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Stereoselective Synthesis of MLN4924, an Inhibitor of NEDD8-Activating Enzyme

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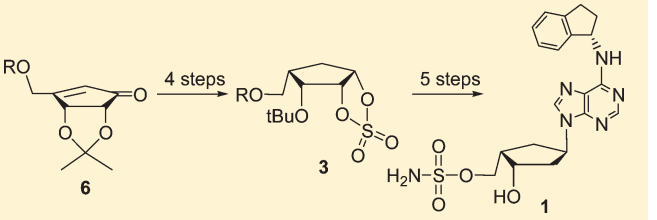
Supporting Information

ABSTRACT: MLN4924 (**1**), which is in clinical trials as an anticancer agent, was stereoselectively synthesized from D-ribose via a route involving stereoselective reduction, regioselective cleavage of an isopropylidene moiety, and selective displacement of a cyclic sulfate moiety as key steps.



The ubiquitin-proteasome system (UPS) plays an important role in the conjugation pathway, which appends ubiquitin to proteins targeted for regulated degradation.[1] The ubiquitinylation pathway is composed of three enzymatic steps (i.e., E1: ubiquitin-activating enzyme, E2: ubiquitin-conjugating enzyme (UBC), and E3: ubiquitin-protein isopeptide ligase).[2] A pathway similar to ubiquitinylation that employs the ubiquitin-like protein NEDD8 (neural precursor cell-expressed developmentally down-regulated 8) has also been identified.[3,4] In the first step, NEDD8 is activated by an E1 enzyme (NEDD8 activating enzyme, NAE). NEDD8 is then transferred to an E2 enzyme (UBC12), and is subsequently conjugated to the protein targeted for degradation. In this pathway, NAE plays an essential role in regulating the activity of cullin-RING (really interesting new gene) ubiquitin ligases, whose substrates play important roles in cellular processes associated with cancer cell growth.[5] Thus NAE is a new target for the development of novel anticancer agents.

MLN4924 (**1**)[6] is a potent and selective inhibitor of NAE and is currently being investigated in phase I clinical trials as an anticancer agent for both solid tumor and hematological malignancies (Figure 1). MLN4924 mimics adenosine 5′-monophosphate (**2**, AMP), which is a tight binding product of the reaction NAE catalyzes.[7,8] MLN4924 inhibits the NAE pathway in cells, which results in S-phase defects, DNA damage, and apoptosis.[6] MLN4924 also damages DNA in mice bearing human HCT-116 tumor xenografts.[6]

Despite its potent anticancer activity, the synthesis of MLN4924 has only been described in a single patent.[9] The aforementioned protocol (Scheme 1S in the Supporting Information) started with cyclopentadiene, from which the synthesis of MLN4924 was achieved in 15 steps and 7.1% overall yields.

Due to the importance of the compound, an efficient stereoselective synthesis of MLN4924 under mild conditions and in good overall yields is our immediate goal. Herein, we report a new method for the stereoselective synthesis of MLN4924 from D-ribose. In particular, the key steps in the synthesis include stereoselective reduction, regioselective cleavage of an isopropylidene moiety, and the selective displacement of a cyclic sulfate moiety.

Scheme 1 shows a retrosynthetic analysis of MLN4924 (**1**). MLN 4924 (**1**) was envisioned to arise by condensing the glycosyl donor, cyclic sulfate **3**, with a purine base. Glycosyl donor **3** could be produced from diol **4**, which in turn could be obtained from cyclopentanone **5** via a stereoselective reduction and a regioselective cleavage of the isopropylidene moiety. Cyclopentanone **5** could arise from cyclopentenone **6** via a stereoselective reduction, and intermediate **6** can be easily obtained from D-ribose using our previously published procedure.[10]

Our synthesis begins with cyclopentenone **6**,[10] which was efficiently synthesized from D-ribose in 6 steps (Scheme 2). Catalytic hydrogenation of cyclopentenone **6** with 10% Pd/C gave cyclopentanone **5** in quantitative yield as a single stereoisomer, due to the incorporation of hydrogen from the convex side of the molecule. Luche reduction[11] of ketone **5** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ afforded alcohol **7** as a single diastereomer. The configuration of the newly created asymmetric center in **7** was easily confirmed by NOESY experiments (see the Supporting Information). The NOE effect between H-1 and H-4 in compound **7** was observed, indicating a *cis* relationship. Regioselective cleavage of the acetonide present in **7** was achieved by treatment with trimethylaluminum,[12] which gave diol **4**. Diol **4** was converted to cyclic sulfate **3** by treatment with thionyl chloride and subsequent oxidation with $RuCl_3$ and $NaIO_4$.[13]

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To complete the synthesis of MLN4924 (**1**), glycosyl donor **3** was reacted with the anion of N^6-indanyl-7-deazaadenine in THF (Scheme 3). After hydrolyzing the resulting sulfate, the desired N^9-isomer **8** (65%) was obtained as a single diastereomer.[14] Treatment of **8** with phenyl chlorothionoformate and further reaction with *n*-Bu_3SnH in the presence of AIBN yielded the 2′-deoxygenated derivative **9**. Compound **9** was treated with pyridine·HF to give a 5′-hydroxyl compound **10**, which was treated with chlorosulfonamide to produce the 5′-sulfonamido derivative **11**. The *tert*-butyl group of **11** was removed with 70% TFA to afford MLN4924 (**1**) in 90% yield.

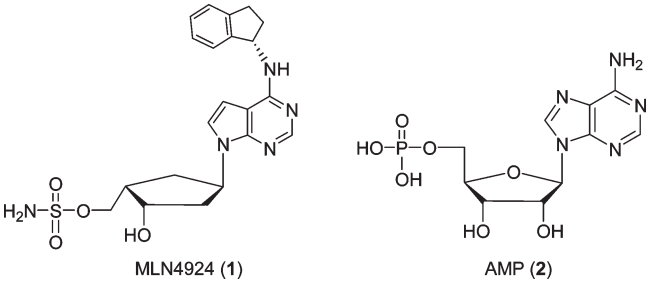
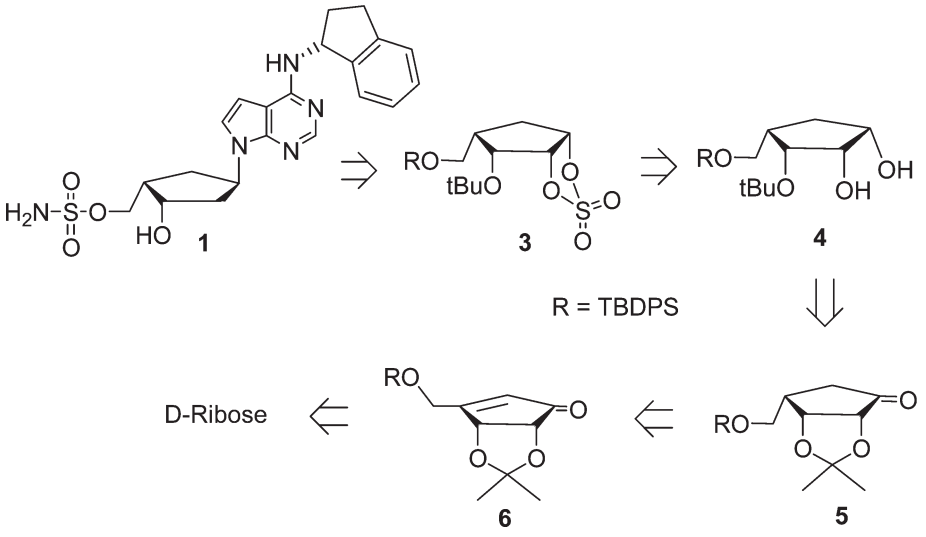


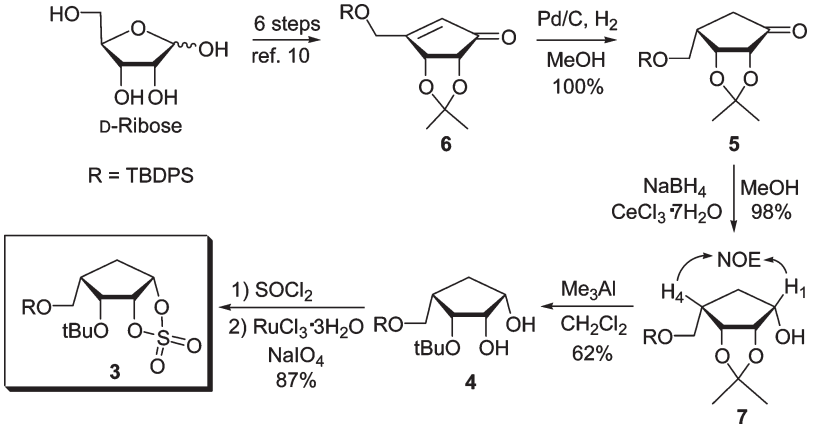
Figure 1. The structure of MLN4924 (**1**), a mimic of AMP.

In summary, we have completed an efficient stereoselective synthesis of MLN4924, a compound in phase I clinical trials as an anticancer agent. Starting from D-ribose, MLN4924 was produced in 15 steps and 11% overall yields under mild conditions. In particular, the key steps of the synthetic sequence included a stereoselective reduction, the regioselective cleavage of an isopropylidene moiety, and the position-selective displacement of a cyclic sulfate moiety. All of the reactions employed in the present synthesis are expected to be very useful in the development of new carbocyclic nucleosides. Structure−activity relationship studies of MLN4920 are currently in progress, and the results will be reported in due course.

Scheme 1. Retrosynthesis of the AMP Mimic MLN4924 (1)



Scheme 2. Synthesis of Glycosyl Donor 3



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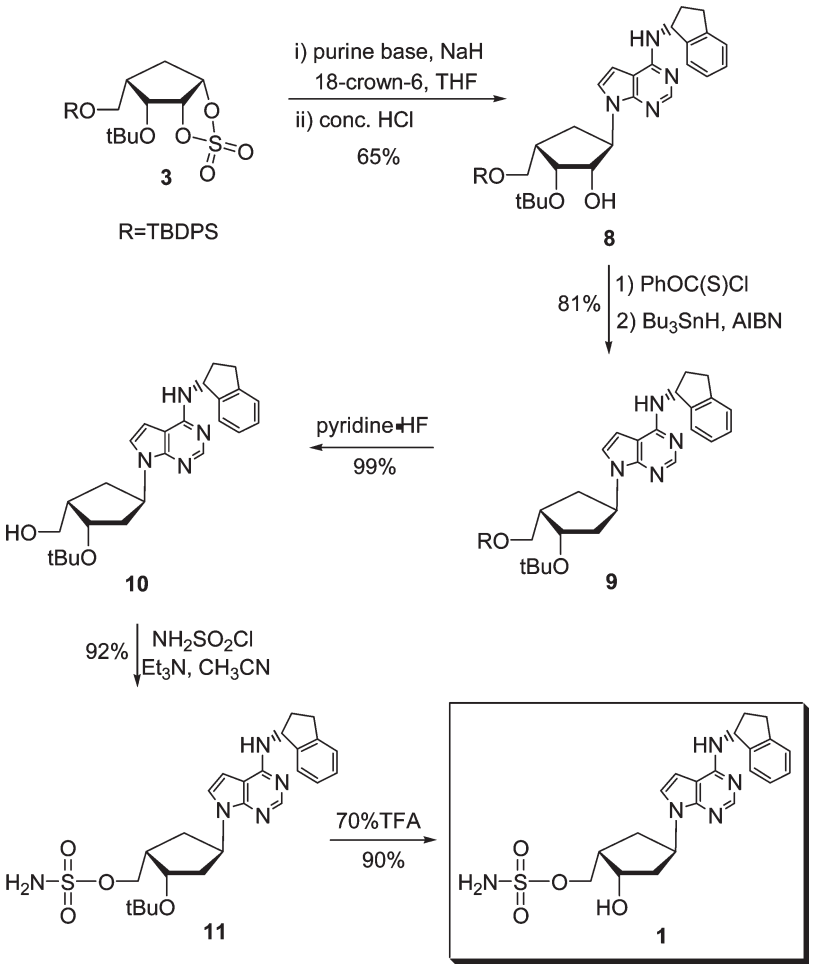
Scheme 3. Synthesis of MLN4924 (1)



EXPERIMENTAL SECTION

6-(*tert*-Butyldiphenylsilanyloxymethyl)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-one (5). 10% Palladium on activated carbon (1.0 g) was added to a suspension of **6** (20.0 g, 47.1 mmol) in methanol (400 mL), and the mixture was stirred overnight at room temperature under an atmosphere of H_2. After filtration, the solvent was removed, and the residue was dissolved in methylene chloride and filtered through a short pad of silica gel. The solvent was evaporated to give **5** (20.1 g, 100%) as a colorless syrup: $[\alpha]^{20}_D$ −28.32 (*c* 1.49, MeOH); HR-MS (ESI) *m*/*z* calcd for $C_{25}H_{32}NaO_4Si$ $[M + Na]^+$ 447.1968, found 447.1956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.40 (m, 6H), 4.84 (t, *J* = 4.4 Hz, 1H), 4.22 (dd, *J* = 1.2, 4.8 Hz, 1H), 3.96 (dd, *J* = 8.0, 10.0 Hz, 1H), 3.82 (dd, *J* = 6.8, 10.0 Hz, 1H), 2.37 (m, 1H), 2.30 (ddd, *J* = 1.2, 8.4, 18.4 Hz, 1H), 2.20 (ddd, *J* = 1.2, 12.0, 18.4 Hz, 1H), 1.37 (s, 3H), 1.35
(s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6, 80.5, 77.6, 77.2, 76.9, 63.6, 38.1, 36.9, 27.1, 27.02, 27.01, 25.3, 19.5. Anal. Calcd for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60. Found: C, 70.79; H, 7.75.

6-(*tert*-Butyldiphenylsilanyloxymethyl)-2,2-dimethyltetrahydrocyclopenta [1,3]dioxol-4-ol (7). Sodium borohydride (2.17 g, 57.4 mmol) and cerium(III) chloride heptahydrate (21.3 g, 57.2 mmol) were added to a suspension of **5** (20.1 g, 47.1 mmol) in methanol (500 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. After the solvent was removed, the residue was partitioned between ethyl acetate and water, and the organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to give **7** (20.86 g, 98%) as a colorless syrup: $[\alpha]^{20}_D$ +34.55 (*c* 0.55, MeOH); HR-MS (ESI) *m*/*z* calcd for $C_{25}H_{34}NaO_4Si$ $[M + Na]^+$ 449.2124, found 449.2110; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.39 (m, 6H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.44 (t, *J* = 5.6 Hz, 1H), 3.89 (dd, *J* = 6.0, 7.6 Hz, 1H), 3.84 (m, 1H), 3.68 (dd, *J* = 6.4, 10.0 Hz, 1H), 1.91 (m, 2H), 1.26 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.2, 134.1, 129.8, 129.7, 127.8, 127.7, 110.6, 79.4, 78.9, 77.6, 77.2, 76.9, 72.5, 62.9, 41.6, 33.4, 27.0, 25.9, 27.0, 25.9, 24.4, 19.5. Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.38; H, 8.03. Found: C, 70.41; H, 8.08.

3-*tert*-Butoxy-4-(*tert*-butyldiphenylsilanyloxymethyl)-cyclopentane-1,2-diol (4). Trimethylaluminum (2.0 M in toluene, 132.1 mL) was added to a solution of **7** (20.86 g, 47.12 mmol) in methylene chloride at 0 °C, and the mixture was stirred at room temperature for 2 d. The mixture was cooled to 0 °C, slowly quenched with saturated aqueous ammonium chloride, filtered, and evaporated. The residue was partitioned between ethyl acetate and water, and the organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to give **4** (13.42 g, 62%) as a colorless syrup: $[\alpha]^{20}_D$ +3.30 (*c* 0.55, MeOH); HR-MS (ESI) *m*/*z* calcd for $C_{26}H_{38}NaO_4Si$ $[M + Na]^+$ 465.2437, found 465.2423; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.41 (m, 6H), 4.05 (dd, J = 4.4, 7.2 Hz, 1H), 3.93 (m, 1H), 3.72 (m, 2H), 3.59 (dd, J = 3.6, 12.0 Hz, 2H), 2.70 (d, J = 20.8 Hz, 1H), 2.10 (m, 2H), 1.60 (m, 1H), 1.20 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 133.5, 130.0, 129.9, 127.9, 127.9, 77.6, 77.2, 76.9, 74.9, 73.8, 72.7, 72.1, 63.3, 42.1, 34.0, 28.5, 27.0, 19.4. Anal. Calcd for $C_{26}H_{38}O_4Si$: C, 70.55; H, 8.65. Found: C, 70.61; H, 8.70.

(4-*tert*-Butoxy-2,2-dioxotetrahydro-2-yl-6-cyclopenta-[1,3,2]dioxathiol-5-ylmethoxy)-*tert*-butyldiphenylsilane (3). Triethyl amine (14.5 mL, 101.0 mmol) and thionyl chloride (3.7 mL, 47.4 mmol) were added to a solution of **4** (13.42 g, 30.3 mmol) in methylene chloride at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was partitioned between methylene chloride and water, and the organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1) to give the cyclic sulfite (14.37 g, 97%) as a white foam: $[\alpha]^{20}_D$ +20.00 (c 0.05, MeOH); HR-MS (ESI) m/z calcd for $C_{26}H_{36}NaO_5SSi$ $[M + Na]^+$ 511.1950, found 511.1929; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.40 (m, 6H), 5.23 (m, 1H), 5.04 (dd, J = 4.4, 6.0 Hz, 1H), 4.01 (t, J = 4.8 Hz, 1H), 3.68 (dd, J = 3.6, 10.4 Hz, 1H), 3.56 (dd, J = 8.0, 10.4 Hz, 1H), 2.07 (m, 2H), 1.96 (m, 1H), 1.14 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.7, 133.9, 133.8, 129.9, 129.9, 127.9, 127.8, 85.7, 83.2, 77.6, 77.2, 76.9, 75.0, 71.1, 62.7, 44.7, 31.4, 28.5, 27.1, 19.4. Anal. Calcd for $C_{26}H_{36}O_5SSi$: C, 63.90; H, 7.42; S, 6.56. Found: C, 63.94; H, 7.45; S, 6.61.

Sodium metaperiodate (18.56 g, 56.4 mmol) and ruthenium chloride (1.72 g, 8.25 mmol) were added to a solution of the cyclic sulfite (14.37 g, 29.4 mmol) in carbon tetrachloride, acetonitrile, and water (1:1:1.5, 210 mL), and the reaction mixture was stirred at room temperature for 10 min. The reaction mixture was partitioned between methylene chloride and water, and the organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to give **3** (13.36 g, 90%) as a white solid: mp 101−104 °C; $[\alpha]^{20}_D$ −80.00 (c 0.05, MeOH); HR-MS (ESI) m/z calcd for $C_{26}H_{36}NaO_6SSi$ $[M + Na]^+$ 527.1900, found 527.1881; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.41 (m, 6H), 5.13 (m, 1H), 4.83 (dd, J = 4.4, 6.8 Hz, 1H), 4.13 (t, J = 4.0 Hz, 1H), 3.92 (dd, J = 6.4, 10.4 Hz, 1H), 3.69 (dd, J = 5.2, 10.4 Hz, 1H), 2.11 (m, 2H), 2.02 (m, 1H), 1.15 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.0, 133.8, 133.7, 130.0, 128.0, 127.9, 83.5, 82.2, 77.6, 77.2, 76.9, 75.4, 70.4, 70.4, 62.2, 43.9, 31.3, 28.2, 27.1, 26.8, 19.4. Anal. Calcd for $C_{26}H_{36}O_6SSi$: C, 61.87; H, 7.19; S, 6.35. Found: C, 61.91; H, 7.14; S, 6.30.

2-*tert*-Butoxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-5-[4-(indan-1-ylamino)pyrrolo[2,3-*d*]pyrimidin-7-yl]cyclopentanol (8). A suspension of N^6-indanyl-7-deazaadenine (8.80 g, 35.2 mmol), sodium hydride (1.38 g, 45.7 mmol), and 18-crown-6 (9.11 g, 45.7 mmol) in THF (200 mL) was stirred at 80 °C. To this reaction mixture was added a solution of **3** (13.36 g, 26.5 mmol) in THF (150 mL), and stirring was continued at 80 °C overnight. The reaction mixture was cooled to 0 °C, and concentrated HCl was added slowly until a pH of 1−2 was attained. Subsequently, the reaction mixture was stirred at 80 °C for an additional 2 h. After neutralization with saturated aqueous $NaHCO_3$, the reaction mixture was partitioned between ethyl acetate and water, and the organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to give **8** (11.62 g, 65%) as a white foam: UV (CH_2Cl_2) λ_{max} 272.5 nm; $[\alpha]^{20}_D$ −8.89 (c 0.45, MeOH); HR-MS (ESI) m/z calcd for $C_{41}H_{51}N_4O_3Si$ $[M + H]^+$ 675.3730, found 675.3717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.70 (m, 4H), 7.41 (m, 6H), 6.92 (d, J = 3.6 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 5.91 (dd, J = 7.6, 14.8 Hz, 1H), 5.14 (br d, J = 6.8 Hz, 1H), 4.77 (m, 1H), 4.36 (t, J = 6.0 Hz, 1H), 4.22 (dd, J = 5.2, 10.8 Hz, 1H), 3.84 (dd, J = 5.6, 10.4 Hz, 1H), 3.73 (dd, J = 8.4, 10.4 Hz, 1H), 3.37 (d, J = 5.6 Hz, 1H), 3.06 (m, 1H), 2.95 (m, 1H), 2.75 (m, 1H), 2.75 (m, 1H), 2.58 (m, 1H), 2.38 (m, 1H), 2.15 (m, 1H), 1.98 (m, 1H), 1.65 (s, 1H), 1.55 (s, 1H), 1.16 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 151.8, 150.3, 144.1, 143.8, 135.9, 134.0, 129.9, 128.2, 127.9, 127.9, 127.0, 125.1, 124.4, 123.3, 103.8, 97.4, 77.8, 77.6, 77.2, 76.9, 74.9, 72.4, 63.5, 62.1, 56.3, 43.9, 34.9, 30.5, 30.5, 28.5, 27.2, 19.5. Anal. Calcd for $C_{41}H_{50}N_4O_3Si$: C, 72.96; H, 7.47; N, 8.30. Found: C, 73.01; H, 7.45; N, 8.36.

{7-[3-*tert*-Butoxy-4-(*tert*-butyldiphenylsilanyloxymethyl)-cyclopentyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}indan-1-yl-amine (9). *N*,*N*-Dimethylaminopyridine (5.64 g, 51.6 mmol) and phenyl chlorothionocarbonate (4.3 mL, 34.4 mmol) were added to a solution of **8** (11.62 g, 17.2 mmol) in methylene chloride (300 mL), and the reaction mixture was stirred overnight at room temperature. After the solvent was removed, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1) to give the thiocarbonate (13.82 g, 99%) as a white foam: UV (MeOH) λ_{max} 271.50 nm; $[\alpha]^{20}_D$ +10.00 (c 0.15, MeOH); HR-MS (ESI) m/z calcd for $C_{48}H_{55}N_4O_4SSi$ $[M + H]^+$ 811.3713, found 811.3687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.61 (dd, J = 1.6, 7.6 Hz, 4H), 7.34 (m, 5H), 7.26 (m, 4H), 7.18 (m, 6H), 6.86 (s, 1H), 6.25 (d, J = 3.2 Hz, 1H), 6.00 (dd, J = 3.2, 8.4 Hz, 1H), 5.83 (d, J = 6.8 Hz, 1H), 5.19 (m, 1H), 5.07 (br s, 1H), 4.48 (t, J = 3.6 Hz, 1H), 3.82 (dd, J = 7.2, 10.4 Hz, 1H), 3.52 (dd, J = 7.2, 10.0 Hz, 1H), 2.99 (m, 1H), 2.88 (m, 2H), 2.69 (m, 2H), 2.18 (dd, J = 11.2, 13.6 Hz, 1H), 1.94 (m, 2H), 1.12 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 153.5, 152.1, 143.9, 135.9, 135.8, 134.1, 129.9, 129.6, 128.3, 127.9, 127.0, 126.7, 125.1, 124.6, 123.2, 122.0, 87.9, 77.6, 77.2, 76.9, 74.6, 70.4, 63.5, 57.3, 42.8, 35.0, 30.7, 30.5, 29.9, 28.7, 27.1, 19.4. Anal. Calcd for $C_{48}H_{54}N_4O_4SSi$: C, 71.08; H, 6.71; N, 6.91; S, 3.95. Found: C, 71.14; H, 6.75; N, 6.95; S, 4.01.

Tri-*n*-butyltinhydride (9.4 mL, 34.1 mmol) and 2,2′-azo-bis-isobutyronitrile (4.32 g, 26.3 mmol) were added to a solution of the thiocarbonate (13.82 g, 17.0 mmol) in toluene (200 mL), and the reaction mixture was stirred at 110 °C for 1 h. After the mixture was cooled, the solvent was removed, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to give **9** (9.21 g, 82%) as a white foam: UV (MeOH) λ_{max} 272.50 nm; $[\alpha]^{20}_D$ −10.00 (c 0.20, MeOH); HR-MS (ESI) m/z calcd for $C_{41}H_{51}N_4O_2Si$ $[M + H]^+$ 659.3781, found 659.3757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.69 (m, 4H), 7.41 (m, 6H), 7.29 (m, 2H), 7.23 (m, 2H), 6.92 (d, J = 3.6 Hz, 1H), 6.31 (d, J = 3.6 Hz, 1H), 5.90 (dd, J = 7.2, 14.8 Hz, 1H), 5.38 (m, 1H), 5.15 (br s, 1H), 4.33 (dd, J = 5.2, 8.4 Hz, 1H), 3.88 (dd, J = 6.4, 10.0 Hz, 1H), 3.68 (dd, J = 7.2, 10.4 Hz, 1H), 3.05 (m, 1H), 2.96 (dd, J = 7.6, 15.6 Hz, 1H), 2.76 (m, 1H), 2.45 (d, J = 5.2 Hz, 1H), 2.29 (m, 2H), 2.06 (m, 1H), 1.95 (m, 2H), 1.55 (s, 1H), 1.13 (s, 9H), 1.06 (s, 9H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 156.3, 151.9, 144.1, 143.9, 135.9, 135.8, 134.3, 129.8, 128.2, 127.8, 127.0, 125.1, 124.6, 121.8, 77.6, 77.2, 76.7, 73.5, 72.2, 63.6, 56.4, 52.8, 46.8, 42.8, 34.9, 34.5, 30.5, 28.6, 27.2, 28.7, 19.4. Anal. Calcd for $C_{41}H_{50}N_4O_2Si$: C, 74.73; H, 7.65; N, 8.30. Found: C, 74.79; H, 7.61; N, 8.25.

2-*tert*-Butoxy-4-[4-(indan-1-ylamino)pyrrolo[2,3-*d*]pyrimidin-7-yl]cyclopentanol (10). Pyridine hydrofluoride (18.42 mL, 190.0 mmol) was added dropwise to a solution of **9** (9.21 g, 13.97 mmol) in THF and pyridine (1:1, 160 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/3) to give **10** (5.63 g, 99%) as a white foam: UV (MeOH) λ_{max} 273.00 nm; $[\alpha]^{20}_D$ −6.36 (c 1.10, MeOH); HR-MS (ESI) m/z calcd for $C_{25}H_{33}N_4O_2$ $[M + H]^+$ 421.2604, found 421.2599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34

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(s, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.2 Hz, 2H), 7.15 (t, J = 6.8 Hz, 1H), 6.88 (d, J = 3.2 Hz, 1H), 6.23 (d, J = 3.6 Hz, 1H), 5.83 (dd, J = 7.2, 15.2 Hz, 1H), 5.28 (m, 1H), 5.06 (m, 1H), 4.47 (dd, J = 5.6, 10.4 Hz, 1H), 3.78 (m, 1H), 3.70 (m, 1H), 3.24 (t, J = 5.2 Hz, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.68 (m, 1H), 2.46 (m, 1H), 2.37 (m, 2H), 1.93 (m, 2H), 1.18(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 151.8, 147.9, 143.9, 143.9, 128.3, 126.9, 125.1, 124.5, 121.9, 97.7, 77.6, 77.2, 76.9, 75.5, 74.9, 63.4, 56.4, 53.8, 44.2, 42.2, 34.9, 33.2, 30.5, 28.6. Anal. Calcd for $C_{25}H_{32}N_4O_2$: C, 71.40; H, 7.67; N, 13.32. Found: C, 71.46; H, 7.60; N, 13.35.

Sulfamic Acid 2-*tert*-Butoxy-4-[4-(indan-1-ylamino)pyrrolo-[2,3-*d*]pyrimidin-7-yl]cyclopentylmethyl Ester (11)

Preparation of a 2.0 M Solution of Chlorosulfonamide in Acetonitrile. Under an atmosphere of nitrogen at 0 °C, formic acid (14.15 mL, 166.0 mmol) was added dropwise to chlorosulfonyl isocyanate (32.0 mL, 162.5 mmol). When the addition was complete, the mixture solidified. Acetonitrile (61.3 mL) was added, and the resulting solution was allowed to stand under a vented source of nitrogen at room temperature overnight.

To a solution of **10** (5.63 g, 13.83 mmol) and triethylamine (9.7 mL, 0.74 mmol) in acetonitrile (278 mL) was added a 2.0 M solution of chlorosulfonamide in acetonitrile (13.83 mL, 27.76 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 45 min. An additional portion of the 2.0 M solution of chlorosulfonamide in acetonitrile (13.83 mL, 27.76 mmol) was added, and the mixture was stirred at room temperature for 15 min. The reaction was quenched with methanol, and the solvent was removed. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to give **11** (6.37 g, 92%) as a white foam: UV (MeOH) λ_{max} 273.00 nm; $[\alpha]^{20}_D$ −18.00 (c 0.50, MeOH); HR-MS (ESI) m/z calcd for $C_{25}H_{34}N_5O_4S$ $[M + H]^+$ 500.2332, found 500.2331; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.22 (m, 2H), 6.95 (d, J = 3.6 Hz, 1H), 6.31 (d, J = 3.2 Hz, 1H), 5.89 (d, J = 6.4 Hz, 1H), 5.10 (s, 2H), 4.41 (m, 2H), 4.26 (m, 1H), 3.05 (m, 1H), 2.94 (m, 1H), 2.76 (m, 2H), 2.27 (m, 3H), 2.06 (m, 1H), 1.97 (m, 1H), 1.76 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 151.9, 149.9, 143.9, 143.8, 128.3, 126.9, 125.1, 124.5, 121.9, 121.9, 103.5, 97.9, 77.4, 77.2, 76.9, 74.3, 71.9, 71.3, 56.4, 53.1, 49.0, 42.3, 34.9, 34.3, 30.5, 28.6. Anal. Calcd for $C_{25}H_{33}N_5O_4S$: C, 60.10; H, 6.66; N, 14.02; S, 6.42. Found: C, 60.15; H, 6.71; N, 13.98; S, 6.39.

Sulfamic Acid 2-Hydroxy-4-[4-(indan-1-ylamino)pyrrolo-[2,3-*d*]pyrimidin-7-yl]cyclopentylmethyl Ester (1). A solution of **11** (6.37 g, 12.72 mmol) in 70% trifluoroacetic acid (149.24 mL) was stirred at room temperature for 2 h. The solvent was removed, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/2) to give **1** (5.08 g, 90%) as a white foam: UV (MeOH) λ_{max} 279.50 nm; $[\alpha]^{20}_D$ −6.41 (c 2.34, MeOH); HR-MS (ESI) m/z calcd for $C_{21}H_{26}N_5O_4S$ $[M + H]^+$ 444.1705, found 444.1706; ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 1.6 Hz, 1H), 7.25 (m, 2H), 7.18 (m, 2H), 6.64 (d, J = 3.6 Hz, 1H), 5.86 (t, J = 7.6 Hz, 1H), 5.46 (m, 1H), 4.49 (d, J = 2.8 Hz, 1H), 3.07 (m, 1H), 2.92 (m, 1H), 2.80 (m, 1H), 2.64 (m, 1H), 2.35 (m, 1H), 2.25 (m, 2H), 2.03 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.1, 145.3, 144.6, 128.8, 127.6, 125.7, 125.2, 122.6, 100.5, 73.1, 70.9, 56.9, 54.0, 44.8, 43.6, 34.9, 34.6, 31.1. Anal. Calcd for $C_{21}H_{25}N_5O_4S$: C, 56.87; H, 5.68; N, 15.79; S, 7.23. Found: C, 56.91; H, 5.73; N, 15.82; S, 7.26.

■ ASSOCIATED CONTENT

Supporting Information. Copies of the NOESY spectrum of **7** and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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