Synthesis and Incorporation into Oligodeoxynucleotides of Carbocyclic *exo*-Amino Nucleosides

Oezlem Yaren, Pascal Röthlisberger, Christian J. Leumann*

Department of Chemistry and Biochemistry, University of Bern, Freiestr. 3, 3012 Bern, Switzerland
Fax +41(31)6313422; E-mail: leumann@ioc.unibe.ch

Received 23 December 2011; revised 31 January 2012

Abstract: The preparation of a series of carbocyclic *exo*-amino nucleosides from selected primary aromatic amines in both the C1′ α- and β-epimeric form as well as the corresponding building blocks for DNA synthesis is described. These nucleosides were incorporated into oligodeoxynucleotides and their base-pairing properties with natural bases and, in part, with themselves investigated. The results obtained confirm that such nucleoside analogues engage in specific interactions with natural nucleotides in DNA duplexes. In addition they can form self-pairs that match or exceed the stability of Watson–Crick base-pairs. Thus, carbocyclic *exo*-amino nucleosides can be taken into consideration in the design of novel base-pairs for the extension of the genetic alphabet, or for other applications in biotechnology.

Key words: nucleosides, oligonucleotides, nucleobases, molecular recognition, medicinal chemistry

1 Introduction

Carbocyclic nucleosides are nucleoside analogues in which the furanose ring oxygen has been replaced by a methylene group (Figure 1). This replacement converts the glycosidic bond into a chemically more stable C–N bond, preventing it from hydrolytic cleavage and rendering the carbocyclic nucleosides metabolically more stable. Such nucleosides are of interest for a variety of reasons. First and foremost, this class of compounds shows interesting antitumor and antiviral properties. Examples of drugs being currently used in therapy include Abacavir, Entecavir, Carbovir, (carbocyclic purine analogues) and carba-BVdU, a pyrimidine analogue with anti HSV-1 activity.[1–4] In addition such nucleosides have been investigated in the past in the context of antisense oligonucleotides,[5–11] or as constituents of aptamers.[12]

A related class of nucleoside analogues are exocyclic amino nucleosides in which the bases are attached to the ribose sugar via a primary aromatic amino function (Figure 1). A natural representative of this class is clitocine, which was first isolated from the mushroom *Clytocybe inversa*,[13] and later found to have potent cytostatic activity against several leukemia cell lines via inhibition of the enzyme adenosine kinase.[14,15] Other examples of such nucleosides include clitocine mimics,[16] as well as the products of oxidative DNA base lesion FapydG, FapydA, and MeFapydG.[17]

exo-Amino nucleosides are relatively unstable due to their hemiaminal bond to a primary aromatic amine. It is therefore a logic extension to replace in this group of analogues the ribofuranose oxygen by a methylene group resulting in stable carbocyclic *exo*-amino nucleosides (Figure 1). The literature on the synthesis and biological profile of this class of nucleoside analogues, however, is scarce.[18,19]

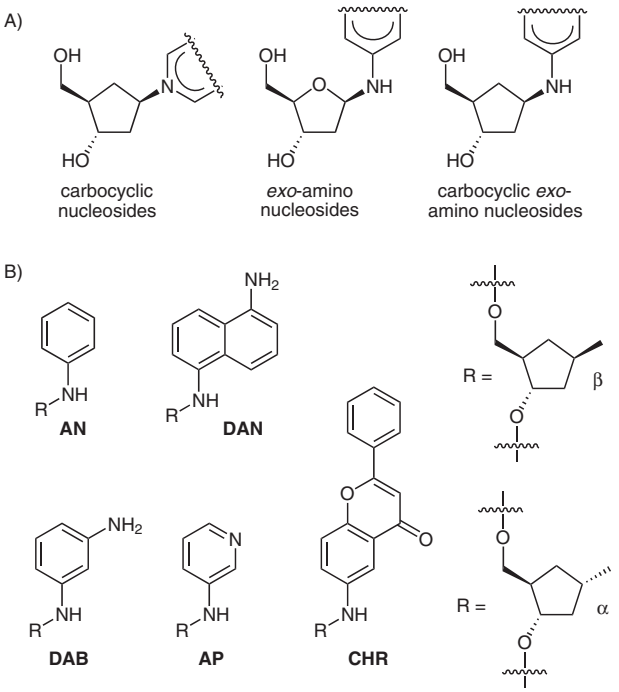


Figure 1 (A) General chemical structures of carbocyclic-, *exo*-amino-, and carbocyclic *exo*-amino nucleosides; (B) carbocyclic α- and β-*exo*-amino nucleosides investigated in DNA base recognition in this study.

In a completely different context there is growing interest in nucleoside analogues that could be used as additional coding units for the expansion of the genetic alphabet.[20–24] For example, an additional replicable, transcribable, and

SYNTHESIS 2012, 44, 1011–1025
Advanced online publication: 02.03.2012
DOI: 10.1055/s-0031-1289737; Art ID: T117811SS

translatable orthogonal base-pair would allow for the introduction of unnatural amino acids into proteins and would, thus, greatly enhance the potential of protein engineering. However, the structural space of DNA base analogues that recognize each other specifically in a Watson–Crick like manner is limited and design rules that are different from classical hydrogen bonding complementarities are largely elusive.

In this context, we recently developed a combinatorial assay for the discovery of novel base surrogates out of a library of aromatic amines.[25] The assay is based on the reversible formation of hemiaminals of primary aromatic amines with a chemically functional abasic site in the center of a DNA duplex in a parallel fashion. Matches were identified by fluorescence-based thermal melting experiments. The resulting structures, after hemiaminal formation, are *exo*-amino nucleosides, which in many cases are likely to be chemically unstable. Again, conferring stability to such nucleosides can be achieved by replacing the deoxyribofuranose by a carbocyclic sugar unit, resulting in carbocyclic *exo*-aminonucleosides (Figure 1).

In this feature article we report on the synthesis of such carbocyclic amino nucleosides with aromatic amines as base surrogates using selected individuals from the library of amines used in the above-mentioned assay. These units were incorporated into oligonucleotides and their pairing properties with the four natural DNA bases and with themselves explored by fluorescence and UV T_m measurements.

2 Synthetic Routes

2.1 Synthesis of Carbocyclic *exo*-Amino Nucleosides and Building Blocks

For the synthesis of the carbocyclic sugar we leaned on a synthetic route developed by Biggadike and Meier.[26,27] Since we were in need of both the α- and β-nucleosides, we decided to attach the aromatic amines via reductive amination to the already known (3*S*,4*R*)-ketone **1** (Scheme 1).[28] The aromatic amines chosen, namely aniline (**AN**), naphthalene-1,5-diamine (**DAN**), benzene-1,3-diamine (**DAB**), pyridin-3-amine (**AP**), and 6-aminoflavone (**CHR**) have been selected from the previously described combinatorial assay.[25]

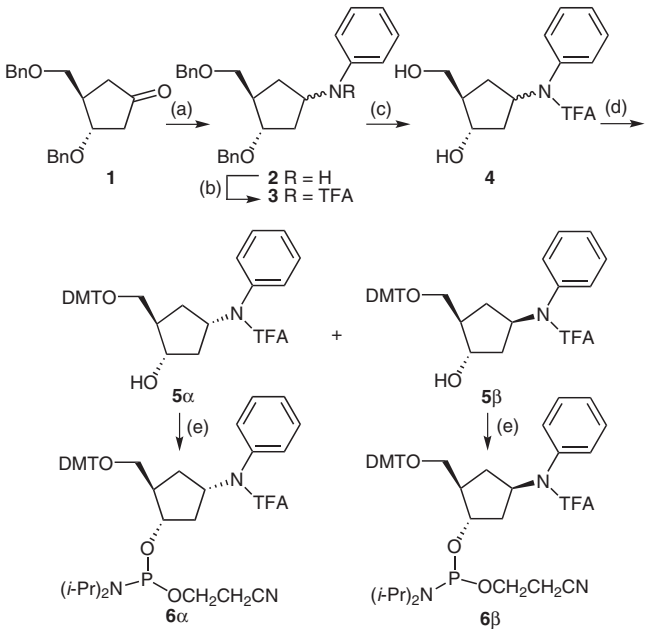
Biographical Sketches

Ozlem Yaren was born in 1982 in Izmir, Turkey. She received her Bachelor's degree in chemistry at Koc University in 2004. After this she moved to Germany where she earned her Master's degree in Material Science at the University of Ulm in 2006. From 2007–2011 she worked on her Ph.D. at the University of Bern, Switzerland, under the guidance of Prof. Christian Leumann. Her Ph.D. work was concerned with the design of a combinatorial assay for the discovery of novel DNA base pairs. Currently she is working as a post-doctoral fellow with Prof. Steven Benner at the Foundation for Applied Molecular Evolution (FfAME) in Gainesville, Florida.

Pascal Röthlisberger was born in 1985 in Bern. After training as a chemistry technician with Hoffmann La-Roche in Basel in 2004, he gained admission to the University of Bern where he earned his B.Sc. degree in chemistry in 2010. He finished his M.Sc. degree in chemistry earlier this year with a Master's thesis under the supervision of Prof. Christian Leumann and is just about to start a Ph.D. in the same group.

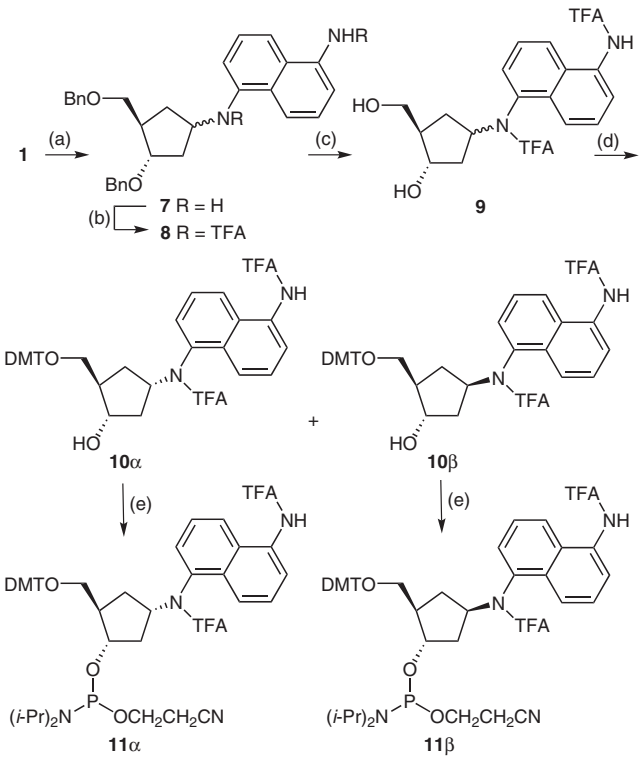
Christian J. Leumann was born in 1958. He obtained his Ph.D. degree in 1986 from the Federal Institute of Technology (ETH) in Zürich, Switzerland, for his work on biomimetic methylation reactions on hexahydroporphyrin derivatives (Prof. A. Eschenmoser). He then moved to the University of Berkeley (1987–1988) as a postdoctoral fellow to investigate catalytic antibodies (Prof. Peter G. Schultz). In 1988 he returned to ETH Zürich to start his independent career. Five years later he was appointed full professor at the University of Bern, Switzerland. His research interests are the synthesis and characterization of base-modified DNA-analogues for applications in nanotechnology, the design, synthesis and characterization of novel backbone modified nucleic acid analogues for oligonucleotide-based therapy, the development of novel tools for DNA-based diagnostics, and research on the biological properties of damaged RNA.

The synthesis of the phosphoramidite building blocks **6α**,**β** (Scheme 1) started with the carbocyclic ketone **1**, which was obtained from cyclopentadiene in four steps and 16% overall yield. Reductive amination of aniline and **1** with sodium cyanoborohydride yielded **2** as a 1:1 mixture of diastereomers in 50% yield that could not be resolved by standard chromatographic techniques. In fact, it turned out that chromatographic separation was only possible on the level of the tritylated compounds **5α**,**β**. This emerged as a recurring feature and was also experienced in the syntheses of the other carbocyclic *exo*-amino nucleosides. In view of the projected oligonucleotide synthesis, we decided to protect the secondary amino function in **2** with trifluoroacetic anhydride, which gave **3** in excellent yields. After Lewis acid promoted removal of the benzyl groups to give **4** followed by standard tritylation to give **5**, the C1′ epimers **5α**,**β** could be isolated separately and the respective configurations were assigned by ^{1}H,^{1}H-ROESY spectroscopy (strong NOE effects between H1′ and H3′ in **5α** and between H1′ and H4′ in **5β** (see Supporting Information). Both, **5α** and **5β** were then separately converted into the phosphoramidite building blocks **6α** and **6β**.

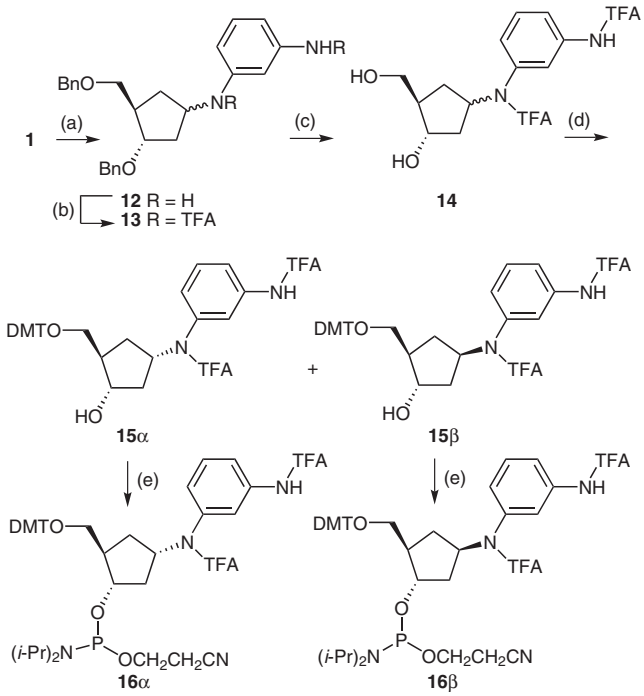


Scheme 1 *Reagents and conditions*: (a) 1. aniline, AcOH, r.t., 2 h, 2. $NaBH_3CN$, r.t., 16 h, 50%, α/β (1:1); (b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 2 h, 94%; (c) 1. 1 M BCl_3, CH_2Cl_2, –78 °C, 6 h, 2. MeOH, –20 °C to r.t., 16 h, 86%; (d) DMT-Cl, pyridine, r.t., 4 h, 56%; (e) (*i*-Pr_2N)PCl(OCH_2CH_2CN), *i*-Pr_2NEt, THF, r.t., 2 h, 48% (**6β**), 68% (**6α**).

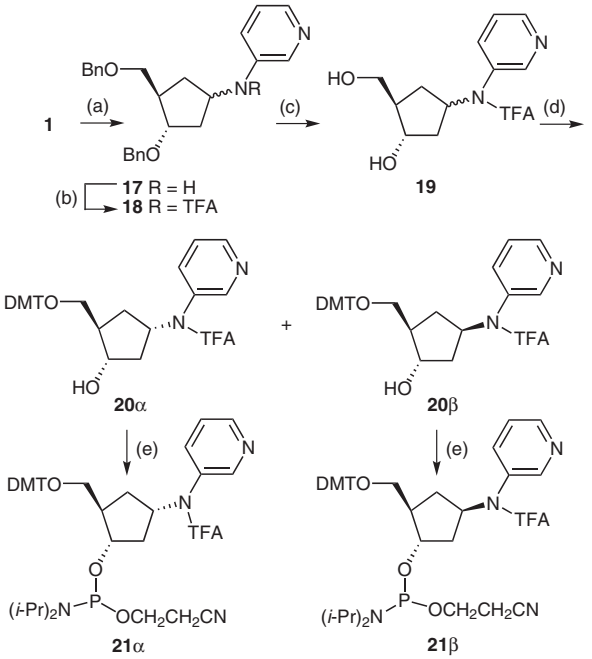
The synthesis of the naphthalene-1,5-diamine containing building blocks **11α**,**β** (Scheme 2) followed the same lines. The reductive amination leading to **7** was slightly less efficient, but yielded again a 1:1 ratio of C1′ epimers. Trifluoroacetic anhydride treatment to give **8** resulted, as expected, in the protection of both amino functions. Inter-



Scheme 2 *Reagents and conditions*: (a) 1. naphthalene-1,5-diamine, AcOH, r.t., 2 h, 2. $NaBH_3CN$, r.t., 16 h, 37%, α/β (1:1); (b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 2 h, 98%; (c) 10% Pd/C, H_2, MeOH, r.t., 2 h, 97%; (d) DMT-Cl, pyridine, r.t., 4 h, 43%; (e) (*i*-Pr_2N)PCl(OCH_2CH_2CN), *i*-Pr_2NEt, THF, r.t., 2 h, 62% (**11β**), 88% (**11α**).



Scheme 3 *Reagents and conditions*: (a) 1. benzene-1,3-diamine, AcOH, 2. $NaBH_3CN$, THF, r.t., 18 h, 38%, α/β (1:1); (b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 1 h, 94%; (c) 10% Pd/C, MeOH, H_2, r.t., 1.5 h, 100%; (d) DMT-Cl, pyridine, r.t., 3.5 h, 40%; (e) (*i*-Pr_2N)PCl(OCH_2CH_2CN), *i*-Pr_2NEt, THF, r.t., 0.5 h, 81% (**16β**), 77% (**16α**).



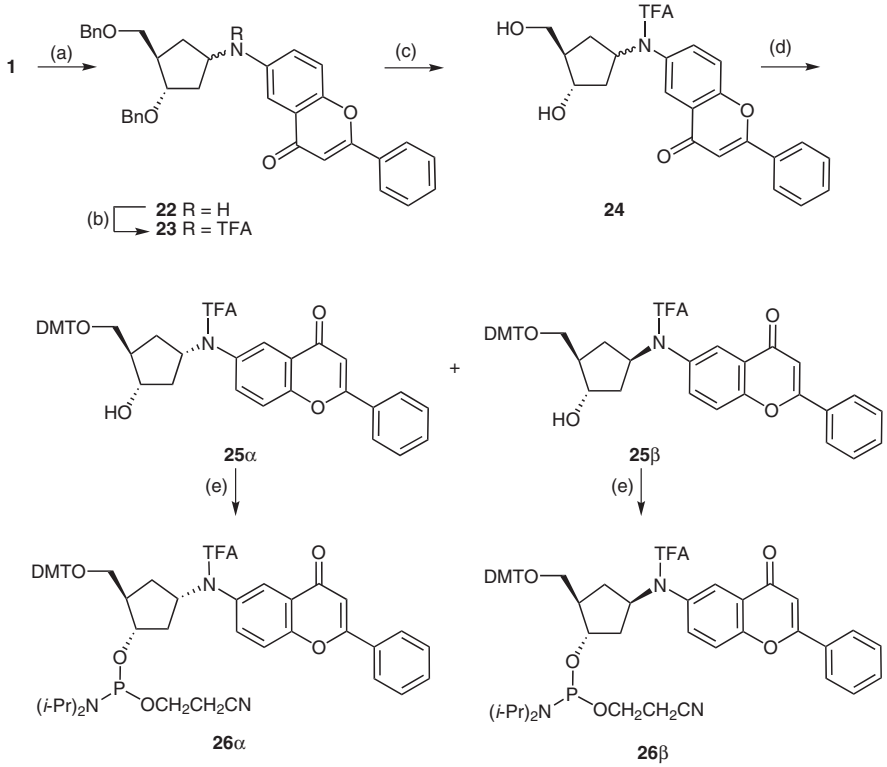
Scheme 4 *Reagents and conditions*: (a) 1. pyridin-3-amine, $Mg(ClO_4)_2$, MeOH, AcOH, 2. $NaBH_3CN$, r.t., 18 h, 50%, α/β (1:1); (b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 1 h, 87%; (c) 10% Pd/C, MeOH, H_2, r.t., 1.5 h, 98%; (d) DMT-Cl, pyridine, r.t., 3.5 h, 55%; (e) (*i*-Pr_2N)PCl(OCH_2CH_2CN), *i*-Pr_2NEt, THF, r.t., 0.5 h, 86% (**21β**), 65% (**21α**).

estingly, the ^1H NMR spectrum of **8** (and the following compounds **9**–**11**) indicated the presence of another set of two minor α- and β-isomers (total of four) arising from isomeric *E*/*Z* forms at the secondary amide function. This additional isomerism was observed with most of the nucleosides prepared in this study as best evidenced by the ^{31}P NMR spectra of the corresponding phosphoramidites that often displayed more than two signals (see Supporting Information). However, only in the case of the tritylated compound **10** could all four isomers be separate by chromatography. The appearance of rotamerism was of no consequence for the synthesis of oligonucleotides as it was only associated with the protecting groups that were removed after oligonucleotide synthesis. For reasons of simplified spectroscopic analysis, we isolated and continued the synthesis only with the major α- and β-isomers of **10**. The assignment of configuration was again performed by ^1H,^1H-ROESY-spectroscopy. Phosphitylation of **10α** and **10β** to give **11α** and **11β** finally concluded this synthesis.

Likewise the syntheses of **16α**,**β**, **21α**,**β**, and **26α**,**β** (Schemes 3– 5) was achieved. In all cases the reductive amination yielded roughly 1:1 mixtures of C1′ epimers in yields of 40–50%.

2.2 Synthesis of Oligonucleotides

Oligonucleotides **ON1**–**12** (Table 1) carrying a fluorescein (FAM) label at the 5′-end or a dabcyl quencher at the 3′-end were prepared on a Pharmacia Gene Assembler plus DNA synthesizer in the DMT-off mode applying classical solid phase phosphoramidite chemistry.[29] Changes applied to the standard synthesis cycle were an



Scheme 5 *Reagents and conditions*: (a) 1. 6-aminoflavone, AcOH, r.t., 2 h, 2. $NaBH_3CN$, r.t., 16 h, 38%, α/β (1:1); (b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 2 h, 74%; (c) 10% Pd/C, H_2, MeOH, r.t., 2 h, 75%; (d) DMT-Cl, pyridine, r.t., 2 h, 80%; (e) (*i*-Pr_2N)PCl(OCH_2CH_2CN), *i*-Pr_2NEt, THF, r.t., 1 h, 69% (**26β**), 63% (**26α**).

extended coupling time of 3.5 minutes for the phosphoramidites **6**, **11**, **16**, **21**, and **26** and the replacement of tetrazole for (ethylthio)tetrazole as the activator.

Oligonucleotides were cleaved from the solid support and deprotected by standard methods (33% aq NH_3, r.t. to 55 °C, 16–24 h). The crude oligonucleotides were purified by either reversed phase or ion exchange HPLC. The structural integrity was controlled by ESI-mass spectrometry. Sequences and analytical data of **ON1–12** are given in Table 1.

Table 1 Sequences and Mass Analytical Data of Oligodeoxynucleotides Synthesized

Sequence of **ON1–10** 5′-(6-FAM-GTCCT**Y**GCTGAG)-3′
Sequence of **ON11**,**12** 5′-(CTCAGC**Y**AGGAC-dabcyl)-3′

	Y =	Yield[a] (%)	MS *m*/*z*	
			Calcd	Found
ON1	α-**AN**	90	4154.3	4154.9
ON2	β-**AN**	95	4154.3	4154.8
ON3	α-**DAN**	50	4217.8	4217.8
ON4	β-**DAN**	42	4217.8	4217.8
ON5	α-**DAB**	75	4168.8	4170.0
ON6	β-**DAB**	79	4168.8	4170.0
ON7	α-**AP**	80	4154.8	4156.0
ON8	β-**AP**	82	4154.8	4156.0
ON9	α-**CHR**	40	4298.6	4298.6
ON10	β-**CHR**	45	4298.6	4298.7
ON11	α-**CHR**	87	4201.1	4201.2
ON12	β-**CHR**	85	4201.1	4201.2

[a] Ratio of OD^{260nm} before and after HPLC.

While the syntheses of oligonucleotides with building blocks **6**, **16**, **21**, and **26** was smooth, that with building block **11** showed some complications. After standard deprotection, the HPLC showed two major peaks in a ratio of 2:3 that could be associated by mass spectrometry with the expected oligonucleotide carrying one trifluoroacetyl group, or one trifluoroacetyl and an acetyl group, respectively. The acetyl group arises from the capping step during synthesis, while the trifluoroacetyl group from incomplete removal during deprotection. We reasoned that this was the consequence of the relatively high nucleophilicity of the naphthalene-1,5-diamine system, where the two amino groups are in a vinylogous hydrazinoid arrangement. Indeed, treatment of the oligonucleotide carrying only the trifluoroacetyl group with a stronger base (1 M NaOH) for two hours lead to the fully deprotected oligonucleotide.

3 Pairing Properties of Oligonucleotides

We performed T_m measurements to determine thermal duplex stabilities with complementary DNA containing all four natural bases opposite the respective residue Y. The natural oligodeoxynucleotides complementary to **ON1–10** were equipped with a 3′-dabcyl label while those complementary to **ON11** and **ON12** contained a 5′-FAM label. Such duplexes contained a fluorescence quencher pair at the end, which was necessary to follow denaturation by fluorescence spectroscopy. The fluorescence measurements (Supporting Information) were performed to comply with the measurements of the previous assay.[25] The UV-measurements were carried out to validate the fluorescence measurements. As expected, we found no significant differences between the T_m-values determined by the two methods. Figure 2 summarizes the T_m data obtained from UV-melting curves (numerical values are given in the Supporting Information).

Interestingly **ON1** gave no sigmoidal transitions in the melting curves in the temperature interval applied (30–70 °C) irrespective of the complementary bases, suggesting that a potential T_m would be below 30 °C. The most discriminating modification was α-**DAB** (**ON5**) which showed T_m differences of up to 4 °C between the strongest (G) and the weakest (C) complementary base. The least discriminating entity was β-**DAN** (**ON4**) with a maximum ΔT_m between all four natural bases of only 1 °C. The highest affinities were obtained with α-**DAN** (**ON3**) indicating that the α-configured naphthalene-1,5-diamine displays the most stabilizing interactions. Interestingly, there are examples where the α-configured nucleotides show stronger binding, as in the case of **DAN**, as well as also the opposite, reflected in the T_ms of **AP**. In all cases the T_ms were lower than that of a classical matched duplex with a T–A (T_m = 54 °C) or a C–G (T_m = 58 °C) instead of a Y–N base-pair.

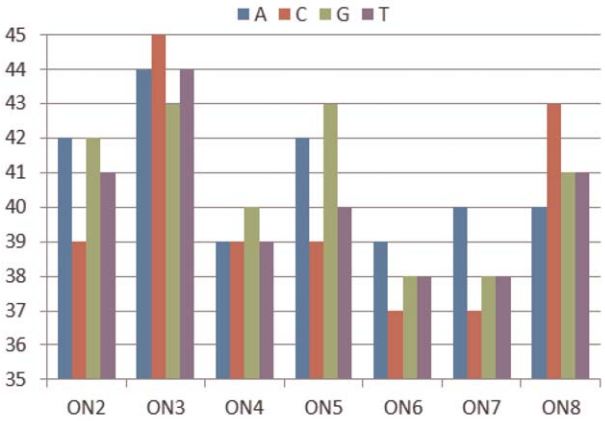


Figure 2 Graphical representation of the T_m values (°C) from UV melting curves (260 nm) of **ON2A–ON8A** with complementary deoxyoligonucleotides presenting each of the four natural bases opposite the modification Y (duplex concd 0.6 μM in 3.5 mM $MgCl_2$, 50 mM KCl, 10 mM tris, pH 8.0).

ON9–12 were prepared to investigate not only complementary binding to the natural bases, but also self-pair formation. The extended aromatic surface of the chromene system calls for interstrand stacking interactions as a duplex stabilizing factor. While such interactions were known to occur with aromatic residues, such as biphenyls and/or phenanthrenes, or other extended chromophores, [30–32] it was unclear whether this may also occur in the series of carbocyclic *exo*-amino nucleosides where the linkage between the aromatic residue and the sugar contains an additional conformationally flexible single bond.

As can be seen from Figure 3, both epimeric forms have a preference for an opposing cytosine base with the α-epimer showing generally slightly higher T_ms compared to the β-epimer. Surprisingly, the thermal duplex stabilities are in all cases as high as that of the control duplex with either an T–A or a C–G base-pair. Thus, the chromene residue is significantly more stabilizing than each of the other aromatic amines. The most stable duplexes are formed when two **CHR** residues are placed against each other. In this series α,α-**CHR** interactions are strongest, α,β- or β,α-**CHR** intermediate and β,β-**CHR** the weakest. All these data are in agreement with the **CHR** residues engaging in interstrand stacking interactions with either natural bases or with themselves.

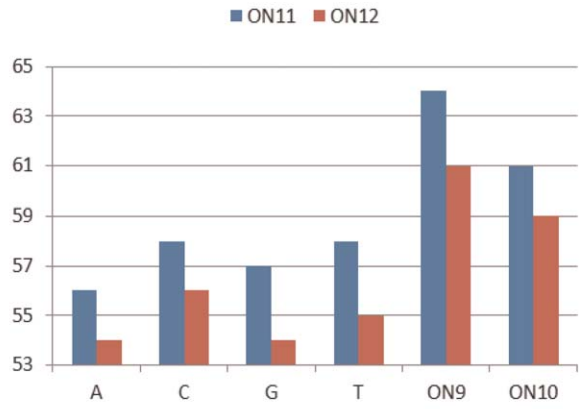


Figure 3 Graphical representation of T_m values of **ON11** and **ON12** paired against natural complements with each of the four natural bases opposite the **CHR** base or against **ON9** and **ON10** exhibiting a **CHR** self-pair. Experimental conditions as for Figure 2.

4 Discussion and Conclusions

In this work we have achieved a synthetic access to a series of carbocyclic *exo*-amino nucleosides and corresponding oligonucleotides. The synthesis relies on a reductive amination procedure to connect the base surrogates with a carbocyclic sugar unit. This reductive amination leads in all cases to nearly 1:1 mixtures of C1′ epimers. We rationalize this lack of selectivity with the *trans* arrangement of the substituents at C3′ and C4′ of the cyclopentanone unit, obstructing hydride attack of the situ formed immonium ion from both sides in the same way. Despite several attempts to optimize this reaction the yields of the reductive amination remained in the range 37–50%. The most prominent side reaction was the reduction of the ketone, indicating that either Schiff base formation or the reactivity of the immonium ion towards hydride reduction was yield determining.

The incorporation of the corresponding building blocks into oligonucleotides via phosphoramidite chemistry was straightforward. The only problem encountered here was that of incomplete removal of the trifluoroacetyl protecting groups during deprotection as well as the introduction of an acetyl group during the capping step in the case of naphthalene-1,5-diamine. We hypothesized that this was due to the high nucleophilicity of the two amino groups that are in a vinylogous hydrazinoid arrangement. The problem of acetylation can be easily prevented by either omitting the capping step or by replacing acetic anhydride as capping reagent by phenoxyacetic anhydride,[33] or trifluoroacetic anhydride that are known to lead to more labile amides with aromatic amines that are cleavable under normal oligonucleotide deprotection conditions.

In terms of molecular recognition in duplex structures we find in general that the T_m-values observed here with the carbocyclic *exo*-amino nucleosides match well with those observed previously in the parallel screen[25] with the (non-carbocyclic) *exo*-amino nucleosides. This validates the methodology of the screen and suggests that there are no significant differences in complementary base recognition as a function of whether there is a CH_2 group or an oxygen atom in the five-membered ring. This complies well with earlier findings on oligonucleotides containing carbocyclic nucleotides with natural bases, where also no major deviations in T_ms were observed as compared to natural nucleosides.[5]

From Figure 2 it becomes clear that both the α- and β-epimeric nucleosides can discriminate between opposing natural bases, which suggests the presence of some level of molecular recognition. In some cases, such as with **DAN** and **DAB**, the α-form leads to higher T_ms whereas in others, for example, with **AP**, the β-epimer leads to higher stabilization. From model considerations of a DNA duplex in the B-conformation it appears that a shift from β to α is associated with a translational shift of the aromatic residue within the plane of the DNA base-pairs. Thus, changing from α to β does not interrupt the base stack, but leads exclusively to a different location of the aromatic residue within the base stack. We, therefore, hypothesize that the differences in stability observed for α- and β-epimers of **AN**, **DAN**, **DAB**, and **AP** are due to differential edge-to-edge interactions of the natural bases by hydrogen bonds and/or hydrophobic interactions.

The situation is somewhat different in the case of the chromene residue **CHR**, where the aromatic surface is too large to permit edge to edge interactions with natural bases. In these cases we believe that recognition occurs by interstrand stacking interactions. The differences between α- and β-epimers is, thus, only a consequence of different

stacking geometries. It is remarkable that such **CHR**/nucleobase pairs are as stable as a matched Watson–Crick base-pair. Into this picture fits also the self-recognition of **CHR**. We note that the T_ms of the self-pairs are higher by up to 6 °C compared to those of duplexes with a C–G pair instead. This is due to the higher hydrophobicity of the aromatic units, avoiding hydration by self-assembly upon duplex formation.

In conclusion we find that carbocyclic *exo*-amino nucleosides show all the characteristics of *exo*-amino nucleosides in DNA base recognition. Despite the structural flexibility imposed by the additional bond between the aromatic and the sugar unit these molecular entities engage in specific interactions with natural nucleotides and can lead to self-pairs that match or exceed the stability of Watson–Crick base-pairs. These are necessary prerequisites for applications as tools in biotechnology. In a completely different context, such carbocyclic *exo*-amino nucleosides may also be of interest in medicinal chemistry. Corresponding testing for antiviral activity will be performed in the near future.

Reactions were carried out under argon. Solvents for reactions were dried by filtration over activated alumina. Solvents for extractions and chromatography were technical grade and distilled before use. All other reagents were purchased from Fluka, Aldrich, Acros Organics, Hänseler, ABCR, and TCI and were of the highest quality available. TLC was carried out using pre-coated silica gel plates SIL-G-25 UV254 (Macherey-Nagel). Visualization was performed under UV-light (254 nm or 350 nm) and by using the following staining reagents; (a): $Ce(SO_4)_2$ (10.5 g), phosphomolybdic acid (21 g), concd H_2SO_4 (60 mL), and H_2O (900 mL), or (b): anisaldehyde (10 mL), concd H_2SO_4 (10 mL), AcOH (2 mL), and EtOH (180 mL). Flash chromatography (FC) was performed on Silica Gel 60 (mesh size: 40–63 μm) from Fluka or SiliCycle. DMT = 4,4′-dimethoxytrityl, TFA = trifluoroacetyl.

NMR spectra were recorded on a Bruker AC-300, Bruker DRX-400, or Bruker DRX-500 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz relative to undeuterated residual solvent [δ = 7.26 ($CDCl_3$), δ = 3.31 (CD_3OD), δ = 2.50 (DMSO-d_6), and δ = 2.05 (acetone-d_6)]. ^{13}C NMR spectra were recorded at 75 MHz or 101 MHz relative to undeuterated residual solvent [δ = 77.16 ($CDCl_3$), δ = 49.00 (CD_3OD), δ = 29.84 and 206.26 (acetone-d_6), and δ = 39.52 (DMSO-d_6)]. Signal assignments were based on DEPT or APT experiments, or on ^{1}H/^{1}H and ^{1}H/^{13}C correlation experiments (COSY/HSQC). ^{1}H/^{1}H-ROESY experiments were recorded at 400 MHz. ^{31}P NMR spectra at 162 MHz relative to 85% H_3PO_4 as the external standard. ^{19}F NMR spectra were recorded at 376 MHz. ESI-MS were recorded either on a Fisons Instrument VG Platform (low resolution) or on an Applied Biosystems, Sciex QSTAR Pulsar (high resolution).

Reductive Aminations; General Procedure

To a soln of **1**[28] (3–10 mmol) in THF (10 mL/mmol) was added glacial AcOH (2 equiv) and amine (2 equiv) at r.t. and the resulting mixture was stirred for 2 h. To this mixture, $NaBH_3CN$ (2 equiv) was added and the mixture was stirred for a further 16 h. The resulting mixture was washed with sat. $NaHCO_3$ and brine, and the aqueous layer was extracted with Et_2O. After evaporation of the solvents, the crude residue was purified by flash chromatography (hexane–EtOAc, 3:1) to yield the desired product **2**, **7**, **12**, or **22**, each as a 1:1 mixture of α/β-epimers as a colorless oil.

***N*-{(3*S*,4*R*)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}aniline (2)**

Starting from **1** (1.8 g, 5.8 mmol); yield: 1.1 g (50%); TLC (hexane–EtOAc, 3:1): R_f = 0.65.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 10 H, H_{arom}), 7.21–7.08 (m, 2 H, $H_{aniline}$), 6.67 (tdt, *J* = 7.4, 4.1, 1.1 Hz, 1 H, $H_{aniline}$), 6.61–6.52 (m, 1 H, $H_{aniline}$), 6.52–6.42 (m, 1 H, $H_{aniline}$), 4.60–4.36 (m, 4 H, CH_2Ph), 4.10–3.86 (m, 2 H, H1′, H3′), 3.57–3.48 (m, 1 H, H5′), 3.48–3.40 (m, 0.5 H, H5′), 3.37 (dd, *J* = 9.2, 6.8 Hz, 0.5 H, H5′), 2.59–2.31 (m, 1.5 H, H4′, H6′), 2.16 (qd, *J* = 13.1, 6.0 Hz, 1 H, H2′), 2.06–1.96 (m, 0.5 H, H6′), 1.91–1.78 (m, 1 H, H2′), 1.71 (ddd, *J* = 13.5, 7.2, 6.4 Hz, 0.5 H, H6′), 1.32 (td, *J* = 13.2, 6.8 Hz, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.64 (d, $C_{aniline}$), 138.41 (d, q-C_{Bn}), 129.19 (s), 128.41 (d), 127.79 (s), 127.71–127.44 (m) (C_{Bn}, $C_{aniline}$), 117.01 (s, $C_{aniline}$), 113.29 (d, $C_{aniline}$), 81.89 (d, C3′), 73.16 (d, *C*H_2Ph), 72.07 (d, C5′), 71.10 (d, *C*H_2Ph), 52.78 (d, C1′), 44.77 (d, C4′), 39.02 (d, C2′), 34.98 (d, C6′).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}NO_2$: 388.2271; found: 388.2271.

***N*^{1}-{(3*S*,4*R*)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}naphthalene-1,5-diamine (7)**

Starting from **1** (3 g, 9.7 mmol); yield: 1.62 g (37%); TLC (hexane–EtOAc, 3:1): R_f = 0.29.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 11 H, H_{arom}, H_{Naphth}), 7.22–7.11 (m, 2 H, H_{Naphth}), 7.07–7.00 (m, 1 H, H_{Naphth}), 6.78–6.68 (m, 1 H, H_{Naphth}), 6.59 (dd, *J* = 20.6, 7.5 Hz, 1 H, H_{Naphth}), 4.63–4.45 (m, 4 H, CH_2Ph), 4.23–4.14 (m, 1 H, H1′), 4.24–4.14 (m, 1 H, H3′), 4.08–4.00 (m, 1 H, H3′), 3.54 (d, *J* = 5.2 Hz, 1 H, H5′), 3.50–3.31 (m, 1 H, H5′), 2.64–2.51 (m, 1 H, H4′, H6′), 2.47–2.39 (m, 0.5 H, H4′), 2.27–2.09 (m, 2 H, H2′, H6′), 1.99 (dt, *J* = 18.1, 6.4 Hz, 0.5 H, H2′), 1.68 (ddd, *J* = 13.1, 9.5, 5.6 Hz, 0.5 H, H6′), 1.52–1.47 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.27 (s, C_{Naphth}), 143.09–142.20 (m, C_{Naphth}), 139.14–138.12 (m, q-C_{Bn}), 129.03–127.07 (m, C_{Bn}, C_{Naphth}), 125.62 (d, C_{Naphth}), 124.88 (d, C_{Naphth}), 124.46–123.60 (m, C_{Naphth}), 110.96 (d, C_{Naphth}), 110.02–108.59 (m, C_{Naphth}), 104.89 (d, C_{Naphth}), 82.35 (d, C3′), 73.14 (d, *C*H_2Ph), 72.04 (d, C5′), 71.21 (d, *C*H_2Ph), 53.04 (d, C1′), 44.79 (d, C4′), 38.87 (d, C2′), 35.54–33.68 (d, C6′).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{33}N_2O_2$: 453.2537; found: 453.2539.

***N*^{1}-{(3*S*,4*R*)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}benzene-1,3-diamine (12)**

Starting from **1** (1 g, 3.2 mmol); yield: 460 mg (36%); TLC (hexane–EtOAc, 1:1): R_f = 0.35.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.39–7.22 (m, 10 H, H_{arom}), 7.69 (q, *J* = 7.9 Hz, 1 H, $H_{phenylene}$), 6.06–5.97 (m, 1.5 H, $H_{phenylene}$), 5.95–5.86 (m, 1 H, $H_{phenylene}$), 5.75 (t, *J* = 2.1 Hz, 0.5 H, $H_{phenylene}$), 4.56–4.37 (m, 5 H, CH_2Ph, H5′), 4.01–3.83 (m, 2 H, H1′, H3′), 3.52–3.31 (m, 1 H, C5′), 2.57–2.30 (m, 1.5 H, H4′, H6′), 2.20–2.06 (m, 1 H, H2′), 2.04–1.95 (m, 0.5 H, H6′), 1.89–1.78 (m, 1 H, H2′), 1.74–1.61 (m, 0.5 H, H6′), 1.37–1.28 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.96 (d, $C_{phenylene}$), 147.57 (s, q-C_{Bn}), 130.15 (d, $C_{phenylene}$), 128.55 (d), 128.01 (s), 127.77 (d), 127.70–127.58 (m) (C_{Bn}), 104.92–104.25 (m, $C_{phenylene}$), 100.27–99.76 (m, $C_{phenylene}$), 82.01 (d, C3′), 73.30 (d, *C*H_2Ph), 72.24 (d, C5′), 71.23 (d, *C*H_2Ph), 52.87 (d, C1′), 44.88 (d, C4′), 39.20 (d, C2′), 35.20 (d, C6′).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{31}N_2O_3$: 403.2380; found: 403.2380.

(3*S*,4*R*)-6-{3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentylamino}-2-phenyl-4*H*-chromen-4-one (22)

Starting from **1** (1.56 g, 5 mmol); yield: 1.00 g (38%); TLC (hexane–EtOAc, 2:1): R_f = 0.27.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.76 (m, 2 H, H_{chrom}), 7.57–7.44 (m, 3 H, H_{chrom}), 7.43–7.30 (m, 11 H, H_{arom}), 7.24 (dd, *J* = 14.5, 2.9 Hz, 1 H, H_{chrom}), 6.92–6.74 (m, 1 H, H_{chrom}), 6.57 (dd, *J* = 9.0, 2.9 Hz, 1 H, H_{chrom}), 4.59–4.44 (m, 4 H, C*H*$_2$Ph), 4.42–4.27 (m, 1 H, NH), 4.04 (dtd, *J* = 11.0, 6.2, 3.7 Hz, 2 H, H1′, H3′), 3.62–3.31 (m, 2 H, H5′), 2.61–2.46 (m, 1 H, H4′), 2.48–2.25 (m, 1 H, H6′), 2.23–2.03 (m, 1 H, H2′), 2.03–1.83 (m, 1 H, H2′), 1.55–1.35 (m, 1 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.61 (d), 162.62 (d), 149.30 (d), 145.25 (d) (C_{chrom}), 139.17–137.65 (m, q-C_{Bn}), 131.74 (d, C_{chrom}), 130.71–127.23 (m, C_{Bn}, C_{chrom}), 126.16 (s), 124.85 (s), 121.87 (d), 118.92 (d), 106.64 (s), 104.00 (d) (C_{chrom}), 81.54 (d, C3′), 73.80 (d, *C*H$_2$Ph), 72.05 (d, C5′), 71.23 (t, *C*H$_2$Ph), 53.12 (d, C1′), 44.76 (d, C4′), 38.73 (d, C2′), 34.75 (d, C6′).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{34}NO_4$: 532.2482; found: 532.2483.

***N*-{(3*S*,4*R*)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl)pyridin-3-amine (17)**

To a soln of **1** (0.1 g, 0.32 mmol, 1 equiv) in anhyd MeOH (1 mL) was added pyridine-3-amine (60 mg, 0.64 mmol, 2 equiv), AcOH (20 μL, 0.32 mmol, 1 equiv), and $Mg(ClO_4)_2$ (4 mg, 0.016 mmol, 0.05 equiv) at r.t. and the mixture was stirred for 2 h. Then $NaBH_3CN$ (24 mg, 0.38 mmol, 1.2 equiv) was added and the mixture stirred for a further 18 h at r.t. The mixture was then quenched with sat. $NaHCO_3$ (8 mL), and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by flash chromatography (hexane–EtOAc, 2:1 to 1:1) to yield **17** (61 mg, 50%) as a colorless oil; ratio α/β 1:1; R_f = 0.35 (hexane–EtOAc, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.78 (m, 2 H, H_{Py}), 7.46–7.26 (m, 10 H, H_{Bn}), 7.13–6.99 (m, 1 H, H_{Py}), 6.87–6.65 (m, 1 H, H_{Py}), 4.65–4.44 (m, 4 H, C*H*$_2$Ph), 4.10–3.92 (m, 2 H, H1′, H3′), 3.62–3.34 (m, 2 H, H5′), 2.60–2.52 (m, 0.5 H, H4′), 2.52–2.37 (m, 1 H, H4′, H6′), 2.14 (m, 1 H, H2′), 2.09–1.98 (m, 0.5 H, H6′), 1.97–1.84 (m, 1 H, H2′), 1.72 (m, 0.5 H, H6′), 1.48–1.36 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.65–143.63 (d, C_{Py}), 139.01–137.89 (m, C_{Py}), 136.65 (d, C_{Py}), 129.09–127.39 (m, C_{Bn}), 123.76 (d, C_{Py}), 119.03 (d, C_{Py}), 82.07 (d, C3′), 73.40 (d, *C*H$_2$Ph), 72.10 (d, C5′), 71.30 (d, *C*H$_2$Ph), 52.81 (d, C1′), 44.86 (d, C4′), 38.94 (d, C2′), 34.88 (d, C6′).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{29}N_2O_2$: 389.2224; found: 389.2224.

Trifluoroacetylation; General Procedure

To a soln of benzylated carbocyclic nucleosides **2**, **7**, **12**, **17**, or **22** (1–3 mmol) in CH_2Cl_2 (30 mL/mmol) at 0 °C was added Et_3N (2 equiv) and TFAA (2 equiv); the mixture was stirred at this temperature for 2 h. After completion of the reaction (TLC monitoring), the mixture was quenched with H_2O. The organic layer was washed with brine and then evaporated under reduced pressure. The resulting residue was purified FC (hexane–EtOAc, 3:1) to yield compound **3**, **8**, **13**, **18**, or **23** as a α/β 1:1 mixture as a yellowish foam.

(3*S*,4*R*)-*N*-{3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}-2,2,2-trifluoro-*N*-phenylacetamide (3)

Starting from **2** (1 g, 2.6 mmol); yield: 1.17 g (94%); TLC (hexane–EtOAc, 4:1): R_f = 0.56.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.21 (m, 15 H, H_{arom}, $H_{aniline}$), 5.27–5.20 (m, 0.5 H, H1′), 5.10–4.90 (m, 0.5 H, H1′), 4.66–4.48 (m, 4 H, C*H*$_2$Ph), 3.92 (dt, 0.5 H, H3′), 3.87–3.74 (m, 0.5 H, H3′), 3.59–3.48 (m, 1 H, H5′), 3.41 (qt, *J* = 18.8, 9.2 Hz, 1 H, H5′), 2.57–2.43 (m, 1 H, H2′, H4′), 2.34 (dtd, *J* = 15.7, 10.7, 6.4 Hz, 1 H, H6′, H4′), 2.26–2.12 (m, 0.5 H, H2′), 2.06–1.91 (m, 0.5 H, H6′), 1.93–1.77 (m, 0.5 H, H6′), 1.73–1.53 (m, 1 H, H2′), 1.50–1.32 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.91 (dd, CF_3C=O), 138.42 (dd, $C_{aniline}$), 135.63 (s, q-C_{Bn}), 134.88 (s, q-C_{Bn}), 130.43 (d), 129.44 (d), 129.02 (d), 128.41 (dd), 127.79–127.37 (m) (C_{Bn}, $C_{aniline}$, CF_3), 79.65 (d, C3′), 73.13 (t, *C*H$_2$Ph), 72.08–71.50 (m C5′), 70.85 (s, *C*H$_2$Ph), 57.48 (s, C1′), 55.29 (s, C1′), 44.28 (s), 43.37 (s) C4′, 36.39 (s), 35.07 (s) C2′, 31.18 (s), 30.46 (s) C6′.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.22 (d, N-TFA).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{29}F_3NO_3$: 484.2093; found: 484.2094.

(3*S*,4*R*)-*N*-{3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}-2,2,2-trifluoro-*N*-[5-(2,2,2-trifluoroacetylamino)naphthalen-1-yl]acetamide (8)

Starting from **7** (1.62 g, 3.6 mmol); yield: 2.3 g (98%); TLC (hexane–EtOAc, 3:1): R_f = 0.48.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, N*H*-TFA), 7.96–7.85 (m, 2 H, H_{Naphth}), 7.78 (ddd, *J* = 10.9, 8.5, 3.1 Hz, 1 H, H_{Naphth}), 7.64–7.48 (m, 2 H, H_{Naphth}), 7.45–7.19 (m, 10 H, H_{Bn}), 7.16–7.07 (m, 1 H, H_{Naphth}), 5.11–4.81 (m, 1 H, H1′), 4.59–4.22 (m, 4 H, C*H*$_2$Ph), 3.89–3.61 (m, 1 H, H3′), 3.49–3.19 (m, 2 H, H5′), 2.74–2.50 (m, 0.5 H, H2′), 2.43–2.23 (m, 1 H, H4′), 2.21–2.04 (m, 1 H, H2′, H6′), 1.98–1.73 (m, 1 H, H2′), 1.66–1.49 (m, 0.5 H, H6′), 1.44–1.29 (m, 0.5 H, H6′), 1.23–1.10 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.30–157.16 (m, CF_3C=O), 156.37–155.30 (m, CF_3C=O), 138.58–138.02 (m, q-C_{Naphth}), 134.54–132.45 (m, q-C_{Bn}), 130.14–126.88 (m, C_{Bn}, C_{Naphth}), 126.35–125.96 (m, CF_3), 122.92 (ddd, C_{Naphth}), 79.67 (dd, C3′), 74.02–72.40 (m, *C*H$_2$Ph), 72.51–71.31 (m, *C*H$_2$Ph), 70.89 (d, C5′), 59.95–59.50 (m, C1′), 57.53 (d, C1′), 44.80–43.11 (m, C4′, 37.44–34.46 (m, C2′), 32.00–29.72 (m, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.90 to –68.73 (m, N-TFA), –74.84 to –75.79 (m, NH-TFA).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{31}F_6N_2O_4$: 645.2183; found: 645.2195.

***N*-{(3*S*,4*R*)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}-2,2,2-trifluoro-*N*-[3-(2,2,2-trifluoroacetamido)phenyl]acetamide (13)**

Starting from **12** (0.96 g, 2.4 mmol); yield: 1.36 g (94%); TLC (hexane–EtOAc, 3:1): R_f = 0.46.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 14.6 Hz, 1 H, NH-TFA), 7.65–7.38 (m, 3 H, $H_{phenylene}$), 7.37–7.14 (m, 10 H, H_{arom}), 7.04 (t, *J* = 7.0 Hz, 1 H, $H_{phenylene}$), 5.04 (s, 0.5 H, C1′), 4.90 (s, 0.5 H, H1′), 4.55–4.32 (m, 4 H, C*H*$_2$Ph), 3.80 (dd, *J* = 12.4, 6.9 Hz, 0.5 H, H3′), 3.72 (s, 0.5 H, H3′), 3.46–3.19 (m, 2 H, H5′), 2.38 (dd, *J* = 15.8, 10.1 Hz, 1 H, H4′, H2′), 2.21 (s, 1 H, H4′, H6′), 2.07 (d, *J* = 18.4 Hz, 0.5 H, H2′), 1.86 (s, 0.5 H, H6′), 1.74 (d, *J* = 17.4 Hz, 0.5 H, H6′), 1.74 (d, *J* = 17.4 Hz, 1 H, H2′), 1.55 (d, *J* = 12.0 Hz, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.35 (m, $C_{phenylene}$), 129.97 (s, $C_{phenylene}$), 128.68–127.76 (m, C_{Bn}, CF_3, $C_{phenylene}$), 122.62 (s), 122.37 (s), 121.34 (s) ($C_{phenylene}$), 79.76 (s, C3′), 73.37 (s), 73.07 (s) (*C*H$_2$Ph), 71.80 (d, *J* = 11.5 Hz, C5′), 70.99 (s, *C*H$_2$Ph), 58.30–57.22 (m, C1′), 56.01–55.09 (m, C1′), 44.36 (s, C4′), 43.56 (s, C4′), 36.55 (s), 35.20 (s) (C2′), 31.26 (s), 30.67 (s) (C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.30 (d, N-TFA), –75.65 (d, NH-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{29}F_6N_2O_4$: 595.2026; found: 595.2026.

N-{(3S,4R)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}-2,2,2-trifluoro-N-(pyridin-3-yl)acetamide (18)

Starting from **17** (0.49 g, 1.3 mmol); yield: 0.53 g (87%); TLC (hexane–EtOAc, 2:1): R_f = 0.42.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (t, *J* = 3.9 Hz, 1 H, H_{Py}), 8.45 (s, 1 H, H_{Py}), 7.67–7.08 (m, 12 H, H_{Bn}, H_{Py}), 5.17–5.01 (m, 0.5 H, H1′), 4.94 (m, 0.5 H, H1′), 4.43 (m, 4 H, C*H*$_2$Ph), 3.81 (s, 0.5 H, H3′), 3.70 (s, 0.5 H, H3′), 3.42–3.20 (m, 2 H, H5′), 2.43–2.30 (m, 0.5 H, H4′), 2.29–2.13 (m, 1 H, H4′, H6′), 2.07 (d, *J* = 18.6 Hz, 1 H, H2′), 1.88 (m, 0.5 H, H6′), 1.67 (m, 0.5 H, H6′), 1.42 (m, 1 H, H2′), 1.29–1.14 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.59 (m, CF_3*C*=O), 150.91 (d, C_{Py}), 139.62–136.43 (d, C_{Py}), 132.16 (d, CF_3), 129.29–126.78 (m, C_{Bn}), 123.70 (d, C_{Py}), 79.56 (s, C3′), 73.23 (d, *C*H$_2$Ph), 71.65 (d, C5′), 71.05 (s, *C*H$_2$Ph), 57.71 (s, C1′), 55.68 (s, C1′), 44.29 (s, C4′), 43.51 (s, C4′), 36.55 (d, C2′), 35.31 (s, C2′), 30.42 (m, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.08 to –67.67 (m, N-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{28}F_3N_2O_3$: 485.2047; found: 485.2047.

N-{(3S,4R)-3-(Benzyloxy)-4-[(benzyloxy)methyl]cyclopentyl}-2,2,2-trifluoro-N-(4-oxo-2-phenyl-4H-chromen-6-yl)acetamide (23)

Starting from **22** (1.03 g, 1.6 mmol); yield: 0.90 g (74%); TLC (hexane–EtOAc, 2:1): R_f = 0.55.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–7.86 (m, 3 H, H_{chrom}), 7.65–7.40 (m, 5 H, H_{arom}, H_{chrom}), 7.39–7.27 (m, 6 H, H_{arom}, H_{chrom}), 7.25–7.07 (m, 4 H, H_{arom}, H_{chrom}), 6.86 (d, *J* = 7.5 Hz, 1 H, H_{chrom}), 5.23–4.87 (m, 1 H, H1′), 4.56–4.35 (m, 4 H, C*H*$_2$Ph), 3.85–3.66 (m, 1 H, H3′), 3.45–3.28 (m, 2 H, H5′), 2.46–2.32 (m, 1 H, H4′), 2.31–2.06 (m, 2 H, H2′, H6′), 2.00–1.67 (m, 1 H, H6′), 1.57–1.42 (m, 1 H, H2′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.21 (s), 163.95 (s) (C_{chrom}), 156.47 (d, CF_3*C*=O), 138.26 (s, C_{chrom}), 136.74–134.60 (m, q-C_{Bn}), 131.68 (d), 130.25–125.55 (m), 125.03–122.90 (m), 119.25 (s), 118.03–117.00 (m), 115.38–113.84 (m), 107.71 (s), (C_{Bn}, C_{chrom}, CF_3), 79.72 (m, C3′), 72.92 (s, *C*H$_2$Ph), 71.51 (s, C5′), 57.94 (d, C1′), 44.18 (d, C4′), 34.69 (d, C2′), 30.85 (d, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.19 (d, N-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{32}F_3NNaO_5$: 651.2125; found: 651.2123.

Debenzylation; General Procedure

To a soln of TFA-protected nucleosides **8**, **13**, **18**, or **23** (1–3 mmol) in MeOH (5 mL/mmol) was added 10% Pd/C (0.11 equiv) at r.t. and the mixture was hydrogenated at atmospheric pressure. When the reaction was complete (TLC monitoring), Pd/C was filtered off. MeOH was evaporated and the resulting residue was purified by FC (5% MeOH–CH_2Cl_2) to yield **9**, **14**, **19**, or **24** as α/β 1:1 mixtures as slightly yellow foam.

2,2,2-Trifluoro-N-(5-{(3S,4R)-[3-hydroxy-4-(hydroxymethyl)cyclopentyl](2,2,2-trifluoroacetyl)amino}naphthalen-1-yl)acetamide (9)

Starting from **8** (2.30 g, 3.6 mmol); yield: 1.60 g (97%); TLC (5% MeOH–CH_2Cl_2): R_f = 0.22.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 (t, *J* = 13.2 Hz, 1 H, H_{Naphth}), 7.89–7.52 (m, 5 H, H_{Naphth}), 5.04–4.82 (m, 0.5 H, H1′), 4.79–4.64 (m, 0.5 H, H1′), 3.78–3.56 (m, 1 H, H3′), 3.44–3.20 (m, 2 H, H5′), 2.42–2.25 (m, 0.5 H, H2′), 2.14–1.93 (m, 0.5 H, H2′), 1.86–1.49 (m, 2.5 H, H4′, H2′, H6′), 1.39–1.08 (m, 1 H, H6′), 0.95–0.67 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 157.20–155.09 (m, CF_3*C*=O), 136.04–134.00 (m, C_{Naphth}), 133.25–131.66 (m, C_{Naphth}, CF_3), 125.14 (d, C_{Naphth}), 71.43–69.61 (m, C3′), 62.12 (s, C5′), 58.13–55.56 (m, C1′), 49.36–45.20 (m, C4′), 38.33–36.51 (m, C2′), 32.13–28.65 (m, C6′).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –67.25 to –67.52 (m, N-TFA), –73.37 (d, NH-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}F_6N_2NaO_4$: 488.1063; found: 488.1070.

2,2,2-Trifluoro-N-[(3S,4R)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-N-[3-(2,2,2-trifluoroacetamido)phenyl]acetamide (14)

Starting from **13** (0.46 g, 0.77 mmol); yield: 0.32 g (100%); TLC (5% MeOH–CH_2Cl_2): R_f = 0.14.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.44 (s, 1 H, NH-TFA), 7.80 (t, *J* = 8.9 Hz, 1 H, $H_{phenylene}$), 7.62 (d, *J* = 12.0 Hz, 1 H, $H_{phenylene}$), 7.53 (q, *J* = 8.2 Hz, 1 H, $H_{phenylene}$), 7.22 (d, *J* = 7.7 Hz, 1 H, $H_{phenylene}$), 4.94 (d, *J* = 5.8 Hz, 0.5 H, H1′), 4.63 (s, 1.5 H, OH), 4.51 (d, *J* = 6.3 Hz, 0.5 H, H1′), 4.45 (s, 0.5 H, OH), 3.70 (s, 1 H, H3′), 3.40 (dd, *J* = 9.8, 5.0 Hz, 0.5 H, H4′), 3.30–3.15 (m, 2 H, H5′), 2.10 (d, *J* = 5.9 Hz, 0.5 H, H6′), 2.02 (d, *J* = 7.0 Hz, 0.5 H, H2′), 1.79–1.37 (m, 2.5 H, H6′, H2′), 1.34–1.18 (m, 0.5 H, H2′), 1.12–0.94 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.52–151.33 (m, CF_3*C*=O), 136.82–134.97 (m, $C_{phenylene}$, CF_3), 129.50 (s), 127.50 (s), 122.25 (s), 121.76 (s) ($C_{phenylene}$), 70.59 (s, C3′), 62.32 (d, C5′), 55.79–54.65 (m, C1′), 47.92–47.07 (m, C4′), 37.72 (s, C2′), 30.38–29.16 (m, C6′).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –66.36 (d, *J* = 8.0 Hz, N-TFA), –73.96 (d, *J* = 12.7 Hz, NH-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}F_6N_2O_4$: 415.1087; found: 415.1087.

2,2,2-Trifluoro-N-[(3S,4R)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-N-(pyridin-3-yl)acetamide (19)

Starting from **18** (642 mg, 1.32 mmol); yield: 395 mg (98%); TLC (5% MeOH–CH_2Cl_2): R_f = 0.27.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.66 (t, *J* = 5.3 Hz, 1 H, H_{Py}), 8.53 (d, *J* = 9.8 Hz, 1 H, H_{Py}), 7.86 (t, *J* = 9.5 Hz, 1 H, H_{Py}), 7.59 (dd, *J* = 12.4, 7.2 Hz, 1 H, H_{Py}), 5.10 (t, *J* = 7.5 Hz, 0.5 H, H1′), 4.83 (m, 0.5 H, H1′), 3.89 (dd, *J* = 11.5, 5.6 Hz, 1 H, H3′), 3.58–3.44 (m, 2 H, H5′), 2.37–2.28 (m, 0.5 H, H2′), 2.20 (dd, *J* = 12.8, 6.7 Hz, 0.5 H, H6′), 1.96 (m, 1.5 H, H2′, H4′, H6′), 1.86–1.71 (m, 1 H, H2′, H4′), 1.69–1.55 (m, 0.5 H, H6′), 1.42 (m, 0.5 H, H2′), 1.21 (m, 0.5 H, H6′).

^{13}C NMR (101 MHz, CD_3OD): δ = 157.27 (CF_3*C*=O), 151.80 (s, C_{Py}), 151.18 (s, C_{Py}), 140.36 (s, C_{Py}), 134.39 (s, CF_3), 125.53 (s, C_{Py}), 73.00 (d, C3′), 64.14 (d, C5′), 58.66 (s, C1′), 57.17 (s, C1′), 49.82 (s, C4′), 48.58 (s, C4′), 39.79 (s, C2′), 38.91 (s, C2′), 32.24 (s, C6′), 31.28 (s, C6′).

^{19}F NMR (376 MHz, CD_3OD): δ = –64.90 (s, N-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}F_3N_2O_3$: 305.1108; found: 305.1108.

2,2,2-Trifluoro-N-[(3S,4R)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-N-(4-oxo-2-phenyl-4H-chromen-6-yl)acetamide (24)

Starting from **23** (900 mg, 1.4 mmol); yield: 470 mg (75%); TLC (5% MeOH–CH_2Cl_2): R_f = 0.31.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.22–8.08 (m, 2 H), 8.04 (d, *J* = 11.9 Hz, 1 H), 7.98–7.78 (m, 2 H), 7.69–7.56 (m, 3 H), 6.94 (d, *J* = 2.9 Hz, 1 H) (H_{chrom}), 5.22–4.83 (m, 1 H, H1′), 3.93 (dd,

J = 40.5, 23.2 Hz, 1 H, H3′), 3.62–3.50 (m, 1 H, H5′), 3.40 (d, J = 5.7 Hz, 1 H, H5′), 2.34–2.15 (m, 1 H, H6′), 1.98 (dd, J = 21.5, 5.2 Hz, 1 H, H4′), 1.91–1.80 (m, 1 H, H2′), 1.76–1.42 (m, 1 H, H2′), 1.39–1.19 (m, 1 H, H6′).

^{13}C NMR (101 MHz, acetone-d_6): δ = 178.14–177.12 (m, C_{chrom}), 165.41–163.87 (m, C_{chrom}), 157.63–156.10 (m, CF_3C=O), 138.41–136.62 (m, C_{chrom}), 130.06 (m, C_{chrom}), 120.98–119.44 (m, C_{chrom}), 118.67–116.79 (m, CF_3, C_{chrom}), 108.05 (s, C_{chrom}), 71.82 (d, C3′), 64.56 (d, C5′), 57.58 (d, C1′), 50.57 (d, C4′), 38.84 (d, C2′), 31.92 (d, C6′).

^{19}F NMR (376 MHz, CD_3OD): δ = –67.80 (d, N-TFA).

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{23}H_{21}F_3NO_5$: 448.1366; found: 448.1347.

2,2,2-Trifluoro-*N*-[(3*S*,4*R*)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-*N*-phenylacetamide (4)

A 1 M soln of BCl_3 in CH_2Cl_2 (33 mL) was slowly added to a soln of **3** (1.165 g, 2.4 mmol) in CH_2Cl_2 (140 mL) at –78 °C. The mixture was stirred for 6 h at –78 °C. The mixture was allowed to warm to –20 °C and MeOH (62 mL) was added slowly and the mixture stirred at r.t. for a further 16 h. The solvents were removed under reduced pressure and the residue was concentrated several times with MeOH. The crude product was purified by flash chromatography (5% to 10% MeOH–CH_2Cl_2) to yield nucleoside **4** (628 mg, 86%) as a colorless oil; ratio α/β 1:1; TLC (5% MeOH–CH_2Cl_2): R_f = 0.35.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.57–7.44 (m, 3 H, $H_{aniline}$), 7.31 (d, J = 7.0 Hz, 2 H, $H_{aniline}$), 5.07 (tt, J = 10.4, 7.4 Hz, 0.5 H, H1′), 4.81 (ddd, J = 15.3, 9.1, 5.6 Hz, 0.5 H, H1′), 3.88 (tt, J = 7.4, 5.1 Hz, 1 H, H3′), 3.65–3.56 (m, 0.5 H, H5′), 3.53–3.47 (m, 0.5 H, H5′), 3.45–3.34 (m, 1 H, H5′), 2.34–2.26 (m, 0.5 H, H2′), 2.26–2.15 (m, 0.5 H, H6′), 2.05–1.99 (m, 0.5 H, H4′), 1.98–1.90 (m, 1 H, H2′, H6′), 1.87–1.80 (m, 1 H, H6′, H4′), 1.67 (ddd, J = 13.3, 10.3, 7.0 Hz, 0.5 H, H2′), 1.48 (td, J = 11.6, 9.2 Hz, 0.5 H, H2′), 1.26 (dt, J = 12.4, 10.2 Hz, 0.5 H, H6′).

^{13}C NMR (101 MHz, CD_3OD): δ = 156.95 (dd, CF_3C=O), 138.67–136.02 (m, $C_{aniline}$), 132.44–129.27 (m, $C_{aniline}$, CF_3), 120.22–115.77 (m, $C_{aniline}$), 73.91–72.37 (m, C3′), 64.43 (d), 64.23 (d) C5′, 58.48 (s), 56.84 (s) C1′, 49.92 (s), 48.33 (s) C4′, 39.74 (s), 38.83 (s) C2′, 32.36 (s), 31.22 (s) C6′.

^{19}F NMR (376 MHz, CD_3OD): δ = –68.80 (s, N-TFA).

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{14}H_{16}F_3NO_3$: 304.1155; found: 304.1161.

DMT Protection; General Procedure

To a soln of the debenzylated carbocyclic nucleosides **4**, **9**, **14**, **19**, or **24** (1–3 mmol) in pyridine (8 mL/mmol) at r.t. was added DMT-Cl (1.3 equiv) in portions over 30 min. The resulting orange mixture was stirred at r.t. for 3–4 h. Pyridine was co-evaporated with toluene under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with brine and the organic phase was dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by flash chromatography (0.2 to 1% MeOH–CH_2Cl_2 or 2 to 30% hexane–EtOAc) to yield both epimers α and β of **5**, **10**, **15**, **20**, or **25** in equal amounts as a colorless foam. The respective configurations were assigned by ^{1}H/^{1}H-ROESY or NOE difference spectroscopy based on H1′H3′ vs H1′–H4′ interactions for α- and β-epimers, respectively.

***N*-[(3*R*,4*S*)-3-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxycyclopentyl]-2,2,2-trifluoro-*N*-phenylacetamide (5)**

Starting from **4** (628 mg, 2.1 mmol); total yield of **5α** and **5β**: 700 mg (56%); ratio α/β 1:1; TLC (CH_2Cl_2 containing 0.5% MeOH): R_f (**5α**) = 0.28, R_f (**5β**) = 0.13.

Epimer 5β

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.33 (m, 4 H, H_{DMT}), 7.33–7.23 (m, 5 H, H_{DMT}, $H_{aniline}$), 7.22–7.10 (m, 5 H, H_{DMT}), 6.86–6.74 (m, 4 H, H_{DMT}), 5.12–4.95 (m, 1 H, H1′), 3.92–3.83 (m, 1 H, H3′), 3.78 (d, J = 3.4 Hz, 6 H, OMe), 3.19 (ddd, J = 13.8, 9.0, 5.0 Hz, 1 H, H5′), 2.91 (dd, J = 8.9, 7.3 Hz, 1 H, H5′), 2.13 (s, OH-C3′), 2.09 (dd, J = 9.0, 4.1 Hz, 1 H, H6′), 2.07–2.03 (m, 1 H, H4′), 1.95 (ddd, J = 11.7, 7.7, 3.9 Hz, 1 H, H2′), 1.81 (dt, J = 13.7, 8.2 Hz, 1 H, H2′), 1.24 (t, J = 4.9 Hz, 1 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.41 (d, CF_3C=O, C_{DMT}), 144.76 (d, C_{DMT}), 136.13–135.66 (m, C_{DMT}), 130.36–130.11 (m, C_{DMT}, $C_{aniline}$), 129.94 (t, $C_{aniline}$), 129.64–128.79 (m, C_{DMT}), 128.29–127.53 (m, C_{DMT}), 126.71 (d, CF_3), 117.94–117.43 (m, $C_{aniline}$), 114.28 (s, $C_{aniline}$), 113.29–113.01 (m, C_{DMT}), 86.15 (s, C_{DMT}), 74.40 (d, C3′), 65.34 (d, C5′), 56.79 (d, C1′), 55.09 (d, OMe), 46.83 (d, C4′), 37.39 (d, C2′), 31.40 (d, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.40 (s, N-TFA).

Epimer 5α

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.34 (m, 5 H, H_{DMT}), 7.34–7.26 (m, 5 H, H_{DMT}, $H_{aniline}$), 7.24–7.13 (m, 4 H, H_{DMT}), 6.87–6.78 (m, 4 H, H_{DMT}), 4.78–4.64 (m, 1 H, H1′), 3.98–3.89 (m, 1 H, H3′), 3.80 (s, 6 H, OMe), 3.22 (dd, J = 9.0, 5.3 Hz, 1 H, H5′), 2.95 (dd, J = 16.0, 7.2 Hz, 1 H, H5′), 2.70 (s, 1 H, OH-C3′), 2.32–2.20 (m, 1 H, H2′), 2.11–1.99 (m, 1 H, H4′), 1.87 (ddd, J = 13.5, 10.2, 8.1 Hz, 1 H, H6′), 1.70 (ddd, J = 12.6, 8.5, 6.3 Hz, 1 H, H6′), 1.61 (dd, J = 10.2, 8.5 Hz, 1 H, H2′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.49 (d, CF_3C=O, C_{DMT}), 144.65 (s, C_{DMT}), 135.73 (d, C_{DMT}), 129.92 (t, $C_{aniline}$), 129.64–129.05 (m, C_{DMT}), 128.21–127.51 (m, C_{DMT}), 126.82 (s, CF_3), 117.43–116.96 (m, $C_{aniline}$), 114.97–114.73 (m, $C_{aniline}$), 113.48–112.88 (m, C_{DMT}), 86.17 (s, C_{DMT}), 75.20 (s, C3′), 65.83 (s, C5′), 56.00 (s, C1′), 55.16 (d, OMe), 45.53 (d, C4′), 37.95 (s, C2′), 29.75 (d, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.42 (s, N-TFA).

HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{35}H_{34}F_3NNaO_5$: 629.2281; found: 629.2295.

***N*-[(3*R*,4*S*)-3-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxycyclopentyl]-2,2,2-trifluoro-*N*-[5-(2,2,2-trifluoroacetylamino)naphthalen-1-yl]acetamide (10)**

Starting from **9** (1.6 g, 0.34 mmol); total yield of **10α** and **10β**: 1.11 g (43%); ratio α/β 1:1; the minor rotamers of **10α** and **10β** were not isolated; TLC (1% MeOH–CH_2Cl_2): R_f (**10α**) = 0.41, R_f (**10β**) = 0.31.

Epimer 10β

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 17.0 Hz, 1 H, N*H*-TFA), 7.90 (dd, J = 19.9, 8.0 Hz, 2 H, H_{Naphth}), 7.78 (d, J = 8.5 Hz, 1 H, H_{Naphth}), 7.64–7.58 (m, 1 H, H_{Naphth}), 7.51 (dd, J = 8.5, 7.4 Hz, 1 H, H_{Naphth}), 7.34–7.27 (m, 4 H, H_{Naphth}, H_{DMT}), 7.24–7.14 (m, 6 H, H_{DMT}), 6.81–6.74 (m, 4 H, H_{DMT}), 5.11–4.94 (m, 1 H, H1′), 4.02–3.88 (m, 1 H, H3′), 3.84–3.75 (m, 6 H, OMe), 3.26–3.15 (m, 1 H, H5′), 3.00–2.87 (m, 1 H, H5′), 2.46–2.30 (m, 1 H, H6′), 2.14–2.07 (m, 1 H, H4′), 1.86–1.76 (m, 1 H, H2′), 1.60–1.42 (m, 2 H, H2′, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.43 (d, CF_3C=O, C_{DMT}), 144.65 (s, C_{DMT}), 135.99 (d, C_{DMT}), 133.37 (d, C_{Naphth}), 129.93 (d, C_{DMT}), 129.28–125.31 (m, C_{DMT}, C_{Naphth}, CF_3), 124.57–121.97 (m, C_{Naphth}), 113.18 (s, C_{DMT}), 86.22 (s, C_{DMT}), 74.42 (s, C3′), 65.26 (s, C5′), 59.04 (s, C1′), 55.30 (d, OMe), 46.79 (s, C4′), 36.99 (s, C2′), 31.91 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.28 to –68.52 (m, N-TFA), –75.05 to –75.43 (m, NH-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{41}H_{36}F_6N_2NaO_6$: 790.2370; found: 790.2382.

Epimer 10α

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 13.4 Hz, 1 H, N*H*-TFA), 7.95 (t, *J* = 8.0 Hz, 1 H, H_{Naphth}), 7.88 (t, *J* = 7.4 Hz, 1 H, H_{Naphth}), 7.75 (t, *J* = 6.5 Hz, 1 H, H_{Naphth}), 7.66–7.58 (m, 2 H, H_{Naphth}), 7.43 (dd, *J* = 10.7, 3.3 Hz, 1 H, H_{Naphth}), 7.41–7.33 (m, 2 H, H_{DMT}), 7.33–7.27 (m, 5 H, H_{DMT}), 7.23–7.17 (m, 2 H, H_{DMT}), 6.86–6.80 (m, 4 H, H_{DMT}), 4.67–4.48 (m, 1 H, H1′), 3.92 (dt, *J* = 14.4, 8.0 Hz, 1 H, H3′), 3.83–3.78 (m, 6 H, OMe), 3.35–3.23 (m, 1 H, H5′), 3.05–2.96 (m, 1 H, H5′), 2.94–2.80 (m, 1 H, OH-C3′), 2.30–2.17 (m, 2 H, H4′, H6′), 2.19–2.10 (m, 1 H, H2′), 2.00–1.86 (m, 1 H, H6′), 1.57–1.41 (m, 1 H, H2′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.09–158.19 (m, C_{DMT}), 158.01–155.53 (m, CF_3*C*=O), 144.60 (s, C_{DMT}), 135.87 (d, C_{DMT}), 134.93 (s, C_{Naphth}), 132.22 (s, C_{Naphth}), 130.66–126.04 (m, C_{DMT}, C_{Naphth}, CF_3), 124.09–122.13 (m, C_{Naphth}), 113.19 (s, C_{DMT}), 86.49 (s, C_{DMT}), 75.39 (s, C3′), 65.85 (s, C5′), 58.97 (s, C1′), 55.24 (d, OMe), 45.80 (s, C4′), 37.33 (s, C2′), 30.99 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.46 (d, N-TFA), –75.07 to –75.42 (m, NH-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{41}H_{36}F_6N_2NaO_6$: 790.2370; found: 790.2382.

***N*-[(3*R*,4*S*)-3-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxycyclopentyl]-2,2,2-trifluoro-*N*-[3-(2,2,2-trifluoroacetamido)phenyl]acetamide (15)**

Starting from **14** (320 mg, 0.70 mmol); yield: **15α** (101 mg, 18%) and **15β** (124 mg, 22%); TLC (hexane–EtOAc, 2:1): R_f (**15α**) = 0.15, R_f (**15β**) = 0.13.

Epimer 15β

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 67.2 Hz, 1 H, NH-TFA), 7.72–7.00 (m, 13 H, H_{DMT}, $H_{phenylene}$), 6.88–6.71 (m, 4 H, H_{DMT}), 5.09–4.92 (m, 1 H, H1′), 3.94 (d, *J* = 14.1 Hz, 1 H, H3′), 3.78 (s, 7 H, OMe), 3.20 (dd, *J* = 9.2, 4.5 Hz, 1 H, H5′), 2.94 (t, *J* = 7.9 Hz, 1 H, H5′), 2.26 (s, 1 H, OH-C3′), 2.09 (d, *J* = 4.2 Hz, 2 H, H4′), 1.96 (d, *J* = 7.9 Hz, 1 H, H6′), 1.80 (dt, *J* = 13.7, 8.3 Hz, 1 H, H2′), 1.68 (s, 1 H, H2′), 1.28–1.16 (m, 1 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.71–155.41 (m, CF_3*C*=O, C_{DMT}), 145.00 (s, C_{DMT}), 136.92 (m, $C_{phenylene}$), 135.93–135.14 (m), 130.21 (d, C_{DMT}), 130.17 (m, $C_{phenylene}$), 128.15–127.05 (s, C_{DMT}, CF_3), 122.39 (s), 121.46 (s) ($C_{phenylene}$), 113.38 (s, C_{DMT}), 86.51 (s, C_{DMT}), 74.51 (s, C3′), 65.63 (s, C5′), 60.69 (s), 57.37 (s, C1′), 55.47 (s, OMe), 47.04 (s, C4′), 37.71 (s, C2′), 31.74 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.15 to –67.72 (m, N-TFA), –74.57 to –76.27 (m, NH-TFA).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{34}F_6N_2NaO_6$: 739.2219; found: 739.2219.

Epimer 15α

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 19.3 Hz, 1 H, NH-TFA), 7.61–6.90 (m, 13 H, H_{DMT}, $H_{phenylene}$), 6.73 (d, *J* = 8.8 Hz, 4 H, H_{DMT}), 4.71–4.52 (m, 1 H, H1′), 3.91–3.79 (m, 1 H, H3′), 3.71 (d, *J* = 3.8 Hz, 6 H, OMe), 3.15 (s, 1 H, H5′), 2.88 (t, *J* = 8.7 Hz, 1 H, H5′), 2.70–2.58 (m, 1 H, OH-C3′), 2.26–2.07 (m, 1 H, H2′), 1.98 (d, *J* = 14.3 Hz, 1 H, H4′), 1.79 (d, *J* = 6.9 Hz, 1 H, H6′), 1.63 (ddd, *J* = 13.8, 8.9, 6.9 Hz, 1 H, H6′), 1.55–1.42 (m, 1 H, H2′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.69–155.12 (m, CF_3*C*=O, C_{DMT}), 144.81 (s, C_{DMT}), 137.12 (m, $C_{phenylene}$), 135.95 (d, C_{DMT}), 130.12 (d, C_{DMT}), 129.28 (s, $C_{phenylene}$), 128.11–127.04 (m, C_{DMT}, CF_3, $C_{phenylene}$), 122.18 (s), 121.38 (s) ($C_{phenylene}$), 113.36 (s, C_{DMT}), 86.64 (s, C_{DMT}), 75.43 (s, C3′), 65.98 (s, C5′), 55.93 (s, C1′), 55.37 (s, OMe), 45.80 (s, C4′), 38.29 (s, C2′), 30.08 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.33 (s, N-TFA), –75.62 (s, NH-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{35}F_6N_2O_6$: 717.2394; found: 716.2312.

***N*-[(3*R*,4*S*)-3-{Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxycyclopentyl]-2,2,2-trifluoro-*N*-(pyridin-3-yl)acetamide (20)**

Starting from **19** (390 mg, 1.3 mmol); yield: **20α** (224 mg, 28%) and **20β** (221 mg, 27%); TLC (hexane–EtOAc, 2:1): R_f (**20α**) = 0.34, R_f (**20β**) = 0.19.

Epimer 20β

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 4.8, 1.5 Hz, 1 H, H_{Py}), 8.37 (s, 1 H, H_{Py}), 7.43 (d, *J* = 8.1 Hz, 1 H, H_{Py}), 7.38–7.04 (m, 11 H, H_{DMT}, H_{Py}), 6.77–6.63 (m, 4 H, H_{DMT}), 4.68 (s, 1 H, H1′), 3.91–3.76 (m, 1 H, H3′), 3.69 (s, 6 H, OMe), 3.13 (s, 1 H, H5′), 2.87 (m, 1 H, H5′), 2.49 (d, *J* = 15.4 Hz, 1 H, H4′), 2.27–2.09 (m, 1 H, H6′), 1.99–1.85 (m, 1 H, H2′, 1.77–1.54 (m, 1 H, H2′), 1.45 (m, 1 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.71 (s, CF_3*C*=O, C_{DMT}), 150.76 (s, C_{Py}), 144.77 (s, C_{DMT}), 139.71–135.91 (d, C_{DMT}, C_{Py}), 130.10 (d, C_{DMT}), 128.12–125.76 (m, C_{DMT}, CF_3), 123.89 (s, C_{Py}), 113.37 (s, C_{DMT}), 86.15 (d, C_{DMT}), 75.17 (s, C3′), 65.96 (s, C5′), 56.69 (s, C1′), 55.37 (s, OMe), 45.78 (s, C4′), 38.21 (s, C2′), 29.9 (s, C6′.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.34 (s, N-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{34}F_3N_2O_5$: 607.2414; found: 607.2414.

Epimer 20α

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 3.6 Hz, 1 H, H_{Py}), 8.31 (s, 1 H, H_{Py}), 7.37 (s, 1 H, H_{Py}), 7.29–7.06 (m, 11 H, H_{DMT}, H_{Py}), 6.71 (t, *J* = 5.8 Hz, 4 H, H_{DMT}), 4.99 (s, 1 H, H1′), 3.79 (d, *J* = 3.1 Hz, 1 H, H3′), 3.69 (s, 6 H, OMe), 3.10 (s, 1 H, H5′), 2.81 (s, 1 H, H5′), 2.11–2.00 (m, 2 H, H4′, H6′), 1.96–1.86 (m, 1 H, H2′), 1.64 (s, 1 H, H2′), 1.07 (q, *J* = 14.0 Hz, 1 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.76 (s, CF_3*C*=O, C_{DMT}), 151.14 (s, C_{Py}), 150.75 (s, C_{Py}), 144.95 (s, C_{DMT}), 137.86 (s, C_{Py}), 136.04–128.17 (m, C_{DMT}), 127.09 (s, CF_3), 123.88 (s, C_{Py}), 113.40 (s, C_{DMT}), 86.55 (s, C_{DMT}), 74.53 (s, C3′), 65.49 (s, C5′), 57.16 (s, C1′), 55.47 (s, OMe), 47.01 (s, C4′), 37.62 (s, C2′), 31.57 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.36 (s, N-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{34}F_3N_2O_5$: 607.2414; found: 607.2414.

***N*-[(3*R*,4*S*)-3-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxycyclopentyl]-2,2,2-trifluoro-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)acetamide (25)**

Starting from **24** (470 mg, 1.05 mmol); total yield of **25α** and **25β**: 623 mg (80%); ratio α/β 1:1; TLC (0.5% MeOH–CH_2Cl_2): R_f (**25α**) = 0.15, R_f (**25β**) = 0.11.

Epimer 25β

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.95 (m, 3 H, H_{chrom}), 7.76–7.43 (m, 6 H, H_{chrom}, H_{DMT}), 7.32–7.13 (m, 8 H, H_{chrom}, H_{DMT}), 6.89–6.78 (m, 5 H, H_{DMT}, H_{chrom}), 5.21 (dd, *J* = 16.9, 7.9 Hz, 1 H, H1′), 4.03 (t, *J* = 21.9 Hz, 1 H, H3′), 3.80 (s, 6 H, OMe), 3.41–3.14 (m, 1 H, H5′), 2.98 (dt, *J* = 55.9, 7.2 Hz, 1 H, H5′), 2.26–2.13 (m, 2 H, H6′, H4′), 2.13–2.00 (m, 1 H, H2′), 1.98–1.77 (m, 1 H, H2′), 1.44–1.26 (m, 1 H, H6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.76 (s, C_{chrom}), 164.37 (s, C_{chrom}), 158.44 (s, CF_3*C*=O), 155.97 (s, C_{DMT}), 144.76 (s, C_{DMT}), 137.40–118.48 (m, C_{DMT}, C_{chrom}, CF_3), 113.09 (s, C_{DMT}), 107.65 (s,

C_{chrom}), 86.32 (s, C_{DMT}), 74.36 (s, C3′), 65.11 (s, C5′), 56.84 (s, C1′), 55.19 (d, OMe), 46.79 (s, C4′), 37.73 (s, C2′), 31.50 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.14 (s, N-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{38}F_3NNaO_7$: 773.2493; found: 773.2508.

Epimer 25α

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 2.3 Hz, 1 H, H_{chrom}), 8.00–7.90 (m, 2 H, H_{chrom}), 7.68 (d, *J* = 8.8 Hz, 1 H, H_{chrom}), 7.60–7.37 (m, 5 H, H_{DMT}, H_{chrom}), 7.33–7.11 (m, 8 H, H_{DMT}, H_{chrom}), 6.85 (dd, *J* = 16.1, 11.5 Hz, 5 H, H_{DMT}, H_{chrom}), 4.87–4.68 (m, 1 H, H1′), 3.97 (s, 1 H, H3′), 3.80 (s, 6 H, OMe), 3.34–3.17 (m, 1 H, H5′), 2.99 (dt, *J* = 17.3, 8.8 Hz, 1 H, H5′), 2.45–2.20 (m, 1 H, H2′), 2.08 (dd, *J* = 10.7, 5.7 Hz, 1 H, H4′), 1.99–1.86 (m, 1 H, H6′), 1.86–1.73 (m, 1 H, H6′), 1.70–1.56 (m, 1 H, H2′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.73 (s, C_{chrom}), 164.48 (s, C_{chrom}), 158.55 (s, CF_3C=O), 155.45 (s, C_{DMT}), 145.54–143.75 (m, C_{DMT}, C_{chrom}), 137.00–123.50 (m, C_{DMT}, C_{chrom}, CF_3), 119.45 (s, C_{chrom}), 113.22 (s, C_{DMT}), 107.73 (s, C_{chrom}), 86.67 (s, C_{DMT}), 75.29 (s, C3′), 65.94 (s, C5′), 55.61 (s, C1′), 55.22 (s, OMe), 45.44 (s, C4′), 37.73 (s, C2′), 29.66 (s, C6′).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.18 (s, N-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{38}F_3NNaO_7$: 773.2493; found: 773.2508.

Phosphoramidites; General Procedure

To a soln of H_{DMT}-protected nucleosides **5α**, **5β**, **10α**, **10β**, **15α**, **15β**, **20α**, **20β**, **25α**, or **25β** (0.1–0.5 mmol) in THF (2.5 mL/mmol) was added *i*-Pr_2NEt (3 equiv) and (2-cyanoethoxy)chloro(diisopropylamino)phosphine (1.2 equiv) at r.t. The resulting mixture was stirred for 0.5–1 h at r.t. When reaction was complete (TLC monitoring), the mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, and the aqueous layers extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by FC (hexane–EtOAc, 2:1) to yield **6α**, **6β**, **11α**, **11β**, **16α**, **16β**, **21α**, **21β**, **26α**, or **26β** as a colorless foam.

(1*S*,2*R*,4*R*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-(2,2,2-trifluoro-*N*-phenylacetamido)cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (6β)

Starting from **5β** (344 mg, 0.57 mmol); yield: 220 mg (48%); TLC (hexane–EtOAc, 2:1): R_f = 0.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.36 (m, 4 H, H_{DMT}), 7.36–7.20 (m, 10 H, H_{DMT}, $H_{aniline}$), 6.84–6.75 (m, 4 H, H_{DMT}), 5.21–5.09 (m, 1 H, H1′), 4.11–3.98 (m, 1 H, H3′), 3.85–3.79 (m, 6 H, OMe), 3.79–3.71 (m, 1 H, $POCH_2$), 3.65–3.48 (m, 3 H, Me_2CH, $POCH_2$), 3.10–2.91 (m, 2 H, H5′), 2.66–2.58 (m, 1 H, CH_2CN), 2.47–2.38 (m, 1 H, CH_2CN), 2.27 (dd, *J* = 20.1, 6.6 Hz, 2 H, H4′, H6′), 2.17–1.97 (m, 1 H, H2′), 1.71–1.58 (m, 1 H, H2′), 1.51–1.31 (m, 1 H, H6′), 1.22–1.03 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.38 (d, C_{DMT}), 156.89 (d, CF_3C=O), 144.99 (s, C_{DMT}), 136.63–136.08 (m, C_{DMT}), 135.36 (d, $C_{aniline}$), 130.33 (t), 130.05 (d), 129.36 (d), 129.01 (t), 128.12 (d), 127.74 (d) (C_{DMT}, $C_{aniline}$), 126.65 (d, CF_3), 121.23–120.35 (m, $C_{aniline}$), 117.64 (d, CN), 114.90 (s, $C_{aniline}$), 113.53–112.48 (m, C_{DMT}), 85.76 (s, C_{DMT}), 74.62 (dd, C3′), 63.79 (d, C5′), 58.18 (dd, $POCH_2$), 56.82 (s, C1′), 55.20 (d, OMe), 46.23 (dd, C4′), 43.14 (dd, Me_2CH), 37.62–36.98 (m, C2′), 31.33 (d, C6′), 24.93–24.05 (m, Me_2CH), 20.27 (dd, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 147.83 (s), 147.31 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.34 (d, N-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{51}F_3N_3NaO_6P$: 829.3360; found: 829.3375.

(1*S*,2*R*,4*S*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-(2,2,2-trifluoro-*N*-phenylacetamido)cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (6α)

Starting from **5α** (76 mg, 0.13 mmol); yield: 70 mg (68%); TLC (hexane–EtOAc, 2:1): R_f = 0.68.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.40 (m, 4 H, H_{DMT}), 7.38–7.30 (m, 5 H, H_{DMT}, $H_{aniline}$), 7.27–7.16 (m, 5 H, H_{DMT}, $H_{aniline}$), 6.91–6.81 (m, 4 H, H_{DMT}), 5.01–4.83 (m, 1 H, H1′), 4.19–3.98 (m, 1 H, H3′), 3.82 (d, *J* = 2.6 Hz, 6 H, OMe), 3.77–3.60 (m, 1 H, $POCH_2$), 3.57–3.41 (m, 3 H, Me_2CH, $POCH_2$), 3.23–3.13 (m, 1 H, H5′), 3.11–2.94 (m, 1 H, H5′), 2.60–2.53 (m, 1 H, CH_2CN), 2.47–2.38 (m, 1 H, CH_2CN), 2.36–2.26 (m, 1 H, H2′), 2.21–2.07 (m, 1 H, H4′), 2.05–1.94 (m, 1 H, H6′), 1.94–1.81 (m, 1 H, H6′), 1.62–1.48 (m, 1 H, H2′), 1.09 (ddt, *J* = 29.4, 24.9, 6.3 Hz, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.43 (d, C_{DMT}), 156.89 (d, CF_3C=O), 144.99 (d, C_{DMT}), 136.35–136.02 (m, C_{DMT}), 135.21 (d, $C_{aniline}$), 130.56 (d), 130.27–130.08 (m), 129.43 (d), 129.08 (d), 128.25 (d), 127.77 (s) (C_{DMT}, $C_{aniline}$), 126.71 (d, CF_3), 120.79–120.65 (m, $C_{aniline}$), 117.65 (d, CN), 114.90 (s, $C_{aniline}$), 113.41–112.94 (m, C_{DMT}), 85.94 (s, C_{DMT}), 74.92 (s, C3′, 73.78 (s, C3′, 63.84 (d, s, C5′, 58.18 (dd, $POCH_2$), 55.62 (s, C1′), 55.21 (d, OMe), 45.36 (dd, C4′), 43.05 (d, Me_2CH), 37.89 (s, C2′), 30.38 (d, C6′), 24.50 (ddd, Me_2CH), 20.22 (dd, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 148.33 (s), 147.91 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.30 (d, N-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{51}F_3N_3NaO_6P$: 829.3360; found: 829.3375.

(1*S*,2*R*,4*R*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-{2,2,2-trifluoro-*N*-[5-(2,2,2-trifluoroacetamido)naphthalen-1-yl]acetamido}cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (11β)

Starting from **10β** (218 mg, 0.28 mmol); yield: 168 mg (62%); TLC (hexane–EtOAc, 2:1): R_f = 0.52.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (s, 1 H, N*H*-TFA), 7.99–7.75 (m, 3 H, H_{Naphth}), 7.71–7.57 (m, 1 H, H_{Naphth}), 7.52–7.43 (m, 1 H, H_{Naphth}), 7.37–7.27 (m, 3 H, H_{Naphth}, H_{DMT}), 7.25–7.10 (m, 7 H, H_{DMT}), 6.81–6.66 (m, 4 H, H_{DMT}), 5.18 (dq, *J* = 15.6, 7.8 Hz, 1 H, H1′), 4.01 (ddd, *J* = 18.3, 5.2, 2.7 Hz, 1 H, H3′), 3.84–3.78 (m, 6 H, OMe), 3.71–3.63 (m, 1 H, $POCH_2$), 3.61–3.46 (m, 3 H, Me_2CH, $POCH_2$), 3.05–2.96 (m, 1 H, H5′), 2.95–2.84 (m, 1 H, H5′), 2.57–2.47 (m, 2 H, C6′, CH_2CN), 2.44–2.35 (m, 1 H, CH_2CN), 2.31 (dd, *J* = 14.7, 10.2 Hz, 1 H, H4′), 1.99–1.80 (m, 1 H, H2′), 1.53 (ddd, *J* = 21.6, 18.6, 9.6 Hz, 1 H, H6′), 1.38–1.23 (m, 1 H, H2′), 1.15–1.01 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.29 (d, CF_3C=O, C_{DMT}), 144.72 (s, C_{DMT}), 136.94–135.50 (m, C_{DMT}), 133.11 (d, C_{Naphth}), 130.83–125.86 (m, C_{DMT}, C_{Naphth}, CF_3), 123.14 (dd, C_{Naphth}), 117.51 (s, CN), 113.03 (t, C_{DMT}), 85.80 (s, C_{DMT}), 74.91 (dd, C3′), 63.82 (d, C5′), 58.64 (d, $POCH_2$), 58.14 (d, C1′), 55.31 (t, OMe), 45.82 (s, C4′), 43.12 (d, Me_2CH), 36.66 (s, C2′), 31.78 (s, C6′), 24.78–24.19 (m, Me_2CH), 20.23 (dd, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 147.66 (s), 147.58 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.34 (d, N-TFA), –75.21 to –75.34 (m, NH-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{50}H_{53}F_6N_4NaO_7P$: 990.3401; found: 990.3411.

(1*S*,2*R*,4*S*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-{2,2,2-trifluoro-*N*-[5-(2,2,2-trifluoroacetamido)naphthalen-1-yl]acetamido}cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (11α)
Starting from **10α** (284 mg, 0.37 mmol); yield: 315 mg (88%); TLC (hexane–EtOAc, 2:1): R_f = 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H, N*H*-TFA), 7.97 (dd, *J* = 8.5, 6.2 Hz, 1 H, H_{Naphth}), 7.89–7.76 (m, 2 H, H_{Naphth}), 7.64–7.54 (m, 2 H, H_{Naphth}), 7.51–7.37 (m, 4 H, H_{Naphth}, H_{DMT}), 7.32–7.14 (m, 6 H, H_{DMT}), 6.92–6.79 (m, 4 H, H_{DMT}), 4.99–4.82 (m, 1 H, H1′), 4.09–3.92 (m, 1 H, H3′), 3.84–3.75 (m, 6 H, OMe), 3.52–3.33 (m, 4 H, Me_2CH, $POCH_2$), 3.11 (dddd, *J* = 26.6, 15.3, 8.9, 5.5 Hz, 2 H, H5′), 2.38–2.24 (m, 4 H, CH_2CN, H6′, H4′), 2.20–2.06 (m, 2 H, H2′, H6′), 1.39–1.22 (m, 1 H, H2′), 1.07–0.75 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.44 (s, C_{DMT}), 157.96–154.82 (m, CF_3C=O), 144.98 (d, C_{DMT}), 137.06–135.74 (m, C_{DMT}), 134.36–132.38 (m, C_{Naphth}), 130.73–125.51 (m, C_{DMT}, C_{Naphth}, CF_3), 124.35–122.15 (m, C_{Naphth}), 118.46–116.98 (m, CN), 113.11 (s, C_{DMT}), 86.01 (d, C_{DMT}), 73.69 (d, C3′), 63.76 (d, C5′), 58.59–58.05 (m, $POCH_2$), 57.84–57.17 (m, C1′), 55.23 (d, OMe), 45.51–45.09 (m, C4′), 42.96 (t, Me_2CH), 36.84 (d, C2′), 31.58 (d, C6′), 24.82–23.96 (m, Me_2CH), 20.04 (dd, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 148.11 (s), 147.95 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.10 to –69.92 (m, N-TFA), –75.07 to –76.89 (m, NH-TFA).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{50}H_{53}F_6N_4NaO_7P$: 990.3401; found: 990.3411.

(1*S*,2*R*,4*R*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-{2,2,2-trifluoro-*N*-[3-(2,2,2-trifluoroacetamido)phenyl]acetamido}cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (16β)
Starting from **15β** (124 mg, 0.16 mmol); yield: 120 mg (81%); TLC (hexane–EtOAc, 2:1): R_f = 0.4.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98–8.03 (m, 1.5 H, NH-TFA, $H_{phenylene}$), 7.87–6.98 (m, 12.5 H, H_{DMT}, $H_{phenylene}$), 6.90–6.66 (m, 4 H, H_{DMT}), 5.01 (d, *J* = 87.9 Hz, 1 H, H1′), 4.12–3.95 (m, 1 H, H3′), 3.86–3.71 (m, 6 H, OMe), 3.64–3.38 (m, 4 H, Me_2CH, $POCH_2$), 2.99 (dt, *J* = 14.6, 8.9 Hz, 2 H, H5′), 2.75–2.56 (m, 1 H, CH_2CN), 2.54–2.33 (m, 1 H, CH_2CN), 2.31–2.11 (m, 2 H, H4′, H6′), 1.87 (m, 0.5 H, H2′), 1.61 (s, 1.5 H, H2′), 1.33–1.19 (m, 1 H, H6′), 1.19–0.97 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.36 –158.51 (s, CF_3C=O, C_{DMT}), 145.17 (s, C_{DMT}), 136.27 (m, $C_{phenylene}$), 130.03 (m), 128.21 (m), 127.78–127.48 (m), 126.80 (s) (C_{DMT}, CF_3), 122.07–120.91 (m, $C_{phenylene}$), 74.86 (s, C3′), 64.46–62.73 (m, C5′), 58.53–56.08 (m, OMe, $POCH_2$), 55.35 (m, C1′), 46.48 (s, C4′), 43.29 (m, Me_2CH), 37.71 (s, C2′), 31.59–28.84 (m, C6′), 25.75–23.77 (m, Me_2CH), 21.19 (s, CH_2CN).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.30 (s, N-TFA), –75.14 (s, NH-TFA).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 150.10–143.17 (m).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{46}H_{52}F_6N_4O_7P$: 917.3472; found: 917.3472.

(1*S*,2*R*,4*S*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-{2,2,2-trifluoro-*N*-[3-(2,2,2-trifluoroacetamido)phenyl]acetamido}cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite(16α)
Starting from **15α** (100 mg, 0.14 mmol); yield: 98 mg (77%); TLC (hexane–EtOAc, 2:1): R_f = 0.38.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03–7.61 (m, 1.5 H, NH-TFA, $H_{phenylene}$), 7.59–6.99 (m, 12.5 H, C_{DMT}, $H_{phenylene}$), 6.86–6.74 (m, 4 H, C_{DMT}), 5.01–4.73 (m, 1 H, H1′), 4.19–4.07 (m, 1 H, H3′), 3.79 (s, 6 H, OMe), 3.66–3.36 (m, 4 H, Me_2CH, $POCH_2$), 3.19–2.94 (m, 2 H, H5′), 2.71–2.56 (m, 1 H, CH_2CN), 2.45–2.34 (m, 1 H, CH_2CN), 2.34 (s, 1 H, H2′), 2.14–1.95 (m, 1 H, H4′), 1.89–1.85 (m, 1 H, H6′), 1.85–1.70 (m, 0.5 H, H6′), 1.64–1.50 (s, 1 H, H2′, 1.25–1.14 (s, 0.5 H, H6′), 1.05–0.84 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.59–155.12 (d, CF_3C=O, C_{DMT}), 145.06 (s, C_{DMT}), 136.06 (d, q-$C_{phenylene}$), 130.31–126.89 (m, C_{DMT}, $C_{phenylene}$, CF_3), 123.10–120.24 (m, $C_{phenylene}$), 113.22 (s, C_{DMT}), 86.81–85.66 (m, C_{DMT}), 75.88 (s, C3′, 63.46 (d, C5′, 58.35–57.28 (d, $POCH_2$), 55.36 (d, OMe), 45.61 (d, C4′, 43.19 (d, Me_2CH), 39.59 (s, C2′), 30.18 (s, C6′), 24.69–24.14 (m, Me_2CH), 21.19 (s, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 153.34–139.04 (m).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.29 (m, N-TFA), –75.66 (s, NH-TFA).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{46}H_{52}F_6N_4O_7P$: 917.3472; found: 917.3472.

(1*S*,2*R*,4*R*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-[2,2,2-trifluoro-*N*-(pyridin-3-yl)acetamido]cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (21β)
Starting from **20β** (108 mg, 0.18 mmol); yield: 124 mg (86%); TLC (hexane–EtOAc, 1:1): R_f = 0.65.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (dd, *J* = 4.7, 1.3 Hz, 1 H, H_{Py}), 8.49 (s, 1 H, H_{Py}), 7.55 (s, 1 H, H_{Py}), 7.49–7.38 (m, 3 H, H_{DMT}), 7.36–7.26 (m, 6 H, H_{DMT}), 7.25–7.14 (m, 1 H, H_{Py}), 6.87–6.75 (m, 4 H, H_{DMT}), 4.95 (dd, *J* = 17.9, 8.3 Hz, 1 H, H1′), 4.12 (q, *J* = 7.1 Hz, 1 H, H3′), 3.79 (d, *J* = 2.3 Hz, 6 H, OMe), 3.77–3.57 (m, 1 H, $POCH_2$), 3.56–3.37 (m, 3 H, Me_2CH, $POCH_2$), 3.14–2.96 (m, 2 H, H5′), 2.56 (t, *J* = 6.3 Hz, 1 H, CH_2CN), 2.39 (t, *J* = 6.4 Hz, 1 H, CH_2CN), 2.37–2.28 (m, 1 H, H2′), 2.11 (dd, *J* = 10.0, 5.1 Hz, 1 H, H4′), 2.03–1.82 (m, 1 H, H6′), 1.80–1.67 (m, 1 H, H6′), 1.48 (d, *J* = 7.6 Hz, 1 H, H2′), 1.19–0.88 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.60 (d, CF_3C=O, C_{DMT}), 151.32 (s, C_{Py}), 150.66 (d, C_{Py}), 145.03 (s, C_{DMT}), 138.13 (s, C_{Py}), 136.23 (d, C_{DMT}), 132.12–127.41 (m, C_{DMT}, CF_3), 126.89 (d, *J* = 4.0 Hz), 123.77 (s, C_{Py}), 117.64 (s, CN), 113.22 (s, C_{DMT}), 86.16 (s, C_{DMT}), 73.68 (s, C3′), 63.59 (s, C5′), 58.49 (d, $POCH_2$), 55.59 (s, C1′), 55.26 (s, OMe), 45.55 (s, C4′), 43.19 (d, Me_2CH), 38.01 (s, C2′), 30.20 (d, C6′), 24.67 (m, Me_2CH), 20.69–20.28 (m, CH_2CN).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.28 (d, N-TFA).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 150.98–145.97 (m).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{43}H_{51}F_3N_4O_6P$: 807.3493, found: 807.3493.

(1*S*,2*R*,4*S*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-[2,2,2-trifluoro-*N*-(pyridin-3-yl)acetamido]cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (21α)
Starting from **20α** (110 mg, 0.18 mmol); yield: 95 mg (65%); TLC (hexane–EtOAc, 1:1): R_f = 0.67.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1 H, H_{Py}), 8.38 (s, 1 H, H_{Py}), 7.42 (d, *J* = 8.1 Hz, 1 H, H_{Py}), 7.35–7.02 (m, 10 H, H_{DMT}, H_{Py}), 6.71 (dd, *J* = 8.8, 6.5 Hz, 4 H, H_{DMT}), 5.07 (s, 1 H, H1′), 4.10–3.87 (m, 1 H, H3′), 3.79–3.61 (m, 7 H, OMe, $POCH_2$), 3.49 (m, 3 H, $POCH_2$, Me_2CH), 2.89 (m, 2 H, H5′), 2.53 (t, *J* = 6.3 Hz, 1 H, CH_2CN), 2.33 (t, *J* = 6.4 Hz, 1 H, CH_2CN), 2.20 (m, 2 H, H4′, H6′), 2.05–1.96 (m, 1 H, H2′), 1.59–1.41 (m, 1 H, H2′), 1.21 (m, 1 H, H6′), 1.12–0.74 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.55 (d, CF_3C=O, C_{DMT}), 151.19 (s, C_{Py}), 150.64 (s, C_{Py}), 145.04 (s, C_{DMT}), 137.87 (s, C_{Py}), 136.13 (s), 132.32 (s), 130.15 (d, *J* = 7.2 Hz), 129.64–127.37 (m), 126.84 (d, *J* = 4.5 Hz), 123.71 (s, C_{Py}), 117.66 (s, CN), 113.18 (s,

C_{DMT}), 85.99 (s, C_{DMT}), 74.52 (s, C3′ 63.88 (d, C5′), 58.22 (d, $POCH_2$), 57.07 (s, C1′), 55.24 (d, OMe), 46.28 (d, C4′), 43.29 (dd, Me_2CH), 38.47–36.56 (m, C2′), 32.84–29.12 (m, C6′), 25.66–23.24 (m, Me_2CH), 21.07–18.80 (m, CH_2CN).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.35 (s, N-TFA).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 149.50–145.10 (m).

HRMS (ESI+): *m*/*z* [M + H] calcd for $C_{43}H_{51}F_3N_4O_6P$: 807.3493; found: 807.3493.

(1*S*,2*R*,4*R*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-[2,2,2-trifluoro-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)acetamido]cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (26β)

Starting from **25β** (150 mg, 0.20 mmol); yield: 138 mg (69%); TLC (hexane–EtOAc, 2:1): R_f = 0.35.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.16–7.94 (m, 3 H, H_{chrom}), 7.74–7.45 (m, 5 H, H_{DMT}, H_{chrom}), 7.31–7.08 (m, 9 H, H_{DMT}, H_{chrom}), 6.97–6.72 (m, 5 H, H_{DMT}, H_{chrom}), 5.31 (d, *J* = 46.7 Hz, 1 H, H1′), 4.25-4.11 (m, 1 H, H3′), 3.85–3.73 (m, 7 H, OMe, $POCH_2$), 3.66 (dd, *J* = 25.5, 18.6 Hz, 3 H, Me_2CH, $POCH_2$), 3.01 (ddd, *J* = 48.2, 39.0, 14.6 Hz, 2 H, H5′), 2.71 (dd, *J* = 11.9, 5.8 Hz, 1 H, CH_2CN), 2.48 (dd, *J* = 12.2, 5.7 Hz, 1 H, CH_2CN), 2.43–2.14 (m, 3 H, H4′, H6′, H2′), 1.81–1.66 (m, 1 H, H2′), 1.53–1.35 (m, 1 H, H6′), 1.40–1.14 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.24 (d, C_{chrom}), 164.57 (d, C_{chrom}), 159.04–157.56 (m, CF_3C=O, C_{DMT}), 145.57 (d, C_{DMT}), 137.00–135.46 (m, C_{DMT}, C_{chrom}), 130.17 (s), 129.21 (s), 129.73–126.38 (m), 127.84 (s), 126.48 (s) (C_{DMT}, C_{chrom}, CF_3), 113.15 (s, C_{DMT}), 108.37 (d, C_{chrom}), 87.08 (d, C_{DMT}), 74.06 (d, C3′), 63.85 (d, C5′, 58.21 (dd, $POCH_2$), 57.39 (s, C1′), 55.04 (d, OMe), 45.77 (dd, C4′), 43.89 (d, Me_2CH), 37.32 (s, C2′), 30.86 (d, C6′), 25.23 (ddd, Me_2CH), 20.18 (dd, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 147.32 (s), 147.43 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.15 (d, N-TFA).

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{53}H_{56}F_3N_3O_8P$: 950.3752; found: 950.3746.

(1*S*,2*R*,4*S*)-2-{[(Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-[2,2,2-trifluoro-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)acetamido]cyclopentyl 2-Cyanoethyl Diisopropylphosphoramidite (26α)

Starting from **25α** (143 mg, 0.19 mmol); yield: 125 mg (63%); TLC (hexane–EtOAc, 2:1): R_f = 0.33.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.14–7.88 (m, 3 H, H_{chrom}), 7.70–7.34 (m, 7 H, H_{DMT}, H_{chrom}), 7.29 (t, *J* = 9.6 Hz, 6 H, H_{DMT}, H_{chrom}), 7.20 (dt, *J* = 12.3, 6.1 Hz, 1 H, H_{chrom}), 6.91–6.74 (m, 5 H, H_{DMT}, H_{chrom}), 4.95 (d, *J* = 8.4 Hz, 1 H, H1′), 4.10–3.98 (m, 1 H, H3′), 3.79 (d, *J* = 1.8 Hz, 6 H, OMe), 3.73–3.57 (m, 1 H, $POCH_2$), 3.54–3.31 (m, 3 H, Me_2CH, $POCH_2$), 3.15–3.10 (m, 1 H, H5′), 3.07–2.94 (m, 1 H, H5′), 2.62–2.50 (m, 1 H, CH_2CN,), 2.46–2.22 (m, 2 H, CH_2CN, H2′), 2.17–2.08 (m, 1 H, H4′), 1.97 (t, *J* = 16.6 Hz, 1 H, H6′), 1.93–1.76 (m, 1 H, H6′), 1.62 (d, *J* = 30.0 Hz, 1 H, H2′), 1.17–0.89 (m, 12 H, Me_2CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.20 (d, C_{chrom}), 164.51 (d, C_{chrom}), 159.04–157.50 (m, CF_3C=O, C_{DMT}), 145.54 (d, C_{DMT}), 137.00–135.46 (m, C_{DMT}, C_{chrom}), 130.17 (s), 129.21 (s), 129.73–126.32 (m), 127.80 (s), 126.41 (s) (C_{DMT}, C_{chrom}, CF_3), 113.08 (s, C_{DMT}), 108.37 (d, C_{chrom}), 88.38 (d, C_{DMT}), 74.08 (d, C3′), 63.84 (d, C5′, 58.19 (dd, $POCH_2$), 55.40 (s, C1′), 54.82 (d, OMe), 45.16 (dd, C4′), 43.15 (d, Me_2CH), 37.50 (s, C2′), 30.99 (d, C6′), 25.34 (ddd, Me_2CH), 20.18 (dd, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 148.37 (s), 148.12 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.12 (d, N-TFA).

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{53}H_{56}F_3N_3O_8P$: 950.3752; found: 950.3745.

Oligonucleotide Synthesis

All oligonucleotides were synthesized on a Pharmacia LKB Gene Assembler Special DNA synthesizer on a 1.3-μmol scale using conventional cyanoethyl phosphoramidite chemistry. Protected natural nucleoside phosphoramidites, solid supports and the 3′-dabcyl CPG were from Glen Research. 6-FAM phosphoramidite was from Nucleic Resources LLC. The concentration of the solns of the natural phosphoramidites was 0.1 M and that of 6-FAM phosphoramidite 0.15 M in MeCN. A soln of 0.25 M 5-(ethylthio)-1*H*-tetrazole in MeCN was used as activator. All other solns and reagents were prepared according to the manufacturer's protocol. After synthesis (trityl-off mode), oligonucleotides were cleaved from the solid support and deprotected with 33% aq NH_3 for 1 h at r.t. followed by 16 h at 55 °C.

Purification and Analytical Characterization of Oligonucleotides

Crude oligonucleotides were purified either by reversed phase (RP) or by ion exchange chromatography using a linear gradient of buffer B in buffer A.

A: RP-HPLC: column; SOURCE 15RPC ST 4.6/100 (Amersham Pharmacia Biotech); buffer A: 0.1 M triethylammonium acetate (TEAA) pH 7.0 in H_2O, buffer B: 0.1 M TEAA (pH 7.0) in MeCN–H_2O 4:1.

B: Anion exchange HPLC: column; Dionex (DNAPac PA200); buffer A: 25 mM Tris HCl in H_2O, pH 8.0; buffer B: 25 mM Tris HCl + 1.25 M NaCl in H_2O, pH 8.0.

Sep-Pak C_{18} (Waters) columns were used for desalting. The column was first washed with MeCN (5 mL) and then conditioned with 0.1 M TEAA buffer (pH 7, 10 mL). Oligonucleotides were loaded as a 0.3 M TEAA soln. The column was washed with 0.1 M TEAA buffer (pH 7, 10 mL) and milli-Q-water (5 mL). Oligonucleotides were then eluted with MeOH–H_2O (3:2, 3–4 mL). Collected fractions were concentrated in a Speed-Vac SC 110 (Savant) and quantified by UV/Vis spectroscopy at 260 nm (Nanodrop ND-1000). The molecular weight of the purified oligonucleotides was confirmed by ESI–mass spectrometry (Table 1).

UV Melting Curves

Thermal denaturation experiments were carried out on a Varian Cary 3E UV/Vis spectrophotometer. Absorbances were monitored at 260 nm and the heating rate was set to 0.5 °C/min. A cooling–heating–cooling cycle in the temperature range of 70–30 °C was applied. Measurements were performed in duplicate. The first derivatives of the melting curves, were calculated directly by the program WinUV 3.0. To avoid evaporation of the soln upon heating, a layer of dimethylpolysiloxane was added on top of the sample soln in the cell.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

The authors gratefully acknowledge financial support by the Swiss National Science Foundation (grant No. 200020-130373).

References

(1) Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; StClair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.;

Reardon, J. E.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082.
(2) Helguera, A. M.; Rodríguez-Borges, J. E.; Caamaño, O.; García-Mera, X.; González, M. P.; Cordeiro, M. N. D. S. *Mol. Inf.* **2010**, *29*, 213.
(3) Hergueta, A. R.; Fernandez, F.; Lopez, C.; Balzarini, J.; De Clercq, E. *Chem. Pharm. Bull.* **2001**, *49*, 1174.
(4) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192.
(5) Sagi, J.; Szemzö, A.; Szécsi, J.; Ötvös, L. *Nucleic Acids Res.* **1990**, *18*, 2133.
(6) Freier, S. M.; Altmann, K. H. *Nucleic Acids Res.* **1997**, *25*, 4429.
(7) Altmann, K. H.; B'Vierre, M. O.; De Mesmaeker, A.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 431.
(8) Altmann, K. H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331.
(9) Altmann, K. H.; Kesselring, R. *Synlett* **1994**, 853.
(10) Altmann, K. H.; Imwinkelried, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 7625.
(11) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739.
(12) Saneyoshi, H.; Mazzini, S.; Aviñó, A.; Portella, G.; González, C.; Orozco, M.; Marquez, V. E.; Eritja, R. *Nucleic Acids Res.* **2009**, *37*, 5589.
(13) Kubo, I.; Kim, M.; Wood, W. F.; Naoki, H. *Tetrahedron Lett.* **1986**, *27*, 4277.
(14) Moss, R. J.; Petrie, C. R.; Meyer, R. B.; Nord, L. D.; Willis, R. C.; Smith, R. A.; Larson, S. B.; Kini, G. D.; Robins, R. K. *J. Med. Chem.* **1988**, *31*, 786.
(15) Fortin, H.; Tomasi, S.; Delcros, J.-G.; Bansard, J.-Y.; Boustie, J. *ChemMedChem* **2006**, *1*, 189.
(16) Varaprasad, C. V.; Habib, Q.; Li, D. Y.; Huang, J. F.; Abt, J. W.; Rong, F.; Hong, Z.; An, H. Y. *Tetrahedron* **2003**, *59*, 2297.
(17) Greenberg, M. M. *Acc. Chem. Res.* **2012**, *45*, DOI: 10.1021/ar2002182.
(18) Agrofoglio, L.; Condom, R.; Guedj, R.; Challand, S. R.; Selway, J. *Nucleosides Nucleotides* **1994**, *13*, 1147.
(19) Agrofoglio, L.; Condom, R.; Guedj, R.; Challand, R.; Selway, J. *Tetrahedron Lett.* **1993**, *34*, 6271.
(20) Wojciechowski, F.; Leumann, C. J. *Chem. Soc. Rev.* **2011**, *40*, 5669.
(21) Seo, Y. J.; Malyshev, D. A.; Lavergne, T.; Ordoukhanian, P.; Romesberg, F. E. *J. Am. Chem. Soc.* **2011**, *133*, 19878.
(22) Seo, Y. J.; Hwang, G. T.; Ordoukhanian, P.; Romesberg, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 3246.
(23) Kool, E. T.; Sintim, H. O. *Chem. Commun.* **2006**, 3665.
(24) Hirao, I.; Kimoto, M.; Mitsui, T.; Fujiwara, T.; Kawai, R.; Sato, A.; Harada, Y.; Yokoyama, S. *Nat. Meth.* **2006**, *3*, 729.
(25) Yaren, O.; Mosimann, M.; Leumann, C. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1935.
(26) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 549.
(27) Ludek, O. R.; Meier, C. *Synthesis* **2003**, 2101.
(28) Huang, H.; Greenberg, M. M. *J. Org. Chem.* **2008**, *73*, 2695.
(29) *Oligonucleotides and Analogues - A Practical Approach*; Oxford University Press: Oxford, **1991**.
(30) Brotschi, C.; Mathis, G.; Leumann, C. J. *Chem. Eur. J.* **2005**, *11*, 1911.
(31) Grigorenko, N. A.; Leumann, C. J. *Chem. Eur. J.* **2009**, *15*, 639.
(32) Matsuda, S.; Fillo, J. D.; Henry, A. A.; Rai, P.; Wilkens, S. J.; Dwyer, T. J.; Geierstanger, B. H.; Wemmer, D. E.; Schultz, P. G.; Spraggon, G.; Romesberg, F. E. *J. Am. Chem. Soc.* **2007**, *129*, 10466.
(33) Hildbrand, S.; Blaser, A.; Parel, S. P.; Leumann, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 5499.

