Stereoselective synthesis of thymine polyoxin C using an allylic trifluoroacetimidate–trifluoroacetamide rearrangement

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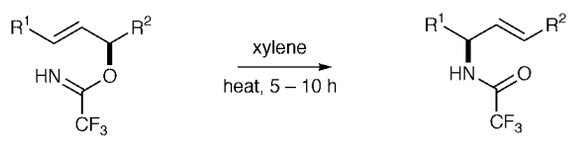
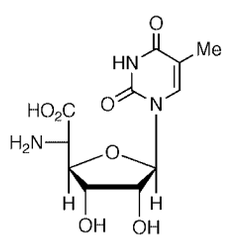
A stereoselective synthesis of thymine polyoxin C **3** is described in which the key step is the [3,3] sigmatropic rearrangement of the trifluoroacetimidate **12** to the trifluoroacetamide **13**. Exchange of the protecting groups followed by ozonolysis and further oxidation then gave the methyl ester **20** which was converted into thymine polyoxin C **3** by introduction of the pyrimidine followed by final deprotection.

The polyoxins are an important group of nucleoside antibiotics which have found use as agricultural fungicides.[1] Because of their biological activities, the synthesis of the polyoxins and the structurally related nikkomycins[2] has been of considerable interest and several total syntheses have been described.[3,4] In the preceeding paper,[5] the [3,3] sigmatropic rearrangement of allylic trifluoroacetimidates **1** to trifluoroacetamides **2** was



1 **2**



3

reported.[6] This was found to be an efficient rearrangement analogous to the well established rearrangement of allylic *trichloro*acetimidates developed by Overman.[7] The trifluoroacetimidate rearrangement proceeds with excellent 1,3-transfer of asymmetry, and was applied to complete total syntheses of polyoxamic acid and derivatives of other α-amino acids. In the present paper we report a total synthesis of thymine polyoxin C **3** in which the key step is a [3,3] sigmatropic rearrangement of an allylic trifluoroacetimidate.[8]

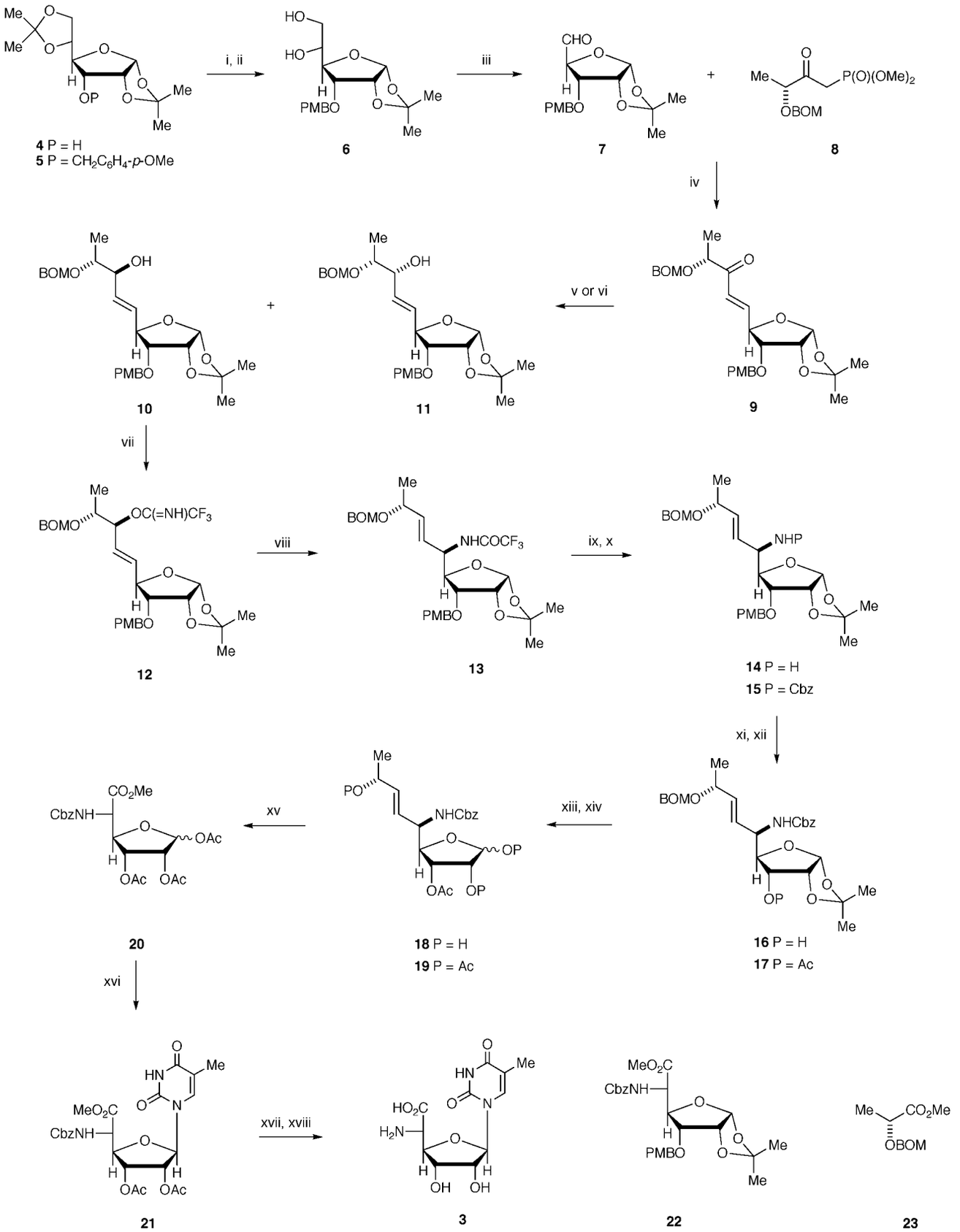
Results and discussion

The alcohol **4** is readily available from diacetone D-glucose by oxidation using pyridinium dichromate followed by reduction using sodium borohydride.[9] Protection using *p*-methoxybenzyl chloride[10] followed by mild acid hydrolysis[11] gave the diol **6** which was cleaved using lead tetraacetate to give the aldehyde **7**, see Scheme 1. This was condensed with the ketophosphonate **8**,[5] which is available from isobutyl (*R*)-lactate in two steps, to give the enone **9**.[12] Reduction of the enone using zinc borohydride gave a mixture of the epimeric alcohols **10** and **11** in which the product of chelation control,[13] isomer **10**, was the major component. The ratio **10**:**11** appeared to be dependent on the scale of the reaction, being ≥98:2 on a small scale (1–2 g), but *ca.* 90:10 for larger scale reactions. When sodium borohydride was used for the reduction, an almost 50:50 mixture of the epimeric alcohols was obtained. The major *anti*-alcohol **10** was converted into its trifluoroacetimidate using a sub-stoicheiometric amount of butyllithium and trifluoroacetonitrile at −78 °C.[5] The rearrangement of the trifluoroacetimidate was then carried out in xylene heated under reflux and was complete after 10 h giving the trifluoroacetamide **13** with excellent stereoselectivity (≥96:4) and in good yield (90%). The configuration of the rearrangement product **13** was not confirmed at this stage but was provisionally assigned by analogy with earlier trifluoroacetimidate rearrangements.[5] It was subsequently confirmed by conversion of the trifluoroacetamide **13** into thymine polyoxin C **3**. The completion of a synthesis of thymine polyoxin C now required functional group manipulation, oxidative cleavage of the alkene and introduction of the pyrimidine base.

The trifluoroacetamide **13** was converted into the amine **14** by treatment with barium hydroxide in methanol and the amine was converted into its benzyloxycarbonyl derivative **15** using standard conditions.[14] Ozonolysis of the alkene **15** followed by oxidation using bromine in methanol[15] gave the methyl esters **22** and **23** in yields of 75% and 65%, respectively. The methyl ester **22** was not taken further in the synthesis, but the isolation of both esters **22** and **23** demonstrates that at least, in principle, the (*R*)-lactate used to prepare the chiral phosphonate **8** can be recovered at this stage, albeit as its methyl ester.

For the synthesis of the thymine polyoxin C, the *p*-methoxybenzyl group was removed using dichlorodicyanoquinone and acetylation of the free hydroxy gave the acetate **17**. Hydrolysis of the dioxolane ring was accompanied by loss of the benzyloxymethyl group and gave the triol **18** which was converted into the tetraacetate **19**. Ozonolysis of the double-bond followed by further oxidation using bromine in methanol[15] then gave the methyl ester **20** together with the lactate **23**, and the ester **20** was converted into the protected thymine polyoxin C **21** using Vorbruggen's conditions.[16] Hydrogenolysis of the benzyloxycarbonyl group followed by saponification of the methyl ester finally gave thymine polyoxin C **3** purified by ion exchange chromatography. The synthetic thymine polyoxin C was found to be identical to an authentic sample by TLC and spectroscopic analysis.[4]

This synthesis of thymine polyoxin C **3** demonstrates the use of the [3,3] sigmatropic rearrangement of allylic trifluoroacetimidates in natural product synthesis. The rearrangement is efficient, proceeds with excellent stereoselectivity and requires less vigorous conditions than rearrangement of the analogous trichloroacetimidates. Although the latter compounds are more



Scheme 1 *Reagents and conditions*: i, sodium hydride, 18-crown-6, 4-methoxybenzyl chloride (92%); ii, 70% aq. acetic acid, 18 h (93%); iii, lead tetraacetate, sodium carbonate, dichloromethane (96%); iv, **8**, lithium chloride, 1,8-diazabicyclo[5.4.0]undec-7-ene, 16 h, room temperature (94%); v, zinc borohydride, ether 6 h (98%; **10**:**11** ≥ 98:2); vi, sodium borohydride, ethanol (95%; **10**:**11** = 47:53); vii, butyllithium, trifluoroacetonitrile, −78 °C (98%); viii, xylene, heat under reflux, 12 h (90%); ix, barium hydroxide, methanol; x, benzyl chloroformate, potassium bicarbonate (96% from **13**); xi, dichlorodicyanoquinone, dichloromethane, *tert*-butyl alcohol (73%); xii, 4-dimethylaminopyridine, triethylamine, acetic anhydride (98%); xiii, aq. acetic acid, 70 °C, 40 h; xiv, 4-dimethylaminopyridine, triethylamine, acetic anhydride (88%); xv, ozone, −78 °C, then dimethyl sulfide followed by bromine, methanol, room temperature, 6 h (74% from **19**); xvi, bis-silylated thymine, trimethylsilyl triflate, 1,2-dichloroethane, heat under reflux, 45 min (82%); xvii, lithium hydroxide, aq. tetrahydrofuran; xviii, 10% Pd/C, methanol, hydrogen (47% from **21**).

accessible, the trifluoroacetimidate rearrangement may be preferred in some cases where rearrangement of the trichloroacetimidate is slow because of the presence of electron withdrawing groups.

Experimental

For general experimental details see the preceding paper.[5]

3-*O*-(4-Methoxybenzyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 5

18-Crown-6 (10 mg) was added to a suspension of sodium hydride (60% dispersion in oil; 800 mg, 20 mmol) in tetrahydrofuran (50 cm^3) and the suspension stirred for 10 min before dropwise addition of the alcohol **4**[9] (2.8 g, 10.7 mmol) in tetrahydrofuran (8 cm^3) at 0 °C. The mixture was stirred at ambient temperature for 1 h and then cooled to 0 °C. 4-Methoxybenzyl chloride (1.8 cm^3, 12.8 mmol) was added and the reaction mixture stirred for a further 32 h at ambient temperature before being poured slowly into water (30 cm^3) and extracted with ethyl acetate (2 × 60 cm^3). The organic extracts were washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (1:2) as eluent afforded the *title compound* **5** (3.76 g, 92%) as a white crystalline solid; mp 77.5–79 °C; $[\alpha]_D^{23}$ +106.6 (*c* 1.1 in $CHCl_3$) (Found: $M^+ - CH_3$, 365.1614. $C_{19}H_{25}O_7$ requires *M*, 365.1600); ν_{max}/cm^{-1} 1614, 1586, 1515, 1461, 1372, 1254 and 1031; δ_H 1.34, 1.36, 1.39 and 1.6 (each 3 H, s, CH_3), 3.80 (3 H, s, OCH_3), 3.86 (1 H, dd, *J* 11, 4.5, 3-H), 3.97 (2 H, m, 6-H_2), 4.12 (1 H, dd, *J* 8.5, 3, 4-H), 4.36 (1 H, dt, *J* 8.5, 3, 5-H), 4.53 (2 H, m, 2-H and ArC*H*H), 4.69 (1 H, d, *J* 11.5, ArCH*H*), 5.74 (1 H, d, *J* 4, 1-H) and 6.88 and 7.20 (each 2 H, d, *J* 8.5, ArH); δ_C 25.3, 26.4, 26.8, 27.0, 55.5, 65.2, 72.0, 74.9, 78.0, 78.2, 104.1, 109.8, 113.1, 114.0, 130.0 and 159.7; *m/z* (EI) 365 ($M^+ - 15$, 7%).

3-*O*-(4-Methoxybenzyl)-1,2-*O*-isopropylidene-α-D-allofuranose 6

A solution of the acetonide **5** (3.5 g, 9.2 mmol) in 70% aqueous acetic acid (60 cm^3) was stirred for 18 h at ambient temperature. Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (1:9) as eluent gave the *title compound* **6** (2.91 g, 93%) as a colourless gum; $[\alpha]_D^{20}$ +104 (*c* 1.2 in $CHCl_3$) (Found: $M^+ + NH_4$, 358.1873. $C_{17}H_{28}NO_7$ requires *M*, 358.1866); ν_{max}/cm^{-1} 3451, 1613, 1589, 1515, 1249 and 1027; δ_H 1.37 and 1.59 (each 3 H, s, CH_3), 2.38 (2 H, br s, 2 × OH), 3.67 (2 H, m, 6-H_2), 3.82 (3 H, s, OCH_3), 3.91 (1 H, dd, *J* 9, 4.5, 3-H), 3.99 (1 H, m, 5-H), 4.09 (1 H, dd, *J* 9, 3.5, 4-H), 4.49 (1 H, d, *J* 11, ArC*H*H), 4.60 (1 H, m, 2-H), 4.73 (1 H, d, *J* 11, ArCH*H*), 5.76 (1 H, d, *J* 3.5, 1-H) and 6.39 and 7.32 (each 2 H, d, *J* 8, ArH); δ_C 26.7, 26.9, 55.4, 63.2, 70.9, 72.0, 76.6, 77.4, 79.3, 104.4, 113.4, 114.2, 128.9, 130.2 and 159.9; *m/z* (CI) 358 ($M^+ + 18$, 2%) and 121 (100).

3-*O*-(4-Methoxybenzyl)-1,2-*O*-isopropylidene-4-formylerythrofuranose 7

Lead tetraacetate (3.9 g, 8.82 mmol) was added to a suspension of the diol **6** (2.5 g, 7.35 mmol) and sodium carbonate (3 g, 28 mmol) in dichloromethane (60 cm^3) at 0 °C. The mixture was stirred for 2 h then diluted with dichloromethane (40 cm^3) and filtered through a pad of Celite® and silica. The solid residue was washed with dichloromethane and the filtrate concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1:5) as eluent gave the *title compound* **7** (2.18 g, 96%) as a colourless gum; $[\alpha]_D^{21}$ +107 (*c* 0.5 in $CHCl_3$) (Found: M^+, 308.1272. $C_{16}H_{20}O_6$ requires *M*, 308.1260); ν_{max}/cm^{-1} 3445, 1736, 1613, 1587, 1515, 1249 and 1032; δ_H 1.37 and 1.62 (each 3 H, s, CH_3), 3.79 (3 H, s, OCH_3), 3.85 (1 H, m, 3-H), 4.47 (1 H, dd, *J* 9.5, 1.5, 4-H), 4.56 (1 H, m, 2-H), 4.58 and 4.69 (each 1 H, d, *J* 12, ArC*H*H), 5.82 (1 H, d, *J* 3.5, 1-H), 6.88 and 7.27 (each 2 H, m, ArH) and 9.61 (1 H, d, *J* 1.5, CHO); δ_C 26.8, 27.1, 55.4, 72.2, 77.7, 78.1, 82.4, 104.9, 114.1, 114.2, 128.9, 129.9, 159.7 and 198.6; *m/z* (CI) 308 (M^+, 18%), 250 (14) and 121 (100).

3-*O*-(4-Methoxybenzyl)-4-[(*R*,*E*)-4-benzyloxymethoxy-3-oxopent-1-enyl]-1,2-*O*-isopropylidene-α-D-erythrofuranose 9

A solution of the ketophosphonate **8**[5] (2.6 g, 8.2 mmol) in acetonitrile (50 cm^3) was added to a suspension of lithium chloride (0.36 g, 8.5 mmol) in acetonitrile (30 cm^3) at 0 °C. The suspension was stirred for 15 min then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.97 cm^3, 7.08 mmol) was added. After 30 min, a solution of the aldehyde **7** (2.18 g, 7.08 mmol) in acetonitrile (5 cm^3) was added and the solution was stirred for 16 h at ambient temperature. Saturated aqueous ammonium chloride (30 cm^3) was added and the mixture extracted with dichloromethane (3 × 50 cm^3). The organic extracts were washed with water (20 cm^3), brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (1:4) as eluent afforded the *title compound* **9** (3.32 g, 94%) as a colourless oil; $[\alpha]_D^{21}$ +75 (*c* 0.3 in $CHCl_3$) (Found: $M^+ + NH_4$, 516.2597. $C_{28}H_{38}NO_8$ requires *M*, 516.2597); ν_{max}/cm^{-1} 1701, 1613, 1515, 1455 and 1028; δ_H 1.31 (3 H, d, *J* 6, 5′-H_3), 1.33 and 1.58 (each 3 H, s, CH_3), 3.46 (1 H, dd, *J* 9, 4, 3-H), 3.77 (3 H, s, OCH_3), 4.32 (1 H, q, *J* 7, 4′-H), 4.55 (6 H, m, 2-H, 4-H, 2 × $ArCH_2$), 4.72 and 4.8 (each 1 H, d, *J* 8, OC*H*HO), 5.73 (1 H, d, *J* 4, 1-H), 6.70 (1 H, dd, *J* 16, 1.5, 2′-H), 6.83 (2 H, m, ArH), 6.94 (1 H, dd, *J* 16.5, 5.5, 1′-H) and 7.22–7.33 (7 H, m, ArH); δ_C 17.8, 26.6, 27.0, 55.4, 70.2, 72.3, 77.6, 77.7, 81.7, 94.1, 104.2, 113.4, 114.1, 124.9, 127.9, 128.0, 128.6, 129.2, 129.9, 137.7, 143.2, 159.8 and 199.5; *m/z* (CI) 516 ($M^+ + 18$, 71%), 499 ($M^+ + 1$, 3), 498 (M^+, 1) and 122 (100).

3-*O*-(4-Methoxybenzyl)-4-[(3*S*,4*R*,1*E*)-4-benzyloxymethoxy-3-hydroxypent-1-enyl]-1,2-*O*-isopropylidene-α-D-erythrofuranose 10

A solution of zinc borohydride in ether (0.17 M; 30 cm^3, 5.04 mmol) was added dropwise to a solution of the enone **9** (2.4 g, 4.82 mmol) in ether (40 cm^3) at −40 °C and the solution stirred for 6 h. Water (25 cm^3) and then a solution of acetic acid (6 cm^3) in water (25 cm^3) were added. The mixture was allowed to warm to ambient temperature and extracted with ether (2 × 75 cm^3). The organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (3:2) as eluent afforded the *title compound* **10** (2.36 g, 98%) as a colourless oil; $[\alpha]_D^{21}$ +13.8 (*c* 0.8 in $CHCl_3$) (Found: $M^+ + NH_4$, 518.2755. $C_{28}H_{40}NO_8$ requires *M*, 518.2754); ν_{max}/cm^{-1} 3477, 1613, 1587 and 1383; δ_H 1.12 (3 H, d, *J* 7, 5′-H_3), 1.33 and 1.59 (each 3 H, s, CH_3), 2.2 (1 H, br s, OH), 3.46 (1 H, dd, *J* 9, 5, 3-H), 3.77 (3 H, s, OCH_3), 3.82 (1 H, dq, *J* 3, 7, 4′-H), 4.15 (1 H, m, 3′-H), 4.55 (6 H, m, 2-H, 4-H, 2 × $ArCH_2$), 4.78 and 4.82 (each 1 H, d, *J* 8, OC*H*HO), 5.70 (2 H, m, 1-H and 1′-H), 5.88 (1 H, ddd, *J* 16, 6, 1, 2′-H), 6.85 (2 H, m, ArH) and 7.23–7.35 (7 H, m, ArH); δ_C 15.4, 26.6, 26.9, 55.5, 70.1, 72.0, 74.3, 77.6, 77.8, 78.5, 81.7, 94.1, 103.7, 113.1, 114.0, 128.0, 128.1, 128.7, 129.2, 129.7, 129.8, 132.6, 137.7 and 159.7; *m/z* (CI) 518 ($M^+ + 18$, 72%), 501 ($M^+ + 1$, 3) and 108 (100). Less than 1% of the (3′*R*)-epimer **11** was present as indicated by ^1H NMR.

3-*O*-(4-Methoxybenzyl)-4-[(3*S*,4*R*,1*E*)-4-benzyloxymethoxy-3-(2,2,2-trifluoroacetimidoyloxy)pent-1-enyl]-1,2-*O*-isopropylidene-α-D-erythrofuranose 12

An intimate mixture of powdered trifluoroacetamide (12 g, 106

mmol) and phosphorus pentoxide (24 g, 148 mmol) was prepared in a 500 cm^3 round bottomed flask equipped with a nitrogen inlet and a water cooled condenser. From the top of the condenser a PTFE tube led first to a trap cooled in an ice–salt mixture, then to a trap cooled to ~−100 °C (ether–liq. N_2) and, finally, *via* a tube packed with calcium chloride, to a scrubber containing aqueous sodium hydroxide. The reaction mixture was heated gradually to 150 °C under a gentle stream of dry nitrogen and held at this temperature for 3 h. Trifluoroacetonitrile distilled out and was collected as a colourless liquid (~6 cm^3) in the low temperature trap before being dissolved in pre-cooled tetrahydrofuran (10 cm^3).

Butyllithium (1.8 M in hexane; 0.72 cm^3, 1.3 mmol) was added to the alcohol **10** (1.64 g, 3.28 mmol) in tetrahydrofuran (20 cm^3) at −78 °C and the mixture stirred for 40 min. The solution of trifluoroacetonitrile prepared above was then added *via* a cannula and the mixture stirred for 1 h then allowed to warm to ambient temperature to allow evaporation of the excess of trifluoroacetonitrile. Ammonium chloride (0.5 g) and light petroleum (60 cm^3) were added, the mixture was filtered and the solid residue washed with diethyl ether. The filtrates were combined and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (1 : 6) as eluent afforded the *title compound* **12** (1.82 g, 98%) as an oil; $[\alpha]_D^{25}$ +79.5 (*c* 1 in benzene) (Found: $M^+ + NH_4$, 613.2745. $C_{30}H_{40}F_3N_2O_8$ requires *M*, 613.2737); ν_{max}/cm^{-1} 3300, 1688, 1613, 1514, 1250, 1200, 1167 and 1027; δ_H (C_6D_6) 1.12 (3 H, d, *J* 6.5, 5′-H_3), 1.27 and 1.59 (each 3 H, s, CH_3), 3.32 (1 H, dd, *J* 9, 4, 3-H), 3.37 (3 H, s, OCH_3), 3.98 (1 H, dq, *J* 3.5, 6.5, 4′-H), 4.18 (1 H, m, 2-H), 4.37–4.76 (6 H, m, OCH_2O, $PhCH_2$ and $ArCH_2$), 4.79 (1 H, dd, *J* 10, 3.5, 4-H), 5.63 (1 H, d, *J* 3.5, 1-H), 5.69 (1 H, m, 3′-H), 6.07 (2 H, m, 1′-H and 2′-H), 6.88 (2 H, d, *J* 10, ArH), 7.1–7.4 (7 H, m, ArH) and 8.02 (1 H, br s, NH); δ_C 15.9, 26.8, 26.9, 54.8, 69.4, 71.7, 73.5, 77.6, 78.3, 79.8, 82.5, 93.3, 104.6, 112.7, 114.1, 116.3, 127.7, 129.5, 130.3, 133.2, 138.6, 157.0 and 160.0; δ_F −75.98; *m*/*z* (CI) 613 (M^+ + 18, 7%).

3-*O*-(4-Methoxybenzyl)-4-[(1*R*,4*R*,2*E*)-4-benzyloxymethoxy-1-(2,2,2-trifluoroacetylamino)pent-2-enyl]-1,2-*O*-isopropylidene-α-D-erythrofuranose 13

A degassed solution of the trifluoroacetimidate **12** (1.4 g, 2.35 mmol) in xylene (30 cm^3) was heated under reflux for 12 h then allowed to cool to ambient temperature and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (1 : 4) as eluent afforded the *title compound* **13** (1.38 g, 98%) as a colourless gum; $[\alpha]_D^{23}$ +108 (*c* 3 in $CHCl_3$) (Found: $M^+ + NH_4$, 613.2740. $C_{30}H_{40}F_3N_2O_8$ requires *M*, 613.2737); ν_{max}/cm^{-1} 3312, 1721, 1613, 1514 and 1250; δ_H 1.21 (3 H, d, *J* 6.5, 5′-H_3), 1.36 and 1.59 (each 3 H, s, CH_3), 3.56 (1 H, dd, *J* 9, 4.5, 3-H), 3.78 (3 H, s, OCH_3), 4.10 (1 H, dd, *J* 9, 4, 4-H), 4.21 (1 H, m, 4′-H), 4.40–4.70 (8 H, m, 1′-H, 2-H, OCH_2O, $PhCH_2$ and $ArCH_2$), 5.54 (2 H, m, 2′-H and 3′-H), 5.68 (1 H, d, *J* 4, 1-H), 6.68 (1 H, br d, *J* 8, NH), 6.88 (2 H, m, ArH) and 7.25–7.40 (7 H, m, ArH); δ_C 21.2, 26.5, 26.8, 52.6, 55.3, 69.5, 71.7, 71.8, 77.2, 78.2, 79.2, 92.0, 104.4, 113.4, 114.0, 115.6, 124.5, 127.8, 127.9, 128.5, 129.0, 129.8, 137.5, 137.9, 156.3 and 159.73; δ_F −77.36; *m*/*z* (CI) 613 (M^+ + 18, 30%) and 458 (35).

3-*O*-(4-Methoxybenzyl)-4-[(1*R*,4*R*,2*E*)-1-benzyloxycarbonylamino-4-benzyloxymethoxypent-2-enyl]-1,2-*O*-isopropylidene-α-D-erythrofuranose 15

Barium hydroxide (3.2 g, 10.2 mmol) was added to a solution of the trifluoroacetamide **13** (1.4 g, 2.35 mmol) in methanol (30 cm^3) at 0 °C. The resulting suspension was stirred for 16 h then filtered through a pad of Celite® and silica and the solid residue washed with ethyl acetate (2 × 50 cm^3). Concentration under reduced pressure afforded the amine **14** (1.17 g, 100%). Water (5 cm^3), ethyl acetate (15 cm^3), potassium bicarbonate (1.2 g, 12 mmol) and benzyl chloroformate (0.32 cm^3, 2.82 mmol) were added and the mixture stirred for 14 h at ambient temperature. The reaction mixture was then diluted with ethyl acetate (100 cm^3), washed with saturated aqueous ammonium hydroxide (2 × 40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (1 : 4) as eluent afforded the *title compound* **15** (1.43 g, 96%) as a colourless gum; $[\alpha]_D^{24}$ +103 (*c* 1.1 in $CHCl_3$) (Found: $M^+ + H$, 634.2990. $C_{36}H_{44}NO_9$ requires *M*, 634.3016); ν_{max}/cm^{-1} 3348, 1721, 1612, 1587, 1514, 1455, 1249 and 1027; δ_H 1.24 (3 H, d, *J* 6.5, 5′-H_3), 1.35, 1.60 (each 3 H, s, CH_3), 3.57 (1 H, m, 3-H), 3.70 (3 H, s, OCH_3), 4.13 (1 H, dd, *J* 9, 4.5, 4-H), 4.24 (1 H, m, 4′-H), 4.41 (1 H, m, 1′-H), 4.51 (1 H, t, *J* 4, 2-H), 4.43–4.76 (6 H, m, $PhCH_2$, OCH_2O and $ArCH_2$), 5.13 (2 H, s, CO_2CH_2), 5.23 (1 H, br d, *J* 9, NH), 5.56 (2 H, m, 2′-H and 3′-H), 5.69 (1 H, d, *J* 3.5, 1-H), 6.88 (2 H, m, ArH) and 7.27–7.45 (12 H, m, ArH); *m*/*z* (FAB) 634 (M^+ + 1, 5%) and 496 (35).

4-[(1*R*,4*R*,2*E*)-1-Benzyloxycarbonylamino-4-benzyloxymethoxypent-2-enyl)-1,2-*O*-isopropylidene-α-D-erythrofuranose 16

Dichlorodicyanoquinone (0.4 g, 1.76 mmol) was added to a solution of the *p*-methoxybenzyl ether **15** (0.66 g, 1.04 mmol) in a mixture of dichloromethane (25 cm^3), pH 7 buffer (4 cm^3) and *tert*-butyl alcohol (1 cm^3). The resulting mixture was stirred for 6 h, a further portion of dichlorodicyanoquinone (0.2 g, 0.88 mmol) was added and the mixture stirred overnight. The resulting suspension was diluted with dichloromethane (60 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), water (20 cm^3) and brine then dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using ethyl acetate–light petroleum (2 : 3) as eluent afforded the *title compound* **16** (0.4 g, 73%) as a colourless gum; $[\alpha]_D^{25}$ +79 (*c* 1.6 in $CHCl_3$) (Found: M^+ + Na, 536.2287. $C_{28}H_{35}NO_8Na$ requires *M*, 536.2261); ν_{max}/cm^{-1} 3343, 3033, 1718, 1612, 1587, 1520 and 1025; δ_H 1.29 (3 H, d, *J* 6.5, 5′-H_3), 1.35 and 1.57 (each 3 H, s, CH_3), 2.56 (1 H, br s, OH), 3.83 (1 H, m, 3-H), 3.88 (1 H, dd, *J* 9, 3.4, 4-H), 4.29 (1 H, m, 4′-H), 4.5 (2 H, m, 1′-H and 2-H), 4.61 and 4.68 (each 1 H, d, *J* 10, Ar*H*CH), 4.77 (2 H, s, CH_2), 5.14 (2 H, s, OCH_2O), 5.32 (1 H, br d, *J* 8, NH), 5.64 (1 H, dd, *J* 8, 3, 2′-H), 5.75 (2 H, m, 1-H and 3′-H) and 7.37 (10 H, m, ArH); δ_C 21.4, 26.5, 26.5, 53.3, 66.9, 69.5, 72.4, 72.7, 78.6, 81.8, 92.1, 103.9, 112.9, 126.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.5, 128.6, 136.0, 136.4, 137.9 and 155.7; *m*/*z* (FAB) 536 (M^+ + 23, 3%), 456 (17), 426 (10), 376 (100) and 318 (43).

3-*O*-Acetyl-4-[(1*R*,4*R*,2*E*)-1-benzyloxycarbonylamino-4-benzyloxymethoxypent-2-enyl)-1,2-*O*-isopropylidene-α-D-erythrofuranose 17

4-Dimethylaminopyridine (10 mg), triethylamine (0.28 cm^3, 2 mmol) and acetic anhydride (0.12 cm^3, 1.3 mmol) were added to a solution of the alcohol **16** (0.51 g, 1 mmol) in dichloromethane (30 cm^3) at 0 °C. The mixture stirred at ambient temperature for 1 h then diluted with ethyl acetate (50 cm^3), washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using ethyl acetate–light petroleum (2 : 3) as eluent afforded the *title compound* **17** (0.54 g, 98%) as a colourless gum; $[\alpha]_D^{20}$ +118 (*c* 0.9 in $CHCl_3$) (Found: $M^+ + NH_4$, 573.2824. $C_{30}H_{41}N_2O_9$ requires *M*, 573.2812); ν_{max}/cm^{-1} 3343, 1742, 1710, 1525, 1375, 1240, 1169 and 1027; δ_H 1.29 (3 H, d, *J* 6.3, 5′-H_3), 1.35 and 1.57 (each 3 H, s, CH_3), 2.12 (3 H, s, $COCH_3$), 4.23 (1 H, dd, *J* 9, 3.5, 4-H), 4.29 (1 H, quintet, *J* 6, 4′-H), 4.45 (1 H, m, 3-H), 4.65–4.76 (6 H, m, 2-H, 1′-H, $ArCH_2$, and CH_2Ph), 5.13 (2 H, s, OCH_2O), 5.20 (1 H, br d, *J* 8, NH), 5.67 (2 H, m, 2′-H and 3′-H), 5.76 (1 H, d, *J* 4, 1-H) and 7.38 (10 H, m, ArH); δ_C 20.6, 21.3, 26.6, 53.0, 67.1, 69.5, 72.0, 72.9, 79.1, 92.0, 104.1, 113.3, 126.0, 127.7, 127.9, 128.2, 128.2,

128.5, 136.2, 136.3, 138.0, 155.5 and 170.1; *m/z* (CI) 573 ($M^+ + 18$, 5%), 466 (24) and 419 (100).

1,2,3-Tri-*O*-acetyl-4-[(1*R*,4*R*,2*E*)-4-acetoxy-1-benzyloxycarbonylaminopent-2-enyl)-D-erythrofuranose 19

A solution of the acetonide **17** (0.76 g, 1.37 mmol) in 70% aqueous acetic acid was heated to 70 °C for 40 h. Concentration under reduced pressure gave the triol **18** which was dissolved in dichloromethane (15 cm^3) and 4-dimethylaminopyridine (5 mg), triethylamine (2 cm^3, 14.2 mmol) and acetic anhydride (0.5 cm^3, 5.3 mmol) were added at 0 °C. The mixture was stirred at ambient temperature for 45 min then diluted with ethyl acetate (50 cm^3), washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using ethyl acetate–light petroleum (2:3) as eluent afforded an anomeric mixture of the *title compound* **19** (0.63 g, 88%) as a colourless gum (Found: $M^+ - OH$, 504.1875. $C_{25}H_{30}NO_{10}$ requires *M*, 504.1870); ν_{max}/cm^{-1} 3340, 1747, 1526, 1372, 1328, 1235, 1078 and 969; δ_H 1.24 (2 H, d, *J* 6, 5′-H_3), 1.26 (1 H, d, *J* 6, 5′-H_3), 1.96–2.09 (12 H, s, 4 × $COCH_3$), 4.26 (0.3 H, m, 4′-H), 4.36 (0.7 H, m, 4′-H), 4.97–5.77 (9 H, m, 2-H, 3-H, 4-H, 1′-H, 2′-H, 3′-H, NH and CH_2Ph), 6.07 (0.3 H, 1β-H), 6.85 (0.7 H, 1α-H) and 7.31 (5 H, m, ArH); *m/z* (CI) 539 ($M^+ + 18$, 25%), 521 (M^+, 100), 504 (41), 444 (23) and 431 (47).

1,2,3-Tri-*O*-acetyl-4-[(*S*)-Benzyloxycarbonylamino(methoxyoxycarbonyl)methyl]-D-erythrofuranose 20

A solution of the tetraacetate **19** (0.42 g, 0.8 mmol) in methanol (20 cm^3) was cooled to −78 °C whilst oxygen was bubbled through the solution. After 10 min, ozone was bubbled into the reaction for 25 min and the mixture purged with oxygen for a further 10 min. Dimethyl sulfide (0.8 cm^3, 10.9 mmol) was added and the reaction mixture allowed to warm to ambient temperature over 1 h then concentrated under reduced pressure. The residual oil was dissolved in methanol (15 cm^3) and water (2 cm^3) and cooled to 0 °C. Sodium hydrogen carbonate (2 g, 23.8 mmol) and bromine (1.56 g, 10 mmol) were added and the resulting suspension stirred at ambient temperature for 6 h. The mixture was then diluted with ether (100 cm^3) and washed with aqueous sodium thiosulfate solution (1.0 M; 2 × 20 cm^3), brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using ethyl acetate–light petroleum (1:1) as eluent afforded an anomeric mixture of the ester **20**[4] (0.28 g, 74%) as a colourless gum (Found: $M^+ - CH_3CO_2H$, 407.1214. $C_{19}H_{21}NO_9$ requires *M*, 407.1216); ν_{max}/cm^{-1} 3354, 1752, 1710, 1526, 1372 and 1224; δ_H 3.8 (3 H, s, OCH_3); *m/z* (EI) 407 ($M^+ - 60$, 1%), 347 (2) and 270 (9).

Thymine polyoxin C 3

Bis-silylated thymine (0.27 g, 1.16 mmol) and trimethylsilyl triflate (0.25 cm^3, 1.27 mmol) were added to a solution of the triacetate **20** (0.18 g, 0.39 mmol) in 1,2-dichloroethane (6 cm^3) and the yellow solution heated under reflux for 45 min. The reaction mixture was allowed to cool to ambient temperature, dichloromethane (50 cm^3) was added, and the mixture was washed with saturated aqueous hydrogen carbonate (2 × 20 cm^3), brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using ethyl acetate–light petroleum (2:3) with 5% methanol as eluent afforded the protected thymine polyoxin C **21**[4] (0.17 g, 82%) as a foam; $[\alpha]_D^{22}$ +16 (*c* 1 in $CHCl_3$) [lit.,[4] +19.8 (*c* 0.56 in $CHCl_3$)] (Found: $M^+ + H$, 534.1718. $C_{24}H_{28}N_3O_{11}$ requires *M*, 534.1724); ν_{max}/cm^{-1} 3295, 1750, 1696, 1528 and 1238; δ_H 1.87 (3 H, br s, 5-CH_3), 2.07 (6 H, s, 2 × $COCH_3$), 3.79 (3 H, s, CO_2CH_3), 4.39 (1 H, dd, *J* 5, 4, 4′-H), 4.81 (1 H, dd, *J* 8.5, 3.5, 5′-H), 5.12 (2 H, s, CH_2Ph), 5.26 (1 H, t, *J* 6, 2′-H), 5.51 (1 H, t, *J* 6, 3′-H), 5.85 (1 H, d, *J* 8.5, NH), 5.92 (1 H, d, *J* 5.5, 1′-H), 7.03 (1 H, br s, 6-H), 7.29 (5 H, m, ArH) and 8.85 (1 H, s, 3-NH); δ_C 12.5, 20.5, 29.7, 53.0, 55.1, 60.4, 67.5, 69.7, 72.3, 77.3, 81.9, 87.6, 112.1, 128.1, 128.4, 128.6, 135.5, 135.8, 150.3, 156.4, 163.2, 169.3, 169.6 and 169.7; *m/z* (CI) 551 ($M^+ + 18$, 4%), 534 ($M^+ + 1$, 10) and 426 (10).

Lithium hydroxide monohydrate (28 mg, 0.67 mmol) was added as a solid to a solution of the diacetate **21** (82 mg, 0.15 mmol) in tetrahydrofuran (6 cm^3) and water (1.5 cm^3) at 0 °C and the resulting yellow solution stirred at 0 °C for 6 h. The mixture was diluted with water (15 cm^3) and extracted with dichloromethane (2 × 20 cm^3). The aqueous phase was cooled to 0 °C, acidified to pH ~2 with aqueous hydrogen chloride (1 M) and extracted with ethyl acetate (5 × 20 cm^3). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow solid (46 mg). A portion of the solid (23 mg, 0.056 mmol) was dissolved in methanol (5 cm^3) and stirred with 10% Pd/C (14 mg) under an atmosphere of hydrogen for 6 h. The suspension was then diluted with methanol (10 cm^3), filtered through a pad of Celite® and the solid residue washed with methanol (2 × 10 cm^3) and water (2 × 10 cm^3). The filtrate was concentrated under reduced pressure to give a yellow solid (15 mg). Ion exchange chromatography (Dowex 50 X8-400, 3 cm^3) eluting with a mixture of pyridine and acetic acid (3:17, pH ~3.1) followed by azeotropic concentration under reduced pressure gave thymine polyoxin C **3**[3,4] (10 mg, 47%) as a pale yellow solid; R_f 0.22, authentic sample R_f 0.22, in $CHCl_3$–MeOH–H_2O (5:4:1); mp 184–187 °C, authentic sample mp 190–193 °C (lit.,[4] 182–185 °C); $[\alpha]_D^{20}$ +8 (*c* 0.3 in H_2O), authentic sample $[\alpha]_D^{20}$ +8.5 (*c* 0.3 in H_2O) [lit.,[4] +8 (*c* 0.37 in H_2O)]; ν_{max}/cm^{-1} (KBr) 3573, 3422 and 3334, 1712, 1688, 1670, 1611, 1323 and 1042; δ_H (D_2O) 1.86 (3 H, s, 5-CH_3), 4.07 (1 H, d, *J* 2.2, 5′-H), 4.29 (2 H, m, 2′-H and 4′-H), 4.57 (1 H, t, *J* 5.5, 3′-H), 5.80 (1 H, d, *J* 5, 1′-H) and 7.45 (1 H, s, 2-H); δ_C 12.5, 56.3, 70.4, 73.6, 83.2, 90.6, 112.7, 138.9, 152.8, 167.4 and 171.3; *m/z* (FAB) 301 (M^+, 100%), 234 (39), 199 (34), 160 (38) and 146 (33).

3-*O*-(4-Methoxybenzyl)-4-[(*S*)-(benzyloxycarbonylamino)(methoxycarbonyl)methyl]-1,2-*O*-isopropylidene-α-D-erythrofuranose 22

Following the procedure outlined for the preparation of the methyl ester **20**, the alkene **15** (0.83 g, 1.32 mmol), after chromatography using light petroleum–ether as eluent (gradient elution), afforded the methyl ester **23** (0.19 g, 65%) as a colourless oil, $[\alpha]_D^{23}$ +67 (*c* 1.3, $CHCl_3$), followed by the *title compound* **22** (0.50 g, 75%) as a white foam, $[\alpha]_D^{24}$ +51 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 3354, 1726, 1605, 1501, 1282, 1259, 1055 and 1024; δ_H 1.34 and 1.58 (each 3 H, s, CH_3), 3.69 (3 H, s, OCH_3), 3.85 (1 H, dd, *J* 9, 5, 3-H), 3.88 (3 H, s, OCH_3), 4.27 (1 H, dd, *J* 9, 4, 4-H), 4.47 (2 H, m, OC*H*H and 2-H), 4.65 (2 H, m, OCH*H* and C*H*-NH), 5.10 (2 H, s, CO_2CH_2), 5.49 (1 H, br d, *J* 7, NH), 5.68 (1 H, d, *J* 3.5, 1-H), 6.85 (2 H, m, ArH) and 7.25–7.60 (7 H, m, ArH).

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