Design and Synthesis of Novel Peptide Nucleic Acid Monomers

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All of the four nucleobases in DNA have replaced the 4-hydroxy group of *N*-[2-(*tert*-butoxycarbonylaminomethyl)-*trans*-4-hydroxy] tetrahydropyrrole acetic acid methyl ester with *cis*-stereochemistry. An efficient route for the synthesis of *N*-[2-(*tert*-butoxycarbonylaminomethyl)-*trans*-4-hydroxy]-tetrahydropyrrole acetic acid methyl ester has been developed. Starting with this intermediate, the protected monomers were synthesized by the Mitsunobu reaction or *via* its tosylate.

Keywords Oligonucleotide, peptide nucleic acids, design, synthesis

Introduction

Oligonucleotides are potentially useful for the regulation of genetic expression by binding with DNA or *m*RNA. The principle, which is known as the antisense principle,[1] provides a way to control protein synthesis at the nucleic acid level. Furthermore, a highly specific inhibition can be achieved by a relatively short antisense oligonucleotide, whose sequence can be derived directly from the sequence of the target nucleic acids. However, to put the antisense principle into practice, the antisense oligonucleotides must be sufficiently stable under physiological conditions, able to pass through the cell membrane, and bind specifically and tightly with the target nucleic acids. Because natural oligonucleotides are readily degraded by nucleases *in vivo*, there is considerable interest in synthetic oligonucleotide analogues, which are stable under physiological conditions. Recently, there has been interest in oligonucleotide analogues in which the sugar phosphate backbone is replaced by a peptide chain[2] after the success of the so-called peptide nucleic acids (PNA).[3,4]

Peptide nucleic acids were first described by Nielsen *et al.* in 1991.[4a] Peptide nucleic acids had advantages over several other chemical modifications of oligonucleotides. Firstly, peptide nucleic acids showed the high bio-stability. They are neither degraded by nucleases nor by proteases. Secondly, peptide nucleic acids showed higher binding capability with DNA or RNA. Thirdly, the protected oligomers can be assembled by well established solid phase peptide synthesis protocols.

In this study, we designed a novel peptide nucleic acid analogue of DNA. The designated PNA composes of alternate *N*-(2-aminomethyl-4-nucleobase) tetrahydropyrrole acetic acid units. The sugar phosphate backbone of a nucleic acid consists of a repeating unit of six atoms. Its configuration and conformation are constrained by the *D*-ribose or 2′-deoxy-*D*-ribose ring. We intend to use the *N*-(aminomethyl-4-nucleobase)tetrahydropyrrole acid unit to replace the *D*-ribose ring in DNA, therefore design the novel peptide nucleic acid monomers (Fig. 1).

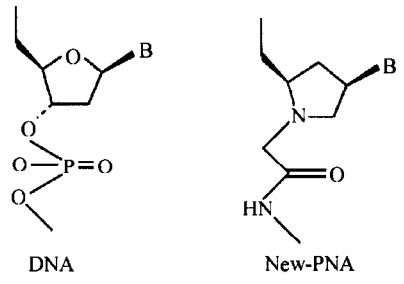

Fig. 1 Comparison of structure of the novel peptide nucleic acids and DNA.

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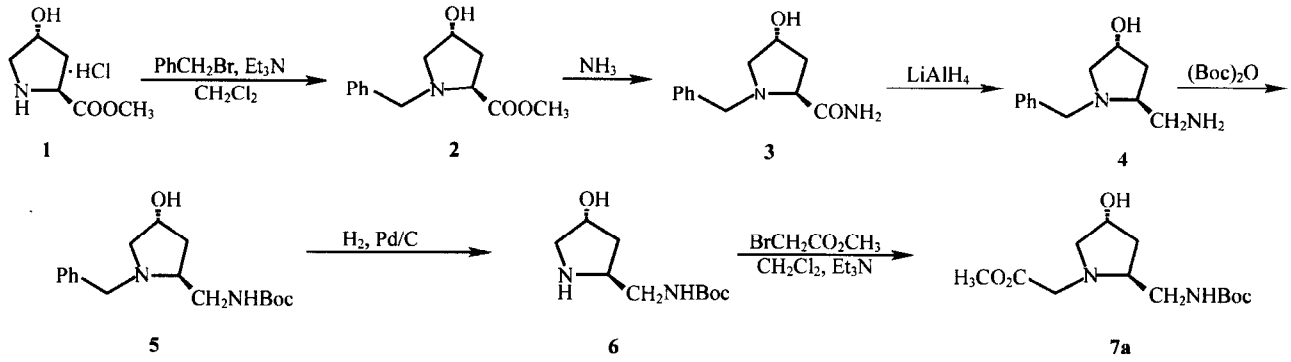
Results and discussion

4-Hydroxy-*trans*-proline methyl ester (**1**) reacted with phenylbromide to give the *N*-phenyl-4-hydroxy-*trans*-proline methyl ester (**2**) in 61% yield. The methyl ester **2** was then treated with ammonia solution (25%) to give *N*-phenyl-4-hydroxy-*trans*-2-tetrahydropyrrole formamide (**3**) in 90% yield. Compound **3** was reduced by lithium aluminum hydride in anhydrous THF to give *N*-phenyl-5-aminomethyl-*trans*-tetrahydropyrrol-3-ol (**4**) in 76% yield. The reaction of **4** with di-*tert*-butyldicarbonate $(Boc)_2O$ in chloroform gave *N*-phenyl-5-(*tert*-butoxylcarbonylaminomethyl) tetrahydropyrrol-3-ol (**5**) in 77% yield. Compound **5** was hydrogenated to give 5-(*tert*-butoxylcarbonylaminomethyl) tetrahydropyrrol-3-ol (**6**) in 69% yield. Treatment of **6** with bromoacetic acid methyl ester gave the intermediate *N*-[2-(*tert*-butoxylcarbonylaminomethyl)-*trans*-4-hydroxy] tetrahydropyrrole acetic acid methyl ester (**7a**) in 65% yield (Scheme 1).

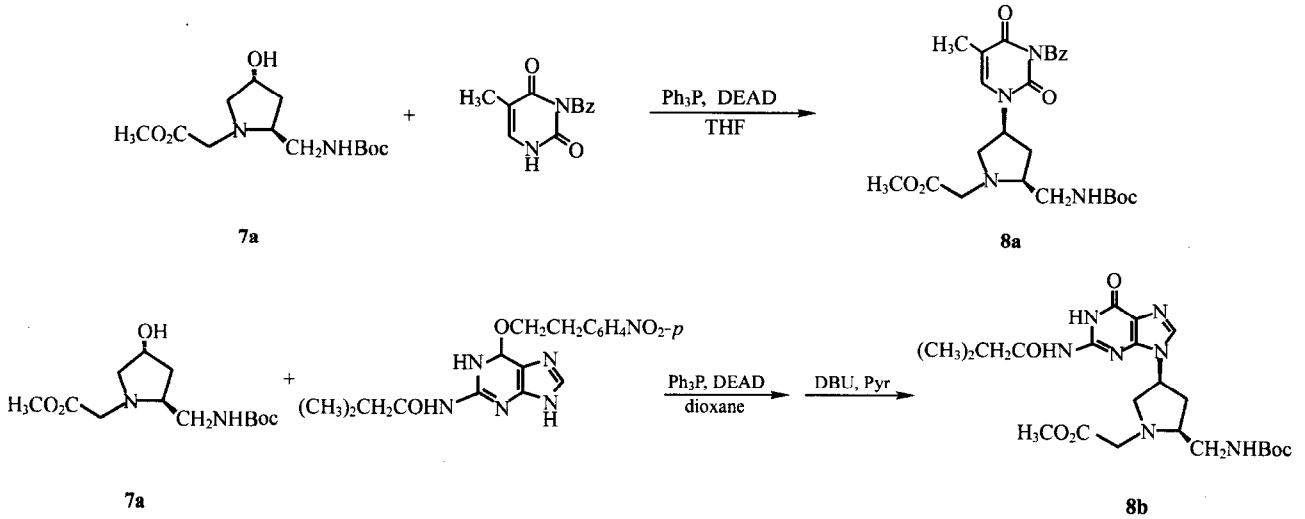
Scheme 1



1 2 3 4 5 6 7a

Recent studies[5,6] suggested that a direct displacement of hydroxy group with a nucleobase by the Mitsunobu reaction[7] was a very versatile method for the preparation of carbocyclic necleosides. Reactions of compound **7a** with N^3-benzoylthimine[8] and N^2-isobutyryl-O^6-(4-nitrophenylethyl)guanine[9] in the presence of triphenylphosphine-diethylazodicarboxylate (DEAD) were carried out to give the desired products **8a** and **8b** (after removal of the O^6-nitrophenylethyl group by treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in pyridine) in 32% and 31% yields, respectively (Scheme 2).

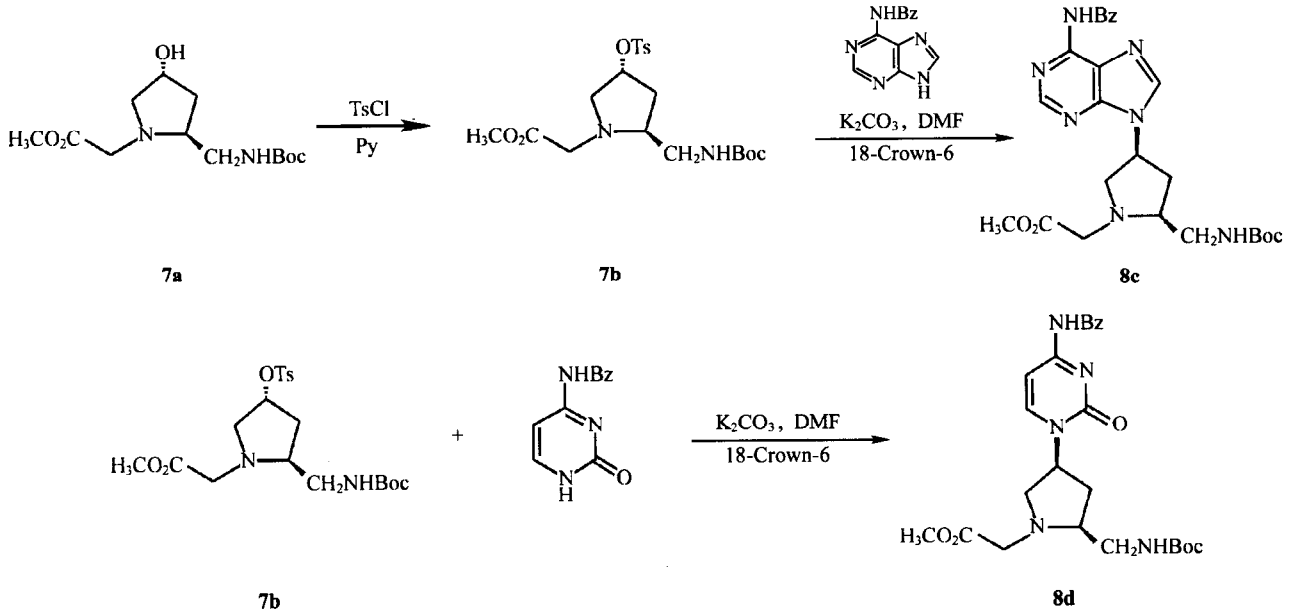
Scheme 2



7a 8a 7a 8b

Compound **7a** was then treated with toluene-*p*-sulfonyl chloride in anhydrous pyridine to give toluene-*p*-sulfonate **7b** in 86% yield. Compound **7b** reacted smoothly with N^6-benzoyladenine[10] (N^6-BzA-K_2CO_3) in dimethylformamide in the presence of 18-crown-6 to give the product **8c** in 26% yield, Analogous reaction with N^4-benzoylcytosine[11] (N^4-BzC) gave the product **8d** in 42% yield (Scheme 3).

Scheme 3



Reactions of compound **7a** with N^6-benzoyladenine (N^6-BzA) were also attempted but the product **8c** was obtained in a lower yield (12%) than that by the displacement reaction of **7b**. However, no product could be obtained from the reaction of compound **7a** and N^4-benzoylcytosine under similar conditions, probably because of the poor solubility of the protected nucleobase in the reaction medium.

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded on a Zabspe FAB mass spectrometer. IR spectra were recorded as KBr discs on a Magna-550 spectrometer.

N-Benzyl-4-hydroxyproline methyl ester (**2**)

A suspension of compound **1** (9.93 g, 54.0 mmol) in dichloromethane (200 mL) was stirred at 0℃, triethylamine (11.0 g, 108 mmol) was added dropwise to the reaction mixture, and then a solution of benzyl bromide (9.30 g, 54.0 mmol) in dichloromethane (50 mL) was added dropwise at 0—5℃. The reaction mixture was stirred at room temperature for three days. The reaction mixture was then diluted with dichloromethane (100 mL) and washed with water (3 × 100 mL). The organic layer was dried ($MgSO_4$), and filtered through celite. The filtrate was evaporated to give an oily product, which was chromatographied on silica gel with ethyl ether-petroleum ether (30—60℃) (1:1) to give **2** (R_f = 0.42) (7.8 g, 61%) as oil; IR ν: 3375 (O—H), 1721(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.63—1.86 (s, 2H), 2.06—2.24 (m, 2H, CH_2(3)), 2.44—2.47 (m, 1H, CH_2(5)), 3.22—3.25 (m, 1H, CH_2(5)), 3.62—3.66 (d, J = 3 Hz, 1H, $PhCH_2$), 3.85 (s, 3H, OCH_3), 3.96—4.00 (d, J = 3 Hz, 1H, $PhCH_2$), 4.41 (m, 1H, CH(2)), 5.34 (m, 1H, CH(4)), 7.26—7.36 (m, 5H). MS *m/z* (%): 235.2 (M^+, 18), 213.5 ($M^+ - H_2O$, 6), 154.3 ($M^+ - PhCH_2$, 4), 91.2 ($PhCH_2^+$, 96). Anal. Calcd for $C_{13}H_{17}NO_3$: C 67.23, H 7.23, N 6.04. Found: C

67.59, H 7.41, N 5.97.

N-Benzyl-4-hydroxy-2-tetrahydropyrrole formamide (**3**)

A solution of **2** (2.35 g, 10 mmol) in ammonia solution (100 mL, 25%) was stirred at room temperature for 48 h. The reaction mixture was evaporated to dryness under reduced pressure to give an oily product, which was chromatographed on silica gel with chloroform-methanol (10:1) to give **3** (R_f = 0.40) as an oil (1.98 g, 90%); IR ν: 3396 (O—H), 3251 (N—H), 1646 (C = O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.60—1.88 (s, 2H), 2.08—2.26 (m, 2H, CH_2(3)), 2.46—2.49 (m, 1H, CH_2(5)), 3.29—3.32 (m, 1H, CH_2(5)), 3.61—3.64 (d, J = 3 Hz, 1H, $PhCH_2$), 3.97—4.00 (d, J = 3 Hz, 1H, $PhCH_2$),4.42 (m, 1H, CH(2)), 5.36 (m, 1H, CH(4)), 7.26—7.36 (m, 5H). MS *m/z* (%): 220.1 (M^+, 3), 202.1 ($M^+ - H_2O$, 4), 176.1 ($M^+ - CONH_2$, 100), 158.1 ($M^+ - CONH_2 - H_2O$, 5), 130.1 ($M^+ - PhCH_2$, 2), 91.1 ($PhCH_2^+$, 98). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C 50.70, H 5.67, N 9.85). Found: C 50.36, H 5.48, N 9.88.

N-Benzyl-5-aminomethyltetrahydropyrrol-3-ol (**4**)

Lithium aluminum hydride (1.90 g, 50 mmol) was added in portions to a solution of **3** (2.20 g, 10 mmol) in dry THF (150 mL). After refluxing for 48 h, the reaction mixture was cooled to room temperature, and then water (4 mL) was added. The mixture was filtered through celite. The filtrate was evaporated to give an oily product, which was chromatographed on silica gel with chloroform-methanol (5:1) to give **4** (R_f = 0.22) as an oil (1.57 g, 76%); IR ν: 3356 (O—H), 3258 (N—H). ^1H NMR ($CDCl_3$) δ: 1.78—2.90 (m, 9H,), 3.16—3.20 (dd, 1H, CH(2)), 3.36—3.39 (d, J = 3 Hz, 1H, $PhCH_2$), 3.91—3.94 (d, J = 3 Hz, 1H, $PhCH_2$), 4.25—4.28 (m, 1H, CH(3)), 7.21—7.28 (m, 5H, C_6H_5). MS *m/z* (%): 207.2 ($M + H^+$, 48), 190.1 ($M - OH + H^+$, 26), 176.1 ($M - CH_2NH_2$, 100), 91.1 ($PhCH_2^+$, 92). Anal. Calcd for $C_{12}H_{18}N_2O$: C 69.87, H 8.79, N 13.58. Found: C 69.60, H 8.70, N 13.45.

N-Benzyl-5-(tert-butoxylcarbonylaminomethyl) tetrahydropyrrol-3-ol (**5**)

To a solution of **4** (8.40 g, 41 mmol) in dichloromethane (150 mL), a solution of di-*tert*-butyldicarbonate (8.90 g, 41 mmol) in dichloromethane (50 mL) was added dropwise at 0℃. The reaction mixture was stirred at 0℃ for 3 h, and at room temperature for 1 h. The solution was evaporated to dryness, and the residue was chromatographied on silica gel with chloroform-methanol (40:1) to give **5** as an oil (R_f = 0.32) (9.6 g, 77%); IR ν: 3409 (O—H), 3343 (N—H), 1686 (C = O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.45 (s, 9H, $C(CH_3)_3$), 1.80—3.12 (m, 8H,), 3.38—3.41 (d, J = 3 Hz, 1H, $PhCH_2$), 3.96—3.99 (d, J = 3 Hz, 1H, $PhCH_2$), 4.26—4.35 (m, 1H, CH(3)), 7.27—7.32 (m, 5H, C_6H_5). MS *m/z* (%): 307.1 ($M + H^+$, 100), 289.1 ($M - H_2O + H^+$, 2), 251.1 ($M - t$-Bu + H^+, 60), 233.0 ($M - t$-BuO, 4), 205.0 (M - Boc, 2), 176.0 ($M - BocNHCH_2$, 58), 158.0 ($M - BocNHCH_2 - H_2O$, 6), 91.0 ($PhCH_2^+$, 54). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C 66.64, H 8.55, N 9.14. Found: C 66.38, H 8.52, N 8.96.

5-(*tert-Butoxylcarbonylaminomethyl*) *tetrahydropyrrol-3-ol* (**6**)

10% Pd-C (0.31 g) was added to a solution of **5** in methanol (30 mL). The reaction mixture was hydrogenated at 4 atmospheric pressure. The reaction mixture was filtered. The filtrate was evaporated to dryness, and the residue was chromatographed on silica gel with chloroform-methanol (10:1) to give **6** as a solid m.p. 78℃ (1.5 g, 60%); IR ν: 3369 (O—H), 3291 (N—H), 1692 (C = O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.39 (s, 9H, $C(CH_3)_3$), 1.68—3.3 (m, 6H), 3.71—3.72 (m, 1H, CH(5)), 4.30—4.44 (m, 1H, CH(2)), 5.38 (m, 1H, CH(3)). MS *m/z* (%): 217.2 ($M + H^+$, 100), 161 ($M - Boc + H^+$, 66). Anal. Calcd for $C_{10}H_{20}N_2O_3$: C 55.53, H 9.93, N 12.95. Found: C 55.02, H 10.12, N 12.64.

N-[2-(tert-Butoxylcarbonylaminomethyl)-trans-4-hydroxy] tetrahydropyrrole acetic acid methyl ester (**7a**)

Triethylamine (1.01 g, 10 mmol) was added dropwise to a solution of **6** (2.16 g, 10 mmol) and bromoacetic acid methyl ester (1.53 g, 10 mmol) in dichloromethane (50 mL) at 0℃. The reaction mixture was warmed to room temperature and was stirred overnight. The reaction mixture was then diluted with

dichloromethane (50 mL) and washed with water (3 × 50 mL). The organic layer was dried ($MgSO_4$), and filtered through celite. The filtrate was evaporated, which was chromatographed on silica gel with chloroform-methanol (40:1) to give **7a** (R_f = 0.3) as an oil (1.87 g, 65%); IR ν: 3398 (O—H), 3118 (N—H), 1733, 1700 (C = O) cm^{-1}. ^1H NMR($CDCl_3$) δ: 1.44 (s, 9H, $C(CH_3)_3$), 2.13—3.67 (m, 10H), 3.72 (s, 3H, OCH_3), 4.41—4.53 (m, 1H, CH(4)), 5.36—5.44 (m, 1H). MS *m/z* (%): 289.0 ($M + H^+$, 100), 233.0 ($M - t$-Bu + H^+, 48), 189.0 (M - Boc + H^+, 5), 158.0 (M - $BocNHCH_2$ - H_2O + H^+, 42). Anal. Calcd for $C_{13}H_{24}N_2O_5$: C 54.15, H 8.39, N 9.72. Found: C 53.97, H 8.65, N 9.43.

N-[2-(*tert-Butoxylcarbonylaminomethyl*)-*trans*-4-(*p-methylphenylsulfonyloxy*)] *tetrahydropyrrole acetic acid methyl esters* (**7b**)

A solution of **7a** (2.88 g, 10 mmol) in dry pyridine (20 mL) was cooled in an ice-bath. Toluene-*p*-sulfonylchloride (2.10 g, 11 mmol) was added with stirring. This solution was kept in a refrigerator at 0℃ for 48 h. The reaction mixture was poured into ice-cold water (50 mL), and extracted with diethyl ether (4 × 50 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to give an oily product, which was chromatographed on silica gel with chloroform-methanol (50:1) to give **7b** (R_f = 0.51) as an oil (3.6 g, 86%); IR ν: 1745, 1709 (C = O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40 (s, 9H, $C(CH_3)_3$), 2.46 (s, 3H, CH_3), 2.17—3.59 (m, 8H,), 3.69 (s, 3H, OCH_3), 4.94—5.06 (m, 1H, CH(4)), 7.36 (d, *J* = 2 Hz, 2H), 7.77 (d, *J* = 2 Hz, 2H). MS *m/z* (%): 443.0 ($M + H^+$, 26), 387.0 ($M - t$-Bu + $2H^+$, 54), 343.0 (M - Boc + $2H^+$, 8), 312.0 (M - $BocNHCH_2$, 100), 287.0 (M - CH_3PhSO_2, 10). Anal. Calcd for $C_{20}H_{30}N_2O_7S$: C 54.28, H 6.83, N 6.33. Found: C 54.60, H 6.53, N 6.45.

N-[2-(*tert-Butoxylcarbonylaminomethyl*)-*cis*-4-(N^3-*benzoylthymin-1-yl*)] *tetrahydropyrrole acetic acid methyl ester* (**8a**)

To a suspension of **7a** (2.88 g, 10 mmol), N^3-benzoylthymine (2.30 g, 10 mmol) and triphenylphosphine (3.03 g, 11 mmol, 95%) in dry THF (10 mL) was added diethylazodicarboxylate (DEAD) (1.82 mL, 11 mmol) dropwise at - 15℃. The reaction mixture was stirred at room temperature overnight. The clear solution was evaporated to dryness, and the residue was purified by column chromatography (chloroform-methanol 50:1) to give **8a** as a foam (R_f = 0.50) (1.6 g, 32%); IR ν: 1736, 1704, 1690 (C = O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.46 (s, 9H, $C(CH_3)_3$), 2.02 (s, 3H, CH_3), 1.89—3.40 (m, 7H), 3.80 (s, 3H, OCH_3), 5.20—5.30 (m, 2H), 7.40—7.93 (m, 5H), 8.12 (s, 1H). MS *m/z* (%): 501.1 ($M + H^+$, 2), 370.0 (M - $BocNHCH_2$, 1), 279.0 (100), 132.8 (Boc-$NHCH_2$ + $2H^+$, 38), 105.0 ($PhCH_2^+$, 14), 77.0 ($C_6H_5^+$, 4), Anal. Calcd for $C_{25}H_{32}N_4O_7$: C 55.99, H 6.44, N 11.19. Found: C 55.62, H 5.99, N 11.58.

N-[2-(*tert-Butoxylcarbonylaminomethyl*)-*cis*-4-(N^2-*isobutyrylguanin-9-yl*)] *tetrahydropyrrole acetic acid methyl ester* (**8b**)

To a suspension of **7a** (0.37 g, 1.0 mmol), N^2-isobutyryl-O^6-[(4-nitrophenyl) ethyl] guanine (0.35 g, 1.3 mmol) and triphenylphosphine (0.36 g, 1.2 mmol) in dry THF (15 mL) was added diethylazodicarboxylate (DEAD) (0.22 mL, 1.3 mmol) dropwise at - 15℃. The reaction mixture was stirred at room temperature overnight. The solution was evaporated to dryness and the residue was purified by column chromatography (chloroform-methanol 2:1) to give the *N*-[2-(*tert*-butoxylcarbonylaminomethyl)-*cis*-4-(N^2-isobutyryl-O^2-nitrophenylethylguanin-9-yl)] tetrahydropyrrole acetic acid methyl ester (R_f = 0.5), which was contaminated with triphenylphosphine oxide. The impure material was dissolved in dry pyridine (10 mL), treated with 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) (0.3 mL, 2.0 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, and washed with water. The organic phase was dried ($MgSO_4$) and evaporated to give the crude product, which was purified by column chromatography (ethyl acetate-methanol 10:1) to give **8b** as a foam (71 mg, 21% from 7a); IR ν: 1709 (C = O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 (m, 6H, $CH(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.78—3.44 (m, 9H), 3.76 (s, 3H, OCH_3), 5.00 (m, 1H, CH(4)), 8.12 (s, 1H). MS *m/z* (%): 492.2 ($M + H^+$, 100), 436.1 ($M - t$-Bu

+2H$^+$, 32), 392.2 (M − Boc + 2H$^+$, 22), 222.0 (44). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C 50.70, H 5.67, N 9.85. Found: C 51.16, H 5.89, N 10.21.

N-[(2-*tert*-*Butoxylcarbonylaminomethyl*)-*cis*-4-(*N*^{6}-*benzoyladenin*-9-*yl*)]*tetrahydropyrrole acetic acid methyl ester* (**8c**)

A mixture of **7b** (1.16 g, 3.17 mmol), *N*^{6}-benzoyladenine (1.06 g, 4.43 mmol), anhydrous K_2CO_3 (0.16 g, 4.43 mmol) and 18-crown-6 (0.35 g) in DMF (50 mL) was stirred at 80℃ overnight. Water (150 mL) was added to the reaction and the suspension was extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give the crude product, which was purified by column chromatography (chloroform-methanol 20∶1) to give **8c** as a foam (R_f = 0.25) (0.42 g, 26%); IR ν: 1746, 1694 (C = O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H, C(CH_3)$_3$), 1.85—3.54 (m, 8H), 3.76 (s, 3H, OCH_3), 5.10—5.22 (m, 1H, CH(4)), 5.38 (m, 1H), 7.51—8.03 (m, 5H), 8.71 (s, 1H), 9.02 (s, 1H). MS *m*/*z* (%): 510.1 (M + H$^+$, 100), 454.0 (M − *t*-Bu + 2H$^+$, 12), 410.0 (M − Boc + 2H$^+$, 8), 379.0 (M-BocNHCH$_2$, 6), 105.5 (PhCO$^+$, 100). Anal. Calcd for $C_{25}H_{31}N_7O_5$: C 58.93, H 6.13, N 19.24. Found: C 59.10, H 6.46, N 18.87.

N-[2-(*tert*-*Butoxylcarbonylaminomethyl*)-*cis*-4-(*N*^{4}-*benzoylcytosin*-1-*yl*)]*tetrahydropyrrole acetic acid methyl ester* (**8d**)

A suspension of **7b** (1.78 g, 4.86 mmol), *N*^{6}-benzoylcytosine (1.58 g, 7.29 mmol), anhydrous K_2CO_3 (2.0 g, 14.58 mmol) and 18-crown-6 (1.0 g) in DMF (50 mL) was stirred at 70—80℃ overnight. The reaction mixture was then diluted with dichloromethane (150 mL) and washed with water (3 × 50 mL). The organic phase was dried ($MgSO_4$), and filtered through celite. The filtrate was evaporated to give an oily product, which was chromatographied on silica gel with chloroform-methanol (20∶1) to give **8d** as a foam (R_f = 0.31) (0.98 g, 41%); IR ν: 1776 (C = O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, C(CH_3)$_3$), 2.01—3.40 (m, 8H), 3.95 (s, 3H, OCH_3), 5.16—5.40 (m, 2H), 7.50—7.63 (m, 5H), 7.92 (d, J = 2 Hz, 1H), 8.56 (d, J = 2 Hz, 1H). MS *m*/*z* (%): 486.1 (M + H$^+$, 25), 429.0 (M − *t*-Bu + H$^+$, 3), 412.0 (M − *t*-BuO, 6), 386.1 (M − Boc + 2H$^+$, 53), 105.0 (PhCO$^+$, 100). Anal. Calcd for $C_{24}H_{31}N_5O_6$: C 59.37, H 6.44, N 14.42. Found: C 59.56, H 6.30, N 14.87.

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