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Synthesis of 6′-Branched Locked Nucleic Acid by a Radical TEMPO-Scavanged Stereoselective Mercury Cyclization

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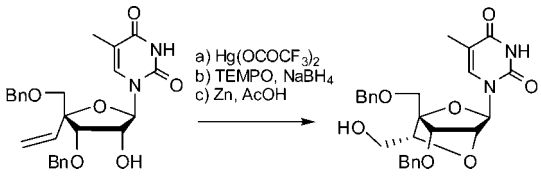

A 6′(*R*)-hydroxymethyl derivative of the locked nucleic acid (LNA)-thymidine monomer has been synthesized by a stereoselective mercury cyclization and subsequent use of TEMPO as a radical scavenger. This compound was converted to an azide derivative, which in a Huisgen-type [3 + 2] cycloaddition afforded a double-headed nucleoside with a triazole linking an additional thymine to the 6′-position of the LNA-nucleoside monomer.

Locked nucleic acid (LNA) has received significant attention as a nucleic acid analogue displaying unprecedented recognition of complementary nucleic acids.[1] Therapeutic antisense properties[2] of LNA are very promising,[3] but also the potential in nanoscale engineering and microarray construction has been recognized.[4] LNA is defined as oligonucleotides containing at least one LNA monomer (Figure 1,) which is a bicyclic nucleoside analogue conformationally locked in the *N*-type conformation and therefore preorganizing the LNA for A-type duplex formation.[5] Hence, the 2′-amino group of amino-LNA (see monomer in Figure 1) has been used as the branching point for a diverse series of functionalized oligonucleotides.[6] The 3′-position of LNA has also been used for functionalization.[7] The carbon atom in the 2′,4′-bridge (herein defined as the 6′-carbon,

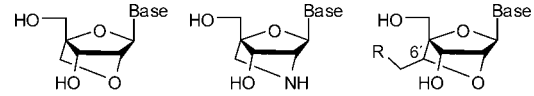

FIGURE 1. An LNA monomer, an amino-LNA monomer, and a 6′-branched LNA monomer.

Figure 1) constitutes a hitherto unexplored center for functionalization. This carbon complements the 2′-amino atom as well as the 3′-position, giving two different positions (*pro-S* and *pro-R*) for displaying nucleic acid decorations in the minor groove. The preparation of a universal building block for branching LNA in the 6′-position is however a challenging task. Herein we demonstrate the first synthesis of a 6′-hydroxymethyl LNA monomer[8] and its conversion into a 6′-azidomethyl analogue, whose potential for Huisgen [3 + 2] cycloaddition is demonstrated in the preparation of a double-headed nucleoside.[9−11]

In the design of a general tool for branching LNA on the 6′-position, we envisioned the synthesis of a 6′-hydroxymethyl derivate as the key goal. The hydroxymethyl group can easily be further derivatized in numerous ways (oxidation, alkylation, activation/substitution). We based the preparation on the known 4′-*C*-vinylribofuranose derivative **1**[12] (Scheme 1), taking advantage of two benzyl protecting groups to be removed simultaneously at the end of the synthesis. Compound **1** was efficiently synthesized in seven steps from 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose using the well-known aldol condensation with formaldehyde[13] as applied in the preparation of LNA,[5] a selective benzylation,[5,14] and a high-yielding oxidation/Wittig olefination sequence.[12] Earlier studies on the preparation of LNA and derivatives thereof have shown that the introduction of the nucleobase cannot be performed after the ring-closing step forming the 2′,4′-bridge.[15] Therefore, compound **1** was converted to the diacetate **2**, which was coupled to thymine using

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(8) Recently, a PCT Int. Appl. demonstrating an alternative synthetic method towards 6′-branching LNA has been published. A non-stereoselective multistep synthesis has been applied based on dihydroxylation of a differently protected analogue of **1** and multiple protecting group manipulations affording 6′-epimeric mixtures: Swayze, E. E.; Seth, P. P. WO2007090071, 2007.

(9) We define nucleosides with two nucleobases as double-headed nucleosides. These have recently been studied as building blocks in oligonucleotides by the group of Herdewijn[10] and us.[11]

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(11) (a) Pedersen, S. L.; Nielsen, P. *Org. Biomol. Chem.* **2005**, *3*, 3570–3575. (b) Christensen, M. S.; Madsen, C. M.; Nielsen, P. *Org. Biomol. Chem.* **2007**, *5*, 1586–1594. (c) Christensen, M. S.; Bond, A.; Nielsen, P. *Org. Biomol. Chem.* **2008**, *6*, 81–91.

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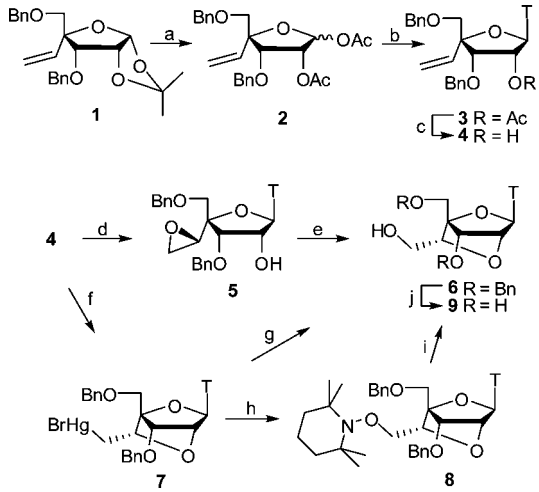
SCHEME 1. Synthesis of the 6′(*R*)-Hydroxymethyl LNA-Thymidine Monomer[a]



[a] Reagents and conditions: (a) Ac_2O, H_2SO_4, AcOH (90%); (b) thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS-triflate, 1,2-DCE (85%); (c) $NaOCH_3$, CH_3OH (95%); (d) *m*CPBA, DCM; (e) CSA, DCM (21% from **4**); (f) $Hg(OCOCF_3)_2$, THF (aq), then 10% NaBr (aq), DCM (98%); (g) $NaBH_4$, O_2, DMF (16% **6** and 55% **4**); (h) $NaBH_4$, TEMPO, DMF (77%); (i) Zn, AcOH, THF (aq) (83%); (j) H_2, $Pd(OH)_2$/C, EtOAc (65%). T = thymin-1-yl.

a Vorbrüggen-type[16] protocol, affording the protected 4′-vinylribonucleoside **3**. Deacetylation gave compound **4** constituting a key material for a ring closure giving the 2′,4′-ring and a 6′-hydroxymethyl group.

Our first attempt was based on the epoxidation of the terminal olefin followed by a ring-opening nucleophilic attack from the 2′-hydroxy group. However, the vinyl group demonstrated a low reactivity toward all attempted reagents, yielding a maximum of 20% of the target epoxide **5** by the application of *m*CPBA. Protocols based on DMDO,[17] *t*BuOOH,[18] or H_2O_2 (Payne oxidation)[19] all failed to improve this situation, though another 20% yield of **5** was obtained with DMDO. Some oxidation of the nucleobase was also detected in all cases. Similar difficulties have been observed with the epoxidation of 5′-olefinated thymidine derivatives.[11b,20] Despite the low yield, compound **5** was obtained as only one stereoisomer, revealing a substrate for the following ring closure. This was performed under acidic conditions using CSA, giving the targeted 6′-hydroxymethyl-LNA monomer **6** in 50% yield. A one-pot epoxidation using *m*CPBA and CSA was optimized to give **6** in 21% overall yield from **4**. The constitution of compound **6** was verified by NMR spectroscopy. The singlets for H1′ and H3′ are characteristics of the constrained *N*-type conformation of an LNA derivative,[5] and the chemical shift for the H1′ at 5.56 ppm is characteristic for LNA (5.51 ppm reported for the thymidine monomer)[5] and not for ENA, for which shifts around 6.0 ppm have been reported.[12] Hence, an alternative ring closure forming a six-membered ring and a secondary alcohol would constitute a hydroxylated analogue of the ring-enlarged analogue of LNA called ENA.[12] Finally, the hydroxy group appeared as a triplet proving a primary alcohol and the LNA-constitution of **6**. The 6′-configuration was not verified at this stage, as NOE-difference spectroscopy was hampered by the overlap of crucial ^{1}H NMR signals. Later derivatization (see below) proved a 6′(*R*)-configuration.

Even though the target ring closure was obtained by the epoxidation method, the yield was too low for any practical use. A protection of the nucleobase as its 4-*O*-(2,6-dimethyl)phenyl derivative did not improve the epoxidation (see Supporting Information). This protecting group has been used by Sekine and co-workers, allowing an efficient dihydroxylation of a 2′-*O*-allyl group of a uridine derivative,[21] but in our case it let to even more pronounced nucleobase oxidation. Dihydroxylation on **4** using OsO_4 afforded also pronounced nucleobase oxidation. Iodocyclization based on the addition of iodine and following ring closure failed to give any product. Electrophilic activation of the double bond based on NBS or NIS also failed. The solution was found in activation by mercury(II) trifluoroacetate.

Hanessian and co-workers have earlier reported the preparation of a six-membered ring forming a bicyclic nucleoside based on a mercury cyclization with mercury(II) acetate.[22] We decided to apply the more reactive trifluoroacetate in a similar protocol and observed a quantitative reaction. The protocol had to be changed, however, in order to extract the mercury bromide derivative **7** from a sodium bromide solution, giving almost quantitative yield. The subsequent reduction of the mercuric derivative by $NaBH_4$ in a solution of DMF saturated by continuous bubbling with oxygen[23] afforded, however, the desired product **6** in only 16% yield as well as the starting compound **4** in 55% yield. Thus, the primary radical formed in the reduction has been reorganized into a more stable form by reopening the constrained ring previously formed. With a large excess of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) in the reduction reaction,[23] however, the primary radical was very efficiently scavenged as the TEMPO-derivative **8** in 77% yield. Cleavage of the oxygen−nitrogen bond occurred thereafter in a good yield by the application of Zn dust in neat acetic acid to give the 6′-hydroxymethyl LNA derivative **6**. The overall yield of **6** was 63% from **4** as compared to the 21% yield obtained by the epoxidation method. The method was completely stereoselective affording the same 6′-epimer as obtained by the epoxidation method. Global debenzylation by hydrogenation afforded the branched LNA-thymidine monomer **9**.

The versatility of the hydroxymethyl compound **6** as the starting point for various modifications was demonstrated by its conversion to the azide (Scheme 2). Hence, mesylation afforded **10**, on which a microwave-heated nucleophilic substitution with sodium azide gave the azide derivative **11**. The azide was reduced to the primary amine **12** by applying Zn dust. The two derivatives **11** and **12** were used in the final solution of the 6′-configuration of the present branched LNA derivatives. Thus, NOE-difference spectroscopy revealed in both cases strong mutual contacts between the H1′ and one of the H7′-protons of 3−4%. No contacts were seen between H1′ and H6′.

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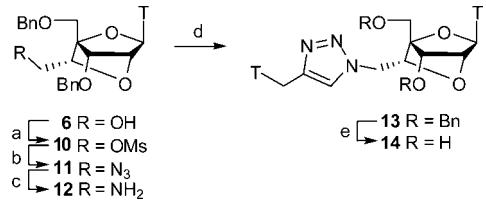
SCHEME 2. Synthesis of the 6′(*R*)-Azidomethyl LNA-Thymidine Monomer and a Double-Headed Nucleoside[a]



[a] Reagents and conditions: (a) MsCl, pyridine, DCM (90%); (b) NaN_3, DMF (57%); (c) Zn, AcOH (31%); (d) N^1-propragylthymine, Na ascorbate, $CuSO_4 \cdot 5H_2O$, *t*BuOH, H_2O (75%); (e) H_2, Pd/C, EtOH (67%).

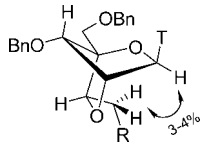


FIGURE 2. *N*-Type conformation and mutual NOE contacts indicated in the 6′-methylenebranched LNA derivatives (based on NMR experiments on **11** and **12**, R = N_3 or NH_2).

Both observations proved the 6′(*R*)-configuration as demonstrated in Figure 2.

Obviously, both the hydroxy group of **6** and the amine of **12** can be used in nucleophilic derivatizations. Nevertheless, we decided to apply the azide functionality of **11** in combination with terminal alkynes in Huisgen-type [3 + 2] cycloadditions, which can be performed with complete regioselectivity, giving only 1,4-disubstituted triazoles by a Cu(I) catalysis.[24] Recently, this reaction type has been intensively applied as a result of the concept of click chemistry introduced by Sharpless and coworkers.[25] The reaction is very robust, it tolerates almost all functional groups, it can be performed in aqueous solutions, and it displays high atom economy giving no side products. In line of our ongoing program on double-headed nucleosides,[9,11] we decided to use the present azide for the decoration of LNA with an additional nucleobase. N^1-Propargylthymine[26] and compound **11** were reacted following a standard protocol with microwave heating[24,27] to give efficiently the double-headed nucleoside **13**. Global deprotection by hydrogenolysis afforded compound **14**. This compound is currently being studied as a building block in nucleic acid secondary structures such as our recently investigated three-way junctions or DNA-zipper motifs.[11]

In summary, we have proved the applicability of mercury(II) trifluoroacetate for forming a 6′-hydroxymethyl modified LNA monomer that is otherwise obtainable only in lower yields and a higher number of steps.[8] Hence, compound **6** was obtained in approximately 22% overall yield over the 13 steps from 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose, whereas the differently protected analogue by Swayze and Seth was obtained in 19% yield as an epimeric mixture over 17 steps.[8] Furthermore, the utility of compound **6** for derivatization was illustrated by the preparation of first the azide **11** and then of the double-headed nucleoside **14** in 26% overall yield over the four steps from **6**. The potential of the 6′(*R*)-position for the design of functional LNA and subsequent nanostructures will be illustrated in the near future. Nevertheless, simple modeling starting from LNA-modified duplexes[1,28] indicates the present *pro-R* position of the 6′-carbon to be the most favorable position of the two pointing into the minor groove. Hence, we consider the present method for stereoselective preparation of 6′(*R*)-branched LNA as extremely convenient, and the application of the key compounds **6**, **11** and **12** for the preparation of functionalized LNA derivatives is in progress.

Experimental Section

Synthesis of (1*R*,3*R*,4*R*,6*S*,7*S*)-7-benzyloxy-1-benzyloxymethyl-6-bromomercurimethyl-3-(thymin-1-yl)-2,5-dioxabicyclo[2.2.1]-heptane (7). To a solution of the olefin **4** (2.82 g, 6.1 mmol) in THF (150 mL) was added mercury(II) trifluoroacetate (3.90 g, 9.11 mmol), and the mixture was stirred for 12 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in DCM (150 mL). A 10% aqueous solution of NaBr (50 mL) was added, and the mixture was stirred vigorously for 30 min. The two phases were separated, and the organic phase was treated with another 10% aqueous solution of NaBr (50 mL). After separation, the organic phase was washed with water (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the product (4.45 g, 98%) as a white foam: R_f 0.42 (EtOAc in hexane, 1:1 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (m, 1H, NH), 7.49 (s, 1H, H-6), 7.31−7.18 (m, 10H, Ph), 5.57 (s, 1H, H-1′), 4.61−4.55 (m, 6H, H-2′, 2 × CH_2Ph, H-6′), 3.99 (s, 1H, H-3′), 3.68 (s, 2H, 2 × H-5′), 2.25 (m, 1H, H-7′), 1.91 (m, 1H, H-7′), 1.55 (s, 3H, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (C-4), 149.9 (C-2), 137.3, 136.8 (Ph), 134.7 (C-6), 128.8, 128.8, 128.7, 128.7, 128.6, 128.3, 128.0, 127.9 (Ph), 110.2 (C-5), 87.3, 86.7 (C-1′, C-4′), 79.8, 78.3, 77.5 (C-2′, C-3′, C-6′), 73.95, 72.5 (2 × *C*H_2Ph), 64.7 (C-5′), 31.9 (C-7′), 12.4 (CH_3); HRMALDI MS *m*/*z* calcd for $C_{26}H_{27}HgBrN_2O_6$ [M + Na]$^+$ 767.0651, found 767.0618.

Synthesis of (1*S*,3*R*,4*R*,6*R*,7*S*)-7-Benzyloxy-1-benzyloxymethyl-6-(2,2,6,6-tetramethylpiperidin-1-yl)oxymethyl-3-(thymin-1-yl)-2,5-dioxabicyclo[2.2.1]heptane (8). To a stirred solution of the mercuric derivative **7** (2.0 g, 2.68 mmol) in anhydrous DMF (13 mL) was added TEMPO (3.15 g, 20.2 mmol). The reaction mixture was stirred at 0 °C, and a solution of sodium boron hydride (477 mg, 12.6 mmol) and TEMPO (3.15 g, 20.2 mmol) in anhydrous DMF (13 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and filtered through celite with precaution to remove the mercury particles. The sinter was rinsed with dichloromethane (150 mL). The combined filtrates were concentrated under reduced pressure and coevaporated with xylene. The residue was purified by column chromatography (20−50% EtOAc in hexane) to afford the product (2.50 g, 77%) as a white foam: R_f 0.46 (EtOAc in hexane, 1:1 v/v); IR (KBr,ν_{max} cm^{-1}) 3433.9, 3187.5, 3065.9, 2929.4, 1693.9, 1455.14, 1361.2, 1269.7, 1103.4, 1055.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H, H-6), 7.36−7.25 (m, 10H, Ph), 5.54 (s, 1H, H-1′), 4.69−4.55 (m, 4H, CH_2Ph), 4.36 (s, 1H, H-2′), 4.31 (m, 1H, H-6′), 4.13−4.08 (m, 2H, H-3′, H-5′), 3.99 (m, 2H, H-7′), 3.79 (d, 1H, J = 11.4 Hz, H-5′), 1.60 (s, 3H, CH_3), 1.43 (br s, 6H, 3 × CH_2), 1.13 (br s, 6H, 2 × CH_3), 1.00 (br s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C-4), 149.7 (C-2), 137.8, 137.0 (Ph), 135.1 (C-6), 128.7, 128.6, 128.3, 128.1, 128.0, 127.7 (Ph), 110.2 (C-5), 87.9 (C-4′), 86.6 (C-1′), 77.6 (C-3′), 76.7 (C-6′), 76.5 (C-2′), 74.0 (*C*H_2Ph), 73.7 (C-7′), 72.6 (*C*H_2Ph), 64.8 (C-5′), 60.1, 60.0 (*C*$(CH_3)_2$), 39.8, 39.7 ($CH_2C(CH_3)_2$), 33.4, 32.8 (C(*C*$H_3)_2$), 20.5, 20.1 (C(*C*$H_3)_2$), 17.2 ($CH_2CH_2CH_2$), 12.4 (CH_3); HRMALDI MS *m*/*z* calcd for $C_{35}H_{45}N_3O_7$ [M + Na]$^+$ 642.3150,

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found 642.3120. Anal. for $C_{35}H_{45}N_3O_7 \cdot 0.25\ H_2O$: found C, 67.35; H, 7.33; N, 6.80; requires C, 67.34; H, 7.35; N, 6.73.

Synthesis of (1*S*,3*R*,4*R*,6*R*,7*S*)-7-Benzyloxy-1-benzyloxymethyl-3-(thymin-1-yl)-6-hydroxymethyl-2,5-dioxabicyclo[2.2.1]heptane (6). To a stirred solution of the TEMPO derivative **8** (1.8 g, 2.97 mmol) in a mixture of AcOH, H_2O, and THF (95 mL, 3:1:1 v/v/v) was added (10 μm) zinc dust (1.67 g, 26.4 mmol) in small portions. The mixture was stirred at 65 °C for 1.5 h and then filtered through a filter (0.45 μm) on a syringe adapter. The filter was washed with THF, and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in EtOAc (250 mL), and the solution was washed with water (50 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL), and brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (20−60% EtOAc in hexane) to afford the product (1.18 g, 83%) as a white foam; R_f 0.20 (EtOAc in hexane, 7:3 v/v); IR (KBr, ν_{max} cm^{-1}) 3437.9, 3183.4, 3065.1, 2926.6, 1690.1, 1455.26, 1365.9, 1271.1, 1105.4, 1057.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.7 (br s, 1H, NH), 7.45 (s, 1H, H-6), 7.36−7.25 (m, 10H, Ph), 5.56 (s, 1H, H-1′), 4.68−4.52 (m, 4H, CH_2Ph), 4.45 (s, 1H, H-2′), 4.32 (m, 1H, H-6′), 4.04 (s, 1H, H-3′), 3.98−3.82 (m, 4H, H-5′, H-7′), 2.25 (m, 1H, OH), 1.62 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (C-4), 150.0 (C-2), 137.4, 136.9 (Ph), 134.8 (C-6), 128.8, 128.7, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8 (Ph), 110.45 (C-5), 87.4 (C-4′), 86.8 (C-1′), 81.0 (C-6′), 77.8 (C-3′), 76.6 (C-2′), 73.9, 72.4 (2 × CH$_2$Ph), 65.0 (C-5′), 60.5 (C-7′), 12.4 (CH_3); HRMALDI MS *m*/*z* calcd for $C_{26}H_{28}N_2O_7$ $[M + Na]^+$ 503.1789, found 503.1782.

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Supporting Information Available: General experimental section including additional experimental procedures and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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