reported in ppm from the central peak of $CDCl_3$ (77.0 ppm) (J values are given in Hz). Assignments were made with the aid of APT data. Combustion analyses were obtained from Microlit Laboratories, Inc., Caldwell, NJ.

5-*O*-(*tert*-Butyldimethylsilyl)-13-*O*-(*p*-toluenesulfonyl)-22,23-dihydroavermectin B_1 Aglycon (2). A 25-mL flask fitted with a nitrogen inlet tube and Teflon-coated stirring bar was charged with 1 (1.28 g, 1.82 mmol), *p*-toluenesulfonic anhydride (1.19 g, 3.65 mmol), *N,N*-diisopropylethylamine (0.95 mL, 0.70 g, 5.5 mmol), DMAP (445 mg, 3.65 mmol), and CH_2Cl_2 (5.1 mL). The resulting solution was stirred at 20 °C for 24 h. (The tosylation can be monitored by removing a 20-μL aliquot, dissolving it in 0.6 mL of $CDCl_3$, obtaining a ^1H NMR, and integrating the signal for H_{13}. H_{13} of 1: 3.98 (br s). H_{13} of 2: 4.82 (br s)). The resulting mixture was cooled to 0 °C, and hexane (10.2 mL) was added followed by aqueous $NaHSO_4$ (10 mL, 1 N) at a rate to maintain the internal temperature at or below 5 °C (~10 min). The resulting pH was ~2. The layers were separated, and the aqueous layer was extracted with 2:1 hexane/CH_2Cl_2 (15 mL). The organic layers were individually washed with 15 mL of saturated aqueous $NaHCO_3$ and 15 mL of water. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to provide 2 (~2 g, impure) as an orange solid. This material was used as is in subsequent reactions after concentrating it from dry toluene (2 × 10 mL).

5-*O*-(*tert*-Butyldimethylsilyl)-13β-nitrooxy-22,23-dihydroavermectin B_1 Aglycon (3). A 25-mL flask fitted with a nitrogen inlet tube and Teflon-coated stirring bar was charged with 2 (~2 g, see above, ~1.82 mmol, crude mixture from previous experimental procedure), tetra-*n*-butylammonium nitrate (1.66 g, 5.45 mmol), and toluene (8 mL). The resulting solution was stirred at 40 °C for 96 h. (The displacement can be monitored by TLC: R_f (starting material) = 0.40; R_f (nitrate ester) = 0.57 in 4:1 hexane/ethyl acetate). The resulting mixture was cooled to 20 °C, concentrated to ~3 mL, and chromatographed twice (5 × 30 cm column; 92:8 hexane/ethyl acetate) to provide 3 (774 mg, 57%). The impurities have slightly higher R_f's than the desired nitrate ester (ΔR_f ~0.07 in 92:8 hexane/ethyl acetate). NMR analysis of the isolated three-component impurity mixture (~5%) was complicated since the individual componenents of this mixture were not readily separable from each other. Data for 3: ^1H NMR δ 5.85 (dd, J = 14.3, 11.4, H_{10}), 5.60 (dt, J = 11.3, 1.9, H_9), 5.42 (m, H_{15}), 5.30 (m, H_3, H_{11}), 5.20 (m, H_{19}),4.95 (d, J = 10.6, H_{13}), 4.65 (dd, J = 14.4, 1.9, H_{8a}), 4.54 (dd, J = 14.4, 1.9, H_{8a}), 4.40 (m, H_5), 4.00 (s, OH), 3.79 (d, J = 5.5, H_6), 3.60 (m, H_{17}), 3.32 (m, H_2), 3.14 (m, H_{25}), 2.55 (m, H_{12}), 2.30 (m, 2 × H_{16}), 1.99 (dd, J = 11.8, 3.6, H_{20eq}), 1.77 (br s, 3 × H_{4a}), 1.55 (s, 3 × H_{14a}), 1.10 (d, J = 6.5, H_{12a}), 0.94 (t, J = 7.3, 3 × H_{28}), 0.90 (s, $SiC(CH_3)_3$), 0.82 (d, J = 6.6, H_{26a}), 0.10 (s, $Si(CH_3)_2$); ^{13}C NMR δ_C 173.6 (C_1), 142.5, 137.5, 133.3 (C_4, C_8, C_{14}), 135.4 (C_{11}), 129.0, 125.5, 118.7, 117.3 (C_3, C_9, C_{10}, C_{15}), 97.5 (C_{21}), 93.1 (C_{13}), 80.2 (C_6), 80.1 (C_7), 77.4 (C_{25}), 69.3, 68.6, 66.6 (C_5, C_{17}, C_{19}), 67.7 (C_{8a}), 45.6 (C_2), 42.3 (C_{20}), 38.3 (C_{12}), 36.6, 35.7, 34.7 (C_{18}, C_{22}, C_{26}), 35.7 (C_{16}), 31.2 (C_{24}), 28.0, 27.5 (C_{23}, C_{27}), 25.6 ($SiC(CH_3)_3$), 20.1, 18.8, 17.5 (C_{4a}, C_{12a}, C_{24a}), 12.6, 11.7, 11.0 (C_{14a}, C_{26a}, C_{28}); MS (EI, 70 eV) 745 (M^+, 5), 503 (18), 307 (30), 225 (30), 223 (32), 195 (70), 151 (72) 137 (72), 95 (100), 75 (70), 73 (80), 69 (66). Anal. Calcd for $C_{40}H_{63}NO_{10}Si$: C, 64.40; H, 8.51; N, 1.88. Found: C, 64.14; H, 8.58; N, 1.79.

5-*O*-(*tert*-Butyldimethylsilyl)-13-*epi*-22,23-dihydroavermectin B_1 Aglycon (4). Zinc (~1 g) was stirred for 5 min in 1 N HCl, filtered, and washed with water (3 × 10 mL; final pH of wash >6), MeOH (2 × 10 mL), and toluene (2 × 5 mL). The resulting material was air dried, and a portion of it was used in the following reduction. A 15-mL flask fitted with a nitrogen inlet tube and Teflon-coated stirring bar was charged with 3 (513 mg, 0.688 mmol), tetrahydrofuran (4.3 mL), and acetic acid (0.7 mL). The solution was stirred in a water bath at 20 °C, and Zn (450 mg, 6.88 mmol, see above) was added in one portion. The resulting suspension was stirred for 10 min as the temperature rose to 25 °C. (The reduction can be monitored by TLC: R_f (nitrate ester) = 0.57; R_f (β-alcohol) = 0.29; R_f (α-alcohol) = 0.19 in 4:1 hexane/ethyl acetate). The resulting mixture was filtered through a coarse glass frit, and the solids were washed with 3 × 7 mL of EtOAc. The washings were combined and cautiously washed with saturated aqueous $NaHCO_3$ (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated, and chromatographed (3 × 30-cm column; 80:20 hexane/ethyl acetate) to provide 4 (425 mg, 88%). The sample of 4 prepared in this manner was identical (TLC, ^1H, ^{13}C NMR) to that previously reported:[2a] ^1H NMR δ 5.75 (m, H_9, H_{10}), 5.30 (m, H_3, H_{11}), 5.20 (m, H_{15}, H_{19}), 4.65 (dd, J = 14.4, 1.9, H_{8a}), 4.54 (dd, J = 14.4, 1.9, H_{8a}), 4.42 (m, H_5), 3.98 (OH), 3.78 (d, J = 5.5, H_6), 3.70 (d, J = 10.0, H_{13}), 3.55 (m, H_{17}), 3.35 (m, H_2), 3.15 (m, H_{25}), 2.35 (m, H_{12}), 1.78 (s, 3 × H_{4a}), 1.55 (s, 3 × H_{14a}), 1.12 (d, J = 6.5, 3 × H_{12a}), 0.94 (t, J = 7.3, 3 × H_{28}), 0.90 (s, $SiC(CH_3)_3$), 0.82 (d, J = 6.6, H_{26a}), 0.10 (s, $Si(CH_3)_2$); ^{13}C NMR δ_C 173.8 (C_1), 140.9, 140.2, 137.4 (C_4, C_8, C_{14}), 138.6 (C_{11}), 123.9, 123.3 (C_9, C_{10}), 119.3, 117.4 (C_3, C_{15}), 97.5 (C_{21}), 83.4 (C_{13}), 80.3 (C_6), 80.1 (C_7), 77.1 (C_{25}), 69.4, 68.7, 67.1 (C_5, C_{17}, C_{19}), 68.0 (C_{8a}), 45.7 (C_2), 41.6 (C_{12}), 41.4 (C_{20}), 36.5, 35.7, 34.5 (C_{16}, C_{18}, C_{22}), 35.5 (C_{26}), 28.1, 27.4 (C_{23}, C_{27}), 25.9 ($SiC(CH_3)_3$)), 20.1, 19.0, 17.5 (C_{4a}, C_{12a}, C_{24a}), 18.4 ($SiC(CH_3)_3$)), 12.5, 11.9, 10.6 (C_{14a}, C_{26a}, C_{28}). Anal. Calcd for $C_{40}H_{64}O_8Si$: C, 68.53; H, 9.20. Found: C, 68.15; H, 9.28.

Acknowledgment. We thank Robert A. Reamer for NMR data on the impurities and E. Tracy Turner Jones and Lawrence F. Colwell for mass spectral data.

Vinylformylation Utilizing Propeniminium Salts

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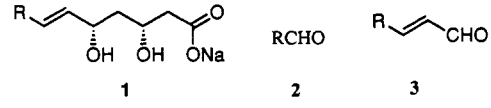
In our efforts to find a practical and efficient method toward a commercial synthesis of dihydroxyheptenoates 1,[1] which are HMG-CoA reductase inhibitors, we investigated two alternative routes. One, a linear strategy,[1] involved the use of dianions derived from acetoacetates and the other, a convergent method,[2] utilized a six-carbon synthon. Trans-α,β-unsaturated aldehydes of the type 3 are used as key intermediates in the linear strategy at Sandoz[1] and by other groups.[3] The need to produce these aldehydes in kilogram quantities led us to a detailed investigation of the Vilsmeier–Haack conditions for vinylformylation, utilizing propeniminium salts as three-carbon synthons.[4]



1 2 3

Earlier reports[5] elaborate on the preparation of α,β-unsaturated aldehydes 3 from aldehydes 2. Concurrent with these studies was a report involving the 2-formylation of substituted indoles.[6] When subjected to $POCl_3$/DMF (Vilsmeier–Haack reagent), 4 gave **4b**, in moderate yield,

(1) Kathawala, F. G. *Med. Res. Rev.* **1991**, *11*, 121 and references cited therein.

(2) (a) Prasad, K.; Chen, K. M.; Repič, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 307–310, and references cited therein. (b) Lee, G. T.; Linder, J.; Chen, K.-M.; Prasad, K.; Repič, O.; Hardtmann, G. E. *SynLett* **1990**, 508.

(3) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L.; Wiggins, J. M. *J. Med. Chem.* **1990**, *33*, 758–765, and references cited therein.

(4) Liebschler, J.; Hardtmann, H. *Synthesis* **1979**, 241.

(5) (a) Kathawala, F. G. World Pat. 1984, 02131; (b) Kathawala, F. G.; Wattanasin, S. World Pat. 1986, 03488.

(6) Walkup, R. E.; Linder, J. *Tetrahedron Lett.* **1985**, *26*, 2155–2158.

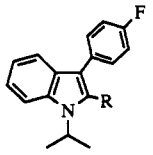
0022-3263/92/1957-3250$03.00/0

Table I. Vinylformylation Utilizing 7

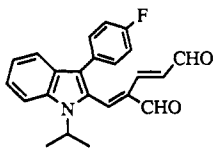
substrate	product (yield, %)	substrate	product (yield, %)
4	**4a** (83[a]) (75[b])	9	**9a** (70[a,c]) (65[b])
8	**8a** (97[a]) (73[b])	10	**10a** (56[a,c])
		11	no reaction

[a] Chromatographed yield. [b] Recrystallized yield. [c] TMP added.

as well as the 5- and 7-formylated regioisomers. This observation was extended to the synthesis of α,β-unsaturated aldehyde **4a** from **4** using (*N,N*-dimethylamino)-acrolein and $POCl_3$.[5a]



4 R = H
4a R = CH=CH-CHO
4b R = CHO

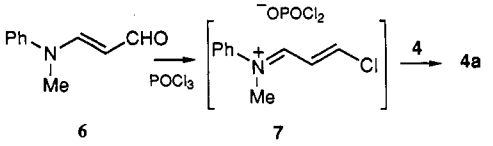


5

Initial large scale preparation of **4a** began with (*N,N*-dimethylamino)acrolein,[7] which is expensive and not readily available. Although we developed an efficient in-house synthesis of this reagent, we quickly realized the limitations of using it on a large scale. The main drawback of (*N,N*-dimethylamino)acrolein is its instability under Vilsmeier–Haack reaction conditions. In order to obtain pure product, chromatography was required. For these reasons, we tried alternative reagents and found that the iminium salt **7**, formed from 3-(*N*-methyl-*N*-phenylamino)acrolein (**6**) and $POCl_3$ reacted smoothly with **4** to give **4a** (Scheme I).[8] A simplified workup, relative to the dimethylamino analogue, was found to be an added advantage. The reaction required just a water quench, and the precipitated product was isolated by filtration, followed by recrystallization.

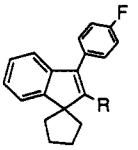
The preparation of **6** had been reported utilizing phosgene, *N*-methyl-*N*-phenylformamide, and ethyl vinyl ether as reagents in dichloromethane.[7b] We modified the above method by using oxalyl chloride and butyl vinyl ether in acetonitrile. With the capability of readily preparing **6** and successfully vinylformylating indole **4** to **4a** on a large scale, we turned our attention to extending these conditions to compounds **8–11** (see Table I). Indene **8**,[5b] when treated with **6**/$POCl_3$ gave a 97% chromatographed yield of **8a** (73% recrystallized). The vinylformylation of pyrimidine **9** proceeded in poor yield[9,10] under the above conditions. We found that with the addition of *sym*-tetramethylpyrazine (TMP), the yield of **9a** dramatically improved to 70%. With TMP, also pyrimidine **10** gave the corresponding vinyl aldehyde **10a** in good yield.[11,12] The role of TMP can be postulated to be a scavenger for HCl and it successfully competes for the proton with starting pyrimidine due to a favorable pK_a. In the absence of TMP, it is presumed that the (dimethylamino)pyrimidine functionality gets protonated, thus diminishing the reactivity

Scheme I

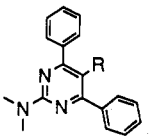


6 **7**

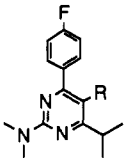
of the aromatic ring towards electrophilic attack. The reaction between **11** and **6**/$POCl_3$ gave no desired product, suggesting that the present vinylformylation method is not applicable to unactivated aromatic systems.



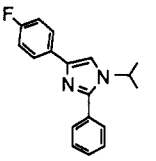
8 R = H
8a R = CH=CH-CHO



10 R = H
10a R = CH=CH-CHO



9 R = H
9a R = CH=CH-CHO



11

Recently, we discovered that reagents of the type **12** (Scheme II), which are intermediates in the preparation of aminoacroleins, when activated with additional amounts of $POCl_3$, could be used directly for vinylformylation of **4**. This eliminates the need for the isolation of β-aminoacroleins.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 300 MHz with Me_4Si as internal standard. IR spectra were measured on KBr pellets.

3-(*N*-Methyl-*N*-phenylamino)acrolein (MPAA) (6). To a precooled (−10 °C) solution of oxalyl chloride (1.056 kg, 8.15 mol, 1.1 equiv) and CH_3CN (480 mL) was added a mixture of *N*-methylformanilide (1.02 kg, 7.39 mol) and butyl vinyl ether (816 g, 7.98 mol, 1.07 equiv) in CH_3CN over 2.5 h while maintaining an internal temperature of −5 to −10 °C. The reaction mixture was warmed to 20 °C over 0.5 h and stirring was allowed to continue for 1 h. The reaction contents were cooled to 0 °C, and a solution of Na_2CO_3 (948 g, 8.94 mol, 1.2 equiv) in water (4.2 L) was added over 45 to 60 min while maintaining an internal temperature of 8–10 °C. Toluene (3.6 L) was added and the solution was stirred at 20–22 °C for 15 min. The solution was allowed to settle for 15 min. The layers were separated and the toluene layer was washed with water (2 × 360 mL). The combined toluene layers were concentrated in vacuo to give 1.16 kg (88%) of a thick stirrable oil.

Purification of 6. The crude 3-(*N*-methyl-*N*-phenylamino)acrolein (MPAA) (1.0 kg, 86.6% purity) was dissolved in 2-propanol (IPA) (445 mL) at 45–50 °C. Hexane (815 mL) was added with continuous stirring. The mixture was cooled to 0 °C over 0.5 h under vigorous agitation. A few seed crystals of MPAA were added and the slurry was further chilled to −15 °C for 1 h. The solid was collected by rapid suction filtration at −10 °C. The product was washed with a cold (−10 °C) solution of IPA/hexane (35/65, 2 × 200 mL). Drying to a constant weight yielded pure **6** (723 g, 82.3%): mp 44–45 °C; IR (KBr) 1641, 1495, 1366, 1159

(7) Some reported preparations of (dimethylamino)acrolein: (a) Arnold, Z.; Sorm, F. Czech. Pat. 90045 (*Chem. Abstr.* **1962**, *27*, 4621). (b) Instituto Chemioterapio Italiano S.p.A. Brit. Pat. 945,536 (*Chem. Abstr.* **1964**, *33*, 10550).

(8) Chen, K.-M.; Kapa, P.; Lee, G. T.; Repič, O.; Hess, P.; Crevoisier, M. Eur. Pat. 363934.

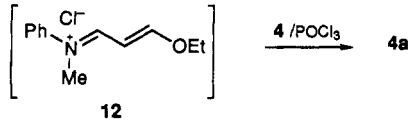
(9) Kucerovy, A.; Mattner, P. G.; Hathaway, S.; Repič, O. *Synth. Commun.* **1990**, *20*, 913–917.

(10) Kucerovy, A.; Mattner, P. G.; Hathaway, S. Unpublished results.

(11) Tetramethylpyrazine was found as a useful additive with selected pyrimidines only.

(12) Tetramethylpyrazine (2.2 equiv) was added as a solution in CH_3CN along with **9** or **10**.

Scheme II



12

cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 190.2, 156.2, 146.0, 129.6, 125.4, 120.5, 105.5, 37.4; MS m/z (NH_3/DCI) 162 (M + 1$^+$). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.42; H, 6.88; N, 8.72.

3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-2(*E*)-propenal (4a). A solution of $POCl_3$ (454 g, 2.96 mol, 2.5 equiv) in CH_3CN (263 mL) was cooled to −5 °C. Crude **6** (471.6 g, 2.49 mol, 2.1 equiv) in CH_3CN (406 mL) was added over a period of 45 min, while maintaining an internal temperature of 5–7 °C. The mixture was stirred at 5–7 °C for 10 min followed by the addition of **4** (300 g, 1.18 mol) over a period of 10 min and then heated to reflux (83 °C) for 3 h. The reaction mixture was cooled to 22 °C and water (2.7 L) was slowly added over 15 min. The mixture was stirred at 35–50 °C for 0.5 h and then heated to 50–55 °C for 1.5 h. After the solution was cooled to 22 °C and stirred for 15 min, the solids were collected by vacuum filtration, washed with water (3 × 600 mL), and vacuum dried for 6 h. Toluene (2.5 L) and cellulose (180 g) were added to the dry solids, and the solution was heated to 50–55 °C for 1.5 h. The slurry was cooled to 22 °C and filtered, washing with toluene (3 × 200 mL). The combined toluene fractions were concentrated in vacuo to give a crude oil. The oil was dissolved in 95% EtOH (280 mL) and concentrated in vacuo. This operation was repeated. The oil was once again dissolved in 95% EtOH (700 mL) and warmed to 78 °C for 15 min, followed by slow cooling to room temperature and then to 0 °C (over 1 h). The solids were collected by suction filtration, washed with cold (0 °C) 95% EtOH (3 × 120 mL), and dried to a constant weight to give **4a** (276.6 g, 75%). Purification was also achieved by column chromatography utilizing EtOAc/hexane as the solvent on SiO_2: mp 129–130 °C; IR (KBr) 1675 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 193.1, 163.9, 160.6, 140.8, 137.5, 131.9, 131.8, 130.4, 129.9, 129.5, 128.4, 124.6, 122.6, 120.9, 115.7, 112.4, 48.2, 21.7; MS m/z (NH_3/DCI) 308 (M + 1$^+$). Anal. Calcd for $C_{20}H_{18}FNO$: C, 78.15; H, 5.90; N, 4.56. Found: C, 78.13; H, 5.90; N, 4.57.

3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-2(*E*)-propenal (4a) (in Situ Procedure). A mixture of oxalyl chloride (330 mL, 3.78 mol, 3.0 equiv) and $POCl_3$ (383 mL, 3.99 mol, 3.1 equiv) was cooled to −10 °C, followed by the addition of a solution of ethyl vinyl ether (355 mL, 3.72 mol, 2.9 equiv) and *N*-methylformanilide (416 mL, 3.37 mol, 2.9 equiv) over 60 to 70 min while maintaining an internal temperature of −5 to −7 °C. The mixture was warmed to 35–40 °C over 30 min and then allowed to stir between 40 and 45 °C for 30 min. The unreacted volatiles were removed at 45–50 °C (40–100 mmHg) over 30 min. The reaction mixture was cooled to 35–40 °C and **4** (334 g, 1.28 mol) and CH_3CN (250 mL) were added. The solution was refluxed (92 °C) for 5.0 h, cooled to 75 °C, and diluted with CH_3CN (400 mL) and water (2.73 L) while maintaining an internal temperature of 35–40 °C. The reaction mixture was heated to 50–55 °C for 1.5 h and then cooled to 22 °C and stirred for 16 h. The solids were collected by filtration and processed as in the previous experiment to give **4a** (258 g, 61%).

3-[3-(4′-Fluorophenyl)spiro[cyclopentane-1,1′-[1*H*]-inden]-1′-yl]-2(*E*)-propenal (8a). A solution of $POCl_3$ (227 g, 2.4 mol, 2.9 equiv) in CH_3CN (175 mL) was cooled between 0 and 5 °C. Reagent **6** (382 g, 2.1 mol, 2.5 equiv) dissolved in CH_3CN (545 mL) was added while maintaining an internal temperature of 0–5 °C. Compound **8** (417.7 g, 0.834 mol) in CH_3CN (280 mL) was added over 5 min. The reaction mixture was heated to reflux (60 °C) for 2 h and then cooled to 40 °C. Celite (450 g) was added, and the solution was stirred for 10 min. Water (4.0 L) was added and the reaction mixture was stirred at 50–55 °C for 1.5 h, cooled to room temperature, and stirred overnight. The solids were collected by suction filtration, washed with water (4.0 L), and dried (25–30 mmHg, rt) overnight. Toluene (3 L) and cellulose (180 g) were added to the solids, and the solution was stirred at 50–55 °C for 1.5 h, cooled to room temperature, and filtered through SiO_2 (420 g). The SiO_2-cellulose pad was washed with toluene (6 L). The toluene filtrates were combined and concentrated in vacuo to give a crude oil. The oil was dissolved in IPA (200 mL) and concentrated in vacuo. Solids were redissolved in IPA (1.4 L) and heated to reflux (82 °C) for 15 min. The mixture was allowed to cool to room temperature and stirred overnight. The solids were collected by suction filtration and dried to a constant weight to give crude **8a** (222.8 g, first recrystallization). Crude **8a** was dissolved in heptane (2.23 L) and refluxed (95 °C) for 15 min, cooled to room temperature, and stirred overnight. The solid was collected by suction filtration, washed with heptane (450 mL), and dried as above to give **8a** (156.4 g). The mother liquors were combined and concentrated in vacuo to give a crude slurry. Product was isolated by recrystallization (as above) to give **8a** (37.4 g, total 193.8 g, 73% yield): mp 120–122 °C; IR (KBr) 1677 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 194.5, 163.9, 161.9, 159.1, 150.1, 145.1, 144.5, 140.8, 131.4, 129.6, 128.5, 128.3, 126.8, 122.1, 116.06, 59.6, 36.2, 27.5; MS m/z (isobutane/DCI) 319 (M + 1$^+$). Anal. Calcd for $C_{22}H_{19}FO$: C, 82.99; H, 6.01. Found: C, 82.90; H, 5.98.

3-[2-(*N*,*N*-Dimethylamino)-4-(4-fluorophenyl)-6-(1-methylethyl)pyrimidin-5-yl]-2(*E*)-propenal (9a). A solution of $POCl_3$ (325.2 g, 2.12 mol, 2.2 equiv) in CH_3CN (175 mL) was cooled to between 0 and 5 °C. A solution of **6** (343 g, 2.12 mol, 2.2 equiv) in CH_3CN (175 mL) was added while maintaining an internal temperature of 0–10 °C. The reaction was stirred for 0.5 h. A solution of **9** (250 g, 2.12 mol, 2.2 equiv) and *sym*-tetramethylpyrazine (288.9 g, 2.12 mol, 2.2 equiv) in CH_3CN (500 mL) was added while maintaining an internal temperature of 5–10 °C. The reaction mixture was heated to 55–60 °C for 4 h, cooled to 30–35 °C, diluted with water (3.5 L), filtered, washed with water (1.2 L), and dried. Toluene (2.0 L) and cellulose (150 g) were added to the solids, and the solution was heated to 50–55 °C for 2.5 h. The reaction mixture was filtered and washed with toluene (1.0 L). The combined toluene filtrates were concentrated in vacuo to give a slurry. The slurry was dissolved in 95% EtOH (600 mL) and concentrated in vacuo. This was repeated twice. The crude slurry was dissolved in 95% EtOH (800 mL) (water bath at 70 °C) and cooled to 0 °C for 1 h. Solids were collected, washed with cold (0 °C) 95% ethanol (300 mL), and dried to a constant weight to give **9a** (176 g). The mother liquors were combined and concentrated in vacuo. Recrystallization as above gave **9a** (20 g, 196 g total, 65% yield). Purification by column chromatography was achieved utilizing EtOAc/hexane on SiO_2: mp 109–110 °C; IR (KBr) 1677 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 193.3, 175.0, 166.1, 164.9, 161.7, 160.6, 149,0, 135.3, 135.2, 131.4, 131.3, 131.2, 115.4, 115.1, 111.8, 36.7, 31.8, 21.6; MS m/z (NH_3/DCI) 314 (M + 1$^+$). Anal. Calcd for $C_{18}H_{20}FN_3O$: C, 68.99; H, 6.43; N, 13.41. Found: C, 68.69; H, 6.45; N, 13.16.

3-[2-(*N*,*N*-Dimethylamino)-4,6-diphenylpyrimidin-5-yl]-2(*E*)-propenal (10a). A solution of $POCl_3$ (1.5 mL, 15.99 mmol, 2.2 equiv) in CH_3CN (2.0 mL) was cooled to 0 to 5 °C. A solution of **6** (2.6 g, 15.99 mmol, 2.2 equiv), **10** (2.0 g, 7.27 mmol), and *sym*-tetramethylpyrazine (2.2 g, 15.99 mmol, 2.2 equiv) in CH_3CN (10 mL) were added while maintaining an internal temperature of 0–5 °C. The reaction mixture was refluxed for 15 h, cooled to room temperature, and diluted with water (15 mL). The mixture was stirred at 60 °C for 2 h, cooled to room temperature, and stirred for an additional 10 h. Toluene (40 mL) was added, and the solution was stirred for 0.5 h. The layers were separated and the aqueous layer was washed with EtOAc/heptane (1:1, 3 × 25 mL). The combined organic phases were concentrated in vacuo to give a crude oil. Purification by column chromatography was achieved using SiO_2 with an EtOAc/hexane solvent system to give **10a** (1.3 g, 56%): mp 197–198 °C; IR (KBr) 1674 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 193.4, 168.5, 160.5, 149.6, 139.1, 130.8, 129.6, 129.2, 128.5, 112.2, 37.0; MS m/z (NH_3/DCI) 330 (M + 1$^+$). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.80; H, 5.90; N, 12.50.

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