Organic & Biomolecular Chemistry

Accepted Manuscript

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ARTICLE

Synthesis of Locked Cyclohexene and Cyclohexane Nucleic Acids (LCeNA and LCNA) with Modified Adenosine Units

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

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We describe the preparation of conformationally locked cyclohexane nucleic acids designed as hybrids between locked nucleic acids (LNA) and cyclohexene nucleic acids (CeNA), which both excel in hybridization with complementary RNAs. We have accomplished the synthesis of these adenine derivatives starting from simple ketoester and installed all four chiral centres by means of total synthesis. The acquired monomers were incorporated into nonamer oligonucleotides.

Introduction

Oligonucleotides with modified sugar moieties have found many applications in modern technologies such as antisense oligonucleotides, RNA interference (RNAi), ribozymes, DNAzymes and aptamers. The stabilization of the duplexes with complementary mRNA of interest is an essential concept for oligonucleotide-mediated regulation of the gene expression. Extensive hybridization with the target sequence and selectivity towards mRNA in comparison with affinity to complementary DNA are important features of the desired technologies.[1]

Although various sugar modifications have led to the enhancement of the hybridization properties of antisense oligonucleotides, probably the most famous modifications are based on monomers with a bridge between the 2' and 4' positions of the ribose ring. This results in the stabilization of the 3'-endo conformation and the formation of bridged nucleic acids (BNA).[2] Imanishi's[3] and Wengel's[4] groups have independently synthesized monomers for 2',4'-bridged nucleic acids/locked nucleic acids (LNA, **1**) and reported their hybridization properties after incorporation into oligonucleotides (Figure **1**). LNAs have also been successfully used for both RNAi[5] and selection of aptamers.[6] Since then, a number of compounds with alternative bridges (e.g. **2**–**4**) have been prepared, especially in order to increase the nuclease resistance of the resulting oligonucleosides.[7] Carba-LNAs (e.g. **2**)[8] have also been prepared. They seem to possess a significantly increased nuclease resistance in comparison with traditional LNAs without dramatic effect on the RNAse H mediated cleavage of the target RNA.[9] Recently LNAs modified on the nucleobase have been reported as well.[10]

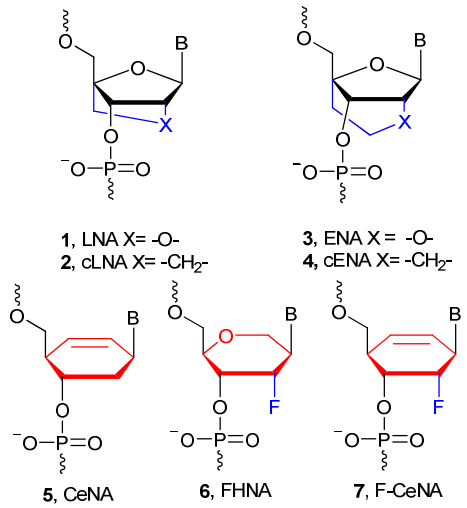


Figure 1 The structures of selected nucleic acids with sugar modification including LNA analogues (**1**–**4**) and six-membered carbohydrate mimics (**5**–**7**).

In contrast to LNA-based oligonucleotides, which usually form stable duplexes with both RNA and DNA, cyclohexene nucleic acids (CeNA, **5**), developed by Herdewijn *et al.*, exert significant selectivity in hybridization with RNA over DNA.[11] The same research team has also suggested that the

cyclohexene moiety can serve as appropriate bioisostere of the natural furanose ring[11b] and proved that this pseudosugar exerts significant flexibility while being incorporated into the structure of oligonucleotides. The crystal structures of duplexes with complementary DNA and RNA oligomers have clearly demonstrated that the cyclohexene moiety can interconvert between two distinct conformations $^2H_3$ (similar to C2'-endo) and $^3H_2$ (similar to C3'-endo).[12,13]

Recently, Seth *et al*. have shown that 2'-fluoro hexitol nucleic acids (FHNA, **6**) exhibit higher duplex stability than 2'-fluoro CeNA (F-CeNA, **7**) due to higher rigidity and superior stabilization in C3'-endo-like conformation.[14,25]

The major objective of our presented study was the preparation of hybrid derivatives merging LNAs and CeNAs in order to stabilize cyclohexene moiety in $^3H_2$ conformation resembling the C3'-endo, which is preferred by CeNA while forming a duplex with complementary RNA strands.[13] In addition, the synthesis of locked cyclohexene nucleic acid (LCeNA) monomers made it easy to obtain saturated monomers bearing a cyclohexane ring instead of the original cyclohexene one (LCNA).

Although the obvious way to reach these compounds in an asymmetric fashion led through extending the synthesis of CeNA by methods for the preparation of LNA from sugar precursors,[15] we decided to explore a synthetic approach, which would result in this type of compounds starting from simple precursors avoiding the use of a chiral pool or enzymatic resolution of synthetically complicated nucleosides. In order to be able to determine the enantiomeric purity of our compounds, we initially performed racemic synthesis of the desired monomers (see the Supplementary Information).

Results and discussion

The retrosynthetic analysis is outlined on the Figure **2.** The crucial step of the synthesis is the construction of the first stereogenic centre by Michael conjugated addition of the acrolein to starting material **8** catalysed by quinine based organocatalyst (Q-PHN-OH) immediately followed by cyclization to build bicyclic ring system (bicyclo[3.2.1]octane). Further tranformations of the functional groups lead to desired final nucleoside **25**.

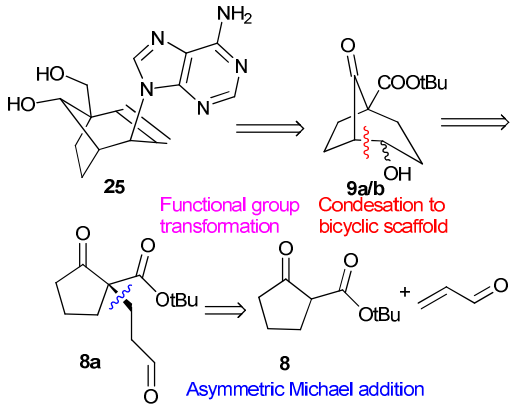
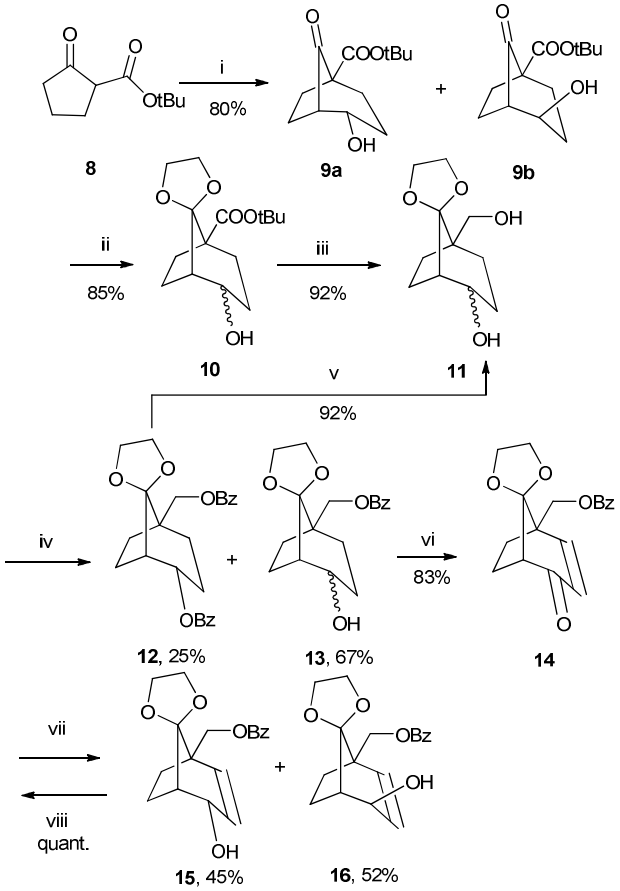


Figure 2 Retrosynthetic analysis.

The asymmetric synthesis of the desired monomers started from the ester **8**[16] (Scheme **1**), which was treated with acrolein together with quinine organocatalyst (Q-PHN-OH) following published synthetic protocol.[17] The crude aldehyde intermediate **8a** was cyclized with cesium carbonate[18] in toluene to afford a mixture of bicyclic compounds **9a** and **9b** (87% yield, 2 steps, ratio ~ 3:2, GC-MS analysis). Alcohols **9a** and **9b** were used as a mixture (Scheme **1**), their keto group protected as a ketal and the ester group of **10** was reduced by lithium aluminum hydride to an inseparable diastereomeric mixture of alcohols **11**. The primary hydroxy group was protected by benzoylation at low temperature and the obtained mixture of the monobenzoylated compounds **13** (**13a**, **13b**, separable) and the dibenzoylated compound **12** (only the compound with an equatorial hydroxyl group was dibenzoylated) was separated. Benzoylation procedure employing BzCN was also attempted but without any improvement of the yields of the monobenzoylated products **13**. Compound **12** can be easily methanolyzed in high yield to the starting diol **11**, which can be re-used in the benzoylation reaction. In one step, the hydroxy group of **13** was oxidized to a keto group and a double bond was introduced to the scaffold by IBX oxidation according to the procedure described by Nicolaou.[19] This procedure went smoothly with an excellent yield (83%). Allylketone **14** was then subjected to the Luche reduction[20] and the obtained alcohols **15** and **16** were easily separated by column chromatography. The undesired alcohol **15** can be oxidized back to ketone **14** by manganese dioxide and thus recycled.

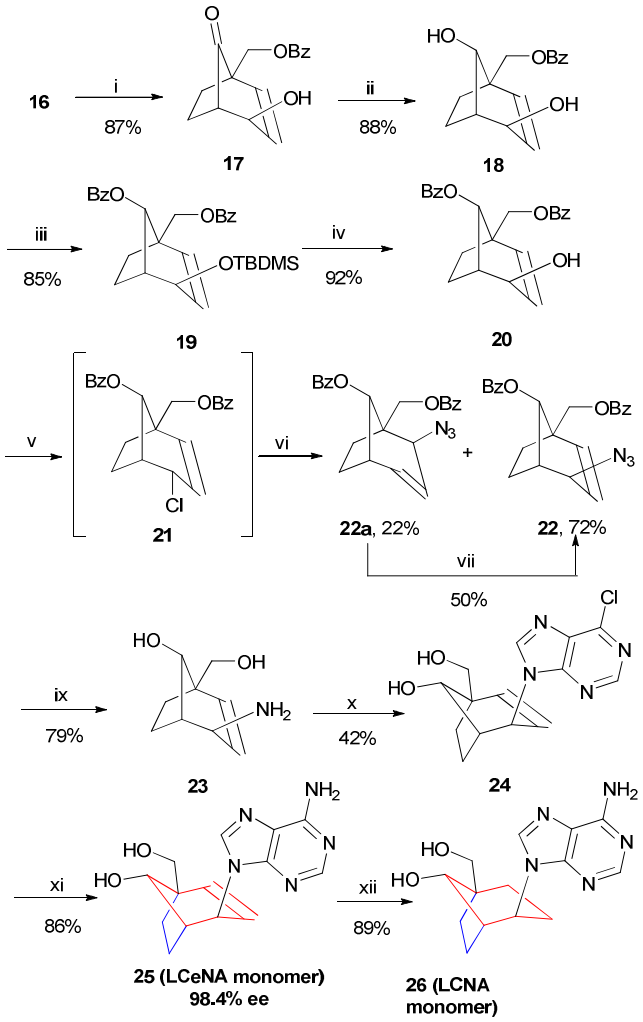


Scheme 1 Synthesis of compound **16**. Reagents and conditions: (i) (a) Q-PHN-OH[17], acrolein, CH_2Cl_2, -25 °C; (b) Cs_2CO_3, toluene, r.t.. (ii) ethyleneglycol, PPTS, benzene, 100 °C; (iii) $LiAlH_4$, Et_2O; (iv) BzCl, pyridine, CH_2Cl_2, -40 °C; (v) MeONa, MeOH; (vi) IBX, DMSO, TsOH, 90 °C; (vii), $NaBH_4$, $CeCl_3$, MeOH, 0 °C; (viii) MnO_2, CH_2Cl_2.

The ketone-protecting group of **16** was easily removed by the reaction with *p*-toluenesulfonic acid in a refluxing acetone-water mixture (Scheme **2**). The keto group of the derivative **17** was then reduced to a hydroxy group by sodium triacetoxyborohydride. The hydroxy group in the position C-4 participates in this reaction and allows to prepare exclusively the product with the desired orientation of the C-8 hydroxy group in diol **18**.[21] Although we tried numerous methodologies for direct introduction of the purine nucleobase (including Tsuji-Trost reaction, Mitsunobu reaction and various direct alkylation methods) using diversely protected derivatives of compound **18** and its congeners with opposite configuration of the allylic hydroxyl, they all failed to give appropriate product either due to low reactivity or undesired allylic rearrangements resulting in complex mixtures of products. Both hydroxy groups were sequentially protected afterwards, the allylic hydroxyl selectively protected by TBDMS group and the C-8 hydroxyl by benzoylation. The TBDMS group was then cleaved by TBAF/acetic acid (reaction mixture is less basic) at elevated temperature (reaction at r.t. is relatively slow) and the free allylic hydroxy group was converted to chloro derivative **21**, followed by the introduction of the azido group by NaN_3. In this stage, we were able to separate isomers **22** and **22a** (a product of the allylic rearrangement) and we also discovered that the undesired isomer **22a** can be easily converted to **22** by standing in acetonitrile solution or better by heating this solution overnight.[22] The allylic rearrangement of **22a** was monitored by ^{1}H NMR spectroscopy (see the Supplementary Information).

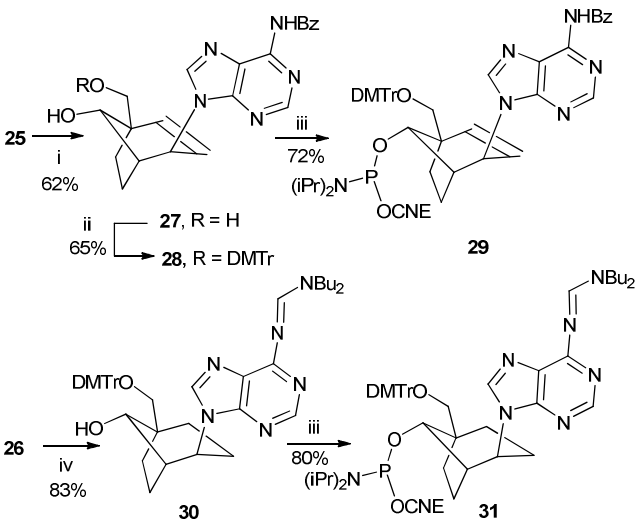
The key amine **23** was prepared by the Staudinger reaction, followed by the removal of the benzoyl protecting groups under basic conditions (Scheme **2**). A purine nucleobase was then introduced in moderate yield (42%) by a recently described MW-assisted build-up protocol.[23] Chloropurine derivative **24** was converted to adenine nucleoside **25** by ammonolysis with ethanolic ammonia under microwave conditions.[23,24] The enantiomeric purity of this LCeNA monomer **25** was determined by chiral HPLC, which assessed the enantiomeric purity above 98%. The saturated analogue **26** was obtained after hydrogenation in high yield (89%). Both nucleosides (**25** and **26**) were used as building blocks for the synthesis of monomeric phosphoramidite units, which were subsequently used for the solid-state oligonucleotide synthesis.

All the compounds were appropriately characterized by ^{1}H and ^{13}C NMR and also by 2D NMR techniques (COSY, HSQC, HMBC). The configuration of the chiral centres at C8 and C4 of compound **25** was confirmed by 2D NMR techniques (COSY, ROESY). In COSY spectrum, 2- and 3-bond spin-spin interactions are visible as crosspeaks. When the hydrogen atoms are in W-like arrangement, it is possible to see 4-bond long-range couplings. Thanks to this fact, it was possible to confirm stereochemistry at C-8, where we found W-like long-range couplings between H8 and H7 (Fig. **3** top). The configuration was also confirmed by ROESY spectrum, where the crosspeaks correspond to the through-space interactions. The H8-H8' crosspeak clearly determined not only configuration at C8 atom, but also the C4 atom; the nucleobase must be above the cycle. For nucleoside **25** we also calculated spin-spin coupling constants by DFT method (B3LYP/6-31+G(d,p)), which were in agreement with experimental data (see Table **S3** in SI).



Scheme 2 Synthesis of nucleosides **25** and **26**. Reagents and conditions: (i) TsOH, acetone-H_2O, reflux; (ii) $NaBH(OAc)_3$, AcOH, CH_3CN, 0 °C to r.t.; (iii) (a) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, (b) BzCl, pyridine, r.t.; (iv) TBAF, AcOH-THF, 60 °C; (v) NCS, °C; PPh_3, CH_2Cl_2, 0 °C; (vi) NaN_3, DMF, 65 °C; (vii) CH_3CN, reflux; (ix) (a) PPh_3, THF, r.t., (b) H_2O, (c) KOH, EtOH-H_2O, reflux; (x) 4,6-dichloro-5-formamidopyrimidine, DIPEA, *n*-BuOH, MW, 160 (xi) NH_3/EtOH, MW, 140 °C; (xii) H_2 (10 bar), $Pd(OH)_2$/C, MeOH, 50 °C

Synthesis of the phosphoramidites **29** and **31** which were used in the solid phase oligonucleotide synthesis is depicted in the Scheme **3**. We used traditional approach and obtained desired compounds in good yields. The obtained phosphoramidites **29** and **31** were then used in classical trityl-off phosphoramidite method for solid-supported oligonucleotide synthesis.



Scheme 3 Synthesis of phosphoramidites **29** and **31**. Reagents and conditions: (i) (a) TMSCl, pyridine, 0 °C, (b) BzCl, pyridine, r.t., (c) aq. NH_3, MeOH; (ii) DMTrCl, pyridine, r.t.; (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, DIPEA, THF, r.t.; (iv) (a) dimethylacetal-*N,N*-dibutylformamide, MeOH, r.t., (b) DMTrCl, pyridine, r.t.; CNE = cyanoethyl.

Hybridization properties of the modified oligonucleotides with their natural DNA and RNA counterparts were evaluated by UV thermal denaturation experiments and the obtained T_m values were compared with those of the corresponding unmodified duplexes (Table **1**).

Table 1. Thermal stability of modified oligonucleotide duplexes[a]

Oligonucleotide	ssRNA T_m (ΔT_m)[b]	ssDNA T_m (ΔT_m)[b]
5′- d(GC$\underline{A}^{25}$T$\underline{A}^{25}$TC$\underline{A}^{25}$C)	22.0 (-4.3 °C)	no comp. form.
5′- r(GC$\underline{A}^{25}$U$\underline{A}^{25}$UC$\underline{A}^{25}$C)	23.0 (-7.7 °C)	22.0 (-4.3 °C)
5′- d(GC$\underline{A}^{26}$T$\underline{A}^{26}$TC$\underline{A}^{26}$C)	no comp. form.	no comp. form.
5′- r(GC$\underline{A}^{26}$U$\underline{A}^{26}$UC$\underline{A}^{26}$C)	no comp. form.	no comp. form.

[a] 4 µM duplex in 50 mM NaH_2PO_4 – Na_2HPO_4 pH 7.2 with 100 mM NaCl; [b] per modification

To our surprise, a striking destabilization effect was observed for both LCeNA and LCNA. Although some destabilization was observed by Migawa *et al.*[25] on structural related cANA derivatives, the drop in affinity is significantly larger in this case and cannot be clarified by the explanation suggested in their work, because the repulsion of the hydrogens in the bridge and the six-membered pseudosugar ring in cANA and LCeNA should lead to opposite effects (Figure **4**). Unfortunately, a similar destabilization effects were observed also for homooligomers prepared from both LCeNA and LCNA subunits while hybridized with complementary oligothymidylates (see the Supporting information).

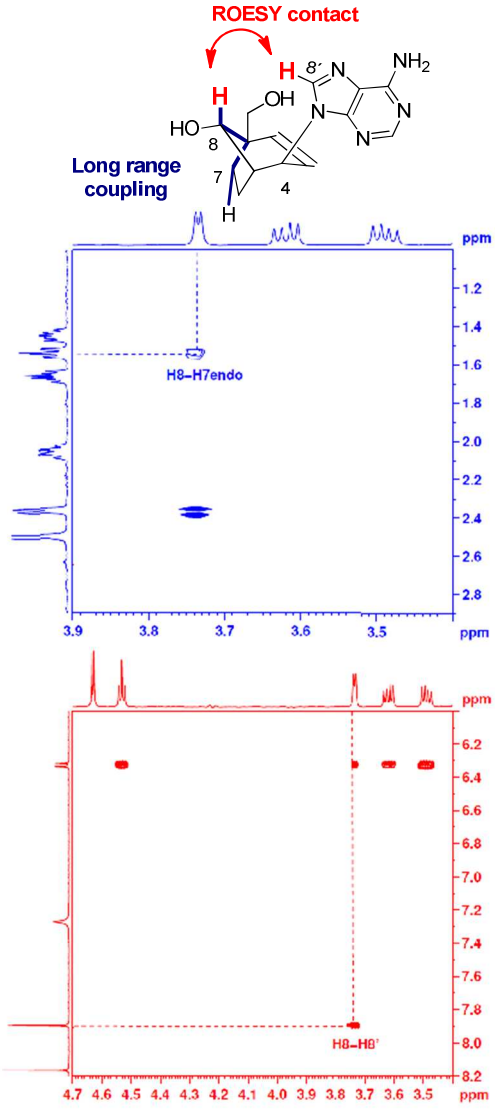


Figure 3 Region of COSY (in blue) and ROESY spectrum (in red) for compound **25**. W-like shaped long-range coupling constant between H8 and H7endo clearly determined configuration at carbon C-8. Through-space interaction H8-H8' confirmed configuration at carbon C-4.

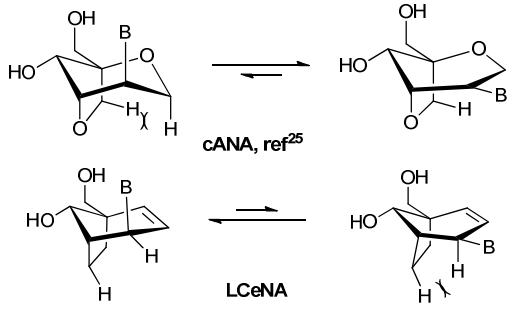


Figure 4 In contrast to the preferred conformation of cANA, LCeNA should adopt a conformation that situates the nucleobase in an "axial-like" orientation due to repulsion of the hydrogen atom of the -CH_2CH_2- bridge and the hydrogen atom vicinal to the nucleobase.

To shed some light on the significant destabilization of the rLCeNA-RNA duplex, we performed the molecular dynamic simulations of RNA duplexes that included normal and locked units. (For a detailed analysis of the calculated results, structural models, and calculation method see Supplementary Information). The values of backbone torsion angles α, γ, and δ calculated for units of RNA oligonucleotides (Figure **S8-S13**) were analysed and statistical distributions of the torsion angles (Figure **S14**) were compared. The calculations unveiled significant structural disorder of modified duplexes as compared to A-RNA structure that was calculated for the duplex that included normal units. The deviations of modified oligonucleotides from canonical A-RNA occurred particularly owing to irregular behaviour of the normal units neighbouring with modified units. The modified units were structurally more rigid though their behaviour was abnormal. In particular, the sugar of modified nucleosides was locked (δ torsion was ca 60°) while the sugar of normal units was flexible (δ torsion ranged from ca 80° to ca 160°). The overall values of α backbone torsions in the neighbourhood of modified residues were smaller by ca 30° as compared to the typical value known for canonical A-RNA. The α-distribution calculated for locked units broadened, which indicated larger amplitudes of motion near phosphate. The α and γ torsions of phosphate groups bridging the locked unit with neighbouring normal units frequently flipped between the values characteristic to A-RNA, $\alpha/\gamma \approx 290°/70°$, and the values calculated owing to locked units, $\alpha/\gamma \approx 180°/180°$. The α-distributions of normal A-RNA duplex were always single-modal and centered at 290° in contrast to bi- or even tri-modal α-distributions calculated in the neighbourhood of locked units (Figure **S14**). The calculations indicated instabilities and structural disorder of the normal residues in the neighbourhoods of modified units. Moreover, the occurrence of α/γ flips depended on positioning of phosphate groups with respect to 3'-end and 5'-end of locked units. The conformationally locked residues of RNA duplexes thus induced particularly irregular behaviour of backbone phosphates in the vicinity of the modified units.

Conclusions

In conclusion, we have prepared novel modified oligonucleotides containing monomers based on bicyclo[3.2.1]octene and octane skeletons as hybrids of CeNA/CNA and LNA. The appropriate monomers were synthesized from a simple achiral precursor – ketoester **8**. As far as we know, this is the first synthesis of the LNA analogues performed by a total synthetic approach. Our molecular dynamic calculations suggest that the surprisingly low affinity of the modified oligonucleotides towards the complementary DNA and RNA results from irregular behaviour of the nucleotides neighbouring with the locked units. The overall structure of the duplex containing locked units was significantly disordered and more conformationally labile in comparison with A-RNA form of a normal duplex.

Experimental section

General

Melting points were determined on a Büchi B-540 apparatus. NMR spectra (δ, ppm; J, Hz) were measured on a Bruker Avance II-600 and/or Bruker Avance II-500 instruments (600.1 or 500.0 MHz for ^{1}H and 150.9 or 125.7 MHz for ^{13}C) in hexadeuterated dimethyl sulfoxide and referenced to the solvent signal (δ 2.50 and 39.70, respectively). Mass spectra were measured on a LTQ Orbitrap XL (Thermo Fisher Scientific) using electrospray ionization (ESI). Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silica gel 60 F254 foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; the compounds were dried at 13 Pa and 50 °C. The elemental analyses were obtained on a Perkin–Elmer CHN Analyzer 2400, Series II Sys (Perkin–Elmer). The elemental compositions for all compounds agreed to within ± 0.4% of the calculated values. For all the tested compounds satisfactory elemental analysis was obtained supporting > 95% purity. Optical rotation was measured on polarimeter Autopol IV (Rudolph Research Analytical) at 589 nm wavelength in chloroform or methanol. Microwave syntheses were carried out in a CEM Discover instrument with a single-mode cavity and focused microwave heating (microwave power supply 0-300 W, 1 W increments, sealed vessel mode, pressure range 0-20 bar). GC-MS analyses were recorded by using a 5975B quadrupole mass spectrometer coupled to a 6890N gas chromatograph (Agilent, Santa Clara, CA, USA) equipped with a Phenomenex ZB-5 HT capillary column (30 m × 0.25 mm, film thickness 0.25 mm); temperature: 60 °C (2 min), then 10 °C/min to 320 °C (10 min).

Preparation of compounds 9a and 9b

To a mixture of starting material **8** (9.05 g, 49.1 mmol) and catalyst Q-PHN-OH[17] (2.40 g, 4.93 mmol, 0.1 eq.) in dry CH_2Cl_2 (100 mL) at - 25 °C under argon atmosphere, a solution of acrolein (8.23 mL, 123 mmol, 2.5 eq.) in CH_2Cl_2 (30 mL) was added dropwise. Reaction mixture was occasionally stirred (>95% of time without stirring) and kept at -25 °C for 24 h. Then the reaction mixture was poured onto silica gel column (200 g, Et_2O) and crude product was eluted with Et_2O. Fractions containing product were collected and evaporated to afford crude intermediate (12.53 g) which was used immediately in the next step. Crude catalyst was then eluted from the column with methanol and recycled (chromatography on silica gel column in CH_2Cl_2:ethanol 25:1). Crude intermediate was dissolved in toluene (350 mL), cesium carbonate (8.48 g, 26 mmol) was added and the reaction mixture was stirred at r.t. overnight. Solids were removed by filtration through Celite and the filtrate was evaporated. Product was purified on a silica gel column (250 g, toluene: ethyl acetate 3:1 → 2:1) to afford 9.416 g (80%) of the mixture **9a** and **9b** (GC chromatogram, Figure **S1**.) Analytical samples of both isomers were obtained by column chromatography of the sample (300 mg of the mixture, 100 g of silica gel, toluene: ethyl acetate 3:1 → 2:1). For determination of the optical purity of this step see the Supplementary Information.

tert-Butyl (1*S*,4*S*,5*S*)-4-hydroxy-8-oxobicyclo[3.2.1]octane-1-carboxylate **(9a)**
Viscous oil. $[\alpha]_D^{20}$ = -22.8 (c 0.325, $CHCl_3$). Found: C, 65.26; H, 8.39. Calc. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%.^{1}H NMR (500 MHz, d6-DMSO): δ 1.39 (s, 9H, *t*Bu), 1.48-1.58 (m, 1H, H-3a), 1.67-1.87 (m, 5H, H-3b, H-7a, H-6ex, H-2), 1.90-1.97 (m, 1 H, H-6en), 2.30-2.36 (m, 1H, H-7b), 2.38 (dd, $J_{5\text{-}4}$ = 3.1, $J_{5\text{-}6ex}$ = 6.7, 1H, H-5), 3.76-3.82 (m, 1H, H-4), 5.14 (d, $J_{OH\text{-}4}$ = 4.5, 1H, OH). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 16.02 (C-6), 26.52 and 26.63 (C-3 and C-7), 27.86 (C(**C**H_3)$_3$), 31.05 (C-2), 54.37 (C-5), 57.05 (C-1), 73.00 (C-4), 80.47 (**C**(CH_3)$_3$), 170.27 (**C**OOtBu), 211.58 (C-8). ESI MS, *m/z*

(rel%): 263 (100) [M+Na]. HRMS: calcd. for [M+Na]: 263.12538, found: 263.12541.

tert-Butyl (1*S*,4*R*,5*S*)-4-hydroxy-8-oxobicyclo[3.2.1]octane-1-carboxylate **(9b)**
Viscous oil. $[\alpha]_D^{20}$ = -5.5 (c 0.381, $CHCl_3$). Found: C, 65.17; H, 8.56. Calc. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.39 (s, 9H, *t*Bu), 1.49 (ddm, $J_{3ax\text{-}2ax}$ = 5.3, J_{gem} = 14.8, 1H, H-3ax), 1.57 (dddd, $J_{6en\text{-}5}$ = 0.8, $J_{6en\text{-}7ex}$ = 4.4, $J_{6en\text{-}7en}$ = 10.8, J_{gem} = 13.3, 1H, H-6en), 1.77-1.85 (m, 2H, H-2eq, H-6ex), 1.87-1.95 (m, 2H, H-7en, H-3eq), 2.25-2.36 (m, 3H, H-5, H-2ax, H-7ex), 4.06-4.09 (m, 1H, H-4), 4.99 (dm, $J_{OH\text{-}4}$ = 2.8, 1H, OH). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 18.67 (C-6), 25.16 (C-7), 25.51(C-7), 27.94 (C(**C**H$_3$)$_3$), 33.35 (C-2), 51.96 (C-5), 57.28 (C-1), 76.38 (C-4), 80.34 (**C**(CH$_3$)$_3$), 170.42 (**C**OOtBu), 211.44 (C-8). ESI MS, *m/z* (rel%): 263 (100) [M+Na]. HRMS: calcd. for [M+Na]: 263.12538, found: 263.12541.

Preparation of compounds 10a and 10b

A mixture of alcohols **9a** and **9b** (9.1 g, 37.9 mmol) was dissolved in benzene (320 mL) and pyridinium *p*-toluenesulfonate (1.97 g, 7.8 mmol) and ethyleneglycol (9.2 mL) were added. Reaction mixture was heated to reflux with Dean-Stark trap for 24 hours and then cooled to r.t., diluted with ethyl acetate (450 mL) and washed with water (300 mL) and saturated aq. sodium bicarbonate (2 x 300 mL). Organic phase was dried over sodium sulfate and evaporated. Residue was purified on a silica gel column (350 g, toluene:ethyl acetate 1:1) to obtain 9.15 g (85%) of the mixture of **10a** and **10b**. Analytical samples of both isomers were obtained after a chromatography of a sample (300 mg of the mixture, toluene:ethyl acetate 3:1 → 2:1).

tert-Butyl (1*S*,4*S*,5*S*)-4-hydroxy-1*H*-spiro[bicyclo[3.2.1]octane-8,2'-[1,3]dioxolane]-1-carboxylate **(10a)**
Viscous oil. $[\alpha]_D^{20}$ = -22.4 (c 0.277, $CHCl_3$). Found: C, 63.24; H, 8.53. Calc. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.14-1.22 (m, 1H, H-3eq), 1.32-1.49 (m, 12H, *t*Bu, H-2eq, H-6ex, H-7en), 1.54-1.60 (m, 1H, H-6en), 1.61-1.67 (m, 1H, H-3ax), 1.82 (dd, $J_{5\text{-}4}$ = 3.1, $J_{5\text{-}6ex}$ = 6.4, 1H, H-5), 1.95-2.02 (m, 1H, H-2ax), 2.17-2.24 (m, 1H, H-7ex), 3.76-3.91 (m, 5H, -OC**H$_2$**C**H$_2$**O-, H-4), 4.45 (d, $J_{OH\text{-}4}$ = 4.6, 1H, OH). ^{13}C NMR (150.92 MHz, d6-DMSO): δ 17.70 (C-6), 26.37 (C-3), 27.80 (C(**C**H$_3$)$_3$), 28.10 (C-7), 29.85 (C-2), 49.23 (C-5), 52.38 (C-1), 63.93 and 65.42 (-O**C**H$_2$**C**H$_2$O-), 67.78 (C-4), 79.26 (**C**(CH$_3$)$_3$), 116.08 (C-8), 172.49 (**C**OOtBu). ESI MS, *m/z* (rel%): 307 (100) [M+Na]. HRMS: calcd. for [M+Na]: 307.15160, found: 307.15163.

tert-Butyl (1*S*,4*R*,5*S*)-4-hydroxy-1*H*-spiro[bicyclo[3.2.1]octane-8,2'-[1,3]dioxolane]-1-carboxylate **(10b)**
Viscous oil. $[\alpha]_D^{20}$ = -21.7 (c 0.373, $CHCl_3$). Found: C, 63.29; H, 8.69. Calc. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.14 (ddd, $J_{6en\text{-}7ex}$ = 4.4, $J_{6en\text{-}7en}$ = 10.0, J_{gem} = 13.0, 1H, H-6en), 1.38 (s, 9H, *t*Bu), 1.39-1.46 (m, 2H, H-2eq, H-3eq), 1.56 (ddd, $J_{7en\text{-}6ex}$ = 4.7, $J_{7en\text{-}6en}$ = 10.8, J_{gem} = 13.3, 1H, H-7en), 1.64-1.73 (m, 2H, H-3ax, H-6ex), 1.91 (dd, $J_{5\text{-}4}$ = 4.0, $J_{5\text{-}6ex}$ = 7.2, 1H, H-5), 2.18 (dddm, $J_{7ex\text{-}6en}$ = 4.4, $J_{7ex\text{-}6ex}$ = 12.5, J_{gem} = 13.3, 1H, H-7ex), 2.32 (tdd, $J_{2ax\text{-}7ex}$ = 1.4, $J_{2ax\text{-}3ax}$ = 5.6, $J_{2ax\text{-}3eq}$ = J_{gem} = 13.7, 1H, H-2ax), 3.67-3.72 (m, 1H, H-4), 3.82-4.03 (m, 4H, -OC**H$_2$**C**H$_2$**O-), 4.14 (d, $J_{OH\text{-}4}$ = 9.6, 1H, OH). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 21.60 (C-6), 25.99 (C-3), 26.38 (C-7), 27.82 (C(**C**H$_3$)$_3$), 29.36 (C-2), 45.37 (C-5), 52.48 (C-1), 63.98 and 65.73 (-O**C**H$_2$**C**H$_2$O-), 72.65 (C-4), 79.48 (**C**(CH$_3$)$_3$), 116.32 (C-8), 172.00 (**C**OOtBu). ESI MS, *m/z* (rel%): 307 (100) [M+Na]. HRMS: calcd. for [M+Na]: 307.15160, found: 307.15165.

Preparation of compounds 13a and 13b

A mixture of alcohols **10a** and **10b** (9.79 g, 34.43 mmol) was dissolved in anhydrous ether (1000 mL) and cooled down with ice bath (argon atmosphere). A solution of $LiAlH_4$ in THF (60.5 mL, 1 M solution, 1.75 eq.) was added dropwise in 30 minutes. Reaction was allowed to slowly reach room temperature and stirred overnight, then cooled again to 0 °C and quenched with ice. Solids were removed by filtration through a Celite pad and thoroughly washed with ethanol. Filtrate was concentrated and residue was chromatographed on a silica gel column (300 g, ethyl acetate:ethanol 20:1) to afford an inseparable mixture of the diols (**11**, 6.86 g, 92%).

(1*S*,5*R*)-1-(Hydroxymethyl)spiro[bicyclo[3.2.1]octane-8,2'-[1,3]dioxolan]-4-ol **(11)**
Viscous oil. Found: C, 61.78; H, 8.43. Calc. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%. CI MS, *m/z* (rel%): 214 (5) [M+H], 197 (100) [M-OH]. HRMS: calcd. for [M+H]: 215.1283, found: 215.1286.

Benzoylation of the diol 11

Compound **11** (7.267 g, 33.9 mmol) was dissolved in CH_2Cl_2 (300 mL) and pyridine was added (5.5 mL, 68 mmol). Reaction mixture was cooled to -40°C and a solution of benzyol chloride (5.9 mL, 50.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise during 1 h and the reaction mixture was stirred at -40 °C for 13 hours. Reaction was quenched with methanol and all volatiles were evaporated. Residue was dissolved in ethyl acetate (700 mL) and washed with water (300 mL), satd. sodium bicarbonate (300 mL), dried with sodium sulfate and evaporated. Residue was chromatographed on silica gel (400 g, toluene:ethyl acetate 4:1 → 1:1) to afford 3.580 g of **12** (25%) and 7.261 g of **13a**+**13b** (67%, mixture). The mixture of monobenzoylated compounds **13a**+**13b** was separated on a small scale by column chromatography (250 mg of the mixture, 100 g, toluene:ethyl acetate 2:1).

(1*S*,4*S*,5*R*)-1-((Benzoyloxy)methyl)spiro[bicyclo[3.2.1]octane-8,2'-[1,3]dioxolan]-4-yl benzoate **(12)**
Light oil. $[\alpha]_D^{20}$ = +0 (c 0.312, $CHCl_3$), $[\alpha]_D^{20}$ = +4.0 (c 0.294, CH_3OH). Found: C, 71.35; H, 6.31. Calc. for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20%. ^{1}H NMR (400 MHz, d6-DMSO): δ 1.60-1.76 (m, 5H, H-2a, H-2b, H-3ax, H-6b, H-7b), 1.78-1.92 (m, 2H, H-6a, H-7a), 1.95-2.02 (m, 1H, H-3eq), 2.27 (dd, $J_{5\text{-}4}$ = 3.1, $J_{5\text{-}6ex}$ = 6.0, 1H, H-5), 3.90-3.99 (m, 4H, -OC**H$_2$**C**H$_2$**O-), 4.22 and 4.29 (2 x d, 2H, J_{gem} = 10.9, BzOC**H$_2$**-), 5.25 (ddd, $J_{4\text{-}5}$ = 3.1, $J_{4\text{-}3eq}$ = 5.8, $J_{4\text{-}3ax}$ = 10.6, H-4), 7.50-7.54 (m, 4H, Ph-*m1*, Ph-*m2*), 7.63-7.69 (m, 2H, Ph-*p1*, Ph-*p2*), 7.94-7.99 (m, 4H, Ph-*o1*, Ph-*o2*). ^{13}C NMR (100.6 MHz, d6-DMSO): δ 19.28 (C-6), 23.29 (C-3), 28.32 (C-7), 28.94 (C-2), 44.98 (C-5), 45.00 (C-1), 64.20 and 65.31 (-O**C**H$_2$**C**H$_2$O-), 66.55 (BzO**C**H$_2$-), 73.07 (C-4), 115.45 (C-8), 128.92 and 129.00 (C-*m1*, C-*m2*), 129.28 (C-*o2*, C-*o1*), 129.98 and 130.17 (C-*i1* and C-*i2*), 133.49 and 133.50 (C-*p1*, C-*p2*), 165.09 and 165.93 (2 x **C**OO). CI MS, *m/z* (rel%): 423 (10) [M+H], 301 (100). HRMS: calcd. for [M+H]: 423.1808, found: 423.1802.

((1*R*,2*R*,5*S*)-2-Hydroxyspiro[bicyclo[3.2.1]octane-8,2'-[1,3]dioxolan]-5-yl)methyl benzoate **(13a)**
Viscous oil. $[\alpha]_D^{20}$ = +6.3 (c 0.158, $CHCl_3$). Found: C, 68.19; H, 7.14. Calc. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97%. ^{1}H NMR (400 MHz, d6-DMSO): δ 1.24 (m, 1H, H-6b), 1.45-1.55 (m, 2H, H-2b, H-3b),

1.60-1.64 (m, 2H, H-7a, H-7b), 1.66-1.64 (m, 2H, H-3a, H-6a), 2.00 (dd, $J_{5\text{-}4}$ = 4.2, $J_{5\text{-}6ex}$ = 6.9, 1H, H-5), 2.06 (m, 1H, H-2a), 3.74 (m, 1H, H-4), 3.84-3.99 (m, 4H, -OC**H**$_2$C**H**$_2$O-), 4.11 (d, $J_{OH\text{-}4}$ = 9.2, 1H, 4-O**H**), 4.18 and 4.24 (2 x d, 2H, J_{gem} = 10.8, BzOC**H**$_2$-), 7.54 (m, 2H, Ph-*m*), 7.66 (m, 1H, Ph-*p*), 7.96 (m, 2H, Ph-*o*). ^{13}C NMR (100.6 MHz, d6-DMSO): δ 22.30 (C-6), 26.21 (C-3), 27.40 (C-7), 27.91 (C-2), 44.30 (C-5), 45.06 (C-1), 63.97 and 65.43 (-O**C**H$_2$**C**H$_2$O-), 66.88 (BzO**C**H$_2$-), 72.74 (C-4), 116.37 (C-8), 128.99 (C-*m*), 129.26 (C-*o*), 130.02 (C-*i*), 133.47 (C-*p*), 165.97 (**C**OO). CI MS, *m/z* (rel%): 319 (25) [M+H], 301 (100). HRMS: calcd. for [M+H]: 319.1545, found: 319.1546.

((1*R*,2*S*,5*S*)-2-Hydroxyspiro[bicyclo[3.2.1]octane-8,2'-[1,3]dioxolan]-5-yl)methyl benzoate (**13b**)
Viscous oil. $[\alpha]_D^{20}$ = +4.9 (c 0.284, $CHCl_3$). Found: C, 67.68; H, 7.21. Calc. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97%. ^{1}H NMR (400 MHz, d6-DMSO): δ 1.21-1.33 (m, 1H, H-3b), 1.42-1.54 (m, 3H, H-2b, H-6b, H-7b), 1.59-1.75 (m, 4H, H-2a, H-3a, H-6a, H-7a), 1.91 (dd, $J_{5\text{-}4}$ = 3.0, $J_{5\text{-}6ex}$ = 6.3, 1H, H-5), 3.83-3.89 (m, 5H, -OC**H**$_2$C**H**$_2$O-, H-4), 4.15 and 4.23 (2 x d, 2H, J_{gem} = 10.8, BzOC**H**$_2$-), 4.45 (d, $J_{OH\text{-}4}$ = 4.7, 1H, 4-O**H**), 7.51-7.56 (m, 2H, Ph-*m*), 7.63-7.68 (m, 1H, Ph-*p*), 7.93-7.96 (m, 2H, Ph-*o*). ^{13}C NMR (100.6 MHz, d6-DMSO): δ 18.46 (C-6), 26.87 (C-3), 28.56 (C-7), 29.12 (C-2), 44.88 (C-1), 48.01 (C-5), 63.94 and 65.15 (-O**C**H$_2$**C**H$_2$O-), 66.96 (BzO**C**H$_2$-), 68.00 (C-4), 115.89 (C-8), 128.98 (C-*m*), 129.25 (C-*o*), 130.04 (C-*i*), 133.46 (C-*p*), 165.96 (**C**OO). CI MS, *m/z* (rel%): 319 (25) [M+H], 301 (100). HRMS: calcd. for [M+H]: 319.1545, found: 319.1544.

Recyclation of diol 11 from 12.

A freshly prepared sodium methoxide in methanol (prepared from 70 mg of sodium and 27 mL of absolute methanol) was added to a solution of the diol **12** (3.4 g, 8.1 mmol) in absolute methanol (55 mL). Reaction mixture was heated to 60 °C for 12 h and evaporated. Residue was chromatographed on a silica gel column (200 g, ethyl acetate) and 1.54 g (89%) of the recycled diol **11** was obtained. This diol was used again for the monobenzoylation reaction.

((1*S*,5*R*)-4-Oxospiro[bicyclo[3.2.1]oct[2]ene-8,2'-[1,3]dioxolan]-1-yl)methyl benzoate (14)

A mixture of alcohols **13a** and **13b** (5.644 g, 17.73 mmol) was dissolved in DMSO (125 mL) and IBX (20.1 g, 71.8 mmol) and *p*-TsOH (1.013 g, 5.33 mmol) was added. Reaction mixture was stirred at r.t. for 1 h and then heated to 90 °C for 16 h. A second portion of IBX (2 g) was added and heating was continued for another 3 h. After cooling, the reaction mixture was carefully poured to a satd. solution of sodium bicarbonate (400 mL) and this mixture was extracted with ethyl acetate (3 x 500 mL). Combined organic phases were washed with satd. solution of sodium bicarbonate (2 x 600 mL), dried with sodium sulfate and evaporated. Product was purified on a silica gel column (250 g) with diethyl ether as a mobile phase to afford 4.618 g (83%) of the product **14**. Analytical sample was obtained by purification on a silica gel column (toluene-ethyl acetate 4:1). Viscous oil. $[\alpha]_D^{20}$ = +139.4 (c 0.307, $CHCl_3$). Found: C, 68.54; H, 5.87. Calc. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.32-1.39 (m, 1H, H-6en), 1.68-1.74 (m, 1H, H-7en), 1.97-2.03 (m, H-7ex), 2.10-2.17 (m, 1H, H-6ex), 2.77 (ddm, 1H, $J_{5\text{-}3}$ = 1.7, $J_{5\text{-}6ex}$ = 7.7, 1H, H-5), 3.73-3.98 (m, 4H, -OC**H**$_2$C**H**$_2$O-), 4.44 and 4.51 (2 x d, 2H, J_{gem} = 11.1, BzOC**H**$_2$-), 6.09 (dd, $J_{3\text{-}5}$ = 1.7, $J_{3\text{-}2}$ = 9.9, 1H, H-3), 7.38 (d, $J_{2\text{-}3}$ = 9.9, 1H, H-2), 7.53-7.56 (m, 2H, Ph-*m*), 7.65-7.69 (m, 1H, Ph-*p*), 7.96-7.98 (m, 2H, Ph-*o*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 20.81 (C-6), 30.76 (C-7), 50.87 (C-1), 57.47 (C-5), 63.67 (BzO**C**H$_2$-), 65.15 and 65.40 (-O**C**H$_2$**C**H$_2$O-), 117.61 (C-8), 128.36 (C-3), 128.97 (C-*m*), 129.35 (C-*o*), 129.75 (C-*i*), 133.60 (C-*p*), 154.23 (C-2), 165.86 (**C**OO), 200.87 (C-4). ESI MS, *m/z* (rel%): 337 (100) [M+Na]. HRMS: calcd. for [M+Na]: 337.10464, found: 337.10469.

Preparation of compounds 15 and 16

To a solution of the starting material **14** (6.293 g, 20.02 mmol) in methanol (330 mL) at 0 °C, cerium(III) chloride heptahydrate (14.65 g, 35.3 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. Sodium borohydride (1.05 g, 27.8 mmol) was added in three portions during 30 minutes, the reaction mixture was stirred at 0 °C for an additional hour, quenched with ice and evaporated. The residue was dissolved in ethyl acetate (600 mL) and washed with water (300 mL). The water phase was extracted with ethyl acetate (600 mL), combined organic phases were dried with sodium sulfate and evaporated. Residue was chromatographed on silica gel (400 g, toluene:ethyl acetate 4:1 → 1:1) to afford 3.293 g of **16** (52%) and 2.827 g of **15** (45%) (Both colourless oils).

((1*S*,4*S*,5*R*)-4-Hydroxyspiro[bicyclo[3.2.1]oct[2]ene-8,2'-[1,3]dioxolan]-1-yl)methyl benzoate **(15)**
$[\alpha]_D^{20}$ = +121.2 (c 0.307, $CHCl_3$). Found: C, 68.01; H, 6.57. Calc. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.51-1.56 (m, 1H, H-6ex), 1.57-1.62 (m, 1H, H-7en), 1.74-1.79 (m, 1H, H-7ex), 1.92 (ddd, $J_{6en\text{-}7ex}$ = 6.6, $J_{6en\text{-}7en}$ = 9.8, J_{gem} = 13.3, 1H, H-6en), 2.09-2.12 (m, 1H, H-5), 3.80-3.93 (m, 4H, -OC**H**$_2$C**H**$_2$O-), 4.26 and 4.33 (2 x d, 2H, J_{gem} = 10.9, BzOC**H**$_2$-), 4.48 (bs, 1H, H-4), 4.80 (d, $J_{OH\text{-}4}$ = 4.5, 1H, OH), 5.49 (dm, $J_{3\text{-}2}$ = 9.7, 1H, H-3), 5.77 (dd, $J_{2\text{-}4}$ = 1.7, $J_{2\text{-}3}$ = 9.7, 1H, H-2), 7.53-7.55 (m, 2H, Ph-*m*), 7.64-7.67 (m, 1H, Ph-*p*), 7.94-7.96 (m, 2H, Ph-*o*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 18.09 (C-6), 33.29 (C-7), 46.62 (C-5), 47.28 (C-1), 64.24 and 65.33 (-O**C**H$_2$**C**H$_2$O-), 64.63 (BzO**C**H$_2$-), 71.01 (H-4), 116.59 (H-8), 128.95 (C-*m*), 129.29 (C-*o*), 129.86 (C-3), 129.97 (C-*i*), 131.21 (C-2), 133.48 (C-*p*), 165.86 (**C**OO). ESI MS, *m/z* (rel%): 339 (100) [M+Na]. HRMS: calcd. for [M+Na]: 339.12029, found: 339.12024.

((1*S*,4*R*,5*R*)-4-Hydroxyspiro[bicyclo[3.2.1]oct[2]ene-8,2'-[1,3]dioxolan]-1-yl)methyl benzoate **(16)**
$[\alpha]_D^{20}$ = +52.6 (c 0.312, $CHCl_3$). Found: C, 68.24; H, 6.40. Calc. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.15 (dddd, $J_{6en\text{-}5}$ = 1.1, $J_{6en\text{-}7ex}$ = 5.9, $J_{6en\text{-}7en}$ = 9.8, J_{gem} = 13.4, 1H, H-6en), 1.56-1.61 (m, 1H, H-7en), 1.70-1.76 (m, 1H, H-7ex), 1.83-1.91 (m, 1H, H-6ex), 2.10 (dm, $J_{5\text{-}6ex}$ = 7.9, 1H, H-5), 3.80-3.98 (m, 6H, -OC**H**$_2$C**H**$_2$O-, H-4, 4-OH), 4.31 and 4.36 (2 x d, 2H, J_{gem} = 11.0, BzOC**H**$_2$-), 5.70 (ddd, $J_{3\text{-}5}$ = 1.5, $J_{3\text{-}4}$ = 3.4, $J_{3\text{-}2}$ = 9.6, 1H, H-3), 5.92 (d, $J_{2\text{-}3}$ = 9.6, 1H, H-2), 7.52-7.55 (m, 2H, Ph-*m*), 7.64-7.68 (m, 1H, Ph-*p*), 7.96-7.98 (m, 2H, Ph-*o*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 22.30 (C-6), 32.06 (C-7), 44.46 (C-5), 47.40 (C-1), 64.22 and 65.14 (-O**C**H$_2$**C**H$_2$O-), 64.77 (BzO**C**H$_2$-), 74.27 (C-4), 115.40 (C-8), 128.49 (C-3), 128.49 (C-*m*), 129.28 (C-*o*), 129.93 (C-*i*), 133.03 (C-*p*), 133.46 (C-2), 165.99 (**C**OO). ESI MS, *m/z* (rel%): 339 (100) [M+Na]. HRMS: calcd. for [M+Na]: 339.12029, found: 339.12026.

Recycling of alcohol 15 to ketone 14

To a solution of allyl alcohol **15** (2.088 g, 6.6 mmol) in CH_2Cl_2 (100 mL) manganese (IV) oxide (6.4 g, 10 eq, activated, ~ 90%) was added in one portion and the reaction mixture was stirred overnight. Solids were removed by filtration on a Celite pad and thoroughly washed with ethyl acetate. Filtrate was evaporated and the crude **15** (quant. yield) was re-used in the Luche reduction. Analytical sample

was obtained by silica gel chromatography (toluene-ethyl acetate 4:1). NMR spectra match those for **14**.

((1*S*,4*R*,5*R*)-4-Hydroxy-8-oxobicyclo[3.2.1]oct-2-en-1-yl)methyl benzoate (17)

p-TsOH (2.38 g, 12.49 mmol) was added to a solution of allyl alcohol **16** (3.293 g, 10.41 mmol) in acetone (180 mL) and water (90 mL) and the reaction mixture was heated to reflux for 10 h and then to 50 °C for another 10 h. Reaction mixture was evaporated to half of the original volume and diluted with ethyl acetate (700 mL). Organic phase was washed with water (300 mL) and saturated aq. sodium bicarbonate (300 mL), dried over sodium sulfate and evaporated. Product was purified on a silica gel column (250 g, toluene:ethyl acetate 4:1 → 2:1) to afford 2.456 g (87%) of **17** as viscous oil. $[\alpha]_D^{20}$ = +15.3 (c 0.326, $CHCl_3$). Found: C, 70.63; H, 6.27. Calc. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.50-1.57 (m, 1H, H-6en), 1.86-1.95 (m, 2H, H-7en, H-7ex), 2.03-2.11 (m, 1H, H-6ex), 2.36 (dm, $J_{5\text{-}6ex}$ = 8.4, 1H, H-5), 4.32 and 4.35 (2 x d, 2H, J_{gem} = 11.3, BzOC**H$_2$**-), 4.55 (bs, 1H, H-4), 5.39 (bs, 1H, 4-OH), 5.75 (ddd, $J_{3\text{-}5}$ = 1.2, $J_{3\text{-}4}$ = 3.8, $J_{3\text{-}2}$ = 9.1, 1H, H-3), 5.96 (d, $J_{2\text{-}3}$ = 9.1, 1H, H-2), 7.51-7.55 (m, 2H, Ph-*m*), 7.65-7.68 (m, 1H, Ph-*p*), 7.92-7.95 (m, 2H, Ph-*o*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 19.35 (C-6), 29.16 (C-7), 49.88 (C-1), 50.10 (C-5), 63.75 (BzO**C**H$_2$-), 79.92 (C-4), 129.01 (C-*m*), 129.39 (C-*o*), 129.56 (C-3), 129.74 (C-*i*), 133.55 and 133.66 (C-*p* and C-2), 165.86 (**C**OO), 212.74 (C-8). ESI MS, *m/z* (rel%): 295 (100) [M+Na]. HRMS: calcd. for [M+Na]: 295.09408, found: 295.09416.

((1*S*,4*R*,5*R*,8*S*)-4,8-Dihydroxybicyclo[3.2.1]oct-2-en-1-yl)methyl benzoate (18)

To an ice-cooled solution of the keto derivative **17** (2.456 g, 9.02 mmol) in a mixture of acetonitrile (170 mL) and acetic acid (5.2 mL), sodium triacetoxyborohydride (2.87 g, 13.5 mmol) was added in four portions during 30 minutes. Reaction mixture was allowed to warm to r.t. and stirring was continued for 12 h. Reaction mixture was quenched with methanol and evaporated. Residue was dissolved in methanol and adsorbed on silica gel. Chromatography on a silica gel column (200 g) in ethyl acetate afforded 2.173 g (88%) of the product **18** as white solid. M.p. 130-131 °C. $[\alpha]_D^{20}$ = -7.1 (c 0.320, $CHCl_3$). Found: C, 69.90; H, 6.60. Calc. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.09-1.15 (m, 1H, H-6en), 1.43-1.48 (m, 1H, H-7en), 1.63-1.70 (m, 1H, H-7ex), 1.88-1.96 (m, 1H, H-6ex), 2.12 (dm, $J_{5\text{-}6ex}$ = 8.0, 1H, H-5), 3.86-3.89 (m, 1H, H-4), 3.99 (d, $J_{8\text{-}OH}$ = 4.0, 1H, H-8), 4.29 and 4.33 (2 x d, 2H, J_{gem} = 10.6, BzOC**H$_2$**-), 4.85 (d, $J_{OH\text{-}8}$ = 4.0, 1H, 8-OH), 4.94 (d, $J_{OH\text{-}4}$ = 5.2, 1H, 4-OH), 5.52 (ddd, $J_{3\text{-}5}$ = 1.6, $J_{3\text{-}4}$ = 3.9, $J_{3\text{-}2}$ = 9.4, 1H, H-3), 5.85 (d, $J_{2\text{-}3}$ = 9.4, 1H, H-2), 7.51-7.55 (m, 2H, Ph-*m*), 7.64-7.68 (m, 1H, Ph-*p*), 7.95-7.97 (m, 2H, Ph-*o*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 23.65 (C-6), 31.33 (C-7), 48.77 (C-5), 49.75 (C-1), 66.44 (BzO**C**H$_2$-), 72.08 (C-8), 73.25 (C-4), 128.12 (C-3), 128.93 (C-*m*), 129.35 (C-*o*), 130.21 (C-*i*), 133.46 (C-*p*), 135.73 (C-2), 166.07 (**C**OO). ESI MS, *m/z* (rel%): 297 (100) [M+Na]. HRMS: calcd. for [M+Na]: 297.10973, found: 297.10972.

((1*S*,4*R*,5*S*,8*S*)-8-(Benzoyloxy)-4-((tert-butyldimethylsilyl)oxy)bicyclo[3.2.1]oct-2-en-1-yl)methyl benzoate (19)

To an ice-cooled solution of diol **18** (2.419, 8.82 mmol) and imidazole (901 mg, 13.23 mmol) in CH_2Cl_2 (53 mL) was added TBDMSCl (total amount 1.6 g, 10.6 mmol) in two portions during 30 minutes and the reaction mixture was stirred at 0 °C for 16 h. Volatiles were evaporated, residue was dissolved in ethyl acetate (700 mL) and the organic phase was washed with water (2 x 300 mL), dried with sodium sulfate, evaporated and co-evaporated with benzene (200 mL). Crude intermediate was dissolved in pyridine (50 mL) and DMAP (catalytic amount) and benzoylchloride (2.05 mL 17.6 mmol) were added. The reaction mixture was left in the dark for 18 h. Reaction was then quenched with water and pyridine was evaporated. The residue was dissolved in ethyl acetate (700 mL) and washed with water (2 x 300 mL) and saturated aq. sodium bicarbonate (2 x 300 mL), dried with sodium sulfate and evaporated. Product was isolated by column chromatography on silica gel (250 g, hexanes:ethyl acetate 20:1) affording 3.691 g (85% over two steps) of **19** as an oil. $[\alpha]_D^{20}$ = +54.4 (c 0.375, $CHCl_3$). Found: C, 70.99; H, 7.36. Calc. for $C_{29}H_{36}O_5Si$: C, 70.70; H, 7.37%. ^{1}H NMR (500 MHz, d6-DMSO): δ 0.07 and 0.08 (2 x s, 2 x 3H, 2 x CH_3), 0.88 (s, 9H, *t*Bu), 1.33-1.39 (m, 1H, H-6en), 1.67-1.73 (m, 1H, H-7en), 1.95-2.01 (m, 1H, H-7ex), 2.04-2.12 (m, 1H, H-6ex), 2.38 (dm, $J_{5\text{-}6ex}$ = 7.9, 1H, H-5), 4.17-4.19 (m, 1H, H-4), 4.34 and 4.41 (2 x d, 2H, J_{gem} = 11.1, BzOC**H$_2$**-), 5.46 (bs, 1H, H-8), 5.64 (ddd, $J_{3\text{-}5}$ = 1.5, $J_{3\text{-}4}$ = 4.1, $J_{3\text{-}2}$ = 9.4, 1H, H-3), 5.96 (d, $J_{2\text{-}3}$ = 9.4, 1H, H-2), 7.45-7.52 (m, 4H, Ph-*m1*, Ph-*m2*), 7.61-7.66 (m, 2H, Ph-*p1*, Ph-*p2*), 7.87-7.89 (m, 2H, Ph-*o2*), 7.95-7.97 (m, 2H, Ph-*o1*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ -4.30 and -4.55 (2 x **C**H$_3$), 17.99 (**C**(CH$_3$)$_3$), 22.92 (C-6), 25.91 (*t*Bu), 31.41 (C-7), 47.00 (C-5), 49.19 (C-1), 65.46 (BzO**C**H$_2$-), 73.87 (C-4), 77.11 (C-8), 127.98 (C-3), 128.87 and 128.96 (C-*m1*, C-*m2*), 129.27 (C-*o2*), 129.44 (C-*o1*), 129.81 and 130.02 (C-*i1* and C-*i2*), 133.54 (C-*p1*, C-*p2*), 135.02 (C-2), 164.93 (**C**OO-1), 165.70 (**C**OO-2). ESI MS, *m/z* (rel%): 515 (100) [M+Na]. HRMS: calcd. for [M+Na]: 515.22242, found: 515.22244.

((1*S*,4*R*,5*R*,8*S*)-8-(Benzoyloxy)-4-hydroxybicyclo[3.2.1]oct-2-en-1-yl)methyl benzoate (20)

Silyl derivative **19** (2.910 g, 5.91 mmol) was dissolved in a mixture of THF (65 mL) and acetic acid (1.2 mL) under argon atmosphere. Reaction mixture was treated with TBAF (8.9 mL, 1 M solution in THF) at r.t.. After 30 minutes the reaction mixture was heated to 60 °C for 24 h and then evaporated. The residue was dissolved in ethyl acetate (700 mL) and washed with water (300 mL). Organic phase was dried with sodium sulfate and evaporated. Chromatography (silica gel 250 g, toluene:ethyl acetate 3:1) of the residue afforded 2.05 g (92%) of **20** as a viscous oil. $[\alpha]_D^{20}$ = +120.60 (c 0.329, $CHCl_3$). Found: C, 72.72; H, 6.10. Calc. for $C_{23}H_{22}O_5$: C, 73.00; H; 5.86%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.31-1.38 (m, 1H, H-6en), 1.69-1.74 (m, 1H, H-7en), 1.93-1.99 (m, 1H, H-7ex), 2.04-2.12 (m, 1H, H-6ex), 2.39 (d, $J_{5\text{-}6ex}$ = 8.2, 1H, H-5), 4.00-4.03 (m, 1H, H-4), 4.32 and 4.38 (2 x d, 2H, J_{gem} = 11.1, BzOC**H$_2$**-), 5.24 (d, 1H, 4-O**H**), 5.48 (bs, 1H, H-8), 5.67 (ddd, $J_{3\text{-}5}$ = 1.5, $J_{3\text{-}4}$ = 3.9, $J_{3\text{-}2}$ = 9.5, 1H, H-3), 5.96 (d, $J_{2\text{-}3}$ = 9.5, 1H, H-2), 7.48-7.53 (m, 4H, Ph-*m1*, Ph-*m2*), 7.62-7.67 (m, 2H, Ph-*p1*, Ph-*p2*), 7.89-7.91 (m, 2H, Ph-*o2*), 7.95-7.97 (m, 2H, Ph-*o1*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 23.46 (C-6), 31.79 (C-7), 46.88 (C-5), 49.18 (C-1), 65.51 (BzO**C**H$_2$-), 72.86 (C-4), 77.22 (C-8), 128.63 (C-3), 128.89 and 128.97 (C-*m1*, C-*m2*), 129.31 (C-*o2*), 129.38 (C-*o1*), 129.76 and 130.04 (C-*i1* and C-*i2*), 133.52 (C-*p1*, C-*p2*), 134.67 (C-2), 165.05 (**C**OO-1), 165.72 (**C**OO-2). ESI MS, *m/z* (rel%): 401 (100) [M+Na]. HRMS: calcd. for [M+Na]: 401.13594, found: 401.13608.

Preparation of compounds 22a and 22

A solution of PPh_3 (2.99 g, 11.4 mmol) and N-chlorosuccinimide (1.53 g, 11.45 mmol) in CH_2Cl_2 (32 mL) was stirred at 0 °C for 30 minutes. A solution of hydroxy derivative **20** (2.155 g, 5.65 mmol) in CH_2Cl_2 (32 mL + 5 mL for rinsing the flask) was then added

dropwise during 30 minutes. Reaction mixture was stirred at 0 °C for 2 h and then treated with methanol (5 mL) and evaporated. Residue was chromatographed on a silica gel column (250 g, hexanes:ethyl acetate 10:1) and the isolated intermediate was immediately used in the following step. Chloro derivative **21** was dissolved in DMF (44 mL) and treated with sodium azide (1.836 g, 28.3 mmol) at 65 °C for 12 h. Volatiles were evaporated, residue was dissolved in ethyl acetate (350 mL) and washed with water (200 mL). Organic phase was dried with sodium sulfate, evaporated and the crude product was chromatographed on a silica gel column (250 g, hexanes:ethyl acetate 20:1 → 10:1) to afford **22a** (505 mg, 22% over 2 steps) and **22** (1.64 g, 72% over 2 steps, both were oils).

(1*R*,4*S*,5*S*,8*S*)-4-Azido-5-((benzoyloxy)methyl)bicyclo[3.2.1]oct-2-en-8-yl benzoate (**22a)**
^{1}H NMR (500 MHz, d6-DMSO): δ 1.69-1.76 (m, 2H, H-7en, H-6ex), 2.11-2.19 (m, 2H, H-6en, H-7ex), 2.76-2.80 (m, 1H, H-1), 4.44 (d, 1H, $J_{4\text{-}3}$ = 4.2, H-4), 4.47 and 4.52 (2 x d, 2H, J_{gem} = 11.0, BzOC**H$_2$**-), 5.19 (s, 1H, H-8), 5.77 (dd, $J_{3\text{-}4}$ = 4.2, $J_{3\text{-}2}$ = 9.3, 1H, H-3), 6.28 (dd, $J_{2\text{-}1}$ = 6.9, $J_{2\text{-}3}$ = 9.3, 1H, H-2), 7.49-7.54 (m, 4H, Ph-*m1*, Ph-*m2*), 7.64-7.69 (m, 2H, Ph-*p1*, Ph-*p2*), 7.97-8.00 (m, 4H, Ph-*o2*, Ph-*o1*). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 29.48 (C-6), 29.92 (C-7), 41.26 (C-1), 50.49 (C-5), 66.14 (C-4), 66.29 (BzO**C**H$_2$-), 77.69 (C-8), 122.20 (C-3), 128.85 and 128.94 (C-*m1*, C-*m2*), 129.34 and 129.42 (C-*o1*, C-*o2*), 129.48 and 129.57 (C-*i1* and C-*i2*), 133.54 and 133.73 (C-*p1*, C-*p2*), 136.22 (C-2), 165.20 (8-**C**OO), 165.63 (-CH$_2$O**C**OO). ESI MS, *m/z* (rel%): 426 (100) [M+Na]. HRMS: calcd. for [M+Na]: 426.14243, found: 426.14233.

(1*S*,4*R*,5*R*,8*S*)-4-Azido-1-((benzoyloxy)methyl)bicyclo[3.2.1]oct-2-en-8-yl benzoate **(22)**
$[\alpha]_D^{20}$ = -10.2 (c 0.275, $CHCl_3$). Found: C, 68.45; H, 5.30; N, 10.11. Calc. for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42%. ^{1}H NMR (500 MHz, d6-$CDCl_3$): δ 1.52 (ddd, $J_{6en\text{-}7ex}$ = 6.2, $J_{6en\text{-}7en}$ = 9.2, J_{gem} = 14.0, 1H, H-6en), 1.89-1.95 (m, 1H, H-7en), 2.04-2.11 (m, 1H, H-7ex), 2.21-2.29 (m, 1H, H-6en), 2.73 (dm, $J_{5\text{-}6ex}$ = 8.1, 1H, H-5), 3.99 (t, $J_{4\text{-}5}$ = 3.3, 1H, H-4), 4.39 and 4.56 (2 x d, 2H, J_{gem} = 11.2, BzOC**H$_2$**-), 5.49 (s, 1H, H-8), 5.73 (ddd, $J_{3\text{-}5}$ = 1.6, $J_{3\text{-}4}$ = 4.1, $J_{3\text{-}2}$ = 9.5, 1H, H-3), 6.20 (d, 1H, $J_{2\text{-}3}$ = 9.5, 1H, H-2), 7.39-7.45 (m, 4H, Ph-*m1*, Ph-*m2*), 7.52-7.58 (m, 2H, Ph-*p1*, Ph-*p2*), 7.99-8.02 (m, 4H, Ph-*o2*, Ph-*o1*). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.96 (C-6), 32.73 (C-7), 44.74 (C-5), 49.15 (C-1), 64.81 (C-4), 65.17 (BzO**C**H$_2$), 76.76 (C-8), 122.80 (C-3), 128.39 and 128.44 (C-*m1*, C-*m2*), 129.56 and 129.64 (C-*o1*, C-*o2*), 129.75 and 129.99 (C-*i1* and C-*i2*), 133.07 and 133.16 (C-*p1*, C-*p2*), 138.46 (C-2), 164.33 (**C**OO-1), 165.40 (**C**OO-2). ESI MS, *m/z* (rel%): 426 (100) [M+Na]. HRMS: calcd. for [M+Na]: 426.14243, found: 426.14229.

Allylic rearrangement of 22a to 22

A solution of compound **22a** (505 mg, 1.25 mmol) in acetonitrile (35 mL) was heated to 95 °C for 24 h. Reaction mixture was evaporated and the residue was chromatographed (100 g, hexanes:ethyl acetate 10:1) to afford 241 mg (48%) of **22**.

(1*S*,4*R*,5*R*,8*S*)-4-Amino-1-(hydroxymethyl)bicyclo[3.2.1]oct-2-en-8-ol (23)

Azido derivative **22** (1.64 g, 4.06 mmol) was dissolved dry THF (20 mL, argon atmosphere) and PPh_3 (1.42 g, 5.41 mmol) was added. Reaction mixture was stirred for 20 h, water (1.23 mL) was added and stirring was continued for another 20 h. The reaction mixture was evaporated and re-dissolved in EtOH-H_2O (18 mL, 1:1). Potassium hydroxide (1.2 g, 21.4 mmol) was added and the reaction mixture was heated to reflux for 5 h, neutralized with aq. HCl and purified on a DOWEX 50 (100 mL, H^+ cycle). The column was washed with water (400 mL), methanol (400 mL) and product was then eluted with aq. NH_3/MeOH (1:4, v/v). Fractions containing product were evaporated and the oily residue was converted to hydrochloride salt with hydrogen chloride in dioxane (2M) (659 mg, 79%, slightly hygroscopic yellowish solid). $[\alpha]_D^{20}$ = -51.4 (c 0.292, CH_3OH). Found: C, 51.21; H, 7.70; N, 6.23. Calc. for $C_9H_{16}ClNO_2$ x 1/3 H_2O: C, 51.06; H, 7.94; N, 6.62%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.26 (ddd, $J_{6en\text{-}7ex}$ = 5.9, $J_{6en\text{-}7en}$ = 9.1, J_{gem} = 13.7, 1H, H-6en), 1.37-1.43 (m, 1H, H-7en), 1.52-1.59 (m, 1H, H-7ex), 1.98-2.06 (m, 1H, H-6ex), 2.24 (d, $J_{5\text{-}6ex}$ = 8.0, 1H, H-5), 3.41 (d, J_{gem} = 10.7, 1H, C**H**bOH), 3.52 (m, 2H, H-4, C**H**aOH), 4.00 (bs, 1H, H-8), 4.62 and 4.89 (2 x bs, 2H, 8-O**H**, CH_2O**H**), 5.48 (dd, $J_{3\text{-}5}$ = 1.7, $J_{3\text{-}4}$ = 3.6, $J_{3\text{-}2}$ = 9.5, 1H, H-3), 6.13 (dd, $J_{2\text{-}4}$ = 0.8, $J_{2\text{-}3}$ = 9.5, 1H, H-2), 8.20 (bs, 3H, NH_3^+). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 25.78 (C-6), 31.86 (C-7), 43.97 (C-5), 51.88 (C-1), 55.09 (C-4), 62.24 (**C**H$_2$OH), 71.21 (C-8), 120.68 (C-3), 142.49 (C-2). CI MS, *m/z* (rel%): 152 (100) [M+H-H_2O]. HRMS: calcd. for [M+H]: 171.1181, found: 170.1176.

(1*S*,4*R*,5*R*,8*S*)-4-(6-Chloro-9*H*-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.2.1]oct-2-en-8-ol (24)

A mixture of amine **23** (1 g, 4.9 mmol), 4,6-dichloro-5-formamido-pyrimidine (1.56 g, 7.35 mmol, prepared according to published procedure[27]) and DIPEA (2.9 mL, 14.7 mmol) in *n*-BuOH (25 mL) was heated in a sealed microwave reactor for 2 h at 140 °C. After evaporation the residue was chromatographed on a silica gel column (400 g) in ethyl acetate → ethyl acetate:toluene:acetone:ethanol (17:4:3:1) to afford **24** (631 mg, 42%). Analytical sample was crystalized from ethanol (white solid). M.p. 176.5-177 °C (decomposition, EtOH). $[\alpha]_D^{20}$ = -18.6 (c 0.297, CH_3OH). Found: C, 54.50; H, 4.91; Cl, 11.30; N, 17.87. Calc. for $C_{14}H_{15}ClN_4O_2$: C, 54.82; H, 4.93; Cl, 11.56; N, 18.26%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.46-1.53 (m, 1H, H-6en), 1.54-1.60 (m, 1H, H-7en), 1.65-1.72 (m, 1H, H-7ex), 2.06-2.13 (m, 1H, H-6ex), 2.42 (dm, $J_{5\text{-}6ex}$ = 7.8, 1H, H-5), 3.51 (dd, $J_{CH\text{-}OH}$ = 5.3, J_{gem} = 10.5, 1H, C**H**bOH), 3.63 (dd, $J_{CH\text{-}OH}$ = 5.3, J_{gem} = 10.5, 1H, C**H**aOH), 3.74 (d, $J_{8\text{-}OH}$ = 3.6, 1H, H-8), 4.53 (t, $J_{OH\text{-}CH2}$ = 5.3, 1H, CH_2O**H**), 4.63 (d, $J_{OH\text{-}8}$ = 3.6, 1H, 8-O**H**), 5.10-5.12 (m, 1H, H-4), 5.76 (ddd, $J_{3\text{-}5}$ = 1.7, $J_{3\text{-}4}$ = 3.9, $J_{3\text{-}2}$ = 9.4, 1H, H-3), 6.40 (dd, $J_{2\text{-}4}$ = 1.2, $J_{2\text{-}3}$ = 9.4, 1H, H-2), 8.49 (s, 1H, H-8´), 8.83 (s, 1H, H-2´). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 25.10 (C-6), 32.31 (C-7), 46.26 (C-5), 51.70 (C-1), 59.74 (C-4), 62.18 (**C**H$_2$OH), 71.81 (C-8), 119.57 (C-3), 131.47 (C-5´), 143.33 (C-2), 145.84 (C-8´), 149.32 (C-6´), 151.48 (C-4´), 151.67 (C-2´). ESI MS, *m/z* (rel%): 329/331 (100/33) [M+Na]. HRMS: calcd. for [M+Na]: 329.07757, found: 329.07771.

(1*S*,4*R*,5*R*,8*S*)-4-(6-Amino-9*H*-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.2.1]oct-2-en-8-ol (25)

A solution of chloropurine derivative **24** (540 mg, 1.76 mmol) was dissolved in ethanolic ammonia (3.5 M, 6 mL) heated in a sealed microwave reactor at 140 °C for 1 h. Reaction mixture was evaporated and chromatographed on a silica gel column (200 g) in ethyl acetate → ethyl acetate:acetone:ethanol:H_2O (19:3:1.8:1.2) to afford 433 mg (86%) of the product **25**. Analytical sample was crystallized from ethanol (white solid).
Enantiomeric purity was determined by chiral HPLC on Chirapak IA (Daicel) column with heptane:ethanol 2:1 + 0.1% Et_2NH as eluent (Fig **S4** and **S5**.)
M.p. 158.5-159.5 °C (EtOH). $[\alpha]_D^{20}$ = -50.1 (c 0.154, CH_3OH). Found: C, 53.48; H, 6.24; N, 22.14. Calc. for $C_{14}H_{17}N_5O_2$ x 1.5 H_2O: C, 53.49; H, 6.41; N, 22.28%. ^{1}H NMR (500 MHz, d6-DMSO): δ

1.41-1.48 (m, 1H, H-6en), 1.51-1.57 (m, 1H, H-7en), 1.63-1.70 (m, 1H, H-7ex), 2.02-2.10 (m, 1H, H-6ex), 2.37 (dm, $J_{5\text{-}6ex}$ = 7.9, 1H, H-5), 3.49 (dd, $J_{CH\text{-}OH}$ = 5.5, J_{gem} = 10.5, 1H, C**Hb**OH), 3.62 (dd, $J_{CH\text{-}OH}$ = 5.5, J_{gem} = 10.5, 1H, C**Ha**OH), 3.73 (d, $J_{8\text{-}OH}$ = 3.5, 1H, H-8), 4.53 (t, $J_{OH\text{-}CH2}$ = 5.3, 1H, CH_2O**H**), 4.63 (d, $J_{OH\text{-}8}$ = 3.5, 1H, 8-O**H**), 4.91-4.93 (m, 1H, H-4), 5.71 (ddd, $J_{3\text{-}5}$ = 1.6, $J_{3\text{-}4}$ = 3.9, $J_{3\text{-}2}$ = 9.5, 1H, H-3), 6.40 (dd, $J_{2\text{-}4}$ = 1.1, $J_{2\text{-}3}$ = 9.5, 1H, H-2), 7.27 (bs, 2H, NH_2), 7.90 (s, 1H, H-8´), 8.17 (s, 1H, H-2´). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 25.20 (C-6), 32.41 (C-7), 46.46 (C-5), 51.77 (C-1), 58.82 (C-4), 62.28 (**C**H_2OH), 71.69 (C-8), 119.39 (C-5´), 120.42 (C-3), 139.06 (C-8´), 142.64 (C-2), 149.18 (C-4´), 151.68 (C-2´), 156.30 (C-6´). ESI MS, *m/z* (rel%): 310 (100) [M+Na]. HRMS: calcd. for [M+H]: 288.14550, found: 288.14557; calcd. for [M+Na]: 310.12745, found: 310.12747.

(1*S*,4*R*,5*R*,8*S*)-4-(6-Amino-9*H*-purin-9-yl)-1-(hydroxymethyl)-bicyclo[3.2.1]octan-8-ol (26)

To a solution of nucleoside **25** (500 mg, 1.74 mmol) in methanol (50 mL) was added $Pd(OH)_2$/C (200 mg) and the reaction mixture was hydrogenated in a steel autoclave (10 bars of hydrogen) at 50 °C for 24 h. Solids were filtered off on a pad of Celite and the residue was chromatographed on a silica gel column (200 g, ethyl acetate → ethyl acetate: acetone: ethanol: H_2O (19:3:1.8:1.2)) to afford 450 mg (89%) of the product **26**. Analytical sample was crystalized from ethanol (white solid). M.p. 241.5-242.5 °C (EtOH). $[\alpha]_D^{20}$ = +54.5 (c 0.301, CH_3OH). Found: C, 56.33; H, 6.46; N; 23.23. Calc. for $C_{14}H_{19}N_5O_2$ x 0.5 H_2O: C, 56.36; H, 6.76; N, 23.47%. ^{1}H NMR (600 MHz, d6-DMSO): δ 1.40-1.45 (m, 1H, H-7en), 1.52-1.58 (m, 3H, H-2eq, H-6en, H-7ex), 1.92-2.02 (m, 2H, H-2ax, H-6ex), 2.07-2.17 (m, 2H, H-3), 2.65 (dd, $J_{5\text{-}4}$ = 3.9, $J_{5\text{-}6ex}$ = 7.0, 1H, H-5), 3.32 (dd, $J_{CH\text{-}OH}$ = 5.0, J_{gem} = 10.5, 1H, C**Hb**OH), 3.38 (d, $J_{8\text{-}OH}$ = 3.5, 1H, H-8), 3.53 (dd, $J_{CH\text{-}OH}$ = 5.0, J_{gem} = 10.5, 1H, C**Ha**OH), 4.32 (t, $J_{OH\text{-}CH2}$ = 5.0, 1H, CH_2O**H**), 4.42 (d, $J_{OH\text{-}8}$ = 3.5, 1H, 8-O**H**), 4.52-4.54 (m, 1H, H-4), 7.21 (bs, 2H, NH_2), 8.14 (s, 1H, H-2´), 8.15 (s, 1H, H-8´). ^{13}C NMR (150.92 MHz, d6-DMSO): δ 21.51 (C-3), 25.63 (C-6), 28.26 (C-7), 31.75 (C-2), 47.10 (C-5), 49.54 (C-1), 56.99 (C-4), 64.92 (**C**H_2OH), 74.66 (C-8), 119.12 (C-5´), 138.98 (C-8´), 149.81 (C-4´), 152.44 (C-2´), 156.21 (C-6´). ESI MS, *m/z* (rel%): 312 (100) [M+Na]. HRMS: calcd. for [M+H]: 290.16115, found: 290.16124; calcd. for [M+Na]: 312.14310, found: 312.14315.

N-(9-((1*R*,2*R*,5*S*,8*S*)-8-Hydroxy-5-(hydroxymethyl)-bicyclo[3.2.1]oct-3-en-2-yl)-9*H*-purin-6-yl)benzamide (27)

Nucleoside **25** (550 mg, 1.91 mmol) was co-evaporated with pyridine (2 x 15 mL), dissolved in pyridine (24 mL), cooled to 0 °C and then TMSCl (1.22 mL, 9.6 mmol) was added dropwise during 10 minutes. Reaction mixture was stirred at 0 °C for 1h and then benzoyl chloride (1.11 mL, 9.6 mmol) was slowly added and the reaction mixture was left at 0 °C for 1 h and at r.t. for another 12 h. The mixture was cooled to 0 °C again, quenched with water (3.5 mL), and after 15 minutes aq. ammonia (6.4 mL, 25%) was added and after further 15 minutes the reaction mixture was evaporated. The residue was re-dissolved in methanol (17 mL) and aq. ammonia (12 mL, 25%) and after 1 h at r.t. evaporated. Residue was chromatographed on a silica gel column (100 g) in ethyl acetate → ethyl acetate: acetone: ethanol: H_2O (21:3:0.6:0.4) to afford **27** (464 mg, 62%) as a yellowish foam. $[\alpha]_D^{20}$ = -86.1 (c 0.296, CH_3OH). Found: C, 63.40; H, 5.46; N, 17.38. Calc. for $C_{21}H_{21}N_5O_3$ x 1/3 H_2O: C, 63.46; H, 5.50; N, 17.62%. ^{1}H NMR (600 MHz, d6-DMSO): δ 1.48-1.54 (m, 1H, H-6en), 1.55-1.60 (m, 1H, H-7en), 1.66-1.73 (m, 1H, H-7ex), 2.07-2.15 (m, 1H, H-6ex), 2.44 (dm, $J_{5\text{-}6ex}$ = 8.0, 1H, H-5), 3.51 (dd, $J_{CH\text{-}OH}$ = 5.1, J_{gem} = 10.5, 1H, C**Hb**OH), 3.64 (dd, $J_{CH\text{-}OH}$ = 5.1, J_{gem} = 10.5, 1H, C**Ha**OH), 3.77 (d, $J_{8\text{-}OH}$ = 3.5, 1H, H-8), 4.54 (t, $J_{OH\text{-}CH2}$ = 5.1, 1H, CH_2O**H**), 4.69 (d, $J_{OH\text{-}8}$ = 3.5, 1H, 8-O**H**), 5.09-5.11 (m, 1H, H-4), 5.77 (ddd, $J_{3\text{-}5}$ = 1.6, $J_{3\text{-}4}$ = 3.9, $J_{3\text{-}2}$ = 9.5, 1H, H-3), 6.39 (dd, $J_{2\text{-}4}$ = 1.1, $J_{2\text{-}3}$ = 9.5, 1H, H-2), 7.53-7.57 (m, 2H, Ph-*m*), 7.63-7.66 (m, 1H, Ph-*p*), 8.04-8.06 (m, 2H, Ph-*o*), 8.24 (s, 1H, H-8´), 8.77 (s, 1H, H-2´), 11.21 (bs, 1H, NH). ^{13}C NMR (150.92 MHz, d6-DMSO): δ 25.16 (C-6), 32.37 (C-7), 46.45 (C-5), 51.72 (C-1), 59.18 (C-4), 62.23 (**C**H_2OH), 71.82 (C-8), 119.96 (C-3), 126.09 (C-5´), 128.61 (C-*m,o*), 132.55 (C-*p*), 133.62 (C-*i*), 142.87 (C-8´), 143.04 (C-2), 150.48 (C-6´), 151.53 (C-2´), 151.98 (C-4´), 165.87 (**C**OO). ESI MS, *m/z* (rel%): 414 (100) [M+Na]. HRMS: calcd. for [M+Na]: 414.15366, found: 414.15359.

N-(9-((1*R*,2*R*,5*S*,8*S*)-5-((Bis(4-methoxyphenyl)-(phenyl)methoxy)methyl)-8-hydroxybicyclo[3.2.1]oct-3-en-2-yl)-9*H*-purin-6-yl)benzamide (28)

Compound **27** (311 mg, 0.79 mmol) was co-evaporated with pyridine (2 x 7 mL) and then dissolved in pyridine (6 mL) and cooled to 0 °C. DMTrCl (404 mg, 1.19 mmol) was added in one portion and the reaction mixture was slowly warmed to r.t. and then stirred for 48 h. Reaction mixture was evaporated and the residue was dissolved in ethyl acetate (300 mL), washed with satd. solution of sodium bicarbonate (2 x 100 mL) and brine (100 mL), dried with sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (150 g, - deactivated with triethylamine, toluene:ethyl acetate 1:3) to afford 358 mg (65%) of the product **28** as a foam (contains some inseparable impurities according ^{13}C NMR, compound was pure enough for the next step). $[\alpha]_D^{20}$ = -8.0 (c 0.313, CH_3OH). Found: C, 72.43; H, 5.83; N, 9.71. Calc. for $C_{42}H_{39}N_5O_5$: C, 72.71; H, 5.67; N, 10.09%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.50-1.56 (m, 1H, H-6en), 1.70 (m, 2H, H-7en, H-7ex), 2.08-2.15 (m, 1H, H-6ex), 2.48 (bs, 1H, H-5), 3.06 and 3.29 (2 x d, J_{gem} = 8.4, 2H, OCH_2), 3.74 (2 x s, 2 x 3H, 2 x OCH_3), 3.88 (bs, 1H, H-8), 4.76 (d, $J_{8\text{-}OH}$ = 3.4, 1H, H-8), 5.13-5.15 (m, 1H, H-4), 5.82 (ddd, $J_{3\text{-}5}$ = 1.6, $J_{3\text{-}4}$ = 3.9, $J_{3\text{-}2}$ = 9.4, 1H, H-3), 6.31 (dd, $J_{2\text{-}4}$ = 1.1, $J_{2\text{-}3}$ = 9.4, 1H, H-2), 6.89-6.92 (m, 4H, H-3´´), 7.21-7.24 (m, 1H, 4´´´), 7.28-7.30 (m, 4H, H-2´´), 7.31-7.34 (m, 2H, H-3´´´), 7.42-7.44 (m, 2H, H-2´´´), 7.54-7.57 (m, 2H, Bz-*m*), 7.63-7.66 (m, 1H, Bz-*p*), 8.04-8.07 (m, 2H, Bz-*o*), 8.28 (s, 1H, H-8´), 8.79 (s, 1H, H-2´), 11.25 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, d6-DMSO): δ 24.99 (C-6), 32.99 (C-7), 46.55 (C-5), 50.48 (C-1), 55.19 and 55.20 (2 x O**C**H_3), 59.20 (C-4), 64.87 (O**C**H_2), 72.14 (C-8), 85.10 (Ph_3**C**O-), 113.30 and 113.31 (2 x C-3´´), 120.00 (C-3), 126.17 (C-5´), 126.75 (C-4´´´), 127.92 and 127.96 (C-2´´´, C-3´´´), 128.64 and 128.66 (Bz-*o*, Bz-*m*), 129.95 and 129.99 (2 x C-2´´), 132.60 (Bz-*p*), 133.61 (Bz-*i*), 135.99 and 136.19 (2 x C-1´´), 142.68 and 142.75 (C-2 and C-8´), 145.51 (C-1´´´), 150.55 (C-6´), 151.61 (C-2´), 152.04 (C-4´), 158.16 and 158.17 (C-4´´), 165.93 (**C**OO). ESI MS, *m/z* (rel%): 716 (100) [M+Na]. HRMS: calcd. for [M+Na]: 716.28434, found: 716.28429.

(1*S*,4*R*,5*R*,8*S*)-4-(6-Benzamido-9*H*-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)bicyclo[3.2.1]oct-2-en-8-yl (2-cyanoethyl) diisopropylphosphoramidite (29)

Compound **28** (358 mg, 0.52 mmol) and DIPEA (0.353 mL, 2.05 mmol) were dissolved in dry THF (5 mL) and the flask was rinsed several times with argon. 2-Cyanoethyl *N,N*-diisopropyl-chlorophosphoramidite (0.21 mL, 0.94 mmol) was added dropwise at r.t. during 15 minutes. The reaction mixture was stirred at r.t. for 3.5 h and then poured to the mixture of satd. solution of sodium bicarbonate with ice (100 mL). Water phase was extracted with ethyl acetate (2 x 200 mL) and the combined organic phases were dried with sodium sulfate and evaporated. Residue was co-evaporated with

benzene (2 x 50 mL) and then chromatographed (100 g - deactivated with triethylamine, toluene:ethyl acetate 1:1 to afford 297 mg (72%) of the product **29** as a white foam. $^{31}P\{^{1}H\}$ NMR (202 MHz, d6-DMSO): 145.73, 145.21. ESI MS, *m/z* (rel%): 916 (100) [M+Na]. HRMS: calcd. for [M+H]: 894.41025, found: 894.41126; calcd. for [M+Na]: 916.39219, found: 916.39245.

N'-(9-((1*R*,2*R*,5*S*,8*S*)-5-((Bis(4-methoxyphenyl)-(phenyl)methoxy)methyl)-8-hydroxybicyclo[3.2.1]octan-2-yl)-9*H*-purin-6-yl)-N,N-dibutylformimidamide (30)

Saturated nucleoside **26** (430 mg, 1.49 mmol) was suspended in methanol (10 mL), dimethylacetal-*N,N*-dibutylformamide (0.87 mL, 3.73 mmol) was added in three portions and the reaction mixture was allowed to stir at r.t. for 11 h. A chromatography on a silica gel column (150 g, ethyl acetate → ethyl acetate:methanol 6:1) afforded a foam, which was directly used for the tritylation. The foam was co-evaporated with pyridine (2 x 10 mL), then dissolved in pyridine (10 mL) and cooled to 0 °C. DMTrCl (636 mg, 1.88 mmol) was added in one portion, the reaction mixture was slowly warmed to r.t. and then stirred for 48 h. Volatiles were evaporated and the residue was dissolved in ethyl acetate (300 mL), washed with satd. solution of sodium bicarbonate (2 x 150 mL) and brine (150 mL), dried with sodium sulfate, evaporated and chromatographed on a silica gel column (200 g, - deactivated with triethylamine, ethyl acetate: acetone 10:1) to afford 727 mg (83%) of **30** as a white foam. $[\alpha]_D^{20}$ = -18.5 (c 0.313, CH_3OH). Found: C, 72.01; H, 7.40; N, 11.17. Calc. for $C_{44}H_{54}N_6O_4$: C, 72.30; H, 7.45; N, 11.50%. ^{1}H NMR (500 MHz, d6-DMSO): δ 0.93 (q, $J_{4\text{-}3}$ = 7.5, 6H, 2 x CH_3), 1.28-1.37 (m, 4H, H-4), 1.46-1.51 (m, 1H, H-7´´ex), 1.55-1.65 (m, 6H, H-2, H-6´´en, H-7´´en), 1.74-1.78 (m, 1H, H-2´´a), 1.94-2.00 (m, 1H, H-6´´en), 2.04-2.11 (m, 1H, H-2´´b), 2.15-2.20 (m, 2H, H-3´´ax, H-3´´eq), 2.71 (dd, $J_{5''\text{-}6''ex}$ = 7.3, $J_{5''\text{-}4''}$ = 3.8, H-5´´), 2.90 and 3.16 (2 x d, J_{gem} = 8.4, 2H, OCH_2), 3.40 (d, $J_{8''OH}$ = 3.9, 1H, H-8´´), 3.42-3.45 and 3.55-3.64 (2 x m, 2 x 2H, H-2), 3.73 (2 x s, 2 x 3H, 2 x OCH_3), 4.59-4.62 (m, 1H, H-4´´), 6.86-6.89 (m, 4H, H-3´´´), 7.19-7.22 (m, 1H, H-p), 7.24-7.27 (m, 4H, H-2´´´), 7.28-7.31 (m, 2H, H-m), 7.39-7.41 (m, 2H, H-p), 8.33 (s, 1H, H-8´), 8.42 (s, 1H, H-2´), 8.96 (s, 1H, N=C**H**-NBu_2). ^{13}C NMR (150.92 MHz, d6-DMSO): δ 13.77 and 13.95 (2 x CH_3), 19.34 and 19.83 (2 x C-3), 21.37 (C-3´´), 25.45 (C-6´´), 28.88 and 30.69 (2 x C-3), 29.22 (C-7´´), 32.62 (C-2´´), 44.55 and 51.07 (2 x C-1), 47.14 (C-5´´), 48.68 (C-1´´), 55.16 (2 x O**C**H_3), 57.12 (C-4´´), 66.45 (O**C**H_2), 74.81 (C-8´´), 84.91 (Ph_3**C**O-), 113.18 (C-3´´´), 125.64 (C-5´), 126.61 and 127.85 and 127.97 (Ph-o, m, p), 129.96 and 129.98 (C-2´´), 136.19 and 136.38 (C-1´´´), 140.98 (C-8´), 145.67 (Ph-i), 151.84 Č-2´), 151.88 (C-4´), 158.07 (C-4´´´), 158.13 (N=**C**H-NBu_2), 159.52 (C-6´). ESI MS, *m/z* (rel%): 731 (100) [M+H]. HRMS: calcd. for [M+H]: 731.42793, found: 731.42774.

(1*S*,4*R*,5*R*,8*S*)-1-((Bis(4-methoxyphenyl) (phenyl)methoxy)methyl)-4-(6-((((dibutylamino) methylene)amino)-9*H*-purin-9-yl)bicyclo[3.2.1]octan-8-yl (2-cyanoethyl) diisopropylphosphoramidite (31)

Compound **30** (680 mg, 0.93 mmol) and DIPEA (0.71 mL, 4.08 mmol) were dissolved in dry THF (10 mL) and the flask was rinsed several times with argon. Then 2-cyanoethyl *N,N*-diisopropylchloro-phosphoramidite (0.42 mL, 1.88 mmol) was added dropwise at r.t. during 15 minutes. Reaction mixture was then stirred at r.t. for 3.5 h and then poured to the mixture of satd. solution of sodium bicarbonate with ice (150 mL). Water phase was extracted with ethyl acetate (2 x 250 mL) and the combined organic phases were dried with sodium sulfate and evaporated. The residue was co-evaporated with benzene (2 x 50 mL) and then chromatographed (100 g - deactivated with triethylamine, toluene:ethyl acetate 1:9) to afford 693 mg (80%) of the product **31** as a white foam. $^{31}P\{^{1}H\}$ NMR (202 MHz, C_6D_6): 147.67, 146.63. ESI MS, *m/z* (rel%): 931 (100) [M+H]. HRMS: calcd. for [M+H]: 931.53578, found: 931.53558; calcd. for [M+Na]: 953.51772, found: 953.51730.

Synthesis of oligonucleotides

The oligonucleotides were synthesised from the appropriate monomers on a ~0.5 µmol scale by a standard trityl-off phosphoramidite method using the LCAA CPG with attached 2'-deoxy-5'-*O*-dimethoxytritylcytidine-3'-*O*-hemisuccinate as the first nucleoside. Deprotection and release of oligonucleotides from CPG was achieved with gaseous ammonia (0.7 MPa) at r.t. for 12 h. Oligonucleotides were purified at 55°C on DNAPac PA100 10 x 250 mm Nucleic Acid Column (Dionex) at a flow rate of 3 mL/min using a linear gradient od sodium chloride (20 mM→500 mM, 60 min) in 50 mM sodium acetate buffer pH 7.0 containing 20% (v) of acetonitrile. Desalting of pure oligonucleotides was performed on 10 µm Luna C18 (2) 10 x 100 mm column (Phenomenex) at a flow rate of 3 mL/min using a gradient of acetonitrile (0→25%, 30 min) in 0.1 M triethylammonium hydrogencarbonate. Desalted oligonucleotides were freeze-dried and characterized by MALDI TOF (Tab. **2**).

Table 2. Analytical data for oligonucleotides

Oligonucleotide	Calcd. mass	Found mass
5´- d(GC**A**^{25}T**A**^{25}TC**A**^{25}C)	2790.82	2790.2
5´- r(GC**A**^{25}U**A**^{25}UC**A**^{25}C)	2858.76	2858.4
5´- d(GC**A**^{26}T**A**^{26}TC**A**^{26}C)	2796.82	2796.2
5´- r(GC**A**^{26}U**A**^{26}UC**A**^{26}C)	2864.76	2864.0

Hybridization study

Thermal experiments with oligonucleotide complexes were performed at 260 nm on a CARY 100 Bio UV Spectrophotometer (Varian Inc.) equipped with a Peltier temperature controller and thermal analysis software. The aqueous solutions of modified and natural complementary strands (4 nmol of each) were mixed, freeze-dried and dissolved in 50 mM NaH_2PO_4 – Na_2HPO_4 pH 7.2 with 100 mM NaCl (1 mL) to give a 4 µM duplex solution. A heating–cooling cycle over a range of 15–60°C with a gradient of 0.5°C/min was applied. The T_m value of each complex was determined from the first derivative plots (dA_{260}/dT versus temperature) as the temperature at a local maximum of dA_{260}/dT.

Acknowledgements

This study was supported by the Czech Science Foundation (grant No. P207/12/P625) and Gilead Sciences, Inc. (Foster City, CA, USA). Subvention for the development of research organization (RVO: 61388963) is also acknowledged.

Notes and references

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Electronic Supplementary Information (ESI) available: details of any supplementary information available should be included here. See DOI: 10.1039/c000000x/

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