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New Synthetic Route to γ-Mercaptomethyl PNA Monomers

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New Synthetic Route to γ-Mercaptomethyl PNA Monomers

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Abstract: Peptide nucleic acids (PNAs) are oligonucleotide mimics widely used as antisense, antigene molecules, and biotechnological tools. Recently, several microarrays and other biosensors based on PNAs have been developed. The construction of PNA molecular beacons or light-up probes for DNA detection requires the labelling of the PNA moiety. Labels are usually attached at the C or N terminal end by a flexible linker or in the middle of a PNA sequence, substituting one PNA base with an artificial base or by attaching fluorophores to a modified PNA backbone. The need to develop simple protocols to label PNAs encouraged us to design a new procedure for the synthesis of γ-mercaptomethyl-modified PNA. Here we propose a new strategy for the synthesis of modified PNAs, bearing amino acid side chains. The synthesis is straightforward and is an improvement to the procedures reported so far, as it uses stable intermediates and proceeds with better yields.

Keywords: Amino acid, PNA, synthesis

Peptide nucleic acids (PNAs) are oligonucleotide mimics widely used as tools for regulating gene expression. In fact, thanks to their ability to hybridize with high affinity and specificity with complementary DNA and RNA and because of their high chemical and enzymatic resistance they have found several applications, such as antisense, antigene molecules and biotechnological tools.[1–5] Recently several microarrays and

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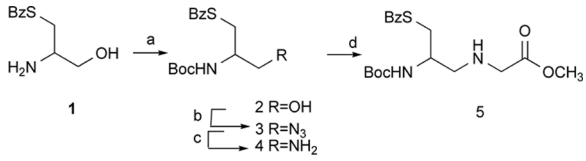
other biosensors based on PNAs were developed; relative to DNA, PNAs are advantageous for the DNA survey in complex mixtures as cell extracts because the hybridization event is not influenced by the ionic strength of the media and by DNA binding proteins.[6] The construction of PNA molecular beacons (MBs) for DNA detection requires the labelling of the PNA moiety at the C and N terminal end with a fluorophore and a fluorescence quencher. Recently, quencher-free DNA-based MBs were synthesized that utilize fluorophores quenched by nucleobases. This strategy allows for the inclusion of fluorophores at various points in the oligonucleotide sequence, not just at the termini, and allows in principle for the incorporation of multiple fluorophores.

The introduction of a label in the middle of a PNA sequence was realized by substituting one PNA base with an artificial base or by attaching fluorophores to a modified PNA backbone. The universal base thiazole orange was successfully inserted into a PNA oligomer by divergent solid-phase synthesis; a doubly labelled PNA conjugate containing one dansyl unit at the C-terminus and one dabsyl unit connected through a linker to the exocyclic amine of an adenine in the middle of a PNA oligomer were obtained.[7,8] A fluorene fluorescent probe was attached at the γ-Lys-modified PNA by solid-phase synthesis.[9] The need to develop simple protocols to label PNA encouraged us to design a new procedure for the synthesis of γ-mercaptomethyl-modified PNA. The nucleophilic SH group, in fact, allows for the selective labelling of unprotected molecules.[10] Molecular dynamic simulations on PNA/DNA duplexes containing L-γ-hydroxymethyl PNA demonstrated that the side chain in the γ position points toward the outer part of the duplex.[11] As is reasonable in a PNA/DNA duplex in which the oligomer contains a Cys-modified PNA monomer, the L-γ-Cys PNA monomer side chain will also be directed to the outer part of the duplex; this will allow for the modification of the PNA by a fluorophore, without hampering the formation of Watson–Crick hydrogen bonds between complementary bases. A cysteine-like PNA monomer at the N-terminus of a chain can be used for chemical ligation purposes, for obtaining either long PNA or PNA-peptide conjugates.[3,12] Furthermore, the presence of Cys-like residues in complementary strands might allow for the stabilization of duplex structures upon disulfide bond formation.

Here we propose a new strategy, an alternative to those reported in the literature, for the synthesis of modified PNA bearing amino acid side chains, starting from amino alcohols.[13,14]. The main advantage of this strategy is represented by the use of more stable intermediates (azides and amines) as compared to those used in the protocols reported so far. Today all the synthetic procedures for Cys-modified PNA monomers



Scheme 1. Regents and condition: a) $(Boc)_2O$, TEA, 98%; b) PPh_3, NaN_3 CCL_4/DMF, 72%; c) H_2, Pd/C, 100%; d) $BrCH_2COOCH_3$, TEA, 55%.

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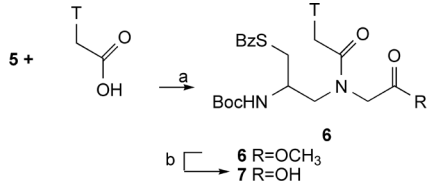
involve the formation of an aldehyde intermediate, which cannot be purified nor stored as it easily racemizes.[15,16] The present protocol overcomes the racemization issue and the need to operate in extremely dry conditions (as required for the N-protected α amino aldheydes synthesis).

The synthesis of the modified monomer was carried out by reactions that do not involve the chiral carbon. Synthesis started out from commercially available S-benzyl cysteinol. The amino alcohol was synthesized following procedures reported in the literature.[17] After protection of the terminal amino group with Boc, the alcohol (**2**) was transformed into the corresponding azide derivative (**3**) by treatment with PPh_3/NaN_3 in CCl_4/DMF (Scheme 1).[18] This reaction is usually employed for the synthesis of azides and amines from alcohols. The reaction proceeds through an intermediate chloride derivative, which is easily transformed into the azide, thanks to the high nucleofilicity of the azide group. Triphenylphosphine is used both for the halogenation reaction and for the reduction of the azide. Attempts to obtain the amine from the alcohol, using either large amounts of phosphines or various phosphine derivatives, were not successful. Reduction of the azide (**3**) was carried out by hydrogenation on palladiated charcoal. The resulting amine (**4**) was then reacted with methyl bromoacetate to give the fully protected backbone (**5**) (Scheme 1). The new backbone was coupled to a functionalized nucleobase, synthesized following procedures reported in the literature (Scheme 2).[19]



Scheme 2. Regents and condition: a) EDC, DMAP, 99%; b)NaOH, 87%.

Reaction of **5** with 1N-carboxymethylthymine afforded in high yield the mercaptomethyl-derivatized PNA monomer (**6**). The same reaction can be carried out with all the DNA bases, functionalized with a carboxymethylene. Deprotection of the ester **6** by treatment with sodium hydroxide afforded the carboxylic acid **7**, which can be used for the solid-phase synthesis of modified PNA oligomers.

All products were characterized by NMR (^{1}H and ^{13}C) and mass spectrometry (ESI). To confirm the chirality of the stereogenic center was maintained, α measurements were carried out on the backbone (**4**).

In conclusion, a new procedure for the synthesis of mercaptomethyl-derivatized PNA monomer was developed starting from a commercially available compound. The synthesis is straightforward and represents an improvement to the procedures reported so far, as it uses stable intermediates and proceeds with better overall yields.

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MATERIALS AND METHODS

All chemicals were purchased at Fluka at the highest purity available and used without further purification. Thin-layer chromatography (TLC) was run on Alugram Sil G/UV$_{254}$ plates developed with ninhydrin or UV visualized. Column chromatography was performed on Fluka silica gel 60 (size: 0.04–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Innova instrument (600 MHz) at room temperature. The signals of the residual protonated solvents ($CDCl_3$ or DMSO d_6) were used as reference signals. High-resolution mass spectra were measured on a Finnigan MSQ mass spectrometer by electrospray ionization.

EXPERIMENTAL

N-Tert-butyloxycarbonyl-S-benzyl-(R)-cysteinol (2)

Triethylamine (2.56 mmol, 359 μL) was added to a solution of S-benzyl-(R)-cysteinol (2.56 mmol, 505 mg) in THF (7.50 mL). After 10 min of stirring, di-tert-butyldicarbonate (2.56 mmol, 558 mg) was added at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The solvent was then evaporated under reduced pressure; the residue was dissolved in ethyl acetate and washed with water. The organic layer was separated, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to yield a colorless oil (744 mg, 98%). R_f: 0.60 (petroleum ether/ethyl acetate 6/4 v/v). Mass spectrum: m/z (ESI), $[M + H]^+$ calcd. 298.14; found 298.12. ^{1}H NMR ($CDCl_3$; δ in ppm): 1.45 (9H, s, CH_3Boc), 2.36 (1H, s, OH), 2.61 (2H, m, CH_2-S), 3.71–3.80 (5H, m, CH_2-OH, Ph-CH_2, C_α),

7.25–7.34 (5H, m, Ph). ^{13}C NMR ($CDCl_3$; δ in ppm): 28.85 (CH_3Boc), 33.09 (SCH_2), 37.04 ($PhCH_2$), 51.99 (Cα), 64.73 (CH_2OH), 127.7, 129.08, 129.4, 138.5 (Ph).

N-Tert-butyloxycarbonyl-2-azido-1-(benzylthiomethyl)ethylamine (3)

A mixture of NH-Boc-S-benzyl-(R)-cysteinol (2.50 mmol, 744 mg), sodium azide (3.00 mmol, 195 mg), and PPh_3 (2.50 mmol, 656 mg) in 28.0 mL of CCl_4/DMF (1/4 v/v) was warmed at 90 °C with stirring. The starting material was completely consumed (TLC monitoring) within 1 h. The reaction mixture was then cooled down to room temperature, diluted with water, and extracted with ether. The organic layer was dried over Na_2SO_4, concentrated on a rotary evaporator, and dried under vacuum to give a crude colorless oil. The residue was purified by flash-column chromatography (petroleum ether/ethyl acetate 95/5 v/v) to give 579 mg (72%) of pure azide. R_f: 0.52 (petroleum ether/ethyl acetate 7/3 v/v). Mass spectrum: m/z (ESI), $[M + H]^+$ calcd. 323.15; found 323.10. ^{1}H NMR ($CDCl_3$; δ in ppm): 1.45 (9H, s, CH_3Boc), 2.57 (2H, m, CH_2S), 3.47– 3.86 (5H, m, 5H, m, CH_2N_3, $PhCH_2$, C_α), 7.25–7.34 (5H, m, Ph). ^{13}C NMR ($CDCl_3$; δ in ppm): 28.82 (CH_3Boc), 33.59 (SCH_2), 36.95 ($PhCH_2$), 49.76 (Cα), 53.51 (CH_2N_3), 127.7, 129.1, 129.4, 138.3 (Ph), 156.3 (C = O).

N-Tert-butyloxycarbonyl-2-(benzylthiomethyl)ethylendiamine (4)

To a solution of **3** (3.11 mmol, 1.00 g) in dry CH_2Cl_2 (20.0 mL) at room temperature was added Pd on charcoal (100 mg); after stirring for 60 min under an atmosphere of hydrogen, the reaction was complete as judged by TLC. The catalyst was filtered off, and the filtrate was concentrated. The product was used in the next step without further purification. R_f: 0.52 (ethyl acetate/methanol 8/2 v/v). Mass spectrum: m/z (ESI), $[M + H]^+$ calcd. 297.16; found 297.10. ^{1}H NMR ($CDCl_3$; δ in ppm): 1.45 (9H, s, CH_3Boc), 2.50–2.65 (2H, m, CH_2S), 2.80 (2H, bs, CH_2NH_2), 3.60–3.73 (3H, bs, CH_2Ph, C_α), 7.25–7.34 (5H, m, Ph). ^{13}C NMR ($CDCl_3$; δ in ppm): 28.88 (CH_3Boc), 34.27 (SCH_2), 37.15 ($PhCH_2$), 44.71 (CH_2NH_2), 52.21 (Cα), 80.01 (CBoc), 127.6, 129.0, 129.5, 138.6 (Ph), 156.2 (C = O).

N-Tert-butyloxycarbonyl-1-(benzylthiomethyl)-N′-methoxycarbonylmethyl-ethylendiamine (5)

To a solution of **4** (3.04 mmol, 900 mg) and Et_3N (3.34 mmol, 470 μL) in dry CH_2Cl_2 (10.0 mL), methyl bromoacetate (3.04 mmol, 279 μL)

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in CH_2Cl_2 (200 μL) was added dropwise. The reaction was stirred overnight, and subsequently aqueous $NaHCO_3$ was added. The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. Purification of the crude oil by silica-gel column chromatography (diethyl ether/ petroleum ether 6/4 to 9/1 v/v) afforded pure **5** as a yellow oil. Yield: 612 mg (55%). R_f: 0.3 (diethyl ether/petroleum ether 85/5 v/v). Mass spectrum: m/z (ESI), $[M+H]^+$calcd. 369.18; found 369.10. ^{1}H NMR ($CDCl_3$; δ in ppm): 1.45 (9H, s, CH_3Boc), 2.52–2.78 (4H, m, CH_2S and CH_2N), 3.37 (2H, dd, NCH_2CO), 3.72 (3H, s, OCH_3), 3.73 (2H, s, CH_2Ph), 3.8 (1H, bs, C_α), 7.25–7.34 (5H, m, Ph).^{13}C NMR ($CDCl_3$; δ in ppm): 28.88 (CH_3Boc), 34.66 (SCH_2), 37.26 ($PhCH_2$), 50.21 (CH_2NH), 51.27 ($CH_2C=O$), 51.86 (OCH_3), 52.27 (Cα), 79.97 (CBoc), 127.5, 129.0, 129.5, 138.7 (Ph), 156.0 (NHC = O).

N-Tert-butyloxycarbonyl-1-(benzylthiomethyl)-N′-methoxycarbonylmethyl-N′-[(thymin-1-yl)acetyl]-ethylendiamine (6)

To a solution of **5** (1.33 mmol, 490 mg) in dry DMF (10.0 mL), thymin-1-ylacetic acid (1.93 mmol, 355 mg), and 4-(dimethylamino)pyridine (DMAP) (0.13 mmol, 15.9 mg) were added, and the mixture was stirred until most of the acid dissolved. Next, N-(3-dimethylaminoproply)-N′-ethylcarbodimide hydrochloride (EDC) (2.93 mmol, 561 mg) was added and the mixture was stirred overnight. The solution was concentrated in vacuo, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with ethyl acetate, and the combined organics were washed with brine and dried (Na_2SO_4). The organic layer was then concentrated on a rotary evaporator and dried under vacuum.

Purification by flash chromatography (ethyl acetate/petroleum ether 95/5 v/v) gave **6** (670 mg, 94%) as a white solid. R_f: 0.55 (diethyl ether/petroleum ether 7/3 v/v). $[\alpha]^{20}_D = -7.4$ (c = 0.02 in $CHCl_3$). Mass spectrum: m/z (ESI), $[M+H]^+$calcd. 535.21; found 535.29. ^{1}H NMR ($CDCl_3$; δ in ppm): two rotamers; major product 1.41 (9H, s, CH_3Boc), 1.66 (1H, s, NH), 1.91 (3H, s, CH_3Thy), 2.48–2.78 (4H, m, CH_2S and CH_2N), 3.43–3.46 (2H, dd, NCH_2CO), 3.72 (3H, s, OCH_3), 3.76 (2H, s, N1ThyCH_2CO), 3.8 (2H, s, CH_2Ph), 4.12–4.16 (1H, m, C_α), 6.98 (1H, s, H6), 7.25–7.32 (5H, m, Ph), 8.35 (1H, s, NHThy). ^{13}C NMR ($CDCl_3$; δ in ppm): two rotamers; major product 12.81 (CH_3Thy), 28.81 (CH_3Boc), 37.41 (SCH_2), 41.61 ($PhCH_2$), 48.00 (CH_2COOMe), 49.42 (Cα), 51.08 (CH_2N1Thy), 52.83 (COOMe), 53.40 (Cα CH_2N), 111.1 (C5Thy), 127.9, 129.2, 129.4, 138.5 (Ph), 151.3 (C(2) = OThy), 164.3 (C(4) = OThy), 169.9 (COOMe).

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N-Tert-butyloxycarbonyl-1-(benzylthiomethyl)-N′-carboxymethyl-N′-[(thymin-1-yl)acetyl]-ethylendiamine (7)

Compound **6** (46. 8 μmol, 25. 0 mg) was dissolved in dioxane (500 μL) and 2 M NaOH (117 μL) was added. After stirring for 20 min, the reaction was complete as shown by TLC. The mixture was acidified by adding 1 N HCl to pH 2–3. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification of an analytical sample (9.7 mg) by reverse-phase HPLC afforded **7** (8.2 mg, 87%) as a white powder. R_f: 0.70 (ethyl acetate/methanol/formic acid 85/10/5 v/v/v). Mass spectrum: m/z (ESI), $[M+H]^+$ calcd. 521.21; found 521.27. ^{1}H NMR ($CDCl_3$; δ in ppm): two rotamers; major product 1.42 (9H, s, CH_3Boc), 1.88 (3H, s, CH_3Thy), 2.48–2.68 (4H, m, CH_2S and CH_2N), 3.48–4.58 (1H, m, C_α), 3.71 (2H, s, NCH_2CO), 3.75 (4H, s, CH_2Ph and N1ThyCH_2CO), 6.97 (1H, s, H6Thy), 7.23–7.32 (5H, m, Ph), 10.1 (1H, s, COOH). ^{13}C NMR (DMSO; δ in ppm): two rotamers; major product 15.85 (CH_3Thy), 32.22 (CH_3Boc), 37.98 (SCH_2), 38.70 ($PhCH_2$), 51.97, 52.43, 54.98, 81.98 (CBoc), 111.9 (C5Thy), 130.6, 132.2, 132.8, 142.6 (Ph), 146.1, 155.0, 159.3, 168.4 (COOH).

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