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Total Synthesis of Carbocyclic Analogues of Coformycin

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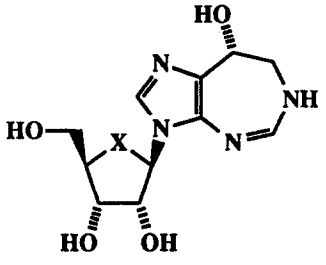
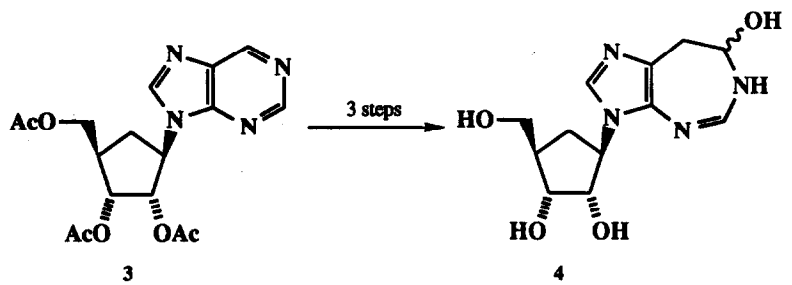
Abstract. Four carbocyclic analogues of the ribonucleoside coformycin, including the recently isolated natural product **2**, have been synthesised in racemic form. The syntheses were achieved in a convergent and direct manner *via* palladium(0) catalysed coupling between diazepinones **15** and **16** and the allylic acetate **5**.

Coformycin (**1**) is a naturally occurring nucleoside of potential use in cancer and viral chemotheraphy,[1] and possesses herbicidal properties of agrochemical interest.[2] Recently workers at Chesterford Park isolated and characterised the carbocyclic analogue **2** of coformycin, which also exhibits herbicidal activity.[3] This paper describes the total synthesis of (±)-carbocyclic coformycin (**2**) and of three other novel carbocyclic analogues of coformycin.



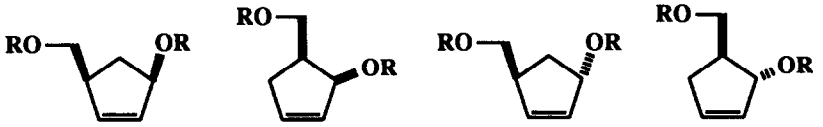
1 X = O
2 X = CH_2

Our initial studies focused on transformation of the carbocyclic purine **3**[4] *via* an analogous route to that previously reported for the conversion of purine ribonucleoside to coformycin (**1**).[5] However, while this route did furnish low yields of carbocyclic isocoformycin (**4**) the desired compound **2** was never detected (Scheme I).[6] Subsequently, we conceived that carbocyclic nucleosides such as **2** would be available *via* a palladium(0) catalysed coupling between the aglycone and the cyclopentenyl acetate **5** or **6**. This approach has recently been successfully exploited by ourselves and several other groups for the synthesis of carbocyclic nucleosides.[7,8,9,10,11]



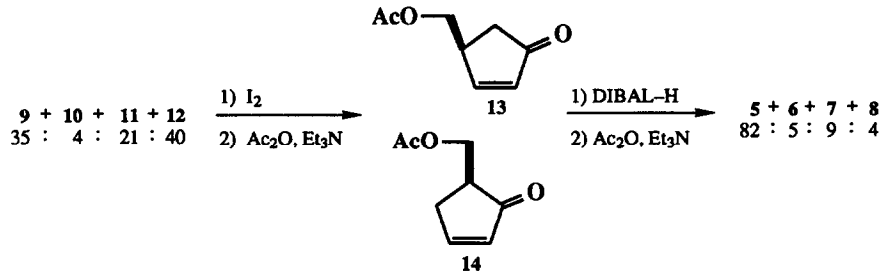
3 4

Scheme I



5 R = Ac, **9** R = H; **6** R = Ac, **10** R = H; **7** R = Ac, **11** R = H; **8** R = Ac, **12** R = H

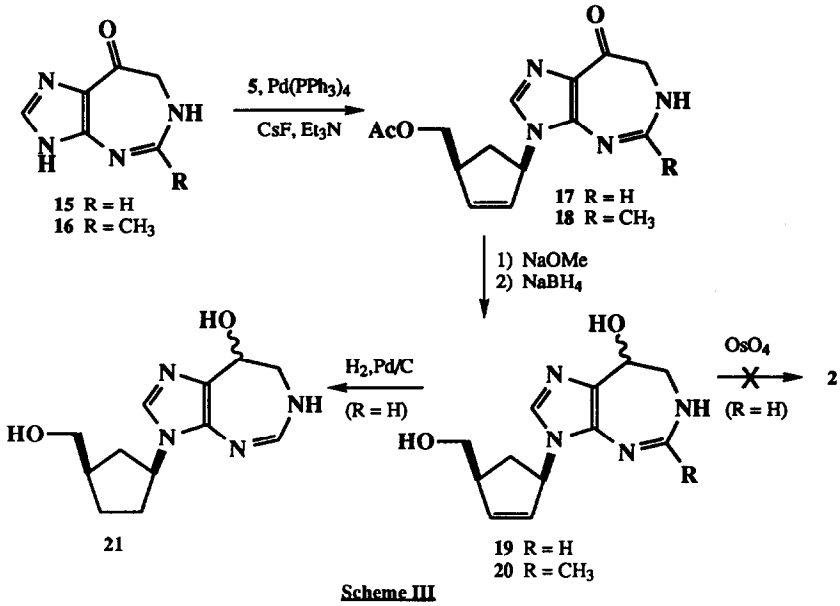
In our early studies into this synthetic approach we utilized a diastereomerically enriched mixture of *cis*-diacetates **5** and **6** prepared *via* a Prins reaction between cyclopentadiene and paraformaldehyde.[7] However, in planning our current work we decided to concentrate on preparing a single diastereoisomer, the 1,4-diacetate **5**, in order to facilitate the possibility of later accessing chiral material. In this regard, Roberts *et al*[8] have recently shown that chiral derivatives of the *cis*-1,4-diol **9** are available in >95% e.e. *via* enzymatic resolution of racemic precursors. Performing the Prins reaction in neat formic acid[12] with a catalytic amount of tosic acid also present, followed by hydrolysis of the resulting formates yielded a 35:4:21:40 mixture of diols **9**:**10**:**11**:**12**. This mixture was separated using HPLC to yield small amounts (1-2 g) of pure 1,4-diol **9**, which was acetylated to give **5**. It is noteworthy that the other major product of this Prins reaction, the *trans*-1,3-diol **12** is also a useful intermediate for the preparation of carbocyclic nucleosides.[13] Alternatively, the mixture of Prins diols can be chemically elaborated as shown in Scheme II to give larger quantities (10-20 g) of isomerically enriched **5**. Thus, oxidation with pyridinium chlorochromate or more conveniently with



Scheme II

iodine,[14] followed by acetylation of the enone-ols, gave a 9:1 mixture of the enone-acetates **13** and **14** in 37% yield. Presumably the enrichment in the 1,4:1,3 ratio observed in this reaction reflects a greater propensity for the 1,3-enone-ol to undergo decomposition *via* ß-elimination and retro-aldol reactions. Reduction of this mixture with DIBAL-H and acetylation of the resulting alcohols then yielded the *cis*-1,4-diacetate **5** along with isomers **6**, **7** and **8** in an 82:5:9:4 ratio and in 47% yield.

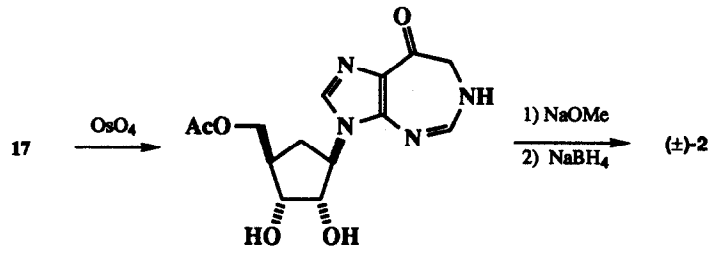
The diazepinones **15** and **16** required for the palladium(0) catalysed coupling reactions with **5** were prepared as described by Showalter and co-workers.[15, 16] All attempts to effect the desired coupling as before, using triethylamine or sodium hydride as base,[7] were completely unsuccessful. Other bases (eg *n*-BuLi, $NaHCO_3$, CsF) were also tried but to no avail, until eventually we discovered that a combination of triethylamine and cesium fluoride facilitated the coupling and afforded the carbocyclic nucleosides **17** and **18** in 17% and 42% yield, respectively (Scheme III). The lower yield of **17** reflects the greater instability of **15**[15] relative to **16** and a greater tendency for **15** to undergo dialkylation. Hydrolysis of the acetate protecting groups and reduction with sodium borohydride then gave carbocyclic 2',3'-didehydro-2',3'-dideoxy coformycin (**19**) in 50% yield and its 5-methyl analogue **20** in 61% yield (both as a 1:1 mixture of diastereoisomers at C-8).



Scheme III

Catalytic hydrogenation of the olefin in diazepinol **19** gave a quantitative yield of carbocyclic 2',3'-dideoxy coformycin (**21**). In contrast, all attempts to effect *cis*-dihydroxylation of this double bond with osmium tetroxide to give carbocyclic coformycin (**2**) met with complete failure. However, by performing the dihydroxylation reaction at an earlier stage, on the diazepinone **17**, we were able to isolate the diol **22**, albeit in low yield (7%) (Scheme IV). Hydrolysis and reduction as described previously, followed by HPLC separation of the C-8 diastereoisomers, then afforded (±)-carbocyclic coformycin (**2**) in 13% yield. This synthetic material had identical physical (UV, ^{1}H NMR, MS, HPLC retention time) and biological (herbicidal) properties to those observed for the natural product.[3] The yield obtained over these last two steps

is of the same order as that reported for comparable steps in the synthesis of coformycin.[17]



Scheme IV

In summary, four carbocyclic analogues of coformycin (1) have been synthesised, including the racemic form of the natural product 2. These syntheses illustrate the versatility of palladium(0) catalysed coupling methodology as a convergent route for the synthesis of carbocyclic nucleosides. Asymmetric variants of the above syntheses should be achievable by coupling an optically active cyclopentenyl acetate[8] with the recently reported chiral tetrahydrodiazepinol.[18]

EXPERIMENTAL

UV spectra were recorded on a Shimadzu UV-2100 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 682 spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker WM-300 spectrometer using residual protic solvent, $CHCl_3$ (δ 7.24 ppm) or HOD (δ 4.63 ppm), as internal reference. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AC-300 spectrometer using CD_3OD (δ 49.0 ppm) as internal reference. Mass spectra were recorded using a VG Trio 2 spectrometer and accurate mass measurements were made using a VG 7070E spectrometer. VPC purity determinations were performed on a Varian 6000 with a FID detector. HPLC purifications were carried out on a Gilson Autoprep system using a UV or RI detector as appropriate. Vacuum flash chromatography[19] was performed on Merck silica gel 60H, Merck aluminium oxide 60G or on Matrex C-18 reverse phase silica 60. All experiments were carried out in oven dried glassware under a nitrogen atmosphere unless otherwise stated. Solvents and reagents were used as purchased, though when necessary solvents were dried over molecular sieves prior to use.

(±)-(1ß,4ß)-1-(Hydroxymethyl)cyclopent-2-en-4-ol (9), (±)-(1ß,2ß)-1-(Hydroxymethyl) cyclopent-3-en-2-ol (10), (±)-(1ß,4α)-1-(Hydroxymethyl)-cyclopent-2-en-4-ol (11) and (±)-(1ß,2α)-1-(Hydroxymethyl)cyclopent-3-en-2-ol (12). A mixture of paraformaldehyde (585 g, 19.5 mol), *p*-toluenesulfonic acid monohydrate (1.3 g, 6.8 mmol) and formic acid (5.5 l) was heated with stirring to 100°C to give a clear solution. This was cooled to 5°C and then freshly cracked cyclopentadiene (696 g, 10.5 mol) was added over 30 min with cooling so as to maintain the temperature below 20°C. The resulting solution was stirred at r.t. for 16 h and then solid sodium bicarbonate (3.0 g, 35.7 mmol) was added. Concentration under reduced pressure, followed by distillation under high vacuum, yielded a mixture

of hydroxymethylcyclopentenol diformates (751 g, 4.4 mol, 42%), b.p. 94-100°C at 0.2 mm Hg (Lit.,[12] b.p. 84°C at 0.1 mm Hg).

This mixture (751 g) was dissolved in ethanol (5 l) and aqueous 10% sodium hydroxide (3.5 l, 8.8 mol) was added. After 1.5 h the mixture was concentrated under reduced pressure and then allowed to stand at r.t. for 2 days after which time a solid crystallised out. Acetone (5 l) was added, the solid was removed by filtration and the filtrate was evaporated *in vacuo*. Distillation under high vacuum then yielded a mixture of hydroxymethylcyclopentenols **9**, **10**, **11** and **12** as a colourless oil, (419 g, 3.7 mol, 83%), b.p. 115-122°C at 1.5 mm Hg (Lit.,[12] b.p. 82°C at 0.05 mm Hg). A portion (5 g) of this mixture was separated by HPLC (250 mm x 41.4 mm Dynamax 60A silica column; eluent 1:9 EtOH:hexane) to give in order of elution:

i) Diol **10** as a colourless oil (183 mg, 4%): IR (Film) υ_{max} 3330 (s), 1615 (w), 1360 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (1H, m, 5-H), 2.43 (2H, m, 1-H and 5-H), 2.68 (1H, br s, OH), 3.01 (1H, br s, OH), 3.78 (2H, m, 6-H), 4.90 (1H, m, 2-H), 5.83 (1H, m, 3-H), 6.01 (1H, m, 4-H); ^{13}C NMR (CD_3OD) δ 135.5, 133.8, 77.3, 63.0, 45.3, 35.83; *m/z* (Cl-MS, isobutane) 113 (M-H, 42%), 96 ($M-H_2O$, 44), 79 (100).

ii) Diol **12** as a colourless oil (1.86 g, 37%): IR (Film) υ_{max} 3320 (s), 1640 (w), 1355 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (1H, m, 5-H), 2.29 (1H, m, 1-H), 2.62 (2H, m, 5-H and OH), 2.73 (1H, d, $J = 6$ Hz, OH), 3.69 (2H, m, 6-H), 4.75 (1H, m, 2-H), 5.77 (1H, m, 3-H), 5.90 (1H, m, 4-H); ^{13}C NMR (CD_3OD) δ 134.9, 133.9, 80.4, 65.1, 50.8, 35.6; *m/z* (Cl-MS, isobutane) 113 (M-H, 13%), 97 (M-OH, 100), 79 (37).

iii) Diol **11** as a colourless oil (981 mg, 20%); IR (Film) υ_{max} 3320 (s), 1615 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (1H, m, OH), 1.67 (1H, m, OH), 1.87 (1H, ddd, J = 3, 8 and 14 Hz, 5-H), 2.00 (1H, ddd, J = 5, 7 and 14 Hz, 5-H) 3.13 (1H, m, 1-H), 3.56 (2H, m, 6-H), 4.88 (1H, m, 4-H), 5.96 (2H, s, 2-H and 3-H); ^{13}C NMR (CD_3OD) δ 137.2; 135.6, 77.5, 66.9, 48.8, 37.8; *m/z* (Cl-MS, isobutane) 113 (M-H, 11%), 97 (M-OH, 100), 79 (33).

iv) Diol **9** as a colourless oil (1.62 g, 32%); IR (Film) υ_{max} 3320 (s), 1640 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (1H, d, J = 13 Hz, 5-H), 2.33 (1H, m, 5-H), 2.87 (1H, m, 1-H), 3.18 (1H, m, OH), 3.41 (1H, d, $J = 9$ Hz, OH), 3.61 (2H, m, 6-H), 4.66 (1H, t, $J = 7$ Hz, 4-H), 5.82 (1H, dd, $J = 2$ and 5 Hz, 3-H), 5.97 (1H, m, 2-H); ^{13}C NMR (CD_3OD) δ 136.1; 135.9, 77.4, 66.7, 48.5, 37.7; *m/z* (Cl-MS, isobutane) 113 (M-H, 16%), 97 (M-OH, 100).

(±)-1-(Hydroxymethyl)cyclopent-2-en-4-one acetate (13). A solution of iodine (28.6 g, 0.11 mol) in dry CH_2Cl_2 (2.4 l) was added to a solution of the hydroxymethylcyclopentenols **9**, **10**, **11** and **12** (60.0 g, 0.53 mol) in dry CH_2Cl_2 (600 ml). After 1.5 h, t.l.c. showed only starting materials and the reaction solution was irradiated with a 300 W tungsten lamp for 15 min causing the mixture to blacken. T.l.c. showed conversion to a less polar spot which stained yellow with 2,4-DNP. The reaction mixture was

cooled in an ice/water bath and triethylamine (183 ml, 1.3 mol), acetic anhydride (44.3 ml, 1.1 mol) and finally 4-dimethylaminopyridine (3.2 g, 26 mmol) were added. After 2 h the black reaction mixture was filtered through Kieselguhr and the filtrate washed with 10% $Na_2S_2O_3$, 1M HCl, water, saturated $NaHCO_3$ and saturated brine. Each aqueous wash was extracted once with fresh CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Vacuum flash chromatography (Silica gel; product eluted with 30-90% EtOAc in hexanes) then yielded a 9:1 mixture (^1H NMR) of the enone acetate **13** and its isomer **14**, (30.0 g, 0.19 mol, 37%): IR (Film) υ_{max} 1730 (s), 1680 (s), 1595 (m) cm^{-1}; ^1H NMR ($CDCl_3$) 2.08 (3H, s, OAc), 2.17 (1H, dd, J = 2 and 18 Hz, 5-H), 2.55 (1H, dd, J = 7 and 18 Hz, 5-H), 3.29 (1H, m, 4-H), 4.12 (1H, dd, J = 6 and 10 Hz, 6-H), 4.26 (1H, dd, J = 6 and 10 Hz, 6-H), 6.26 (1H, dd, J = 2 and 6 Hz, 2-H), 7.61 (1H, dd, J = 2 and 6 Hz, 3-H); Anal. calcd for $C_8H_{10}O_3$ requires: C, 62.32; H, 6.54. Found: C, 62.54; H, 6.71%.

(±)-(1ß,4ß)-1-(Hydroxymethyl)cyclopent-2-en-4-ol diacetate (5). a) By acylation of the diol (9): Acetic acid anhydride (1.60 ml, 17 mmol) was added dropwise to a solution of the pure diol (**9**) (0.51 g, 4.47 mmol) in dry pyridine (3.5 ml) under nitrogen. After stirring at room temperature for 4 h, the reaction mixture was concentrated *in vacuo* and last traces of reagents and acetic acid were removed by co-evaporation with toluene (2 x 15 ml) to give the diacetate **5** (0.86 g, 4.34 mmol, 97%): IR (Film) υ_{max} 1740 (s), 1370 (s), 1240 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (1H, dt, J = 4 and 14 Hz, 5-H), 2.02 (3H, s, OAc), 2.05 (3H, s, OAc), 2.47 (1H, dt, J = 7 and 14 Hz, 5-H), 2.93 (1H, m, 1-H), 4.02 (2H, d, J = 7 Hz, 6-H), 5.58 (1H, m, 4-H), 5.89 (1H, m, 2-H), 5.99 (1H, m, 3-H); HR-MS calcd for $C_8H_{10}O_2$ requires 138.0681. Found 138.0679 $[M\text{-}AcOH]^+$.

b) **By reduction and acylation of the enone (13):** A solution of diisobutyl-aluminium hydride (1.5 M solution in toluene, 67.2 ml, 0.10 mol) was instilled into a cold (-78°C), stirred solution of the enones **13** and **14** (14.6 g, 94.7 mmol, 9:1 mixture) in dry THF (200 ml) over a period of 30 min so as to maintain the internal reaction temperature below -70°C. After a further 1 h the mixture was allowed to warm to -10°C and water (30 ml) followed by silica gel (150 g) was added. The resulting slurry was allowed to warm to r.t., filtered and evaporated *in vacuo*. The crude product (10.6 g) was dissolved in dry CH_2Cl_2 (250 ml) and then dry Et_3N (19.0 ml, 0.14 mol), acetic anhydride (11.5 ml, 0.12 mol) and 4-dimethylaminopyridine (0.83 g, 6.8 mmol) were added sequentially. After 2 h the reaction mixture was washed with 1M HCl, water, saturated $NaHCO_3$ and saturated NaCl, then dried ($MgSO_4$) and evaporated *in vacuo*. Vacuum flash chromatography (Silica gel; product eluted with 20% EtOAc in hexanes) yielded the *cis*-1,4-diacetate **5** along with isomers **6**, **7** and **8** (8.91 g, 45.0 mmol, 47%) in an 82:5:9:4 ratio as determined by VPC (12 m x 0.33 mm BP1 column, 80°C for 5 min, increasing at 10°C min^{-1} to 250°C).

(±)-3-[(1ß,4ß)-4-(Acetoxymethyl)cyclopent-2-enyl]-6,7-dihydroimidazo[4,5-d][1,3] diazepin-8(3H)-one (17). To a stirred suspension of the diazepinone **15**[15] (mono-DMSO solvate, mono-HCl salt; 1.32 g, 5.0 mmol) in dry DMF (11.5 ml) was added dry triethylamine (1.05 ml, 7.5 mmol), cesium fluoride (0.76 g, 5.0 mmol) and tetrakis(triphenyl-phosphine)palladium(0) (0.58 g, 0.50 mmol). The mixture was heated to 60°C in an oil bath and then a solution of the diacetate **5** (0.99 g, 5.0 mmol) in dry

DMF (1.5 ml) was added dropwise over 1 h *via* a motorised syringe pump. After a further 30 min the reaction mixture was poured into ether (40 ml) and the precipitated solids were removed by filtration and washed with ether. Evaporation *in vacuo* yielded a brown gum (3.0 g) which was redissolved in CH_2Cl_2 (50 ml), washed twice with saturated $NaHCO_3$ (25 ml), dried ($MgSO_4$) and re-evaporated. The crude product mixture (1.6 g) was purified by HPLC (250 mm x 41.4 mm Dynamax 60A silica column; eluent 1:9 MeOH: CH_2Cl_2) to yield the carbocyclic nucleoside **17** as a sticky gum (0.24 g, 0.83 mmol, 17%): UV (MeOH) λ_{max} 303, 340 (sh) nm; IR (KBr) υ_{max} 1740 (s), 1660 (s), 1600 (m), 1235 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (1H, m, 5'-H), 2.03 (3H, s, OAc), 2.83 (1H, m, 5'-H), 3.12 (1H, m, 4'-H), 3.96 (2H, s, 7-H), 4.10 (2H, m, 6'-H), 5.66 (1H, m, 1'-H), 5.88 (1H, m, 3'-H), 6.09 (1H, m, 2'-H), 7.34 (1H, d, J = 4 Hz, 5-H), 7.50 (1H, s, 2-H).

(±)-3-[(1ß,4ß)-4-(Acetoxymethyl)cyclopent-2-enyl]-6,7-dihydro-5-methylimidazo-[4,5-d][1,3]diazepin-8(3H)-one (18). To a stirred suspension of the diazepinone **16**[16] (mono-HCl salt; 10.0 g, 50 mmol) in dry DMF (90 ml) was added dry triethylamine (10.4 ml, 75 mmol), cesium fluoride (7.60 g, 50 mmol), tetrakis(triphenylphosphine)palladium(0) (1.73 g, 1.5 mmol) and a solution of the diacetate **5** (9.8 g, 50 mmol) in dry DMF (10 ml). The mixture was heated at 60°C in an oil bath for 16 h and then allowed to cool to r.t.. The solids were removed by filtration and washed with ether. The combined organics were evaporated under high vacuum at 50°C. The residue (20.5 g) was dissolved in CH_2Cl_2 (350 ml), washed twice with saturated $NaHCO_3$ (200 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product (15.7 g) was purified by vacuum flash chromatorgaphy (Silica gel; product eluted with 6-15% EtOH in MeCN containing 1% Et_3N) to give the carbocyclic nucleoside **18** (6.36 g, 21 mmol, 42%): UV (MeOH) λ_{max} 304, 340 (sh) nm; IR (KBr) 1740 (s), 1660 (s), 1600 (m), 1235 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (1H, m, 5'-H), 2.04 (3H, s, OAc), 2.30 (3H, s, 5-CH_3), 2.81 (1H, m, 5'-H), 3.12 (1H, m, 4'-H), 3.86 (2H, s, 7-H), 4.10 (2H, m, 6'-H), 5.67 (1H, m, 1'-H), 5.87 (1H, m, 3'-H), 6.07 (1H, m, 2'-H), 7.56 (1H, s, 2-H); HR-MS calcd for $C_{15}H_{18}N_4O_3$ requires 302.1379. Found 302.1378 $[M]^+$.

(±)-3-[(1ß,4ß)-4-(Hydroxymethyl)cyclopent-2-enyl]-3,6,7,8-tetrahydroimidazo[4,5-d][1,3]diazepin-8-ol (19). Sodium methoxide (51 mg, 0.94 mmol) was added to a cold (0°C) solution of the acetate **17** (0.18 g, 0.62 mmol) in dry methanol (16 ml). After 2 h, t.l.c. showed conversion to a more polar product and the pH of the reaction mixture was adjusted to *ca.* 7 by adding solid CO_2. Evaporation *in vacuo* at 40°C yielded a sticky solid (0.2 g) which was redissolved in 4:1 water:methanol (40 ml) and cooled to 0°C. Sodium borohydride (24 mg, 0.62 mmol) was added and the mixture was allowed to warm to r.t.. After 2 h, t.l.c. showed conversion to a more polar product and solid CO_2 was added until the pH was 7-8 and then the mixture was evaporated *in vacuo*. The crude product was purified by vacuum flash chromatography (reverse phase C18 silica; product eluted with 30-40% MeOH in water) to give the carbocyclic nucleoside **19** (77 mg, 0.31 mmol, 50%): UV (MeOH) λ_{max} 284 nm; IR (KBr) υ_{max} 3330 (s), 1650 (s), 1600 (m) cm^{-1}; ^1H NMR (D_2O) δ 1.30 (1H, m, 5'-H), 2.52 (1H, m, 5'-H), 2.80 (1H, m, 4'-H), 3.12 (1H, m, 7-H), 3.38 (3H, m, 7-H and 6'-H), 4.92 (1H, m, 8-H), 5.20 (1H, m, 1'-H), 5.72 (1H, m, 3'-H), 5.97 (1H, m, 2'-H),

6.99 (1H, s, 5-H), 7.22 (1H, s, 2-H); HR-FABMS (NBA + $NaHCO_3$ matrix) calcd for $C_{12}H_{17}N_4O_2$ requires 249.1352. Found 249.1304 $[M + H]^+$.

(±)-3-[(1ß,4ß)-4-(Hydroxymethyl)cyclopent-2-enyl]-3,6,7,8-tetrahydro-5-methyl-imidazo [4,5-d][1,3]diazepin-8-ol (20). Sodium methoxide (0.45 g, 8.2 mmol) was added in portions over 10 min to a cooled (5°C) solution of the acetate **18** (1.66 g, 5.5 mmol) in dry methanol (110 ml). The mixture was then allowed to warm to r.t. and after 35 min solid CO_2 was added to neutralise the base. The solvent was evaporated *in vacuo* and the product was purified by vacuum flash chromatography (reverse phase C18 silica; product eluted with 20-60% MeOH in water) to give (±)-3-[(1ß,4ß)-4-(hydroxymethyl)cyclopent-2-enyl]-6,7-dihydro-5-methyimidazol[4,5-d][1,3]diazepin-8(3H)-one (1.19 g, 4.5 mmol, 84%): ^1H NMR (D_2O) δ 1.32 (1H, m, 5'-H), 2.10 (3H, s, 5-CH_3), 2.58 (1H, m, 5'-H), 2.85 (1H, m, 4'-H), 3.43 (2H, m, 6'-H), 3.62 (2H, s, 7-H), 5.41 (1H, m, 1'-H), 5.71 (1H, m, 3'-H), 6.00 (1H, m, 2'-H), 7.48 (1H, s, 2-H); HR-MS calcd for $C_{13}H_{16}N_4O_2$ requires 260.1273. Found 260.1274 $[M]^+$.

The above alcohol (1.12 g, 4.3 mmol) was dissolved in 4:1 water:methanol (215 ml) and sodium borohydride (0.32 g, 8.5 mmol) was added in portions over 6 h. The reaction mixture was adjusted to neutral pH by adding solid CO_2 and then the solvent was evaporated *in vacuo*. Purification by vacuum flash chromatography (reverse phase C18 silica; product eluted with 20-40% MeOH in water) yielded the carbocyclic nucleoside **20** (0.83 g, 3.2 mmol, 73%): UV (MeOH) λ_{max} 284 nm; IR (KBr) υ_{max} 3320 (s), 1655 (s), 1600 (m) cm^{-1}; ^1H NMR (D_2O) δ 1.29 (1H, m, 5'-H), 2.00 (3H, s, 5-CH_3), 2.59 (1H, m, 5'-H), 2.81 (1H, m, 4'-H), 3.12 (1H, m, 7-H), 3.23 (1H, m, 7-H), 3.41 (2H, m, 6'-H), 4.88 (1H, m, 8-H), 5.31 (1H, m, 1'-H), 5.71 (1H, m, 3'-H), 5.97 (1H, m, 2'-H), 7.25, 7.26 (1H, 2s, 2-H); HR-MS calcd for $C_{13}H_{18}N_4O_2$ requires 262.1430. Found 262.1431 $[M]^+$.

(±)-3-[(1ß,4ß)-4-(Hydroxymethyl)cyclopentyl]-3,6,7,8-tetrahydroimidazo[4,5-d]-[1,3] diazepin-8-ol (21). The alkene **19** (50 mg, 0.2 mmol) was dissolved in 9:1 ethanol:water (2.5 ml) and 10% palladium on charcoal (24 mg) was added and the mixture was subjected to hydrogenation at atmospheric pressure for 2.25 h (*ca.* 5 ml H_2 absorbed). The reaction mixture was filtered through kieselguhr and evaporated *in vacuo* to yield the carbocyclic nucleoside **21** (51 mg, 0.2 mmol, 99%): UV (MeOH) λ_{max} 283 nm; ^1H NMR (D_2O) δ 1.16-2.12 (7H, m, 2',3',4' and 5'-H), 3.05 (1H, d, J = 12 Hz, 7-H), 3.28 (3H, m, 7-H and 6'-H), 4.34 (1H, m, 1'-H), 4.88 (1H, m, 8-H), 6.90 (1H, s, 5-H), 7.32 (1H, s, 2-H); HR-FABMS (NBA matrix) calcd for $C_{12}N_{19}N_4O_2$ requires 251.1508. Found 251.1493 $[M + H]^+$.

(±)-3-[(1ß,2α,3α,4ß)-4-(Acetoxymethyl)cyclopentyl]-6,7-dihydroimidazo[4,5-d]-[1,3] diazepin-8(3H)-one (22). A 0.5 M solution of osmium tetroxide in toluene (0.62 ml, 0.32 mmol) was added in two equal portions after 0 h and 3 h to a solution of the alkene **17** (0.30 g, 1.04 mmol) and N-methylmorpholine N-oxide (0.28 g, 2.06 mmol) in 10:1 propan-2-one:water (2 ml). After a total of 6.5 h, solid $Na_2S_2O_5$ (0.6 g, 3.1 mmol) was added and then 5 min later, CH_2Cl_2 (5 ml) and solid Na_2SO_4. The mixture was filtered through kieselguhr and then subjected to vacuum flash chromatography (neutral alumina;

product eluted with MeOH) to yield a sticky solid (0.25 g). Further purification by HPLC (250 mm x 46 mm Dynamax 60A reverse phase C-18 silica column; eluent 7:93 MeCN:water) yielded the desired diol **22** (23 mg, 0.071 mmol, 7%): UV (MeOH) λ_{max} 304, 345 (sh) nm; ^{1}H NMR (D_2O) δ 1.45 (1H, m, 5'-H),1.94 (3H, s, OAc), 2.21 (1H, m, 5'-H), 2.72 (1H, m, 4'-H), 3.80 (2H, s, 7-H), 3.89 (1H, m, 3'-H), 3.99 (2H, d, J = 5 Hz, 6'-H), 4.18 (1H, m, 2'-H), 4.68 (1H, m, 1'-H), 7.31 (1H, s, 5-H), 7.61 (1H, s, 2-H).

8R-3-[(1R,2S,3R,4R)- and 8S-3-[(1S,2R,3S,4S)-2,3-Dihydroxy-4-(hydroxymethyl) cyclopentyl]-3,6,7,8-tetrahydroimidazo[4,5-d][1,3]diazepin-8-ol (2). Sodium methoxide (2.5 mg, 0.046 mmol) was added to a cold (0°C) solution of the acetate **22** (10 mg, 0.031 mmol) in dry methanol (0.6 ml). The mixture was allowed to warm to r.t. and after 1.5 h t.l.c. showed conversion to a more polar spot. Solid CO_2 was added until the pH was *ca.* 7 and the solvent was evaporated *in vacuo* to yield a yellow solid (16.6 mmg). A freshly prepared 0.11 M solution of sodium borohydride in methanol (0.1 ml, 0.011 mmol) was added to a cold (0°C) solution of the above solid (5.7 mg) in 4:1 methanol:water (0.75 ml). The mixture was allowed to warm to r.t. and after 3 h solid CO_2 was added until the pH was 7-8. Evaporation *in vacuo* followed by HPLC purification (250 mm x 46 mm Dynamax 60A reverse phase C-18 silica column; eluent water) yielded pure (±)-carbocyclic coformycin (**2**) (0.4 mg, 0.0014 mmol, 13%). This material had identical UV, ^{1}H NMR and MS spectra to those obtained for the natural product[3] and co-chromatographed with the natural material upon HPLC coinjection.

A second (not completely pure) compound tentatively assigned as the C-8 epimer of **2** was also isolated from the HPLC column (0.6 mg); ^{1}H NMR (D_2O) δ 1.30 (1H, m, 5'-H), 2.02 (1H, m, 4'-H), 2.25 (1H, m, 5'-H), 3.20 (1H, d, J = 14 Hz, 7-H), 3.34 (1H, dd, J = 3 and 14 Hz, 7-H), 3.50 (2H, d, J = 6 Hz, 6'-H), 3.84 (1H, m, 3'-H), 4.15 (1H, m, 2'-H), 4.52 (1H, m, 1'-H), 4.98 (1H, s, 8-H), 7.02 (1H, s, 5-H), 7.50 (1H, s, 2-H).

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