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Stereoselective synthesis of 3′-substituted 2′-deoxy C-nucleoside pyrazolo[1,5-*a*]-1,3,5-triazines and their 5′-phosphate nucleotides

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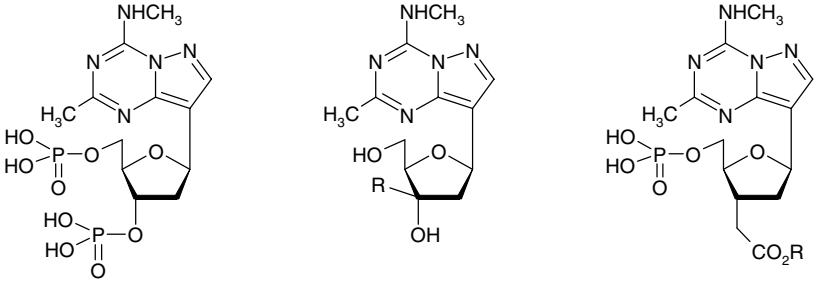
Abstract—An efficient synthesis of novel 3′-substituted 2′,3′-dideoxynucleoside analogues in the pyrazolotriazine series was developed from the corresponding 3′-ketonucleoside via the Wittig reaction. On the other hand, a highly stereoselective addition of alkynylcerium reagents to the same precursor led to the 3′-alkynyl-2′-deoxynucleosides in one step with the natural stereochemistry. Applications to produce novel $P2Y_1$ receptor antagonists or new anti-retroviral nucleoside analogues are suggested.

1. Introduction

In our efforts to design novel purinergic $P2Y_1$ receptor antagonists as potent platelet aggregation inhibitors with enhanced metabolic stability, we have recently reported the synthesis of 8-(2′-deoxy-β-D-ribofuranosyl)-2-methyl-4-(*N*-methylamino)pyrazolo[1,5-*a*]-1,3,5-triazine-3′,5′-bisphosphate (**1**).[1] With the goal to improve potency of antagonists at the $P2Y_1$ receptor, we have adopted an efficient chemical pathway to introduce substituents at the 3′-position on the glycosyl moiety leading to intermediate **2** in a diastereoselective manner. In the second part of this work, we have focused our interest on replacement of the 3′-phosphate group by another functionality with increased in vivo stability. A similar strategy consisting of uncharged substitution of the phosphate group on an adenine scaffold has been recently described.[2] However, to the best of our knowledge, there is no example of substitution at the 3′-position on pyrazolotriazine C-nucleoside (Fig. 1).

2. Chemical synthesis

In an earlier publication, we have reported the synthesis of compound **4a** as a key intermediate leading to



1 2 3

Figure 1. Nucleotide analogues acting on the $P2Y_1$ receptor and a 3′-substituted precursor.

Keywords: C-Nucleoside pyrazolotriazines; Nucleotides; Wittig reaction; Stereoselective addition.
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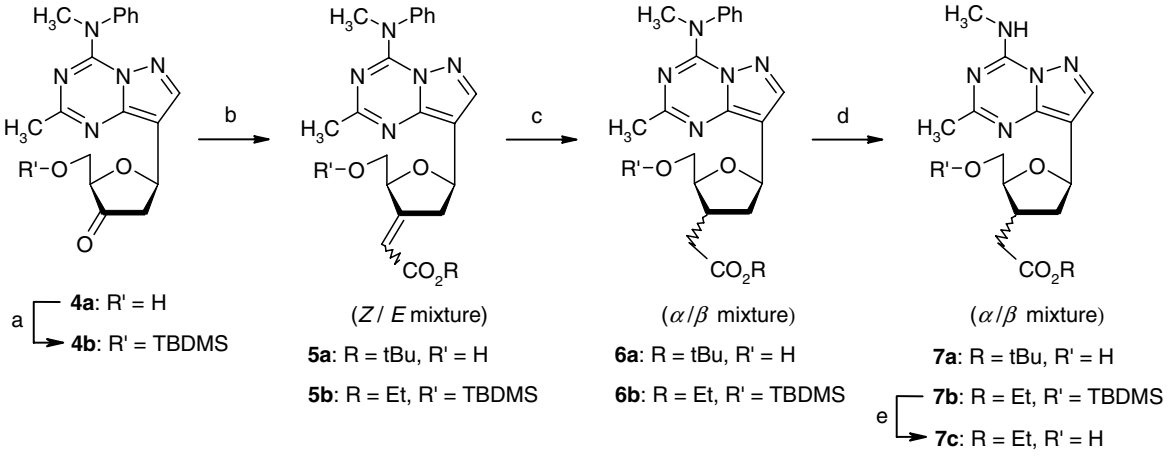
bisphosphate **1**.[1] The electrophilic carbonyl at the 3′-position on the glycosyl moiety allowed versatile reactivity and was an ideal group for the introduction of substitutions and functionalities.

Compound **4a** may be protected as 5′-*O*-*tert*-butyldimethylsilyl derivative **4b** in good yield, followed by Wittig reaction with stabilized ylide[3] in toluene (Scheme 1).[4] Protection of the 5′-hydroxyl was not necessary for this reaction, but the less polar 5′-*O*-*tert*-butyldimethylsilyl adducts were more easily separated from excess ylide and triphenylphosphine oxide by column chromatography. In each case, the Wittig reaction led to a *Z*/*E* mixture of α,β-unsaturated esters **5a** and **5b** in excellent yields. The next step consisted of hydrogenation of the double bond in good yields.[5] Both the bulky 1′-pyrazolotriazinyl and the 5′-*O*-*tert*-butyldimethylsilyl groups generated steric hindrance, which favourably directed reduction under the glycosyl face leading to an unseparable 3′-α/β-diastereomeric mixture in a 2/3 ratio. Displacement of the *N*-methyl-*N*-phenylamino group by methylamine in a sealed tube afforded compounds **7a** and **7b** in variable yields.[6] 5′-O-Silylated derivative **7b** was deprotected with fluoride ion generating nucleoside **7c** in good yield. At this stage, 3′-α/β-diastereomeric mixture **7c** may be eventually separated by column chromatography.

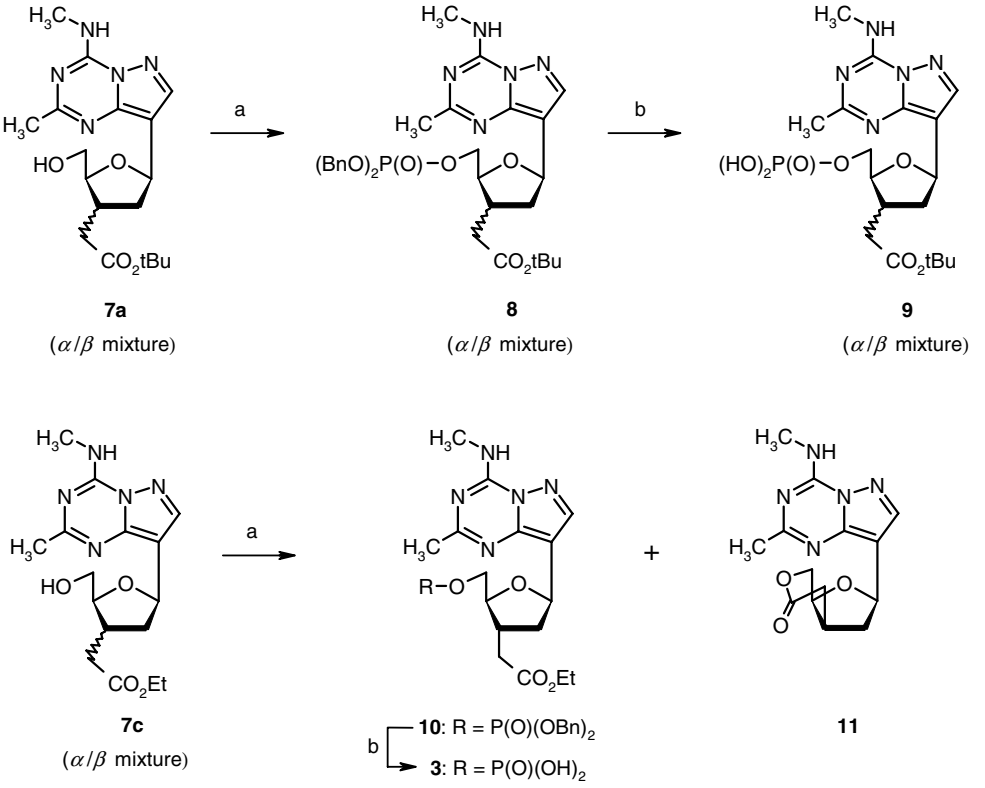
As shown in Scheme 2, nucleosides **7a** and **7c** were phosphorylated[7] in variable yields using the tetrabenzyl pyrophosphate (TBPP) procedure,[8] followed by hydrogenation to remove the benzyl groups. In the case of *tert*-butyl ester **7a**, this methodology afforded the 3′-α/β-diastereomers mixture of nucleotide **9**, which needed preparative HPLC methods to separate them.[9] However, the reactivity observed for ethyl ester **7c** was different. The 3′-α-diastereomer nucleoside was transformed to 3′-α-diastereomer nucleotide **3**, whereas the 3′-β-diastereomer nucleoside was cyclized into lactone **11** under basic conditions.[10] The relative configuration of this lactone was unambiguously established by NOESY experiments. These experiments revealed a strong NOE effect between the 3′-H and the 4′-H of the sugar and between the 3′-*C*–CH_2 and the 5′-H. The six member ring lactone was obtained in this case due to the greater electrophilicity of the ethyl ester relative to the *tert*-butyl ester under kinetic conditions. Thus, starting from a α/β-diastereomeric mixture of nucleoside **7c**, dibenzyl phosphate **10** was easily separated from lactone **11** by flash column chromatography affording only the target final nucleotide **3** after hydrogenolysis.[11]

An efficient procedure for the preparation of 3′-*C*-branched nucleosides starting from the corresponding 3′-ketonucleosides has been reported by Biellmann and co-workers.[12] This approach consisted of a highly stereoselective addition of an alkynylcerium reagent to 3′-ketonucleosides, affording the 3′-alkynylnucleosides with the required stereochemistry. The remarkable stereoselectivity observed in adenosine and uridine series, was attributed to chelation control of the 5′-hydroxyl, which acted as a β-face directing group. Thus, this strategy allowed efficient substitution of the 3′-position on the glycosyl moiety and keeping the 3′-hydroxyl group in the natural configuration. Our system differed from adenosine by the nature of the base and the absence of the 2′-hydroxyl group.

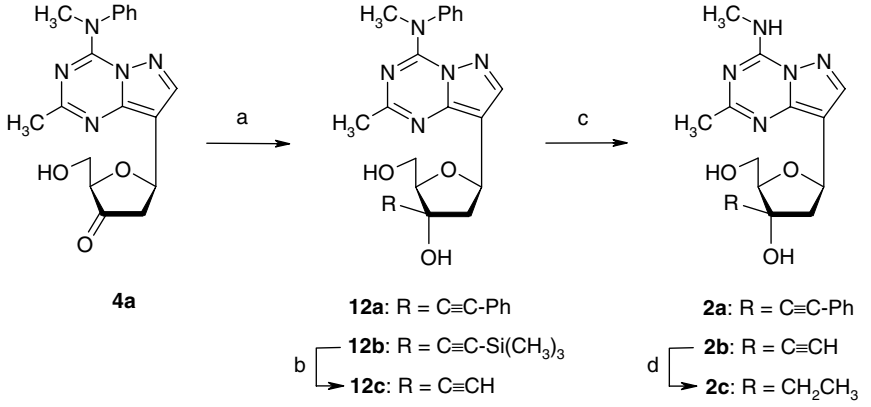
As shown in Scheme 3, the addition of alkynylcerium–lithium reagents onto 3′-ketonucleoside **4a** (synthesis of **4a** reported in an earlier publication)[1] afforded compounds **12a**,**b** in good yield and was highly diastereoselective (only a trace amount of the other diastereomer was detected by TLC).[13] The alkynylcerium–lithium reagents were prepared from phenylacetylene or (trimethylsilyl)acetylene as described in the literature.[12] At this stage, the NOESY experiments did not allow to establish the relative configuration of adducts **12a**,**b** because the phenyl or the trimethylsilyl groups borne by the triple bond were too far from the sugar moiety. Nevertheless, the coupling constant observed between the 1′-H and the 2′-β-H of the glycosyl moiety (approximately 5.5 Hz) was in agreement with an *erythro* 3′-substituted 2′-deoxynucleoside configuration.[14] After deprotection of ethynyl derivative **12b** by tetrabutylammonium fluoride, the *N*-methyl-*N*-phenyl-



Scheme 1. Reagents and conditions: (a) TBDMS-Cl, imidazole, DMF, 35 °C, 16 h, 73%; (b) $Ph_3P{=}CH{-}CO_2R$, toluene reflux, 18 h, 86–90%; (c) H_2, Pd/C, MeOH, 60 psi, rt, 24 h, 62–93%; (d) $MeNH_2$, EtOH, sealed tube, 100 °C, 16 h, 46–98%; (e) TBAF, THF, rt, 1 h, 86%.



Scheme 2. Reagents and conditions: (a) *t*BuOK, TBPP, THF, −40 °C, 30 min, 50–87%; (b) H_2, Pd/C, MeOH, 60 psi, rt, 20 h, 93–99%.



Scheme 3. Reagents and conditions: (a) R–Li/$CeCl_3$, THF, −78 °C, 1–3 h, 86–90%; (b) TBAF, THF, rt, 1 h; (c) $MeNH_2$, EtOH, sealed tube, 100 °C, 16 h, 81–89%; (d) H_2, Pd/C, MeOH, 60 psi, rt, 20 h, 99%.

amino group was displaced by methylamine in a sealed tube to afford products **2a** and **2b** in good yields.[15] A catalytic hydrogenation of compound **2b** was finally carried out with the aim to confirm the relative configuration of these nucleosides by NOESY experiments.[16] Especially the NOE effect observed between 3′-*C*–CH_2 and 5′-H, as well as between the methyl of 3′-*C*–CH_2CH_3 and 5′-H confirmed the presence of the 3′-*C*-substituent at the β-face of the pentofuranose ring. These 3′-substituted 2′-deoxynucleoside analogues obtained in pyrazolotriazine series appeared as the direct precursors of novel $P2Y_1$ receptor antagonists. They could also interfere with the biosynthesis of nucleic acids, since 3′-*C*-branched deoxynucleotides could act as slow substrates or inhibitors of HIV reverse transcriptase during viral DNA chain elongation.[17]

In conclusion, we have developed an expedient and efficient procedure for the synthesis of novel 3′-substituted 2′,3′-dideoxynucleoside analogues in the pyrazolotriazine series via the Wittig reaction. Reduction of the double bond leads to a α/β-diastereomeric mixture of the 3′-substituted nucleoside. The scope of this strategy results in a different reactivity of each diastereomer affording only the final nucleotide in the desired configuration. These novel compounds are currently under biological evaluation for their platelet aggregation inhibition properties as $P2Y_1$ receptor antagonists. On

the other hand, a stereoselective addition of alkynylcerium reagents allows us to synthesize in one step the 3′-alkynyl-2′-deoxynucleosides with the required stereochemistry from the corresponding 3′-ketonucleoside. These findings represent useful methodologies for the synthesis of analogue systems of adenine nucleosides and nucleotides.

Acknowledgement

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References and notes

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4. A typical procedure for the Wittig reaction: A solution of **4a** (300 mg, 0.849 mmol) and *tert*-butyl triphenylphosphoranylidene acetate (1.28 g, 3.40 mmol) in toluene (10 mL) was refluxed overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 1/2) to afford **5a** (*Z*/*E* mixture, 330 mg, 86%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H, $C(CH_3)_3$), 2.55 (s, 3H, 2-CH_3), 2.76 (dd, $J = 5.3$, 16.1 Hz, 1H, 2′-H^A), 3.26–3.44 (m, 1H, 2′-H^B), 3.73 (s, 3H, N–CH_3), 3.98–4.23 (m, 2H, 5′-H), 4.63–4.68, 5.31–5.36 (m, 1H, 4′-H), 5.02, 5.16 (dd, $J = 5.5$, 11.4 Hz, 1H, 1′-H), 5.78, 5.86 (s, 1H, C=CH), 6.30 (br s, 1H, OH), 7.12–7.18, 7.33–7.45 (m, 5H, Ph), 7.61 (s, 1H, 7-H). MS: *m*/*z* 452 $(M+H)^+$.
5. A typical procedure for the reduction: A mixture of **5a** (320 mg, 0.709 mmol) and 10% Pd/C (75 mg) in MeOH (100 mL) was shaken in a hydrogenation apparatus under 60 psi pressure at room temperature for 24 h. The catalyst was removed by filtration and washed with MeOH and CH_2Cl_2. The filtrate was concentrated to dryness and the product was purified by trituration in Et_2O to furnish **6a** (α/β-diastereomeric mixture, 300 mg, 93%) as a white solid; mp 49–51 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H, $C(CH_3)_3$), 2.14–2.51, 2.70–2.89 (m, 5H, 2′-H+3′-H+3′-CH_2), 2.55 (s, 3H, 2-CH_3), 3.72 (s, 3H, N–CH_3), 3.89–4.06 (m, 2H, 5′-H), 4.20–4.27 (m, 1H, 4′-H), 5.03 (dd, $J = 5.4$, 11.1 Hz, 1H, 1′-H), 6.60 (br s, 1H, OH), 7.10–7.18, 7.33–7.41 (m, 5H, Ph), 7.60 (s, 1H, 7-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.1 ($C(CH_3)_3$), 37.2, 38.1 (CH_2), 40.0 (2′-C), 62.1 (5′-C), 71.0 (1′-C), 81.2 (4′-C), 108.5 (8-C), 125.9 (C^{meta}), 127.2 (C^{para}), 129.0 (C^{ortho}), 143.2 (7-C), 144.0 (9-C), 149.1 (4-C), 162.4 (2-C). MS: *m*/*z* 454 $(M+H)^+$.
6. A typical procedure for the *N*-methyl-*N*-phenylamino group displacement: A solution of **6a** (298 mg, 0.657 mmol) and 2 M methylamine solution (2.0 mL, 4.00 mmol) in ethanol (5 mL) was stirred at 100 °C in a sealed tube for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/CH_2Cl_2/EtOH 4/5/1) to yield **7a** (α/β-diastereomeric mixture, 113 mg, 46%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46, 1.47 (s, 9H, $C(CH_3)_3$), 2.04–2.13 (m, 1H, 2′-H^A), 2.24–2.33 (m, 1H, 2′-H^B), 2.55 (s, 3H, 2-CH_3), 2.45–2.66 (m, 3H, 3′-H+3′-CH_2), 3.21 (d, $J = 5.0$ Hz, 3H, N–CH_3), 3.51–3.57, 3.61–3.69 (m, 1H, 5′-H^A), 3.75–3.82 (m, 1H, 5′-H^B), 4.05–4.14 (m, 1H, 4′-H), 4.74 (dd, $J = 2.5$, 11.6 Hz, 1H, 1′-H), 6.52 (br s, 1H, NH), 7.94 (s, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 (2-CH_3), 27.2 (N–CH_3), 28.1 ($C(CH_3)_3$), 36.7, 37.4 (CH_2), 40.0 (2′-C), 49.4, 49.8 (3′-C), 63.7 (5′-C), 71.1 (1′-C), 81.2 (4′-C), 109.5 (8-C), 143.3 (7-C), 145.9 (9-C), 149.0 (4-C), 163.6 (2-C), 173.4 (CO_2tBu). MS: *m*/*z* 378 $(M+H)^+$.
7. A typical procedure for the phosphorylation: 1.0 M potassium *tert*-butoxide solution in THF (0.19 mL, 0.190 mmol) was added dropwise to a stirred solution of **7a** (60 mg, 0.159 mmol) in anhydrous THF (5 mL) at −40 °C. After 5 min, tetrabenzyl pyrophosphate (103 mg, 0.190 mmol) was added and the resulting mixture was stirred at −40 °C for 30 min. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL) and the mixture was allowed to warm to room temperature. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/CH_2Cl_2/EtOH 4/5/1) to give **8** (α/β-diastereomeric mixture, 50 mg, 49%) as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42, 1.44 (s, 9H, $C(CH_3)_3$), 2.08–2.43 (m, 4H, 2′-H+3′-CH_2), 2.52, 2.54 (s, 3H, 2-CH_3), 2.68–2.77 (m, 1H, 3′-H), 3.19 (d, $J = 4.9$ Hz, 3H, N–CH_3), 3.55–3.66 (m, 1H, 5′-H^A), 3.74–3.81 (m, 1H, 5′-H^B), 4.18–4.29 (m, 1H, 4′-H), 4.71–4.81 (m, 1H, 1′-H), 5.03, 5.10 (d, 4H, 2 × CH_2Ph), 6.69 (br s, 1H, NH), 7.32, 7.35 (s, 10H, 2 × Ph), 7.91 (s, 1H, 7-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9 (2-CH_3), 27.2 (N–CH_3), 28.1 ($C(CH_3)_3$), 36.7, 37.8 (CH_2), 38.9 (2′-C), 60.4 (5′-C), 69.4, 69.5 (2 × CH_2Ph), 70.5 (1′-C), 80.6 (4′-C), 109.0 (8-C), 128.0, 128.5, 128.6 (2 × Ph), 143.2 (7-C), 146.0 (9-C), 148.9 (4-C), 163.8 (2-C), 171.1 (CO_2tBu). ^{31}P NMR (121 MHz, $CDCl_3$): δ −0.75 (s, α-diastereomer), −0.55 (s, β-diastereomer). MS: *m*/*z* 638 $(M+H)^+$.
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9. A typical procedure for the hydrogenolysis: A suspension of **8** (45 mg, 70.6 μmol) and 10% Pd/C (15 mg) in MeOH (70 mL) was shaken in a hydrogenation apparatus under 60 psi pressure at room temperature for 24 h. The catalyst was removed by filtration and washed with MeOH and CH_2Cl_2. The filtrate was concentrated to dryness and the product was purified by recrystallization from EtOH and Et_2O to give **9** (α/β-diastereomeric mixture, 30 mg, 93%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.41 (s, 9H, $C(CH_3)_3$), 1.95–2.23 (m, 4H, 2′-H+3′-CH_2), 2.42 (s, 3H, 2-CH_3), 2.75–2.83 (m, 1H, 3′-H), 3.01 (d, $J = 4.1$ Hz, 3H, N–CH_3), 3.58–3.68, 3.72–3.77 (m, 1H, 5′-H^A), 3.85–3.94 (m, 1H, 4′-H), 4.08 (dd, $J = 4.4$, 10.6 Hz, 1H, 5′-H^B), 4.61–4.69 (m, 1H, 1′-H), 8.08 (s, 1H, 7-H), 8.66 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.0 (2-CH_3), 27.6 (N–CH_3), 28.2 ($C(CH_3)_3$), 70.5 (1′-C), 80.4 (4′-C), 109.0 (8-C), 143.6 (7-C), 145.8 (9-C), 149.2 (4-C), 163.0 (2-C), 171.6 (CO_2tBu). ^{31}P NMR (81 MHz, DMSO-d_6): δ −0.50 (s, β-diastereomer), −0.33 (s, α-diastereomer).
10. Physical data for lactone **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (ddd, 1H, 2′-H^A), 2.52–2.61 (m, 1H, 2′-H^B), 2.56 (s, 3H, 2-CH_3), 2.64 (d, $J = 4.9$, 2H, 3′-CH_2), 3.02–3.13

(m, 1H, 3′-H), 3.22 (d, $J = 5.2$ Hz, 3H, N–CH_3), 4.23 (dd, $J = 2.6$, 12.4 Hz, 1H, 5′-H^A), 4.43 (ddd, 1H, 4′-H), 4.51 (dd, $J = 2.1$, 12.4 Hz, 1H, 5′-H^B), 5.15 (dd, $J = 4.5$, 10.9 Hz, 1H, 1′-H), 6.49 (br s, 1H, NH), 7.99 (s, 1H, 7-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0 (2-CH_3), 27.2 (N–CH_3), 33.5 (3′-CH_2), 35.2 (3′-C), 39.4 (2′-C), 69.4 (5′-C), 71.5 (1′-C), 74.2 (4′-C), 106.9 (8-C), 143.5 (7-C), 146.7 (9-C), 149.0 (4-C), 164.0 (2-C), 171.8 (CO_2R). MS: m/z 304 $(M+H)^+$.

11. Physical data for nucleotide **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $J = 7.1$ Hz, 3H, CH_3), 1.98–2.12 (m, 1H, 2′-H^A), 2.23–2.32 (m, 1H, 2′-H^B), 2.38–2.49 (m, 1H, 3′-H), 2.57 (s, 3H, 2-CH_3), 2.61–2.75 (m, 2H, CH_2), 3.19 (d, 3H, N–CH_3), 3.80–3.88 (m, 1H, 4′-H), 3.94–4.09 (m, 2H, 5′-H), 4.10 (q, $J = 7.1$ Hz, 2H, CH_2), 5.28–5.36 (m, 1H, 1′-H), 6.50 (br s, 1H, NH), 8.04 (s, 1H, 7-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.6 (CH_3), 26.1 (2-CH_3), 27.5 (N–CH_3), 29.5 (3′-CH_2), 37.5 (2′-C), 60.4 (CH_2), 66.9 (5′-C), 70.9 (1′-C), 109.5 (8-C), 144.1 (7-C), 146.1 (9-C), 149.2 (4-C), 162.9 (2-C), 172.3 (CO_2Et). ^{31}P NMR (81 MHz, DMSO-d_6): δ 0.18 (s).
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13. A typical procedure for the stereoselective addition: A suspension of anhydrous $CeCl_3$ (174 mg, 0.707 mmol) in dry THF (1.5 mL) under argon was stirred at room temperature overnight. Independently, 1.6 M BuLi solution in hexane (0.44 mL, 0.707 mmol) was added dropwise to a stirred solution of phenylacetylene (78 μL, 0.707 mmol) in dry THF (2 mL) under argon at −78 °C. The reaction temperature was raised to −20 °C over a 1 h period. This lithium acetylide solution was cooled to −78 °C and added, via a cannula, to the $CeCl_3$ suspension at the same temperature (prepared above). The mixture was stirred for 1 h and a cooled solution (−78 °C) of **4a** (50 mg, 0,141 mmol) in dry THF (1.5 mL) was rapidly added via a cannula. After 3 h at −78 °C, the reaction was quenched by adding saturated aqueous NH_4Cl (10 mL) and the mixture was allowed to warm to room temperature. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexane 1/1) to give **12a** (55 mg, 86%) as a white solid, mp: 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 3H, 2-CH_3), 2.71 (dd, $J = 5.7$, 13.9 Hz, 1H, 2′-H^A), 2.97 (dd, $J = 9.5$, 13.9 Hz, 1H, 2′-H^B), 3.75 (s, 3H, N–CH_3), 4.02–4.07 (m, 1H, 5′-H^A), 4.12–4.19 (m, 2H, 5′-H^B+4′-H), 5.22 (dd, $J = 5.7$, 9.5 Hz, 1H, 1′-H), 7.14–7.19, 7.31–7.42, 7.47–7.53 (m, 10H, N–Ph+C≡C–Ph), 7.67 (s, 1H, 7-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2 (2-CH_3), 42.3 (N–CH_3), 48.9 (2′-C), 61.8 (5′-C), 70.7 (1′-C), 75.2 (3′-C), 86.4 (4′-C), 88.7, 122.4 (C≡C), 107.4 (8-C), 126.2 (N–Ph, C^{meta}), 127.4 (N–Ph, C^{para}), 128.2 (C≡C–Ph, C^{meta}), 128.5 (C≡C–Ph, C^{para}), 129.0 (N–Ph, C^{ortho}), 131.8 (C≡C–Ph, C^{ortho}), 144.3 (7-C), 147.8 (9-C), 149.1 (4-C), 162.8 (2-C). MS: m/z 456 $(M+H)^+$. Physical data for compound **12b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 9H, $Si(CH_3)_3$), 2.52 (s, 3H, 2-CH_3), 2.59 (dd, $J = 5.6$, 13.9 Hz, 1H, 2′-H^A), 2.86 (dd, $J = 9.4$, 13.9 Hz, 1H, 2′-H^B), 3.74 (s, 3H, N–CH_3), 3.91–3.96 (m, 1H, 5′-H^A), 4.03–4.10 (m, 2H, 5′-H^B+4′-H), 5.15 (dd, $J = 5.6$, 9.4 Hz, 1H, 1′-H), 7.13–7.19, 7.32–7.43 (m, 5H, Ph), 7.64 (s, 1H, 7-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.12 ($Si(CH_3)_3$), 25.1 (2-CH_3), 42.3 (N–CH_3), 48.8 (2′-C), 61.7 (5′-C), 70.6 (1′-C), 74.9 (3′-C), 86.4 (4′-C), 89.4, 104.9 (C≡C), 107.3 (8-C), 126.1 (C^{meta}), 127.4 (C^{para}), 129.0 (C^{ortho}), 144.3 (7-C), 147.7 (9-C), 149.0 (4-C), 162.7 (2-C). MS: m/z 452 $(M+H)^+$.
14. Körner, S.; Bryant-Friedrich, A.; Giese, B. *J. Org. Chem.* **1999**, *64*, 1559–1564.
15. For a typical procedure see Ref. 6. Physical data for compound **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 3H, 2-CH_3), 2.73 (dd, $J = 6.1$, 13.7 Hz, 1H, 2′-H^A), 3.01 (dd, $J = 9.0$, 13.7 Hz, 1H, 2′-H^B), 3.25 (d, $J = 5.1$ Hz, 3H, N–CH_3), 4.07–4.12 (m, 1H, 5′-H^A), 4.13–4.18 (m, 2H, 5′-H^B+4′-H), 5.29 (dd, $J = 6.1$, 9.0 Hz, 1H, 1′-H), 6.63 (br s, 1H, NH), 7.30–7.36, 7.46–7.53 (m, 5H, Ph), 7.91 (s, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5 (2-CH_3), 27.3 (N–CH_3), 49.1 (2′-C), 61.9 (5′-C), 70.7 (1′-C), 75.2 (3′-C), 86.5 (4′-C), 88.7, 122.4 (C≡C), 109.0 (8-C), 128.2 (C^{meta}), 128.5 (C^{para}), 131.8 (C^{ortho}), 144.5 (7-C), 145.5 (9-C), 149.1 (4-C), 164.0 (2-C). MS: m/z 380 $(M+H)^+$. Physical data for compound **2b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H, 2-CH_3), 2.62 (s, 1H, C≡CH), 2.65 (dd, $J = 5.9$, 13.9 Hz, 1H, 2′-H^A), 2.92 (dd, $J = 9.3$, 13.9 Hz, 1H, 2′-H^B), 3.24 (d, $J = 5.1$ Hz, 3H, N–CH_3), 3.95–4.02 (m, 1H, 5′-H^A), 4.07–4.12 (m, 2H, 5′-H^B+4′-H), 5.25 (dd, $J = 5.9$, 9.3 Hz, 1H, 1′-H), 6.62 (br s, 1H, NH), 7.89 (s, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5 (2-CH_3), 27.3 (N–CH_3), 48.8 (2′-C), 61.7 (5′-C), 70.6 (1′-C), 73.1, 83.7 (C≡C), 74.5 (3′-C), 86.3 (4′-C), 108.9 (8-C), 144.5 (7-C), 145.5 (9-C), 149.1 (4-C), 164.0 (2-C). MS: m/z 304 $(M+H)^+$.
16. For a typical procedure see Ref. 5. Physical data for compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, $J = 7.3$ Hz, 3H, 3′-CH_2CH_3), 1.76–1.88 (m, 1H, 3′-CH_2^A), 1.59–1.72 (m, 1H, 3′-CH_2^B), 2.35 (dd, $J = 7.6$, 13.4 Hz, 1H, 2′-H^A), 2.51 (dd, $J = 8.1$, 13.4 Hz, 1H, 2′-H^B), 2.53 (s, 3H, 2-CH_3), 3.21 (d, $J = 5.0$ Hz, 3H, N–CH_3), 3.71–3.76 (m, 1H, 5′-H^A), 3.93–4.00 (m, 2H, 5′-H^B+4′-H), 5.06 (t, $J = 7.9$ Hz, 1H, 1′-H), 6.81 (br s, 1H, NH), 7.84 (s, 1H, 7-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.3 (CH_3), 25.5 (2-CH_3), 27.3 (N–CH_3), 30.9 (3′-CH_2), 46.7 (2′-C), 63.0 (5′-C), 70.5 (1′-C), 81.7 (3′-C), 84.8 (4′-C), 110.0 (8-C), 144.3 (7-C), 145.5 (9-C), 149.1 (4-C), 163.7 (2-C). MS: m/z 308 $(M+H)^+$.
17. Fedorov, I. I.; Kazmina, E. M.; Novicov, N. A.; Gurskaya, G. V.; Bochkarev, A. V.; Jasko, M. V.; Victorova, L. S.; Kukhanova, M. K.; Balzarini, J.; De Clercq, E.; Krayevsky, A. A. *J. Med. Chem.* **1992**, *35*, 4567–4575.