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2′-Fluoro-3-deazaaristeromycin

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ABSTRACT

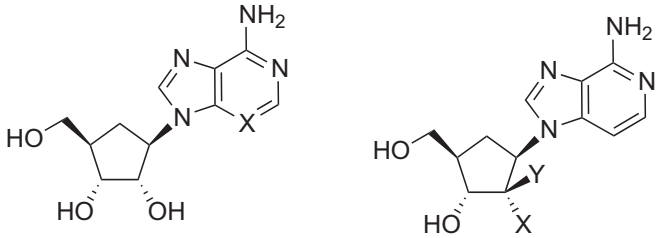
The carbocyclic nucleoside 3-deazaaristeromycin has shown biological promise but a library of its derivatives upon which to expand this property is lacking. To address this situation, the synthesis of the two diastereomers of 2′-fluoro-3-deazaaristeromycin is described in a multistep convergent process that calls upon D-ribose for construction of the cyclopentyl fluoro units.

1. Introduction

The carbocyclic nucleoside aristeromycin (**1**) represents a unique structure among nature's library of small molecules.[1] Its potential as a medicinal agent has been limited due to associated toxicity.[2] However, its synthetic partner 3-deazaaristeromycin (**2**)[3] has demonstrated less restrictive properties but its further development has been lacking. To address this situation, we have undertaken a more extensive investigation of **2** by preparing a variety of derivatives. Our recent attention was drawn to fluoro substituted targets because of their potential biological significance.[4] Here we report the synthesis of the two diastereomers of 2′-fluoro-3-deazaaristeromycin **3** and **4** (Fig. 1).

The retrosynthetic analysis guiding the synthesis of **3** and **4** (Scheme 1) required the preparation of the unknown cyclopentylidene protected cyclopentenone **5**, which was selected over the more common isopropylidene cyclopentenone,[5] because **5** would be less volatile under the planned reaction pathways. Thus, beginning with D-ribose (**6**, Scheme 2) and, following established conditions,[5] **5** was realized via a Grubbs metathesis conversion[5] (step e).

With **5** in hand, we moved to appending the 5′-hydroxylmethylene precursor (arrow, Scheme 1) prior to bringing the fluoro atoms into the process. In that regard, treatment of **5** vinylmagnesium bromide in the presence of cuprous bromide gave the 1,4-adduct **11** (Scheme 3). Subsequent keto reduction (to **12**) and



1, X=N
2, X=CH

3, X=F,Y=H
4, X=H,Y=F

Fig. 1. Aristeromycin and related compounds.

protection of the resultant secondary alcohol via the *p*-methoxybenzyl accessory provided **13**. To expose the C-2 center for introducing the desired fluorine atom, **13** was deprotected to the diol **14** that was, in turn, selectively mono-protected at the C-2 and C-3 hydroxyls as *tert*-butyldiphenylsilyl units (i.e., **15** and **16**).

To proceed toward **3**, the free hydroxyl of **16** was inverted by a Mitsunobu reaction[6] (to **17**) and, subsequent, lithium hydroxide saponification resulted in **18**. Fluroination (DAST) to **19** was followed by construction of the C-4 protected hydroxymethylene that proceeded via (i) oxidative glycolization (NMO), cleavage ($NaIO_4$), and reduction ($NaBH_4$) (to **20**), (ii) protection as the *tert*-butyldiphenylsilyl derivative (**21**), and (iii) removal of the *p*-methoxybenzyl provided the requisite cyclopentanol **22** for coupling with an appropriate 3-deazapurine.

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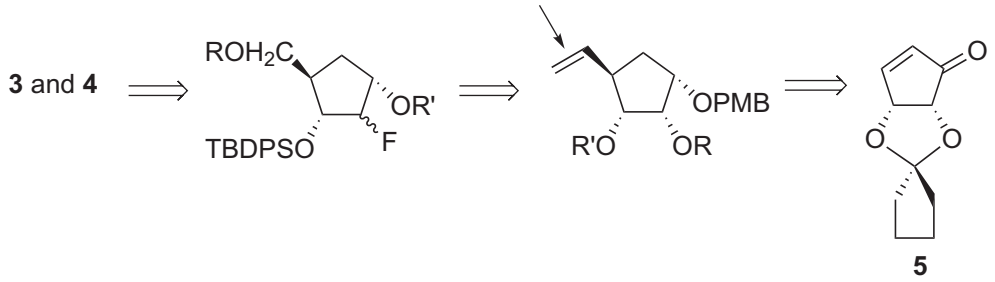
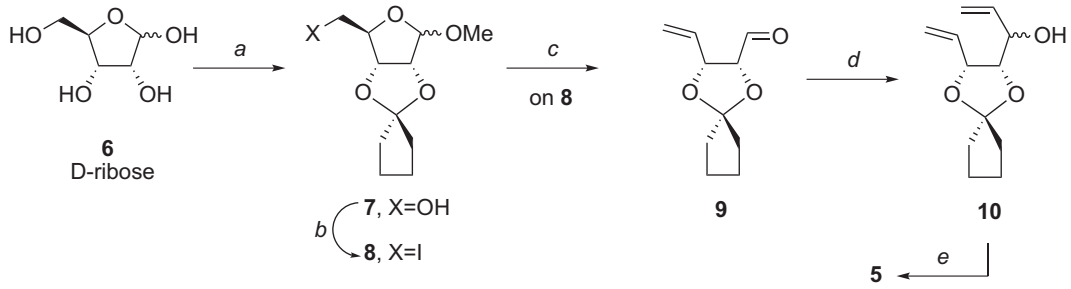


Scheme 1. Retrosynthetic approach to **3** and **4**.



Reaction conditions: *a*, cyclopentanone, $HC(OMe)_3$, MeOH, H_2SO_4, 78%; *b*, I_2, PPh_3, MeCN/toluene, imidazole, rt, 80%; *c*, Zn, MeOH/AcOH, reflux, 80%; *d*, CH_2=$CHMgBr$, CH_2Cl_2,THF, 84%; *e*, (i) Grubbs 1st generation catalyst, CH_2Cl_2, rt; (ii) MnO_2, CH_2Cl_2, 70% for 2 steps.

Scheme 2. Preparation of cyclopentenone **5**.

The C-2 α-fluoro coupling partner **26** was achieved beginning with **16** (Scheme 4) via the same sequence that was described for **22** from **16** except, of course, for the initial inversion necessitated in the latter process to carry out the DAST fluorination.

The target syntheses (Scheme 5) were completed by subjecting **22**/**26** to a Mitsunobu coupling[7] with the Boc protected 3-deazaadenine **27**[8] to **28a**/**28b**. Removal of the protecting groups of these latter products with HCl in methanol gave **3** and **4**, respectively.[9]

The availability of **3** and **4** adds to the growing list of fluoro nucleosides of potential biological relevance.[4]

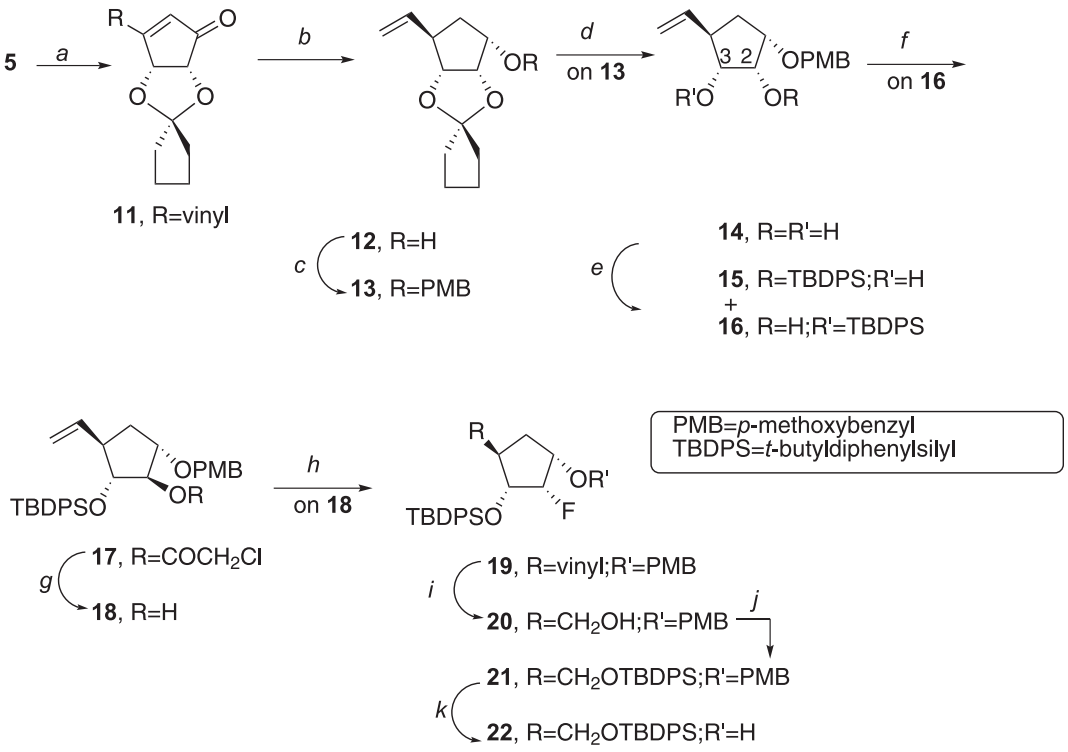
2. Experimental

2.1. General

^1H and ^{13}C NMR spectra were measured on a Bruker AV-400 spectrometer or Bruker AC-250 spectrometer. ^1H chemical shifts are reported relative to $CDCl_3$ at δ 7.27 ppm (or MeOD at δ 3.51 ppm or DMSO-d_6 at δ 2.51 ppm) and tetramethylsilane as an internal standard. ^{13}C chemical shifts are reported in relative to $CDCl_3$/MeOD/DMSO-d_6. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets). Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60 F_{254} precoated silica gel plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 mm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in an N_2 atmosphere under anhydrous conditions.

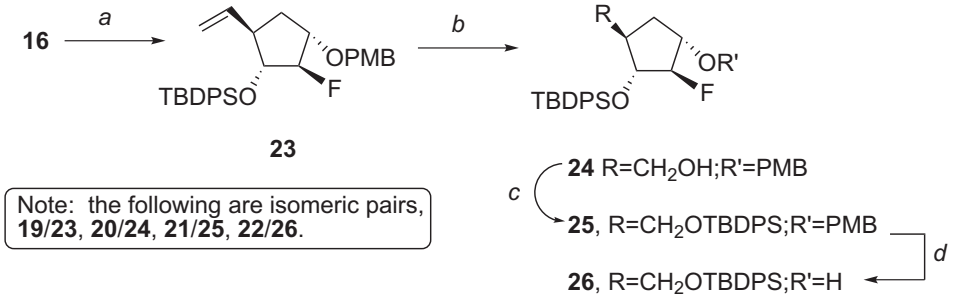
*2.1.1. ((3a′R,6′R,6a′R)-4′-Methoxytetrahydrospiro[cyclopentane-1,2′-furo[3,4-d]-[1,3]dioxole]-6′-yl)methanol (**7**).* D-Ribose (**6**, 15 g, 100 mmol), cyclopentanone (88 mL, 1 mol), MeOH (100 mL), and trimethyl orthoformate (55 mL, 500 mmol) were added to a 500 mL flask. To this, concd H_2SO_4 (0.5 mL) was added carefully. The mixture was stirred at room temperature for 2 days. Ammonium hydroxide (29.6%) was added to neutralize the mixture. The solvent was removed under reduced pressure and the residue dissolved in EtOAc, which was, in turn, washed with brine, dried (Na_2SO_4), and concentrated to give **7** as yellow oil (17.8 g, 78.0%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.79 (d, J=6.0 Hz, 1H), 4.55 (d, J=6.0 Hz, 1H), 4.44 (t, J=2.8 Hz, 1H), 3.67 (m, 2H), 3.44 (s, 3H), 3.29 (dd, J=3.6, 9.6 Hz, 1H), 1.95 (m, 2H), 1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 121.8, 109.8, 88.2, 85.6, 81.5, 64.1, 55.6, 35.8, 35.7, 23.8, 23.3. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.27; H, 7.96.

*2.1.2. (3a′S,4′S,6a′R)-4′-Iodomethyl-6′-methoxytetrahydrospiro[cyclopentane-1,2′-furo[3,4-d][1,3]dioxole] (**8**).* Compound **7** (17.81 g, 78 mmol) was dissolved in MeCN/toluene (1:1, 250 mL). To this imidazole (7.97 g, 117 mmol) and triphenylphosphine (TPP) (22.5 g, 86 mmol) were added. This was followed by the addition of I_2 (21.8 g, 86 mmol) in portions until the solution turned black. The resulting solution was stirred at room temperature for 2 h. Water (100 mL) and sodium thiosulfate (5 g) were then added until the solution became clear. The organic layer was separated, dried (Na_2SO_4), concentrated, and the residue purified with column chromatography (hexanes/EtOAc=5:1). The product **8** was isolated as colorless oil (21.13 g, 80.1%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (s,



Reaction conditions: *a*, CH_2=CHMgBr, CuBr•Me_2S in THF then TMSCl, HMPA, -78 °C then rt, 66%; *b*, $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH, 0 °C then rt, 95%; *c*, PMBCl, NaH, DMF, 0°C to rt, 86%; *d*, HCl, MeOH, 87%; *e*, TBDPSCl, imidazole, DMAP, CH_2Cl_2, 0°C to rt, 41% for **15**, 34% for **16**; *f*, $ClCH_2CO_2H$, DIAD, PPh_3, THF, -40 °C then 60 °C, 66%; *g*, LiOH, MeOH, 25 °C, 85%; *h*, DAST, py, CH_2Cl_2, rt, 64%; *i*, (i) NMO, MeOH then $NaIO_4$, 0 °C followed by OsO_4 at 0 °C; (ii) $NaBH_4$, MeOH, 58% for 2 steps; *j*, see step *e*, 92%; *k*, DDQ, CH_2Cl_2, rt, 64%.

Scheme 3. Synthesis of precursor to **3**.

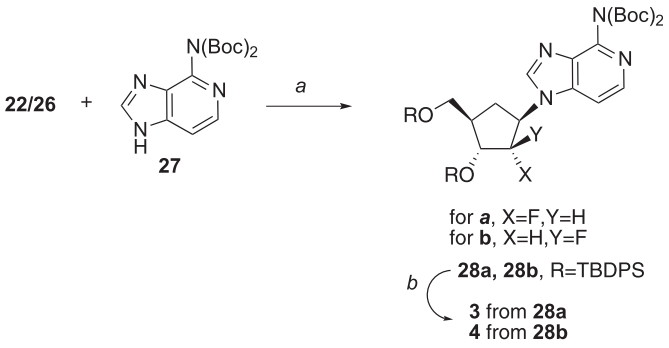


Reaction conditions: *a*, see step *h of* Scheme 3, 65%; *b*, see step *i* of Scheme 3, 59% for 2 steps; *c*, see step *e* of Scheme 3, 94%; *d*, see step *k* of Scheme 3, 66%.

Scheme 4. Synthesis of precursor to **4**.

1H), 4.71 (d, *J*=5.6 Hz, 1H), 4.7 (d, *J*=5.6 Hz, 1H), 4.45 (m, 1H), 3.37 (s, 3H), 3.3 (m, 1H), 3.18 (m, 1H), 1.90 (m, 2H), 1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 123.1, 109.9, 87.9, 85.8, 82.7, 55.2, 35.8, 35.7, 23.6, 23.2, 6.7. Anal. Calcd for $C_{11}H_{17}O_4I$: C, 38.84; H, 5.04. Found: C, 39.08; H, 5.09.

*2.1.3. (3aR,6aR)-3aH-Spiro[cyclopenta[d][1,3]dioxole-2,1′-cyclopentan]-4(6aH)-one (**5**).* To a stirred solution of iodide **8** (21.13 g, 62 mmol) in MeOH (200 mL) at room temperature was added zinc powder (4.47 g, 68 mmol, Aldrich, dust, <10 μ) in one batch. This was followed by the addition of AcOH (0.23 mL, 7.5 mmol) in one portion via syringe. The resultant reaction mixture was heated to reflux for 5 h followed by cooling to room temperature, filtering through a short plug of Celite, and washing with a mixture of THF/hexanes (1:1, 100 mL). The filtrate was concentrated in vacuo to provide a colorless oil, which was purified by silica gel column chromatography (hexanes/EtOAc, 2:1) to afford (2*R*,3*R*)-3-vinyl-1,4-dioxaspiro[4.4]nonane-2-carbaldehyde (**9**) (9.07 g, 80.1%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J*=3.2 Hz, 1H), 5.75 (m, 1H), 5.3–5.5 (m, 2H), 4.76 (m, 1H), 4.34 (m, 1H), 2.09 (m,



Reaction conditions: *a*, DIAD, PPh_3, THF, -40 °C to rt then to 60 °C; *b*, HCl, MeOH, rt, 18.7% for **3** and 23.3% for **4** for both steps *a* and *b*.

Scheme 5. Final steps in the preparation of **3** and **4**.

2H), 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 131.2, 121.1, 120.0, 81.9, 79.4, 36.9, 36.8, 24.1, 23.3.

Compound **9** (9.07 g, 49.8 mmol) was dissolved in CH_2Cl_2 (50 mL) and to this vinylmagnesium bromide (59.7 mL, 59.7 mmol, 1 M in THF) was added at −78 °C. The resultant mixture was warmed to 0 °C and saturated aqueous NH_4Cl (40 mL) added to quench the reaction. The organic layer was separated, dried (Na_2SO_4), and concentrated using a rotavapor (bath temperature <10 °C). The residue was purified by silica gel column chromatography (hexanes/EtOAc, 5:1) to give 1-((2*S*,3*R*)-3-vinyl-1,4-dioxaspiro[4.4]nonan-2-yl)prop-2-en-1-ol (**10**) as colorless oil (8.77 g, 83.8%, as a mixture of two diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (m, 1H), 5.79 (m, 1H), 5.35 (m, 4H), 4.55 (m, 1H), 4.2 (m, 1H), 4.02 (m, 1H), 2.01 (m, 2H), 1.65 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 137.7, 136.9, 134.0, 133.9, 119.8, 119.0, 118.7, 117.2, 116.6, 80.7, 80.6, 79.0, 78.7, 71.3, 70.9, 37.1, 37.0, 36.9, 36.6, 24.2, 24.1, 23.4, 23.3.

Compound **10** (8.77 g, 41.7 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and through this solution N_2 was bubbled for 30 min to remove O_2. To this was added Grubbs first generation catalyst (343 mg, 0.417 mmol) and the solution stirred at room temperature for 12 h. Then the solution was cooled to 0 °C and then warmed to 60 °C for the addition of activated MnO_2 powder (10.88 g, 125 mmol, commercially available). The mixture was cooled to room temperature, stirred overnight, and H_2O (200 mL) was added. The organic layer was separated, filtered, dried (Na_2SO_4), concentrated under reduced pressure, and purified by silica gel column chromatography (hexanes/EtOAc, 2:1) to give **5** as white solid (5.28 g, 70.2%), mp 53–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J*=2.4, 4.8 Hz, 1H), 6.28 (d, *J*=6.0 Hz, 1H), 5.23 (dd, *J*=2.0, 5.2 Hz, 1H), 4.40 (d, *J*=5.2 Hz, 1H), 1.86 (m, 2H), 1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.0, 159.9, 135.5, 124.3, 78.2, 76.2, 37.9, 37.4, 24.1, 23.3. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.79; H, 7.02.

*2.1.4. (3aR,6R,6aR)-6-Vinyldihydro-3aH-spiro[cyclopenta[d][1,3]dioxole-2,1′-cyclopentan]-4(6aH)-one (**11**).* Vinylmagnesium bromide (17.34 mL, 17.34 mmol, 1.0 M in THF) was added, dropwise by syringe, to a suspension of CuBr·Me_2S (0.285 g, 1.39 mmol) in anhydrous THF (20 mL) at −78 °C. This reaction mixture was stirred at the same temperature for 30 min before a solution of **10** (2.5 g, 13.9 mmol), TMSCl (3.68 mL, 29.1 mmol), and HMPA (6.28 mL, 36.1 mmol) in THF (20 mL) was added dropwise via a cannula. The reaction mixture was kept stirring at −78 °C for 5 h and then warmed to room temperature. Saturated aqueous NH_4Cl (15 mL) and tetra-*N*-butylammonium fluoride (TBAF, 3.0 mL) were added to quench the reaction and this mixture stirred for 30 min. The reaction mixture was diluted with EtOAc (100 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 4:1) to afford **11** as a colorless oil (1.92 g, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.17–5.08 (m, 2H), 4.56 (d, *J*=5.6 Hz, 1H), 4.18 (d, *J*=5.2 Hz, 1H), 3,13 (m, 1H), 2.85 (dd, *J*=8.40 Hz, 1H), 2.32 (m, *J*=18.0 Hz, 1H), 1.94–1.65 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 137.3, 122.3, 116.5, 81.6, 77.7, 40.0, 38.8, 36.3, 36.2, 23.9, 23.1. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.34; H, 7.8.

*2.1.5. 2,3-(Cyclopentylidenedioxy)-4-vinylcyclopentanol (**12**).* To a stirred solution of cyclopentenone **11** (1.92 g, 9.2 mmol) and $CeCl_3 \cdot 7H_2O$ (2.93 g, 10.1 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (0.698 g, 18.4 mmol) in small portions. After stirring at room temperature for 1 h the mixture was neutralized with concd HCl, reduced to 2:3 volume, extracted with brine and Et_2O, and the organic layers combined, dried ($MgSO_4$), and concentrated to give **12** as a colorless oil (1.84 g, 94.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.06–5.10 (m, 2H), 4.4 (m, 2H), 4.07–4.13 (m, 1H), 2.76 (m, 1H), 2.41 (d, *J*=7.6 Hz, 1H), 1.89–1.96 (m, 4H), 1.7 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 121.6, 115.3, 84.4, 79.0, 71.3, 44.3, 36.3, 35.7, 35.5, 24.2, 23.1. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.33; H, 8.60.

*2.1.6. (3aS,4S,6R,6aR)-4-(4-Methoxybenzyloxy)-6-vinyltetrahydro-3aH-spiro-[cyclopenta[d][1,3]dioxole-2,1′-cyclopentane] (**13**).* Compound **12** (3.00 g, 14.3 mmol) was dissolved in dry DMF (15 mL) and this solution cooled to 0 °C. Then, NaH (685 mg, 17.1 mmol, 60% in mineral oil) was added in one portion. The resultant solution was stirred for 30 min and then *p*-methoxybenzyl chloride (PMBCl) (4.15 mL, 28.5 mmol) added at 0 °C in one portion. The solution was stirred at room temperature for 3 h and then the solvent was removed under reduced pressure. To this saturated aqueous NH_4Cl solution (40 mL) was added and the mixture extracted with EtOAc (3×50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue purified by silica gel column chromatography (hexanes/EtOAc, 8:1) to provide **13** as a colorless oil (4.06 g, 86.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 5.68 (m, 1H), 5.03 (m, 1H), 4.97 (m, 1H), 4.65 (d, *J*=10.4 Hz, 1H), 4.55 (d, *J*=10.4 Hz, 1H), 4.43 (t, *J*=6.4, 5.6 Hz, 1H), 4.30 (d, *J*=5.6 Hz, 1H), 3.81 (m, 4H), 2.66 (t, *J*=7.2 Hz, 6.75, 1H), 2.03–2.16 (m, 2H), 1.70–1.94 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 138.9, 130.8, 129.7, 121.0, 115.0, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.1, 35.8, 35.6, 32.1, 24.3, 23.3. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.35; H, 8.01.

*2.1.7. (1R,2R,3S,5R)-3-(4-Methoxybenzyloxy)-5-vinylcyclopentane-1,2-diol (**14**).* Compound **13** (4.06 g, 12.29 mmol) was dissolved in 3 N HCl (0.41 mL) in MeOH and stirred at 25 °C overnight. Neutralization of this solution with $NaHCO_3$ was conducted and the

mixture filtered. The filtrate was removed under reduced pressure, and the residue purified by silica gel column chromatography (hexanes/EtOAc, 3:1) to provide **14** as a colorless oil (2.82 g, 86.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J=8.8 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 5.77 (m, 1H), 5.05 (m, 1H), 4.97 (m, 1H), 4.65 (d, J=11.6 Hz, 1H), 4.55 (d, J=11.6 Hz, 1H), 4.02 (t, J=6.4, 5.6 Hz, 1H), 3.99 (m, 1H), 3.81 (s, 3H), 3.66 (t, J=6.4, 7.6, 1H), 2.63–2.7 (m, 1H), 2.05–2.09 (m, 1H), 1.59–1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.7, 131.1, 129.5, 121.1, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.3, 32.2. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.14; H, 7.52.

*2.1.8. (1R,2R,3S,5R)-2-(tert-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-5-vinylcyclopentanol (**15**) and (1S,2R,3R,5S)-2-(tert-butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-3-vinylcyclopentanol (**16**).* Compound **14** (2.82 g, 10.67 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and to this 4-(dimethylamino) pyridine (DMAP) (65 mg, 0.53 mmol) was added. The resultant solution was treated with imidazole (726 mg, 10.67 mmol) and TBDPSCl (3.0 mL, 11.74 mol) at 0 °C. This was followed by warming the solution to room temperature and stirring for an additional 2 h. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by silica gel column chromatography (hexanes/EtOAc, 5:1) to provide **15** (2.2 g, 41%) and **16** (1.82 g, 34%) as colorless oil. Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.71 (m, 4H), 7.27–7.42 (m, 6H), 7.25 (d, J=2 Hz, 2H), 6.86 (d, J=2 Hz, 2H), 5.32–5.42 (m, 1H), 4.83 (m, 1H), 4.71–4.81 (m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.42 (d, J=11.6 Hz, 1H), 3.78 (m, 5H), 2.74–2.8 (m, 1H), 2.7 (s, 1H), 2.02–2.12 (m, 1H), 1.55–1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 138.4, 135.5, 133.5, 131.1, 130.1, 129.7, 127.6, 121.1, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.3, 32.2, 25.3, 19.3. Anal. Calcd for $C_{31}H_{38}O_4Si$: C, 74.06; H, 7.62. Found: C, 74.01; H, 7.53. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.71 (m, 4H), 7.34–7.43 (m, 6H), 7.25 (d, J=4.8 Hz, 2H), 6.85 (d, J=4.8 Hz, 2H), 5.30–5.42 (m, 1H), 4.8–4.92 (m, 2H), 4.41–4.49 (m, 2H), 3.79 (s, 3H), 3.71–3.79 (m, 2H), 2.81–2.9 (m, 1H), 2.49 (s, 1H), 2.02–2.12 (m, 1H), 1.55–1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 136.3, 134.1, 133.1, 131.2, 130.3, 129.2, 128.1, 120.9, 114.3, 85.2, 79.3, 77.9, 72.8, 55.5, 47.3, 33.3, 27.2, 19.4. Anal. Calcd for $C_{31}H_{38}O_4Si$: C, 74.06; H, 7.62. Found: C, 74.15; H, 7.59.

*2.1.9. (1R,2R,3R,5S)-2-(tert-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-3-vinylcyclopentanol (**18**).* Compound **16** (2 g, 3.98 mmol) was dissolved in THF (20 mL) and to this chloroacetic acid (489 mg, 5.17 mmol) and Ph_3P (2.09 g, 7.96 mmol) were added. The resultant solution was cooled to −40 °C and diisopropyl azodicarboxylate (DIAD) (1.16 mL, 5.97 mmol) added dropwise. The mixture was warmed to room temperature, and then heated to 60 °C for 24 h. The solvent was removed under reduced pressure and the residue purified by silica column chromatography (hexanes/EtOAc, 6:1) to give (1*R*,2*R*,3*R*,5*S*)-2-(*tert*-butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-3-vinyl cyclopentyl 2-chloroacetate (**17**) as colorless oil (1.52 g, 66%). The crude product, which was contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

Compound **17** (1.72 g, 2.97 mmol) was dissolved in 1 N LiOH (5.9 mL) in MeOH (20 mL) and this solution stirred at 25 °C for 2 h. To this, 0.5 N HCl (aqueous) solution was added to neutralize the solution. This was followed by the addition of H_2O (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and purified by silica gel column chromatography (hexanes/EtOAc, 6:1) to provide **18** as a colorless oil (1.27 g, 84.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.72 (m, 4H), 7.35–7.42 (m, 6H), 7.24 (d, J=4.8 Hz, 2H), 6.84 (d, J=4.8 Hz, 2H), 5.35–5.44 (m, 1H), 4.7–4.93 (m, 2H), 4.42–4.48 (m, 2H), 3.8 (s, 3H), 3.73–3.79 (m, 2H), 2.82–2.89 (m, 1H), 2.5 (s, 1H), 2.01–2.09 (m, 1H), 1.56–1.61 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 136.2, 134.2, 133.2, 131.3, 130.2, 129.3, 128.1, 120.9, 114.2, 85.1, 79.2, 77.8, 72.7, 55.4, 47.2, 33.2, 27.1, 19.4. Anal. Calcd for $C_{31}H_{38}O_4Si$: C, 74.06; H, 7.62. Found: C, 74.03; H, 7.51.

*2.1.10. tert-Butyl((1R,2S,3S,5R)-2-fluoro-3-(4-methoxybenzyloxy)-5-vinylcyclo-pentyloxy)diphenylsilane (**19**).* Compound **18** (1.5 g, 2.98 mmol) was dissolved in dry CH_2Cl_2 (12 mL) and to this pyridine (0.7 mL, 8.95 mmol) and DAST (0.59 mL, 4.48 mmol) were added. The resultant solution was warmed to room temperature under N_2 for 12 h and then reaction quenched with saturated aqueous Na_2CO_3 solution (15 mL). The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers dried (Na_2SO_4), concentrated under reduced pressure, and purified by silica gel column chromatography (hexanes/EtOAc, 6:1) to provide **19** as a colorless oil (0.956 g, 63.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.72 (m, 4H), 7.27–7.42 (m, 6H), 7.25 (d, J=2 Hz, 2H), 6.86 (d, J=2 Hz, 2H), 5.32–5.42 (m, 1H), 4.83–4.92 (m, 2H), 4.39–4.44 (m, 2H), 3.81–3.92 (m, 2H), 3.76 (s, 3H), 2.80–2.86 (m, 1H), 2.5 (s, 1H), 2.02–2.12 (m, 1H), 1.55–1.65 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 138.6, 135.4, 133.4, 130.9, 130.3, 129.5, 127.6, 121.2, 114.1, 85.3, 79.3, 78, 71.6, 55.4, 44.3, 33.1, 25.2, 19.5. Anal. Calcd for $C_{31}H_{37}FO_3Si$: C, 73.77; H, 7.39. Found: C, 73.82; H, 7.33.

*2.1.11. ((1R,2R,3S,4S)-2-(tert-Butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxybenzyloxy)cyclopentyl)methanol (**20**).* Compound **19** (2.2 g, 4.36 mmol) was dissolved in MeOH (20 mL) and to this 4-methylmorpholine *N*-oxide (1.8 mL, 8.72 mmol, 50% in water), H_2O (14 mL), and $NaIO_4$ (2.05 g, 9.59 mmol) were added. The mixture was cooled to 0 °C and OsO_4 (55 mg, 0.218 mmol, 5 mol%) was added. This mixture was stirred at 0 °C for 2 h and then filtered followed by removing the MeOH under reduced pressure. The residue was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (20 mL) and to this was added $NaBH_4$ (412 mg, 10.9 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C for 1 h and saturated aqueous NH_4Cl solution (20 mL) was added. The mixture was filtered through Celite and the filtrate removed under reduced pressure. The residue was extracted with EtOAc (3×15 mL) and the combined organic layers dried (Na_2SO_4), then concentrated to give a residue that was purified by silica column chromatography (hexanes/EtOAc, 5:1) to provide **20** as a colorless oil (1.29 g, 58.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.70 (m, 4H), 7.28–7.41 (m, 6H), 7.25 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 4.41–4.48 (m, 2H), 3.80–3.88(m, 2H), 3.74 (s, 3H), 3.69–3.72(m, 2H), 2.81–2.89 (m, 1H), 2.5 (s, 1H), 1.71–1.85 (m, 2H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 138.3, 133.4, 131.2, 129.8, 129.6, 127.5, 121.2, 85.3, 79.1, 77.8, 71.5, 61.4, 55.2, 44.2, 32.8, 25.4, 19.6. Anal. Calcd for $C_{30}H_{37}FO_4Si$: C, 70.83; H, 7.33. Found: C, 70.63; H, 7.44.

*2.1.12. tert-Butyl(((1R,2R,3S,4S)-2-(tert-butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxybenzyloxy)cyclopentyl)methoxy)diphenylsilane (**21**).* Compound **20** (1.1 g, 2.16 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and to this DMAP (13 mg, 0.11 mmol) was added. To the solution was then added with imidazole (177 mg, 2.59 mmol) and TBDPSCl (0.66 mL, 2.59 mol) at 0 °C. Following the additions, the solution was warmed to room temperature and stirred for 2 h. Water (10 mL) was added to quench the reaction and the mixture extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by silica gel column chromatography (hexanes/EtOAc, 8:1) to provide **21** as a colorless oil (1.49 g, 92%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.69–7.72 (m, 8H), 7.23–7.33 (m, 12H), 7.26 (d, J=8.4 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 4.57 (d, J=5.6 Hz, 1H), 4.47–4.51 (m, 2H), 4.26 (m, 1H), 3.75 (s, 3H), 3.66–3.72 (m, 2H), 3.41 (m, 1H), 2.19–2.23 (m, 2H), 1.81–1.89 (m, 1H), 0.94 (s, 9H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 138.3, 134.2, 133.4, 132.2, 131.2, 130.4, 130.1, 129.7, 128.6, 127.5, 121.2, 85.2, 79.2, 77.9, 71.8, 61.2, 55.6, 44.3, 33.2, 25.3, 25.1, 19.2, 19.0. Anal. Calcd for $C_{46}H_{55}O_4FSi_2$: C, 73.95; H, 7.42. Found: C, 73.78; H, 7.32.

*2.1.13. (1S,2S,3R,4R)-3-(tert-Butyldiphenylsilyloxy)-4-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopentanol (**22**).* Compound **21** (1.5 g, 2.39 mmol) was dissolved in CH_2Cl_2 (20 mL). To this, DDQ (652 mg, 2.87 mmol) was added in one portion and the mixture stirred at room temperature for 2 h. Saturated aqueous Na_2CO_3 solution (20 mL) was added. The mixture was then extracted with EtOAc (3×15 mL) and the organic layers combined, washed with saturated aqueous Na_2CO_3 solution (20 mL), brine (20 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified by silica gel column chromatography (hexanes/EtOAc, 5:1) to provide **22** as a colorless oil (1.14 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.73 (m, 8H), 7.32–7.42 (m, 12H), 4.66 (d, J=5.6 Hz, 1H), 4.28–4.31 (m, 1H), 3.71–3.79 (m, 2H), 3.23–3.26 (m, 1H), 2.29–2.32 (m, 2H), 1.82–1.92 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 134.1, 133.5, 132.1, 131.3, 130.3, 130.7, 127.6, 85.2, 79.2, 77.2, 61.3, 44.3, 33.2, 25.3, 25.2, 19.3, 19.0. Anal. Calcd for $C_{38}H_{47}O_3FSi_2$: C, 72.80; H, 7.56. Found: C, 72.81; H, 7.44.

*2.1.14. tert-Butyl((1R,2R,3S,5R)-2-fluoro-3-(4-methoxybenzyloxy)-5-vinylcyclopentyloxy)diphenylsilane (**23**).* Following the procedure for preparing **19**, compound **16** (1.4 g, 2.78 mmol) provided **23** as a colorless oil (0.911 g, 64.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7–7.74 (m, 4H), 7.29–7.42 (m, 6H), 7.26 (d, J=2 Hz, 2H), 6.87 (d, J=2 Hz, 2H), 5.34–5.43 (m, 1H), 4.83–4.92 (m, 2H), 4.4–4.45 (m, 2H), 3.81–3.90(m, 2H), 3.73 (s, 3H), 2.81–2.86 (m, 1H), 2.51 (s, 1H), 2.06–2.14 (m, 1H), 1.53–1.63 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 137.5, 135.1, 133.3, 130.9, 130.3, 129.6, 127.6, 121.3, 114.2, 85.3, 79.3, 78.0, 71.5, 55.6, 44.3, 33.2, 25.1, 19.5. Anal. Calcd for $C_{31}H_{37}O_3FSi$: C, 73.77; H, 7.39. Found: C, 73.71; H, 7.29.

*2.1.15. ((1R,2R,3R,4S)-2-(tert-Butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxybenzyloxy)cyclopentyl)methanol (**24**).* By following the procedure for preparing **20**, compound **23** (2.15 g, 4.26 mmol) yielded **24** as a colorless oil (1.287 g, 59.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.70 (m, 4H), 7.27–7.38 (m, 6H), 7.25 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 4.42–4.48 (m, 2H), 3.82–3.89(m, 2H), 3.73 (s, 3H), 3.69–3.72(m, 2H), 2.82–2.88 (m, 1H), 2.49 (s, 1H), 1.71–1.85 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 138.3, 133.3, 131.2, 130.1, 129.5, 127.5, 121.3, 85.4, 79.1, 77.9, 71.5, 61.4, 55.3, 44.3, 32.7, 25.5, 19.7. Anal. Calcd for $C_{30}H_{37}O_4FSi$: C, 70.83; H, 7.33. Found: C, 70.71; H, 7.41.

*2.1.16. tert-Butyl(((1R,2R,3R,4S)-2-(tert-butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxybenzyloxy)cyclopentyl)methoxy)diphenylsilane (**25**).* Calling on the procedure that gave **22**, compound **24** (1.5 g, 2.95 mmol) led to **25** as a colorless oil (2.07 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7–7.74 (m, 8H), 7.25–7.33 (m, 12H), 7.26 (d, J=8.4 Hz, 2H), 6.92 (d, J=8.4 Hz, 2H), 4.56 (d, J=5.6 Hz, 1H), 4.46–4.50 (m, 2H), 4.25 (m, 1H), 3.75 (s, 3H), 3.64–3.70 (m, 2H), 3.40 (m, 1H), 2.17–2.22 (m, 2H), 1.82–1.89 (m, 1H), 0.93 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.3, 134.2, 133.3, 132.1, 131.1, 130.3, 130.1, 129.5, 128.4, 127.1, 121.1, 85.4, 79.5, 77.3, 71.8, 61.1, 55.4, 44.2, 33.2, 25.3, 25.1, 19.2, 19.0. Anal. Calcd for $C_{46}H_{55}FO_4Si_2$: C, 73.95; H, 7.42. Found: C, 73.87; H, 7.36.

*2.1.17. (1S,2R,3R,4R)-3-(tert-Butyldiphenylsilyloxy)-4-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopentanol (**26**).* Employing the same procedure for obtaining **22**, compound **25** (1.45 g, 2.31 mmol) provided **26** as a colorless oil (1.14 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.70 (m, 8H), 7.28–7.37 (m, 12H), 4.62 (d, J=5.6 Hz, 1H), 4.24–4.27 (m, 1H), 3.71–3.76 (m, 2H), 3.21–3.25 (m, 1H), 2.29–2.3 (m, 2H), 1.81–1.88 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 134.5, 133.4, 132.1, 131.4, 130.2, 130.8, 127.5, 85.3, 79.1, 77.1, 61.3, 44.1, 32.9, 25.4, 25.2, 19.3, 19.2. Anal. Calcd for $C_{38}H_{47}O_3Si_2F$: C, 72.80; H, 7.56. Found: C, 72.68; H, 7.53.

*2.1.18. (1R,2S,3R,5R)-3-(4-Amino-1H-imidazo[4,5-c]pyridin-1-yl)-2-fluoro-5-(hydroxylmethyl)cyclopentanol (**3**).* Compound **22** (2 g, 3.19 mmol) was dissolved in THF (20 mL) and to this deazapurine **27**[8] (1.6 g, 4.79 mmol) and Ph_3P (1.67 g, 6.38 mmol) were added. The solution was cooled to −40 °C and diisopropyl azodicarboxylate (DIAD) (0.93 mL, 4.79 mmol) was added dropwise. The mixture was warmed to room temperature, and then heated to 60 °C for 24 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (hexanes/EtOAc, 2:1) to give crude 1-((1*R*,2*S*,3*R*,4*R*)-3-(*tert*-butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-2-fluorocyclopentyl)-4-(*N*,*N*-di-(*tert*-butyl-*O*-carbonyl)amino)-1*H*-imidazo[4,5-*c*]pyridine (**28a**) as yellow oil (1.01 g). This crude product, which was contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

Crude **28a** (0.9 g, 0.954 mmol) was dissolved in 1 N HCl (0.174 mL) in MeOH and stirred at 25 °C overnight. Amberlite IRA-400(Cl) ion exchange resin was then added to neutralize the solution to pH 7. The mixture was filtered and the filtrate removed under reduced pressure giving a residue that was purified by silica gel column chromatography (EtOAc/MeOH/NH_4OH, 20:2:1) to provide **3** as a white solid (0.14 g, 18.7% for two steps). Mp 238–241 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.69 (d, J=6 Hz, 1H), 6.84 (d, J=6 Hz, 1H), 6.14 (br, 2H), 5.46 (d, J=2 Hz, 1H), 4.81–4.92 (m, 2H), 4.80 (d, J=2 Hz, 1H), 3.92–4.00 (m, 2H), 3.71–3.79 (m, 2H), 2.32–2.37 (m, 1H), 1.98–2.02 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.8, 141.5, 141.3, 135.5, 135.1, 108.6, 94.1, 78.8, 72.8, 62.8, 32.4, 24.9. Anal. Calcd for $C_{12}H_{15}N_4O_2F$: C, 54.13; H, 5.68; N, 21.04. Found: C, 54.14; H, 5.61; N, 20.93.

*2.1.19. (1R,2R,3R,5R)-3-(4-Amino-1H-imidazo[4,5-c]pyridin-1-yl)-2-fluoro-5-(hydroxylmethyl)cyclopentanol (**4**).* In the same way that **3** was achieved, **26** (1.8 g, 2.87 mmol) gave crude 1-((1*R*,2*R*,3*R*,4*R*)-3-(*tert*-butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-2-fluorocyclopentyl)-4-(*N*,*N*-di-(*tert*-butyl-*O*-carbonyl) amino)-1*H*-imidazo[4,5-*c*]pyridine (**28b**) as yellow oil (1.11 g). This crude product, which contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

As with **28a**, crude **28b** (1 g, 1.06 mmol) yielded **4** as a white solid (0.16 g, 23.3% for two steps), mp 239–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.67 (d, J=6 Hz, 1H), 6.82 (d, J=6 Hz, 1H), 6.15 (br, 2H), 5.44 (d, J=2 Hz, 1H), 4.79–4.89 (m, 2H), 4.75(d, J=2 Hz, 1H), 3.90–3.97 (m, 2H), 3.70–3.79 (m, 2H), 2.31–2.36 (m, 1H), 1.98–2.02 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.6, 141.3, 141.1, 135.1, 135.0, 107.9, 94.4, 78.6, 72.5, 62.6, 32.4, 24.8. Anal. Calcd for $C_{12}H_{15}N_4O_2F$: C, 54.13; H, 5.68; N, 21.04. Found: C, 54.05; H, 5.59; N, 20.94.

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