (d, J = 5 Hz), 28.61 (d, J = 4 Hz), 20.18 (d, J = 12 Hz), 17.43 (d, J = 5 Hz). ^{31}P-NMR δ: 23.64, 23.45. FAB HRMS: calcd for $C_{22}H_{29}NO_7P$ (MH^+) 450.1680, found 450.1682.

Methyl D-2-[[[(*R*,*S*)-1-[*N*-(Benzyloxycarbonyl)amino]-2-methylpropyl]hydroxyphosphoryl]oxy]-3-methylbutyrate (3m). ^{1}H-NMR ($CDCl_3$/DMF-d_7) δ: 7.34 (m, 5 H), 6.91 (s, 1 H), 5.91 (m, 0.5 H), 5.58 (m, 0.5 H), 5.11 (s, 2 H), 4.68 (m, 1 H), 4.04 (m, 1 H), 3.70 (s, 3 H), 2.28 (m, 1 H), 2.18 (m, 1 H), 0.96 (m, 12 H). ^{13}C-NMR (CD_3OD) δ: 172.19 (d, J = 6 Hz), 158.90 (d, J = 5 Hz), 138.25, 129.48, 129.02, 128.90, 79.83 (d, J = 7 Hz), 79.76 (d, J = 4 Hz), 67.88, 55.23 (d, J = 156 Hz), 55.07 (d, J = 156 Hz), 52.78, 52.66, 33.03 (d, J = 5 Hz), 32.86 (d, J = 6 Hz), 30.55 (d, J = 4 Hz), 30.48 (d, J = 7 Hz), 21.16 (d, J = 3 Hz), 21.00 (d, J = 3 Hz), 18.92, 18.79, 18.61, 18.53, 18.46, 17.24 (d, J = 11 Hz). ^{31}P-NMR δ: 24.23, 23.94. FAB HRMS: calcd for $C_{18}H_{29}NO_7P$ (MH^+) 402.1680, found 402.1682.

General Procedure for the Preparation of Benzylphosphonate Diesters. To a solution of benzylphosphonic acid (0.5 mmol), alcohol (1.25 mmol), and triphenylphosphine (1.25 mmol) dissolved in anhydrous THF (5 mL) was added diisopropyl azodicarboxylate (1.25 mmol). After 30 min the reaction mixture was concentrated under vacuum and then the triphenylphosphineoxide crystallized with acetone/pentane and removed by filtration. The filtrate was concentrated under vacuum and purified by chromatography (HOAc/EtOAc). The compounds obtained by this method are listed below.

Dimethyl Benzylphosphonate (5a). Spectral characterization in agreement with ref 30. ^{1}H-NMR ($CDCl_3$) δ: 7.30 (m, 5 H), 3.67 (d, J = 11 Hz, 6 H), 3.18 (d, J = 22 Hz). ^{13}C-NMR ($CDCl_3$) δ: 131.05 (d, J = 9 Hz), 129.61 (d, J = 6 Hz), 128.53, 126.91 (d, J = 3 Hz), 52.85 (d, J = 7 Hz), 32.73 (d, J = 138 Hz). ^{31}P-NMR δ: 28.92. FAB HRMS: calcd for $C_9H_{14}O_3P$ (MH^+) 201.0680, found 201.0681.

Diisopropyl Benzylphosphonate (5b). ^{1}H-NMR ($CDCl_3$) δ: 7.30 (m, 5 H), 4.61 (m, J = 7 Hz, 2 H), 3.12 (d, J = 22 Hz, 2 H), 1.28 (d, J = 6 Hz, 6 H), 1.16 (d, J = 6 Hz, 6 H). ^{13}C-NMR ($CDCl_3$) δ: 131.74 (d, J = 9 Hz), 129.75 (d, J = 6 Hz), 128.22 (d, J = 3 Hz), 126.58 (d, J = 4 Hz), 70.54 (d, J = 7 Hz), 34.60 (d, J = 140 Hz), 23.92 (d, J = 4 Hz), 23.63 (d, J = 5 Hz). ^{31}P-NMR δ: 27.46. FAB HRMS: calcd for $C_{13}H_{22}O_3P$ (MH^+) 257.1305, found 257.1307.

Dibenzyl Benzylphosphonate (5c). Spectral characterization in agreement with ref 31. ^{1}H-NMR ($CDCl_3$) δ: 7.26 (m, 15 H), 4.91 (d, J = 8 Hz, 4 H), 3.17 (d, J = 22 Hz, 2 H). ^{13}C-NMR ($CDCl_3$) δ: 136.23 (d, J = 6 Hz), 131.78 (d, J = 9 Hz), 129.77 (d, J = 7 Hz), 128.49, 128.42, 128.23, 127.81, 126.86 (d, J = 4 Hz), 67.52 (d, J = 7 Hz), 33.97 (d, J = 138 Hz). ^{31}P-NMR δ: 24.70. FAB HRMS: calcd for $C_{21}H_{22}O_3P$ (MH^+) 353.1305, found 353.1307.

Supplementary Material Available: ^{13}C-NMR spectra of compounds **3b–3m** as their 1-adamantanamine salts and **5b** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(30) Lee, S.; Bentrude, W. G. *Phosphorus Sulfur* **1988**, *35*, 219.
(31) Thorsett, E. D.; Harris, E. E.; Peterson, E. R.; Greenlee, W. J.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 2176.

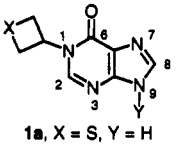
Synthesis of *N*-Thietan-3-yl-α-oxo Nitrogen Heterocycles from Imino Thioethers. A Novel Transformation

Jeffery B. Press,* James J. McNally, Zoltan G. Hajos, and Rebecca A. Sawyers

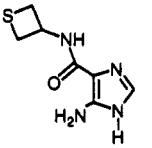
The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477

Received August 2, 1991 (Revised Manuscript Received August 5, 1992)

We recently reported the novel formation of thietane derivative **1a** during the course of synthetic studies on 6-mercaptopurine.[1] The structure of **1a** was deduced from analysis of NMR, IR, and HRMS data as well as chemical transformations to **1b**, **1c** and most notably the formation of imidazole derivative **2**. The structure of **2** was fully determined by X-ray crystallographic analysis.[1]



1a, X = S, Y = H
1b, X = SO_2, Y = H
1c, X = S, Y = $COCH_3$



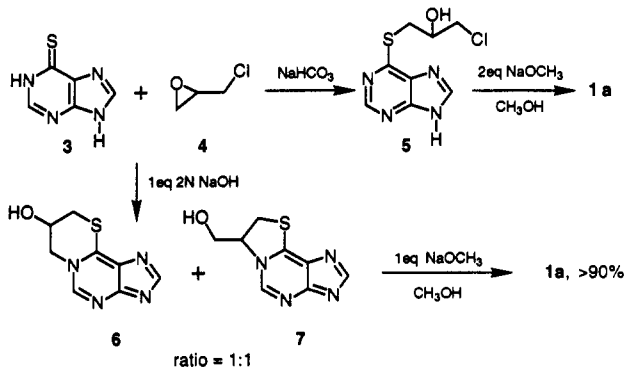
2

Compound **1a** is prepared by alkylation of 6-mercaptopurine (**3**) with epichlorohydrin (**4**) to form **5** which subsequently rearranges in base to give **1a** (Scheme I). We reported that **1a** was isolated in modest (≈35%) yield as the sole product from **5** and proposed a mechanism wherein an intermediate bicyclic thiazoline forms by intramolecular alkylation at N-1.[1] Since this rearrangement seemed quite remarkable, we undertook a study to in-

(1) Press, J. B.; Hajos, Z. G.; Sawyers, R. A. *Tetrahedron Lett.* **1990**, *31*, 1373.

0022-3263/92/1957-6335$03.00/0

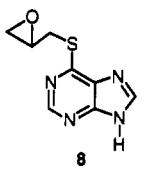
Scheme I



vestigate the generality of this thietane-forming process using other heterocyclic 2-imino thioethers as well as to gain further insight into the mechanism.

Careful control of the reagent amounts used in the reaction of 6-mercaptopurine gives some support to our hypothesis of the processes leading to formation of **1a** (Scheme I). When only 1 equiv of sodium hydroxide is used, 6-mercaptopurine is converted in good yield to a mixture of very insoluble **6** and **7** in essentially equal amounts. Tricyclic **7** was characterized by ^{1}H and ^{13}C NMR and UV while **6** was determined by DEPT NMR analysis of the mixture. Compound **7** converts to **1a** upon exposure to 1 equiv of sodium methoxide. From these results, it is probable that the relatively low mass balance and yield initially reported for the conversion of **5** to **1a** might arise from competitive formation of hypoxanthine[1] as well as from formation of **6**. As a consequence of their high polarity and poor solubility, both the 6-ring product **6** as well as hypoxanthine may easily be lost during column chromatography.

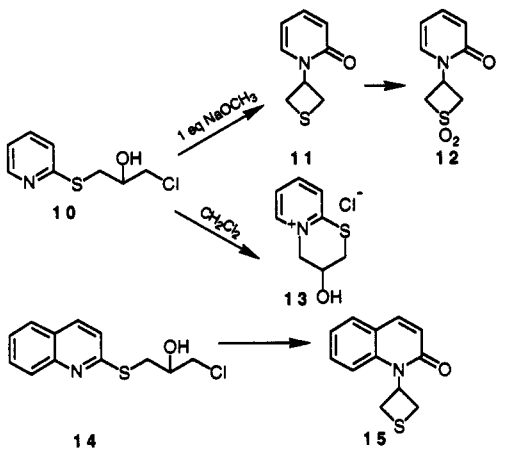
The intermediacy of epoxide **8** would seem likely in this transformation. Unfortunately, numerous reactions to isolate **8** failed to give isolable material. Not surprisingly,



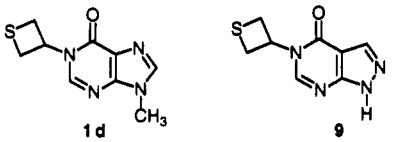
treatment of **5** with varying amounts of a variety of bases leads only to mixtures of **5**, **1a**, and **6** without detectable formation of **8**. Reaction of 6-mercaptopurine with alkylating agents that either can form the epoxide more easily (epibromohydrin) or contain the preformed epoxide moiety (glycidyl tosylate or glycidyl 3-nitrobenzenesulfonate) gives intractable mixtures of products. Alkylation of 6-mercaptopurine with allyl bromide gives 6-allylthiopurine[2] but attempts to epoxidize the allyl group to form **8** lead either to oxidation of the nitrogens of the purine nucleus, sulfur or no reaction at all.[3]

With these reaction requirements and outcome from 6-mercaptopurine, we were interested in the scope of this reaction to form 3-N-substituted thietane derivatives.

Scheme II

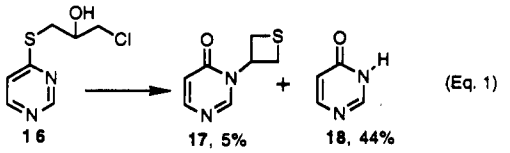


Reaction of 9-methyl-6-mercaptopurine[4] does give **1d** but in only 2.5% isolated yield. It appears that anionic assistance from N-9 of the purine ring of **5** is required for sufficient N-1 nitrogen nucleophilicity to facilitate reaction and gives insight into the need for 2 equiv of base in reaction of **3**. Reaction of the isomeric 4-mercaptopyrazolo[3,4-*d*]pyrimidine occurs analogously to **3** to give **9** in similar yield (≈35%).



The most general form that this reaction could take would be the transformation of 2-mercaptopyridine as shown in Scheme II. In fact, the reaction occurs as for the formation of **1a** to give **11** in 58% yield. Thietane **11** has the expected spectral similarities to 1-methyl-2-pyridone. It was further characterized by conversion to sulfone **12** using potassium permanganate. The moderate yield of **11** is a consequence of competitive formation of the intramolecular cyclized product **13**, analogous to the formation of **6** in the case of purine. Formation of a dihydrothiazino[3,2-*a*]pyridinium system has already been reported from 3-hydroxy-2-mercaptopyridine.[5] However, a major difference in this current example is that, if the chloride **10** were allowed to stand for even 1 day prior to the rearrangement reaction, **13** forms essentially quantitatively. Compound **13** is unchanged by treatment with base. It would seem that the increased nucleophilic character of pyridine vis-à-vis purine, enhances not only the formation of the the thietane in base but also the 6-ring formation under essentially neutral conditions. The less nucleophilic nitrogen of **14** (derived from 2-mercaptoquinoline) forms the thietane **15** in reduced yield (41%).

As the nucleophilic character of the ring nitrogen involved in the initial displacement reaction decreases further, thietane formation suffers significantly. For example, in the case of 4-mercaptopyrimidine, chlorohydrin **16** forms in the expected manner, but treatment with base gives **17** in low yields (eq 1). The majority of the reaction results



(Eq. 1)

(2) Johnston, T. P.; Holum, L. B.; Montgomery, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 6265.

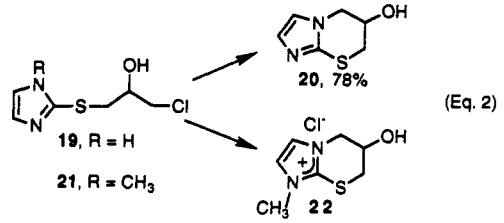
(3) Oxidation of 6-allylthiopurine. Dioxirane: Adam, W.; Chan, Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. Iodine, water, silver oxide: Parrilli, M.; Barone, G.; Adinolfi, M.; Mangoni, L. *Tetrahedron Lett.* **1976**, 207. Benzonitrile, hydrogen peroxide: Payne, G. B. *Tetrahedron* **1962**, *18*, 763. Sodium hydroxide, hydrogen peroxide: Henbest, H. B.; Jackson, W. R. *J. Chem. Soc.* **1967**, 2459. *m*-Chloroperbenzoic acid: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1968; Vol. 1, p 135.

(4) Elion, G. B. *J. Org. Chem.* **1962**, *27*, 2478.

(5) Undheim, K.; Reistad, K. R. *Acta Chem. Scand.* **1970**, *24*, 2949.

from apparent hydrolysis of the imino thioether to form **18**. The low reactivity of 4-mercaptopyrimidines unactivated by hydroxyl substitution has already been noted for other ring closures.[6] When 2-mercaptopyrimidine is used, very little isolable product of any kind may be isolated. Hydrolysis of the imino thioether is also the only isolable product from the reaction of 2-mercaptobenzoxazoline under the reaction conditions.

When imidazoles are used instead of pyrimidines, only 6-ring-fused product formation is observed. Thus, 2-mercaptoimidazole gives chlorohydrin **19** which, in turn, ring closes to give only **20** in high yield (eq 2). No thie-



(Eq. 2)

tane-containing products are evident despite extensive high-field ^{1}H NMR analysis. Even when a charged product forms (**22**), no thietane is produced. Presumably, the strain of the proposed intermediate bicyclo[3.3] system overwhelms the increased nucleophilic character of the imidazole nitrogen.

In summary, the novel formation of *N*-thietan-3-yl-substituted lactams has some generality and may be added to the other methods of preparing 3-aminothietanes.[7,8] Competitive reaction manifolds, including the formation of 6-ring-fused products as well as hydrolysis of the imino thioether intermediates to give unsubstituted lactams, serve to decrease the generality of the reaction. The nucleophilicity of the ring-nitrogen involved in the course of the rearrangement as well as potential ring-strain of presumed intermediates also seem to play a role in the reaction outcome. While we have attempted to rearrange an acyclic example of this reaction, no isolable products were obtained although further examination of acyclic reaction is probably warranted. Overall, this is a unique addition to the few methods available to prepare relatively unusual substituted thietane derivatives.[9-11]

Experimental Section

Purifications using flash chromatography on 230–400 mesh E. Merck silica gel were run under positive nitrogen pressure. All compounds were homogeneous by thin-layer chromatographic analysis. In general, the noncrystalline nature of compounds in this report precluded isolation of completely anhydrous material in spite of prolonged drying.

6-[(1-Chloro-2-hydroxy-3-propanyl)thio]purine (5). To 6-mercaptopurine (25 g, 0.15 mol) dispersed in ethanol (350 mL) with anhydrous $NaHCO_3$ (13.5 g, 0.16 mol) was added epichlorohydrin (16.0 mL, 0.20 mol) in ethanol (200 mL) dropwise over 45 min at room temperature. After 1 week, the inorganics were removed by filtration and the solvent was evaporated in vacuo. The solid residue was triturated in water and dried to give the crude **5** (11.63 g, 32%). A portion was purified by flash chromatography to give **5**, mp 143–145 °C. MS (CI): 245 (MH^+); ^{1}H NMR (DMSO-d_6): δ 8.7 (s, 1 H), 8.45 (s, 1 H), 4.0 (m, 1 H), 3.7 (m, 2 H), 3.4 (m, 2 H), 3.2 (br s, 2 H, exchanges with D_2O). IR (KBr): 1568, 1437, 1338, 1326, 1237, 10.87 cm^{-1}. UV (MeOH): λ_{max} 214 nm (ϵ 9326), 286 nm (ϵ 13 618); compared to 6-methylthiopurine λ_{max} 290 (ϵ 17 600).[4] Anal. Calcd for $C_8H_9ClN_4OS$: C, 39.26; H, 3.71; N, 22.89. Found: C, 38.99; H, 3.73; N, 22.65.

6-Oxo-1-(thietan-3-yl)purine (1a). A methanol suspension (20 mL) of **5** (2.25 g, 9.2 mmol) was treated with 0.5 M sodium methoxide in methanol (37 mL, 18.4 mmol) over a 20-min period at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 24 h. The suspension was cooled to 0 °C and neutralized with 2 N aqueous hydrochloric acid (9.2 mL, 18.4 mmol). The mixture was allowed to warm to rt and was filtered through Celite. The filtrate was evaporated in vacuo to give 1.87 g of a solid which was purified by flash chromatography using 10% methanol/methylene chloride to give **1a** (0.61 g, 32%), mp 258–260 °C dec. HRMS: 208.0505 (208.0496 calcd). ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1 H), 8.1 (s, 1 H), 5.9 (m, 1 H), 4.05 (t, J = 8.8 Hz, 2 H), 3.38 (t, J = 8.8 Hz, 2 H), 3.2 (br s, 1 H, exchanges with D_2O). ^{13}C NMR (DMSO-d_6): δ 154.78, 153.00, 144.61, 142.04, 119.00, 51.70, 33.53 (two superimposed methylene carbons, reversed in DEPT experiment). IR (KBr) 3122, 3107, 3047, 1698, 1630, 1365, 1216 cm^{-1}. UV (MeOH) λ_{max} 205 nm (ϵ 26 324), 251 nm (ϵ 8875); compare to hypoxanthine λ_{max} 251 (ϵ 9400).[4] Anal. Calcd for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.91; Found: C, 45.74; H, 4.04; N, 26.99.

6-Oxo-1-(1,1-dioxythietan-3-yl)purine (1b). To **1a** (425 mg, 2 mmol) in water (10 mL) was added 1 N aqueous sodium hydroxide (2.0 mL, 2 mmol) at room temperature, and the resulting solution was treated with potassium permanganate (348 mg, 2.2 mmol) in water (50 mL) added dropwise over approximately 20 min. The resulting suspension was filtered through Celite to give a light-yellow filtrate which was carefully acidified with 2 N aqueous hydrochloric acid to pH 5.0. The resulting precipitate was collected by filtration to give **1b**, 310 mg (65%), mp 268–269 °C dec. HRMS 240.0282 (240.0315 calcd). ^{1}H NMR (DMSO-d_6): δ 8.4 (s, 1 H), 8.2 (2, 1 H), 5.42 (m, 1 H), 4.95 (dd, 2 H), 4.65 (dd, 2 H), 3.2 (br s, 1 H, exchanges with D_2O). IR (KBr) 1693, 1515, 1533, 1394, 1344, 1314, 1369, 1226, 1136 cm^{-1}. UV (EtOH): λ_{max} 253 nm (ϵ 3040). Anal. Calcd for $C_8H_8N_4O_3S$: C, 39.98; H, 3.36; N, 23.32. Found: C, 39.80; H, 3.49; N, 23.27.

9-Acetyl-6-oxo-1-(thietan-3-yl)purine (1c). To **1a** (312 mg, 1.5 mmol) was added DMF (2.0 mL), acetic anhydride (1.0 mL, 10 mmol), and DMAP (60 mg, 0.5 mmol) successively and the mixture was stirred at rt for 16 h. The precipitate was collected by filtration, triturated with ether, and purified by flash chromatography using ethyl acetate/acetone as the eluant to give 170 mg (50%) of **1c**, mp 175–178 °C dec. ^{1}H NMR (DMSO-d_6): δ 8.47 (s, 1 H), 8.43 (s, 1 H), 6.12 (q, J = 8 Hz, 1 H), 3.80 (t, J = 8 Hz, 2 H), 3.64 (t, J = 8 Hz, 2 H), 2.85 (s, 3 H); IR (KBr) 1738, 1700 cm^{-1}. UV (CH_2Cl_2): λ_{max} 229 nm (ϵ 6663), 298 nm (ϵ 5274). Anal. Calcd for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.66; H, 4.00; N, 22.29.

5-Amino-4-[[(thietan-3-yl)amino]carbonyl]imidazole (2). A solution of **1a** (1.2 g, 4.76 mmol) in 2 N aqueous sodium hydroxide (30 mL, 60 mmol) was stirred and heated to reflux under nitrogen for 5 h. It was cooled to 0 °C, and carefully neutralized by the dropwise addition of concentrated hydrochloric acid (4 mL, 48 mmol) and 2 N hydrochloric acid (2 mL, 4 mmol). The solvent was removed in vacuo, and the residue was purified by flash chromatography using 10% methanol/methylene chloride to give **2** as a light beige powder 530 mg (56%), mp 173–176 °C dec. HRMS: (M^+) 198.0568 (198.0575 calcd). ^{1}H NMR (DMSO-d_6): δ 11.4 (br s, 1 H, exch. with D_2O), 8.03 (d, J = 8.5 Hz, 1 H exch. with D_2O), 7.03 (s, 1 H), 5.58 (br s, 2 H, exch. with D_2O), 5.14 (m, 1 H), 3.57 (t, J = 8.8 Hz, 2 H), 3.14 (t, J = 8.2 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 162.78, 143.14, 127.12, 111.6, 45.86, 35.3 (two superimposed methylene carbons, reversed in DEPT experiment). IR (KBr): 1625, 1598, 1568, 1534, 1497 cm^{-1}. UV (EtOH): λ_{max} 275 nm (13 290). Anal. Calcd for $C_7H_{10}N_4OS$: C, 42.41; H, 5.08; N, 28.26; S, 16.17. Found: C, 42.39; H, 5.26; N, 28.33; S, 16.11. This structure was further confirmed by X-ray crystallography.[1]

8-(Hydroxymethyl)-7,8-dihydrothiazolo[2,3-*i*]purine (7) and 8-Hydroxy-7,8-dihydro-9*H*-1,3-thiazino[2,3-*i*]purine (6). To 6-mercaptopurine (3.4 g, 20 mmol) dispersed in methanol (20 mL) was added 2 N NaOH (10.0 mL, 20.0 mmol) with stirring at rt under nitrogen. To the resulting very fine suspension was added epichlorohydrin (1.8 mL, 22 mmol) dissolved in methanol

(6) Undheim, K.; Röe, J. *Acta Chem. Scand.* **1969**, *23*, 2437.
(7) Dittmer, D. C.; Christy, M. E. *J. Am. Chem. Soc.* **1962**, *84*, 399.
(8) Dittmer, D. C.; Chang, R. L.-F.; Davis, F. A.; Iwanami, M.; Stamos, I. K.; Takahashi, K. *J. Org. Chem.* **1972**, *37*, 1111.
(9) Block, E. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W.; Ed.; Pergamon Press: Oxford, England, 1984; Vol. 7, p 403.
(10) Kelly, J. W.; Robinson, P. L.; Evans, S. A., Jr. *J. Org. Chem.* **1986**, *51*, 4473.
(11) Oda, K.; Machida, M. *Heterocycles* **1988**, *27*, 2417.

(10 mL) dropwise over 5 min at 0 °C. The reaction mixture was stirred for 24 h at rt and filtered through Celite. The filtrate was evaporated in vacuo to give a light yellow powder, 3.54 g (85%) which was a 1:1 mixture of **6** and **7** by ^{1}H NMR analysis. A portion of the mixture was purified by preparative HPLC (C_{18} reversed-phase column, using methanol/water as the eluant) to give the product **7** as a colorless solid, mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 8.88 (s, 1 H), 8.32 (s, 1 H), 5.5 (m, 1 H, exchanges with D_2O), 5.40 (m, 1 H), 4.02 (m, 1 H), 3.90 (m, 1 H), 3.67–3.80 (m, 2 H). ^{13}C NMR (DMSO-d_6): δ 162.1, 161.5, 149.9, 141.4, 130.3, 68.5, 61.2, 32.5 (61.2 and 32.5 inverted in DEPT experiment, relative to 162.1, 141.4 and 68.5. HRMS: $C_8H_8N_4OS$ 208.0427 (calcd 208.0419). IR (KBr): 1610, 1492, 1427, 1387, 1354 cm^{-1}. UV (MeOH): λ_{max} 222 nm (ε 5414), 294 nm (ε 3860).

NMR data of compound **6** determined from mixture of **6** and **7** and deleting peaks for compound **7**. ^{1}H NMR (DMSO-d_6): δ 8.73 (s, 1 H), 8.21 (s, 1 H), 6.15 (s, 1 H, exchanges with D_2O), 4.70 (m, 1 H), 4.57 (m, 1 H), 4.40 (m, 1 H), 3.55 (m, 1 H), 3.27 (m, 1 H); ^{13}C NMR (DMSO-d_6): δ 160.9, 158.4, 149.5, 145.0, 131.6, 58.9, 53.9, 32.0. Peaks at 53.9 and 32.0 inverted in DEPT spectrum relative to 58.9, 145.0, and 160.9.

Conversion of 7 to 1a. To **7** (190 mg, 0.91 mmol) in methanol (5.0 mL) was added 0.5 M sodium methoxide in methanol (2.0 mL, 1.0 mmol), and the mixture was stirred at rt for 24 h. 1 N HCl was added to the mixture, and the solvent was evaporated in vacuo. The resulting solid was purified by flash chromatography using 5% methanol in methylenechloride as the eluant to give the product (170 mg, 90%) which was identical in all respects to **1a** prepared previously.

6-[(1-Chloro-2-hydroxy-3-propanyl)thio]-9-methylpurine. Epichlorohydrin (1.41 mL, 18.0 mmol) was added to a mixture of 9-methyl-6-mercaptopurine[4] (3.0 g, 18.0 mmol) and sodium bicarbonate (1.53 g, 18.0 mmol) in ethanol (50 mL) and stirred at rt for 1 day. The reaction was worked up as described for **10**. The product was purified by flash chromatography using 5–10% methanol in methylene chloride as the eluant to give the product as a colorless solid, 1.5 g (32%), mp 99–105 °C. ^{1}H NMR ($CDCl_3$): δ 3.56–3.70 (m, 4 H), 3.91 (s, 3 H), 4.26 (br s, 2 H), 8.01 (s, 1 H), 8.69 (s, 1 H). IR (KBr): 3220, 1567, 1330 cm^{-1}. MS (CI): 259 (MH^+). Anal. Calcd for $C_9H_{11}ClN_4OS$: C, 41.78; H, 4.29; N, 21.65. Found: C, 41.86; H, 3.97; N, 21.62.

9-Methyl-1-(thietan-3-yl)hypoxanthine (1d). Sodium methoxide in methanol (1.2 M, 4.8 mL, 5.76 mmol) was added to a solution of 6-[(1-chloro-2-hydroxy-3-propanyl)thio]-9-methylpurine (1.48 g, 5.72 mmol) in methanol (25 mL) and stirred at rt for 2.5 days. The reaction was worked up as described for **11**. The product was further purified by medium-pressure chromatography using 3% methanol in methylene chloride to give **1d** as a colorless solid, 33 mg (2.5%). ^{1}H NMR ($CDCl_3$): δ 3.56–3.60 (m, 2 H), 3.93 (m, 2 H), 3.82 (s, 3 H), 6.16 (q, J = 8.7 Hz, 1 H), 7.75 (s, 1 H), 8.34 (s, 1 H). MS (CI): 223 (MH^+). HRMS calcd for $C_9H_{10}N_4OS$: 222.0589 (222.0575 calcd).

4-Oxo-1-(thietan-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (9). 1*H*-Pyrazolo[3,4-*d*]pyrimidine (15.2 g, 0.1 mol) was dissolved in ethanol (200 mL) and treated sequentially with sodium bicarbonate (8.4 g, 0.1 mol) and epichlorohydrin (10.62 g, 0.11 mol) in ethanol (30 mL) at rt. After being stirred for 2 days, the mixture was filtered and the filtrate evaporated to give an oil (25.7 g) which was purified by flash chromatography using 10% methanol in methylene chloride to give the chlorohydrin as a solid, 8.3 g (34%), mp 101–103 °C. DCI/MS: 245 (MH^+). ^{1}H NMR (DMSO-d_6): δ 8.73 (s, 1 H), 8.3 (s, 1 H), 5.78 (s, 2 H, exchanges with D_2O), 4.03 (m, 1 H), 3.70 (m, 2 H), 3.49 (m, 2 H). Anal. Calcd for $C_9H_9ClN_4OS$: C, 39.26; H, 3.71; N, 22.90. Found: C, 39.45; H, 3.73; N, 23.07.

To the chlorohydrin (8.24 g, 0.034 mol) in methanol (100 mL) was added 0.5 M sodium methoxide in methanol (150 mL, 0.075 mol), and the mixture was stirred for 1 week. The mixture was neutralized with 2 N hydrochloric acid, filtered, and concentrated to give a gum (20 g) which was dissolved in 30% methanol in methylene chloride (100 mL), filtered, and purified by flash chromatography using 10% methanol in methylene chloride to give **9** as a white solid (2.9 g, 38%), mp 192–195 °C. MS (MH^+) 209. IR (KBr): 1684 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.46 (s, 1 H), 8.05 (s, 1 H), 5.8 (m, 1 H), 4.05 (m, 2 H), 3.35 (m, 2 H), 3.2 (br s, 1 H, exchanges with D_2O). Anal. Calcd for $C_8H_8N_4OS \cdot 0.25H_2O$: C, 45.16; H, 4.03; N, 26.34. Found: C, 45.47; H, 4.16; N, 25.84.

2-[(1-Chloro-2-hydroxy-3-propanyl)thio]pyridine (10). Epichlorohydrin (3.6 mL, 46 mmol) was added to a mixture of 2-mercaptopyridine (5.0 g, 45 mmol) and sodium bicarbonate (4.0 g, 47.2 mmol) in ethanol (100 mL) at rt and stirred for 16 h. The solvent was evaporated in vacuo, and the residue was taken up in methylene chloride. The inorganics were removed by filtration, and the product was purified by flash chromatography using 1–5% methanol in methylene chloride as the eluant to give **10** (8.52 g, 93%) as an amber oil. ^{1}H NMR ($CDCl_3$): δ 3.35–3.50 (m, 2 H), 3.63–3.66 (m, 2 H), 4.13–4.18 (m, 1 H), 6.69 (d, J = 3.8 Hz, 1 H, exchanges with D_2O), 7.05–7.10 (m, 1 H), 7.32–7.39 (m, 1 H), 7.52–7.60 (m, 1 H), 8.35–8.37 (m, 1 H). IR (neat): 3189, 1584, 1560, 1456, 1417 cm^{-1}. MS (CI): 204 (MH^+). Anal. Calcd for $C_8H_{10}NOSCl$: C, 47.17; H, 4.95; N, 6.88. Found: C, 47.07; H, 4.99; N, 6.78. This material converts to **13** on standing.

1-(Thietan-3-yl)-1*H*-2-pyridone (11). Sodium methoxide (1 N, 12 mL, 12 mmol) was added to a solution of 2-[(1-chloro-2-hydroxy-3-propanyl)thio]pyridine (**10**, 2.42 g, 11.9 mmol) in methanol (50 mL) at 0 °C over 15 min and stirred at rt for 2 days. The solution was cooled to 5 °C and neutralized with several drops of concentrated hydrochloric acid. The solvent was evaporated in vacuo, and the resultant residues was taken up in methylene chloride. The inorganics were removed by filtration. The product was purified by flash chromatography using 1–5% methanol in methylene chloride as the eluant to give **11** (1.16 g, 58%) as a colorless solid, mp 50–53 °C. ^{1}H NMR (DMSO-d_6): δ 3.26–3.36 (m, 2 H), 3.80–3.86 (m, 2 H), 5.78–5.90 (m, 1 H), 6.26–6.35 (m, 1 H), 6.37–6.38 (m, 1 H), 7.38–7.45 (m, 1 H), 7.87 (m, 1 H). IR (KBr): 1659, 1584, 1536 cm^{-1}. MS (CI): 168 (MH^+). Anal. Calcd for C_8H_9NOS: C, 57.46; H, 5.42; N, 8.37. Found: C, 57.18; H, 5.43; N, 8.16.

2-Oxo-1-(thietan-3-yl)pyridine *S*,*S*-Dioxide (12). To **11** (1 g, 6 mmol) in water (10 mL) was added 1 N sodium hydroxide (6 mmol, 6 mL) at room temperature, and potassium permanganate (1.04, 6.6 mmol) dissolved in water (125 mL) was added dropwise over 15 min. The suspension was filtered through Celite. The filtrate was acidified with 2 N hydrochloric acid (pH ≈ 5.0) and concentrated to give a white solid (1.30 g). This solid was washed with methanol (3 × 25 mL) and purified on silica gel using 5% methanol in methylene chloride to give sulfone **12** (560 mg, 47.0%) as a white solid, mp 125–128 °C. DCI/MS: 200 (MH^+). ^{1}H NMR (DMSO-d_6): δ 7.85 (d, 1 H, J = 7 Hz), 7.5 (m, 1 H), 6.45 (d, 1 H, J = 9 Hz), 6.35 (t, J = 6.8 Hz, 1 H), 5.35 (m, 1 H), 4.7 (m, 4 H). Anal. Calcd for $C_8H_9O_3S$: C 48.22, H 4.55, N 7.03. Found: C 48.27, H 4.60, N 6.97.

3,4-Dihydro-3-hydroxy-2*H*-thiazino[3,2-*a*]pyridinium Chloride (13). A sample of **10** (1.13 g) was stirred in methylene chloride (10 mL) overnight. Product **13** crystallized as a white solid which was triturated with pentane to give pure **13**, 1.06 g (99%), mp 75–76 °C. ^{1}H NMR (DMSO-d_6): δ 8.81 (d, 1 H, J = 6 Hz), 8.25 (m, 1 H), 8.04 (d, 1 H, J = 6 Hz), 7.72 (m, 1 H), 6.24 (br s, 1 H, exchanges with D_2O), 4.75 (m, 2 H), 4.52 (m, 1 H), 3.61 (m, 1 H), 3.34 (m, 1 H). Anal. Calcd for $C_8H_{10}NOSCl \cdot 0.75H_2O$: C, 44.23; H, 5.33; N, 6.45. Found: C, 44.00; H, 5.31; N, 6.20.

2-[(1-Chloro-2-hydroxy-3-propanyl)thio]quinoline (14). Epichlorohydrin (2.5 mL, 32.1 mmol) was added to a mixture of 2-quinolinethiol (5.03 g, 31.2 mmol) and sodium bicarbonate (2.78 g, 32.8 mmol) in ethanol (70 mL) at rt and stirred for 16 h. The reaction was worked up as described for **10** to give **14** as an amber oil, 5.27 g (67%). ^{1}H NMR ($CDCl_3$): δ 3.50–3.74 (m, 4 H), 4.25–4.32 (m, 1 H), 7.25 (br s, 1 H, exchanges with D_2O), 7.33–7.97 (m, 6 H). IR (neat): 3350, 1615, 1594, 1558, 1498, 1420 cm^{-1}. MS (CI): 254 (MH^+). Anal. Calcd for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.77; N, 5.52. Found: C, 56.47; H, 4.87; N, 5.50.

1-(Thietan-3-yl)-1*H*-quinol-2-one (15). Compound **14** (3.4 g, 13.4 mmol) was treated with 1 N sodium methoxide (14 mL, 14 mmol) at rt and stirred for 3 days. The reaction was worked up as described for **11** to give **15**, 1.2 g (41%), as a colorless solid after recrystallization from 2-propanol, mp 128–30 °C. ^{1}H NMR ($CDCl_3$): δ 3.48–3.54 (m, 2 H), 4.24 (t, J = 9.0 Hz, 2 H), 6.62 (d, J = 4.2 Hz, 1 H), 6.87–7.00 (m, 1 H), 7.26–7.31 (m, 1 H), 7.57–7.69 (m, 3 H), 8.22 (d, J = 8.6 Hz, 1 H). IR (KBr): 1652, 1588, 1565, 1461 cm^{-1}. MS (CI): 218 (MH^+). Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.38; H, 4.83; N, 6.42.

4-[(1-Chloro-2-hydroxy-3-propanyl)thio]pyrimidine (16). Epichlorohydrin (1.9 mL, 24.5 mmol) was added to a mixture of 4-mercaptopyrimidine (2.5 g, 22.3 mmol) and sodium bicarbonate (1.99 g, 24.5 mmol) in ethanol (50 mL) and stirred at rt for 4 d. The mixture was worked up as described for **10** to give the product (1.02 g, 22%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.41–3.69 (m, 4 H), 4.16–4.20 (m, 1 H), 4.9 (br s, 1 H, exchanges with D_2O), 7.29 (dd, J = 1.4, 5.5 Hz, 1 H), 8.39 (d, J = 5.5 Hz, 1 H), 8.91 (d, J = 1.4 Hz, 1 H). IR (neat): 3300, 1571, 1447 cm^{-1}. MS(CI): 205 (MH^+).

1-(Thietan-3-yl)-1*H*-pyrimidin-6-one (17) and -4(3*H*)-pyrimidone (18). Sodium methoxide (1.2 N, 4.1 mL, 4.9 mmol) was added to a solution of **16** (1.0 g, 4.9 mmol) in methanol (25 mL) at 0 °C. The resultant solution was stirred at rt for 16 h and worked up as described for **11** to give **17** as a colorless solid after flash chromatography using 5% methanol in methylene chloride as the eluant, 40 mg (5%), mp 48–50 °C. ^{1}H NMR ($CDCl_3$): δ 3.42–3.48 (m, 2 H), 3.55–3.61 (m, 2 H), 5.86–5.95 (m, 1 H), 6.70 (d of d, J = 1.1, 5.8 Hz, 1 H), 8.45 (d, J = 5.8 Hz, 1 H), 8.74 (s, 1 H); MS (CI): 169 (MH^+). Anal. Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found: C, 50.26; H, 4.65; N, 16.43.

The pyrimidone **18** was eluted with 5–15% methanol in methylene chloride to give 208 mg (44%) as a colorless solid which was identical to an authentic sample (Aldrich).

2-[(1-Chloro-2-hydroxy-3-propanyl)thio]imidazole (19). Epichlorohydrin (3.66 mL, 46.8 mmol) was added to a mixture of 2-mercaptoimidazole (4.6 g, 45.9 mmol) and sodium bicarbonate (4.46 g, 52.4 mmol) in ethanol (100 mL) and stirred at rt for 16 h. The reaction mixture was worked up as described for **10** to give **19** as a colorless oil, 5.28 g (60%). ^{1}H NMR: δ 3.21–3.37 (m, 2 H), 3.65–3.68 (m, 2 H), 4.20–4.23 (m, 1 H), 5.3 (br s, 2 H), 7.02 (s, 2 H). MS (CI): 193 (MH^+). Anal. Calcd for $C_6H_9ClN_2OS$: C, 37.41; H, 4.71; N, 14.54. Found: C, 37.01; H, 4.83; N, 14.17.

3,4-Dihydro-3-hydroxy-2*H*-thiazino[3,2-*a*]imidazole (20). A solution of sodium methoxide (1.0 M, 12 mL, 12 mmol) was added to a solution of **19** (2.32 g, 12.0 mmol) in methanol and stirred at rt for 16 h. The mixture was worked up as described for **11** and purified by flash chromatography using 5% methanol in methylene chloride as the eluant to give **20** as a colorless solid, 1.47 g (78%), mp 202–205 °C. ^{1}H NMR ($CDCl_3$): δ 3.17–3.22 (m, 2 H), 3.95–4.00 (m, 1 H), 4.10–4.15 (m, 1 H), 4.20–4.30 (m, 1 H), 5.25 (br s, 1 H, exchanges with D_2O), 6.87 (d, J = 1.3 Hz, 1 H), 6.96 (d, J = 1.3 Hz, 1 H). MS (CI): 157 (MH^+). Anal. Calcd for $C_6H_8N_2OS$: C, 46.14; H, 5.16; N, 17.93. Found: C, 46.38; H, 5.02; N, 18.11.

2-[(1-Chloro-2-hydroxy-3-propanyl)thio]-1-methylimidazole (21). Epichlorohydrin (3.5 mL, 45.1 mmol) was added to a mixture of 2-mercapto-1-methylimidazole (5.0 g, 43.8 mmol) and sodium bicarbonate (4.1 g, 48.2 mmol) in ethanol (100 mL) and stirred at rt for 16 h. The mixture was worked up as described for **10** to give **21** 8.13 g (90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.31–3.36 (m, 2 H), 3.61 (s, 3 H), 3.64–3.68 (m, 2 H), 4.17–4.27 (m, 1 H), 6.87 (d, J = 1.4 Hz, 1 H), 6.94 (d, J = 1.4 Hz, 1 H), 7.76 (br s, 1 H, exchanges with D_2O). IR (neat): 1460 and 1280 cm^{-1}. MS (CI): 207 (MH^+). Anal. Calcd for $C_7H_{11}ClN_2OS$: C, 40.68; H, 5.36; N, 13.55. Found: C, 40.50; H, 5.17; N, 13.19.

3,4-Dihydro-3-hydroxy-7-methyl-2*H*-thiazino[3,2-*a*]imidazolium Chloride (22). A solution of **21** (2.0 g, 9.67 mmol) in methylene chloride (40 mL) was stirred at rt for 2 weeks. The crystalline precipitate was collected by filtration and dried in vacuo to give **22** as a colorless solid, 0.197 g (10%): mp 178–180 °C; ^{1}H NMR (DMSO-d_6) δ 3.40–3.58 (m, 2 H), 3.66 (s, 3 H), 4.20 (m, 2 H), 4.53–4.54 (m, 1 H), 6.10–6.20 (d, J = 3.7 Hz, 1 H, exchanges with D_2O), 7.74 (s, 2 H). IR (KBr): 3207, 3067, 1570, 1475, 1435 cm^{-1}. Anal. Calcd for $C_7H_{11}ClN_2OS$: C, 40.68; H, 5.36; N, 13.55. Found: C, 40.63; H, 5.21; N, 13.44.

Alternatively, a solution of **21** (3.14 g, 15.2 mmol) in methanol (50 mL) was treated with 1 N sodium methoxide in methanol (15.2 mL, 15.2 mmol) and stirred at rt for 16 h. The mixture was neutralized with concentrated hydrochloric acid, the solvent was evaporated in vacuo, and the solid residue was triturated in methylene chloride. Filtration gave a colorless solid (3.82 g) which was a mixture of sodium chloride and 3,4-dihydro-3-hydroxy-7-methyl-2*H*-thiazino[3,2-*a*]imidazolium chloride.

2-[(1-Chloro-2-hydroxy-3-propanyl)thio]benzoxazole. Epichlorohydrin (2.7 mL, 34.7 mmol) was added to a mixture of 2-mercaptobenzoxazole (5.0 g, 33.1 mmol) and sodium bicarbonate (2.81 g, 33.1 mmol) in ethanol (100 mL) and stirred at rt for 24 h. The reaction was worked up as described for **10** to give the product as a colorless solid, 6.06 g (75%), mp 45–47 °C. ^{1}H NMR ($CDCl_3$): δ 3.46–3.63 (m, 2 H), 3.72 (d, J = 5.8 Hz, 2 H), 4.31–4.36 (m, 1 H), 4.85 (d, J = 4.8 Hz, 1 H, exchanges with D_2O), 7.24–7.33 (m, 2 H), 7.44–7.48 (m, 1 H), and 7.55–7.59 (m, 1 H). IR (KBr): 1500, 1454, 2140 cm^{-1}. MS (CI): 244 (MH^+). Anal. Calcd for $C_{10}H_{10}ClNO_2S$: C, 49.28; H, 4.14; N, 5.75. Found: C, 49.14; H, 4.21; N, 5.60.

2-Benzoxazolinone. A 1 N solution of sodium methoxide in methanol (13.2 mL, 13.2 mmol) was added to a solution of 2-[(1-chloro-2-hydroxy-3-propanyl)thio]benzoxazole (3.22 g, 13.2 mmol) in methanol (50 mL) at 0 °C and allowed to stir at rt for 16 h. The resultant mixture was neutralized with concentrated hydrochloric acid, and the solvent was evaporated in vacuo. The residue was dissolved in methylene chloride, and the inorganic materials were removed by filtration. The solution was dried over magnesium sulfate, and the solvent was evaporated to give the product as a colorless solid, 1.5 g (84%), mp 134–138 °C. ^{1}H NMR ($CDCl_3$): δ 7.08–7.26 (m, 4 H) and 8.2–8.9 (br s, 1 H, exchanges with D_2O). IR (KBr): 1778, 1736, 1481 cm^{-1}. MS (CI): 136 (MH^+). This material was identical to an authentic sample (Aldrich).

Acknowledgment. We thank Dr. Gary Caldwell and Ms. Diane Gauthier for detailed NMR measurements. High-resolution mass spectrometry was done by Mr. Richard Dunfey. Preparative HPLC was performed by Ms. Mary Evangelisto.

Registry No. 1a, 129205-12-5; **1b**, 129205-13-6; **1c**, 129205-14-7; **1d**, 143746-42-3; **2**, 129205-15-8; **3**, 50-44-2; **4**, 106-89-8; **5**, 129205-11-4; **6**, 143746-29-6; **7**, 129205-16-9; **9**, 143746-30-9; **10**, 143746-31-0; **11**, 143746-32-1; **12**, 143746-33-2; **13**, 143746-34-3; **14**, 143746-35-4; **15**, 143746-36-5; **16**, 143746-37-6; **17**, 143746-38-7; **18**, 4562-27-0; **19**, 143746-39-8; **20**, 34035-41-1; **21**, 143746-40-1; **22**, 143746-41-2; 9-methyl-6-mercaptopurine, 1006-20-8; 6-[(1-chloro-2-hydroxy-3-propanyl)thio]-9-methylpurine, 143746-43-4; 4-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine, 5334-23-6; 4-[(1-chloro-2-hydroxy-3-propanyl)thio]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 143746-44-5; 2-mercaptopyridine, 2637-34-5; 2-quinolinethiol, 2637-37-8; 4-mercaptopyrimidine, 1450-86-8; 2-mercaptoimidazole, 872-35-5; 2-mercapto-1-methylimidazole, 60-56-0; 2-mercaptobenzoxazole, 2382-96-9; 2-[(1-chloro-2-hydroxy-3-propanyl)thio]benzoxazole, 143746-45-6; 2-benzoxazolinone, 2637-37-8.

Diastereoselective Synthesis of Anti and Syn α,β-Dihydroxy Thioesters by Titanium Enolate Aldol Condensation

Rita Annunziata, Mauro Cinquini,* Franco Cozzi,* and Andrea Lombardi Borgia

Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Universita', via C. Golgi 19, 20133 Milano, Italy

Received July 2, 1992

The aldol condensation between α-alkoxy esters (or their synthetic equivalents) and aldehydes represents a versatile entry to the 1,2-diol unit. However, while syn configurated compounds are efficiently obtained by several of these processes,[1] precedents for highly stereocontrolled anti diol

(1) (a) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Mark, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161. (b) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247. (c) Gray, B. D.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1985** 20. (d) Oesterle, T.; Simchen, G. *Justus Liebigs Ann. Chem.* **1987**, 693. (e) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506. (f) Sugano, Y.; Naruto, S. *Chem. Pharm. Bull.* **1989**, *37*, 840. (g) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157. (h) Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1991**, 1901.

0022-3263/92/1957-6339$03.00/0