Synthesis of Four Candidate Metabolites of the Phosphorothioate Insecticide DOWCO 429

Gary A. Roth* and E. Lynn McClymont

Environmental Chemistry Laboratory, 9001 Building, DowElanco, Midland, Michigan 48641-1706

Four candidate metabolites of the insecticide *O,O*-diethyl *O*-[2-(1,1-dimethylethyl)-5-pyrimidinyl] phosphorothioate (DOWCO 429, **1**) are prepared via coupling of the appropriately substituted amidines with the biselectrophilic reagent *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate, followed by additional functional group manipulations. Each of the metabolite standards retains the heterocyclic ring but contains oxidized alkyl side chains at the 2-position of the pyrimidine.

DOWCO 429, common name Butathiophos, is an insecticide currently under development at DowElanco. During the course of animal metabolism studies on DOWCO 429 (**1**), several polar metabolites have been isolated from goat urine. Preliminary mass spectrometry analyses indicated that hydrolysis of the phosphorothioate and biological oxidation of the aliphatic side chain may have occurred, resulting in the formation of 2-(1,1-dimethyl-2-hydroxyethyl)-5-pyrimidinol (**2**). It is therefore chemically reasonable that 2-(1,1-dimethyl-1-carboxymethyl)-5-pyrimidinol (**4**) may be a secondary metabolite produced via oxidation of the corresponding alcohol.

Aqueous photolysis studies on DOWCO 429 (**1**) have led to the isolation of three major photoproducts. Utilization of gas chromatography/mass spectrometry techniques provided tentative identification of two of the products as *O,O*-diethyl *O*-[2-(hydroxymethyl)-5-pyrimidinyl] phosphorothioate (**3**) and *O,O*-diethyl *O*-[2-(2-hydroxy-2-methylpropyl)-5-pyrimidinyl] phosphorothioate (**5**). This paper describes the synthesis and spectroscopic properties of the proposed metabolites **2**–**5** (Figure 1).

RESULTS AND DISCUSSION

The synthesis of metabolite standard **2** is outlined in Scheme I. Commercially available methyl 2,2-dimethyl-3-hydroxypropionate (**6**) was protected as the benzyl ether **7** under carefully controlled reaction conditions. Hydrolysis of **7**, acid chloride formation, and treatment with aqueous ammonia in dichloromethane provided amide **8**. Dehydration of **8** was effected with phosphorus oxychloride in refluxing acetonitrile to afford nitrile **9**. Conversion of **9** to pyrimidine **10** was carried out by using a modification of the procedure developed by Reifschneider (1984). Treatment of **9** with anhydrous hydrogen chloride in ethanol/toluene (sealed tube) provided the corresponding debenzylated imino ester. It has been observed that higher yields of imino esters are achieved when the reaction is conducted under sealed conditions in the presence of excess hydrogen chloride than under atmospheric conditions (McKendry, 1986). Reaction of the imino ester with anhydrous ammonia in methanol yielded the desired amidine, which was converted to **10** by using *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate (reagent A in Scheme V; Holy and Arnold, 1973) and potassium carbonate in refluxing acetonitrile. Debenzylation of **10** under transfer hydrogenolysis conditions provided the desired metabolite standard **2**.

The metabolite candidate **4** was prepared by starting with pyrimidine **10** as depicted in Scheme II. Swern (1978) oxidation of **10** to the corresponding aldehyde followed by treatment of the crude aldehyde with benzyltriethylammonium permanganate (Scholz, 1979) in dichloromethane/acetic acid gave acid **11**. Deprotection of **11** under transfer hydrogenolysis conditions yielded the desired metabolite candidate **4**.

Scheme III outlines the synthesis of metabolite standard **3**. Commercially available benzoyloxyacetyl chloride (**12**)

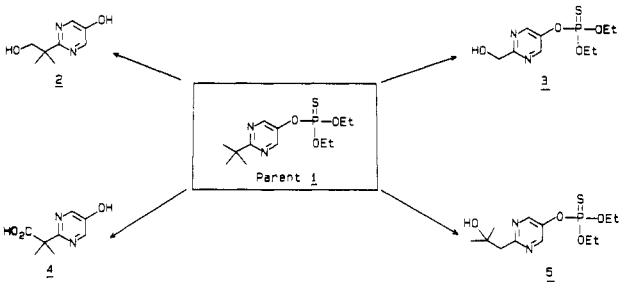
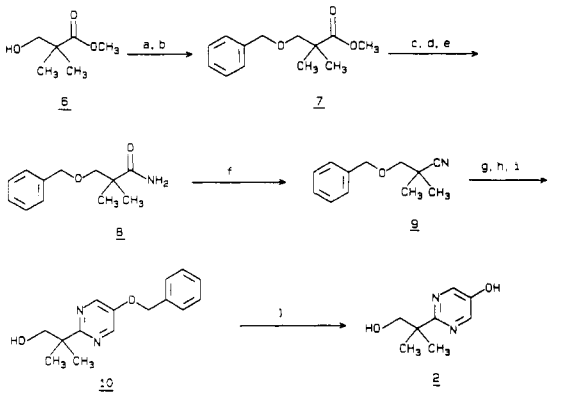


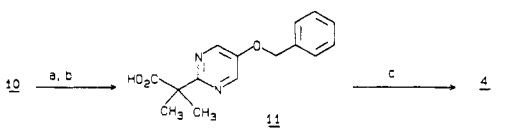
Figure 1. Potential metabolites of DOWCO 429.

Scheme I[a]



[a] Key: (a) NaH, THF; (b) BnBr; (c) NaOH, THF, CH_3OH; (d) $SOCl_2$, PhH; (e) NH_4OH, H_2O, CH_2Cl_2; (f) $POCl_3$, CH_3CN; (g) HCl, EtOH, toluene; (h) NH_3, CH_3OH; (i) *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate, K_2CO_3, CH_3CN; (j) $Pd(OH)_2/C$, cyclohexene.

Scheme II[a]



[a] Key: (a) $(COCl)_2$, DMSO, CH_2Cl_2 NEt_3; (b) benzyltriethylammonium permanganate, CH_2Cl_2, HOAc; (c) cyclohexene, $Pd(OH)_2/C$, EtOH.

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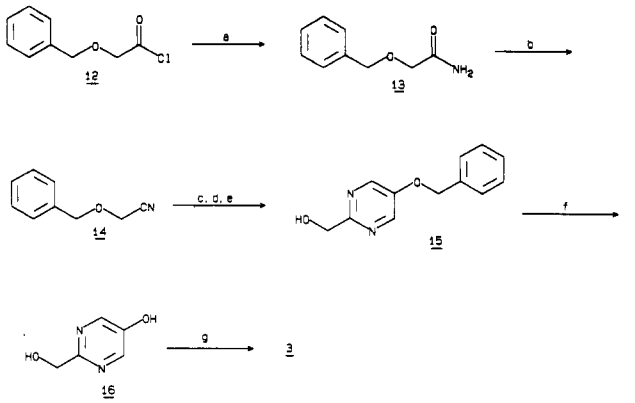
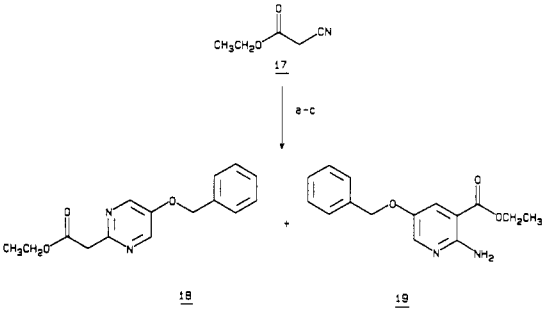
Scheme III[a]



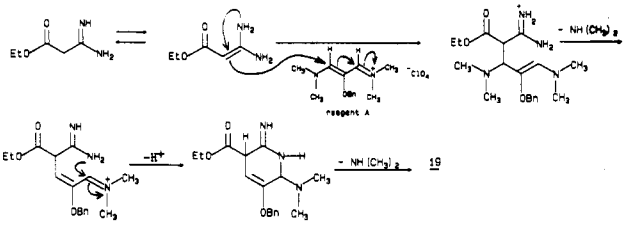
[a] Key: (a) NH_4OH, CH_2Cl_2; (b) $POCl_3$; (c) HCl, EtOH, toluene; (d) NH_3CH_3OH; (e) *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate, K_2CO_3, CH_3CN; (f) cyclohexene, $Pd(OH)_2/C$, EtOH; (g) Diethyl chlorothiophosphate, CH_3CN, K_2CO_3.

Scheme IV[a]



[a] Key: (a) HCl, EtOH; (b) NH_3, EtOH; (c) *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate, K_2CO_3, CH_3CN.

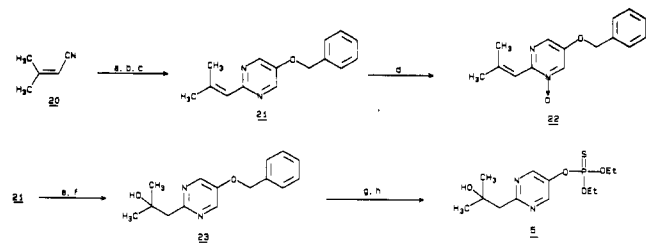
Scheme V



was converted to the analogous nitrile **14** (Quarterman, 1955) under standard conditions. Imino ester formation from **14** provided the desired product with concomitant removal of the benzyl protecting group. The pyrimidine **15** was obtained following the standard reaction sequence previously described. Debenzylation using transfer hydrogenolysis conditions afforded the pyrimidinol **16**, which upon selective phosphorylation at the pyrimidinol site afforded the hydroxymethyl metabolite candidate **3**.

Our initial attempts at the synthesis of metabolite standard **5** are shown in Scheme IV. Dry hydrogen chloride was sparged into a solution of ethyl cyanoacetate (**17**) in ethanol and the resulting imino ester treated with ammonia/ethanol to provide the corresponding amidine. Reaction of this material with *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate afforded both the desired pyrimidine **18** and the pyridine **19**. A possible reaction pathway leading to the formation of **19** is outlined in Scheme V. Several attempts at addition of methylorganometallic reagents to the ester of **18** failed to give any of the desired tertiary alcohol due to competitive deprotonation.

Scheme VI[a]



[a] Key: (a) HCl, EtOH; (b) NH_3, EtOH; (c) *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate, K_2CO_3, CH_3CN; (d) MCPBA; (e) $Hg(OAc)_2$, H_2O, THF; (f) $NaBH_4$, NaOH; (g) cyclohexene, $Pd(OH)_2/C$, EtOH; (h) diethyl chlorothiophosphate, K_2CO_3, CH_3CN.

Metabolite candidate **5** was successfully prepared as outlined in Scheme VI. The nitrile **20** (Piechucki, 1974) was converted to the benzyl-protected pyrimidinol **21** according to the standard reaction sequence. Our attempts to prepare tertiary alcohol **23** via epoxidation of **21** followed by reductive opening at the less hindered position were thwarted due to our inability to oxidize the double bond of **21**. Attempted epoxidations of **21** yielded, as the only isolable product, the *N*-oxide **22** as determined by ^1H NMR and mass spectrometry. The tertiary alcohol **23** was eventually secured via Markovnikov addition of water across the double bond of **21**. This was accomplished by using the oxymercuration/demercuration procedure developed by Brown and Geoghegan (1970). Thus, treatment of **21** with mercuric acetate in water/tetrahydrofuran, followed by reduction of the organomercurial with sodium borohydride in dilute sodium hydroxide, resulted in clean formation of the desired tertiary alcohol **23**. Debenzylation of **23** followed by selective phosphorylation yielded the desired metabolite candidate **5**.

EXPERIMENTAL SECTION

Thin-layer chromatography (TLC) was routinely used to monitor reactions and to check purities. TLC was conducted by using 2.5 × 10 cm Analtech silica gel GF (UV 254) plates. Low-field ^1H NMR spectra were obtained by using a Varian EM-390 (90 MHz) spectrometer using the solvent noted and tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (δ scale) downfield from TMS. Significant ^1H NMR data are tabulated in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, number of protons, assignment. Mass spectra were obtained by using a Finnigan 4615 instrument operated in the positive ion mode. All mass spectra were obtained by using a direct exposure probe and an ionization potential of 70 eV (electron impact). Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. All nonaqueous reactions were conducted under an atmosphere of nitrogen or under a calcium sulfate drying tube. All reactions were magnetically stirred. Solvents and reagents were used as received from commercial suppliers. Infrared spectra were recorded on a Perkin-Elmer Model 1310 spectrophotometer. High-resolution mass spectrometry analyses (HRMS) were obtained by using a VG 70SQ instrument operated at 70-eV electron impact ionization potential using a direct insertion probe. HRMS were obtained at the Mass Spectrometry Center of the University of South Carolina.

Methyl 2,2-Dimethyl-3-(benzyloxy)propionate (7). To a stirred, cooled (−23 °C) suspension of sodium hydride (8.4 g, 60%, 0.21 mol) in THF (200 mL) was added the alcohol **6** (25 g, 0.19 mol) in THF (20 mL) dropwise over 30 min. The mixture was stirred at −23 °C for 2 h and then warmed to room temperature and stirred for 0.5 h. Benzyl bromide (24 mL, 0.20 mol) was added dropwise and the mixture stirred at room temperature for 18 h. Ether (100 mL) was added and stirring continued for an

additional 6 h. The mixture was diluted with ether (150 mL), and the organics were washed with water (1 × 250 mL) and half-saturated brine (2 × 250 mL). After drying ($MgSO_4$) and filtration, the solvents were removed on the rotary evaporator to leave a yellow liquid. The liquid was distilled through a 15-cm Vigreux column and the product collected at 100–105 °C and 0.7 mmHg as a pale yellow liquid (24 g, 57%): ^{1}H NMR ($CDCl_3$) 1.2 (s, 6 H, 2-CH_3), 3.5 [s, 2 H, OCH_2C(CH_3)$_2$], 3.7 (s, 3 H, OCH_3), 4.5 (s, 2 H, ArCH_2O), 7.3 (s, 5 H, ArH's); IR (film) 3100–2800, 1740 cm^{-1}.

2,2-Dimethyl-3-(benzyloxy)propionamide (8). To a solution of ester **7** (19 g, 85.6 mmol) in CH_3OH (50 mL), THF (20 mL), and water (15 mL) was added sodium hydroxide (4.6 g, 115 mmol). The mixture was heated at reflux for 1.25 h and then allowed to cool to room temperature. Most of the CH_3OH/THF was removed on the rotary evaporator and the mixture diluted with water (100 mL). The aqueous mixture was extracted with ether (2 × 50 mL) and then acidified to pH 2 with concentrated HCl (13 mL). The aqueous phase was extracted with ether (3 × 75 mL), and the combined extracts were dried ($MgSO_4$), filtered, and evaporated to afford the carboxylic acid as a white solid (mp 70–73 °C). The solid was dissolved in benzene (80 mL) and treated with $SOCl_2$ (11 mL). The mixture was heated at reflux for 3 h and then cooled to room temperature. The volatiles were removed on the rotary evaporator (40 °C at 35 mmHg) to leave a yellow liquid. The liquid was dissolved in CH_2Cl_2 (50 mL) and added dropwise to a mixture of concentrated NH_4OH (25 mL) and CH_2Cl_2 (50 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction was warmed to room temperature and stirred for 15 h. The CH_2Cl_2 layer was separated, washed with half-saturated brine (50 mL), dried ($MgSO_4$) and filtered. Removal of the solvent on the rotary evaporator and final drying at 0.5 mmHg provided **8** as a white solid (ca. 80 mmol): mp 37–41 °C; ^{1}H NMR ($CDCl_3$) 1.2 (s, 6 H, 2-CH_3), 3.45 [s, 2 H, OCH_2C(CH_3)$_2$], 4.6 (s, 2 H, ArCH_2O), 6.3 (bd, 2 H, NH_2), 7.3 (s, 5 H, ArH's); homogeneous by TLC, R_f = 0.25 in 1/1 hexane/EtOAc; IR (KBr) 3310–3040, 1665 cm^{-1}.

2,2-Dimethyl-3-(benzyloxy)propionitrile (9). The amide **8** (ca. 80 mmol) was dissolved in acetonitrile (100 mL) and treated with $POCl_3$ (10 mL). The mixture was heated at reflux for 3 h and then cooled to room temperature. The CH_3CN was removed on the rotary evaporator and the residue dissolved in Et_2O (ca. 50 mL) and cooled to 0 °C. Water (ca. 50 mL) was added and the two-phase mixture stirred at 0 °C for 15 min, warmed to room temperature, and stirred for 20 min. The layers were separated, the organic phase was washed once with water (50 mL) and dried ($MgSO_4$), and the solvent was removed on the rotary evaporator to leave the crude product as a yellow liquid. The material was purified via silica gel chromatography (400 g of 230–400 mesh, benzene) to afford the product as a pale yellow liquid (9.8 g, 61% from **7**): ^{1}H NMR ($CDCl_3$) 1.3 (s, 6 H, 2-CH_3), 3.35 [s, 2 H, OCH_2C(CH_3)$_2$], 4.6 (s, 2 H, ArCH_2O), 7.3 (s, 5 H, ArH's); IR (film) 2250 cm^{-1}; MS (m/e) 189 (M$^+$, 10%), 107 (7%), 91 (100%).

2-(1,1-Dimethyl-2-hydroxyethyl)-5-(benzyloxy)pyrimidine (10). Nitrile **9** (8.0 g, 42.3 mmol) was dissolved in toluene (25 mL) and ethanol (3.0 mL) in a 50-mL ampule. The mixture was cooled to −78 °C under a N_2 stream and then HCl gas sparged in for 15 min. The ampule was sealed and allowed to warm to room temperature. The ampule was heated at 50 °C oil bath temperature with good stirring for 18 h. After cooling to −78 °C, the ampule was opened and allowed to warm slowly to room temperature. The contents of the ampule were transferred to a 500-mL round-bottom flask by using CH_2Cl_2. The solvents were removed on the rotary evaporator to leave a white solid. The solid was triturated with hexane, filtered, washed with hexane, and dried (0.5 mmHg, room temperature). The white solid was dissolved in CH_3OH (100 mL) and anhydrous ammonia sparged in for 20 min. After the solution was stirred for an additional 1.5 h, the solvent was removed on the rotary evaporator to afford the amidine as a white crystalline solid. The solid was slurried in acetonitrile (200 mL) and treated with *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate (13.3 g, 40 mmol) and K_2CO_3 (25 g, 180 mmol). The mixture was heated at 75 °C for 18.5 h and then allowed to cool to room temperature. The mixture was poured into water (250 mL) and extracted with EtOAc (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and filtered and the solvents removed on the rotary evaporator to leave the crude product as an amber oil. The oil was purified by chromatography on silica gel (250 g of 230–400 mesh, 1/1 hexane/EtOAc) to provide **10** as a light amber oil which crystallized on standing (8.8 g, 81%): mp 49–51 °C; ^{1}H NMR ($CDCl_3$) 1.35 (s, 6 H, 2-CH_3), 3.7 (bs, 2 H, CH_2OH), 4.2 (bs, 1 H, OH), 5.2 (s, 2 H, OCH_2Ph), 7.4 (s, 5 H, ArH's), 8.4 (s, 2 H, 2-heteroaromatic H's); MS (m/e) 258 (M$^+$, 2.7%), 240 (7.2%), 228 (24.5%), 145 (17.7%), 137 (27.2%), 91 (100%); IR (KBr) 3500 (b), 3050, 2920 cm^{-1}.

2-(1,1-Dimethyl-2-hydroxyethyl)-5-pyrimidinol (2). Benzyl ether **10** (1.2 g, 4.65 mmol) was dissolved in ethanol (6 mL) and treated with cyclohexene (950 μL, 14 mmol) and palladium hydroxide on carbon (250 mg). The mixture was heated at reflux for 0.5 h and then cooled to room temperature. The mixture was filtered through a pad of Celite and the filter rinsed well with ethanol. The ethanol was removed on the rotary evaporator to leave a thick yellow oil. The oil was treated with toluene (20 mL) and the solvent removed on the rotary evaporator with final drying at 0.5 mmHg to provide **2** as a pale yellow solid (790 mg, 100%): mp 120–121 °C; ^{1}H NMR (DMSO-d_6) 1.25 (s, 6 H, 2-CH_3), 3.6 (s, 2 H, CH_2OH), 4.3 (bs, 1 H, OH), 8.2 (s, 2 H, 2-heteroaromatic H's), 10.1 (s, 1 H, OH); MS (m/e) 168 (M$^+$, 0.5%), 150 (M$^+$ − H_2O, 36%), 138 (100%), 123 (42%), 110 (17%); IR (KBr) 3700–2500 (b), 1430, 1270, 1040 cm^{-1}. HRMS, m/e, exact mass calcd for $C_8H_{12}N_2O_2$: 168.0899. Found: 168.0901.

2-(1,1-Dimethyl-1-carboxymethyl)-5-(benzyloxy)pyrimidine (11). To a solution of oxalyl chloride (350 μL, 4 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DMSO (567 μL, 8 mmol) dropwise. After the solution was stirred for 5 min, the alcohol **10** (800 mg, 3.1 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was warmed to −43 °C (CH_3CN/CO_2 bath) and stirred for 45 min. Triethylamine (2.1 mL) was added and the reaction allowed to warm slowly to 0 °C. The mixture was diluted with CH_2Cl_2 (ca. 20 mL), and the organics were washed with ice-cold water (3 × 15 mL), dried (Na_2SO_4), filtered, and evaporated to leave a pale yellow oil. The oil was dissolved in CH_2Cl_2 (35 mL) and acetic acid (5 mL) and treated with benzyltriethylammonium permanganate (1.0 g, 3 mmol). After the solution was stirred at room temperature for 1 h, ether (200 mL) was added. The mixture was stirred for 10 min and then filtered through Celite. The organics were washed with water (2 × 100 mL), treated with charcoal/Na_2SO_4, filtered, and evaporated to provide an acetic acid solution of the product. Aqueous NaOH (20 mL of 20%) and water (10 mL) were added, and the basic aqueous phase was extracted with ether (2 × 20 mL). The aqueous layer was taken to pH 2 with concentrated HCl/ice and the resulting precipitate collected and washed with water. Drying at 0.5 mmHg (room temperature) for 14 h afforded **11** as a white solid (244 mg, 29%): mp 124–125 °C; ^{1}H NMR ($CDCl_3$) 1.65 (s, 6 H, 2-CH_3's), 5.2 (s, 2 H, OCH_2Ar), 7.35 (s, 5 H, Ar H's), 8.5 (s, 2 H, heteroaromatic H's), 10.0 (bs, OH); MS (m/e) 272 (M$^+$, 0.8%), 254 (0.2%), 228 (17.3%), 137 (9.7%), 91 (100%); IR (KBr) 3350 (b), 2980, 2500 (b), 1700 cm^{-1}.

2-(1-Carboxy-1-methylethyl)-5-pyrimidinol (4). The carboxylic acid **11** was slurried in ethanol (2 mL) and treated with cyclohexene (110 μL) and palladium hydroxide on carbon (25 mg). The mixture was heated at reflux for 1 h and then filtered through Celite. The filter was rinsed with hot ethanol (2 mL), and the solvents were removed on the rotary evaporator to leave a pale yellow solid. The solid was recrystallized from CH_2CN (1.5 mL) to afford, after drying, the product as a pale yellow solid (26 mg, 39%): mp 162 °C; MS (m/e) 182 (M$^+$, 2.8%), 164 (14.5%), 149 (7.2%), 138 (80.5%), 137 (100%), 136 (32.4%), 135 (18.3%), 123 (47.4%); ^{1}H NMR (DMSO-d_6, 200 MHz), 1.45 (s, 6 H, 2-CH_3's), 3.34 (bs, 1 H, OH), 8.27 (s, 2 H, heteroaromatic H's), 11.0 (bs, 1 H, OH); IR (KBr) 3360 (b), 1690 cm^{-1}. HRMS, m/e, exact mass calcd for $C_8H_{10}N_2O_3$: 182.0691. Found: 182.0694.

(Benzyloxy)acetamide (13). (Benzyloxy)acetyl chloride (**12**, 25 g, 0.136 mol) was dissolved in CH_2Cl_2 (85 mL) and added dropwise to a concentrated solution of NH_4OH (43 mL) in CH_2Cl_2 (85 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then warmed to room temperature and stirred for 16 h. The reaction mixture was transferred to a separatory funnel, and the CH_2Cl_2 layer was removed. The CH_2Cl_2 layer was dried ($MgSO_4$),

and the solvent was removed on the rotary evaporator with additional drying at 1.0 mmHg (room temperature) for 1.5 h to provide a fluffy white solid (22.3 g, 99% yield): mp 85–87 °C [lit. 89–91 °C (Quarterman, 1955)]; ^{1}H NMR (90 MHz, $CDCl_3$) 3.9 (s, 2 H, $COCH_2O$), 4.6 (s, 2 H, OCH_2Ph), 6.3–7.0 (bs, 2 H, NH_2), 7.3 (s, 5 H, Ar *H*'s); IR (KBr) 3200–3050, 1660 cm^{-1}.

(Benzyloxy)acetonitrile (14). Amide **13** (22.0 g, 0.133 mol) was dissolved in CH_3CN (170 mL) and treated with $POCl_3$ (17 mL). The mixture was heated at reflux under a $CaSO_4$ drying tube for 3 h and then cooled to room temperature and allowed to stand for an additional 15 h. The CH_3CN was removed on the rotary evaporator, resulting in an oil. The oil was dissolved in ether (100 mL) and cooled to 0 °C. Water (50 mL) was added, and the mixture was stirred at 0 °C for 20 min and then at room temperature for 20 min. The organic phase was removed and placed on the rotary evaporator, resulting in a two-phase oil. The oil was filtered through silica gel (200 g, 230–400 mesh) with ether (500 mL). The ether was removed on the rotary evaporator. The residual oil was dissolved in CH_2Cl_2 (100 mL), dried (Na_2SO_4/$MgSO_4$), and filtered and the CH_2Cl_2 removed on the rotary evaporator with final drying at 1.0 mmHg (room temperature) for 1 h to provide the product as a yellow liquid (15.4 g, 79%): ^{1}H NMR (90 MHz, $CDCl_3$) 4.15 (s, 2 H, OCH_2CN), 4.65 (s, 2 H, OCH_2Ph), 7.35 (s, 5 H, Ar *H*'s); IR (film) 2245 (weak) cm^{-1}.

5-(Benzyloxy)-2-(hydroxymethyl)pyrimidine (15). The nitrile **14** (5 g, 34 mmol) was dissolved in toluene (21 mL) and ethanol (2.5 mL) in a 50-mL ampule. The ampule was cooled to −78 °C (CH_2Cl_2/dry ice), HCl gas was sparged into the reaction mixture for 15 min, and then the ampule was sealed. (NOTE: Prior to the ampule being sealed, the reaction was allowed to warm slightly, at which point HCl gas came out of solution causing the loss of approximately half of the reaction mixture.) The sealed ampule was warmed to room temperature and then stirred at 50 °C for 20 h. The resulting mixture was cooled to −78 °C and opened. The reaction was stirred at room temperature until all effervescing had ceased. The resulting mixture was transferred to a flask by using CH_2Cl_2 and CH_3OH. The solvents were removed on the rotary evaporator to provide a yellow solid. The solid was triturated with hexane and filtered, and the precipitate was dried at 1.0 mmHg overnight, yielding a light yellow solid. The solid was dissolved in CH_3OH (50 mL). Gaseous NH_3 was sparged into the solution for 20 min at room temperature. The resulting mixture was stirred at room temperature for 1.5 h. The solvents were removed on the rotary evaporator, resulting in an off-white solid. The solid and *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate (1.1 g, 3.3 mmol) were combined with K_2CO_3 (1.7 g) and anhydrous CH_3CN (20 mL). The mixture was refluxed for 4 h. The CH_3CN was removed on the rotary evaporator, resulting in a brown oil that was partitioned between H_2O (50 mL) and ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated, aqueous brine (2 × 50 mL), dried with $MgSO_4$, and evaporated on the rotary evaporator. The resulting brown mixture was chromatographed on silica gel (230–400 mesh) wih a 2/1 ethyl acetate/hexane eluent to provide the product as a light yellow solid (345 mg): mp 73–75 °C; MS (70 eV, DEP) 216 (M^+, 7.2%), 91 (100%), 65 (9.1%); ^{1}H NMR (90 MHz, $CDCl_3$) 3.5 (bt, 1 H, O*H*), 4.8 (bd, 2 H, *J* = 3 Hz, CH_2OH), 5.2 (s, 2 H, OCH_2Ph), 8.5 (s, 5 H, Ar *H*'s), 8.5 (s, 2 H, pyrimidine *H*'s); IR (KBr) 3320 (b) cm^{-1}.

2-(Hydroxymethyl)-5-pyrimidinol (16). Pyrimidine **15** (265 mg, 1.23 mmol) was dissolved in EtOH (5 mL) and combined with $Pd(OH)_2$ (100 mg, 20% on carbon) and cyclohexene (370 μL, 3.7 mmol). The reaction was refluxed. After 1 h, TLC (3/1 ethyl acetate/hexane) indicated that no reaction had occurred. Therefore, 200 mg of $Pd(OH)_2$ and 2 mL of cyclohexene were added, and the reaction was refluxed for an additional 2 h, at which time TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite and the filter washed with EtOH (20 mL). The EtOH was removed from the mixture on the rotary evaporator to provide a light yellow-green liquid (150 mg, 100% yield): MS (70 eV, DEP) 126 (3%), 126 (69%, M^+), 125 (40%), 97 (100%); IR (KBr) 3410 (b) cm^{-1}; ^{1}H NMR (90 MHz, DMSO) 5.7 (bs, 2 H, CH_2OH), 8.5 (s 2 H, pyrimidine *H*'s).

***O,O*-Diethyl *O*-[2-(Hydroxymethyl)-5-pyrimidinyl] Phosphorothioate (3).** Pyrimidinol **16** (150 mg, 1.23 mmol) was combined with anhydrous CH_3CN (7 mL), K_2CO_3 (509 mg, 3.7 mmol), and diethyl chlorothiophosphate (232 μL, 1.48 mmol) and refluxed at 80 °C for 1.5 h. Upon completion, the CH_3CN was evaporated with a stream of N_2 gas. The resulting mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The H_2O layer was washed with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layers were filtered through Na_2SO_4 and $MgSO_4$. The solvents were removed on the rotary evaporator. The resulting oil was chromatographed on silica gel (230–400 mesh) by using 10/1 CH_2Cl_2/ethyl acetate, affording the product as a light yellow liquid (177 mg, 53% yield from **4**): IR (film) prominent peaks at 3420 (broad) and 2980 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 1.4 (t, 6 H, *J* = 8 Hz, OCH_2CH_3), 3.6 (bs, 1 H, O*H*), 4.3 (m, 4 H, OCH_2CH_3), 5.85 (s, 2 H, CH_2OH), 8.7 (s, 2 H, pyrimidine *H*'s); MS (70 eV, DEP) 278 (91%, M^+), 249 (59%), 221 (24%), 125 (38%), 109 (48%), 97 (100%). HRMS, *m/e*, exact mass calcd for $C_9H_{15}N_2O_4PS$: 278.0490. Found: 278.0495.

2-[(Carbethoxy)methyl]-5-(benzyloxy)pyrimidine (18) and 2-Amino-5-(benzyloxy)-3-carbethoxypyridine (19). Ethyl cyanoacetate (**17**, 21.3 mL, 0.2 mol) was dissolved in EtOH (20 mL) in a flask connected to a NaOH trap. HCl gas was sparged into the stirring mixture for 1.25 h while the reaction temperature was maintained below 40 °C. The resulting mixture was heated at 50 °C for 1 h, at which point a white precipitate formed. The reaction was cooled to room temperature and placed on the rotary evaporator to leave a white solid. NH_3 gas (5.1 g) was sparged into EtOH (100 mL) at room temperature. The NH_3/EtOH solution was then added dropwise to the aforementioned white solid dissolved in EtOH (100 mL). The reaction temperature was kept at or below 25 °C. The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 13 h to produce a precipitate. The mixture was filtered, and the filtrate was evaporated on the rotary evaporator (40 °C water bath), resulting in a brown oil (26.66 g, 0.2 mol). This oil (4.5 g, 34.7 mmol) was combined with *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate (10.5 g, 31.6 mmol), K_2CO_3 (7.4 g), and anhydrous CH_3CN (150 mL). The mixture was refluxed at 90 °C for 4 h and then cooled to room temperature. The solvents were removed on the rotary evaporator to leave a dark brown oil. The oil was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The H_2O layer was washed with an additional 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$) and filtered, and the solvent was removed on the rotary evaporator. The resulting oil was chromatographed on silica gel (70–230 mesh) with 3/1 hexane/ethyl acetate as the eluent. All fractions containing only **18** (by TLC) were combined and placed on the rotary evaporator to provide a yellow oil. All fractions with a mixture of **18** and **19** were combined, and the solvents were removed on the rotary evaporator to leave an oil that was then dissolved in ether (50 mL) and washed with 1 N HCl (3 × 5 mL). The ether layer was dried ($MgSO_4$), filtered, and placed on the rotary evaporator to yield only **18**. The two quantities of **18** were combined in a tared flask, and solvent was removed on the rotary evaporator with additional drying at 0.5 mmHg for 1 h, resulting in a light orange oil that, upon refrigeration overnight, formed yellow crystals (2.96 g, 10.9 mmol, 34% yield). The reaction also resulted in a significant amount of **19** (600 mg) as yellow crystals.

Data for **18**: IR spectrum showed a broad set of peaks from 2860 to 3120 cm^{-1} and a very prominent peak at 1730 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_2$) 1.2 (t, 3 H, *J* = 7 Hz, CH_3CH_2O), 3.95 (s, 2 H, $CH_3CH_2CO_2CH_2$), 4.2 (q, 2 H, *J* = 7 Hz, CH_3CH_2O), 5.1 (s, 2 H, OCH_2Ph), 7.4 (s, 5 H, Ar*H*'s), 8.4 (s, 2 H, pyrimidinyl *H*'s).

Data for **19**: IR spectrum showed a broad set of peaks from 2860 to 3540 cm^{-1} and prominent peaks at 1690 and 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 1.4 (t, 3 H, *J* = 8 Hz, OCH_2CH_3), 4.3 (q, 2 H, *J* = 8 Hz, OCH_2CH_3), 5.0 (s, 2 H, OCH_2Ph), 6.1 (bs, 2 H, NH_2), 7.4 (s, 5 H, Ar *H*'s), 7.8 (d, 1 H, *J* = 3 Hz, pyridine *H*), 8.1 (d, 1 H, *J* = 3 Hz, pyridine *H*).

2-(2-Methyl-1-propenyl)-5-(benzyloxy)pyrimidine (21). 3,3-Dimethylacrylonitrile (**20**, 2.5 g, 30.9 mmol) was dissolved in CH_3OH (30 mL). The resulting solution was sparged with anhydrous HCl gas for 1 h while the reaction temperature was maintained below 40 °C. The mixture was stirred at 50 °C for 1 h and then at room temperature for 18 h. The resulting mixture was placed on the rotary evaporator to leave a yellow-green oil. Anhydrous

NH_3 was sparged into CH_3OH (30 mL) for 20 min. The NH_3/CH_3OH solution was added dropwise to the previously mentioned yellow-green oil in CH_3OH (30 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 2 h. Excess solvents were removed on the rotary evaporator to provide an off-white solid. The solid was dissolved in anhydrous CH_3CN (50 mL) and combined with K_2CO_3 (2.9 g, 20.8 mmol) and *N*-[3-(dimethylamino)-2-(benzyloxy)-2-propylidene]-*N*-methylmethaminium perchlorate (2.5 g, 10.4 mmol). The mixture was refluxed for 4 h and cooled to room temperature, and the CH_3CN was removed on the rotary evaporator. The resulting mixture was partitioned between H_2O (100 mL) and Et_2O (100 mL). The aqueous layer was washed with additional Et_2O (2 × 100 mL). The Et_2O layers were combined, dried ($MgSO_4$), filtered, and placed on the rotary evaporator to remove the Et_2O. The resulting brown solid was dissolved in CH_2Cl_2 and chromatographed on silica gel (230–400 mesh, 10/1 hexane/EtOAc), providing the product as a white solid (826 mg, 3.4 mmol, 11% yield): mp 73–74 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) 1.9 (s, 3 H, CH_3), 2.2 (s, 3 H, CH_3), 5.1 (s, 2 H, CH_2Ph), 6.4 (bs, 1 H, olefin *H*), 7.4 (s, 5 *H*, Ph *H*'s), 8.4 (s, 2 H, pyrimidine *H*'s); IR showed prominent peaks at 1690, 2910, 2970, and 3040 cm^{-1}; MS (70 eV, EI) 240 (22.7%, M$^+$), 149 (51.6%), 120 (13.6%), 91 (100%).

2-(2-Hydroxy-2-methylpropyl)-5-(benzyloxy)pyrimidine (23). Mercuric acetate (1.1 g, 3.4 mmol) was dissolved in H_2O (5 mL), and THF (5 mL) was added, causing the solution to become yellow. To this solution was added the olefin **21** (826 mg, 3.4 mmol). The mixture was stirred at room temperature for 2 h, at which point the reaction became colorless. $NaBH_4$ (65 mg, 1.7 mmol) was dissolved in 2.5 M NaOH (4 mL) and added dropwise to the reaction mixture. Saturated, aqueous brine was added to the resulting mixture, which was then extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and dried ($MgSO_4$), and the solvent was removed on the rotary evaporator with additional drying at 1 mmHg for 18 h to afford a light yellow oil. The oil was dissolved in CH_2Cl_2 (6 mL) and chromatographed on silica gel (230–400 mesh) by using 1/1 hexane/ethyl acetate to provide the product as a clear colorless oil (738 mg, 2.86 mmol, 84% yield): ^{1}H NMR ($CDCl_3$, 90 MHz) 1.3 [s, 6 H, $(CH_3)_2$], 3.1 (s, 2 H, CH_2 pyrimidine), 5.2 (s, 2 H, CH_2Ph), 7.4 (s, 5 H, aromatic *H*'s), 8.4 (s, 2 H, pyrimidine *H*'s); IR (KBr) 2990, 3430 cm^{-1}; MS (70 eV, EI) 259 (0.2%), 258 (0.2%, M$^+$), 200 (40.8%), 109 (44.1%), 91 (100%).

***O,O*-Diethyl *O*-[(2-Hydroxy-2-methylpropyl)-5-pyrimidinyl] Phosphorothioate (5).** The (benzyloxy)pyrimidine **23** (738 mg, 2.86 mmol) was dissolved in EtOH (20 mL). Cyclohexene (875 μL, 8.6 mmol) and $Pd(OH)_2$ (290 mg) were added, and the mixture was refluxed for 1.5 h, at which point the reaction was complete as determined by TLC (1/1 hexane/ethyl acetate). The resulting mixture was filtered hot through Celite and the filter rinsed with 10 mL of EtOH. The EtOH was removed on the rotary evaporator (30 °C water bath) with additional drying at 1.0 mmHg for 0.5 h. The resulting yellow oil was dissolved in CH_3CN (30 mL) and combined with diethyl chlorothiophosphate (906 μL, 5.7 mmol) and K_2CO_3 (1.2 g, 8.6 mmol). This mixture was refluxed at 80 °C for 3 h and then cooled to room temperature. The CH_3CN was removed on the rotary evaporator. The resulting mixture was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted further with 2 × 50 mL of CH_2Cl_2. The CH_2Cl_2 layers were combined and dried, and the solvent was removed on the rotary evaporator. The resulting brown oil was chromatographed on silica gel (230–400 mesh) using 2/1 hexane/ethyl acetate as the eluent. The 97+% pure fractions by TLC and GC were combined, and the solvents were removed on the rotary evaporator to provide the product as a yellow oil (507 mg, 1.58 mmol, 55.2% yield): ^{1}H NMR (90 MHz, $CDCl_3$) 1.4 [t, 12 H, J = 6 Hz, $C(CH_3)_2$ and $(OCH_2CH_3)_2$], 3.2 (s, 2 H, CH_2 pyrimidine), 4.3 [m, 4 H, $(OCH_2CH_3)_2$], 4.9 (bs, 1 H, O*H*), 8.6 (s, 2 H, pyrimidine *H*'s); IR 2980, and 3450 cm^{-1} (broad); MS (70 eV, EI) 321 (15.1%), 320 (3.6%, M$^+$), 305 (19.1%), 262 (100%), 206 (23.7%), 126 (40.3%). HRMS, *m/e*, exact mass calcd for $C_{12}H_{21}N_2O_4PS$: 320.0960. Found: 320.0960.

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