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Carbocyclic 4′-*epi*-formycin

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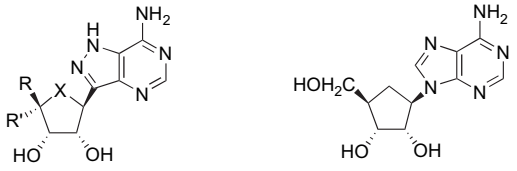
Abstract—Formycin is a naturally occurring biologically responsive C-nucleoside. In pursuing the design and syntheses of novel C-nucleosides, convenient access to carbocyclic C-nucleosides based on the formycin framework was a goal. One such target was carbocyclic 4′-*epi*-formycin (**4**). This compound is reported via a procedure based on an asymmetric aldol/ring closure metathesis strategy. To provide a preliminary glimpse into the biological characterization of **4** an antiviral assay was conducted. Target **4** was found to be inactive and to lack cytotoxicity to the host cells.

1. Introduction

Formycin A (**1**) is the C-nucleoside isomer of adenosine, which has achieved a place of potential that has not been fully developed for its value in medicinal agent discovery.[1] Similarly, but more thoroughly studied, is the carbocyclic adenine derivative aristeromycin (**2**).[2] Little attention[3] has been devoted to combining these two structural features into carbocyclic C-nucleosides (e.g., carbocyclic formycin A, **3**) as a source for a new chemotherapeutic library. Our goal is to gain access to representatives of this latter group of compounds. The 4′-epimer of **3** (i.e., **4**), which is an analog of α-L-lyxoadenosine,[4] is a member of that series and it is described herein (Fig. 1).



1, R=CH_2OH;R'=H;X=O
3, R=CH_2OH;R'=H;X=CH_2
4, R=H;R'=CH_2OH;X=CH_2

2

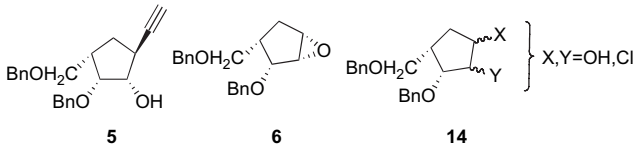
Figure 1.

2. Chemistry

The plan to **4** required the availability of the cyclopentyl alkyne **5** as the starting material for construction of the requisite pyrazolo[4,3-*d*]pyrimidine base unit.[3d,e,5a–c,e] Because of the numerous examples of stereoselective epoxide ring openings as synthetic sequence components,[6] **5** (Fig. 2) was seen as being accessible from the chiral **6** and an alkynyl organoaluminum reagent.[7] To gain access to **6**, we adapted literature conditions[8–10] beginning with (*R*)-4-benzyl-2-oxazolidinone (**8**) (Scheme 1) and called on asymmetric aldol/ring closure metathesis steps.

With **6** in hand, its reaction with diethyl[(trimethylsilyl)-ethynyl]aluminum resulted in **13** (Scheme 2) and minor side-products assigned as **14**.[11] Desilylation of **13** yielded **5**, whose X-ray crystallographic analysis (Fig. 3) confirmed that the hydroxy, benzyloxy, and benzyloxymethyl were on same face of cyclopentyl ring and opposite to the alkynyl unit.

Formylation of **5** and subsequent reaction of the resultant substituted propargylic aldehyde with hydrazine, and then acetylation provided **15**.[3d,e] Debenzylation (boron tribromide was superior to catalytic hydrogenolysis) of **15** and then acetylation (to **16**) was followed by nitration and *cine*-cyano substitution[3d,e,5c–e] to yield **17**. Hydrogenation of **17** gave **18**. Deacetylation of **18** (to **19**) and subsequent treatment with formamidine[3d,e,5c,e] produced the fused pyrimidine target **4**.



5 **6** **14**

Figure 2.

Keywords: Cyclopentyl; C-nucleoside; Pyrazolo[4,3-*d*]pyrimidine; Diastereomeric aldol.
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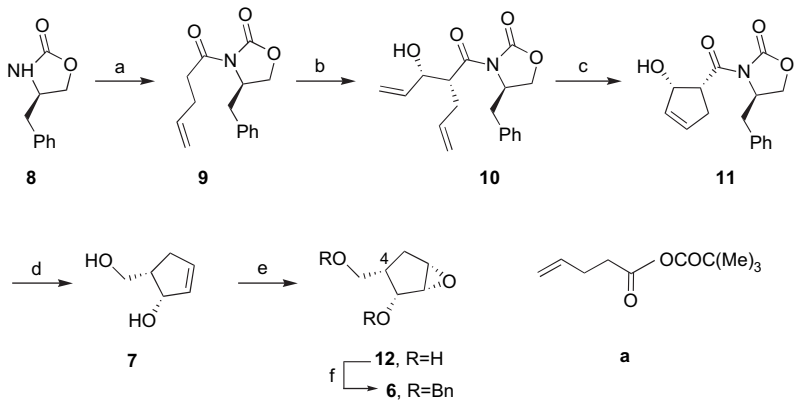
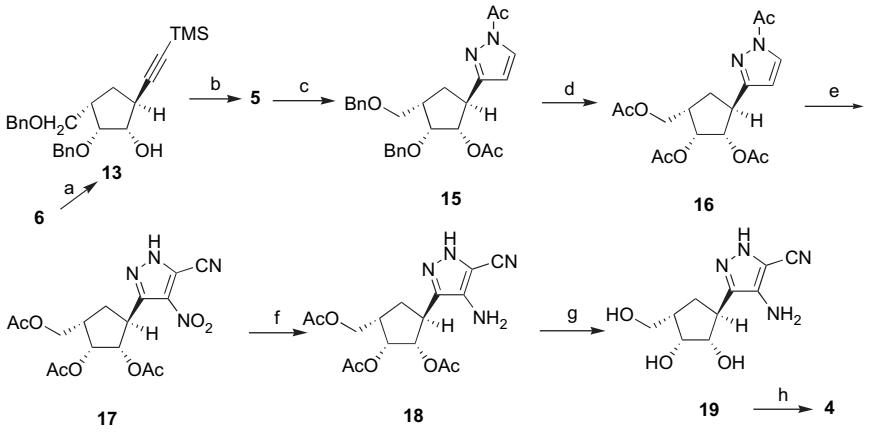


Scheme 1. Reaction conditions: (a) (i) *n*-BuLi/hexanes, THF; (ii) **a**, TBME, 100% for two steps; (b) (i) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; (ii) acrolein, −78 °C, CH_2Cl_2, 92% for two steps; (c) Grubbs catalyst, CH_2Cl_2, 59%; (d) $LiBH_4$, MeOH, THF, 0 °C, 66%; (e) *m*-CPBA, CH_2Cl_2; (f) NaH, BnBr, TBAI, THF, 72% (for steps (e) and (f)).



Scheme 2. Reaction conditions: (a) Me_3SiCCH, BuLi, −78 °C, N_2 followed by Et_2AlCl, 0 °C, 62%; (b) TBAF, THF, 92%; (c) (i) *n*-BuLi/hexanes, TBME followed by DMF; (ii) hydrazine monohydrate, AcOH; (iii) Ac_2O, pyridine, DMAP, 85% for three steps; (d) (i) BBr_3, CH_2Cl_2, (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 76%; (e) (i) ammonium nitrate, TFA, TFAA; (ii) KCN, EtOH/EtOAc, 88% for two steps; (f) H_2, Pd/C, MeOH, 92%; (g) NH_3, MeOH, 88%; (h) formamidine acetate, EtOH, 60%.

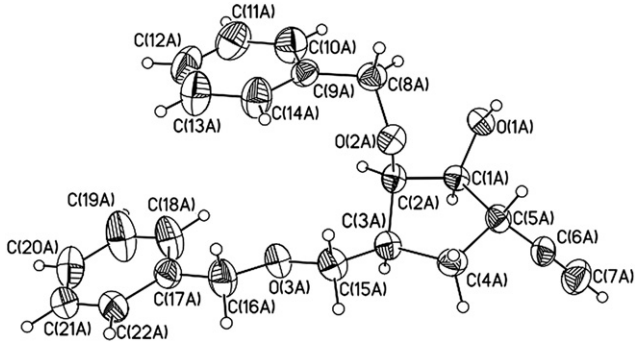


Figure 3. X-ray structure for compound **5**.

3. Antiviral analysis

To gain preliminary insight into the biological potential of **4**, it was subjected to antiviral screening versus herpes simplex-1, herpes simplex-2, herpes simplex-1 (TK^-), vaccinia, vesicular stomatitis, coxsackie B4, respiratory syncytial, parainfluenza 3, reovirus-1, Sindbis, and Punta Toro.[12] No activity was found. Also, no cytotoxicity arose in the cell lines used in the antiviral assays: human erythroleukemia (HEL), HeLa, and Vero.

4. Conclusion

A straightforward chiral synthesis of carbocyclic 4′-*epi*-formycin has been achieved using practical means and avails a rare example of a 4′-*epi*-carbocyclic nucleoside.[13] The absence of antiviral activity with **4** may be the consequence of its failure to undergo conversion to the 5′-nucleotide derivative, an efficient intracellular process for the parent formycin,[14] and/or its lack of inhibitory effect on *S*-adenosylhomocysteine hydrolase, a site of action of aristeromycin (**3**).[2]

5. Experimental

5.1. Materials and methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer or Bruker AC-250 spectrometer. All ^1H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet),

q (quartet), m (multiplet) and br (broad), dd (doublet of doublet). 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 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in an N_2 atmosphere under anhydrous conditions.

5.1.1. (4*R*)-Benzyl-3-(pent-4-enoyl)oxazolidin-2-one (9). Triethylamine (15.3 mL, 0.11 mol) was added to a solution of 4-pentenoic acid (11.6 mL, 11.3 g, 0.11 mol) in *t*-butyl methyl ether (800 mL) cooled to −78 °C. The solution was stirred for 5 min, and pivaloyl chloride (13.5 mL, 0.11 mol) was added. After 15 min, the bath was removed and replaced by an ice H_2O bath. The heterogeneous mixture (containing **a**) was mechanically stirred at 0 °C for 1 h. In a separate flask, a solution of (*R*)-4-benzyl-2-oxazolidinone (**8**, 19.2 g, 0.11 mol) in THF (200 mL) was cooled to −78 °C, whereupon *n*-BuLi (44.0 mL, 2.5 M in hexanes, 0.11 mol) was added slowly. This solution was stirred for 10 min at −78 °C. The flask containing the mixed anhydride was cooled to −78 °C, and the lithiated oxazolidinone transferred via cannula into the mixed anhydride **a**. After being stirred at −78 °C for 15 min, the reaction mixture was warmed to 0 °C and stirred for 30 min, then the reaction was quenched by addition of aqueous, saturated NH_4Cl. After extraction twice with CH_2Cl_2, the combined organic phases were dried (anhyd Na_2SO_4), filtered, and the filtrate concentrated. Purification by flash silica gel column chromatography (hexanes/EtOAc, 3:1) gave **9** (28.5 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (m, 2H), 2.76 (dd, 1H, *J*=9.4, 13.4 Hz), 3.03 (m, 2H), 3.24 (dd, 1H, *J*=10.1, 13.4 Hz,), 4.12 (m, 2H), 4.64 (m, 1H), 5.04 (m, 2H), 5.86 (m, 1H), 7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 35.2, 38.2, 55.5, 66.6, 116.0, 127.7, 129.3, 129.8, 135.8, 137.2, 153.8, 172.8. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.44; H, 6.65; N, 5.31.

5.1.2. [3(2*R*,3*S*),4*R*]-3-(2-Allyl-3-hydroxypent-4-enoyl)-4-benzyloxazolidin-2-one (10). To a solution of **9** (26 g, 0.10 mol) in CH_2Cl_2 (50 mL) at −78 °C under N_2 atmosphere was added diisopropylethylamine (39 mL, 0.22 mol) followed by dibutylboron triflate (200 mL, 0.20 mol, 1.0 M solution in CH_2Cl_2). The reaction mixture was allowed to stir for 1 h at room temperature. After re-cooling to −78 °C, a solution of acrolein (16 mL, 0.22 mol) in CH_2Cl_2 (100 mL) was added dropwise. The mixture was stirred for 2 h at −78 °C. Then, the reaction mixture was slowly warmed to room temperature and allowed to stir overnight. It was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (anhyd Na_2SO_4), filtered, and the filtrate evaporated under reduced pressure. Purification of the residue via silica gel flash chromatography (gradient elution from 10% to 25% EtOAc/hexanes) afforded **10** (29 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (m, 1H), 2.66 (m, 2H), 2.86 (br s, 1H), 3.31 (m, 1H), 4.18 (m, 2H), 4.29 (m, 1H), 4.47, (br s, 1H), 4.73 (m, 1H), 5.24 (m, 4H), 5.91 (m, 2H), 7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 38.1, 47.4, 55.7, 66.1, 73.4, 116.9, 117.4, 127.5, 129.1, 129.6, 135.3, 135.4, 137.4, 153.7, 174.5. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.20; H, 7.07; N, 4.11.

5.1.3. [3(1*R*,2*S*),4*S*]-4-Benzyl-3-(2-hydroxycyclopent-3-enecarbonyl)oxazolidin-2-one (11). A solution of compound **10** (22.2 g, 70.4 mmol) in CH_2Cl_2 (300 mL) was degassed by passing through a stream of N_2 for 25 min and 0.5 mol % of Grubbs catalyst (first generation) was then added under an atmosphere of N_2. After stirring overnight, the reaction mixture was exposed to air for 1 h, and purified by flash silica gel column chromatography (hexanes/EtOAc, 1:1) to yield **11** (12 g, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (m, 1H), 2.76 (m, 1H), 2.86 (d, 1H, *J*=7.5 Hz), 3.14 (m, 1H), 3.27 (m, 1H), 4.09 (m, 1H), 4.22 (m, 1H), 4.40 (m, 1H), 4.69, (m, 1H), 5.10 (br s, 1H), 5.72 (m, 1H), 5.99 (m, 1H), 7.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 37.9, 47.2, 55.4, 66.2, 76.9, 127.2, 128.8, 129.4, 130.9, 134.4, 135.5, 153.7, 172.0. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.69; H, 6.04; N, 4.71.

5.1.4. (1*S*,5*S*)-5-Hydroxymethyl-2-cyclopenten-1-ol (7). A solution of $LiBH_4$ (1.0 g, 43.0 mmol) in THF (55 mL) cooled at 0 °C was added into a solution of **11** (11.0 g, 38.3 mmol) in THF (150 mL) and MeOH (1.7 mL). The reaction mixture was stirred at 0 °C for 45 min and then allowed to warm to room temperature. After 1 h, 10% NaOH (61 mL) was added, and stirring continued until both phases were clear. The mixture was extracted with Et_2O. The organic phase was washed with brine, dried (anhyd Na_2SO_4), filtered, and the filtrate concentrated in vacuo. Purification by silica gel flash chromatography (gradient elution from 50% to 70% EtOAc/hexanes) yielded **7** (2.9 g, 66.3%) as a colorless liquid, $[\alpha]_D^{22.8}$ 124.0 (*c* 0.26, methanol) (lit.[10] reported $[\alpha]_D^{24}$ −125.1 (*c* 0.47, CH_2Cl_2) for the enantiomer of **7**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (m, 1H), 2.37 (m, 2H), 3.75 (br s, 2H), 4.24 (d, 2H, *J*=16.8 Hz), 4.85 (br s, 1H), 5.81 (m, 1H), 5.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 42.7, 62.2, 76.9, 132.4, 134.7. Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.04; H, 8.98.

5.1.5. (1*S*,2*R*,3*S*,4*S*)-1-Benzyloxymethyl-2-benzyloxy-3,4-epoxyclopentane (6). A solution of **7** (2.1 g, 18.4 mmol), *m*-chloroperoxybenzoic acid (7.2 g), and CH_2Cl_2 (100 mL) was stirred at room temperature overnight. The solvent was removed and the residue partitioned between Et_2O and H_2O. The solvent was then removed in vacuo to obtain **12** (2.2 g), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (m, 1H), 2.13 (m, 1H), 2.43 (m, 1H), 3.40 (m, 2H), 3.52 (m, 1H), 3.61 (m, 1H), 3.69 (m, 2H), 4.60 (dd, 1H, *J*=1.5, 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 37.8, 56.2, 61.5, 64.0, 75.2.

To a solution of **12** (2.2 g) in anhyd THF (50 mL) at 0 °C, NaH (2 g, 50 mmol, 60% dispersion in mineral oil) was added in several portions. After 30 min, benzyl bromide (6.1 mL, 51.3 mmol) and a catalytic amount of

tetrabutylammonium iodide were added. The reaction mixture was then allowed to stir at room temperature overnight. After the starting material was no longer present (TLC), ice H_2O was added to quench the reaction. The resultant mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (anhyd Na_2SO_4), filtered, and the filtrate concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexanes/EtOAc, 4:1) affording **6** (4.1 g, 72% over two steps) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (m, 1H), 2.32 (d, 1H, J=14.9 Hz), 2.53 (m, 1H), 3.48 (m, 1H), 3.58 (m, 2H), 3.90 (dd, 1H, J=4.7, 9.2 Hz), 4.23 (dd, 1H, J=1.2, 8.5 Hz), 4.56 (s, 2H), 4.70 (q, 2H, J=12.0 Hz), 7.41 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 35.7, 54.9, 57.8, 72.5, 72.6, 73.7, 80.9, 127.6, 127.7, 127.9, 128.0, 128.5, 128.6, 138.3, 138.9. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.42; H, 7.10.

5.1.6. (1*S*,2*R*,3*S*,5*S*)-2-Benzyloxy-3-benzyloxymethyl-5-(trimethylsilylethynyl)cyclopentanol (13). To a solution of trimethylsilylacetylene (15.3 mL, 108.2 mmol) in anhydrous toluene (390 mL) with stirring at −78 °C under N_2 was added *n*-butyllithium (43.3 mL, 108.3 mmol, 2.5 M solution in hexanes), and the reaction mixture was stirred at the same temperature for 30 min. Then, a solution of diethylaluminum chloride (60.1 mL, 108.2 mmol, 1.8 M solution in toluene) was added at 0 °C. Upon the addition a slow precipitation of LiCl was observed. The reaction mixture was stirred for 5 h at 10 °C. A solution of epoxide **6** (6.6 g, 21.3 mmol) in toluene (20 mL) was then added immediately. The reaction mixture was stirred at 0 °C for 45 min and 3 h at room temperature, monitored by TLC analysis, and quenched with MeOH (*caution*: gas evolution). After adding H_2O (4.2 mL), 15% NaOH solution (4.2 mL), and H_2O (12.6 mL), the reaction mixture was filtered, washed with CH_2Cl_2, and the organic layer then washed with brine, and dried (anhyd Na_2SO_4). The solvent was evaporated, and the crude residue was purified by silica gel column chromatography (hexanes/EtOAc, 6:1) to give **13** (5.4 g, 62%) as a white solid, mp 47–48 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.24 (s, 9H), 1.98 (m, 2H), 2.64 (m, 1H), 2.91 (m, 1H), 3.33 (m, 1H), 3.62 (m, 2H), 4.21 (m, 2H), 4.61 (s, 2H), 4.74 (d, 2H, J=2.8 Hz), 7.41 (m, 10H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 0.46, 31.8, 36.7, 39.8, 69.4, 73.6, 78.4, 80.9, 85.9, 109.2, 128.0 (2C), 128.1(2C), 128.5 (2C), 128.7 (2C), 138.6. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.36; H, 7.93.

Further elution of the column gave **14** (1.8 g, 24.4%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (m, 1H), 2.31 (m, 1H), 2.65 (m, 1H), 3.48 (dd, 1H, J=5.7, 9.1 Hz), 3.56 (dd, 1H, J=4.3, 9.1 Hz), 3.75 (m, 1H), 4.15 (m, 2H), 4.30 (dd, 1H, J=4.1, 7.7 Hz), 4.51 (s, 2H), 4.60 (dd, 2H, J=11.4, 36.9 Hz), 7.31 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7, 38.7, 62.2, 68.6, 73.2, 73.5, 78.3, 79.3, 127.8 (2C), 128.0 (2C), 128.6 (2C), 137.7, 138.2. Anal. Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.68. Found: C, 69.17; H, 6.73.

5.1.7. (1*S*,2*R*,3*S*,5*S*)-2-Benzyloxy-3-benzyloxymethyl-5-ethynylcyclopentanol (5). To a solution of **13** (3.2 g, 7.8 mmol) in THF (60 mL) under N_2 was added tetrabutylammonium fluoride (7.8 mL, 7.8 mmol, 1 M solution in THF) by injection at 0 °C. The mixture was stirred overnight at room temperature. The solution was absorbed on silica gel, and the crude product purified by silica gel flash column chromatography (hexanes/EtOAc, 4:1) to give **5** (2.4 g, 92%) as a white solid, mp 66–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (m, 1H), 1.96 (m, 1H), 2.11 (d, 1H, J=2.5 Hz), 2.54 (m, 1H), 2.78 (m, 1H), 3.19 (d, 1H, J=8.7 Hz), 3.53 (m, 2H), 4.12 (m, 2H), 4.51 (m, 2H), 4.64 (dd, 2H, J=11.5, 13.7 Hz), 7.30 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 35.4, 39.7, 69.3, 69.9, 73.5, 73.6, 78.3, 80.9, 86.6, 127.9 (2C), 128.6 (2C), 128.7 (2C), 138.1, 138.5. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.56; H, 7.22.

5.1.8. (1*S*,2*R*,3*S*,5*S*)-1-Acetyl-5-(1-acetyl-1*H*-pyrazol-3-yl)-2-benzyloxy-3-(benzyloxymethyl)cyclopentane (15). To a solution of **5** (2.4 g, 7.1 mmol) in anhydrous *t*-butyl methyl ether (90 mL) with stirring at −78 °C under N_2 was added *n*-butyllithium (7.1 mL, 17.8 mmol, 2.5 M solution in hexanes), and the reaction mixture stirred at the same temperature for 30 min. An excess of DMF (2.7 mL, 35.0 mmol) was added in one portion and the cold bath removed. The reaction mixture was allowed to warm to room temperature and aged for 30 min. The TBME solution was poured into a vigorously stirred, biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (45 mL) and TBME (45 mL) cooled over ice to ca. +5 °C. The resulting layers were separated and the organic extract was washed with H_2O. The combined aqueous layers were back extracted with TBME. The combined organic layers were dried (anhyd Na_2SO_4), filtered, and the filtrate concentrated to give the crude acetylenic aldehyde as an oil. The crude product thus isolated was used to the next step without further purification.

To a solution of crude aldehyde (from the previous process) in glacial AcOH (78 mL) was added a solution of hydrazine monohydrate (3.7 g, 34.9 mmol) in glacial AcOH (38 mL). The resulting solution was heated at reflux for 8 h and then concentrated in vacuo to afford a dark brown oil. This crude product was dissolved in pyridine (20 mL), and Ac_2O (9.3 mL, 98.4 mmol) and DMAP were added. The resulting solution was stirred for 16 h at room temperature. The solvent was removed in vacuo, and the crude residue dissolved in EtOAc (800 mL), washed with 10% HCl and brine, dried (anhyd Na_2SO_4), concentrated, and purified by silica gel column chromatography to afford **15** (2.8 g, 85% over three steps) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.00 (m, 2H), 2.63 (s, 3H), 2.95 (m, 1H), 3.48 (dd, 1H, J=6.4, 9.0 Hz), 3.60 (m, 1H), 3.72 (t, 1H, J=8.7 Hz), 4.29 (t, 1H, J=4.0 Hz), 4.50 (dd, 2H, J=11.9, 13.6 Hz), 4.60 (q, 2H, J=11.6 Hz), 5.20 (dd, 1H, J=3.7 9.4 Hz), 6.28 (d, 1H, J=2.8 Hz), 7.29 (m, 10H), 8.14 (d, 1H, J=2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.8, 29.9, 39.3, 40.4, 69.8, 73.3, 74.1, 79.6, 80.5, 108.7, 127.7, 127.7, 127.8, 127.8, 128.5, 128.5, 129.1, 138.5, 138.9, 159.0, 169.6, 170.8. Anal. Calcd for $C_{27}H_{30}N_2O_5$: C, 70.11; H, 6.54; N, 6.06. Found: C, 70.10; H, 6.48; N, 6.08.

5.1.9. (1*S*,2*R*,3*S*,5*S*)-1,2-Diacetoxy-5-acetoxymethyl-3-(1-acetyl-1*H*-pyrazol-3-yl)cyclopentane (16). To a stirred solution of **15** (2.0 g, 4.3 mmol) in anhyd CH_2Cl_2 (180 mL)

was added boron tribromide (43.2 mL, 43.2 mmol, 1.0 M solution in CH_2Cl_2) at −78 °C and the reaction mixture stirred at the same temperature for 1 h. To this mixture was added MeOH (400 mL) and the reaction mixture neutralized with Ag_2CO_3 and filtered through a pad of Celite. The filtrate was evaporated and the crude product dissolved in CH_2Cl_2 (300 mL). To this triethylamine (4.8 mL), Ac_2O (1.9 mL) and a catalytic amount of DMAP were added, and the resulting solution stirred overnight. The mixture was then washed with brine, dried (anhyd Na_2SO_4), concentrated, and the residue chromatographed (silica gel, hexanes/EtOAc, 3:1) to afford **16** (1.2 g, 76% over two steps) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (m, 11H), 2.66 (m, 3H), 3.56 (m, 1H), 4.11 (m, 3H), 5.35 (m, 1H), 5.55 (m, 1H), 6.30 (m, 1H), 8.18 (d, 1H, J=2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.0, 21.1, 21.9, 29.8, 37.9, 39.3, 62.9, 73.3, 78.1, 108.6, 129.5, 157.8, 170.3 (2C), 170.4, 171.2. Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.05. Found: C, 55.85; H, 6.19; N, 7.67.

5.1.10. (1*S*,2*R*,3*S*,5*S*)-1,2-Diacetoxy-5-acetoxymethyl-3-(5-cyano-4-nitro-1*H*-pyrazol-3-yl)cyclopentane (17). Trifluoroacetic anhydride (2.1 mL) was added dropwise to a stirred solution of **16** (0.99 g, 2.7 mmol) and ammonium nitrate (1.9 g) in TFA (30 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. The solvent was evaporated in vacuo at room temperature and then diluted with CH_2Cl_2, washed with H_2O, saturated aqueous $NaHCO_3$ solution and brine, dried (anhyd Na_2SO_4), and the organic phase concentrated in vacuo to give the 1,4-dinitro pyrazole derivative (1.1 g) as a syrup. The crude product thus isolated was used to the next step without further purification.

At room temperature, a solution of the 1,4-dinitro compound in EtOH (9.3 mL) and EtOAc (9.3 mL) was added dropwise over 5 min to a stirred solution of KCN (1.3 g, 19.5 mmol) in EtOH (23.0 mL) and H_2O (5.5 mL). Following an additional 5 min at room temperature, the reaction mixture was neutralized with AcOH (2.0 mL). After evaporation of the solvent in vacuo, the residue was diluted with EtOAc (110 mL), washed with H_2O and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo to a residue that was subjected to chromatographic purification (silica gel, CH_2Cl_2/MeOH, 20:1) to afford **17** (0.94 g, 88% over two steps) as a light yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.09 (s, 3H), 2.11 (m, 2H), 2.21 (s, 3H), 2.36 (m, 1H), 2.96 (m, 1H), 4.21 (m, 3H), 5.58 (m, 1H), 5.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 20.7, 20.8, 30.0, 36.9, 37.8, 62.5, 72.9, 76.4, 110.7, 122.6, 133.9, 145.0, 170.6, 171.4, 171.8. Anal. Calcd for $C_{16}H_{18}N_4O_8$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.29; H, 4.59; N, 13.90.

5.1.11 (1*S*,2*R*,3*S*,5*S*)-1,2-Diacetoxy-3-acetoxymethyl-5-(4-amino-5-cyano-1*H*-pyrazol-3-yl)cyclopentane (18). A catalytic amount of Pd/C was added to a solution of **17** (0.83 g, 2.1 mmol) in MeOH (30 mL). The resulting mixture was shaken under 30 psi of H_2 overnight. After the reaction was complete, the solvent was evaporated in vacuo and the product purified by silica gel chromatography (CH_2Cl_2/EtOAc/MeOH, 8:1:0.5) to afford **18** (0.7 g, 92%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (m, 14H), 2.72 (m, 1H), 3.51 (m, 1H), 4.12 (m, 2H), 5.28 (m, 1H), 5.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (2C), 21.1, 28.7, 36.4, 37.8, 63.1, 73.1, 78.0, 110.1, 112.6, 133.8, 135.7, 170.4, 171.0, 171.4. Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.81; H, 5.89; N, 15.62.

5.1.12. (1*S*,2*R*,3*S*,5*S*)-1,2-Dihydroxy-3-hydroxymethyl-5-(4-amino-5-cyano-1*H*-pyrazol-3-yl)cyclopentane (19). Anhyd NH_3 was introduced to a solution of compound **18** (0.59 g, 1.6 mmol) in MeOH (80 mL) at 0 °C. The reaction mixture was stirred at room temperature. After the starting material was no longer present (TLC), the solvent was removed in vacuo and the residue purified by silica gel chromatography (CH_2Cl_2/MeOH, 6:1) to afford **19** (0.33 g, 88%) as a light yellow solid, mp 174–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 2H), 2.08 (m, 1H), 3.18 (m, 1H), 3.37 (m, 1H), 3.60 (m, 1H), 3.89 (m, 2H), 4.34 (m, 3H), 4.52 (m, 1H), 4.75 (m, 1H), 13.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 37.1, 41.9, 61.0, 72.7, 79.1, 114.1, 115.4, 131.7, 132.9. Anal. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.39; H, 6.03; N, 23.35.

5.1.13. (1*S*,2*R*,3*S*,5*S*)-1,2-Dihydroxy-3-hydroxymethyl-5-(7-amino-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)cyclopentane (4). A solution of **19** (0.25 g, 1.0 mmol) in EtOH (30 mL) was stirred with formamidine acetate (0.16 g, 1.5 mmol) under reflux for 50 min. The resulting white precipitate was isolated by filtration, washed with EtOH, and dried to afford analytically pure **4** (0.16 g, 60%) as a white solid, mp 269–270 °C (dec), $[\alpha]_D^{22.5}$ −53.5 (*c* 0.26, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (m, 2H), 2.28 (m, 1H), 3.41 (m, 2H), 3.62 (m, 1H), 3.98 (m, 1H), 4.34 (m, 3H), 4.94 (s, 1H), 7.24 (br s, 2H), 8.13 (s, 1H), 12.37 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 40.1, 42.8, 61.3, 73.3, 79.0, 122.2, 139.8, 148.2, 150.8, 151.2. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.00; H, 5.83; N, 26.30.

5.2. X-ray data for compound 5

Crystallographic data (excluding structure factors) for **5** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 642212. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)1223 336033 or e mail: deposit@ccdc.cam.ac.uk].

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