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Synthesis by conjugate radical addition of new heterocyclic amino acids with nucleobase side chains

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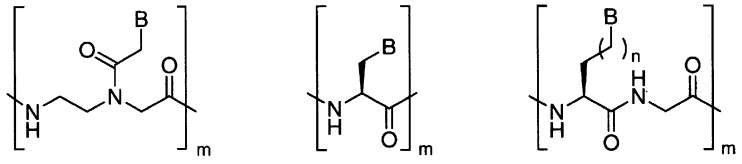
Abstract—*N*-(2-iodoethyl) and *N*-(3-iodopropyl)pyrimidines and purines undergo stereoselective conjugate radical addition with an optically active oxazolidinone acceptor to give *syn*-adducts that can be converted into amino acids carrying pyrimidine and purine (nucleobase) side chains.

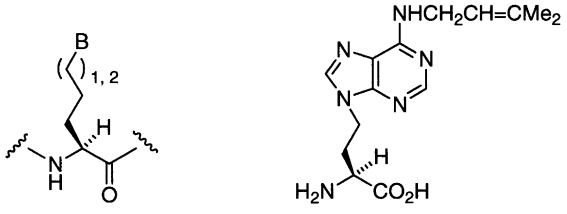
1. Introduction

Peptide-based nucleic acid analogues (PNAs; sometimes called 'Peptide Nucleic Acids') have attracted much attention as molecules with the potential to interact with nucleic acid chains.[1] Suggested applications include antisense properties.[2] Indeed, Nielsen's classical PNA **1** (B=pyrimidine or purine base) has been shown to form duplexes with the complementary DNAs (with higher affinity than the corresponding DNA–DNA), and to self-hybridize, or to form triplexes PNA–PNA–DNA (or –PNA).[1] In contrast, DNA recognition using analogues with a 'real' peptide backbone has proved more elusive. It has been reported that the substituted alanine oligomers **2** and **3**, and homologue **4** (termed α-PNA[3]) of the latter, do not demonstrate hybridisation with DNA, and insufficient flexibility of the polypeptide chain has been suggested as the cause.[4] In contrast, triplex formation between tetrapeptides of type **4** and poly(dT) or poly(dU) has been reported.[5]

Our interest in unusual amino acids led us to propose the homologous amino acids **6** carrying the nucleic acid bases (nucleobases) with a 3- or 4-methylene tether to the peptide backbone, as components for PNA variants **5**. Residues **6** are also analogues of naturally occurring bioactive pyrimidine and purine amino acids such as discadenine **7**.[6] We report herein our flexible methodology which is based on stereoselective radical chemistry.[7,8]



1 **2** **3**; n = 0 **4**; n = 1 **5**; n = 2, 3



6 **7**

Keywords: nucleic acid analogues; amino acids; radical reactions.

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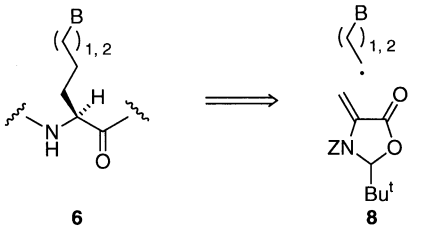


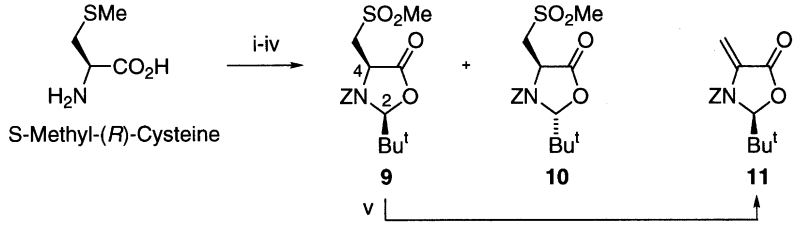
Scheme 1.

2. Results and discussion

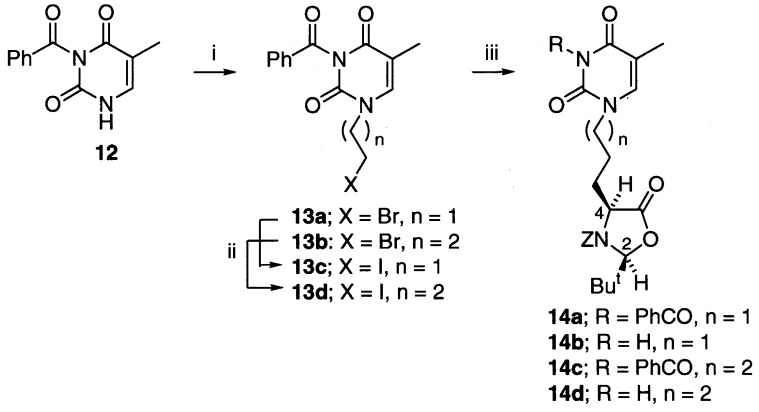
In contrast to published routes to residues with two-carbon tethers,[3,5,9] we determined to link preformed heterocycles with the peptide backbone by forming a *carbon–carbon* bond in the tether, and proposed the analysis shown in Scheme 1; this generates the C(β)–C(γ) bond by conjugate radical addition to chiral acceptor **8**.[10] The *N*-benzyloxycarbonyl (Z) acceptor was selected in order to ultimately provide Z-amino acids suitable for peptide couplings.

The (*S*)-acceptor **11** was prepared from *S*-methyl-(*R*)-cysteine as outlined in Scheme 2, by adaptation of a sequence published for synthesis of the *N*-benzoyl analogue.[11] Thus *S*-methyl-(*R*)-cysteine as its dried sodium carboxylate salt was converted into a Schiff base (Bu^{t}CHO, hexane, Dean–Stark water removal) that when acylated with benzyl chloroformate underwent cyclization to afford the 4-methylthiomethyloxazolidinones as an inseparable mixture of diastereomers, estimated as 10:1.3 based on the SMe singlets in the ^{1}H NMR spectrum (major isomer δ 2.10, minor isomer δ 2.02). These were oxidised (oxone®, MeCN) to generate the corresponding mixture of sulfones **9** and **10** (57% overall from *S*-methyl-(*R*)-cysteine). *syn*-Sulfone **9** was formed as a 10:1.5 mixture with its *anti*-diastereoisomer **10**, again estimated from the ^{1}H NMR spectrum (SO_2Me singlets for major isomer δ 3.09, minor isomer δ 2.87), that was easily separated by column chromatography;[11] major isomer *syn*-**9** was further crystallised to ensure diastereomeric purity. The *syn* configuration was supported by nOe studies, inter alia mutual enhancements between C–2(H) and C–4(H), and is in accord with other related reports. The minor isomer *anti*-**10** lacked this interaction and instead displayed mutual enhancements between C–4(H) and the *tert*-butyl group. Base treatment (DBU, CH_2Cl_2, 0°C, 1 h) of major sulfone **9** afforded (*S*)-oxazolidinone **11** (96%) as a crystalline solid [the (*R*)-enantiomer would be available either from unnatural *S*-methyl-(*S*)-cysteine, or from minor sulfone **10**].

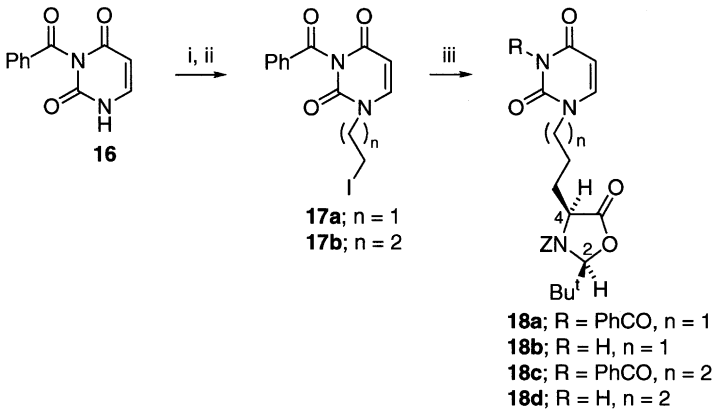
The radical precursors for additions to acceptor **11** were to be haloalkyl pyrimidines and purines, prepared from the appropriately protected heterocyclic base and ω-haloalcohols by a Mitsunobu procedure.[12] Thus 3-benzoylthymine **12**[13] was prepared by treatment of thymine with benzoyl chloride (2.2 mol equiv., MeCN–pyridine 5:2 v/v, 20°C) to afford 1,3-dibenzoylthymine, which was not isolated but treated directly with base (K_2CO_3, dioxane–water) to complete selective mono-debenzoylation (67% overall) at N-1. 3-Benzoylthymine **12** was then coupled with 2-bromoethanol or 3-bromopropanol (DIAD, Ph_3P, 0⟶20°C) to afford the 1-(ω-bromoalkyl) derivatives **13a** (89%) and **13b** (92%), respectively (Scheme 3). Our attempts to generate radicals from these bromides proved fruitless (using method B, see below), so they were converted directly to the corresponding iodoalkyl compounds **13c** and **13d**, respectively (NaI, propanone reflux; each 95%).



Scheme 2. *Reagents*: i, NaOH aq.; ii, Bu^{t}CHO, Dean–Stark; iii, $PhCH_2OCOCl$ (ZCl); iv, oxone®, MeCN–H_2O; v, DBU.

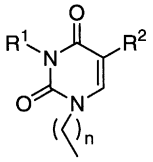


Scheme 3. *Reagents*: i, $HO(CH_2)_nBr$, $Pr^iO_2CN{=}NCO_2Pr^i$, Ph_3P; ii, NaI, Me_2CO reflux; iii, Method C: **11** (1 mol equiv.), Bu_3SnH (1 mol equiv.), AIBN (0.1 mol equiv.), toluene reflux; method D: **11** (2 mol equiv.), Bu_3SnCl (0.3 mol equiv.), $NaBH_3CN$ (2 mol equiv.), AIBN (0.1 mol equiv.).



Scheme 4. *Reagents*: i, ii as in Scheme 3; iii, Method D.

Iodide **13c** was treated under two protocols differing in the method for generation of a radical,[10] namely (1) method C (see Section 3): with oxazolidinone **11** (1 mol equiv.) in toluene at reflux containing AIBN (0.1 mol equiv.) and dropwise addition of Bu_3SnH (1 mol equiv.); or (2) method D: with oxazolidinone **11** (2 mol equiv.), Bu_3SnCl (0.3 mol equiv.), $NaBH_3CN$ (2 mol equiv.) and AIBN (0.1 mol equiv.) in *tert*-BuOH at reflux. Method C (concentration of iodide **13c** approx. 0.01 M) afforded the conjugate addition product **14a** (26%) and reduction product **15a** (24%). On the other hand, method D after 16 h afforded 54% of conjugate addition products consisting of the adduct **14a** (24%) and the 3-debenzoylated derivative **14b** (30%), with no reduced material. The extent of debenzoylation was time dependent; a reaction time of 40 h led to **14b** as the sole addition product (47%). This tentatively suggests the deacylation may be via hydride-mediated reduction of the out-of-plane benzoyl carbonyl group, a possibility supported by observations of a decrease in debenzoylation when less $NaBH_3CN$ is used in method D, and that debenzoylation of **13** occurs in the presence of $NaBH_3CN$ alone. When 1-iodopropylthymine derivative **13d** was treated under method D for 40 h, adduct **14c** was not found and deacylated adduct **14d** was isolated (25%) along with reduction product **15b** (21%).

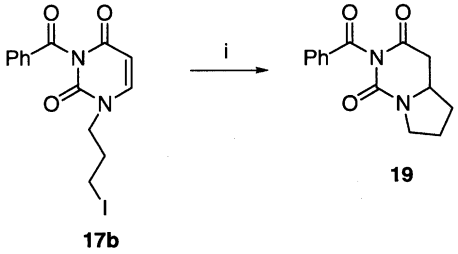


15a; R^1 = PhCO, R^2 = Me, n = 1
15b: R^1 = H, R^2 = Me, n = 2
15c; R^1 = PhCO, R^2 = H, n = 1
15d: R^1 = R^2 = H, n = 2
15e; R^1 = PhCO, R^2 = H, n = 2

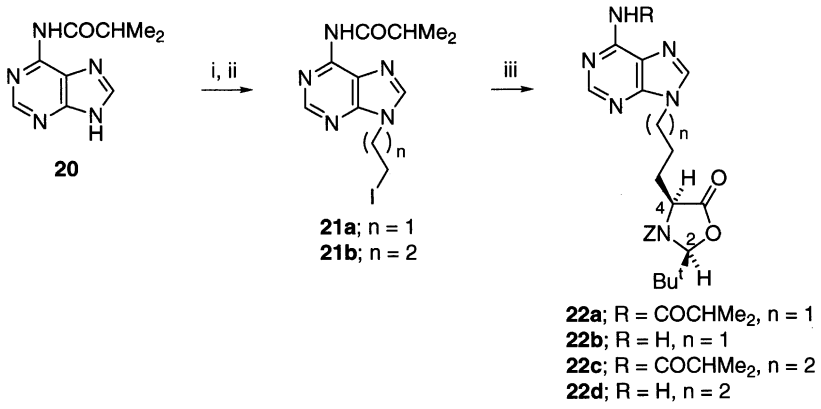
We elected to extend these standard conjugate radical addition protocols (methods C and D; method D preferred) to other pyrimidines and purines rather than to separately optimise each conjugate addition. 3-Benzoyluracil **16**[12] was prepared from uracil (62% overall) using similar methods as for 3-benzoylthymine, i.e. dibenzoylation with benzoyl chloride (2.2 mol equiv., MeCN–pyridine 5:2 v/v, 0°C) and mono-debenzoylation (K_2CO_3, dioxane–water). The 3-benzoyluracil **16** was converted into the 1-iodoalkyl derivatives **17a** and **17b** as suitable precursors for the radical addition reactions, using the Mitsunobu protocol with 2-bromoethanol or 3-bromopropanol as above (82 and 84%, respectively) followed by iodide substitution for bromide (each 96%) (Scheme 4).

Conjugate addition method D when applied to iodoethyl compound **17a** with a reaction time of 7 h afforded addition product **18a** (47%) and reduction product **15c** (46%). When the reaction was left for 40 h, deacylated addition product **18b** (51%) was isolated and no benzoylated material was observed; reduction product was present but not purified from this reaction. Homologue **17b** after 40 h gave debenzoylated adduct **18d** (44%) with reduced material **15d** (51%). The yield of **18d** could be increased to 62% by using 5 mol equiv. of acceptor **11** in method D, but we preferred to routinely use 2 mol equiv. of this valuable optically active intermediate. When less than 2 mol equiv. $NaBH_3CN$ was used, some of the benzoylated adduct **18c** was isolated, for example, 1 mol equiv. $NaBH_3CN$ affording after 8 h **18c** (21%) and reduction product 3-benzoyl-1-propyluracil **15e** (27%).

During our investigations of the effect of using less $NaBH_3CN$ in reactions with iodopropyluracil **17b**, an unexpected result was observed. From a reaction using method D but with less oxazolidinone **11** (1.2 mol equiv.) and less $NaBH_3CN$ (0.3 mol equiv.), and after a reaction time of only 30 min, unchanged acceptor **11** (82%) and iodo compound **17b** (80%) were recovered along with the pyrrolopyrimidinedione **19** (87% based on recovered **17b**), the result of a 5-*exo* trig cyclisation of the radical formed from the iodoalkyl compound, followed by hydrogen atom



Scheme 5. *Reagents*: i, Bu_3SnH (1 mol equiv.), AIBN (0.1 mol equiv.), toluene reflux.

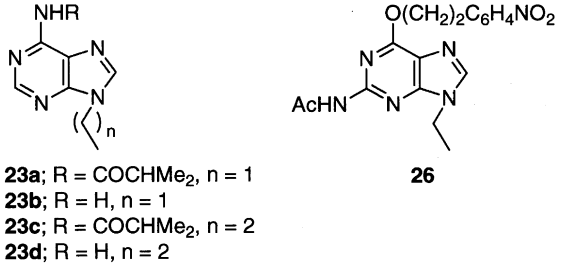


Scheme 6. *Reagents*: i and ii as in Scheme 3; iii, Methods C or D (see text).

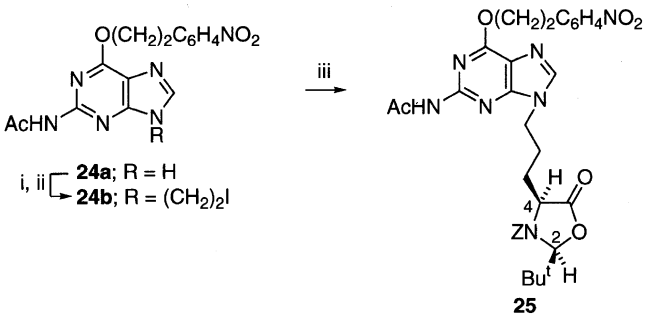
capture. In a further experiment using the method C for radical generation but in the absence of any oxazolidinone **11**, the pyrrolopyrimidinedione **19** was isolated in 53% yield (Scheme 5). Related cyclizations have been reported,[14] although in those cases the initial radical from intramolecular conjugate addition underwent oxidation or led to *ipso* substitution.

In the purine series, adenine was treated with excess 2-methylpropionic anhydride (3 mol equiv., DMF, reflux) followed by removal of one 2-methylpropionyl group (H_2O–EtOH, 1:1 v/v, reflux) to afford N^6-(2-methylpropionyl)adenine **20**[15] (71% overall) and the 9-iodoalkyladenines **21a** and **21b** were prepared from protected adenine **20** in the standard way, by Mitsunobu coupling with 2-bromoethanol or 3-bromopropanol as above (each 76%) followed by iodide substitution for bromide (86 and 81%, respectively) (Scheme 6). Application of method D with a 16 h reaction time to iodoethyl compound **21a** led to the expected mixture of conjugate addition [40%; acylated **22a** (26%) and deacylated **22b** (14%)] and reduction [36%; acylated **23a** (17%) and deacylated **23b** (19%)]. The deacylated adduct **22b** and acylated reduction product **23a** were isolated as an inseparable mixture, the contents of which were quantified from the result of the subsequent hydrolysis step (see below). The iodopropyl derivative **21b** similarly gave adducts using method D for 16 h [22%; acylated **22c** (12%) and deacylated **22d** (10%)] along with reduced compounds [24%; acylated **23c** (11%) and deacylated **23d** (23%)]. For comparison, method C when applied to iodopropyl compound **21b** led to acylated adduct **22c** (23%) and reduction product **23c** (45%).

Finally, a protected guanine **24a**[16] was prepared (53% overall) by treatment of guanine with excess acetic anhydride (3 mol equiv., DMF, reflux) followed by reaction of the 9,N^2-diacetylguanine with 2-(4-nitrophenyl)ethanol under Mitsunobu conditions (DIAD, Ph_3P, 0→20°C) and monodeacetylation by selective hydrolysis (H_2O–dioxane 1:1 v/v, reflux). The guanine derivative **24a** was converted into the 9-iodoethyl derivative **24b** as usual by Mitsunobu coupling with 2-bromoethanol (67%) and substitution of iodide for bromide (85%) (Scheme 7). Conjugate addition by method C led to adduct **25** (21%) and reduction to **26** (20%).



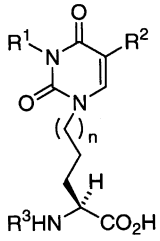
The illustrated conjugate radical addition products were all *syn*-adducts, as determined by nOe studies, in which for example mutual enhancements were observed between C–2(H) and C–4(H). Only one diasteroisomer was visible in the ^{1}H- and ^{13}C NMR spectra. The diastereoselectivity has been found to be dependent on the nature of the *N*-substituent in the oxazolidinone;[10] a preference for *syn*-adducts, i.e. hydrogen atom capture from the face of the presumed radical intermediate (after conjugate addition) opposite



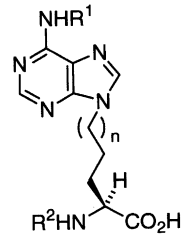
Scheme 7. *Reagents*: i and ii as in Scheme 3; iii, Method C.

to the *tert*-butyl substituent, is expected for *N*-carbamate derivatives.

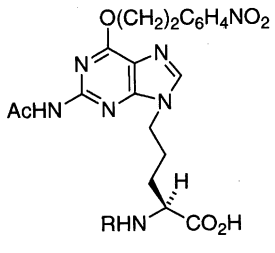
The *syn*-oxazolidinones could be easily and efficiently converted into the corresponding *N*-benzyloxycarbonyl-(*S*)-amino acids (suitable for peptide coupling technology) by base hydrolysis (2 mol equiv. LiOH, H_2O–THF, 3:1 v/v, 0°C, 30–60 min). Thus the three thymine-substituted Z-amino acids **27a**–**c** (having 3- or 4-carbon tethers for the pyrimidine) were prepared from the adducts **14a**, **14b**, and **14d** (92, 96 and 87%, respectively). The uracil Z-amino acids **27d**–**f** were likewise prepared from adducts **18b**–**d** (69, 96 and 52%, respectively), as were adenine derivatives **28a**–**d** from adducts **22a**–**d** (72, 87, 89 and 86%, respectively) and guanine Z-amino acid **29** from adduct **25** (87%). To monitor optical purity, the benzyloxycarbonyl group was removed by hydrogenolysis (Pd–C, EtOH–H_2O 7:3 v/v; 8 h) to afford the amino acids **27g**–**j** (74, 79, 75, and 90%, respectively), **28e** and **28f** (75 and 61%, respectively).



27a; R^1 = PhCO, R^2 = Me, R^3 = Z, n = 1
27b; R^1 = H, R^2 = Me, R^3 = Z, n = 1
27c; R^1 = H, R^2 = Me, R^3 = Z, n = 2
27d; R^1 = R^2 = H, R^3 = Z, n = 1
27e; R^1 = PhCO, R^2 = H, R^3 = Z, n = 2
27f; R^1 = R^2 = H, R^3 = Z, n = 2
27g; R^1 = H, R^2 = Me, R^3 = H, n = 1
27h; R^1 = H, R^2 = Me, R^3 = H, n = 2
27i; R^1 = R^2 = R^3 = H, n = 1
27j; R^1 = R^2 = R^3 = H, n = 2



28a; R^1 = $COCHMe_2$, R^2 = Z, n = 1
28b; R^1 = H, R^2 = Z, n = 1
28c; R^1 = $COCHMe_2$, R^2 = Z, n = 2
28d; R^1 = H, R^2 = Z, n = 2
28e; R^1 = $COCHMe_2$, R^2 = H, n = 1
28f; R^1 = $COCHMe_2$, R^2 = H, n = 2



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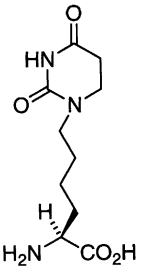
Amino acid **27j** was obtained after hydrogenolysis of Z-amino acid **27f** for 5 h; prolonged hydrogenolysis for 16 h led to the 5,6-dihydrouracil amino acid **30** (88%).

The amino acids were analysed by esterification (AcCl, EtOH, reflux) and subsequent conversion to the 'Mosher amides' **31** [(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride, Et_3N, CH_2Cl_2, 20°C].[17] In some cases diamide derivatives were also isolated and used for spectral analysis. A very major and a rather minor diastereoisomer were observed in the ^1H NMR spectra, and analysis of the CF_3 signals in the ^{19}F NMR spectra revealed very good enantiomeric excesses for the amino acids **27g** (85%), **27h** (88%), **27i** (90%), **27j** (89%) and **28f** (86%).[18]

We have thus made available a range of novel optically active pyrimidinyl and purinyl amino acids for application, for example, in PNA variants.



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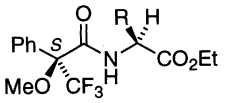

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3. Experimental

3.1. General

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded using a Perkin–Elmer 1710 FT-IR spectrometer. ^{19}F NMR spectra were obtained at 376 MHz on a JEOL JNM-EX400 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 300 MHz or at 75 MHz, respectively, on a JEOL JNM-LA300 spectrometer. Low resolution mass spectra were recorded on a VG Micromass VG20-250 spectrometer, or by the EPSRC National Mass Spectrometry Service Centre (University of Wales Swansea) who also performed the accurate mass measurements. All reagents were purified by distillation or recrystallisation where appropriate, or according to standard procedures.[19] Column chromatography was carried out using Fluka Silica Gel 60 (220–440 mesh).

3.1.1. (2*S*,4*R*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one 9 and (2*R*,4*R*)-isomer 10. *S*-Methyl-(*R*)-cysteine (27 g, 0.2 mol) was treated with aqueous sodium hydroxide (8.0 g, 0.2 mol, in 130 cm^3 water), and after 5 min the solution was evaporated to dryness under reduced pressure to leave a white solid. A solution of 2,2-dimethylpropanal (21.7 cm^3, 17.2 g, 0.2 mol) in hexane (300 cm^3) was added, and the suspension was stirred and heated under reflux with Dean–Stark water removal for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure, and the white solid suspended in dry dichloromethane (250 cm^3). Benzyl

chloroformate (42.8 cm^3, 51.1 g, 0.3 mol) was added dropwise to the stirred suspension at 0°C over 3 h. After stirring the mixture at room temperature for a further 36 h, aqueous sodium bicarbonate (10% w/v, 100 cm^3) was added and rapid stirring was continued for 4 h. The layers were then separated and the dichloromethane solution was dried ($MgSO_4$), filtered and evaporated. To the residue stirred in acetonitrile (200 cm^3) was added oxone® (95 g, 0.15 mol) in water (500 cm^3). After 24 h at room temperature, water (200 cm^3) was added, the mixture was extracted with dichloromethane (3×200 cm^3), and the combined extracts were dried($MgSO_4$), filtered and evaporated. Careful purification by column chromatography (hexane–ethyl acetate, 9:1 to 3:1 v/v) gave the *title compounds* (42 g, 57% overall yield), *syn-diastereoisomer* **9** as an oil, white crystals from hexane, mp 151–152°C (38.19 g, 52%) that was used in the following step without further purification, and *anti-diastereoisomer* **10** as a clear oil (3.80 g, 5%). (2*S*,4*R*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)-oxazolidin-5-one **9** (major *syn* diastereoisomer): $[\alpha]_D^{22}$=+27.0 (*c*, 2.00 in EtOH); Found: MH^+ 370.1323. $C_{17}H_{23}NO_6S$ requires: MH 370.1324; ν_{max} (film/cm^{-1}) 3441, 3056, 2980, 2877, 1796, 1729, 1635, 1397, 1316, 1266, 1131 and 1041; δ_H (300 MHz; $CDCl_3$) 0.95 (9H, s, C*Me*$_3$), 3.11 (3H, s, SO_2Me), 3.41 (1H, dd, *J*=3.80, 15.20 Hz, C*H*HSO_2Me), 3.59 (1H, dd, *J*=8.01, 15.20 Hz, CH*H*SO_2Me), 4.99 (1H, dd, *J*=3.80, 8.01 Hz, C*H*CH_2), 5.23 (2H, 2×d, *J*=11.91 Hz, C*H*$_2$Ph), 5.62 (1H, s, C*H*CMe_3) and 7.33–7.43 (5H, m, ArH); δ_C (75 MHz; $CDCl_3$) 24.6 (C*Me*$_3$), 37.2 (*C*Me_3), 42.5 (SO_2CH_3), 53.5 (*C*HCH_2), 57.2 (*C*H_2SO_2Me), 68.9 (*C*H_2Ph), 96.8 (CHO), 128.7, 128.8 and 128.8 (ArCH), 134.8 (ArC), 155.3 and 170.65 (CO). (2*R*,4*R*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one **10** (minor *anti*-diastereoisomer): $[\alpha]_D^{22}$=+72.8 (*c*, 0.32 in EtOH); Found: MH^+ 370.1319. $C_{17}H_{23}NO_6S$ requires: MH 370.1324; ν_{max} (film/cm^{-1}) 3415, 3056, 2973, 2877, 1797, 1713, 1639, 1413, 1354, 1317, 1266, 1127, 1035, 1015 and 975; δ_H (300 MHz; $CDCl_3$) 0.94 (9H, s, C*Me*$_3$), 2.91 (3H, s, SO_2Me), 3.57 (2H, d, *J*=14.1 Hz, C*H*$_2SO_2Me$), 4.45 (1H, br s, C*H*CH_2), 5.00 (2H, 2×d, *J*=11.90 Hz, C*H*$_2$Ph), 5.68 (1H, s, C*H*CMe_3) and 7.23–7.47 (5H, m, ArH); δ_C (75 MHz; $CDCl_3$) 24.7 (C*Me*$_3$), 39.3 (*C*Me_3), 43.7 (SO_2CH_3), 53.6 (*C*HCH_2), 61.2 (*C*H_2SO_2Me), 68.3 (*C*H_2Ph), 96.0 (CHO), 128.7, 128.7 and 129.0 (ArCH), 134.9 (ArC), 152.9 and 170.4 (CO).

3.1.2. (2*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one 11. (2*S*,4*R*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-(methylsulfonylmethyl)oxazolidin-5-one **9** (2.85 g, 7.72 mmol) in dry dichloromethane (40 cm^3) was treated dropwise with DBU (1.39 cm^3, 1.41 g, 9.27 mmol) and stirred at 0°C for 1 h before addition of water (40 cm^3). The layers were separated and the dichloromethane solution was washed with water, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was filtered through a short column of silica gel to give a colourless oil crystallised from hexane to yield the *title compound* **11** (2.13 g, 95%) as a colourless crystalline solid, mp 69–71°C, $[\alpha]_D^{20}$=−65.4 (c, 0.4 in EtOH); Found: MH^+ 290.1394. $C_{16}H_{19}NO_4$ requires: MH 290.1392; ν_{max} (KBr/cm^{-1}) 3093, 3068, 3052, 1790, 1724, 1680, 1391, 1369, 1329, 1272, 1257, 1162, 1133, 1095, 1036 and 1012; δ_H (300 MHz; $CDCl_3$) 0.93 (9H, s, *CMe*$_3$), 5.27 (2H, s, C*H*$_2$Ph), 5.63 (2H, s, C=C*H*$_2$), 5.71 (1H, s, C*H*CMe_3), 7.26–7.39 (5H, m, ArH); δ_C (75 MHz; $CDCl_3$) 24.3 (*CMe*$_3$), 38.6 (*C*Me_3), 68.7 (*C*H_2Ph), 93.9 (*C*$HCMe_3$), 104.2 (C=*C*H_2), 128.65, 128.7 and 128.81 (ArCH), 130.2 and 134.7 (*C*=CH_2 and ArC), 152.3 and 164.5 (C=O).

3-Benzoylthymine **12** and 3-benzoyluracil **16** were prepared by the method of Reese et al.[13] N^6-(2-Methylpropionyl)-adenine **20**[15] and N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]-guanine **24a**[16] were prepared according to the methods of Shevlin et al.

3.2. General procedure for Mitsunobu reaction, for preparation of *N*-(ω-bromoalkyl) nucleobase derivatives (method A)[12]

To a suspension of suitably protected nucleobase (1 mol equiv.), triphenylphosphine (1.2 mol equiv.) and the ω-bromoalcohol (1.2 mol equiv.) in dry dioxane at 0°C was added DIAD (1.2 mol equiv.) dropwise over 3 h. The mixture was then stirred under argon at room temperature overnight to yield a clear solution. The solvent was removed and the residue purified by column chromatography to give the *N*-(ω-bromoalkyl) nucleobase derivative.

3.3. General procedure for conversion of *N*-(ω-bromoalkyl) nucleobase derivatives into *N*-(ω-iodoalkyl) derivatives (method B)

The *N*-(ω-bromoalkyl) nucleobase derivative (1 mol equiv.) and dry sodium iodide (5 mol equiv.) were heated in dry acetone (100 cm^3) at reflux under argon overnight in the dark (aluminium foil). After cooling, the acetone was removed under reduced pressure and the residue taken up in ethyl acetate (100 cm^3) and water (100 cm^3). The organic layer was separated and washed with aqueous sodium thiosulfate solution (2% w/v, 2×50 cm^3). The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the *N*-(ω-iodoalkyl) derivative.

3.3.1. 3-Benzoyl-1-(2-bromoethyl)thymine 13a. Prepared following method A, using 3-benzoylthymine **12** (4.0 g, 17.4 mmol), triphenylphosphine (5.47 g, 20.9 mmol), 2-bromoethanol (1.48 cm^3, 2.61 g, 20.9 mmol), dioxane (150 cm^3) and DIAD (4.11 cm^3, 4.22 g, 20.9 mmol). Purification by column chromatography (hexane–ethyl acetate 6:4 v/v) gave the *title compound* **13a** as a white amorphous solid (5.22 g, 89%), mp 183–184°C; Found: MNH_4^+ (^{79}Br; CI) 354.0453. $C_{14}H_{13}{}^{79}BrN_2O_3$ requires: MNH_4 354.0455; ν_{max} (KBr/cm^{-1}) 2926, 2854, 2723, 1752, 1700, 1659, 1441, 1378 and 1360; δ_H (300 MHz; $CDCl_3$) 1.95 (3H, d, *J*=1.1 Hz, CH_3), 3.64 and 4.09 (each 2H, t, *J*=5.9 Hz, CH_2CH_2), 7.18 (1H, q, *J*=1.1 Hz, C*H*=CCH_3), 7.50 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.92 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 12.35 (CH_3), 29.3 and 50.7 (CH_2), 110.3 (C-5), 129.2, 130.4, 131.4 and 135.2 (ArCH and C-6), 140.9 (ArC), 149.6, 163.1 and 168.8 (CO); *m*/*z* (EI) 339.1 (MH; ^{81}Br, 100%), 337.1 (MH; ^{79}Br, 96), 310.1 (93), 308.1 (100), 268.1 (28), 266 (31).

3.3.2. 3-Benzoyl-1-(2-iodoethyl)thymine 13c. Prepared

following method B, using 3-benzoyl-1-(2-bromoethyl)-thymine **13a** (4.0 g, 11.4 mmol) and sodium iodide (8.56 g, 57.1 mmol) to yield the *title compound* **13c** as a yellow powder (4.32 g, 95%), mp 138–139°C; Found: MH^+ 385.0049. $C_{14}H_{13}IN_2O_3$ requires: MH 385.0053; ν_{max} (KBr/cm^{-1}) 3119, 1754, 1746, 1694, 1650, 1434, 1364 and 1193; δ_H (300 MHz; $CDCl_3$) 1.95 (3H, s, CH_3), 3.4 and 4.07 (each 2H, t, J=6.2 Hz, CH_2CH_2), 7.14 (1H, s, C*H*=CCH_3), 7.52 (2H, m, ArH), 7.66 (1H, m, ArH) and 7.93 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 12.35 (CH_3), 41.85 and 50.85 (CH_2), 110.4 (C-5), 129.2, 130.4, 131.4 and 135.1 (ArCH and C-6), 141.1 (ArC), 149.7, 163.1 and 168.7 (CO); *m/z* 385 (MH^+, 62%), 356 (100), 314 (18), 229 (20) and 202 (60).

3.3.3. 3-Benzoyl-1-(3-bromopropyl)thymine 13b. Prepared following method A, using 3-benzoylthymine **12** (3.0 g, 13.0 mmol), triphenylphosphine (4.11 g, 15.7 mmol), 3-bromo-1-propanol (1.42 cm^3, 2.18 g, 15.7 mmol) in dry dioxane (150 cm^3) and DIAD (3.08 cm^3, 3.17 g, 15.7 mmol). Purification by column chromatography (hexane–ethyl acetate 1:1 v/v) gave the *title compound* **13b** as a white solid (4.20 g, 92%), mp 89–90°C; Found: MH^+ (CI) 351.0343. $C_{15}H_{15}BrN_2O_3$ requires MH 351.0344; ν_{max} (KBr/cm^{-1}) 3079, 2966, 1753, 1698, 1664, 1648, 1597, 1463, 1348, 1257 and 1179; δ_H (300 MHz, $CDCl_3$) 1.97 (3H, d, 1.0 Hz, CH_3), 2.28 (2H, apparent quintet, J=6.58 Hz, $CH_2CH_2CH_2$), 3.91 (2H, t, J=6.22 Hz, CH_2Br), 4.09 (2H, t, J=6.78 Hz, NCH_2), 7.18 (1H, q, J=1.0 Hz, C*H*=CCH_3), 7.50 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.92 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 12.35 (CH_3), 29.3, 31.0 and 50.7 (CH_2), 110.3 (C-5), 129.2, 130.4, 135.2 and 131.4 (ArCH and C-6), 140.9 (ArC), 149.6, 163.1 and 168.8 (CO); *m/z* 351 (M^+, 10%), 322 (100), 282 (40), 243 (80), 229 (10) and 216 (25).

3.3.4. 3-Benzoyl-1-(3-iodopropyl)thymine 13d. Prepared following method B, using 3-benzoyl-1-(3-bromopropyl)-thymine **13b** (4.0 g, 11.4 mmol) and sodium iodide (8.56 g, 57.1 mmol) to yield the *title compound* **13d** as a yellow powder (4.32 g, 95%), mp 91–92°C; Found: MH^+ 399.0213. $C_{15}H_{15}IN_2O_3$ requires: MH 399.0205; ν_{max} (KBr/cm^{-1}) 3479, 1746, 1651, 1600, 1439, 1353, 1239 and 1176; δ_H (300 MHz; $CDCl_3$) 1.97 (3H, s, CH_3), 2.25 (2H, apparent quintet, J=6.90 Hz, $CH_2CH_2CH_2$), 3.21 (2H, t, J=6.43 Hz, CH_2I), 3.82 (2H, t, J=6.79 Hz, NCH_2), 7.17 (1H, s, C*H*=CCH_3), 7.45 (2H, m, ArH), 7.62 (1H, m, ArH) and 7.93 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 1.6 (CH_2I) 12.4 (CH_3), 31.8 and 49.5 (CH_2), 110.9 (C-5), 129.1, 130.4 and 131.5 and 135.0 (ArCH and C-6), 140.2 (ArC), 149.8, 163.0 and 168.9 (C=O); *m/z* 398 (M^+, 15%), 370 (30), 328 (20), 277 (100), 243 (60) and 167 (18).

3.3.5. 3-Benzoyl-1-(2-bromoethyl)uracil. Prepared following method A, using 3-benzoyluracil **16** (4.2 g, 19.4 mmol), triphenylphosphine (6.12 g, 23.3 mmol) and 2-bromoethanol (1.65 cm^3, 2.92 g, 23.3 mmol) in dry dioxane (150 cm^3) and DIAD (4.59 cm^3, 4.72 g, 23.3 mmol). Purification by column chromatography (hexane–ethyl acetate 6:4 v/v) gave the *title compound* as a white solid (5.15 g, 82%), mp 183–184°C; Found: MNH_4^+ (ES^+; ^{79}Br) 340.0290. $C_{13}H_{11}{}^{79}BrN_2O_3$ requires: MNH_4 340.0297; ν_{max} (KBr/cm^{-1}) 3110, 1744, 1699, 1664, 1449, 1349 and 1258; δ_H (300 MHz; $CDCl_3$) 3.65 and 4.13 (each 2H, t, J=5.88 Hz, CH_2CH_2), 5.74 and 7.31 (each 1H, d, J=7.70 Hz, CH=CHCO), 7.48 (2H, m, ArH), 7.65 (1H, m, ArH), 7.93 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 29.4 and 51.1 (CH_2), 101.8 (C-6), 129.25, 130.5, 131.3 and 135.3 (ArCH and C-5), 144.9 (ArC), 149.6, 162.3 and 168.45 (CO); *m/z* 324 (M^+, ^{81}Br, 100%) and 322 (M^+, ^{79}Br, 100).

3.3.6. 1-(2-Iodoethyl)-3-benzoyluracil 17a. Prepared following method B, using 3-benzoyl-1-(2-bromoethyl)uracil (5.0 g, 15.5 mmol) and sodium iodide (11.64 g, 77.6 mmol) to yield the *title compound* **17a** as a yellow powder (5.52 g, 96%), mp 190–191°C; Found: MH^+ (CI) 370.9892. $C_{13}H_{11}IN_2O_3$ requires: MH 370.9892; ν_{max} (KBr/cm^{-1}) 3109, 1743, 1700, 1663, 1447, 1344 and 1178; δ_H (300 MHz; $CDCl_3$) 3.44 and 4.13 (each 2H, t, J=6.16 Hz, CH_2CH_2), 5.84 and 7.23 (each 1H, d, J=7.90 Hz, CH=CHCO), 7.49 (2H, m, ArH), 7.66 (1H, m, ArH) and 7.95 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 21.9 and 51.5 (CH_2), 101.9 (C-5), 129.25, 130.5, 131.3, 135.2 (ArCH and C-6), 144.3 (ArC), 149.5, 162.25 and 168.44 (CO); *m/z* 370 (MH^+, 4%), 342 (100), 277 (30), 215 (40), 188 (60) and 155 (50).

3.3.7. 3-Benzoyl-1-(3-bromopropyl)uracil. Prepared following method A, using 3-benzoyluracil **16** (3.5 g, 16.2 mmol), triphenylphosphine (5.10 g, 19.4 mmol) and 3-bromo-1-propanol (1.77 cm^3, 2.70 g, 19.4 mmol) in dry dioxane (150 cm^3) and DIAD (3.08 cm^3, 3.83 g, 19.4 mmol). Purification by column chromatography (hexane–ethyl acetate, 1:1 v/v) gave the *title compound* as a white solid (4.57 g, 84%), mp 89–90°C; Found: MH^+ (CI) 337.0188. $C_{14}H_{13}BrN_2O_3$ requires: MH 337.0188; ν_{max} (KBr/cm^{-1}) 1738, 1699, 1654, 1598, 1446, 1389, 1341 and 1256; δ_H (300 MHz; $CDCl_3$) 2.28 (2H, apparent quintet, J=6.40 Hz, $CH_2CH_2CH_2$), 3.44 (2H, t, J=6.07 Hz, CH_2Br), 3.94 (2H, t, J=6.61 Hz, NCH_2), 5.80 and 7.35 (each 1H, d, J=8.05 Hz, CH=CHCO), 7.51 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.93 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 29.7, 30.95 and 47.9 (CH_2), 102.2 (C-5), 129.2 and 130.45 (ArCH), 131.4 (ArC), 135.2 and 144.5 (ArCH and C-6), 149.8, 162.35 and 168.75 (CO); *m/z* 337 (MH^+, 40%), 276 (30), 259 (40), 172 (100), 155 (46), 139 (44) and 105 (34).

3.3.8. 3-Benzoyl-1-(3-iodopropyl)uracil 17b. Prepared following method B, using 3-benzoyl-1-(3-bromopropyl)-uracil (4.5 g, 13.4 mmol) and sodium iodide (10.0 g, 67.0 mmol) to yield the *title compound* **17b** as a yellow gum (5.0 g, 96%); Found: MH^+ 385.0052. $C_{14}H_{13}IN_2O_3$ requires: MH 385.0049; ν_{max} (KBr/cm^{-1}) 3056, 1751, 1708, 1669, 1440 and 1266; δ_H (300 MHz; $CDCl_3$) 2.21 (2H, apparent quintet, J=6.61 Hz, $CH_2CH_2CH_2$) 3.14 (2H, t, J=6.61 Hz, CH_2I), 3.82 (2H, t, J=6.79 Hz, NCH_2), 5.74 and 7.33 (each 1H, d, J=7.97 Hz, CH=CHCO), 7.49 (2H, m, ArH), 7.65 (1H, m, ArH) and 7.91 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 1.53, 31.7 and 49.7 (CH_2), 102.0 (C-5), 129.2 and 130.3 (ArCH), 131.3 (ArC), 135.2 and 144.6 (ArCH and C-6), 149.7, 162.3 and 168.8 (CO); *m/z* 384 (M^+, 8%), 356 (50), 328 (8), 314 (10), 263 (100) and 257 (65).

3.3.9. 9-(2-Bromoethyl)-N^6-(2-methylpropionyl)adenine. Prepared following method A, using N^6-(2-methylpropionyl)-adenine **20** (5.0 g, 24.4 mmol), triphenylphosphine (7.68 g, 29.3 mmol), 2-bromoethanol (2.07 cm^3, 3.66 g, 29.3 mmol),

dioxane (150 cm^3) and DIAD (5.76 cm^3, 5.92 g, 29.3 mmol). Purification by column chromatography (hexane–ethyl acetate, 4:1 v/v) gave the *title compound* as a white solid (5.76 g, 76%), mp 148–149°C (from ethanol); Found: MH^+ 312.0462. $C_{11}H_{14}N_5OBr$ requires: MH 312.0460; ν_{max} (KBr/cm^{-1}) 3339, 3281, 3117, 2973, 1689, 1611, 1516, 1489, 1201 and 1152; δ_H (300 MHz; $CDCl_3$) 1.34 (6H, d, J=6.93 Hz, CH*Me*$_2$), 3.28 (1H, septet, J=6.93 Hz, C*H*Me$_2$), 3.79 and 4.69 (each 2H, t, J=5.88 Hz, CH_2CH_2), 8.12 and 8.70 (each 1H, s, 2-CH and 8-CH), 9.06 (1H, s, CONH); δ_C (75 MHz; $CDCl_3$) 19.4 (CH_3), 29.65 (CH_2Br), 36.0 (*C*HMe$_2$), 45.8 (NCH_2), 122.3 and 143.0 (ArC), 149.5 and 151.4 (C-2 and C-8), 152.6 (ArC) and 176.4 (CO); *m/z* 313 (M^+, 100%), 311 (M^+, 100%), 270 (12) and 268 (20).

3.3.10. 9-(2-Iodoethyl)-N^6-(2-methylpropionyl)adenine 21a. Prepared following method B, using 9-(2-bromoethyl)-N^6-(2-methylpropionyl)adenine (5.0 g, 16.1 mmol) and sodium iodide (12.0 g, 80.4 mmol) to yield the *title compound* **21a** as a yellow powder (4.96 g, 86%), mp 162–163°C; Found: MH^+ 360.0315. $C_{11}H_{14}N_5OI$ requires MH 360.0321; ν_{max} (KBr/cm^{-1}) 3339, 2871, 3040, 3064, 2971, 2928, 2363, 1794, 1611, 1527, 1471, 1348, 1322, 1237, 1191, 1152 and 1111; δ_H (300 MHz; $CDCl_3$) 1.33 (6H, d, J=6.89 Hz, CH*Me*$_2$), 3.24 (1H, septet, J=6.89, C*H*Me$_2$), 3.63 and 4.64 (each 2H, t, J=6.52 Hz, CH_2CH_2), 8.14 and 8.71 (each 1H, s, 2-CH and 8-CH) and 8.93 (1H, s, NHCO); *m/z* 359 (M^+, 20%), 289 (20), 205 (20), 135 (100) and 108 (15).

3.3.11. 9-(3-Bromopropyl)-N^6-(2-methylpropionyl)adenine. Prepared following method A, using N^6-(2-methylpropionyl)-adenine **20** (4.5 g, 22.0 mmol), triphenylphosphine (6.91 g, 26.3 mmol), 3-bromo-1-propanol (2.39 cm^3, 3.66 g, 26.3 mmol), dioxane (170 cm^3) and DIAD (5.19 cm^3, 5.33 g, 26.3 mmol). Purification by column chromatography (hexane–ethyl acetate 4:1 v/v) gave the *title compound* as a white solid (5.42 g, 76%), mp 110–111°C (from toluene); Found: MH^+ (ES^+) 326.0621. $C_{12}H_{16}N_5OBr$ requires: MH 326.0616; ν_{max} (KBr/cm^{-1}) 3283, 3137, 3068, 3047, 2970, 2930, 1689, 1663, 1485, 1406, 1350, 1234 and 1227; δ_H (300 MHz; $CDCl_3$) 1.31 (6H, d, J=6.50 Hz, CH*Me*$_2$), 2.49 (1H, septet, J=6.50 Hz, C*H*Me$_2$), 3.30 (2H, apparent quintet, $CH_2CH_2CH_2$), 3.37 (2H, t, J=6.22 Hz, CH_2Br), 4.49 (2H, t, J=6.58 Hz, NCH_2), 8.14 and 8.73 (each 1H, s, 2-CH and 8-CH) and 8.85 (1H, s, NHCO); δ_C (75 MHz; $CDCl_3$) 19.25 (CH_3), 29.5 and 31.7 (CH_2), 36.0 (*C*HMe$_2$), 42.3 (CH_2), 122.4 (ArC), 143.1 (CH), 149.5 and 151.7 (ArC), 152.5 (CH) and 176.6 (CO); *m/z* 325 (M^+, 20%), 257 (20), 205 (20), 176 (40), 149 (100) and 71 (38).

3.3.12. 9-(3-Iodopropyl)-N^6-(2-methylpropionyl)adenine 21b. Prepared following method B, using 9-(3-bromopropyl)-N^6-(2-methylpropionyl)adenine (5.3 g, 16.3 mmol) and sodium iodide (12.2 g, 81.5 mmol) to yield the *title compound* **21b** as a yellow gum (4.93 g, 81%); Found: MH^+ (ES^+) 374.0473. $C_{12}H_{16}N_5OI$ requires: MH 374.0478; ν_{max} (film/cm^{-1}) 3413, 2981, 2360, 2342, 1610, 1588, 1459 and 908; δ_H (300 MHz, $CDCl_3$) 1.31 (6H, d, J=6.69 Hz, CH*Me*$_2$), 2.43 (1H, septet, J=6.69 Hz, C*H*Me$_2$), 3.12 (2H, t, J=6.61 Hz, CH_2I), 3.24 (2H, apparent quintet, J=6.61 Hz, $CH_2CH_2CH_2$), 4.42 (2H, t, J=5.58 Hz, NCH_2), 8.09 and 8.73 (each 1H, s, 2-CH and 8-CH), 8.75 (1H, s, NHCO); δ_C (75 MHz; $CDCl_3$) 1.65 (CH_2), 19.2 (CH_3), 32.3 (CH_2), 36.1 (*C*HMe$_2$), 44.5 (CH_2), 122.3 (ArC), 142.9 (CH), 149.4 and 151.6 (ArC), 152.57 (CH) and 176.9 (CO); *m/z* 373 (M^+, 10%), 277 (80), 199 (28), 149 (54) and 77 (100).

3.3.13. 9-(2-Bromoethyl)-N^2-acetyl-O^6-[2-(4-nitrophenyl)-ethyl]guanine. Prepared following method A, using N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]guanine **24a** (5.0 g, 14.6 mmol), 2-bromoethanol (1.24 cm^3, 2.19 g, 17.5 mmol), triphenylphosphine (4.6 g, 17.5 mmol), dioxane (100 cm^3) and DIAD (3.54 g, 3.45 cm^3, 17.5 mmol). Purification by flash chromatography (EtOAc–hexane, 4:1 v/v) gave the *title compound* as a white solid (4.39 g, 67%), mp 181–182°C; Found: MH^+ (FAB) 449.0573. $C_{17}H_{17}BrN_6O_4$ requires: MH 449.0579; ν_{max} (KBr/cm^{-1}) 3206, 3133, 1665, 1610, 1589, 1510, 1460, 1415, 1383, 1352, 1327, 1309, 1226 and 1025; δ_H (300 MHz; DMSO-d_6) 1.97 (3H, s, CH_3 ArC*H*$_2$), 3.28 (2H, t, J=6.80 Hz, ArC*H*$_2$), 3.95 and 4.55 (each 2H, t, J=6.04 Hz, NCH_2CH_2Br), 4.77 (2H, t, J=6.80 Hz, OCH_2), 7.60 and 8.20 (each 2H, d, J=8.21 Hz, ArH), 8.29 (1H, s, 8-CH), 10.42 (1H, s, NHCO); δ_C (75 MHz; DMSO-d_6) 24.7 (CH_3), 31.0, 34.2, 44.85 and 66.4 (CH_2), 116.65 (ArC), 123.4, 130.3 and 142.8 (ArCH), 146.21, 146.4, 152.0, 152.9 and 159.6 (ArC) and 169.10 (CO); *m/z* 449 (MH^+, 65%), 343 (20), 300 (75), 258 (35), 178 (50), 151 (100) and 133 (52).

3.3.14. 9-(2-Iodoethyl)-N^2-acetyl-O^6-[2-(4-nitrophenyl)-ethyl]guanine 24b. Prepared using a modification of method B. 9-(2-Bromoethyl)-N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]guanine (0.77 g, 1.72 mmol) and dry sodium iodide (1.29 g, 8.58 mmol) in dry acetone (50 cm^3) was heated at reflux in the dark (aluminium foil) under argon overnight. After cooling, the acetone was removed under reduced pressure and the residue taken up in dichloromethane (50 cm^3) and water (50 cm^3). The organic layer was separated and washed with aqueous sodium thiosulfate solution (2% w/v, 2×25 cm^3), dried ($MgSO_4$) and the solvents were removed under reduced pressure to yield the *title compound* **24b** as a yellow gum (0.72 g, 85%); Found: MH^+ (FAB) 497.0412. $C_{17}H_{17}IN_6O_4$ requires: MH 497.0408; ν_{max} (KBr/cm^{-1}) 3387, 3093, 1685, 1677, 1656, 1605, 1515, 1493, 1381, 1344, 1327, 1213, 1048 and 1023; δ_H (300 MHz; DMSO-d_6) 2.25 (3H, s, CH_3), 3.32 (2H, t, J=6.80 Hz, ArC*H*$_2$), 3.70 and 4.51 (each 2H, t, J=6.58 Hz, NCH_2CH_2I), 4.79 (2H, t, J=6.80 Hz, OCH_2,), 7.56 and 8.18 (each 2H, d, J=8.29 Hz, ArH), 8.26 (1 H, s, 8-CH), 10.42 (1H, s, NHCO); δ_C (75 MHz; DMSO-d_6) 3.65 (CH_2), 24.7 (CH_3), 34.2, 45.3 and 66.35 (CH_2), 116.8 (ArC), 123.3, 130.3 and 142.6 (ArCH), 146.2, 146.4, 152.9, 152.8 and 159.6 (ArC) and 169.0 (CO); *m/z* 497 (MH^+, 75%), 348 (55), 279 (26), 193 (65), 151 (100) and 107 (73).

3.4. General procedure for conjugate radical addition to oxazolidinone 11 (method C)

To the iodoalkyl derivative (1.0 mol equiv.), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (1.2 mol equiv.) and AIBN (0.1 mol equiv.) in degassed toluene (200 cm^3), warmed to 80°C and stirred under a positive atmosphere of argon, was added tributyltin hydride (1.2 mol equiv.) dropwise via syringe pump over 2 h. Heating and stirring were continued until reflux and for a further

12 h. After cooling, the toluene was removed under reduced pressure and the residue purified by flash column chromatography (EtOAc–hexane, 1:4 to 4:1 v/v) to give the conjugate adduct.

3.5. General procedure for conjugate radical addition to oxazolidinone 11 (method D)

The iodoalkyl derivative (1.0 mol equiv.), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (2 mol equiv.), tributyltin chloride (0.3 mol equiv.), sodium cyanoborohydride (2 mol equiv.) and AIBN (0.1 mol equiv.) in *tert*-butanol (40 cm^3/g of **11**) per were heated at reflux under a positive atmosphere of argon for 40 h. After cooling, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (EtOAc–hexane, 1:4 to 4:1 v/v) to yield the conjugate adduct.

3.5.1. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(3-benzoyl-1-thyminyl)propyl]oxazolidin-5-one 14a. Performed following method C, using 3-benzoyl-1-(2-iodoethyl)thymine **13c** (0.66 g, 17.2 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (497 mg, 17.2 mmol), AIBN (ca. 10 mg) and tributyltin hydride (0.555 cm^3, 0.60 g, 20.6 mmol) to give the *conjugate adduct* **14a** as a colourless oil (244 mg, 26%) and *3-benzoyl-1-ethylthymine* **15a** as a white solid (106 mg, 24%), mp 169–171°C. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(3-benzoyl-1-thyminyl)propyl]oxazolidin-5-one **14a**: Found: MH^+ (CI) 548.2387. $C_{30}H_{33}N_3O_7$ requires: MH 548.2397; ν_{max} (neat/cm^{-1}) 3431, 2361, 2342, 1790, 1749, 1701, 1657, 1440 and 1266; δ_H (300 MHz; $CDCl_3$) 0.94 (9H, s, CMe_3), 1.74–2.04 (7H, m, 2×$NCH_2CH_2CH_2$ and $CH{=}CCH_3$), 3.69 and 3.81 (each 1H, m, NCH_2), 4.31 (1H, t, J=6.79 Hz, $CHCH_2$), 5.17 (2H, s, CH_2Ph), 5.56 (1H, s, $CHBu^t$), 7.11 (1H, s, $CH{=}CCH_3$), 7.34–7.38 (5H, m, ArH), 7.49 (2H, m, ArH), 7.64 (1H, m, ArH) and 7.91 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 12.4 ($CH{=}CCH_3$), 24.9 (CMe_3), 25.8 ($NCH_2CH_2CH_2$), 29.9 ($CHCH_2$), 36.9 (CMe_3), 47.7 (NCH_2), 56.6 ($CHCH_2$), 68.7 (CH_2Ph), 96.5 ($CHBu^t$), 110.9 ($CH{=}CCH_3$), 128.6, 128.8, 128.8, 129.1, 130.4 and 131.7 (ArCH), 134.95 and 135.0 (ArC), 139.9 ($CH{=}CCH_3$), 149.8, 156.1, 163.1, 169.0 and 172.3 (CO); *m*/*z* 547 (M^+, 100%), 490 (50), 442 (30), 398 (60), 315 (70) and 286 (45). 3-Benzoyl-1-ethylthymine **15a**: Found: (CI) 259.1083. $C_{14}H_{14}N_2O_3$ requires: MH^+ 259.1082; ν_{max} (KBr/cm^{-1}) 1366, 1346, 1266, 1248 and 1193; δ_H (300 MHz) 1.30 (3H, t, J=7.15 Hz, CH_2CH_3), 1.95 (3H, s, $CH{=}CCH_3$), 3.77 (2H, q, J=7.15 Hz, CH_2CH_3), 7.12 (1H, s, $CH{=}CCH_3$), 7.49 (2H, m, ArH), 7.64 (1H, m, ArH) and 7.91 (2H, m, ArH); *m*/*z* 258 (M^+, 15%), 230 (100) and 188 (40).

3.5.2. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(3-benzoyl-1-thyminyl)propyl]oxazolidin-5-one 14a and (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4[3-(1-thyminyl)propyl]oxazolidin-5-one 14b. Performed following method D, using 3-benzoyl-1-(2-iodoethyl)thymine **13c** (1.13 g, 2.94 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (1.70 g, 5.89 mmol), tributyltin chloride (0.239 cm^3, 0.287 g, 0.882 mmol), sodium cyanoborohydride (0.370 g, 5.89 mmol) and AIBN (0.29 mmol), but heating at reflux for 16 h to yield the *conjugate adduct* **14a** as a colourless oil (1.29 g, 24%) identical with the sample prepared by method C, and the *debenzoylated conjugate adduct* **14b** as a white solid (0.391 g, 30%), mp (decomp.) 78–80°C. No reduced products were isolated. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4[3-(1-thyminyl)propyl]oxazolidin-5-one **14b**: Found: MH^+ (CI) 444.2132. $C_{23}H_{29}N_3O_6$ requires: MH 444.2134; ν_{max} (KBr/cm^{-1}) 3204, 3037, 2964, 1792, 1708, 1680, 1467, 1397, 1363, 1348, 1229, 1198 and 1125; δ_H (300 MHz; $CDCl_3$) 0.95 (9H, s, CMe_3), 1.85–1.99 (7H, m, CH_2CH_2 and $CH{=}CCH_3$), 3.68 and 3.76 (each 1H, m, NCH_2), 4.32 (1H, t, J=6.79 Hz, $CHCH_2$), 5.18 (2H, 2×d, J=11.93 Hz, CH_2Ph), 5.56 (1H, s, $CHBu^t$), 7.00 (1H, s, $CH{=}CCH_3$), 7.34–7.38 (5H, m, ArH) and 9.57 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) 12.3 ($CH{=}CCH_3$), 24.9 (CMe_3), 25.8 ($NCH_2CH_2CH_2$), 29.8 ($CHCH_2$), 36.9 (CMe_3), 47.4 (NCH_2), 56.7 ($CHCH_2$), 68.6 ($PhCH_2$), 96.5 ($CHBu^t$), 110.8 ($CH{=}CCH_3$), 128.6, 128.7 and 128.8 (ArH), 135.0 (ArC), 140.2 ($CH{=}CCH_3$), 172.3, 171.2, 164.5 and 156.1 (CO); *m*/*z* 443 (M^+, 60%), 386 (70), 308 (75), 286 (100), 264 (35), 250 (35), 208 (80) and 194 (48).

When the reaction time was extended to 40 h, using 3-benzoyl-1-(2-iodoethyl)thymine **13c** (6.84 g, 17.8 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one (10.3 g, 35.6 mmol), tributyltin chloride (1.45 cm^3, 1.74 g, 5.34 mmol), sodium cyanoborohydride (2.24 g, 35.6 mmol) and AIBN (1.78 mmol), purification by column chromatography gave only the adduct **14b** as a white solid (3.68 g, 47%), data as above. Reduced products were not isolated.

3.5.3. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[4-(1-thyminyl)butyl]oxazolidin-5-one 14d. Prepared following method D, using 3-benzoyl-1-(3-iodopropyl)thymine **13d** (3.12 g, 7.84 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (4.53 g, 15.7 mmol), tributyltin chloride (0.638 cm^3, 0.765 g, 2.35 mmol), sodium cyanoborohydride (0.98 g, 15.7 mmol) and AIBN (0.78 mmol) to yield the *debenzoylated conjugate adduct* **14d** as a thick oil (900 mg, 25%) and *1-propylthymine* **15b** as a white solid (276 mg, 21%), mp 134–135°C. (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(1-thyminyl)-butyl]oxazolidin-5-one **14d**: Found: MH^+ 458.2287. $C_{24}H_{31}N_3O_6$ requires: MH 458.2291; ν_{max} (film/cm^{-1}) 3489, 3201, 3068, 2964, 1789, 1710, 1690, 1480, 1398, 1348, 1289, 1269, 1225, 1125, 1043 and 1013; δ_H (300 MHz; $CDCl_3$) 0.95 (9H, s, CMe_3), 1.56–2.05 (9H, m, $CH(CH_2)_3CH_2N$ and $CH{=}CCH_3$), 3.49–3.69 (2H, m, NCH_2), 4.23–4.28 (1H, t, J=6.79 Hz, $CHCH_2$), 5.17 (2H, s, CH_2Ph), 5.55 (1H, s, $CHBu^t$), 6.89 (1H, s, $CH{=}CCH_3$), 7.32–7.44 (5H, m, ArH) and 9.08 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) 12.3 ($CH{=}CCH_3$), 23.2 (CH_2), 24.9 (CMe_3), 28.4 and 32.6 (CH_2), 37.0 (CMe_3), 48.2 (NCH_2), 56.8 ($CHCH_2$), 68.5 (CH_2Ph), 96.4 ($CHBu^t$), 110.7 (CCH_3), 128.5, 128.55 and 128.7 (ArCH), 135.2 (ArC), 140.4 ($CH{=}CCH_3$), 150.8, 156.0, 164.3 and 172.6 (CO); *m*/*z* 457 (M^+, 10%), 400 (20), 300 (30), 91 (25), 84 (100) and 47 (20). 1-Propylthymine **15b**:[20] Found: MH^+ 169.0980. $C_8H_{12}N_2O_2$ requires: MH 169.0977; ν_{max} (KBr/cm^{-1}) 3163, 3099, 3027, 2970, 1704, 1649 and 1245; δ_H (300 MHz; $CDCl_3$) 0.94 (3H, t, J=7.51 Hz, CH_2CH_3), 1.71 (2H, apparent sextet,

J=7.33 Hz, $NCH_2CH_2CH_3$), 1.93 (3H, s, CH=CCH_3), 2.91 (2H, t, J=6.25 Hz, NCH_2CH_2), 6.99 (1H, s, CH=CCH_3) and 9.37 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) 10.9 (CH_2CH_3), 12.3 (CH=CCH_3), 22.35 (CH_2CH_3), 50.05 (NCH_2), 110.5 (CH=$C$$CH_3$), 140.5 ($C$H=$CCH_3$), 151.1 and 164.4 (CO); m/z 168 (M^+, 90%), 126 (90), 96 (100), 55 (37) and 41 (40).

3.5.4. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(3-benzoyl-1-uracilyl)propyl]oxazolidin-5-one 18a. Prepared following method D, using 3-benzoyl-1-(2-iodoethyl)uracil **17a** (0.76 g, 2.05 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (1.19 g, 4.11 mmol), tributyltin chloride (0.167 cm^3, 0.201 g, 0.616 mmol), sodium cyanoborohydride (0.258 g, 4.11 mmol) and AIBN (0.205 mmol), but heating at reflux for 7 h to yield the *conjugate adduct* **18a** as a colourless oil (510 mg, 47%) and 3-benzoyl-1-ethyluracil **15c** as a white amorphous gum (230 mg, 46%) that was incompletely characterized. No debenzoylated products were observed in the mixture. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(3-benzoyl-1-uracilyl)propyl]oxazolidin-5-one **18a**: Found: MH^+ (CI) 534.2237. $C_{29}H_{31}N_3O_7$ requires: MH 534.2240; ν_{max} (film/cm^{-1}) 3404, 3369, 1790, 1749, 1704, 1665, 1497, 1439, 1392, 1347, 1255, 1235 and 1041; δ_H (300 MHz; $CDCl_3$) 0.94 (9H, s, Bu^t), 1.82–2.01 (4H, m, $CHCH_2CH_2$), 3.69–3.85 (2H, m, NCH_2), 4.30 (1H, t, J=6.79 Hz, $CHCH_2$), 5.16 (2H, s, CH_2Ph), 5.56 (1H, s, $CHBu^t$), 5.75 (1H, d, J=7.87 Hz, CH=$CHCO$), 7.24–7.40 (6H, m, ArH and CH=CHCO), 7.46–7.52 (2H, m, ArH), 7.61–7.67 (1H, m, ArH) and 7.90 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 24.9 (CMe_3), 25.7 ($CH_2CH_2CH_2N$), 29.8 ($CHCH_2$), 36.9 (CMe_3), 48.0 (NCH_2), 56.6 ($CHCH_2$), 68.7 (CH_2Ph), 96.5 ($CHBu^t$), 102.15 (CHCO), 128.4, 128.6, 128.8, 128.8, 129.2 and 130.4 (ArCH), 131.5 and 135.1 (ArC), 144.1 (CH=CHCO), 149.8, 156.1, 162.4, 168.8 and 172.3 (CO); m/z 533 (MH^+, 20%), 476 (30), 404 (25), 376 (50), 301 (40) and 198 (50). 3-Benzoyl-1-ethyluracil **15c**: ν_{max} (film/cm^{-1}) 3413, 3058, 2984, 2328, 2178, 1788, 1749, 1665, 1601, 1485, 1439, 1391, 1346, 1266, 1178 and 1122; δ_H (300 MHz; $CDCl_3$) 1.29 (3H, t, J=7.15 Hz, NCH_2CH_3), 3.79 (2H, q, J=7.15 Hz, NCH_2CH_3), 5.81 (1H, d, J=7.90 Hz, 5-CH), 7.20–7.52 (4H, m, ArH and 6-CH), 7.89 (2H, m, ArH); m/z 244 (M^+, 5%), 216 (30), 199 (20), 183 (15), 105 (100) and 77 (88).

3.5.5. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(-1-uracilyl)propyl]oxazolidin-5-one 18b. Prepared following method D, using 3-benzoyl-1-(2-iodoethyl)uracil **17a** (5.45 g, 14.7 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (8.51 g, 29.5 mmol), tributyltin chloride (1.20 cm^3, 1.44 g, 4.42 mmol), sodium cyanoborohydride (1.85 g, 29.5 mmol) and AIBN (1.47 mmol) to yield the *debenzoylated conjugate adduct* **18b** as a colourless oil (3.24 g, 51%). No benzoylated product was isolated; reduction product was present but not purified from this experiment. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(-1-uracilyl)propyl]oxazolidin-5-one **18b**: Found: MNH_4^+ (ES^+) 447.2255. $C_{22}H_{27}N_3O_6$ requires: MNH_4 447.2244; ν_{max} (film/cm^{-1}) 3691, 3055, 2360, 2342, 1791, 1713, 1689 and 1266; δ_H (300 MHz; $CDCl_3$) 0.92 (9H, s, Bu^t), 1.83–2.10 (4H, m, $CHCH_2CH_2$), 3.26–3.82 (2H, m, NCH_2), 4.43 (1H, t, J=6.75 Hz, $CHCH_2$), 5.16 (2H, s, CH_2Ph), 5.54 (1H, s, $CHBu^t$), 5.82 (1H, d, J=7.54 Hz, CH=CHCO), 7.32–7.34 (6H, m, ArH and CH=CHCO) and 9.92 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) 24.9 (CMe_3), 26.7 ($CH_2CH_2CH_2N$), 28.9 ($CHCH_2$), 36.8 (CMe_3), 47.6 (NCH_2), 56.7 ($CHCH_2$), 68.9 (CH_2Ph), 96.8 ($CHBu^t$), 102.5 (CHCO), 128.7, 135.0 (ArCH), 146.15 and 147.1 (ArC), 151.4 (CH=CHCO), 156.4, 165.5, 171.0 and 173.3 (CO); m/z 430 (MH^+, 30%), 279 (20), 254 (100), 238 (30) and 220 (90).

3.5.6. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[4-(3-benzoyl-1-uracilyl)butyl]oxazolidin-5-one 18c. Prepared following a modified method D, using 3-benzoyl-1-(3-iodopropyl)uracil **17b** (2.40 g, 6.25 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (1.51 g, 5.21 mmol), tributyltin chloride (0.424 cm^3, 0.509 g, 1.56 mmol), sodium cyanoborohydride (0.427 g, 6.79 mmol) and AIBN (0.52 mmol) but heated at reflux in degassed ethanol (50 cm^3) for 8 h to yield the *conjugate adduct* **18c** as a colourless oil (598 mg, 21%) and 3-benzoyl-1-propyluracil **15e** as a white gum (362 mg, 27%) that was incompletely characterized. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[4-(3-benzoyl-1-uracilyl)butyl]oxazolidin-5-one **18c**: Found: MH^+ (CI) 548.2390. $C_{30}H_{33}N_3O_7$ requires: MH 548.2397; ν_{max} (KBr/cm^{-1}) 2962, 2362, 1791, 1749, 1703, 1664, 1438, 1371, 1348, 1256 and 1235; δ_H (300 MHz; $CDCl_3$) 1.00 (9H, s, CMe_3), 1.64–2.02 (6H, m, $CH(CH_2)_3CH_2N$), 3.74 (2H, m, NCH_2), 4.31 (1H, t, J=6.97 Hz, $CHCH_2$), 5.21 (2H, s, CH_2Ph), 5.60 (1H, s, $CHBu^t$), 5.81 and 7.25 (each 1H, d, J=7.44 Hz, CH=CHCO), 7.42–7.44 (5H, m, ArH), 7.55 (2H, m, ArH) 7.70 (1H, m, ArH) and 7.97 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 22.0 (CH_2), 24.8 (CMe_3), 28.1 and 32.4 (CH_2), 36.81 (CMe_3,), 48.7 (NCH_2), 53.4 ($CHCH_2$), 68.3 (CH_2Ph), 96.3 ($CHBu^t$), 101.9 (CHCO), 128.4, 128.6, 128.7, 129.1 and 130.3 (ArCH), 131.4 (ArC), 135.0 (ArCH), 135.1 (ArC), 144.2 (CH=CHCO), 149.6, 155.8, 162.35, 168.8 and 172.4 (CO); m/z 547 (M^+, 20%), 490 (50), 446 (30), 418 (50), 390 (60), 286 (40) and 198 (100). 3-Benzoyl-1-propyluracil **15e**: δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, J=7.51 Hz, CH_2CH_3), 1.72 (2H, apparent sextet, J=7.36 Hz, $NCH_2CH_2CH_3$), 3.68 (2H, t, J=7.33 Hz, NCH_2), 5.80 and 7.20 (each 1H, d, J=7.05 Hz, CH=CHCO) and 7.47–7.68 (5H, m, ArH).

3.5.7. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[4-(1-uracilyl)butyl]oxazolidin-5-one 18d. Prepared following method D, using 3-benzoyl-1-(3-iodopropyl)uracil **17b** (1.98 g, 5.16 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (2.98 g, 10.3 mmol), tributyltin chloride (0.420 cm^3, 503 mg, 1.55 mmol), sodium cyanoborohydride (648 mg, 10.3 mmol) and AIBN (0.516 mmol) to yield the *debenzoylated conjugate adduct* **18d** as an amorphous solid (1.00 g, 44%), mp (decomp.) 151–153°C, and *1-propyluracil* **15d** as a white gum (0.405 g, 51%). (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[4-(1-uracilyl)-butyl]oxazolidin-5-one **18d**: Found: MH^+ 444.2125. $C_{23}H_{29}N_3O_6$ requires: MH 444.2134; δ_H (300 MHz; CD_3OD) 0.93 (9H, s, CMe_3), 1.52–2.01 (6H, m, $CH(CH_2)_3CH_2N$), 3.58–3.73 (2H, m, NCH_2), 4.35 (1H, t, J=7.54 Hz, $CHCH_2$), 5.16 (2H, s, CH_2Ph), 5.56 (1H, s, $CHBu^t$), 5.62 (1H, d, J=7.69 Hz, CH=CHCO) and 7.30–7.50 (6H, m, ArH and CH=CHCO); δ_C (75 MHz; CD_3OD) 24.2 (CH_2), 25.4 (CMe_3), 29.2 and 33.8 (CH_2), 37.8 (CMe_3,), 48.5 (NCH_2), 58.2 ($CHCH_2$), 69.4 (CH_2Ph), 97.8

(*C*HBu^t), 102.2 (CH=*C*HCO), 128.75, 129.5 and 129.6 (ArCH), 137.1 (ArC), 147.3 (*C*H=CHCO), 152.8, 157.9, 166.8 and 174.6 (CO); *m/z* 444 (MH^+, 80%) and 430 (20). 1-Propyluracil **15d**: Found: M^+ (EI) 154.0734. $C_7H_{10}N_2O_2$ requires: M 154.0742; δ_H (300 MHz, $CDCl_3$) 0.91 (3H, t, *J*=7.33 Hz, CH_2CH_3), 1.72 (2H, sextet, *J*=7.33 Hz, $NCH_2CH_2CH_3$), 3.70 (2H, t, *J*=7.33 Hz, NCH_2CH_2), 5.72 (1H, d, *J*=7.88 Hz, CH=C*H*CO), 7.16 (1H, d, *J*=7.88 Hz, C*H*=CHCO) and 9.20 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) 10.9 (CH_2CH_3), 22.3 (CH_2CH_3), 50.45 (NCH_2), 102.0 (C-5), 144.7 (C-6), 164.0 and 171.2 (CO); *m/z* 154 (M^+, 50%), 126 (15), 112 (60), 82 (100), 69 (50) and 55 (40).

This experiment was repeated but using 5 mol equiv. of acceptor **11**, i.e. 3-benzoyl-1-(3-iodopropyl)uracil **17b** (1.98 g, 5.16 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (7.45 g, 25.8 mmol), tributyltin chloride (0.420 cm^3, 503 mg, 1.55 mmol), sodium cyanoborohydride (648 mg, 10.3 mmol) and AIBN (0.516 mmol) to yield the *debenzoylated conjugate adduct* **18d** as an amorphous solid (1.42 g, 62%), identical to the above sample.

3.5.8. 2-Benzoyloctahydropyrrolo[1,2-*c*]pyrimidine-1,3-dione 19. Prepared following method D, using 3-benzoyl-1-(3-iodopropyl)uracil **17b** (0.86 g, 2.24 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (777 mg, 2.69 mmol), tributyltin chloride (0.182 cm^3, 219 mg, 0.67 mmol), sodium cyanoborohydride (42 mg, 0.67 mmol) and AIBN (0.2 mmol) but heated at reflux for 30 min. to yield recovered oxazolidinone **11** (640 mg, 82%) and uracil **17b** (690 mg, 80%), and the *title compound* **19** (99 mg, 17%; 87% based on recovered uracil **17b**) as a white amorphous solid, mp 157–158°C; Found: MH^+ (CI) 259.1084. $C_{14}H_{14}N_2O_3$ requires: MH 259.1083; ν_{max} (KBr/cm^{-1}) 3963, 3926, 2361, 1743, 1704, 1681, 1438, 1370, 1349, 1278, 1258, 1240 and 980; δ_H (300 MHz, $CDCl_3$) 1.64–1.76 (1H, m, $COCH_2CHCHH$), 1.94–2.00 and 2.09–2.15 (each 1H, ddddd, *J*=2.37, 4.78, 6.97, 9.70 and 11.93 Hz, NCH_2CH_2), 2.32–2.38 (1H, m, $COCH_2CHCHH$), 2.57 (1H, dd, *J*=13.22 and 15.95 Hz, COCHH), 2.95 (1H, dd, *J*=3.85 and 15.95 Hz, COCHH), 3.50–3.71 (2H, m, NCH_2), 3.91–3.95 (1H, m, NCH), 7.49 (2H, m, ArH), 7.62 (1H, m, ArH) and 7.89–7.92 (2H, m, ArH); δ_C (300 MHz, $CDCl_3$) 23.2 ($NCH_2CH_2CH_2$), 33.2 ($CHCH_2$), 38.3 ($COCH_2$), 45.3 (NCH_2), 52.9 (CH), 129.2 and 130.5 (ArCH), 132.7 (ArC), 134.5 (ArCH), 149.9, 168.9 and 170.0 (CO).

An experiment following method C, using 3-benzoyl-1-(3-iodopropyl)uracil **17b** (0.43 g, 1.12 mmol), AIBN (ca. 10 mg), toluene (150 ml) and tributyltin hydride (0.361 cm^3, 0.391 g, 1.34 mmol), but without using the chiral acceptor **11**, gave the *title compound* **19** as a colourless oil (152 mg, 53%), having spectral data as above. The reduction product 3-benzoyl-1-propyluracil was not observed.

3.5.9. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{3-[N^6-(2-methylpropionyl)-9-adeninyl]propyl}oxazolidin-5-one 22a and (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[3-(9-adeninyl)propyl]oxazolidin-5-one 22b. Prepared following method D, using 9-(2-iodoethyl)-N^6-(2-methylpropionyl)-adenine **21a** (3.29 g, 9.16 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (5.30 g, 18.3 mmol), tributyltin chloride (0.746 cm^3, 895 mg, 2.75 mmol), sodium cyanoborohydride (1.15 g, 18.3 mmol) and AIBN (0.92 mmol) but heated at reflux for 16 h to yield the *conjugate adduct* **22a** as a colourless oil (1.17 g, 26%), a mixture of *deacylated conjugate adduct* **22b** (580 mg, 14%, calculated from the following hydrolysis step) and 9-ethyl-N^6-(2-methylpropionyl)adenine **23a** (360 mg, 17%, calculated from the hydrolysis step), and *9-ethyladenine* **23b** (280 mg, 19%) as a white solid, mp 180–182°C (lit.,[21] 184–186°C). (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{3-[N^6-(2-methylpropionyl)-9-adeninyl]propyl}oxazolidin-5-one **22a**: Found: MH^+ 523.2670. $C_{27}H_{34}N_6O_5$ require: MH 523.2669; δ_H (300 MHz; $CDCl_3$) 0.91 (9H, s, C*Me*$_3$), 1.33 (6H, d, *J*=6.97 Hz, CH*Me*$_2$), 1.87–2.24 (4H, m, $CHCH_2CH_2$), 3.28 (1H, septet, *J*=6.79 Hz, C*H*Me$_2$), 4.27–4.34 (3H, m, C*H*CH_2 and NCH_2), 5.15 (2H, s, CH_2Ph), 5.52 (1H, s, C*H*Bu^t), 7.26 (5H, m, ArH), 8.12 and 8.71 (each 1H, s, adenine-H), 9.74 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) 19.0 (CH*Me*$_2$), 24.6 (C*Me*$_3$), 26.7 ($CHCH_2CH_2$), 29.0 ($CHCH_2$), 33.85 (*C*HMe$_2$), 35.8 (*C*Me$_3$), 43.2 (NCH_2), 56.5 ($CHCH_2$), 68.6 (CH_2Ph), 96.5 (*C*HBu^t), 122.0 (ArC), 128.5, 128.65 and 128.7 (ArCH), 134.9 (ArC), 143.0 (ArCH), 149.55 and 151.7 (ArC), 152.4 (ArCH), 156.1, 172.25 and 176.8 (CO); *m/z* 522 (M^+, 2%), 395 (2), 359 (25) and 91 (100). (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[3-(9-adeninyl)propyl]oxazolidin-5-one **22b** (data from the mixture of **22b** and **23a**): δ_H (300 MHz; $CDCl_3$) 0.91 (9H, s, C*Me*$_3$), 1.79–2.25 (4H, m, $CHCH_2CH_2$), 4.22 (2H, t, *J*=6.97 Hz, NCH_2), 4.36 (1H, m, C*H*CH_2), 5.15 (2H, s, CH_2Ph), 5.56 (1H, s, C*H*Bu^t), 7.26–7.38 (5H, m, ArH), 7.83 and 8.36 (each 1H, s, adenine-H). 9-Ethyl-N^6-(2-methylpropionyl)adenine **23a** (data from the mixture of **22b** and **23a**): δ_H (300 MHz; CD_3OD) 1.26 (6H, d, *J*=6.96 Hz, CH*Me*$_2$), 1.51 (3H, t, *J*=7.33 Hz, CH_2CH_3) 2.91 (1H, septet, *J*=6.96 Hz, C*H*Me$_2$) and 4.31 (2H, q, *J*=7.33 Hz, CH_2CH_3), 8.37 and 8.63 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 15.6 and 19.7 (CH_3), 37.1 (*C*HMe$_2$), 40.3 (CH_2CH_3), 127.05 (ArC), 145.3 (C-2 or C-8), 150.6 (ArC), 152.9 (C-8 or C-2), 153.2 (ArC) and 178.23 (CO). 9-Ethyladenine **23b**:[21] Found: M^+ (EI) 163.0857. $C_7H_9N_5$ requires: M 163.0858; ν_{max} (KBr/cm^{-1}) 3268, 3191, 1675, 1601, 1573, 1480, 1415, 1327, 1308, 1249, 1214 and 1197; δ_H (300 MHz; $CDCl_3$) 1.62 (3H, t, *J*=7.32 Hz, CH_2CH_3), 4.26 (2H, q, *J*=7.32 Hz, CH_2CH_3), 6.09 (2H, s, NH), 7.86 and 8.37 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 15.55 (CH_3), 38.9 (CH_2), 121.0 (ArC), 140.0 (C-2 or C-8), 150.4 (ArC), 152.8 (C-8 or C-2) and 155.5 (ArC); *m/z* 163 (M^+, 60%), 135 (100) and 108 (70).

3.5.10. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{4-[N^6-(2-methylpropionyl)-9-adeninyl]butyl}oxazolidin-5-one 22c. Prepared following method C, using 9-(3-iodopropyl)-N^6-(2-methylpropionyl)adenine **21b** (0.31 g, 8.31 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (240 mg, 8.31 mmol), AIBN (ca. 10 mg) and tributyltin hydride (0.268 ml, 0.290 g, 9.97 mmol) to give the *conjugate adduct* **22c** as a colourless oil (102 mg, 23%) and N^6-(*2-methylpropionyl*)-*9-propyladenine* **23c** as a white gum (92.4 mg, 45%). (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{4-[N^6-(2-methylpropionyl)-9-adeninyl]butyl}oxazolidin-5-one **22c**: Found: MH^+ 537.2811. $C_{28}H_{36}N_6O_5$ requires: MH 537.2747; ν_{max} (KBr/cm^{-1}) 3343, 3055, 2975, 2875, 2359,

1790, 1718, 1615, 1586, 1462, 1402, 1372, 1349 and 1267; δ_H (300 MHz; $CDCl_3$) 0.94 (9H, s, C*Me*$_3$), 1.31 (6H, d, *J*=6.87 Hz, CH*Me*$_2$), 1.52–2.03 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$), 3.22 (1H, septet, *J*=6.87 Hz, C*H*Me$_2$), 4.18–4.26 (3H, m, C*H*CH$_2$ and NCH$_2$), 5.15 (2H, s, C*H*$_2$Ph), 5.54 (1H, s, C*H*Bu^t), 7.29–7.39 (5H, m, ArH), 7.92 and 8.55 (each 1H, s, 2-CH and 8-CH) and 8.72 (1H, s, CONH); δ_C (75 MHz; CD_3OD) 19.7 (CH*Me*$_2$), 24.4 (CHCH$_2$*C*H$_2$), 25.6 (C*Me*$_3$), 30.2 (CHCH$_2$CH$_2$*C*H$_2$), 33.65 (CH*C*H$_2$), 37.15 (*C*HMe$_2$), 37.8 (*C*Me$_3$), 44.75 (NCH$_2$), 58.1 (*C*HCH$_2$), 69.3 (*C*H$_2$Ph), 97.7 (*C*HBu^t), 129.5, 129.6 and 129.9 (ArCH), 137.0 (ArC), 143.0 (ArCH), 149.8 and 150.7 (ArC), 153.1 (ArCH), 153.4 (ArC), 157.8, 174.55 and 176.25 (CO); *m*/*z* 537 (MH$^+$, 100%), 515 (6), 379 (15), 260 (16), 202 (16) and 148 (25). N^6-(2-Methylpropionyl)-9-propyladenine **23c**: Found: MH$^+$ 248.1511. $C_{12}H_{17}N_5O$ requires: MH 248.1516; δ_H (300 MHz; CD_3OD) 0.94 (3H, t, *J*=7.15 Hz, CH$_2$C*H*$_3$), 1.38 (6H, d, *J*=6.86 Hz, CH*Me*$_2$), 1.88 (2H, sextet, *J*=7.15 Hz, CH$_2$C*H*$_2$CH$_3$), 3.31 (1H, septet, *J*=6.86 Hz, C*H*Me$_2$), 4.29 (2H, t, *J*=7.15 Hz, NC*H*$_2$CH$_2$), 8.38 and 8.62 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 11.3 (CH$_2$*C*H$_3$), 19.65 (CH*Me*$_2$), 24.2 (*C*H$_2$CH$_3$), 37.1 (*C*HMe$_2$), 46.7 (NCH$_2$), 124.0 (ArC), 145.75 (ArCH), 150.65 (ArC), 152.9 (ArCH), 153.4 (ArC) and 178.2 (CO); *m*/*z* 247 (M$^+$, 50%), 177 (60), 149 (58), 138 (100), 108 (30) and 84 (30).

3.5.11. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{4-[N^6-(2-methylpropionyl)-9-adeninyl]butyl}oxazolidin-5-one 22c and (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(9-adeninyl)butyl]oxazolidin-5-one 22d. Prepared following method D, using 9-(3-iodopropyl)-N^6-(2-methylpropionyl)adenine **21b** (1.86 g, 4.99 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (2.88 g, 9.97 mmol), tributyltin chloride (0.406 cm^3, 487 mg, 1.50 mmol), sodium cyanoborohydride (627 mg, 9.97 mmol) and AIBN (0.5 mmol) but heated at reflux for 16 h to yield the conjugate adduct **22c** as a colourless oil (0.31 g, 12%), *deacylated conjugate adduct* **22d** as a colourless oil (0.22 g, 14%), N^6-(2-methylpropionyl)-9-propyladenine **23c** as a white gum (0.13 g, 11%) and *9-propyladenine* **23d** also as a white gum (0.2 g, 23%). Data for (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-{4-[N^6-(2-methylpropionyl)-9-adeninyl]butyl}oxazolidin-5-one **22c** and for N^6-(2-methylpropionyl)-9-propyladenine **23c** were identical to those given above. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-[4-(9-adeninyl)butyl]oxazolidin-5-one **22d**: Found: MH$^+$ (ES$^+$) 467.2401. $C_{24}H_{30}N_6O_4$ requires: MH 467.2407; ν_{max} (KBr/cm^{-1}) 3323, 3300, 2874, 1790, 1718, 1645, 1600, 1481, 1396, 1348 and 1082; δ_H (300 MHz; CD_3OD) 0.91 (9H, s, C*Me*$_3$), 1.35–2.22 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$), 4.15 (2H, t, *J*=6.96 Hz, NC*H*$_2$), 4.32 (1H, t, *J*=6.97 Hz, C*H*CH$_2$), 5.10 (2H, s, C*H*$_2$Ph), 5.54 (1H, s, C*H*Bu^t), 7.24–7.35 (5H, m, ArH), 8.04 and 8.19 (each 1H, s, adenine-H); δ_C (75 MHz; CD_3OD) 24.4 (CHCH$_2$*C*H$_2$), 25.4 (C*Me*$_3$), 30.4 (CHCH$_2$CH$_2$*C*H$_2$), 33.7 (CH*C*H$_2$), 37.8 (*C*Me$_3$), 44.6 (NCH$_2$), 58.15 (*C*HCH$_2$), 69.3 (*C*H$_2$Ph), 97.7 (*C*HBu^t), 120.1 (ArC), 129.5, 129.6 and 129.9 (ArCH), 137.0 (ArC), 142.7 (ArCH), 150.7 (ArC), 153.7 (ArCH), 157.3 (ArC), 157.8 and 174.55 (CO); *m*/*z* 466 (M$^+$, 80%), 409 (100), 365 (40) and 287 (70). 9-Propyladenine **23d**:[21] Found: MH$^+$ (ES$^+$) 178.1091. $C_8H_{11}N_5$ requires: MH 178.1092; ν_{max} (film/cm^{-1}) 3408, 3055, 2985, 2361, 1636, 1474, 1418, 1327, 1266 and 896; δ_H (300 MHz; $CDCl_3$) 0.94 (3H, t, *J*=7.15 Hz, CH$_2$C*H*$_3$), 1.90 (2H, sextet, *J*=7.15 Hz, CH$_2$C*H*$_2$CH$_3$), 4.20 (2H, t, *J*=7.15 Hz, NCH$_2$), 6.23 (2H, s, NH$_2$), 7.82 and 8.35 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 11.2 (CH$_2$*C*H$_3$), 22.8 (*C*H$_2$CH$_3$), 46.6 (NCH$_2$), 119.6 (ArC), 140.45 (ArCH), 150.1 (ArC), 152.9 (ArCH) and 155.7 (ArC); *m*/*z* 177 (M$^+$, 55%), 148 (88), 135 (100) and 108 (60).

3.5.12. (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-(3-{N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]-9-guaninyl}propyl)oxazolidin-5-one 25. Prepared following method C, using 9-(2-iodoethyl)-N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]guanine **24b** (1.0 g, 2.02 mmol), (2*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-methyleneoxazolidin-5-one **11** (587 mg, 2.02 mmol), AIBN (ca. 10 mg) and tributyltin hydride (0.651 cm^3, 0.704 g, 2.42 mmol)) in toluene (200 cm^3) to give the *conjugate adduct* **25** as a yellow oil (279 mg, 21%) and *9-ethyl*-N^2-*acetyl*-O^6-*[2-(4-nitrophenyl)ethyl]guanine* **26** as a white solid (149 mg, 20%). (2*S*,4*S*)-3-Benzyloxycarbonyl-2-*tert*-butyl-4-(3-{N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]-9-guaninyl}propyl)oxazolidin-5-one **25**: Found: MH$^+$ (CI) 660.2787. $C_{33}H_{37}N_7O_8$ requires: MH 660.2782; δ_H (300 MHz; $CDCl_3$) 0.91 (9 H, s, C*Me*$_3$), 1.72–2.13 (4 H, m, CHC*H*$_2$C*H*$_2$), 2.53 (3H, s, CH$_3$CO), 3.32 (2H, t, *J*=6.70 Hz, C*H*$_2$Ar), 4.18 (2H, m, NCH$_2$), 4.37 (1H, t, *J*=7.54 Hz, C*H*CH$_2$), 4.79 (2H, t, *J*=6.70 Hz, OCH$_2$), 5.16 (2H, s, C*H*$_2$Ph), 5.56 (1H, s, C*H*Bu^t), 7.29–7.35 (5H, m, ArH), 7.50 (2H, d, *J*=8.62 Hz, ArH), 7.77 (1H, s, guanine-H), 7.85 (1H, s, CONH) and 8.19 (1H, d, *J*=8.62 Hz, ArH); δ_C (75 MHz; $CDCl_3$) 24.9 (C*Me*$_3$), 25.2 (CO*C*H$_3$), 26.6 (CHCH$_2$*C*H$_2$), 30.05 (CH*C*H$_2$), 35.1 (CH$_2$), 36.9 (*C*Me$_3$), 43.1 (NCH$_2$), 56.5 (*C*HCH$_2$), 66.9 (CH$_2$), 68.7 (*C*H$_2$Ph), 96.5 (*C*HBu^t), 117.75 (ArC), 123.8, 128.6, 128.7 and 128.8 (ArCH) 128.9 (ArC), 130.0 (ArCH), 134.9 (ArC), 141.6 (ArCH), 145.7, 146.9, 152.0 and 153.15 (ArC), 156.1, 160.6 and 172.25 (CO); *m*/*z* 660 (MH$^+$, 20%), 602 (100), 511 (60), 480 (40), 410 (40), 368 (30), 261 (70) and 193 (80). 9-Ethyl-N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]guanine **26**: Found: M$^+$ (EI) 370.1390. $C_{17}H_{18}N_6O_4$ requires: M 370.1390; ν_{max} (KBr/cm^{-1}); δ_H (300 MHz; $CDCl_3$) 3.60 (3H, t, *J*=7.30 Hz, CH$_2$C*H*$_3$), 2.53 (3H, s, CH$_3$CO), 3.31 (2H, t, *J*=6.60 Hz, CH$_2$Ar), 4.22 (2H, q, *J*=7.30 Hz, C*H*$_2$CH$_3$), 4.78 (2H, t, *J*=6.60 Hz, OCH$_2$), 7.50 (2H, d, *J*=8.56 Hz, ArH), 7.82 (1H, s, guanine-H), 7.87 (1H, s, CONH) and 8.18 (2H, d, *J*=8.56 Hz, ArH); *m*/*z* 370 (MH$^+$, 100%), 341 (20), 328 (70), 277 (50), 262 (40) and 234 (84).

3.6. General procedure for conversion of 4-substituted oxazolidinones into *N*-benzyloxycarbonyl-(*S*)-amino acids by base hydrolysis (method E)

The oxazolidinone conjugate adduct in THF–water (3:1 v/v, 40 cm^3) was cooled in an ice-bath and treated with lithium hydroxide monohydrate (2 mol equiv.). After stirring for 1 h at 0°C, water was added (50 cm^3) and the THF removed under reduced pressure. The solution was acidified to pH 2–3 by careful addition of 1 M hydrochloric acid, and the mixture was extracted with ethyl acetate (3×50 cm^3). The combined organic extracts were dried (MgSO$_4$), filtered, and evaporated to give the Z-amino acids.

3.6.1. (2*S*)-Benzyloxycarbonylamino-5-(3-benzoyl-1-thyminyl)pentanoic acid 27a. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[3-(3-benzoyl-1-thyminyl)propyl]oxazolidin-5-one **14a** (210 mg, 0.384 mmol) and lithium hydroxide monohydrate (0.768 mmol, 32 mg) to yield the title compound **27a** (0.170 g, 92%) as a thick colourless oil that was incompletely characterized; $[\alpha]_D^{25}=-13.3$ (*c*, 0.24 in EtOH); δ_H (300 MHz; $CDCl_3$) 1.62–1.96 (7H, m, CHC*H*$_2$C*H*$_2$ and CH=CC*H*$_3$], 3.65–3.74 (2H, t, *J*=6.61 Hz, NC*H*$_2$), 4.20 (1H, m, NHC*H*CH$_2$), 5.10 (2H, s, C*H*$_2$Ph), 5.58 (1H, d, *J*=7.90 Hz, N*H*CHCH$_2$), 7.09 (1 H, s, C*H*=CCH$_3$), 7.30–7.34 (5H, m, ArH), 7.44 (2H, m, ArH), 7.61 (1H, m, ArH), 7.87 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 12.3 (CH=C*C*H$_3$), 24.8 (CH$_2$*C*H$_2$CH$_2$), 29.2 (*C*H$_2$CH$_2$CH$_2$N), 48.1 (CH$_2$CH$_2$*C*H$_2$N), 53.0 (*C*HCH$_2$), 67.2 (*C*H$_2$Ph), 110.0 (CH=*C*CH$_3$), 125.3, 128.1, 128.2, 128.6, 129.0 and 129.2 (ArCH), 130.4 and 135.15 (ArC), 140.4 (*C*H=CCH$_3$), 150.0, 156.3, 163.3, 169.1 and 175.0 (CO).

3.6.2. (2*S*)-Benzyloxycarbonylamino-5-(1-thyminyl)pentanoic acid 27b. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[3-(1-thyminyl)-propyl]oxazolidin-5-one **14b** (210 mg, 0.474 mmol) and lithium hydroxide monohydrate (0.948 mmol, 40 mg) to yield the *title compound* **27b** (0.170 g, 96%) as a white amorphous solid, mp (decomp.) 199–100°C; $[\alpha]_D^{25}=-11.3$ (*c*, 0.32 in EtOH); Found: MNH_4^+ (ES^+) 393.1777. $C_{18}H_{21}N_3O_6$ requires: MNH_4 393.1774; ν_{max} (KBr/cm^{-1}) 3306, 3191, 3062, 3035, 2959, 1654, 1531, 1358, 1217, 1133, 1066 and 910; δ_H (300 MHz; $CDCl_3$) 1.55–1.84 (7H, m, CHC*H*$_2$C*H*$_2$ and CH=C(C*H*$_3$), 3.65–3.81 (2H, t, *J*=6.61 Hz, NC*H*$_2$), 4.27 (1H, m, NHC*H*CH$_2$), 5.02 (2H, s, C*H*$_2$Ph), 5.99 (1H, d, *J*=7.69 Hz, N*H*CHCH$_2$), 7.00 (1H, s, C*H*=CCH$_3$), 7.23–7.47 (5H, m, ArH), 10.25 (1H, s, CONH); δ_C (75 MHz; $CDCl_3$) 12.2 [CH=C(*C*H$_3$)], 21.1 (CH$_2$*C*H$_2$CH$_2$), 29.2 (*C*H$_2$CH$_2$CH$_2$N), 48.0 (CH$_2$CH$_2$*C*H$_2$N), 53.2 (*C*HCH$_2$), 67.0 (*C*H$_2$Ph), 110.95 (CH=*C*CH$_3$), 128.0, 128.2 and 128.5 (ArCH), 136.2 (ArC), 141.0 (*C*H=CCH$_3$), 151.5, 165.2, 156.4 and 151.5 (CO); *m*/*z* 393 (MNH_4^+, 100%), 376 (80), 349 (55), 332 (40) and 285 (70).

3.6.3. (2*S*)-Benzyloxycarbonylamino-6-(1-thyminyl)hexanoic acid 27c. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(1-thyminyl)-butyl]oxazolidin-5-one **14d** (310 mg, 0.678 mmol) and lithium hydroxide monohydrate (85 mg, 2.04 mmol) to yield the *title compound* **27c** as a thick colourless oil (230 mg, 87%); Found: MNH_4^+ 407.1940. $C_{19}H_{23}N_3O_6$ requires: MNH_4 407.1931; ν_{max} (film/cm^{-1}) 3430, 2959, 2348, 1657, 1546, 1501, 1467, 1129 and 1070; δ_H (300 MHz; $CDCl_3$) 1.21–1.88 (9H, m, CH(C*H*$_2$)$_3$CH$_2$N and CH=CC*H*$_3$), 3.66 (2H, m, NC*H*$_2$), 4.37 (1H, m, C*H*CH$_2$), 5.79 (1H, d, *J*=7.87 Hz, N*H*CH), 6.98 (1H, s, C*H*=CCH$_3$), 7.26–7.37 (5H, m, ArH) and 10.17 (1H, s, CONH); δ_C (75 MHz; DMSO-d_6) 12.2 (CH=C*C*H$_3$), 21.7, 28.35 and 31.7 (CH$_2$), 48.0 (NCH$_2$), 53.4 (*C*HCH$_2$), 67.0 (*C*H$_2$Ph), 110.9 (CH=*C*CH$_3$), 128.0, 128.15 and 128.5 (ArCH), 136.3 (ArC), 140.9 (*C*H=CCH$_3$), 151.45, 156.2, 165.1 and 175.6 (CO); *m*/*z* 390 (M^+, 75%), 363 (90), 346 (100), 299 (88) and 282 (80).

3.6.4. (2*S*)-Benzyloxycarbonylamino-5-(1-uracilyl)pentanoic acid 27d. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[3-(-1-thyminyl)propyl]-oxazolidin-5-one **18b** (2.34 g, 5.45 mmol) and lithium hydroxide monohydrate (687 mg, 16.4 mmol) to yield the *title compound* **27d** (1.35 g, 69%) as a thick oil; $[\alpha]_D^{25}=-71.6$ (*c*, 0.10 in EtOH); Found: MH^+ 362.1352. $C_{17}H_{19}N_3O_6$ requires: MH 362.1352; ν_{max} (film/cm^{-1}) 3426, 3056, 1660 and 1266; δ_H (300 MHz; CD_3OD) 1.55–1.82 (4H, m, CHC*H*$_2$C*H*$_2$), 3.65 (2H, t, *J*=6.43 Hz, NC*H*$_2$), 4.11 (1H, m, C*H*CH$_2$), 4.98 (2H, s, C*H*$_2$Ph), 5.52 (1H, d, *J*=7.80 Hz, CH=C*H*CO), 7.17–7.26 (5H, m, ArH) and 7.51 (1H, d, *J*=7.80 Hz, C*H*=CHCO); δ_C (75 MHz; CD_3OD) 21.5 (CH$_2$*C*H$_2$CH$_2$), 29.65 (*C*H$_2$CH$_2$CH$_2$N), 48.7 (CH$_2$CH$_2$*C*H$_2$N), 54.8 (*C*HCH$_2$), 67.6 (*C*H$_2$Ph), 102.3 (CH=*C*HCO), 128.8, 129.0 and 129.5 (ArCH), 138.2 (ArC), 147.15 (*C*H=CHCO), 152.8, 158.6, 166.7 and 175.4 (CO); *m*/*z* 361 (M^+, 100%), 344 (40), 318 (55) and 296 (20).

3.6.5. (2*S*)-Benzyloxycarbonylamino-6-(3-benzoyl-1-uracilyl)hexanoic acid 27e. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(3-benzoyl-1-uracilyl)butyl]oxazolidin-5-one **18c** (112.6 mg, 0.206 mmol) and lithium hydroxide monohydrate (17 mg, 0.412 mmol) to yield the *title compound* **27e** as a thick colourless oil (95 mg, 96%); Found: MNH_4^+ 497.2038. $C_{25}H_{25}N_3O_7$ requires: MNH_4 497.2036; ν_{max} (KBr/cm^{-1}) 3436, 2096, 1654 and 1266; δ_H (300 MHz, $CDCl_3$) 1.23–2.04 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$), 3.66 (2H, m, NC*H*$_2$), 4.32 (1H, m, C*H*CH$_2$), 5.02 (2H, s, C*H*$_2$Ph), 5.59 and 6.98 (each 1H, d, *J*=7.99 Hz, CH=CHCO), 7.13–7.32 (5H, m, ArH), 7.46 (2H, m, ArH) 7.72 (1H, m, ArH) and 7.87 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 21.8, 28.1 and 31.4 (CH$_2$), 48.6 (NCH$_2$), 53.3 (*C*HCH$_2$), 67.1 (*C*H$_2$Ph), 101.8 (CH=*C*HCO), 128.0, 128.2, 128.5, 129.2 and 130.3 (ArCH), 131.2 (ArC), 135.2 (ArCH), 136.0 (ArC), 144.6 (*C*H=CHCO), 149.7, 156.2, 162.8, 168.8 and 175.38 (CO). *m*/*z* 479 (M^+, 15%), 374 (20), 153 (25) and 121 (100).

3.6.6. (2*S*)-Benzyloxycarbonylamino-6-(1-uracilyl)hexanoic acid 27f. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(1-uracilyl)-butyl]oxazolidin-5-one **18d** (250 mg, 0.564 mmol) and lithium hydroxide monohydrate (47 mg, 1.13 mmol) to yield the *title compound* **27f** as a white solid (110 mg, 52%), mp (decomp.) 182–183°C; $[\alpha]_D^{25}=-150$ (*c*, 0.032 in EtOH); Found: MH^+ 376.1513. $C_{18}H_{21}N_3O_6$ requires: MH 376.1508; ν_{max} (KBr/cm^{-1}) 3213, 2364, 1715, 1688, 1541, 1466, 1364, 1257, 1200 and 1072; δ_H (300 MHz, DMSO-d_6) 1.15–1.56 (6H, m, CH C*H*$_2$C*H*$_2$C*H*$_2$), 3.62 (2H, t, *J*=6.79 Hz, NC*H*$_2$), 3.89 (1H, m, C*H*CH$_2$), 5.02 (2H, s, C*H*$_2$Ph), 5.50 (1H, d, *J*=7.85 Hz, CH=C*H*CO), 7.31–7.34 (5H, m, ArH), 7.55 (1H, d, *J*=7.78 Hz, CHN*H*) 7.61 (1H, d, *J*=7.85 Hz, C*H*=CHCO) and 11.21 (1H, s, uracil-NH); δ_C (75 MHz; $CDCl_3$) 22.4, 27.9 and 30.3 (CH$_2$), 47.1 (NCH$_2$), 53.6 (*C*HCH$_2$), 65.3 (*C*H$_2$Ph), 100.7 (CH=*C*HCO), 127.6, 127.7 and 128.2 (ArCH), 136.9 (ArC), 145.55 (*C*H=CHCO), 150.8, 156.0, 163.6 and 173.7 (CO); *m*/*z* 376 (MH^+, 80%), 332 (70), 285 (90), 268 (100), 244 (100) and 226 (50).

3.6.7. (2*S*)-Benzyloxycarbonylamino-5-[*N*^{6}-(2-methylpropionyl)-9-adeninyl]pentanoic acid 28a. Prepared following

method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-{3-[N^6-(2-methylpropionyl)-9-adeninyl]propyl}oxazolidin-5-one **22a** (0.91 g, 1.74 mmol) and lithium hydroxide monohydrate (219 mg, 5.23 mmol) to yield the *title compound* **28a** as a white amorphous solid (0.57 g, 72%), mp (decomp.) 147–150°C; Found: MH^+ 455.2043; $C_{22}H_{26}N_6O_5$ requires: MH 455.2052; δ_H (300 MHz; $CDCl_3$) 1.28 (6H, d, *J*=6.78 Hz, CH*Me*$_2$), 1.74–2.27 (4H, m, CHC*H*$_2$C*H*$_2$), 3.03 (1H, septet, *J*=6.78 Hz, C*H*Me$_2$), 4.36 (2H, m, NCH$_2$), 4.52 (1H, m, C*H*CH$_2$), 5.11 (2H, s, C*H*$_2$Ph), 5.73 (1H, d, *J*=7.51 Hz, CHN*H*), 7.33 (5H, m, ArH), 8.17 and 8.69 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; $CDCl_3$) 19.2 (CH*Me*$_2$), 25.5 (CHCH$_2$*C*H$_2$), 28.6 (CH*C*H$_2$), 36.0 (*C*HMe$_2$), 43.4 (NCH$_2$), 53.5 (*C*HCH$_2$), 67.1 (*C*H$_2$Ph), 122.0 (ArC), 128.1, 128.3 and 128.6 (ArCH), 136.8 (ArC), 143.1 (ArCH), 149.3 and 151.6 (ArC), 152.9 (ArCH), 156.2, 172.8 and 176.5 (CO); *m*/*z* 455 (M+H, 70%), 347 (100), 277 (30), 206 (62) and 196 (70)

3.6.8. (2*S*)-Benzyloxycarbonylamino-5-(9-adeninyl)pentanoic acid 28b. Prepared following a modified method E, using a mixture (see earlier) calculated to comprise (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[3-(9-adeninyl)propyl]-oxazolidin-5-one **22b** (580 mg, 1.28 mmol), 9-ethyl-N^6-(2-methylpropionyl)adenine **23a** (360 mg, 1.55 mmol) and lithium hydroxide monohydrate (162 mg, 3.85 mmol), and extracting with dichloromethane (3×20 cm^3) to yield 9-ethyl-N^6-(2-methylpropionyl)adenine **23a** (360 mg, 17% based on iodo-compound **21a**). Acidification and extraction of the aqueous layer as usual gave the *title compound* **28b** as a white solid (430 mg, 87%), mp 193–94°C; Found: MH^+ (ES^+) 385.1629. $C_{18}H_{20}N_6O_4$ requires: MH 385.1624; ν_{max} (KBr/cm^{-1}) 3395, 1611, 1542, 1459, 1408, 1323 and 1221; δ_H (300 MHz; CD_3OD) 1.61–2.05 (4H, m, CHC*H*$_2$C*H*$_2$), 4.22 (1H, m, C*H*CH$_2$), 4.43 (2H, m, NCH$_2$), 5.02 (2H, s, C*H*$_2$Ph), 7.23–7.31 (5H, m, ArH), 8.50 and 8.58 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 27.4 and 29.4 (CH$_2$), 45.1 (NCH$_2$), 54.8 (*C*HCH$_2$), 67.6 (*C*H$_2$Ph), 119.8 (ArC), 128.6, 128.9 and 129.4 (ArCH), 138.0 (ArC), 145.1 and 145.7 (ArCH), 150.0 and 151.2 (ArC), 158.5 and 174.0 (CO); *m*/*z* 385 (MH^+, 15%), 251 (5), 190 (46), 126 (70), 111 (100) and 84 (90).

3.6.9. (2*S*)-Benzyloxycarbonylamino-6-[N^6-(2-methylpropionyl)-9-adeninyl]hexanoic acid 28c. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-{4-[N^6-(2-methylpropionyl)-9-adeninyl]butyl}oxazolidin-5-one **22c** (0.32 g, 0.597 mmol) and lithium hydroxide monohydrate (84 mg, 0.199 mmol) to yield the *title compound* **28c** as a white amorphous solid (0.250 g, 89%), mp 147–150°C; Found: MH^+ (ES^+) 469.2208; $C_{23}H_{28}N_6O_5$ requires: MH 469.2199; ν_{max} (KBr/cm^{-1}) 3322, 3054, 2974, 2556, 1723, 1683, 1609, 1590, 1540, 1457, 1402, 1350, 1072, 1050 and 968; δ_H (300 MHz; CD_3OD) 1.28 (6H, d, *J*=6.88 Hz, CH*Me*$_2$), 1.34–2.21 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$), 2.91 (1H, septet, *J*=6.88 Hz, C*H*Me$_2$), 4.14 (1H, m, C*H*CH$_2$), 4.31 (2H, t, *J*=6.96 Hz, NCH$_2$), 5.04 (2H, s, C*H*$_2$Ph), 7.26–7.32 (5H, m, ArH), 8.35 and 8.63 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 19.2 (CH*Me*$_2$), 23.9, 28.9 and 32.11 (CH$_2$), 37.1 (*C*HMe$_2$), 44.8 (NCH$_2$), 53.73 (*C*HCH$_2$), 67.6 (*C*H$_2$Ph), 123.75 (ArC), 128.7, 128.9 and 129.4 (ArCH), 138.15 (ArC), 145.6 (ArCH), 150.5 (ArC), 152.9 (ArCH), 153.3 (ArC), 158.6, 175.7 and 178.2 (CO); *m*/*z* 469 (MH^+, 100%), 399 (40), 361 (50), 335 (30) and 291 (42).

3.6.10. (2*S*)-Benzyloxycarbonylamino-6-(9-adeninyl)hexanoic acid 28d. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-[4-(9-adeninyl)-butyl]oxazolidin-5-one **22d** (0.27 g, 0.579 mmol) and lithium hydroxide monohydrate (73 mg, 1.74 mmol) to yield the *title compound* **28d** as a white amorphous gum (0.197 g, 86%); Found: MH^+ (ES^+) 399.1778. $C_{19}H_{22}N_6O_4$ requires: MH 399.1781; ν_{max} (KBr/cm^{-1}) 3327, 2971, 2361, 2342, 1704, 1515, 1266 and 1202; δ_H (300 MHz; CD_3OD) 1.38–1.98 (6H, m, CHC*H*$_2$C*H*$_2$C*H*$_2$), 4.14 (1H, m, C*H*CH$_2$), 4.25 (2H, t, *J*=6.96 Hz, NC*H*$_2$), 5.06 (2H, s, C*H*$_2$Ph), 7.25–7.33 (5H, m, ArH), 8.18 and 8.26 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 23.9 (CHCH$_2$*C*H$_2$), 30.45 (CHCH$_2$CH$_2$*C*H$_2$), 32.1 (CH*C*H$_2$), 44.9 (NCH$_2$), 55.0 (*C*HCH$_2$), 67.6 (*C*H$_2$Ph), 126.15, 128.8, 129.0 and 129.5 (ArCH), 138.2, 139.2 and 143.9 (ArC), 150.2 (ArCH), 155.0 (ArC),158.6 and 176.15 (CO); *m*/*z* 399 (MH^+, 100%), 355 (15), 291 (60), 265 (60) and 247 (40).

3.6.11. (2*S*)-Benzyloxycarbonylamino-5-{N^2-acetyl-O^6-[2-(4-nitrophenyl)ethyl]-9-guaninyl}pentanoic acid 29. Prepared following method E, using (2*S*,4*S*)-3-benzyloxycarbonyl-2-*tert*-butyl-4-(3-{N^2-acetyl-O^6-[2-(4-nitrophenyl)-ethyl]-9-guaninyl}propyl)oxazolidin-5-one **25** (60 mg, 0.091 mmol) and lithium hydroxide (10 mg, 0.18 mmol) to yield the *title compound* **29** as a yellow solid (47 mg, 87%), mp 143–144°C; Found: MH^+ 592.2156. $C_{28}H_{29}N_7O_8$ requires; MH 592.2154; ν_{max} (KBr/cm^{-1}) 3466, 2961, 2363, 2345, 1719, 1687, 1664, 1610, 1518, 1345 and 1236; δ_H (300 MHz; DMSO-d_6) 1.45–1.85 (4H, m, CHC*H*$_2$C*H*$_2$), 2.20 (3H, s, CH$_3$CO), 3.35 (2H, t, *J*=6.70 Hz, CH$_2$Ar), 3.60 (1H, m, C*H*CH$_2$), 4.20 (2H, m, NCH$_2$), 4.75 (2H, t, *J*=6.70 Hz, OCH$_2$), 4.97 (2H, br s, C*H*$_2$Ph), 6.43 (1H, s, guanine-H), 7.20–7.40 (5H, m, ArH), 7.60 and 8.19 (each 2H, d, *J*=8.60 Hz, ArH) and 10.35 (1H, s, CONH); *m*/*z* 592 (MH^+, 60%), 562 (40), 546 (38), 516 (100), 484 (40) and 428 (65).

3.7. General procedure for removal of a benzyloxycarbonyl group (Z) by hydrogenolysis to afford amino acids (method F)

The *Z*-protected amino acid (1 mol equiv.) in ethanol (140 cm^3) and water (60 cm^3) was degassed with a stream of argon for 15 min. Palladium-charcoal catalyst (10 mol%, 0.1 mol equiv.) was added and a stream of hydrogen was passed through the solution under vigorous stirring for 8h. The solution was then again degassed with a stream of argon for 15 min, and the catalyst was filtered and washed with a small amount of ethanol and water. The solvents were removed under reduced pressure, toluene (20 cm^3) was added and removed under reduced pressure (3 times) to eliminate traces of water. The crude residue was dried under vacuum to yield the free amino acid.

3.7.1. (2*S*)-Amino-5-(1-thyminyl)pentanoic acid 27g. Prepared following method F, using (2*S*)-benzyloxycarbonylamino-5-(1-thyminyl)pentanoic acid **27b** (1.61 g, 4.29 mmol) and Pd–C (200 mg) to yield the *title compound*

27g as a white solid (760 mg, 74%), mp (decomp.) 124–125°C; Found: MH^+ (ES^+) 242.1144. $C_{10}H_{15}N_3O_4$ requires: MH 242.1141; ν_{max} (KBr/cm^{-1}) 3448, 3153, 3034, 2362, 1685, 1674, 1600, 1475, 1460, 1420 and 1220; δ_H (300 MHz, D_2O) 1.57–1.91 (7H, m, $CHCH_2CH_2$ and $CH{=}CCH_3$), 3.57–3.71 (2H, m, NCH_2), 3.85 (1H, t, J=5.50 Hz, $CHCH_2$) and 7.29 (1 H, s, $CH{=}CCH_3$); δ_C (75 MHz; D_2O) 11.7 ($CH{=}CCH_3$), 24.3 ($CHCH_2CH_2CH_2$), 27.2 ($CHCH_2CH_2CH_2$), 48.2 (CH_2N), 53.45 ($CHCH_2$), 111.3 (ArC), 143.4 ($CH{=}CCH_3$), 152.7, 167.3 and 173.1 (CO); *m/z* 242 (MH^+, 50%), 198 (100), 169 (53), 146 (52), 127 (54), 113 (44) and 70 (70).

3.7.2. (2*S*)-Amino-6-(1-thyminyl)hexanoic acid 27h. Prepared following method F, using (2*S*)-benzyloxycarbonylamino-6-(1-thyminyl)hexanoic acid **27c** (1.32 g, 3.39 mmol) and Pd–C (300 mg) to yield the *title compound* **27h** as a white solid (680 mg, 79%), mp 219–220°C; Found: MH^+ (ES^+) 256.1296. $C_{11}H_{17}N_3O_4$ requires: MH 256.1297; ν_{max} (KBr/cm^{-1}) 3432, 3050, 2955, 2362, 1685, 1476, 1413, 1356 and 1130; δ_H (300 MHz; D_2O) 1.21–1.29 (2H, m, $CHCH_2CH_2$), 1.52–1.62 (2H, apparent quintet, J=7.36 Hz, $CHCH_2CH_2CH_2$), 1.66–1.75 (5H, m, $CHCH_2$ and $CH{=}CCH_3$), 3.48 (1H, t, J=6.61 Hz, $CHCH_2$), 3.61 (2H, t, J=6.98 Hz, NCH_2) and 7.33 (1 H, s, $CH{=}CCH_3$); δ_C (75 MHz; D_2O) 12.1 ($CH{=}CCH_3$), 22.2 ($CHCH_2CH_2CH_2$), 28.6 ($CHCH_2CH_2CH_2$), 30.9 ($CHCH_2$), 48.9 (CH_2N), 55.2 ($CHCH_2$), 111.5 (ArC), 144.0 ($CH{=}CCH_3$), 153.2, 167.9 and 175.6 (CO); *m/z* 256 (MH^+, 70%), 212 (100), 197 (30), 183 (34), 169 (60), 146 (28), 127 (28) and 84 (42).

3.7.3. (2*S*)-Amino-5-(1-uracilyl)pentanoic acid 27i. Prepared following method F, using (2*S*)-benzyloxycarbonylamino-5-(1-uracilyl)pentanoic acid **27d** (1.23 g, 3.41 mmol) and Pd–C (150 mg) to yield the *title compound* **27i** as a white solid (580 mg, 75%), mp 208–209°C; Found: M−H (ES^-) 226.0833. $C_9H_{13}N_3O_4$ requires: M-H 226.0828; ν_{max} (KBr/cm^{-1}) 3513, 3457, 3090, 1692, 1673, 1609, 1418, 1387, 1249 and 1237; δ_H (300 MHz; D_2O) 1.47–1.82 (4H, m, $CHCH_2CH_2$), 3.59 (1H, t, J=5.86 Hz, $CHCH_2$), (2H, m, NCH_2), 5.67 and 7.48 (each 1H, d, J=7.81 Hz, CH=CH); δ_C (75 MHz; D_2O) 24.6 ($CHCH_2CH_2$), 27.9 ($CHCH_2$), 48.9 (CH_2N), 54.9 ($CHCH_2$), 102.2 and 147.8 (CH=CH), 152.9, 167.5 and 174.8 (CO); *m/z* 226 (M-H, 58%), 183 (20), 153 (30), 121 (100), 11 (40) and 90 (60).

3.7.4. (2*S*)-Amino-6-(1-uracilyl)hexanoic acid 27j. Prepared following method F, using (2*S*)-benzyloxycarbonylamino-6-(1-uracilyl)hexanoic acid **27f** (110 mg, 0.293 mmol) and Pd–C (30 mg) for 5 h to yield the *title compound* **27j** as a white solid (60 mg, 90%), mp (decomp.) 187–205°C, that was incompletely characterized; ν_{max} (KBr/cm^{-1}); δ_H (300 MHz, D_2O) 1.26–1.93 (6H, m, $CHCH_2CH_2CH_2$), 3.67 (1H, t, J=6.43 Hz, $CHCH_2$), 3.74 (2H, t, J=7.33 Hz, NCH_2), 5.75 and 7.58 (each 1H, d, J=7.81 Hz, CH=CH); δ_C (75 MHz; D_2O) 22.1 ($CHCH_2CH_2$), 28.5 ($CHCH_2CH_2CH_2$), 30.8 ($CHCH_2$), 49.3 (CH_2N), 55.4 ($CHCH_2$), 102.3 and 148.1 (CH=CH), 153.2, 167.7 and 175.4 (CO).

3.7.5. (2*S*)-Amino-5-[N^6-(2-methylpropionyl)-9-adeninyl]-pentanoic acid 28e. Prepared following method F, using (2*S*)-benzyloxycarbonylamino-5-[N^6-(2-methylpropionyl)-9-adeninyl]pentanoic acid **28a** (190 mg, 0.419 mmol) and Pd–C (200 mg) to yield the *title compound* as a white solid (100 mg, 75%), mp (decomp.) 110–112°C; Found: MH^+ (ES^+) 321.1680. $C_{14}H_{20}N_6O_3$ requires: MH 321.1675; ν_{max} (KBr/cm^{-1}) 3386, 2971, 2934, 2377, 1794, 1774, 1611, 1459, 1219 and 966; δ_H (300 MHz; D_2O) 1.13 (6H, d, J=6.97 Hz, $CHMe_2$), 1.58 (2H, m, $CHCH_2CH_2$), 1.77 (2H, m, $CHCH_2$), 2.75 (1H, septet, J=6.97 Hz, $CHMe_2$), 3.35 (1H, m, $CHCH_2$), 4.22 (2H, m, NCH_2), 8.27 and 8.53 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; CD_3OD) 26.9 ($CHCH_2CH_2$), 29.3 ($CHCH_2$), 37.1 ($CHMe_2$), 44.65 (NCH_2), 49.0 ($CHCH_2$), 124.5 (ArC), 128.8 and 129.4 (ArCH), 145.7 and 151.0 (ArC), 153.0 and 178.0 (CO); *m/z* 321 (MH^+, 35%), 206 (30), 165 (55), 152 (65), 133 (64) and 115 (72).

3.7.6. (2*S*)-Amino-6-[N^6-(2-methylpropionyl)-9-adeninyl]-hexanoic acid 28f. Prepared following method F, using (2*S*)-benzyloxycarbonylamino-6-[N^6-(2-methylpropionyl)-9-adeninyl]hexanoic acid **28c** (230 mg, 0.491 mmol) and Pd–C (200 mg) to yield the *title compound* as a white hygroscopic solid (100 mg, 61%); Found: MH^+ (ES^+) 335.1824. $C_{15}H_{22}N_6O_3$ requires: MH 335.1831; δ_H (300 MHz; D_2O) 0.60 (6H, d, J=6.87 Hz, $CHMe_2$), 1.28 (2H, m, $CHCH_2CH_2$), 1.06–1.31 (4H, m, $CHCH_2$ and NCH_2CH_2), 2.20 (1H, septet, J=6.87 Hz, $CHMe_2$), 3.07 (1H, t, J=5.86 Hz, $CHCH_2$), 3.61 (2H, t, J=7.15 Hz, NCH_2), 7.66 and 7.87 (each 1H, s, 2-CH and 8-CH); δ_C (75 MHz; D_2O) 19.25 ($CHCH_2CH_2$), 22.4 ($NCH_2CH_2CH_2$), 30.7 ($CHCH_2$), 36.7 ($CHMe_2$), 44.5 (NCH_2), 55.3 ($CHCH_2$), 123.6 (ArC), 146.1 (ArCH), 149.2 (ArC), 152.0 (ArCH) 152.2 (ArC), 176.5 and 181.2 (CO); *m/z* 335 (MH^+, 80%), 291 (80), 265 (100), 221 (90), 204 (60), 178 (100), 149 (40) and 136 (80).

3.7.7. (2*S*)-Amino-6-(5,6-dihydro-1-uracilyl)hexanoic acid 30. This was prepared following method F, using (2*S*)-benzyloxycarbonylamino-6-(1-uracilyl)hexanoic acid **27f** (150 mg, 0.40 mmol) and Pd–C (100 mg) but for 16 h to yield the *title compound* **30** as a white solid (86 mg, 88%), mp (decomp.) 219–220°C; Found: MH^+ (ES^+) 244.1297. $C_{10}H_{17}N_3O_4$ requires: MH 244.1297; ν_{max} (KBr/cm^{-1}) 3484, 2954, 2931, 2344, 2362, 1729, 1466, 1288, 1275, 1044 and 971; δ_H (300 MHz, D_2O) 1.10–1.75 (6H, m, $CHCH_2CH_2CH_2$), 2.63 (2H, t, J=7.16 Hz, CH_2CO), 3.22 (2H, t, J=7.33 Hz, CH_2N), 3.35 (2H, t, J=7.16 Hz, CH_2CH_2CO) and 3.94 (1H, m, $CHCH_2$); δ_C (75 MHz; D_2O) 22.5 ($CHCH_2CH_2$), 27.1 ($CHCH_2CH_2CH_2$), 30.7 (CH_2CO), 31.5 ($CHCH_2$), 42.5 (CH_2CH_2CO), 47.5 (CH_2N), 51.4 ($CHCH_2$), 155.0 and 175.1 (CO); *m/z* 244 (MH^+, 18%), 198 (20), 155 (30), 141 (40), 116 (34) and 84 (100). Traces of (2*S*)-amino-6-(1-uracilyl)hexanoic acid **27f** were also isolated.

3.8. General method for conversion of an amino acid into a (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (Mosher amide) (method G)

Acetyl chloride (10 mol equiv.) was added dropwise at 0°C to the amino acid (~50 mg) stirred in ethanol (50 cm^3). The mixture was then stirred overnight at 25°C, heated at reflux for 4 h, cooled and the solvent evaporated under reduced pressure to give the ethyl ester hydrochloride salt which was further dried under vacuum overnight.

(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPA-Cl) was added dropwise at room temperature to the ester hydrochloride stirred in dichloromethane (4 cm^3) and triethylamine (4 cm^3). The mixture was stirred overnight, water (20 cm^3) was added and the mixture extracted with ethyl acetate (3×20 cm^3). The combined ethyl acetate layers were washed with saturated sodium bicarbonate solution (3×10 cm^3), dried with magnesium sulphate and evaporated under reduced pressure. The crude material was then purified by column chromatography (ethyl acetate/hexane) to yield the desired Mosher amide.

3.8.1. Ethyl (2*S*)-amino-5-(1-thyminyl)pentanoate (*S*)-MTPA amide. Prepared following method G from amino acid **27i** to yield the *title compound* as a colourless oil; Found: MH^+ (ES^+) 486.1856. $C_{22}H_{26}F_3N_3O_6$ requires: MH 486.1852; δ_H (300 MHz, $CDCl_3$) major and minor* diastereoisomers: 1.30 and 1.26* (3H, t, *J*=7.06 Hz, CH_2CH_3), 1.53–1.96 (7H, m, $CHCH_2CH_2$ and $CH{=}CCH_3$), 3.45 and 3.35* (3 H, s, OCH_3), 3.56–3.78 (2H, m, NCH_2), 4.24 (2H, q, *J*=7.06 Hz, CH_2CH_3), 4.66 (1H, dt, *J*=4.60 and 8.26 Hz, $CHCH_2$), 6.85 and 7.05* (1H, s, $CH{=}CCH_3$), 7.35–7.44 (4H, m, NHCH and ArH), 7.54–7.57 (2H, m, ArH), 9.04 and 9.00* (1H, s, ArNH); δ_C (75 MHz; $CDCl_3$) major diastereomer 12.3 ($CH{=}CCH_3$), 14.1 (CH_2CH_3), 24.9 ($CHCH_2CH_2$), 29.5 ($CHCH_2CH_2$), 47.4 (NCH_2), 51.1 ($CHCH_2$), 55.3 (OCH_3), 62.1 (CH_2CH_3), 110.8 ($CH{=}CCH_3$), 127.2, 128.6 and 129.6 (ArCH), 132.8 (ArC), 140.2 ($CH{=}CCH_3$), 150.8, 164.2, 166.7 and 171.2 (CO); *m/z* 486 (M^+, 10%), 296 (100), 268 (20), 222 (90), 189 (70) and 105 (80); δ_F (376 MHz, $CDCl_3$) minor diastereoisomer −69.074, major diastereoisomer −68.790, ee: 85%.

3.8.2. Ethyl (2*S*)-amino-6-(1-thyminyl)hexanoate (*S*)-MTPA amide and ethyl (2*S*)-amino-6-(1-thyminyl)hexanoate (*S*)-MTPA diamide. Prepared following method G from amino acid **27j** to yield the *title monoamide* and the *title diamide*, both as colourless oils. Ethyl (2*S*)-amino-6-(1-thyminyl)hexanoate (*S*)-MTPA amide: Found: MH^+ (ES^+) 500.2019. $C_{23}H_{28}F_3N_3O_6$ requires: MH 500.2008; δ_H (300 MHz; $CDCl_3$) major and minor* diastereoisomers: 1.28 and 1.21* (3H, t, *J*=7.15 Hz, CH_2CH_3), 1.59–1.97 (9H, m, $CHCH_2CH_2CH_2$ and $CH{=}CCH_3$), 3.34* and 3.54 (3H, s, OCH_3), 3.61 (2H, t, *J*=6.79 Hz, NCH_2), 4.16 (2H, q, *J*=7.15 Hz, CH_2CH_3), 4.56 (1H, dt, *J*=5.13 and 8.15 Hz, $CHCH_2$), 6.89 and 6.98* (1H, s, $CH{=}CCH_3$), 7.10 (1H, d, *J*=8.15 Hz, NHCH), 7.31–7.36 (3H, m, ArH), 7.61–7.63 (2H, m, ArH) and 8.51 (1H, s, ArNH); δ_C (75 MHz; $CDCl_3$) major diastereomer 12.3 ($CH{=}CCH_3$), 14.1 (CH_2CH_3), 22.1, 28.3 and 31.6 (CH_2), 47.8 (NCH_2), 51.7 ($CHCH_2$), 55.3 (OCH_3), 61.84 (CH_2CH_3), 110.8 ($CH{=}CCH_3$), 127.2, 128.5 and 129.6 (ArCH), 133.0 (ArC), 140.1 ($CH{=}CCH_3$), 150.7, 163.9, 166.45 and 171.5 (CO); *m/z* 499 (M^+, 100%), 426 (70)374 (30), 354 (20), 338 (40) and 324 (28). δ_F (376 MHz, $CDCl_3$) minor diastereoisomer −69.325, major diastereoisomer −68.869, ee: 88%. Ethyl (2*S*)-amino-6-(1-thyminyl)hexanoate (*S*)-MTPA diamide: Found: MNH_4^+ (ES^+) 733.2668. $C_{33}H_{35}F_6N_3O_8$ requires: MNH_4 733.2672; δ_H (300 MHz; $CDCl_3$) major and minor* diastereoisomers: 1.26 and 1.22* (3H, t, *J*=7.15 Hz, CH_2CH_3), 1.61–1.94 (9H, m, $CHCH_2CH_2CH_2$ and $CH{=}CCH_3$), 3.34* and 3.45 and 3.49 (6H, s, 2×OCH_3), 3.61 (2H, t, *J*=6.79 Hz, NCH_2), 4.21 (2H, q, *J*=7.15 Hz, CH_2CH_3), 4.62 (1H, dt, *J*=5.13 and 8.17 Hz, $CHCH_2$), 6.91 and 6.99* (1H, s, $CH{=}CCH_3$), 7.17 (1H, d, *J*=8.17 Hz, NHCH), 7.26–7.45 (6H, m, ArH), 7.54–7.57 (2H, m, ArH) and 7.68–7.71 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 12.3 ($CH{=}CCH_3$), 14.1 (CH_2CH_3), 22.1, 28.2 and 31.85 (CH_2), 48.4 (NCH_2), 51.6 ($CHCH_2$), 54.7 and 55.3 (OCH_3), 61.9 (CH_2CH_3), 110.55 ($CH{=}CCH_3$), 127.3, 128.3, 128.5, 128.6 and 129.65 (ArCH), 132.8 and 131.2 (ArC), 139.9 ($CH{=}CCH_3$), 149.2, 162.6, 166.4, 171.5 and 171.9 (CO); *m/z* 716 (M^+, 16%), 517 (100), 500(80), 468 (50), 391 (20), 337 (65) and 286 (70). δ_F (376 MHz; $CDCl_3$) minor diastereoisomer −69.206 and −70.136, major diastereoisomer −68.830 and −70.017, ee: 88%.

3.8.3. Ethyl (2*S*)-amino-5-(1-uracilyl)pentanoate (*S*)-MTPA amide. Prepared following method G from amino acid **27l** to yield the *title compound* as a colourless oil; Found: MNH_4^+ (ES^+) 489.1959. $C_{21}H_{24}F_3N_3O_6$ requires: MNH_4 489.1961; δ_H (300 MHz, $CDCl_3$) major and minor* diastereoisomer: 1.30 and 1.26* (3H, t, *J*=7.06 Hz, CH_2CH_3), 1.50–1.96 (4H, m, $CHCH_2CH_2$), 3.45 and 3.34* (3H, s, OCH_3), 3.48–3.77 (2H, m, NCH_2), 4.23 (2H, q, *J*=7.06 Hz, CH_2CH_3), 4.67 (1H, m, $CHCH_2$), 5.54 and 5.69* (1H, d, *J*=7.78 or 7.88* Hz, $CH{=}CHCO$), 6.92 and 7.21* (1H, *J*=7.78 or 7.88* Hz, $CH{=}CHCO$), 7.34–7.59 (5H, m, ArH) and 9.38 (1H, s, ArNH); δ_C (75 MHz; $CDCl_3$) major diastereomer 14.1 (CH_2CH_3), 24.6 ($CHCH_2CH_2$), 29.5 ($CHCH_2$), 47.9 (NCH_2), 50.85 ($CHCH_2$), 55.2 (OCH_3), 62.2 (CH_2CH_3), 101.9 ($CH{=}CHCO$), 128.55, 128.7 and 129.5 (ArCH), 132.6 (ArC), 143.9 (ArCH), 149.1, 161.7, 166.8 and 171.1 (CO); *m/z* 472 (MH^+, 65%), 398 (100), 346 (80) and 296 (28); δ_F (376 MHz; $CDCl_3$) minor diastereoisomer −69.737, major diastereoisomer −69.122, ee: 90%.

3.8.4. Ethyl (2*S*)-amino-6-(1-uracilyl)hexanoate (*S*)-MTPA amide. Prepared following method G from amino acid **27n** to yield the *title compound* as a colourless oil, incompletely characterized; Found: MNH_4^+ 491.2117. $C_{21}H_{24}N_3O_6F_3$ requires: MNH_4 491.2111; δ_F (376 MHz, $CDCl_3$) minor diastereoisomer −69.134, major diastereoisomer −68.869, ee: 89%.

3.8.5. Ethyl (2*S*)-amino-6-(9-adeninyl)hexanoate (*S*)-MTPA diamide. Prepared following method G from amino acid **28f** to give the *title compound*; Found: MH) (ES^+) 725.2516. $C_{33}H_{34}N_6O_6F_6$ requires: MH 725.2522; δ_H (300 MHz; $CDCl_3$) minor* and major diastereoisomers: 1.26* and 1.29 (3H, t, *J*=7.15 Hz, CH_2CH_3), 1.58–1.91 (6H, m, $CHCH_2CH_2CH_2$), 3.32* and 3.46 (3H, s, OCH_3), 3.47 and 3.52* (3H, s, OCH_3), 3.76 (2H, m, NCH_2), 4.22 (2H, q, *J*=7.15 Hz, CH_2CH_3), 4.58 (1H, dt, *J*=5.32 and 8.17 Hz, $NHCHCH_2$), 7.13 (1H, d, *J*=8.17 Hz, NHCH), 7.37–7.67 (10H, m, ArH), 7.92 and 8.00* (1H, s, ArH), 8.78 and 8.80* (1H, s, ArH) and 9.60 (1H, s, NH); δ_C (75 MHz; $CDCl_3$) major diastereomer 14.2 (CH_2CH_3), 22.4, 29.3 and 31.7 (CH_2), 47.7 (NCH_2), 51.6 ($CHCH_2$), 55.3 and 55.6 (OCH_3), 122.8 (ArC), 127.2, 127.7, 128.4, 128.5, 128.75 and 129.6 (ArCH), 131.7 and 132.9 (ArC), 143.1 (ArCH), 148.2 and 152.2 (ArC), 152.5 (ArCH), 163.7, 166.4 and 171.4 (CO); *m/z* 725 (MH^+, 100%), 535 (5), 189 (20) and 105 (8); δ_F (376 MHz; $CDCl_3$) major diastereoisomer

−68.871 and −69.423; minor diastereoisomer −69.181 and −69.277; ee. 86%.

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