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1

Tricyclanos: conformationally constrained nucleoside analogues with a new heterotricycle obtained from a D-ribofuranose unit

Máté Kicsák, Attila Mándi, Szabolcs Varga, Mihály Herczeg, Gyula Batta, Attila Bényei, Anikó Borbás* and Pál Herczegh*

Nucleoside analogues having a new N,O-containing tricycle in place of the ribose unit have been prepared by a diastereoselective cyclocondensation of tris(hydroxymethyl)aminomethane and dialdehydes obtained from ribofuranosyl nucleosides by periodate oxidation.
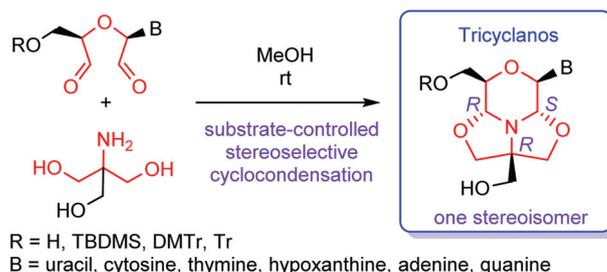
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PAPER

Tricyclanos: conformationally constrained nucleoside analogues with a new heterotricycle obtained from a D-ribofuranose unit†

Máté Kicsák,[a] Attila Mándi, [b] Szabolcs Varga,[a] Mihály Herczeg,[a] Gyula Batta,[b] Attila Bényei,[c] Anikó Borbás *[a] and Pál Herczegh*[a]

A novel type of nucleoside analogue in which the sugar part is replaced by a new tricycle, 3,7,10-trioxa-11-azatricyclo[5.3.1.0^{5,11}]undecane has been prepared by substrate-controlled asymmetric synthesis. 1,5-Dialdehydes obtained from properly protected or unprotected uridine, ribothymidine, cytidine, inosine, adenosine and guanosine by metaperiodate oxidation reacted readily with tris(hydroxymethyl)aminomethane to provide the corresponding tricyclic derivatives with three new stereogenic centers. Through a double cyclisation cascade process the tricyclic compounds were obtained in good to high yields, with very high diastereoselectivity. Formation of one stereoisomer, out of the eight possible, was observed in all cases. The absolute configuration of the new stereotriad-containing tricyclic systems was aided by conventional NMR experiments followed by chemical shift calculations using an X-ray crystal structure as reference that was in good agreement with H−H distances obtained from a new ROESY NMR method. The synthesis was compatible with silyl, trityl and dimethoxytrityl protecting groups. A new reagent mixture containing $ZnCl_2$, Et_3SiH and hexafluoroisopropanol was developed for detritylation of the acid-sensitive tricyclano nucleosides.
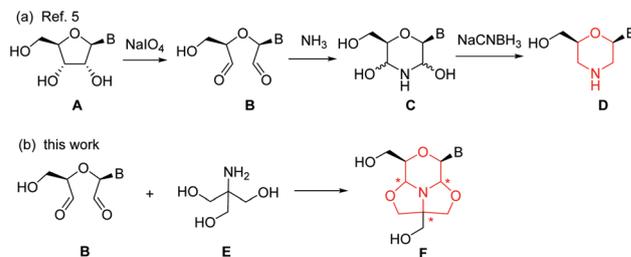
Introduction

Nucleoside analogues are able to interfere with the replication of viruses or with the proliferation of cancer cells by competing with their natural counterparts. Therefore, chemically modified nucleosides and nucleotides have attracted considerable attention and numerous therapeutically important derivatives have been developed over the past few decades.[1–3]

Azanucleosides are nucleoside analogues in which the furanose unit has been replaced by a nitrogen-containing ring including pyrrolidine, piperidine, morpholine, etc. Some azanucleosides are in advanced clinical trials as anticancer drugs, and others have promising antimalarial, antitrypanosomal and antibacterial properties.[4]

In the 1990s, Summerton devised and began developing morpholinos, an important group of azanucleosides having the morpholine ring in the place of ribose moieties.[5] The morpholino monomers can be prepared from simple ribonucleosides by periodate oxidation and a subsequent reductive amination (Scheme 1a). In these compounds the morpholine ring is connected to the heterocyclic base recognition moieties of RNA (adenine, cytosine, uracil and guanine). Oligonucleotide analogues were prepared from these morpholino derivatives by coupling the morpholine nitrogen to the phosphoramidite moiety derived from the primary hydroxyl of another monomer.[6] The phosphorodiamidate connected morpholino oligomers (PMOs) inhibit the translation of target mRNA by steric blocking and they are resistant to enzymatic degradation. PMOs proved to be effective antivirals against RNA viruses.[7] They also exhibited antibacterial and anticancer activities as well as inhibited in-stent restenosis after the

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†Electronic supplementary information (ESI) available: Experimental details, characterization of all reported compounds, DFT and computational data. CCDC 1571164. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob02296d

Scheme 1 Synthesis of (a) morpholinos and (b) proposed synthesis of morpholine-containing tricyclanos.

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implantation of coronary stents and proved to be promising therapeutic agents in the treatment of Duchenne muscular dystrophy.[8,9] Modified oligonucleotides containing a single morpholino unit also show potent gene-silencing activity and prolonged action time.[10]

The 2′-amino-locked nucleosides, bearing a –CH₂–NH- bridge between the C2′ and C4′ atoms, also represent notable members of the azanucleoside family.[11,12] These nucleoside derivatives are also a kind of bicyclic morpholine analogue containing a bridged morpholine ring connected to the nucleobase. The incorporation of amino-locked nucleosides and other conformationally restricted bi-, tri- or tetracyclic monomers into oligonucleotides has been a widely used approach to produce nucleic acid analogues with increased duplex stability and high enzymatic stability.[13–16] Given the potential of morpholinos and other azanucleosides as drug leads, the development of new analogues is an important area in medicinal and synthetic chemistry. Inspired by both the gene silencing activity and the special structure of morpholinos, we envisioned the synthesis of a novel type of nucleoside analogue having structure **F**, in which the ribose unit is substituted with a morpholine-containing tricyclic ring system (Scheme 1b). Due to the two primary hydroxyl groups, these analogues can be coupled to each other and can be incorporated into DNA or RNA oligonucleotides at any desired position using standard phosphoramidite chemistry. Moreover, the rigidity of the tricyclic sugar mimic could endow the synthetic oligonucleotides with an increased stability against nucleases.

Cyclocondensation of aminoalcohols and monoaldehydes is a long-known reaction[17] which has been used extensively for the synthesis of bis-oxazolidine bicyclic systems.[18] It was demonstrated for the first time by Broadbent *et al.*[19] that the condensation of 2-amino-1,3-propanediols and 1,4-diketones led to the formation of pyrrolidino-bis-oxazolidine tricycles. However, the reaction required harsh conditions and use of *p*-toluenesulfonic acid in refluxing toluene, and only moderate yields were achieved. Giovenzana *et al.*[20] described that a completely stereoselective 2 : 2 condensation of glyoxal and tris (hydroxymethyl)aminomethane (Tris) took place in aqueous medium without acid catalysis to give a pentacyclic derivative in high yield. We assumed that under such mild conditions cyclocondensation between the 1,5-dialdehyde derivative of nucleosides (**B**) and Tris (**E**) could proceed in a stereoselective manner providing the desired heterotricyclic derivative (**F**).

Herein, we present the synthesis and structural determination of uridine-, ribothymidine-, inosine-, cytidine-, adenosine- and guanosine-derived members of the new nucleoside family which we suggest to call tricyclanos, by analogy of Summerton's morpholinos.

Results and discussion

Synthesis

Our initial experiments were carried out with unprotected uridine (**1**), which was oxidized with the metaperiodate form
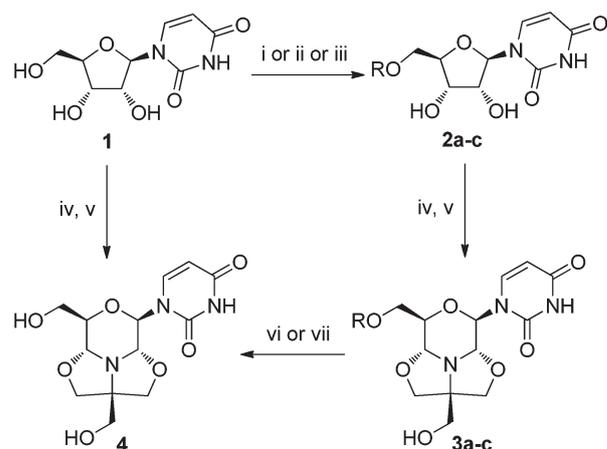
Scheme 2 Synthesis of uracil-tricyclano **4** without protecting groups and using the 5′-TBDMS, DMTr and Tr protecting groups. Reagents and conditions: (i) TBDMSCl, imidazole, dry DMF, rt, overnight, **2a**: 64%; (ii) DMTrCl, dry Et₃N, dry C₅H₅N, rt, overnight, **2b**: 81%; (iii) TrCl, dry C₅H₅N, rt, overnight, **2c**: 83%; (iv) IO₄⁻ resin, MeOH, rt, dark, overnight; (v) **E**, 3 Å MS, dry MeOH, rt, **3a**, **3b**: overnight, **3c**: 2 days, **3a**: 72% (2 steps from **2a**), **3b**: 76% (2 steps from **2b**), **3c**: 76% (2 steps from **2c**), **4**: 58% (2 steps from **1**); (vi) TBAF, dry THF, rt, overnight, **4**: 48% (from **3a**); (vii) ZnCl₂, (F₃C)₂CHOH, H₃CNO₂, Et₃SiH, rt, 2 h, **4**: 71% from **3b**, 66% from **3c**. **2a**, **3a**: R = TBDMS; **2b**, **3b**: R = DMTr; **2c**, **3c**: R = Tr.

of an anion exchange resin, and the obtained crude dialdehyde was reacted directly with Tris (**E**) in methanol at room temperature (Scheme 2). The reaction proceeded cleanly providing compound **4**, one of the eight possible diastereoisomers, in 58% yield after column chromatographic purification. No other product could be isolated from the reaction mixture. The moderate yield was caused by the incomplete conversion of **1** and the difficulty of purification of the product. In order to discriminate the two primary hydroxyl groups of the resulting tricyclano and in hope of higher yield, we decided to block the 5′-hydroxyl function of uridine. Therefore, **1** was regioselectively reacted with *tert*-butyldimethylsilyl (TBDMS) chloride and the partially blocked **2a**[21] was subjected to the two-step transformation including oxidation and condensation with Tris. To our delight, the cyclocondensation reaction between **E** and the dialdehyde[22] took place with both high efficacy and stereoselectivity to give **3a** in 72% yield over two steps, in completely stereo pure form. Removal of the TBDMS protecting group by TBAF afforded uracil-tricyclano **4** that was identical to the compound obtained *via* dialdehyde without protecting the 5′-hydroxyl group.

Our literature survey revealed that the heterotricyclic ring system formed by the condensation of the ribose-derived dialdehyde and tris(hydroxymethyl)aminomethane has not been described until now. The new tricycle has been named as 3,7,10-trioxa-11-azatricyclo[5.3.1.0⁵,¹¹]undecane (Fig. 1). The absolute configuration of the new stereogenic centers C2, C5 and C8 could be determined by means of X-ray crystallography, experimental and theoretical NMR methods (*vide infra*).

As our aim was to prepare nucleoside analogues which can be incorporated into short oligonucleotides, we tested the
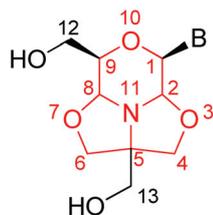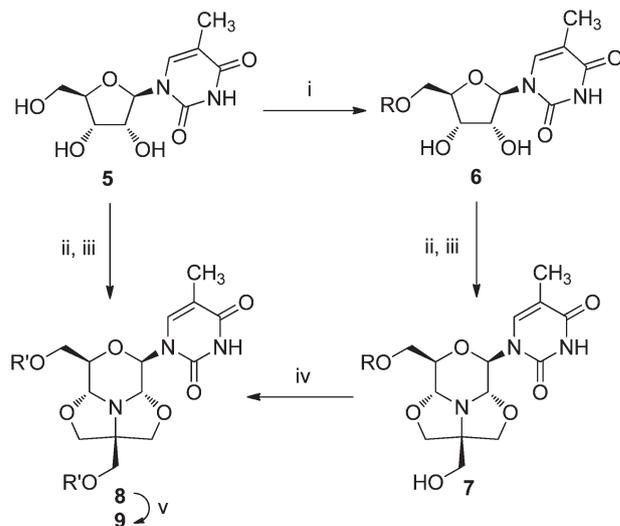
Fig. 1 Numbering of tricyclano nucleosides having the 3,7,10-trioxa-11-azatricyclo[5.3.1.0^{5,11}]undecane core.

Scheme 3 Synthesis of thymine-tricyclano **8** without protecting groups and using the 5′-Tr protecting groups. Reagents and conditions: (i) TrCl, dry C_5H_5N, rt, overnight, 75%; (ii) IO_4^- resin, MeOH, rt, dark, overnight; (iii) **E**, 3 Å MS, dry MeOH, rt, overnight, **7**: 64% (2 steps from **6**), **8**: 53% (2 steps from **5**); (iv) $ZnCl_2$, $(F_3C)_2CHOH$, H_3CNO_2, Et_3SiH, rt, 1 h, **8**: 55% (from **7**); (v) Ac_2O, dry C_5H_5N, rt, overnight, 73%. **6**, **7**: R = Tr; **8**: R′ = H; **9**: R′ = Ac.

compatibility of tricyclano synthesis with 4,4′-dimethoxytrityl (DMTr), the standard protecting group in the solid phase nucleic acid synthesis. Thus, the known compound **2b**[10] was prepared and converted to the DMTr-protected uracil-tricyclano **3b** in 76% yield over two steps (Scheme 2). The condensation of the intermediate dialdehyde with **E** proceeded, again, with the same diastereoselectivity as observed with the unprotected and 5′-silyl protected dialdehydes, revealing that the protecting group has no influence on the stereochemical outcome of the cyclisation.

Removal of the DMTr group from **3b** having an acid-sensitive double aminal structure was a critical part of the reaction path. Attempted experiments under standard conditions[23] using dichloroacetic acid led to partial decomposition of the tricycle of **3b**. Hence, our attention was turned to find a new method for DMTr cleavage which the acid sensitive tricyclano could survive. For this purpose we have recently elaborated a complex system of reagents including a Lewis acid (boron trifluoride diethyl etherate), a reducing quenching agent (triethylsilane) and the mild protic acid, 1,1,1,3,3,3-hexafluoroisopropanol. This reagent cocktail, due to synergistic effect of the components, proved to be efficient for rapid and clean deprotection of a large variety of trityl- and dimethoxytrityl-protected compounds.[24] However, applying this method for removal of the DMTr group of **3b**, partial decomposition has been observed. Since the Lewis acid is a variable component of the reagent combination, by exchanging $BF_3 \cdot Et_2O$ with the milder Lewis acid zinc chloride, fine tuning of the reactivity was achieved. Treating **3b** with the reagent cocktail containing zinc chloride the DMTr deprotection went to completion within half an hour without noticeable decomposition, providing **4** in 71% yield.

The synthesis of the uracil-tricyclano was also carried out using the cheap trityl (Tr) protecting group which resulted in the corresponding tricyclano **3c** with 76% overall yield from **2c**. To our delight, the $ZnCl_2$-containing reagent cocktail also cleaved the Tr protecting group of tricyclano **3c** without damaging the acid-sensitive tricyclic system (Scheme 2). This result suggested that the O-DMTr protecting group can be changed to the less expensive Tr group in our further experiments.

The tricyclano derivative of ribothymidine was also prepared using the Tr protecting group at position 5′ (Scheme 3). First, **6**[25] was synthesized and converted to **7** in two steps including oxidation with metaperiodate followed by the con-

densation reaction with **E**. Finally, the trityl protecting group was successfully cleaved by our detritylating reagent combination to result in **8** that was also prepared from unprotected **5**. Acetylation of **8** furnished **9** which was used for structural determination studies.
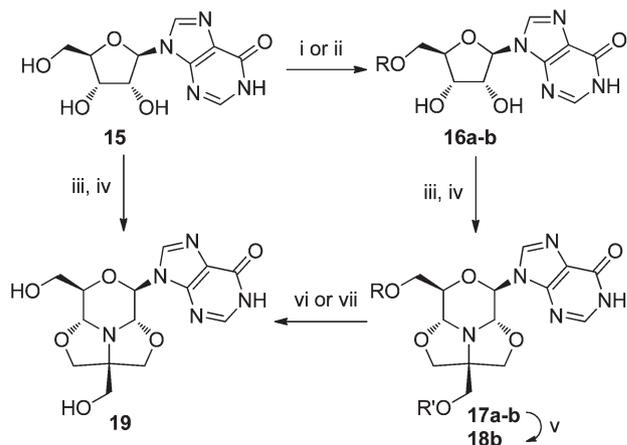
We envisioned that the synthesis of the cytosine-tricyclano can be easily accomplished by using O,N-bistrityl protection. Unexpectedly, simultaneous tritylation of the 5′ hydroxyl and the amino group of **10** proved to be very sluggish and inefficient providing the bisprotected **11a** in only 30% yield after a ten-day reaction (Scheme 4). The usual oxidation and tricyclization procedure showed similar efficacy as in the cases of uridine and thymidine congeners to provide the cytosine-tricyclano **13a** in 65% isolated yield. Unfortunately, our new detritylation method was not completely successful. Despite the high excess of $ZnCl_2$ (8 equiv.) only the O-Tr group could be cleaved in a 5-hour reaction to give **14a** in 56% yield. Longer exposure of **13a** to the detritylation conditions led to decomposition of the tricyclic system rather than N-deprotection. Therefore, we decided to change the N-trityl to the more acid-sensitive N-DMTr protecting group. First, the amino group of **10** was selectively protected with DMTr, then the obtained **11b**[26] was selectively O-tritylated at the primary position to result in **12b** in 56% overall yield from **10**. After periodate oxidation, the resulting dialdehyde was reacted with **E** to produce **13b** in a good 72% yield over two steps. Finally, **13b** was successfully treated with our detritylation cocktail to result in **14b**. Although TLC monitoring of the reaction showed clean and efficient deprotection, **14b** could only be isolated in 26% yield because the purification process was difficult due to the very poor solubility of the product.

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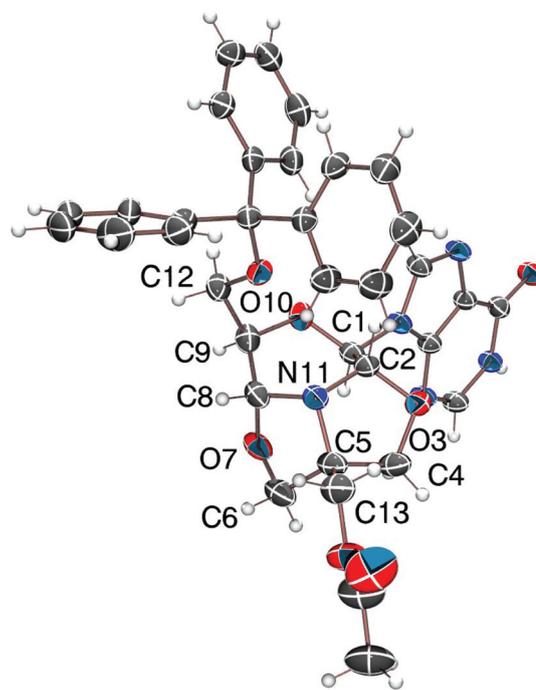
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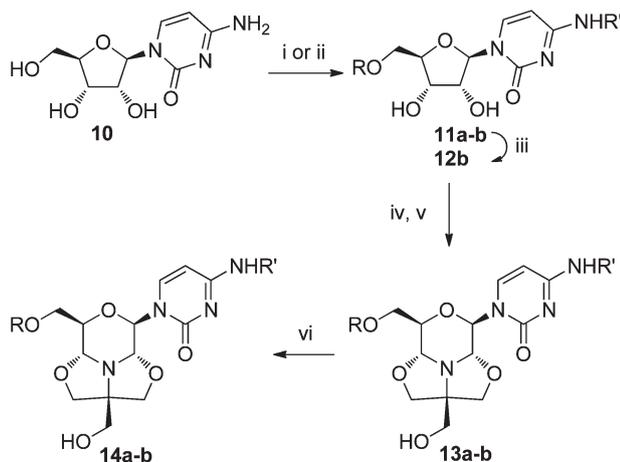
Scheme 4 Synthesis of cytosine-tricyclano using the *O*- and *N*-bis trityl (including Tr and DMTr) protecting groups. Reagents and conditions: (i) TrCl, DMAP, Et₃N, dry DMF, 50 °C, 10 days, **11a**: 30%; (ii) TMSCl, DMTrCl, dry C₅H₅N, rt, 4 days, **11b**: 82%; (iii) TrCl, dry C₅H₅N, rt, 7 days, **12b**: 68%; (iv) IO₄⁻ resin, MeOH : CH₂Cl₂ (**13a**: 3 : 1, **13b**: 1 : 1), rt, dark, **13a**: overnight, **13b**: 3 days; (v) E, 3 Å MS, dry MeOH, rt, **13a**: 2 days, **13b**: overnight, **13a**: 65% (2 steps from **11a**), **13b**: 72% (2 steps from **12b**); (vi) ZnCl₂, (F₃C)₂CHOH, H₃CNO₂, Et₃SiH, rt, 5 h, **14a**: 56% (from **13a**), 7 h, **14b**: 26% (from **13b**); **11a**, **13a**: R = R′ = Tr; **11b**: R = H, R′ = DMTr. **12b**, **13b**: R = Tr, R′ = DMTr; **14a**: R = H, R′ = Tr; **14b**: R = R′ = H.
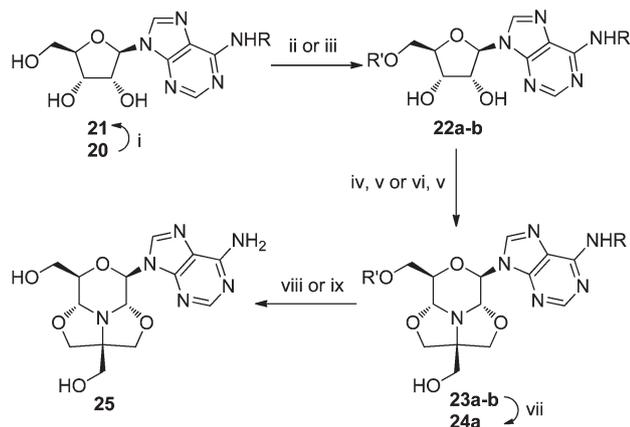
Scheme 5 Synthesis of hypoxanthine-tricyclano **19** *via* unprotected, TBDMS- and Tr-protected dialdehyde intermediates. Reagents and conditions: (i) TBDMSCl, imidazole, dry DMF, rt, overnight, **16a**: 54%; (ii) TrCl, dry C₅H₅N, dry DMF, dry DMSO, 60 °C, 4 days, **16b**: 39%; (iii) IO₄⁻ resin, MeOH, rt, dark, overnight; (iv) E, 3 Å MS, dry MeOH, rt, overnight, **19**: 38% (2 steps from **15**), **17a**: 52% (2 steps from **16a**), **17b**: 42% (2 steps from **16b**); (v) Ac₂O, dry C₅H₅N, rt, overnight, **18b**: 86% (from **17b**); (vi) TBAF, dry THF, rt, overnight, **19**: 56% (from **17a**); (vii) ZnCl₂, (F₃C)₂CHOH, H₃CNO₂, Et₃SiH, rt, 2 h, **19**: 58% (from **17b**). **16a**: R = TBDMS; **16b**: R = Tr; **17a**: R = TBDMS, R′ = H; **17b**: R = Tr, R′ = H; **18b**: R = Tr, R′ = Ac.

To further explore the scope of the novel synthetic pathway parallel to the synthesis of pyrimidine-based tricyclano, similar experiments with inosine, adenosine, and guanosine towards purine tricyclanos were also carried out. First, the impact of the purine base on the cyclocondensation was studied in the case of inosine (Scheme 5). The reaction between Tris and the 5′-TBDMS- or Tr-protected dialdehyde derivatives obtained from inosine *via* **16a**[27] or **16b**[28] afforded **17a** or **17b**, respectively, as the only products. Formation of other stereoisomers was not visible, and the moderate yields (52% for **17a** and 42% for **17b** over two steps) can be explained mainly by the difficulty in purification of the tricyclic products and, to a lesser extent, by the incomplete conversions of dialdehydes. The usual deprotection of both **17a** and **17b** yielded efficiently the unprotected hypoxanthine-tricyclano **19**, which can also be obtained directly from **15** without protecting the 5′ position. **17b** was acetylated to afford the crystalline **18b** which was recrystallized from i-PrOH. Fortunately, the obtained crystal was good for X-ray diffraction and thereby gave us the key for determination of the absolute configuration of the new tricyclic ring system. The crystal structure of **18b** is shown in Fig. 2.

To get access to adenine-tricyclano, **20** was *N*-benzoylated (**21**),[29] silylated (**22a**)[30] and subsequently transformed into **23a** (Scheme 6). The cyclocondensation led to the formation of a single stereoisomer; however, partial loss of the benzoyl group was observed, owing to the nucleophilicity of the Tris reactant. The desilylation of **23a** with TBAF and subsequent debenzoylation of the resulting **24a** in methanolic ammonia took place smoothly to provide the desired free tricyclano **25** in 86%

Fig. 2 ORTEP view of the structure of compound **18b**, at 40% probability level with a partial numbering scheme. One of the molecules from the asymmetric unit is shown and the solvent molecules are omitted for clarity.

overall yield. In order to test the applicability of our new detritylation method in a purine-containing tricyclano, the 6-*N*,5′-*O*- bis tritylated adenosine derivative **22b**[31] was prepared. Next,

4 | *Org. Biomol. Chem.*, 2017, **00**, 1–9

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Scheme 6 Synthesis of adenine-tricyclano **25** using *O*-TBDMS and *N*-benzoyl or the *O*- and *N*-bis trityl protecting group. Reagents and conditions: (i) TMSCl, Bz$_2$O, dry C$_5$H$_5$N, rt, overnight, then H$_2$O, cc. NH$_3$, **21**: 96%; (ii) TBDMSCl, DMAP, 4 Å MS, dry C$_5$H$_5$N, rt, overnight, **22a**: 83% (from **21**); (iii) TrCl, dry C$_5$H$_5$N, 60 °C, overnight, **22b**: 63% (from **20**); (iv) IO$_4^-$ resin, MeOH, rt, dark, overnight; (v) **E**, 3 Å MS, dry MeOH, rt, overnight, **23a**: 24% (2 steps from **22a**), **23b**: 70% (2 steps from **22b**); (vi) IO$_4^-$ resin, MeOH : CH$_2$Cl$_2$ (3 : 2), rt, dark, overnight; (vii) TBAF, dry THF, rt, overnight, **24a**: 92% (from **23a**); (viii) cc. NH$_3$, MeOH, rt, overnight, **25**: 95% (from **24a**); (ix) ZnCl$_2$, (F$_3$C)$_2$CHOH, H$_3$CNO$_2$, Et$_3$SiH, rt, 24 h, 63% (from **23b**); **20**: R = H; **21**: R = Bz; **22a**, **23a**: R = Bz, R' = TBDMS; **22b**, **23b**: R = R' = Tr; **24a**: R = Bz, R' = H.

22b was converted to **23b** using the usual two-step reaction including oxidation followed by cyclocondensation of the obtained dialdehyde with Tris. The complete deprotection of **23b** required an overnight treatment with the detritylating cocktail containing 8 equiv. of ZnCl$_2$. Fortunately, despite the long reaction time and high excess of Lewis acid, neither depurination nor decomposition of the tricyclic core occurred in a noticeable amount and compound **25** was isolated in 63% yield.

Finally, in order to extend our synthetic method to all ribonucleosides, guanine-tricyclano **29** was also prepared (Scheme 7). First, guanosine **26** was selectively tritylated at the primary hydroxyl and the amino group of the heterocyclic base to obtain **27a**,[32] which was transformed into the tricyclano **28a** in high efficacy (73% yield) by the usual two-step procedure. Unexpectedly, complete deprotection required a three-day reaction with the detritylating cocktail, upon which decomposition also occurred, and the desired product could not be isolated. To avoid decomposition upon deprotection, the above synthetic route from **26** to **28** was carried out by the use of the more acid-labile DMTr protecting group. For this purpose, **26** was treated with TMSCl and DMTrCl to produce the required *O*- and *N*-bis(dimethoxytrityl) derivative **27b**[33] in 47% yield, together with the mono-*N*-protected by-product **27c**. Transformation of **27b** into the tricyclano derivative was carried out in the usual manner to obtain **28** in 80% yield. To our great delight, treatment of **28b** with our mild reagent combination led to a satisfactory level of *O*-and *N*-deprotection within 5 hours and the required fully deprotected guanosine derivative **29**, the last member of the tricyclano family, could
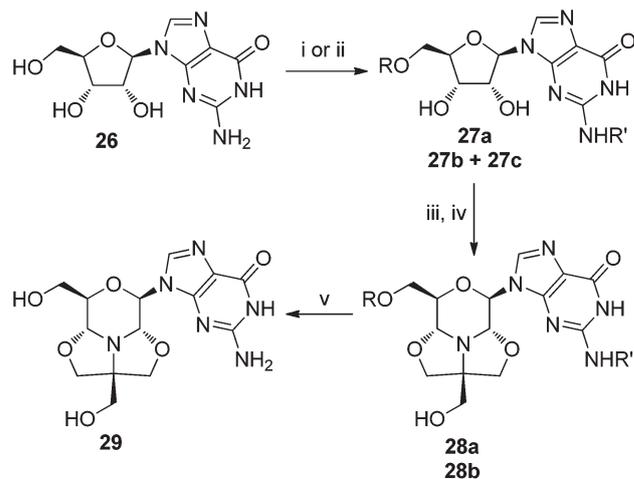
Scheme 7 Synthesis of guanine-tricyclano **29** with *O*- and *N*-bis trityl and the *O*- and *N*-bis(dimethoxytrityl) protecting groups. Reagents and conditions: (i) TrCl, DMAP, Et$_3$N, dry DMF, 50 °C, 10 days, **27a**: 49%; (ii) TMSCl, DMTrCl, dry DMF, dry C$_5$H$_5$N, 4 days, **27b**: 47%, **27c**: 30%; (iii) NaIO$_4$, MeOH : H$_2$O (3 : 1) or IO$_4^-$ resin, MeOH : CH$_2$Cl$_2$ (2 : 3), rt, dark, overnight; (iv) **E**, 3 Å MS, dry MeOH, rt, **28a**: 2 days, **28b**: overnight, **28a**: 73% (2 steps from **27a**), **28b**: 80% (2 steps from **27b**); (v) ZnCl$_2$, (F$_3$C)$_2$CHOH, H$_3$CNO$_2$, Et$_3$SiH, rt, 5 h, 20% (from **28b**). **27a**, **28a**: R = R' = Tr; **27b**, **28b**: R = R' = DMTr; **27c**: R = H, R' = DMTr; **29**: R = R' = H.

successfully be isolated and characterised. We assume that the moderate yield of **29**, which was mainly caused by incomplete deprotection, can be increased by further fine tuning of the detritylation conditions.

Determination of the absolute configuration

Simple NMR methods (*e.g.* $^3J_{HH}$ coupling constants) were insufficient to unambiguously disclose the stereochemistry around the three new stereocenters which might be due to the conformational diversity predicted theoretically (see Fig. S4 in the ESI†). Finally, the combined use of X-ray crystallography, a new NMR ROESY method for H–H distance determination and chemical shift calculations based on theoretical conformational distribution and comparison with NMR data gave satisfactory results.

X-ray studies

X-ray quality crystals of **18b** were grown from i-propanol. Details of data collection and summary of parameters are given in the ESI, Table S1.† In the structure, hydrogen atoms were placed into geometric positions except for the N–H and O–H protons which could be located in the difference electron density maps but the N–H and O–H distances were restrained. The O–H hydrogen atoms of the solvent i-propanol were shifting between two orientations and the small disorder of the solvent molecule was not modelled as chemical evidence indicated the presence of i-propanol molecules. However this did not affect the overall correctness of the structure determination. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the

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Org. Biomol. Chem., 2017, **00**, 1–9 | 5

atom they were bonded to. Refinement of the non-hydrogen atoms was carried out with anisotropic temperature factors. The selected bond lengths and angles of compound **18b** are shown at Tables S2 and S3,† respectively. The space group was non-centrosymmetric and the results unambiguously support that the sample is enantiopure. The high sensitivity of the detector made it possible to determine the absolute configuration reliably on the basis of the anomalous dispersion effect. The Flack parameter for 4034 quotients was found to be 0.03(12).[34]

The absolute configuration for both **18b** molecules is (1*R*,2*S*,5*R*,8*R*,9*R*). The structure is stabilized by weak C–H⋯O and C–H⋯N hydrogen bonds. There are also hydrogen bonds between the i-propanol molecules and O–H bond of one of the i-propanol molecules and carbonyl oxygen of the hypoxanthine moiety (O96). Altogether bond length and bond distance data correspond to the expected values[35] and distance of N11 from the C2–C5–C8 plane is 0.497 and 0.515 Å for the two molecules, respectively. Ring puckering analysis[36] of the structure revealed that the 5-membered rings of N11–C2–O3–C4–C5 and N11–C8–O7–C6–C5 have envelope conformation on O3 and O7, respectively (Fig. S165†). However, the six membered ring of N11–C2–C1–O10–C9–C8 is very strained as the C1–C2–N11–C8 atoms are in one plane (Fig. S166†) while C9 and O10 are at the same side of the plane resembling a half chair conformation. The C1–C2 and C51–C52 distances are both 1.516(7) Å indicating sp^3 carbons. The angle of C1–O10 and C1–C2–N11–C8 planes is 58 degrees (52 degrees for the other molecule in the asymmetric unit). A search of the Cambridge Structural Database (Ver. 5.38, update May, 2017)[37] resulted in around 2600 hits for the morpholine ring moiety in organic compounds. The histogram for the angle of the said planes is shown in Fig. S165† clearly demonstrating that our system with a 52–58 degree angle is rather unique.

DFT NMR calculations

For the DFT NMR studies all possible 8 : 8 stereoisomers of **3c** and **9**, the proven one of **18b** and the presumed one of **13a** were utilized. For each stereoisomer an OPLS (Optimized Potentials for Liquid Simulations)[38] conformational search was carried out for CHCl$_3$ and conformers were saved in a 21 kJ mol^{-1} energy window. These conformers were reoptimized at the B3LYP/6-31+G(d,p) level and NMR shift values were computed for conformers over 1% Boltzmann population at the mPW1PW91/6-311+G(2d,p) level.[39] Corrected C and H-NMR data[40] were compared to the experimental shift values. While for **9** the C-NMR data (Table S7†) alone were rather persuasive, for **3c** a combination of C (Table S5†) and H-NMR data (Table S6†) was necessary to distinguish between the 8 stereoisomers resulting in the same diastereomer elucidated by X-ray crystallography for **18b**. Corrected mean absolute error (CMAE) values[41] and largest deviations from the experimental data of **18b** and **13a** were similar for the single investigated stereoisomers as for the best stereoisomers of **3c** and **9** (Tables S9–S12†). Therefore, from the computational NMR results for all tricyclanos the products are homochiral with the X-ray-determined compound **18b**.

Newly developed distance-based experimental NMR method to elucidate stereochemistry

A recently introduced zero-quantum suppressed off-resonance ROESY method[42] (an easy-ROESY variant) proved to be especially useful to corroborate stereochemical conclusions. Since the method is less sensitive to zero-quantum artifacts present between scalar-coupled nuclei (*e.g.* the CH$_2$ groups or the aromatic *ortho* protons used for distance calibration), good distance agreement was found between NMR and X-ray techniques (Fig. S167–S169 and Table S4†) where an independent X-ray structure was available (**18b**). Interestingly, theoretical calculations showed conformational diversity of the tricyclic ring and the side chains that prevents the possibility of direct comparison with *ad hoc* selected conformers. Conformational diversity was recently shown to persist in "rigid" molecules like strychnine.[43] For the 500 MHz off-resonance ROESY spectra, typically a magic tilt angle of theta = 54.7° was used, with a spin lock field strength of 8.33 kHz (p_{90} = 30 us) at ±5.9 kHz offsets applied in the two halves of the mixing time of 200 ms. For zero quantum filtering adiabatic chirp pulses of 30 and 50 ms with simultaneous spoil gradients were used as described in ref. 42.

Mechanism

We suppose that the formation of the new tricycle can be described as a series of consecutive reactions (Scheme 8). First a Schiff base (**i2**) is formed through a hemiaminal (**i1**) followed by an intramolecular addition of one of the primary alcohols resulting in the oxazolidine **i3**. A second hemiaminal (**i4**) is formed by the addition of the NH group to the second aldehyde. The final step is the addition of the second hydroxyl group onto the iminium intermediate **i5**. The stereoselectivity of the reaction is controlled by the two chiral centers of the dialdehyde. Since the water side product is continuously removed with molecular sieves there is no equilibration in the particular reaction steps. Therefore, we postulate that formation of the kinetic product is preferred resulting in the high stereoselectivity of the reaction. The observed stereochemistry at C2 and C8 is in accordance with the polar Felkin–Anh model generally applied for the addition reactions of alde-
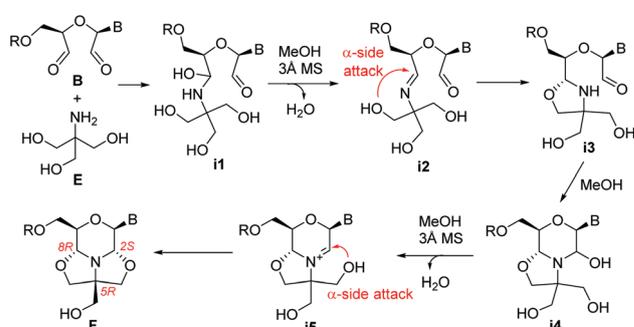
Scheme 8 Proposed mechanism of the imine-oxazolidine and iminium-oxazolidine cascade reactions. (The first attack of the amine on one of the two aldehyde moieties is interchangeable.)

6 | *Org. Biomol. Chem.*, 2017, **00**, 1–9

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hydes or ketones with an electronegative group.[44] Chiral centers at C2 and C5 (or at C8 and C5) form simultaneously in the final cyclisation step.

Conclusions

In conclusion, we developed a new type of nucleoside analogue by the stereoselective transformation of the ribose unit of nucleosides to a novel, specific heterotricyclic system comprising a morpholine ring and two 1,3-oxazolidine rings. The implemented synthesis is very simple including an oxidation step followed by a cyclocondensation of the resulting dialdehyde with the commercially available and cheap reagent Tris. The highly efficient and stereoselective formation of one isomeric form of the newly generated stereotriade observed in the condensation reactions can be explained by the induced fitting of the reactants. The reaction proceeds through two consecutive hemiaminal–oxazolidine cascade reactions and the stereoselectivity is governed by the two stereogenic centers of the nucleoside-derived dialdehydes. The stereochemistry was unambiguously proved by single crystal X-ray diffraction for **18b** in agreement with NMR ROESY and computational methods that allowed assigning absolute configuration in the absence of X-ray structures. A combined approach was necessary because of the theoretically predicted flexibility of the tricycle. The synthetic method is compatible with both purine and pyrimidine bases as well as bulky protecting groups like TBDMS, Tr or DMTr. Using a ZnCl$_2$-Et$_3$SiH-(F$_3$C)$_2$CHOH-containing reagent system, due to the beneficial synergism of the components, the Tr and DMTr protecting groups of tricyclanos could efficiently be cleaved in most cases – except for the *N*-trityl group of cytosine and guanine – and this mild deprotection method neither affected the acid-sensitive double aminal system nor caused depurination.

Studies towards the synthesis of tricyclano-containing oligonucleotide derivatives and utilisation of the tricyclisation method for producing new N-containing heterotricyclic systems are under way.

Experimental

Typical procedure for the cyclocondensation reaction between the nucleoside dialdehyde and Tris: 12′-*O*-trityl-uracil-tricyclano (3c)

To a solution of **2c** (2.00 g, 4.13 mmol) in MeOH (100 mL) the IO$_4^-$-form of anion exchange resin (8.0 g) was added and stirred overnight in the dark. The next day the resin was filtered off through a short pad of Celite® and washed successively with MeOH and CH$_2$Cl$_2$. The solvent was evaporated in vacuum. The residue was dissolved in dry MeOH (100 mL) and 3 Å molecular sieves (2 g) were added to the reaction. After stirring for half an hour, Tris (747 mg, 6.17 mmol, 1.5 equiv.) was added to the mixture. The next day another portion of Tris (249 mg, 2.06 mmol, 0.5 equiv.) was added to the stirred reaction mixture. After a total reaction time of 2 days the molecular

sieves were filtered off through a short pad of Celite® and washed successively with MeOH and CH$_2$Cl$_2$. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 98 : 2 → 98 : 3 → 97 : 3) to yield compound **3c** (1.78 g, 76%, over two steps) as a white foam. R_f = 0.42 (CH$_2$Cl$_2$/MeOH 95 : 5); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 9.77 (s, 1H, N*H*), 7.48 (d, *J* = 8.2 Hz, 1H, uracil C*H*-6), 7.43 (d, *J* = 7.3 Hz, 6H, 6 × Tr Ar–H), 7.29 (t, *J* = 7.4 Hz, 6H, 6 × Tr Ar–H), 7.23 (t, *J* = 7.2 Hz, 3H, 3 × Tr Ar–H), 6.14 (d, *J* = 4.7 Hz, 1H, H-1′), 5.67 (d, *J* = 8.2 Hz, 1H, uracil C*H*-5), 4.80 (d, *J* = 4.6 Hz, 1H, H-8′), 4.68 (d, *J* = 4.7 Hz, 1H, H-2′), 4.21 (q, *J* = 4.4 Hz, 1H, H-9′), 3.87 (d, *J* = 9.0 Hz, 2H, H-6′a, H-4′a), 3.78 (d, *J* = 8.9 Hz, 1H, H-6′b), 3.77 (d, *J* = 8.8 Hz, 1H, H-4′b), 3.64 (d, *J* = 5.5 Hz, 2H, H-13′a,b), 3.38 (d, *J* = 4.3 Hz, 2H, H-12′a,b), 2.90 (t, *J* = 5.8 Hz, 1H, O*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 163.4 (1C, uracil C*O*-4), 150.5 (1C, uracil C*O*-2), 143.5 (3C, 3 × Tr Ar–C), 139.9 (1C, uracil C*H*-6), 128.7, 128.0, 127.3 (15C, 15 × Tr Ar-C*H*), 103.0 (1C, uracil C*H*-5), 90.3 (1C, C-2′), 88.4 (1C, C-8′), 87.1 (1C, Tr C$_q$), 77.7 (1C, C-1′), 75.3 (1C, C-5′), 73.9 (1C, C-9′), 72.0 (1C, C-4′), 71.3 (1C, C-6′), 63.7 (1C, C-13′), 63.6 (1C, C-12′); ESI-TOF-MS: *m/z* calcd for C$_{32}$H$_{31}$N$_3$NaO$_7$ [M + Na]$^+$ 592.206, found 592.205.

Typical deprotection procedure using the three-component detritylating cocktail: uracil-tricyclano (4)

3c (342 mg, 0.60 mmol) was added to the mixture of ZnCl$_2$ (342 mg, 2.51 mmol, 4.2 equiv.), hexafluoroisopropanol (6 mL), MeNO$_2$ (3 mL) and Et$_3$SiH (600 μL, 3.76 mmol, 6.3 equiv.). After 2 hours a saturated NaHCO$_3$-solution was added and the solvents were evaporated. The crude product was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 9 : 1 → 8 : 1 → 85 : 15 → 8 : 2) to yield **4** (129 mg, 66%) as a white foam. R_f = 0.45 (CH$_2$Cl$_2$/MeOH 85 : 15); ^{1}H NMR (400 MHz, D$_2$O + CD$_3$OD) δ = 7.78 (d, *J* = 8.1 Hz, 1H, uracil C*H*-6), 6.04 (d, *J* = 5.0 Hz, 1H, H-1′), 5.88 (d, *J* = 8.1 Hz, 1H, uracil C*H*-5), 4.77 (d, *J* = 5.1 Hz, 1H, H-2′), 4.70 (d, *J* = 4.1 Hz, 1H, H-8′), 4.15 (dd, *J* = 3.9, 1.3 Hz, 1H, H-9′), 4.00 (d, *J* = 9.1 Hz, 1H, H-6′a), 3.93–3.86 (m, 2H, H-4′a,b), 3.85–3.71 (m, 3H, H-6′b, H-12′a,b), 3.69 (s, 2H, H-13′a,b); ^{13}C NMR (100 MHz, D$_2$O + CD$_3$OD) δ = 166.6 (1C, uracil C*O*-4), 152.3 (1C, uracil C*O*-2), 142.6 (1C, uracil C*H*-6), 103.8 (1C, uracil C*H*-5), 90.8 (1C, C-2′), 89.1 (1C, C-8′), 79.1 (1C, C-1′), 75.9 (1C, C-9′), 75.6 (1C, C-5′), 73.0 (1C, C-4′), 72.2 (1C, C-6′), 63.6 (1C, C-13′), 62.7 (1C, C-12′); ESI-TOF-MS: *m/z* calcd for C$_{13}$H$_{17}$N$_3$NaO$_7$ [M + Na]$^+$ 350.096, found 350.093.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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Org. Biomol. Chem., 2017, **00**, 1–9 | 7

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Org. Biomol. Chem., 2017, **00**, 1–9 | **9**