Asymmetric total synthesis of (+)-carbocyclic uracil polyoxin C

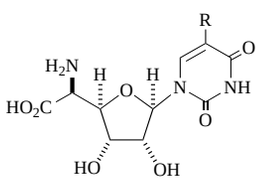
Varinder K. Aggarwal* and Nuno Monteiro

Department of Chemistry, University of Sheffield, Sheffield, UK S3 7HF

A short, practical, asymmetric synthesis of carbocyclic uracil polyoxin C is described. The key step in the synthesis is a regio- and stereo-selective palladium-mediated substitution reaction of an α-amino substituted unsaturated lactone with bis-silylated uracil. Critical to the success of this reaction is the use of trimethylsilyl chloride in the reaction mixture which substantially enhances the reactivity of the lactone. The final stages involve dihydroxylation of 1,4-disubstituted cyclopentene which is essentially non-selective. The factors surrounding the poor selectivity of this reaction are discussed.

Introduction

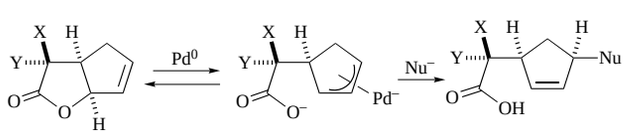
Polyoxins and nikkomycins (neopolyoxins) form an important class of peptidyl nucleosides which are potent inhibitors of chitin synthetase.[1] Polyoxin C constitutes the basic amino acid nucleoside common to most members of the polyoxins (*e.g.* **1a**–**c**) and nikkomycin dipeptides. They have been the focus of



1a R = H Uracil Polyoxin C
1b R = Me Thymine Polyoxin C
1c R = CH_2OH Polyoxin C

recent synthetic efforts[2,3] but little attention has been given to the carbocyclic analogues of the nikkomycins or polyoxins.[4] The potential advantage in the therapeutic use of these compounds includes greater metabolic stability and in some cases *increased* biological activity compared to nucleosides.

In our earlier studies[5] we showed that C-4 substituted 2-oxabicyclo[3.3.0]oct-7-en-3-ones can undergo efficient palladium-catalysed substitution reactions with various nucleophiles. In this process the regio- and stereo-chemistry of the 1,4-disubstituted cyclopentene is totally controlled (Scheme 1). We felt that this methodology could be applied to

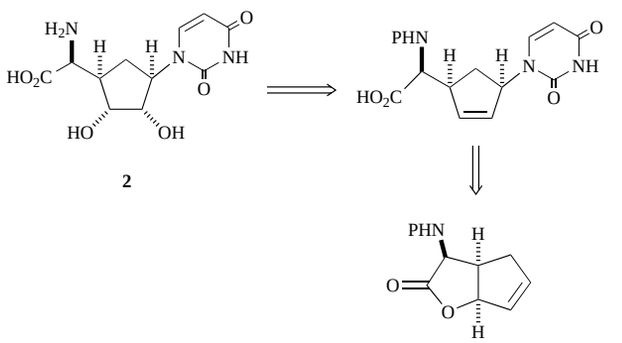


Scheme 1

the allylation of nucleoside bases providing a short and convenient access to carbocyclic analogues of nucleosides, in particular the polyoxin and nikkomycin analogues. In this paper we describe in full the successful execution of this strategy in a synthesis of carbocyclic uracil polyoxin C **2** (Scheme 2).[6]

Results and discussion

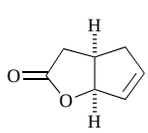
The palladium(0)-catalysed substitution of cyclopentenyl acetates and related compounds by nucleoside bases has been



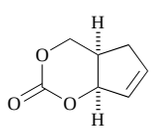
2

Scheme 2

investigated[7] and such bases have been shown to be very poor nucleophiles. High temperatures are often required due to the poor solubility of the corresponding salts. Problems related to the regioselectivity obtained at the heterocyclic ring have also been reported particularly when two amide groups are present as in the case for pyrimidines such as uracil[8] and so protecting groups are often required. There are no examples of palladium-catalysed substitution reactions of unsaturated lactones (*e.g.* **3**)



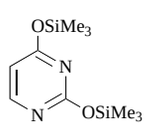
3



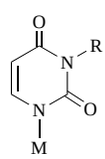
4

with nucleoside bases. However there is an example where the bicyclic carbonate **4** was used in a carbonucleoside synthesis.[9] Carbonates are much more reactive than acetates (which are themselves more reactive than lactones) and evidently are able to couple with poor nucleophiles including nucleoside bases.

We have recently shown that unsaturated lactones can undergo palladium-catalysed substitution reactions.[5] The efficiency of the reaction is dependent on the nucleophile used and the nature and stereochemistry of the substituent α to the carbonyl group. In model studies we reacted lactone **3** with a range of uracil derivatives **5**[10] and **6**[11] under a variety of conditions



5



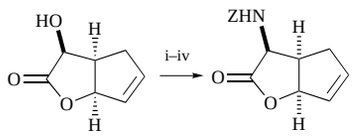
6

R = H or Bz
M = Na, K, Cs

* E-Mail: V.Aggarwal@Sheffield.ac.uk

(range of solvents DMF, DMSO, CH_3CN–H_2O; 80 °C) using catalytic amounts of palladium(0) complexes [$Pd(PPh_3)_4$, $Pd(OPr^i)_4$, $Pd(dppe)_2$, $Pd(dba)_2$] but without any success.

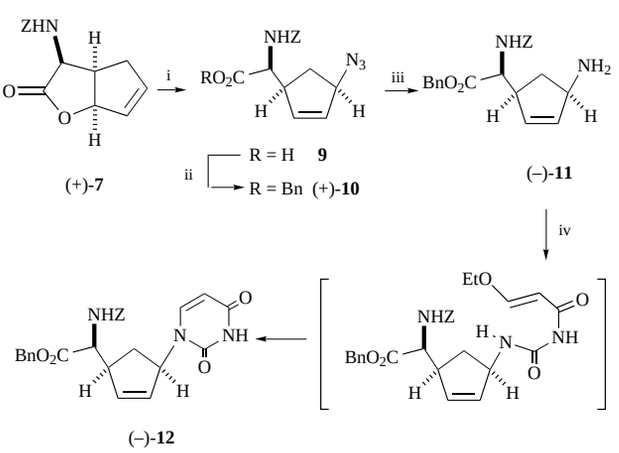
Our model reaction with the simple lactone **3** was perhaps not a good choice because it is a poorer electrophile in palladium-catalysed substitution reactions than the amino lactone **7** required for the synthesis of polyoxins. We have previously shown that the presence of an electron withdrawing group α to the carbonyl group of lactones enhances rates of substitution and that further rate increases can be achieved using an *endo* substituent.[5] The amino lactone **7** possesses both features and was therefore prepared from (−)-hydroxy lactone **8**[12] (Scheme 3). However, all reactions of (+)-**7** with uracil



(-)-**8** (+)-**7**

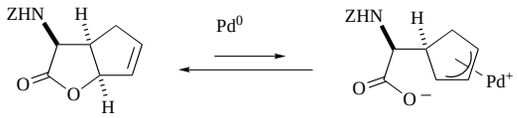
Scheme 3 *Reagents and conditions*: i, $ZnBr_2$, PPh_3, DEAD, THF, room temp., 60%; ii, NaN_3, DMSO, RT, 87%; iii, PPh_3, THF–H_2O, room temp., 92%; iv, ZCl, $NaHCO_3$, THF–H_2O, 0 °C, 94%

derivatives **5** or **6** under a range of conditions were still unsuccessful. Assuming that the problem lay in attempting to couple a poor nucleophile with a still relatively poor electrophile, we decided to use a superior nucleophile that could ultimately be converted to the uracil base.[13] We were particularly interested in the use of di-*tert*-butyl iminodicarbonate [$HN(Boc)_2$],[14d] and sodium azide[14e] because such nitrogen nucleophiles had been used in palladium-catalysed substitution reactions as ammonia substitutes.[14] Although lactone **7** did not react with the sodium or potassium salts of $HN(Boc)_2$ we were pleased to find that reaction of sodium azide in the presence of 5 mol% $Pd(PPh_3)_4$ in THF at room temperature afforded the cyclopentene acid derivative **9** as the sole product (94% yield). The carboxy function was subsequently protected[15b] as a benzyl ester **10** and after reduction[16] of the azido group to the amine the uridine derivative **12** was obtained in two steps from **11** and in 75% overall yield (Scheme 4).



Scheme 4 *Reagents and conditions*: i, NaN_3, $Pd(PPh_3)_4$, THF–H_2O, room temp., 94%; ii, BnBr, $NaHCO_3$, DMF, RT, 96%; iii, PPh_3, THF–H_2O, room temp., 81%; iv, EtOCH=CHCONCO, benzene–DMF, −10 °C to room temp., 85% then 1 M H_2SO_4, dioxane, reflux, 88%

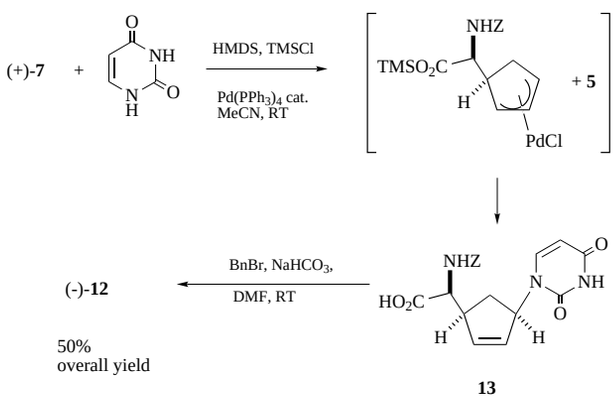
However, the additional steps and linearity of the synthesis made it less efficient and less flexible than the direct coupling of uracil with lactone **7**. We reasoned that if we could increase the reactivity of the lactone, it might then couple with poor nucleophiles like uracil. Assuming that the low reactivity of the lactone was due to the position of the equilibrium favouring the closed lactone rather than the π-allyl palladium species (Scheme 5) we sought to push the equilibrium towards the π-allyl



Scheme 5

palladium intermediate by trapping the carboxylate released with a good oxophilic species and considered the use of trimethylsilyl chloride (TMSCl).

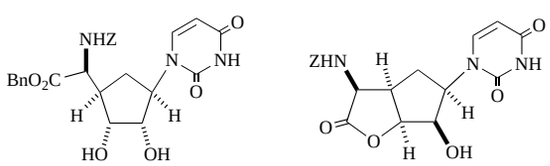
We therefore treated lactone **7** with the silylated uracil **5** in the presence of palladium(0) and one equivalent of TMSCl and were pleased to observe direct coupling. Following benzylation of acid **13**, (−)-**12** was obtained although in low yield (32%, two steps). As TMSCl is known to accelerate silylation reactions when using hexamethyldisilazane (HMDS), especially when these are performed at unusually low temperatures,[17] we considered a simpler procedure in which the silylated uracil was prepared *in situ* at room temperature. Thus simply mixing stoichiometric amounts of uracil, TMSCl, HMDS at room temperature followed by lactone **7** and palladium(0) we obtained the coupled product in improved yield. Following benzylation, **12** was isolated in 50% overall yield (Scheme 6).



Scheme 6

The ^1H and ^{13}C NMR spectral data as well as the optical rotation of the product matched those obtained by the previously described linear approach.

The penultimate step in the synthesis was stereocontrolled dihydroxylation of the cyclopentene. The stereocontrolled dihydroxylation of 3-substituted cyclopentenes in good yield remains a challenging problem:[18] selective attack from the less hindered face is rarely observed due to either directive effects[19] of allylic groups or conformational effects[20] of the five membered ring. A range of reaction conditions using NMO monohydrate with catalytic OsO_4 were examined[21] but this always led to a mixture of compounds **14** and **15** (Table 1, entries



(+)-**14** (+)-**15**

1–4), the latter arising from lactonisation of the unwanted all-*cis* diol. In line with previous results[20a] a marked solvent effect was observed; the *syn* isomer was always favoured except when the reaction was performed in THF (entry 4) which gave a 1:1 ratio of **14**:**15** (90% yield) from which **14** could be isolated in 44% yield by conventional chromatography. This method was ultimately used[22] though the use of $NaIO_4$ with catalytic RuO_4 gave the highest selectivity in favour of the desired diol (2:1) but in only 59% overall yield (entry 10).

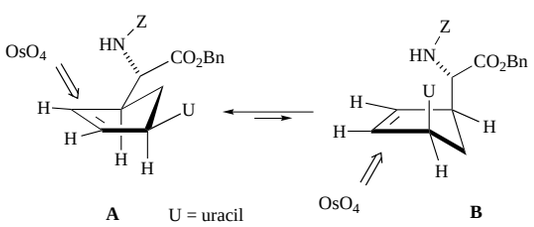
Table 1 Results from the dihydroxylation of **12**[a]

Entry	Catalyst[b]	Equiv.	Additive[c]	Solvent	Reaction time	Yield (%)	Ratio **14**:**15**[d]
1	OsO_4	0.04	—	Pr^iOH	>24 h	29[e]	17:83
2	OsO_4	0.04	—	CH_2Cl_2	7 h	92	22:78
3	OsO_4	0.04	—	Me_2CO	3 h	96	43:57
4	OsO_4	0.04	—	THF	15 h	90	50:50
5[f]	OsO_4	0.04	$(DHQ)_2PHAL$	$Bu^tOH–H_2O$ (1:1)	—	0	—
6[f]	OsO_4	0.04	$(DHQ)_2PHAL$	THF–H_2O (1:1)	—	0	—
7	OsO_4	0.04	$(DHQ)_2PHAL$	THF	15 h	84	47:53
8	OsO_4	0.04	$(DHQ)_2PHAL$	THF	15 h	87	35:65
9	OsO_4	1	—	THF–H_2O (10:1)	20 h	80	40:60
10	OsO_4	1	quinidine	THF–H_2O (10:1)	20 h	—[g]	—
11	OsO_4	1	$(DHQ)_2PHAL$	THF–H_2O (10:1)	20 h	—[g]	—
12[h]	RuO_4	0.07	—	AcOEt–MeCN–H_2O	<5 min	59	67:33
13	OsO_4	0.07	—	AcOEt–MeCN–H_2O	20 h	92	44:56

[a] Reactions conducted at room temperature under a nitrogen atmosphere. [b] $NMO·H_2O$ and $NaIO_4$ were used as co-oxidants respectively for OsO_4 and RuO_4. [c] Ligands: $(DHQ)_2PHAL$ = dihydroquinine 1,4-phtalazinediyl diether; $(DHQD)_2PHAL$ = dihydroquinidine 1,4-phtalazinediyl diether; 0.25 equiv. or 2 equiv. were used respectively when catalytic or stoichiometric amounts of osmium tetroxide were used. [d] Complete lactonisation of the *syn* diastereoisomer was ensured by treatment of the crude mixture with cat. *p*-TsOH (see Experimental section for details). Ratios were determined by ^{1}H NMR spectroscopy (250 MHz, $[^2H]_6$DMSO) on the purified mixture (flash chromatography) by integration of the vinyl doublets of the pyrimidine ring; (δ 7.61 for **14** and 7.52 ppm for **15**). [e] Only 36% conversion after 24 h due to poor solubility of the starting material in the solvent at this temperature. [f] $K_3Fe(CN)_6$ was used as co-oxidant in the presence of K_2CO_3 and $CH_3SO_2NH_2$. [g] A mixture of products was obtained (see text). [h] Reaction conducted at 0 °C.

Attempts to influence the diastereoselectivity of the dihydroxylation through reagent control were unsuccessful. Under the conditions required for the Sharpless asymmetric dihydroxylation (AD)[23] reaction no diol was obtained (entries 5 and 6). By using UpJohn's procedure with added quinine/quinidine based ligands clean dihydroxylation was achieved but still without significant enhancement of the diastereoselectivity (entries 7 and 8). Using stoichiometric amounts of OsO_4 with additional ligands gave an intractable mixture of products presumably resulting from competitive osmylation of the uracil moiety[24] as indicated by the disappearance in ^{1}H NMR of the uracil double bond protons (entries 10 and 11). All attempts in using potassium permanganate[25] as oxidant failed. Under basic or neutral aqueous conditions[25b] essentially no diols were obtained whereas use of quaternary ammonium salts as additives under anhydrous conditions[25c] again led to intractable mixtures of products.

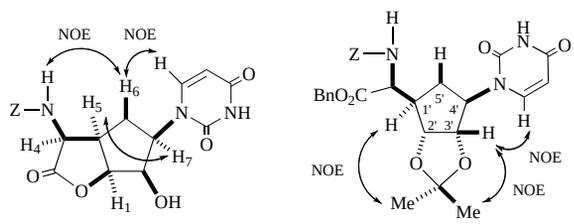
The preferred formation of the all-*cis* diol can be rationalised on the basis of the preferred conformation of the cyclopentene and consideration of non-bonded interactions using the model developed by Poli.[20a] Cyclopentene **12** should preferentially adopt conformation **A** in which the two groups are pseudo-equatorial to avoid 1,3-interactions (Scheme 7). In this conformation attack from the lower face is blocked by the axial C–H groups whereas attack on the top face can occur unimpeded. Conformer B would be expected to be oxidised on the less hindered α face.



Scheme 7

The stereochemistry of the dihydroxylation as well as that of the outcome of the palladium catalysed reactions were confirmed by COSY and ROESY experiments on lactone (+)-**15** and the acetonide derivative (+)-**16**.

Fig. 1 shows the significant NOEs. In compound **15** all hydrogen atoms on the β face are related which confirms the all-*cis* stereochemistry of the cyclopentane ring. Further indications come from strong NOEs between H-6 and both the hydrogen on the nitrogen bearing the Z group and one of the vinyl hydrogens at the uracil moiety. This also confirmed the stereochemistry at C–4. The separation between the signals corresponding to H-4 and H-5 was too small to allow further confirmation. Compound **16** showed strong NOEs between the vinyl hydrogen of the uracil ring and both $H_{2'}$ and $H_{3'}$. These two hydrogens also showed a strong NOE to one of the methyl groups of the acetonide and the other methyl group showed a strong NOE with $H_{1'}$. Finally, hydrogenolysis of both benzyl protecting groups[15a] gave carbocyclic uracil polyoxin C **2** in essentially quantitative yield.



(+)-**15** (+)-**16**

Fig. 1

Conclusion

We have described a short, practical, asymmetric synthesis of carbocyclic uracil polyoxin C based on a regio- and stereoselective palladium-mediated substitution reaction of an α-amino substituted unsaturated lactone with bis-silylated uracil. Critical to the success of this reaction is the use of TMSCl in the reaction mixture which substantially enhances the reactivity of the lactone. As a wide range of silylated heterocyclic bases can be prepared,[10,26] this reaction should find broader applications.

Experimental

General procedures

Unless otherwise noted all reactions were carried out under a nitrogen atmosphere in oven dried glassware using standard syringe, cannula and septa techniques. Reagents purchased commercially were used without further purification. Tetrahydrofuran was distilled from $LiAlH_4$. Dimethylformamide, benzene and acetonitrile were distilled from CaH_2. Analytical TLC was performed with 0.2 mm silica gel $60F_{254}$ plates. Flash

chromatography was performed using BDH flash silica gel (40–63 μm). Melting points were determined on a Reichert hot stage micro melting point apparatus and are uncorrected. ^{1}H (250 MHz) and ^{13}C (63 MHz) NMR spectra were recorded in $CDCl_3$ on a Bruker AC-250 instrument using $CDCl_3$ as internal standard. Chemical shifts (δ) are given in ppm downfield. *J* Values are given in Hz. Infrared spectra were run on a Perkin-Elmer 684 Spectrophotometer. Mass spectra were recorded on a VG-ProSpec instrument operating in EI, CI or FAB mode. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to the fraction with bp 40–60 °C.

(−)-4-*exo*-Bromo-2-oxabicyclo[3.3.0]oct-7-en-3-one

The hydroxy lactone (−)-**8** (2.80 g, 20 mmol) and triphenylphosphine (15.80 g, 60 mmol) were dissolved in anhydrous THF (250 ml) under nitrogen. Anhydrous zinc bromide (4.50 g, 20 mmol) and diethyl azodicarboxylate (DEAD) (9.40 ml, 60 mmol) were added at room temperature consecutively. The mixture was stirred at room temperature for 30 min and then was filtered through Celite. The solid residue was carefully washed with ethyl acetate and the filtrate condensed *in vacuo*. Purification by chromatography on silica gel using ethyl acetate–light petroleum (1:4) as eluent gave in the first fractions the exo-*bromo lactone* (2.43 g, 60%) as a white solid; mp 39.5–40.5 °C; $[\alpha]_D^{20}$ −55.6 (*c* 1, $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 3030, 2985 and 1755; δ_H(250 MHz, $CDCl_3$) 6.13 (1H, dt, *J* 2.0 and 5.5, 7-H or 8-H), 5.82 (1H, dq, *J* 2.0 and 5.5, 7-H or 8-H), 5.57 (1H, dt, *J* 2.0 and 7.0, 1-H), 4.24 (1H, d, *J* 4.5, 4-H), 3.30 (1H, ddt, *J* 4.5, 7.0 and 9.0, 5-H), 2.84 (1H, dddt, *J* 1.0, 2.0, 9.0 and 17.5, 6-H) and 2.39 (1H, ddt, *J* 2.0, 7.0 and 17.5, 6-H); δ_C(63 MHz, $CDCl_3$) 172.8 (C-3), 138.0 (C-7 or C-8), 128.5 (C-7 or C-8), 87.9 (C-1), 47.5 (C-4), 43.4 (C-5) and 37.3 (C-6); *m*/*z* (EI) 79 (100%) (Found: C, 41.38; H, 3.27; Br, 39.30. Calc. for $C_7H_7BrO_2$: C, 41.41; H, 3.47; Br, 39.35%).

(−)-4-*endo*-Azido-2-oxabicyclo[3.3.0]oct-7-en-3-one

Sodium azide (2.60 g, 40 mmol) was added to a solution of the above *exo*-bromo lactone (4.06 g, 20 mmol) in DMSO (20 ml). The solution was stirred for 24 h at room temperature, diluted with ethyl acetate and washed with brine. The organic layer was dried (Na_2SO_4) and condensed *in vacuo*. The crude product was purified by chromatography on silica gel using ethyl acetate–light petroleum (3:7) as eluent to give the endo-*azido lactone* (2.87 g, 87%) as a colourless oil; $[\alpha]_D^{20}$ −257.7 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3060, 2940, 2110, 1770 and 1620; δ_H(250 MHz, $CDCl_3$) 6.19 (1H, dt, *J* 2.2 and 5.5, 7-H or 8-H), 5.89 (1H, dq, *J* 2.2 and 5.5, 7-H or 8-H), 5.34 (1H, dt, *J* 2.2 and 6.5, 1-H), 4.55 (1H, d, *J* 9.5, 4-H), 3.20 (1H, dddd, *J* 6.0, 6.5, 9.0 and 9.5, 5-H), 2.64 (1H, ddt, *J* 2.2, 6.0 and 18.0, 6-H) and 2.48 (1H, ddt, *J* 2.2, 9.0 and 18.0, 6-H); δ_C(63 MHz, $CDCl_3$) 173.14 (C-3), 140.29 (C-7 or C-8), 127.59 (C-7 or C-8), 86.99 (C-1), 59.52 (C-4), 39.45 (C-5) and 32.33 (C-6); *m*/*z* (EI) 165 (M$^+$, 1%) and 137 (M − N_2, 100) (Found: C, 51.00; H, 4.39; N, 25.45. Calc. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44%).

(−)-4-*endo*-Amino-2-oxabicyclo[3.3.0]oct-7-en-3-one

Triphenylphosphine (4.73 g, 18 mmol) was added in small portions to a solution of the above *endo*-azido lactone (2.97 g, 18 mmol) in tetrahydrofuran (18 ml) and rapid evolution of nitrogen occurred. After complete reaction, water (1.62 g, 90 mmol) was added and the mixture was stirred at room temperature for 24 h. After removal of the solvent, the crude product was purified by chromatography on silica gel (gradient of solvent ethyl acetate–methanol) to give the corresponding endo-*amino lactone* (2.30 g, 92%) as a pale yellow solid; mp 59–60 °C; $[\alpha]_D^{20}$ −48.6 (*c* 1, MeOH); ν_{max}(KBr disc)/cm^{-1} 3375, 2970, 1755, 1665 and 1620; δ_H(250 MHz, $CDCl_3$) 6.13 (1H, dt, *J* 2.2 and 5.5, 7-H or 8-H), 5.85 (1H, dq, *J* 2.2, 5.5, 7-H or 8-H), 5.21 (1H, dt, *J* 2.2 and 6.5, 1-H), 3.95 (1H, d, *J* 9.5, 4-H), 3.06 (1H, tt, *J* 6.5 and 9.5, 5-H), 2.49 (1H, ddt, *J* 2.2, 6.5 and 18.0, 6-H), 2.37 (1H, ddt, *J* 2.2, 9.5 and 18.0, 6-H) and 1.72 (2H, br s, NH_2); δ_C(63 MHz, $CDCl_3$) 178.3 (C-3), 140.3 (C-7 or C-8), 128.2 (C-7 or C-8), 86.0 (C-1), 53.2 (C-4), 41.2 (C-5) and 31.3 (C-6); *m*/*z* (EI) 95 (98%), 94 (100), 80 (53), 67 (52) and 66 (44) (Found: C, 60.16; H, 6.44; N, 9.81. Calc. for $C_7H_9NO_2$: C, 60.42; H, 6.52, N, 10.06%).

(+)-4-*endo*-Benzyloxycarbonylamino-2-oxabicyclo[3.3.0]oct-7-en-3-one 7

Sodium hydrogen carbonate (2.70 g, 32 mmol) and benzyl chloroformate (2.46 ml, 16 mmol) were added to a solution of the above amino lactone (2.22 g, 16 mmol) in THF–H_2O (1:3, 64 ml) at 0 °C. The reaction was allowed to warm to room temperature (1 h) and was quenched with saturated aqueous ammonium chloride. The reaction mixture was extracted with ethyl acetate and the combined organic layers were dried (Na_2SO_4) and condensed *in vacuo*. Filtration of the crude product through silica gel using ethyl acetate–light petroleum (3:7) as eluent gave the *carbamate* (+)-**7** (4.11 g, 94%) as a white solid; mp 146–147 °C; $[\alpha]_D^{20}$ +35.0 (*c* 1, $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 3320, 3025, 2960, 1770 and 1690; δ_H(400 MHz, $CDCl_3$, 220 K, too broad at 293 K) 7.37 (5H, br s, Ar*H*), 6.22 (1H, dt, *J* 2.2 and 5.5, 7-H or 8-H), 5.97 (1H, d, *J* 6.0, N*H*), 5.92 (1H, dq, *J* 2.2 and 5.5, 7-H or 8-H), 5.33 (1H, dt, *J* 2.2 and 6.0, 1-H), 5.07 (2H, AB, *J* 11.0, CH_2Ph), 4.78 (1H, dd, *J* 6.0 and 9.0, 4-H), 3.37 (1H, tt, *J* 6.0 and 9.0, 5-H), 2.46 (1H, ddt, *J* 2.2, 9.0 and 18.0, 6-H) and 2.34 (1H, ddt, *J* 2.2, 6.0 and 18.0, 6-H); δ_C(63 MHz, $CDCl_3$) 174.1 (C-3), 156.2 (NC=O), 140.7 (=CH), 136.0 (=C−), 128.6 (=CH), 128.3 (=CH), 128.1 (=CH), 127.9 (=CH), 87.0 (C-1), 67.4 (*C*H_2Ar), 53.7 (C-4), 40.5 (C-5) and 32.0 (C-6); *m*/*z* (EI) 274 (M + H$^+$, 1%), 167 (M − PhCH_2O, 85), 123 (60), 107 (100), 92 (60) and 91 (74) (Found: C, 65.81; H, 5.40; N, 5.04. Calc. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12%).

(+)-(3*R*,5*S*)-3-Azido-5-[(*S*)-benzyloxycarbonyl(benzyloxycarbonylamino)methyl]cyclopent-1-ene 10

Sodium azide (1.04 g, 16 mmol), dissolved in water (8 ml), was added to a solution of the carbamate **7** (2.18 g, 8 mmol) and $Pd(PPh_3)_4$ (0.48 g, 0.4 mmol) in THF (16 ml). The solution was stirred at room temperature for 1 h then acidified with aqueous HCl (1 M). The reaction mixture was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and condensed *in vacuo*. The residue was filtered through a short pad of silica gel using ethyl acetate–light petroleum (1:1) as eluent to give the crude acid **9** (2.37 g, *ca.* 94%); δ_H(250 MHz, $CDCl_3$) 7.35 (5H, s, Ar*H*), 5.95 (1H, br d, *J* 5.5, =C*H*), 5.82 (1H, br d, *J* 5.5, =C*H*), 5.25 (1H, d, *J* 9.0, N*H*Z), 5.15 (2H, s, CH_2Ar), 4.55–4.40 (2H, br m, C*H*NHZ and C*H*N_3), 3.35 (1H, br m, =CH−C*H*), 2.56 (1H, dt, *J* 8.5 and 14.0, C*H*H) and 1.73 (1H, dt, *J* 5.0 and 14.0, CH*H*). The crude product was dissolved in DMF (80 ml) and sodium hydrogen carbonate (1.34 g, 16 mmol) was added followed by benzyl bromide (4.80 ml, 40 mmol). The mixture was allowed to react for 24 h at room temperature. Water was then added and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4) and condensed *in vacuo*. Purification by percolation through a silica gel column eluting with ethyl acetate–light petroleum (1:4) gave the protected *amino acid* **12** (2.92 g, 90% from **7**) as a colourless viscous oil; $[\alpha]_D^{20}$ +19.5 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3330, 3070, 3040, 2980, 2100 and 1720; δ_H(250 MHz, $CDCl_3$) 7.32 (10H, s, Ar*H*), 5.89 (1H, dt, *J* 2.2 and 5.5, =C*H*), 5.72 (1H, br d, *J* 5.5, =C*H*), 5.32–5.10 (5H, m, N*H*Z and 2 × CH_2Ar), 4.54 (1H, dd, *J* 4.5 and 9.0, C*H*NHZ), 4.44 (1H, br m, C*H*N_3), 3.28 (1H, br m, =CH−C*H*), 2.49 (1H, dt, *J* 8.5 and 14.0, C*H*H) and 1.72 (1H, dt, *J* 5.0 and 14.0, CH*H*); δ_C(63 MHz, $CDCl_3$) 171.0 (C=O), 156.4 (NHC=O), 136.1 (=C−), 135.1 (=C−), 133.6 (=CH), 133.1 (=CH), 128.7 (=CH), 128.6 (=CH), 128.5 (=CH), 128.4 (=CH), 128.2 (=CH), 128.1 (=CH), 67.4 (*C*H_2Ar), 67.2 (*C*H_2Ar), 66.2 (CH), 56.0 (CH), 47.1 (CH) and 32.3 (CH_2); *m*/*z* (FAB) 407 (M + H$^+$,

30%), 379 (23), 364 (100), 228 (32) and 213 (63) (Found: C, 64.88; H, 5.34; N, 13.57. Calc. for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.45; N, 13.78%).

(−)-(3*R*,5*S*)-3-Amino-5-[(*S*)-benzyloxycarbonyl(benzyloxycarbonylamino)methyl]cyclopent-1-ene 11

Triphenylphosphine (1.32 g, 5 mmol) was added in small portions to a solution of azide **10** (2.03 g, 5 mmol) in THF (5 ml). After completion of the addition, water (0.45 ml, 25 mmol) was added and the mixture was stirred at room temperature for 24 h. The solvent was then removed *in vacuo* and the crude product was purified by chromatography on silica gel (gradient of solvent ethyl acetate–methanol) to give the *amine* **11** (1.54 g, 81%) as a colourless gum; $[a]_D^{20}$ −69.2 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3350, 3070, 3040, 2980 and 1720; δ_H(250 MHz, $CDCl_3$) 7.35 (10H, s, Ar*H*), 5.78 (1H, br d, *J* 5.5, =C*H*), 5.46 (1H, br d, *J* 5.5, =C*H*), 5.25–5.05 (4H, m, 2 × CH_2Ar), 4.35 (1H, br d, *J* 4.0, C*H*NHZ), 3.91 (1H, br m, C*H*NH_2), 3.21 (1H, br m, =CH−C*H*), 2.37 (1H, dt, *J* 8.0 and 13.5, C*H*H) and 1.27 (1H, dt, *J* 5.0 and 13.5, CH*H*); δ_C(63 MHz, $CDCl_3$) 171.6 (C=O), 156.6 (NHC=O), 138.3 (=CH), 136.3 (=C−), 135.4 (=C−), 130.4 (=CH), 128.6 (=CH), 128.5 (=CH), 128.4 (=CH), 128.4 (=CH), 128.1 (=CH), 67.1 (*C*H_2Ar), 67.0 (*C*H_2Ar), 56.7 (CH), 56.3 (CH), 46.8 (CH) and 36.5 (CH_2); *m*/*z* (EI) 380.1732 (5%) (M^+, $C_{22}H_{24}N_2O_4$ requires 380.1736), 229 (27), 91 (100) and 82 (55).

(−)-1-{(1′*R*,4′*S*)-4′-[(*S*)-Benzyloxycarbonyl(benzyloxycarbonylamino)methyl]cyclopent-2′-enyl}uracil 12

From 11. A stirred suspension of silver cyanate (2.0 g, 13.5 mmol) in dry benzene (13.5 ml) was refluxed for 0.5 h and 3-ethoxypropenoyl chloride[13] (0.9 g, 6.75 mmol) in benzene (4.5 ml) was added dropwise to the refluxing mixture. The mixture was heated for an additional 0.5 h and stirred at room temperature for 2.5 h. The solid was allowed to settle and 14.4 ml of the solution (containing theoretically 5.4 mmol of 3-ethoxypropenoyl cyanate) were added dropwise at −10 °C to a stirred solution of the amine **11** (1.71 g, 4.5 mmol) in dry DMF (18 ml). The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was then removed *in vacuo* and the residue was filtered through a short pad of silica gel using ethyl acetate as solvent to give the crude intermediate acylurea (2.0 g, *ca*. 85%) as a light brown solid; δ_H(250 MHz, $CDCl_3$) 9.52 (1H, s, N*H*CO), 8.69 (1H, d, *J* 8.0, N*H*CO), 7.47 (1H, d, *J* 12.0, =C*H*OEt), 7.27 (10H, s, Ar*H*), 5.77 (1H, dt, *J* 2.0 and 6.0, =C*H*), 5.52 (1H, br d, *J* 6.0, =C*H*), 5.34 (1H, d, *J* 9.0, N*H*Z), 5.23 (1H, d, *J* 12.0 =C*H*CO), 5.07 (4H, m, 2 × CH_2Ar), 4.79 (1H, br m, C*H*NH), 4.40 (1H, dd, *J* 4.0 and 9.0, C*H*NHZ), 3.82 (2H, q, *J* 7.0, C$H_2$$CH_3$), 3.17 (1H, br m, =CH−C*H*), 2.49 (1H, dt, *J* 9.0 and 14.0, C*H*H), 1.49 (1H, dt, *J* 7.0 and 14.0, CH*H*) and 1.24 (3H, t, *J* 7.0, CH_2CH_3). The crude acylurea was dissolved in dioxane–sulfuric acid (1 M) (1:1, 60 ml) and the solution was refluxed for 1 h. The reaction mixture was then extracted with chloroform; the combined extracts were washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and condensed *in vacuo*. The residue was purified by column chromatography on silica gel using ethyl acetate–light petroleum (4:1) as solvent to give the *uridine derivative* **12** (1.6 g, 75% from **11**) as a white powder; mp 154–155 °C; $[a]_D^{20}$ −104.5 (*c* 1, MeOH); ν_{max}(KBr)/cm^{-1} 3325, 3060, 2945, 1740, 1715, 1690 and 1670; δ_H(250 MHz, $CDCl_3$) 9.25 (1H, s, NH_{uracil}), 7.30 (10H, br s, Ar*H*), 6.96 (1H, d, *J* 8.0, =C*H*N), 6.81 (1H, br d, *J* 5.5, =C*H*), 5.61 (1H, dt, *J* 2.2 and 5.5, =C*H*), 5.55 (1H, m, C*H*N), 5.45 (1H, d, *J* 8.0, =C*H*CO), 5.32 (1H, d, *J* 9.0, N*H*Z), 5.13 (2H, AB, *J* 12.0, CH_2Ar), 5.01 (2H, s, CH_2Ar), 4.46 (1H, dd, *J* 4.5 and 9.0, C*H*NHZ), 3.21 (1H, br m, =CH−C*H*), 2.67 (1H, dt, *J* 8.0 and 14.0, C*H*H) and 1.39 (1H, dt, *J* 7.0 and 14.0, CH*H*); δ_C(63 MHz, $CDCl_3$) 171.0 (C=O), 163.5 (C=O), 156.4 (C=O), 151.1 (C=O), 140.5 (=CH), 136.0 (=CH), 135.8 (=C−), 134.9 (=C−), 132.0 (=CH), 128.7 (=CH), 128.7 (=CH), 128.5 (=CH), 128.3 (=CH), 102.7 (=CH), 67.6 (*C*H_2Ar), 67.5 (*C*H_2Ar), 60.9 (CH), 56.1 (CH), 47.4 (CH) and 33.5 (CH_2); *m*/*z* (EI) 475.1743 (13%) (M^+, $C_{26}H_{25}N_3O_6$ requires 475.1743), 177 (83), 113 (57) and 91 (100).

From 7. To a suspension of dry uracil (224 mg, 2 mmol) in CH_3CN (6 ml) were added freshly distilled hexamethyldisilazane (HMDS) (0.4 ml, 2 mmol) and trimethylsilyl chloride (TMSCl) (0.25 ml, 2 mmol) and the resulting mixture was stirred for 30 min at room temperature. A solution containing lactone **7** (546 mg, 2 mmol) and $Pd(PPh_3)_4$ (120 mg, 0.1 mmol) in CH_3CN (4 ml) was then added and the mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was filtered through a short silica gel column using ethyl acetate–methanol (9:1) as eluent. After removal of the solvent the residue containing crude acid **15** was dissolved in DMF (4 ml) and sodium hydrogen carbonate (0.34 g, 4 mmol) was added followed by benzyl bromide (0.25 ml, 2 mmol) and the mixture was allowed to react 24 h at room temperature. The solvent was then removed *in vacuo* and the crude mixture was purified by percolation through a silica gel column eluting with ethyl acetate–light petroleum (4:1) to give the uridine derivative **12** (480 mg, 50% from **7**) which had identical analytical data as above.

(+)-1-{(1′*R*,2′*S*,3′*R*,4′*R*)-4′-[(*S*)-Benzyloxycarbonyl(benzyloxycarbonylamino)methyl]-2′,3′-dihydroxycyclopentyl}uracil 14

Catalytic dihydroxylations by osmium tetroxide. General procedure. A solution of the uridine **12** (475 mg, 1 mmol) in the chosen solvent (20 ml) was charged with *N*-methylmorpholine *N*-oxide monohydrate (NMO·H_2O) (200 mg, 1.5 mmol) and was stirred for 10 min. A 2.5% (w/w) solution of osmium tetroxide in Bu^{t}OH (0.6 ml, 0.04 mmol) was then added and the mixture was stirred for the appropriate time (monitored by TLC) at room temperature. The reaction mixture was then treated with saturated aqueous sodium metabisulfite (1 ml) and stirred for an additional 10 min. Anhydrous sodium sulfate was added and the mixture was filtrated through a short pad of Celite. The solvent was removed *in vacuo* and the residue was dissolved in THF (5 ml) and treated with a catalytic amount of *p*-TsOH for 15 min. The solvent was then removed and the residue was percolated through a short pad of silica gel using ethyl acetate as eluent to give a mixture of compounds **14** and **15**. Ratios were determined by ^{1}H NMR spectroscopy (250 MHz, $[^2H]_6$DMSO) by integration of the vinyl doublets of the pyrimidine ring (δ 7.61 for **14** and 7.52 for **15**). The compounds can alternatively be separated by conventional chromatography using ethyl acetate as eluent to give in the first fractions the *lactone* **15** as a white powder; mp 230–232 °C; $[a]_D^{20}$ +165.5 (*c* 0.5, THF); ν_{max}(KBr)/cm^{-1} 3365, 1770 and 1685; δ_H(400 MHz, $[^2H]_6$DMSO) 11.29 (1H, s, NH_{uracil}), 7.74 (1H, d, *J* 9.5, N*H*Z), 7.52 (1H, d, *J* 8.0, =CH−N), 7.35 (5H, br m, Ar*H*), 5.61 (1H, d, *J* 4.5, O*H*), 5.56 (1H, d, *J* 8.0, =C*H*−CO), 5.08 (2H, AB, *J* 12.0, CH_2Ar), 4.87 (1H, dd, *J* 5.0 and 8.0, C*H*OCO), 4.84 (1H, t, *J* 9.5, C*H*NHZ), 4.67 (1H, ddd, *J* 5.0, 7.0 and 13.0, C*H*N), 4.13 (1H, q, *J* 5.0, C*H*OH), 3.03 (1H, ddt, *J* 8.0, 9.5 and 10.0, C*H*), 2.13 (1H, ddd, *J* 10.0, 12.0 and 13.0, C*H*H) and 1.70 (1H, ddd, *J* 7.0, 8.0 and 12.0, CH*H*); δ_C(100 MHz, $[^2H]_6$DMSO) 175.0 (C=O), 163.2 (C=O), 156.4 (C=O), 151.3 (C=O), 143.6 (=*C*H), 136.7 (=C−), 128.4 (=*C*H), 127.9 (=*C*H), 127.8 (=*C*H), 99.7 (=*C*H), 79.9 (*C*H), 68.8 (*C*H), 65.9 (*C*H_2Ar), 55.8 (*C*H), 51.7 (*C*H), 36.3 (*C*H) and 26.3 (*C*H_2); *m*/*z* (EI) 401.1229 (7%) (M + H^+, $C_{19}H_{19}N_3O_7$ requires 401.1223), 108 (100), 107 (67), 91 (91), 79 (68) and 77 (59); and in the later fractions the *diol* **14** as a crystalline white solid; mp 86–88 °C; $[a]_D^{20}$ +13.5 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3420, 2925 and 1690; δ_H(250 MHz, $[^2H]_6$DMSO) 11.30 (1H, s, NH_{uracil}), 7.83 (1H, d, *J* 7.5, N*H*Z), 7.61 (1H, d, *J* 8.0, =C*H*−N), 7.35 (10H, s, Ar*H*), 5.60 (1H, d, *J* 8.0, =C*H*CO), 5.15–4.99 (4H, m, 2 × CH_2Ar), 4.96 (1H, d, *J* 6.5, O*H*), 4.72 (1H, d, *J* 5.0, O*H*), 4.54 (1H, dt, *J* 9.0 and 11.0, C*H*N), 4.25 (1H, t, *J* 7.5, C*H*NHZ), 4.00 (1H, dt, *J* 6.5 and 9.0, C*H*OH), 3.82 (1H, br q, *J* 5.0, C*H*OH), 2.21 (1H, m, CH_2–C*H*),

1.92 (1H, ddd, *J* 8.0, 9.0 and 12.0, C*H*H) and 1.37 (1H, dt, *J* 11.0 and 12.0, CH*H*); δ_C(100 MHz, $CDCl_3$) 171.6 (C=O), 164.2 (C=O), 156.7 (C=O), 151.6 (C=O), 142.9 (=CH), 136.1 (=C−), 135.2 (=C−), 128.6 (=CH), 128.5 (=CH), 128.3 (=CH), 128.1 (=CH), 128.1 (=CH), 102.3 (=CH), 73.8 (CH), 70.8 (CH), 67.4 (CH_2Ar), 67.1 (CH_2Ar), 63.0 (CH), 55.5 (CH), 45.2 (CH) and 27.5 (CH_2); *m*/*z* (FAB) 510.1877 (32%) (M + H^+, $C_{26}H_{28}N_3O_8$ requires 510.1876), 391 (100), 307 (63).

Oxidation by ruthenium tetroxide. A solution of sodium metaperiodate (32 mg, 0.15 mmol) and $RuCl_3 \cdot 3H_2O$ (7 mol%) in water (0.2 ml) was added to a vigorously stirred solution of the uridine **12** (48 mg, 0.1 mmol) in ethyl acetate–acetonitrile (1:1, 1.2 ml) cooled at 0 °C. The two phase mixture was stirred for 5 min and saturated aqueous sodium thiosulfate (0.1 ml) was added followed after 10 min by anhydrous sodium sulfate. The mixture was filtered through a short pad of Celite. The solvent was removed *in vacuo* and the residue was percolated through silica gel using ethyl acetate as eluent to give a 2:1 mixture of compounds **14** and **15** (59%).

(+)-1-{(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Isopropylidenedioxy-4′-[(*S*)-benzyloxycarbonyl(benzyloxycarbonylamino)methyl]cyclopentyl}uracil 16

To a solution of the diol **14** (70 mg, 0.137 mmol) in acetone (1.5 ml) and 2,2-dimethoxypropane (85 μl) was added a catalytic amount of *p*-TsOH·H_2O and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the crude product purified on silica gel using ethyl acetate–light petroleum (7:3) as eluent to give the protected *diol* **16** (65 mg, 86%) as a white solid; mp 65–66 °C; $[\alpha]_D^{20}$ +2.1 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3330, 3060, 2985 and 1690; δ_H(250 MHz, $CDCl_3$) 9.80 (1H, s, NH_{uracil}), 7.35 (10H, m, Ar*H*), 7.01 (1H, d, *J* 8.0, =C*H*N), 6.44 (1H, d, *J* 7.5, NC*H*Z), 5.68 (1H, dd, *J* 2.0 and 8.0, =C*H*−CO), 5.20 (2H, AB, *J* 12.0, CH_2Ar), 5.10 (2H, AB, *J* 12.0, CH_2Ar), 4.76 [1H, dd, *J* 3.5 and 7.0, C*H*OC(CH_3)$_2$], 4.62 [1H, t, *J* 7.0, C*H*OC(CH_3)$_2$], 4.49 (1H, t, *J* 7.5, C*H*NHZ), 4.25 (1H, m, C*H*N), 2.47 (1H, m, C*H*), 2.10 (1H, m, C*H*H), 1.85 (1H, m, CH*H*), 1.43 (3H, s, CH_3) and 1.22 (3H, s, CH_3); δ_C(63 MHz, $CDCl_3$) 171.8 (C=O), 163.2 (C=O), 156.5 (C=O), 150.8 (C=O), 143.8 (=CH), 136.2 (=C−), 135.0 (=C−), 128.6 (=CH), 128.5 (=CH), 128.4 (=CH), 128.2 (=CH), 113.5 [−*C*(CH_3)$_2$], 102.6 (=CH), 82.9 (CH), 80.1 (CH), 67.7 (CH_2Ar), 67.2 (CH_2Ar), 65.1 (CH), 54.5 (CH), 47.2 (CH), 32.3 (CH_2), 27.6 (CH_3) and, 25.4 (CH_3); *m*/*z* (FAB) 550.2183 (82%) (M + H^+, $C_{29}H_{32}N_3O_8$ requires 550.2189), 492 (81), 307 (100).

(+)-1-{(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dioxy-4′-[(*S*)-amino(carboxyl)-methyl]cyclopentyl}uracil (carbocyclic uracil polyoxin C) 21

A round-bottom flask containing a mixture of diol **14** (118 mg, 0.23 mmol) and 10% Pd/C (50 mg) in ethanol–water (9:1, 10 ml) was degassed and then pressurised with hydrogen (1 atm). After stirring at 20 °C for 2 h the mixture was filtered through Celite. The filtrate residue was washed with water (4 × 5 ml) and the filtrate concentrated to dryness to give the *amino acid* **2** (66 mg, 100%) as a white powder; mp 195–202 °C (decomp.); $[\alpha]_D^{20}$ +13.0 (*c* 0.5, H_2O); ν_{max}(KBr)/cm^{-1} 3435, 1730, 1685 and 1635; δ_H(400MHz, D_2O) 7.51 (1H, d, *J* 8.0, =C*H*N), 5.73 (1H, d, *J* 8.0, =C*H*CO), 4.48 (1H, ddd, *J* 6.5, 7.5 and 11.0, C*H*N), 4.18 (1H, t, *J* 6.5, C*H*OH), 4.12 (1H, t, *J* 6.5, C*H*OH), 3.75 (1H, d, *J* 6.5, C*H*NH_2), 2.23 (1H, ddt, *J* 6.5, 7.5 and 11.0, C*H*), 2.10 (1H, dt, *J* 7.5 and 13.0, C*H*H) and 1.55 (1H, dt, *J* 11.0, 13.0, CH*H*); δ_C(100 MHz, D_2O) 171.5 (C=O), 166.3 (C=O), 152.2 (C=O), 144.5 (=CH), 102.0 (=CH), 73.0 (CH), 72.3 (CH), 62.7 (CH), 56.5 (CH), 43.5 (CH) and 26.6 (CH_2); *m*/*z* (FAB) 286.1043 (8%) (M + H^+, $C_{11}H_{16}N_3O_6$ requires 286.1039), 277 (100).

Acknowledgements

We thank the European Commission for a Fellowship to N. M. (No. ERB4001GT933280), and Dr M. F. Wang for preliminary studies. We thank Chiroscience for a generous supply of (−)-**7a** and Glaxo-Welcome for a generous supply of ethyl 3-ethoxypropenoate.

References

1 M. Kaneko, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 989; R. E. Boehme, A. D. Borthwick and P. G. Wyatt, *Annu. Rep. Med. Chem.*, 1994, **29**, 145; E. Cabib, *Antimicrob. Agents Chemother.*, 1991, **35**, 170; H. Decker, H. Zahner, H. Heitsch, W. A. Konig and H. P. Fiedler, *J. Gen. Microbiol.*, 1991, **137**, 1805; S. Milewski, F. Mignini and E. Borowski, *J. Gen. Microbiol.*, 1991, **137**, 2155; T. C. Schuz, H. P. Fiedler, H. Zahner, M. Rieck and W. A. Konig, *J. Antibiot.*, 1992, **45**, 199; T. Chapman, O. Kinsman and J. Houston, *Antimicrob. Agents Chemother.*, 1992, **36**, 1909; J. P. Gaughran, M. H. Lai, D. R. Kirsch and S. J. Silverman, *J. Bacteriol.*, 1994, **176**, 5857; Y. Aoki, M. Kondoh, M. Nakamura, T. Fujii, T. Yamazaki, H. Shimada and M. Arisawa, *J. Antibiot.*, 1994, **47**, 909.

2 A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1990, **55**, 3853; A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1990, **55**, 5818; Y. Auberson and P. Vogel, *Tetrahedron*, 1990, **46**, 7019; A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1991, **56**, 4875; N. Chida, K. Koizumi, Y. Kitada, C. Yokoyama and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 1994, 111; A. Dondoni, F. Junquera, F. L. Merchan, P. Merino and T. Tejero, *Tetrahedron Lett.*, 1994, **35**, 9439; C. Mvondo Evina and G. Guillerm, *Tetrahedron Lett.*, 1996, **37**, 163; B. M. Trost and Z. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 3037.

3 The polyoxins consist of an amino acid nucleoside linked to an N-terminal amino acid. The preparation of the latter amino acid has already been described: S. Knapp, *Chem. Rev.*, 1995, **95**, 1859.

4 For reviews on carbocyclic nucleosides see: V. E. Marquez and M. I. Lim, *Med. Res. Rev.*, 1986, **6**, 1; A. D. Borthwick and K. Biggadike, *Tetrahedron*, 1992, **48**, 571; D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745; L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl and R. Guedj, *Tetrahedron*, 1994, **50**, 10 611; a partial synthesis of racemic nikkomycin Z has been reported: H. Baumgartner, C. Marschner, R. Pucher, M. Singer and H. Griengl, *Tetrahedron Lett.*, 1992, **33**, 6443.

5 V. K. Aggarwal, N. Monteiro, G. J. Tarver and R. McCague, *J. Org. Chem.*, in press.

6 For a preliminary account of this work see: V. K. Aggarwal, N. Monteiro, G. J. Tarver and S. D. Lindell, *J. Org. Chem.*, 1996, **61**, 1192.

7 For general studies see: L. L. Gundersen, T. Benneche, F. Rise, A. Gogoll and K. Undheim, *Acta Chem. Scand.*, 1992, **46**, 761; G. Jähne, A. Müller, M. Kroha, O. Holzhäuser, C. Meichsner, M. Helsberg, I. Winkler and G. Rieß, *Tetrahedron Lett.*, 1992, **33**, 5335; for recent examples see: S. W. Schneller and M. Koga, *J. Org. Chem.*, 1993, **58**, 6471; A. L. Margolin, D. R. Borcherding, W.-D. Kugel and N. Margolin, *J. Org. Chem.*, 1994, **59**, 7214; L. B. Akella and R. Vince, *Tetrahedron*, 1996, **52**, 2789. See also ref. 18.

8 S. Sigismondi, D. Sinou, M. Pérez, M. Moreno-Mañas, R. Pleixats and M. Villarroya, *Tetrahedron Lett.*, 1994, **35**, 7085 and references cited therein.

9 T. Hildebrand, T. Troxler and R. Scheffold, *Helv. Chim. Acta*, 1994, **77**, 1236; M. T. Crimmins and B. W. King, *J. Org. Chem.*, 1996, **61**, 4192.

10 T. Nishimura and I. Iwai, *Chem. Pharm. Bull.*, 1964, **12**, 352.

11 K. A. Cruickshank, J. Jiricny and C. B. Reese, *Tetrahedron Lett.*, 1984, **25**, 681.

12 Optically pure (−)-**8** has been prepared. See R. A. MacKeith, R. McCague, H. F. Olivo, S. M. Roberts, S. J. C. Taylor and H. Xiong, *Biorg. Med. Chem. Lett.*, 1994, 387; F. Burlina, P. Clivio, J.-L. Fourrey, C. Riche and M. Thomas, *Tetrahedron Lett.*, 1994, **35**, 8151; for examples related to its use in synthesis see: P. A. Grieco, K. J. Henry, J. J. Nunes and J. E. Matt Jr., *J. Chem. Soc., Chem. Commun.*, 1992, 368; R. A. MacKeith, R. McCague, H. F. Olivo, C. F. Palmer and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1993, 313; R. A. MacKeith, R. McCague, H. F. Olivo and S. M. Roberts, *Tetrahedron Lett.*, 1993, **34**, 3785; G. Casy, G. Gorins, R. McCague, H. F. Olivo and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 1994, 1085; A. Toyota, N. Katagiri and C. Kaneko, *Heterocycles*, 1994, **38**, 27. Amino lactones of type **7** can also be obtained in racemic form by skeletal rearrangement of 2-azabicyclo[2.2.1]hept-5-ene-3-carbocyclic acid derivatives. See T. Kobayashi, K. Ono, H. Kato, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 61; M. B. Hursthouse, K. M. Abdul Malik, D. E. Hibbs, S. M. Roberts,

A. J. H. Seago, V. Sik and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2419.
13 The pyrimidine ring can be built up from a primary amine using standard procedures: G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1958, 153; G. Shaw and R. N. Warrener, *J. Chem. Soc*., 1958, 157. For more recent examples see Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem*., 1976, **13**, 1015; L. J. J. Hronowski and W. A. Szarek, *Can. J. Chem*., 1985, **63**, 2787. See also ref 4.
14 (*a*) B. M. Trost and E. J. Keinan, *J. Org. Chem*., 1979, **44**, 3451; (*b*) Y. Inoue, M. Tagushi, M. Toyofuku and H. Hashimoto, *Bull. Chem. Soc. Jpn*., 1984, **57**, 3021; (*c*) S. E. Bystrom, R. Aslanian and J. E. Bäckvall, *Tetrahedron Lett*., 1985, **26**, 1749; (*d*) R. D. Connel, T. Rein, B. Åkermark and P. Helquist, *J. Org. Chem*., 1988, **53**, 3845; (*e*) S. I. Murahashi, Y. Taniguchi, Y. Imada and Y. Tanigawa, *J. Org. Chem*., 1989, **54**, 3292; (*f*) M. Takagi and K. Yamamoto, *Chem. Lett*., 1989, 2123; (*g*) R. O. Hutchins, J. Wei and S. J. Rao, *J. Org. Chem*., 1994, **59**, 4007.
15 (*a*) V. Bocchi, G. Casnati, A. Dossena and R. Marchelli, *Synthesis*, 1979, 957; (*b*) V. Bocchi, G. Casnati, A. Dossena and R. Marchelli, *ibid*, 961.
16 N. Knouzi, M. Vaultier and R. Carrié, *Bull. Soc. Chim. Fr*., 1985, 815.
17 These reactions are usually performed in refluxing HMDS. See J. Cossy and P. Pale, *Tetrahedron Lett*., 1987, **28**, 6039 and references cited therein. For examples related to the use of TMSCl in the silylation of nucleoside bases see H. Vorbrüggen, K. Krolikiewics and B. Bennua, *Chem. Ber*., 1981, **114**, 1234 and ref. 10.
18 For examples related to carbocyclic nucleoside synthesis see: E. A. Saville-Stones, S. D. Lindell, N. S. Jennings, J. C. Head, M. J. Ford, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2603; S. M. Roberts and K. A. Shoberu, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2605; F. Liotta, C. R. Unelius, J. Kozak and T. Norin, *Acta Chem. Scand*., 1992, **46**, 686; B. M. Trost, L. Li and S. D. Guile, *J. Am. Chem. Soc*., 1992, **114**, 8745; A. D. Da Silva, E. S. Coimbra, J.-L. Fourrey, A. S. Machado and M. Robert-Géro, *Tetrahedron Lett*., 1993, **34**, 6745; T. Hildebrand, C. Leumann and R. Scheffold, *Helv. Chim. Acta*, 1996, **79**, 702. See also J. P. Whitten, J. R. McCarthy and M. R. Whalon, *J. Org. Chem*., 1985, **50**, 4399.
19 U. Hacksell, G. D. Daves, *J. Org. Chem*., 1983, **48**, 4144; B. M. Trost, G. H. Kuo and T. Benneche, *J. Am. Chem. Soc*., 1988, **110**, 621; A. R. Ritter and M. J. Miller, *J. Org. Chem*., 1994, **59**, 4602; S. B. King and B. Ganem, *J. Am. Chem. Soc*., 1994, **116**, 562; D. Zhang, A. Ghosh, C. Süling and M. J. Miller, *Tetrahedron Lett*., 1996, **37**, 3799.
20 (*a*) G. Poli, *Tetrahedron Lett*., 1989, **30**, 7385 and references cited therein; (*b*) C. F. Palmer, R. McCague, G. Ruecroft, S. Savage, S. J. C. Taylor and C. Ries, *Tetrahedron Lett*., 1996, **34**, 4601.
21 V. VanRheenan, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett*., 1976, **19**, 1973.
22 T. K. M. Shing, E. K. W. Tam, V. M. F. Tai, I. H. F. Chung and Q. Jiang, *Chem. Eur. J*., 1996, **2**, 50.
23 For a review see: H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev*., 1994, **94**, 2483.
24 M. R. Barvian and M. M. Greenberg, *J. Org. Chem*., 1993, **58**, 6151 and references cited therein.
25 (*a*) A. J. Fatiadi, *Synthesis*, 1987, 85; (*b*) K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc*., 1957, **79**, 2822; (*c*) T. Ogino and K. Mochizuki, *Chem. Lett*., 1979, 443.
26 For an example of their recent use in synthesis see: H. Sugimura, K. Osumi, Y. Kodaka and K. Sujino, *J. Org. Chem*., 1994, **59**, 7653 and references cited therein. See also ref. 3.

Paper 7/02323E
Received 4*th April* 1997
Accepted 29*th April* 1997