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SYNTHESIS OF TRIAZOL C_n-RIBONUCLEOSIDE PHOSPHORAMIDITES USING β-RIBOFURANOSYL-C_n-ACETYLENES FOR RNA CATALYSIS PROBING

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Abstract – Novel C4-linked triazol C_0-, C_1- and C_2-ribonucleoside phosphoramidites for RNA catalysis probing were synthesized from β-ribofuranosyl-C_n-acetylenes (n = 0–2), which were efficiently prepared by fragmentation of tetrazoles derived from cyanophosphates. *N*-Pivaloyloxymethyl moiety was selected for the protection of triazole-*N*, whose properties under acidic and basic conditions were investigated.

INTRODUCTION

We have recently reported the efficient synthesis of C4-linked C_0- to C_3-imidazole ribonucleoside phosphoramidites [Imz-C_n-PAs (**1a**–**d**)], which could be introduced in RNA using solid-phase *t*-BDMS chemistry implemented on an automated synthesizer, as shown in Figure 1.[1] During the synthesis of these phosphoramidites, pivaloyloxymethyl (POM)[1b] and cyanoethyl (CE)[1c] groups were employed successfully as suitable protecting groups for the imidazole τ-nitrogen and sugar 2'-hydroxy functions, respectively. Since imidazoles (p*K*a of 14.2) are both good proton donors and acceptors,[2] we developed a novel chemogenetic approach using Imz-C_n-PAs **1** for the study of the catalytic mechanism of Varkud satellite (VS)[3a] and hairpin ribozymes,[3b] where conventional nucleobases are replaced by imidazoles as a powerful tool to probe general acid–base catalysis in the active sites of ribozymes.[4] The results from this approach indicated that the chemical mechanisms of VS and hairpin ribozymes involve general acid–base catalysis via a combination of specific adenine (A) and guanine (G) nucleobases (e.g., A756 and G638 in

the VS ribozyme).[1c,3] Of particular interest is the modified VS ribozyme (G638C_2Imz), obtained from a two-carbon-elongated homologue [Imz-C_2-PA (**1c**)], which shows significantly greater catalytic activity than G638C_0Imz, suggesting that the flexible C_2-methylene spacer is a better structural mimic of the purine nucleobase.[1c] However, it is impossible to determine by this approach which nucleobases function particularly as acids or bases when imidazole species are employed as nucleobases. On the other hand, tetrazoles with p*K*a of 4.9 are often used as metabolism-resistant isomeric replacements for carboxylic acids in medicinal chemistry.[5] Therefore, after preparation of ribose-$(CH_2)_n$-tetrazole (Tez) PAs **2a**–**c** (n = 0–2) (Figure 2–A),[6] C5-linked C_0- and C_2-tetrazoles were incorporated successfully into the VS ribozyme substrate to determine more specifically which nucleobases of the ribozyme function as general acids in the chemistry of the natural ribozyme.[6a] However, the tetrazole-containing VS ribozymes exhibited poor

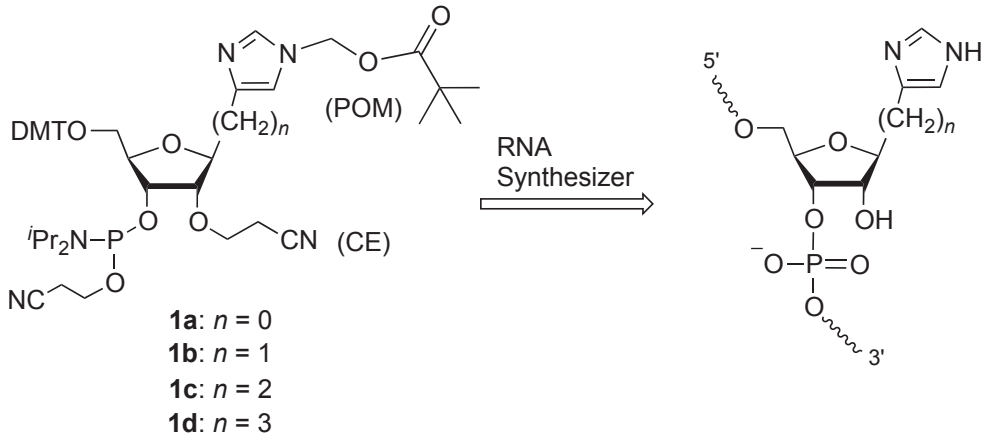


Figure 1. Incorporation of a C_n-imidazole to a ribozyme using PAs **1a**–**d** employing solid-phase RNA synthesis

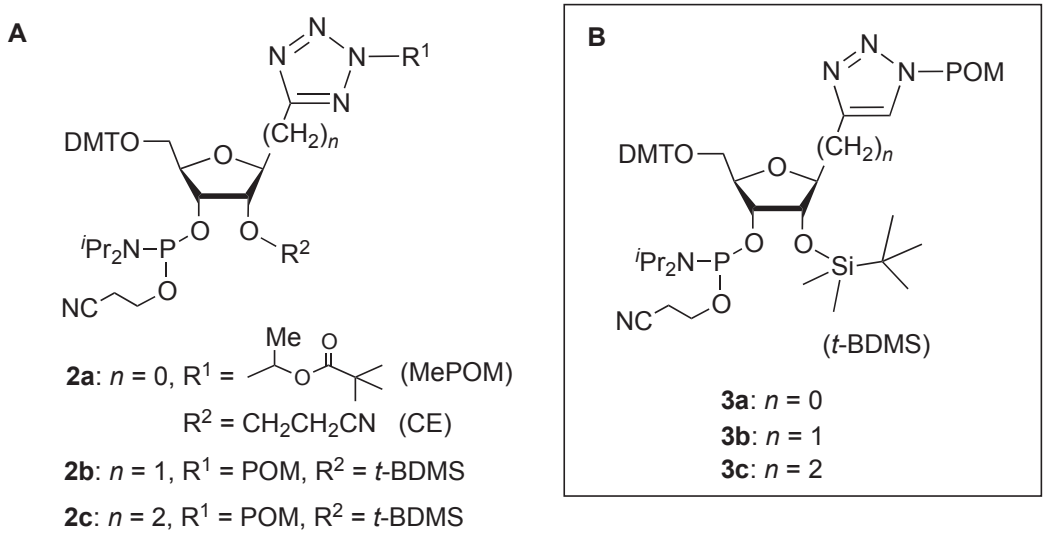
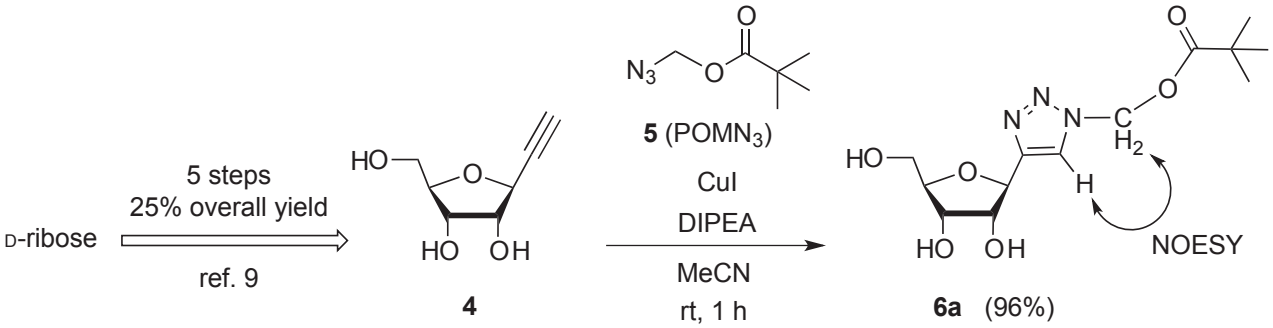


Figure 2. (A) Structure of C5-linked tetrazole-C_n-ribonucleoside PAs
(B) Structure of C4-linked triazole-C_n-ribonucleoside PAs

catalytic activity. This might be attributed to the potent acidic nature of tetrazoles, producing the corresponding salt between the tetrazole and nucleobase. With these results in hand, we directed our attention to 1,2,3-triazoles as alternative acid surrogates, since triazoles are less acidic (p*K*a of 9.3).[7] We herein describe the synthesis of novel C4-linked C_0-, C_1-, and C_2-triazole ribonucleoside PAs **3a**–**c** (Figure 2–B). In this study, β-ribofuranosyl-C_n-acetylenes **15a**–**c** (*n* = 0, 1, and 2) were employed as key intermediates, efficiently prepared by [1,2]-rearrangement of alkylidene carbenes generated upon fragmentation of tetrazoles derived from cyanophosphates.



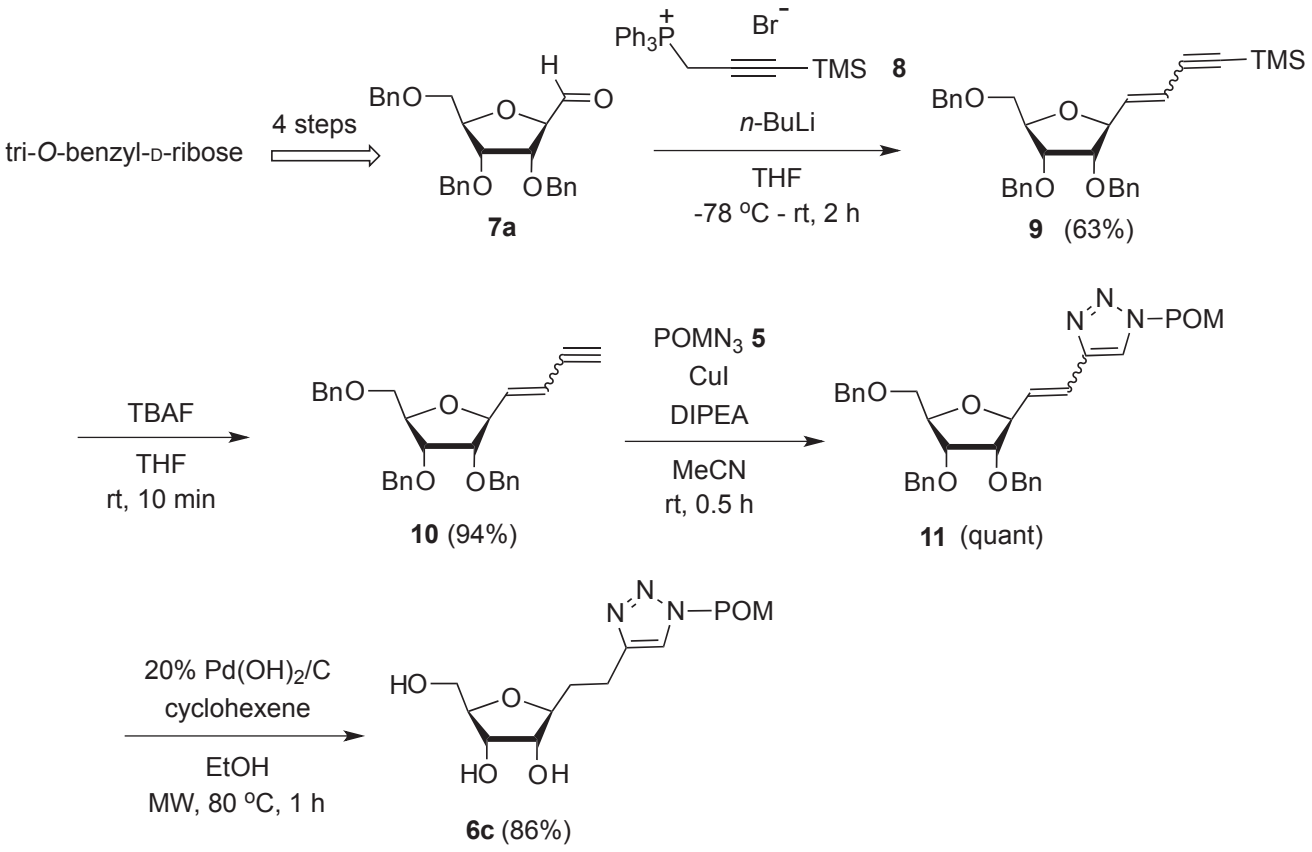
Scheme 1. Synthesis of *N*-POM protected triazole-C-nucleoside **6a** using 1-acetylenyl-β-D-ribofuranose **4**

RESULTS AND DISCUSSION

We first carried out a Huisgen 1,3-dipolar cycloaddition 'click' reaction[8] between 1-acetylenyl-β-D-ribofuranose **4**[9] and azidomethyl pivaloate ($POMN_3$, **5**)[10] for the construction of C4-linked 1,2,3-triazole-C-nucleoside **6a**, which is a key intermediate for C_0-triazole PA **3a** (Scheme 1). The terminal alkyne **4** was prepared through an alkynylglycosylation reaction reported by Lubin-Germain and co-workers,[9] starting from D-ribose, over five steps in 25% overall yield. The following Cu(I)-catalyzed [3+2] azide–alkyne cycloaddition (CuAAC) reaction[8] of alkyne **4** with $POMN_3$ **5** under standard CuI and diisopropylethylamine (DIPEA) conditions afforded the *N*-POM-protected triazole-C-nucleoside **6a** in 96% yield. The position of the POM group on the triazole-*N* was assigned as 1,4-disubstituted fashion by ^{13}C-NMR (δ: 125.6 ppm)[11] and ^{1}H-^{1}H NOESY analyses, as shown in Scheme 1.

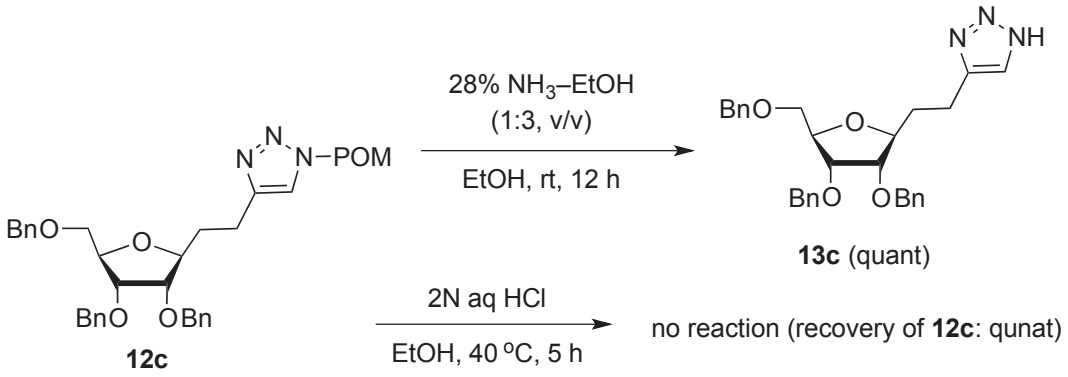
Alternatively, the corresponding triazole C_2-nucleoside **6c** was synthesized starting from D-ribofuranosyl carbaldehyde **7a**, prepared by our previously reported procedure[1c] in 52% overall yield from commercially available 2,3,5-tri-*O*-benzyl-D-ribose in four steps. Wittig olefination (63%) of **7a** using (3-trimethysilyl-2-propynyl)triphenylphosphonium bromide (**8**) followed by treatment with tetra-*n*-butylammonium fluoride (TBAF) provided three-carbon-elongated D-ribosyl-but-3-en-1-yne **10** (94%, *E*/*Z* = 3/2). Click reaction of the resulting terminal alkyne **10** with $POMN_3$ **5** afforded *N*-POM-vinyltriazole **11** quantitatively. Subsequent debenzylation and reduction of the double bond with

Pd(OH)$_2$-C/cyclohexene furnished *N*-POM-triazole-C$_2$-ribonucleoside **6c** (86%) in 51% overall yield from **7a**.



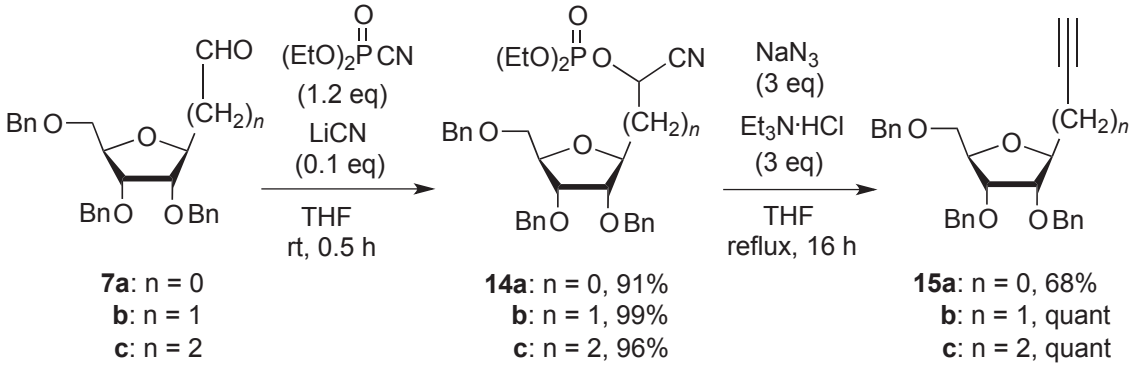
Scheme 2. Synthesis of *N*-POM-triazole C$_2$-ribonucleoside **6c** using D-ribosyl-but-3-en-1-yne **10** as an intermediate

Since there is limited literature information regarding *N*-POM azoles (see reference 12), we examined the use of POM as a protecting group for the triazole nitrogen during RNA synthesis by the *t*-BDMS approach.[13] Oligonucleotide base-protecting groups are conventionally removed in the final step of RNA synthesis by an ammonia and ethanol mixture [28% aq NH_3–EtOH (3:1, v/v)] at 60 °C for 16 h.[13] As shown in Scheme 3, the triazol-*N*-POM group of **12c** was quantitatively removed by aq NH_3–EtOH (1:3, v/v) at room temperature (rt) in 12 h affording a C$_2$-triazole **13c** (quant), which are faster and milder conditions than those of the standard deprotection procedure mentioned above.[1b] Therefore, this result confirmed POM as a suitable triazol-*N* protecting group for RNA synthesis.[12] In contrast, the *N*-POM groups of triazole C-nucleosides **12c** remained intact under 2*N* HCl–EtOH (1:2, v/v; 40 °C, 5 h) (Scheme 3). In addition, the *N*-POM groups of triazole C-nucleosides **12** tolerated satisfactorily the debenzylation–conditions using Pd(OH)$_2$-C/cyclohexene, as illustrated in Scheme 6 by the conversion of tribenzyl compounds **12** to triols **6**.



Scheme 3. Chemistry of *N*-POM triazole **12c** under acidic and basic conditions

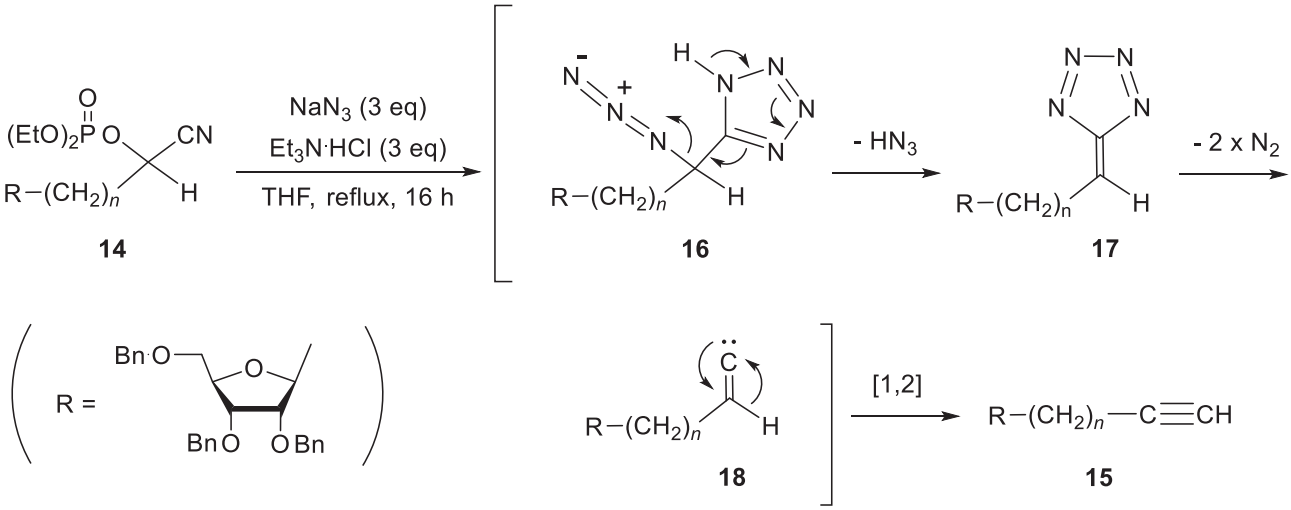
Although triazole C_0- and C_2-ribonucleosides **6a** and **6c** were successfully obtained as described above, the preparation of terminal acetylenes **4** and **10** was not so straightforward. Accordingly, a systematic approach to C_n-ribonucleoside acetylenes was required. If easy access to terminal alkynes **15** was made from β-D-ribofuranosyl-C_n-aldehydes **7**, triazole PAs **3** could be feasibly obtained by Huisgen 1,3-dipolar cycloaddition reactions between acetylenes **15** and $POMN_3$ **5**. Indeed, we have recently developed a novel transformation of carbonyl compounds into C_1-elongated alkyne homologs via cyanophosphates (CPs),[14a] which have been widely employed as synthetic intermediates in a variety of organic syntheses (Scheme 4).[15] In this work, reaction of aldehydes **7a**–**c** with diethyl phosphorocyanidate (DEPC, 1.2 equiv)[15] in the presence of LiCN (0.1 equiv) easily afforded CPs **14a**–**c** (91–99%).[16] Subsequent reaction of the CPs with NaN_3–Et_3N·HCl (3.0 equiv)[14b] in refluxing THF furnished alkynes **15a**–**c** (68% to quant.).[14a]



Scheme 4. Synthesis of terminal alkynes **15a**–**c** via cyanophosphates **14a**–**c** as intermediates

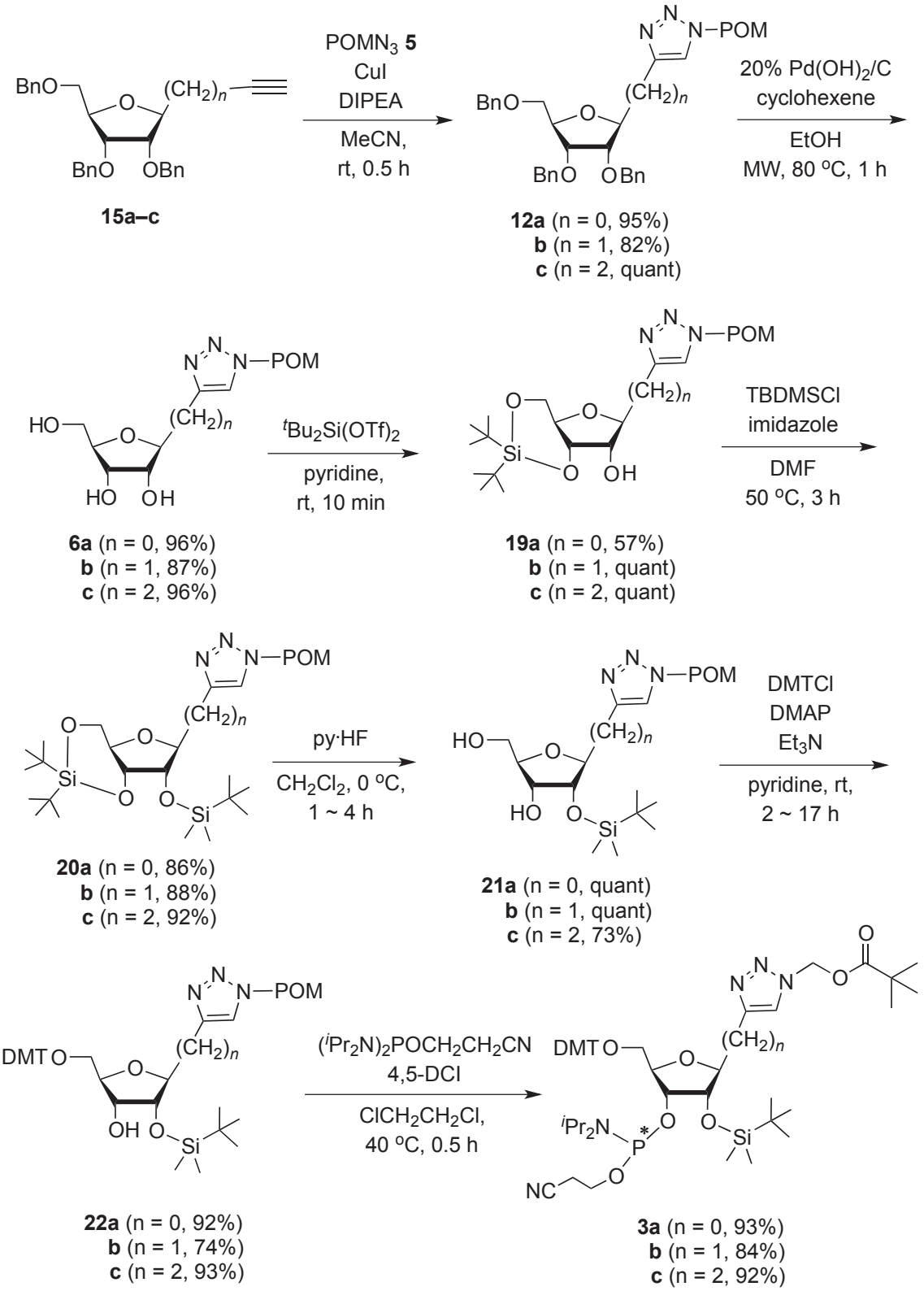
As a proposed mechanism for the alkyne formation, reaction of the CN moiety of CPs **14** with the azide source would generate azidotetrazoles **16**, as illustrated in Scheme 5.[14a] The resulting tetrazoles **16** would then spontaneously lead to alkynes **15** upon tetrazole–fragmentation: elimination of HN_3 from azidotetrazoles **16**, the formation of unstable tetraazafulvenes **17**, and loss of 2 moles of N_2 generating alkylidene carbenes **18**, which would finally undergo a [1,2]-rearrangement to furnish alkynes **15**.[14] These

reactions would take place under neutral conditions and could be successfully extended to obtain alkynes that are not usually accessible from the corresponding carbonyl compounds by the Ohira–Bestmann (dimethyl 1-diazo-2-oxopropylphosphonate/K_2CO_3/MeOH) or Shioiri [TMSC(Li)N_2] procedures, both of which require basic conditions.[14,17]



Scheme 5. Proposed mechanism for the formation of alkynes **15** mediated upon fragmentation of azidotetrazoles **16**

With the C_0-, C_1-, and C_2-ribonucleoside acetylenes **15a**–**c** in hand,[14a] we turned our attention to the synthesis of C_n-triazole-ribonucleoside PAs **3a**–**c** (n = 0–2), as shown in Scheme 6.[18] *N*-POM-1,2,3-triazole-C_n-nucleosides **12a**–**c** (82%–quant) were prepared via 1,3-dipolar cycloaddition of the terminal acetylenes **15** and $POMN_3$ **5**. Subsequent debenzylation of **12a**–**c** with $Pd(OH)_2$-C/cyclohexene under microwave (MW) irradiation furnished *N*-POM-triazole-C_n-nucleosides **6a**–**c** (87–96%).[6] 3',5'-*O*-Di-*tert*-butylsilanediyl (DTBS) protection of C-nucleosides **6a**–**c** afforded 3',5'-*O*-protected compounds **19a**–**c** (57%–quant), allowing for the selective introduction of 2'-hydroxy protecting groups. Silylation reaction of **19a**–**c** with *tert*-butyldimethylsilyl chloride (TBDMSCl) afforded fully protected intermediates **20a**–**c** (86–92%). The DTBS group of **20a**–**c** was selectively removed by treatment with pyridine·HF to give 3',5'-unprotected ribonucleoside derivatives **21a**–**c** (73%–quant). After dimethoxytritylation under standard conditions, the 3'-hydroxy groups of derivatives **22a**–**c** (74–93%) were subjected to phosphitylation. Treatment of **22a**–**c** with 2-*O*-cyanoethyl- *N*,*N*,*N'*,*N'*-tetraisopropylphosphordiamidite in the presence of 4,5-dicyanoimidazole (4,5-DCI) in dichloromethane proceeded smoothly at 40 °C for 0.5 h to afford the final product C4-linked-C_n-triazole PAs **3a**–**c** (84–93%). Among them, the crude PA **3a** (n = 0) was subjected to chromatography on basic(NH)-silica gel affording **3a** (93%) as a diastereomeric mixture, which could be partially resolved. ^{31}P-NMR analysis of **3a** revealed two P-diastereomers at δ



Scheme 6. Synthesis of C_0-, C_1-, and C_2-triazole-ribonucleoside PAs **3a**–**c** from terminal acetylenes **15**

148.9 and 150.7 ppm ($CDCl_3$). We have recently reported a reliable MS analysis of nucleoside PAs using a matrix system [triethanolamine (TEOA)-NaCl] on a liquid secondary ion (LSI) MS or fast atom bombardment (FAB) MS instrument equipped with a double-focusing mass spectrometer.[19] The present method provided a consistent composition formula {$C_{49}H_{70}N_5O_9PSi$+Na [$(M+Na)^+$]; calculated: 954.4578, found 954.4574}. In a similar manner, the structures of **3b** and **3c** were characterized by ^{31}P-NMR and MS analyses. In addition, purified triazole PAs **3a**–**c** could be stored in a vial for at least one year at -20 ^oC without significant spectral changes. Subsequent studies on triazole-modified VS and hairpin ribozymes using triazole PAs **3a**–**c** are underway in our laboratory and will be published in due course.

EXPERIMENTAL

Reactions with air- and moisture-sensitive compounds were carried out under Argon atmosphere. MW-assisted reactions were performed in a Milestone MultiSYNTH multimodal reactor with thermal control. Anhydrous solvents were purchased from WAKO Chemical Co. All solvents were removed in a rotary evaporator under reduced pressure. Fuji Silysia FL-60D silica gel was used for flash column chromatography and Chromatorex NH-DM 1020 (Fuji Silysia Chemical Ltd.) was used for basic (NH) silica gel chromatography. TLC was performed on pre-coated TLC plates (Merck $60F_{254}$). ^{1}H- and ^{13}C-NMR spectra were measured using tetramethylsilane (TMS) as the internal standard on Varian Mercury-300 or Agilent 400-MR-DD2 spectrometers. The coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{31}P-NMR spectra were recorded at 121 MHz (Varian Mercury-300) and the chemical shifts were measured relative to 85% H_3PO_4 as the external standard. High resolution MS analysis was performed on a JMS-700(2) double-focusing magnetic sector mass spectrometer (JEOL Ltd., Tokyo, Japan) in positive ion mode with 3-nitrobenzylalcohol (NBA) or triethanolamine (TEOA)-NaCl as the matrix.[19] IR spectra were recorded on a Shimadzu IR-435 spectrometer.

Synthesis of triazole C-nucleoside 6a (Scheme 1)

[4-(β-D-Ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (6a)

$POMN_3$ **5** (28 mg, 0.18 mmol), CuI (86 mg, 0.45 mmol), and DIPEA (58 mg, 0.45 mmol) were added to a solution of **4** (24 mg, 0.15 mmol) in MeCN (2 mL). After stirring at rt for 1 h, the volatiles were removed to obtain a residue, which was then purified by column chromatography on silica gel (MeOH/AcOEt = 5:95, v/v) to give **6a** (45 mg, 96%) as a colorless oil.

^{1}H-NMR (CD_3OD): δ 1.17 (s, 9H), 3.65 (dd, J = 12.0, 4.4 Hz, 1H), 3.77 (dd, J = 12.0, 3.6 Hz, 1H), 3.97 (ddd, J = 4.8, 4.4, 3.6 Hz, 1H), 4.11 (t-like, J = 4.8 Hz, 1H), 4.18 (t-like, J = 5.6 Hz, 1H), 4.90 (d, J = 5.6 Hz, 1H), 6.31 (s, 2H), 8.16 (s, 1H) ppm; ^{13}C-NMR (CD_3OD): δ 27.1, 39.7, 63.3, 71.3, 72.5, 77.3, 78.2, 86.4, 125.6, 148.7, 178.5 ppm; HRMS (FABMS: NBA) calcd for $C_{13}H_{22}N_3O_6$ [$(M+H)^+$] 316.1508, found

316.1501.

Synthesis of triazole C_2-nucleoside 6c (Scheme 2)

[(2,3,5-Tri-*O*-benzyl-*β*-D-ribofuranosyl)-but-3-en-1-yn-1-yl]trimethylsilane (9)

A 1.6 M *n*-BuLi solution in hexane (6.4 mL, 10.3 mmol) was added dropwise over a period of 20 min to a solution of (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide **8** (4.90 g, 10.8 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for 30 min at the same temperature, and a solution of aldehyde **7a** (4.06 g, 9.4 mmol) in THF (20 mL) was added dropwise over a period of 20 min. The reaction mixture was allowed to warm up to rt and further stirred for 2 h. The reaction was quenched upon addition of water (1 mL) and the volatiles were then evaporated. The obtained residue was purified by column chromatography on silica gel (AcOEt/hexane = 5:95) to give a 3:2 mixture (3.12 g, 63%) of the (*E*)- and (*Z*)-isomers of **9** as a colorless oil. The 3:2 ratio of the *E* and *Z* isomers of **9** was assigned based on the following ^{1}H-NMR data.

^{1}H-NMR ($CDCl_3$): δ 0.18 (s, 3.6H), 0.19 (s, 5.4H), 3.47–3.57 (m, 1.4H), 3.66–3.71 (m, 1H), 3.77 (dd, J = 5.2, 3.2 Hz, 0.4), 3.88–3.95 (m, 1H), 4.20–4.25 (m, 1H), 4.38 (d, J = 12.0 Hz, 0.4H), 4.47–4.60 (m, 6H), 4.82 (d, J = 12.0 Hz, 0.4H), 5.17 (ddd, J = 8.8, 2.8, 0.8 Hz, 0.4H), 5.60 (ddd, J = 10.8, 0.8, 0.4 Hz, 0.4H), 5.86 (dd, J = 16.0, 1.2 Hz, 0.6H), 5.87 (dd, J = 10.8, 8.8 Hz, 0.4H), 6.13 (dd, J = 16.0, 6.0 Hz, 0.6H), 7.22 (m, 15H) ppm; ^{13}C-NMR ($CDCl_3$): δ -0.1, 69.5, 70.2, 71.3, 71.9, 72.0, 72.3, 73.3, 73.4, 77.4, 77.6, 80.4, 80.9, 80.9, 81.3, 81.4, 95.6, 100.7, 101.7, 103.1, 111.2, 111.6, 127.5, 127.5, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.2, 128.3, 128.3, 128.3, 128.4, 137.6, 137.7, 137.7, 137.8, 138.0, 138.2, 142.2, 142.3 ppm; HRMS (FABMS: TEOA+NaCl): calcd for $C_{33}H_{38}O_4Si$+Na [$(M+Na)^+$] 549.2438, found 549.2440.

(2,3,5-Tri-*O*-benzyl-*β*-D-ribofuranosyl)-but-3-en-1-yne (10)

A 1.0 M TBAF solution in THF (8.9 mL, 8.9 mmol) was added to a solution of **9** (3.12 g, 5.9 mmol) in THF (10 mL) at rt, and the resulting mixture was stirred for 10 min. AcOEt (100 mL) was added to the mixture, which was subsequently washed with H_2O (50 mL). The organic layers dried over Na_2SO_4, and filtrated off were then evaporated. The residual oil was purified by column chromatography (AcOEt/hexane = 10:90) to afford **10** (2.53 g, 94%) as an oil, which could be partially isolated.

***E*-10**

^{1}H-NMR ($CDCl_3$): δ 2.91 (d, J = 2.4 Hz, 1H), 3.50 (dd, J = 10.4, 4.0 Hz, 1H), 3.55 (dd, J = 10.4, 4.0 Hz, 1H), 3.69 (dd, J = 6.0, 5.2 Hz, 1H), 3.90 (t, J = 4.8 Hz, 1H), 4.23 (q, J = 4.0 Hz, 1H), 4.46–4.60 (m, 7H), 5.82 (ddd, J = 16.0, 2.4, 1.6 Hz, 1H), 6.18 (dd, J = 16.0, 7.0 Hz, 1H), 7.26–7.36 (m, 15H) ppm; ^{13}C-NMR ($CDCl_3$): δ 70.1, 72.0, 72.3, 73.4, 77.3, 78.3, 80.8, 81.3, 81.5, 81.6, 110.7, 127.6, 127.6, 127.8, 127.9, 127.9, 128.0, 128.4, 128.4, 137.6, 137.7, 138.0, 143.0 ppm; HRMS (FABMS: TEOA+NaCl): calcd for $C_{30}H_{30}O_4$+Na [$(M+Na)^+$] 477.2042, found 477.2044.

***Z*-10**

^{1}H-NMR ($CDCl_3$): δ 3.22 (dd, J = 2.4, 0.8 Hz, 1H), 3.52 (dd, J = 10.8, 4.0 Hz, 1H), 3.63 (dd, J = 10.8, 3.2 Hz, 1H), 3.78 (t, J = 5.2 Hz, 1H), 3.93 (dd, J = 6.4, 5.2 Hz, 1H), 4.21–4.25 (m, 1H), 4.43–4.61 (m, 5H), 4.73 (d, J = 12.0 Hz, 1H), 5.11 (ddd, J = 8.8, 4.4, 0.8 Hz, 1H), 5.58 (dq, J = 11.2, 1.2 Hz, 1H), 5.93 (ddd, J = 11.2, 8.8, 0.8 Hz, 1H), 7.24–7.38 (m, 15H) ppm; ^{13}C-NMR ($CDCl_3$): δ 69.7, 71.6, 72.0, 73.4, 77.6, 79.3, 79.9, 80.9, 81.2, 84.0, 110.7, 127.5, 127.7, 127.7, 127.9, 128.0, 128.3, 137.8, 137.8, 138.2, 143.3 ppm; HRMS (FABMS: TEOA+NaCl): calcd for $C_{30}H_{30}O_4$+Na [$(M+Na)^+$] 477.2042, found 477.2044.

{4-[2-(2,3,5-Tri-*O*-benzyl-*β*-D-ribofuranosyl)vinyl]-triazol-1-yl}methyl-2,2-dimethylpropionate (11)

A mixture of **10** (2.50 g, 5.50 mmol), $POMN_3$ **5** (1.0 mL, 6.60 mmol), CuI (2.09 g, 11.00 mmol), and DIPEA (2.80 mL, 16.50 mmol) in MeCN (12 mL) was stirred at rt for 0.5 h. The volatiles were evaporated and the obtained residue was partitioned between AcOEt and H_2O (each 120 mL). The organic layer was further washed with aq. NH_4Cl, dried, and evaporated to afford a residue, which was then purified using column chromatography (AcOEt/hexane = 15:85) to yield **11** (3.52 g, quant) as an oil. The *E* and *Z* isomers of **11** could be partially isolated.

***E*-11**

^{1}H-NMR ($CDCl_3$): δ 1.19 (s, 9H), 3.56 (dd, J = 10.4, 4.0 Hz, 1H), 3.61 (dd, J = 10.4, 4.0 Hz, 1H), 3.80 (t, J = 5.2 Hz, 1H), 3.97 (t, J = 5.2 Hz, 1H), 4.27 (dd, J = 8.8, 4.0 Hz, 1H), 4.49–4.67 (m, 7H), 6.17 (d, J = 11.8 Hz, 1H), 6.21 (d, J = 11.8 Hz, 1H), 6.44 (dd, J = 16.0, 6.8 Hz, 1H), 6.70 (dd, J = 16.0, 1.2 Hz, 1H), 7.25–7.36 (m, 15H), 7.54 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ 26.8, 38.8, 69.5, 70.2, 72.0, 72.2, 73.4, 77.4, 81.2, 81.4, 119.8, 121.9, 127.6, 127.6, 127.8, 127.9, 128.0, 128.4, 130.8, 137.7, 137.8, 138.1, 145.7, 177.8 ppm; HRMS (FABMS: NBA): calcd for $C_{36}H_{42}N_3O_6$ [$(M+H)^+$] 612.3073, found 612.3071.

***Z*-11**

^{1}H-NMR ($CDCl_3$): δ 1.16 (s, 9H), 3.54 (dd, J = 10.4, 4.0 Hz, 1H), 3.58 (dd, J = 10.4, 4.0 Hz, 1H), 3.88 (t, J = 5.6 Hz, 1H), 4.02 (t, J = 4.8 Hz, 1H), 4.27 (q, J = 4.0 Hz, 1H), 4.49–4.64 (m, 5H), 4.72 (d, J = 12.0 Hz, 1H), 5.10 (ddd, J = 8.4, 6.0, 1.2 Hz, 1H), 5.75 (dd, J = 11.6, 8.8 Hz, 1H), 6.11 (d, J = 10.4 Hz, 1H), 6.16 (d, J = 10.4 Hz, 1H), 6.61 (dd, J = 11.6, 1.2 Hz, 1H), 7.25-7.36 (m, 15H), 8.04 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ 26.8, 38.7, 69.7, 70.1, 72.0, 73.4, 77.8, 81.6, 82.0, 120.7, 124.1, 127.5, 127.6, 127.7, 127.7, 127.9, 128.0, 128.3, 128.3, 132.0, 137.9, 137.9, 138.1, 144.2, 177.4 ppm; HRMS (FABMS: NBA): calcd for $C_{36}H_{42}N_3O_6$ [$(M+H)^+$] 612.3073, found 612.3071.

{4-[(*β*-D-Ribofuranosyl)ethyl]-triazol-1-yl}methyl 2,2-dimethylpropionate (6c)

A mixture of **11** (611 mg, 1.0 mmol), 20% $Pd(OH)_2/C$ (360 mg), and cyclohexene (3.0 mL, 30.0 mmol) in EtOH was exposed to MW irradiation at 100 °C for 1 h.[6] After filtration through Celite, the filtrates were evaporated to give a residue, which was purified by column chromatography on silica gel (AcOEt) to afford **6c** (295 mg, 86%) as an oil.

^{1}H-NMR (CD_3OD): δ 1.16 (s, 9H), 1.80–1.90 (m, 1H), 1.95–2.05 (m, 1H), 2.77–2.94 (m, 2H), 3.56 (dd, J = 12.0, 4.8 Hz, 1H), 3.67 (dd, J = 12.0, 3.6 Hz, 1H), 3.70–3.75 (m, 2H), 3.78 (dd, J = 8.4, 4.8 Hz, 1H), 3.93 (t, J = 4.8 Hz, 1H), 6.27 (s, 2H), 7.90 (s, 1H) ppm; ^{13}C-NMR (CD_3OD): δ 22.6, 27.2, 34.2, 39.7, 63.6, 71.2, 72.9, 76.3, 83.0, 85.8, 124.4, 149.2, 178.5 ppm; HRMS (FABMS: NBA): calcd for $C_{15}H_{26}N_3O_6$ [$(M+H)^+$] 344.1821, found 344.1819.

Synthesis of C_0-, C_1- and C_2-triazole ribonucleoside PAs 3a–c (Scheme 6)

[4-(2,3,5-*O*-Tribenzyl-β-D-ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (12a)

$POMN_3$ **5** (0.34 mL, 2.24 mmol), CuI (711 mg, 3.74 mmol), and DIPEA (0.95 mL, 5.61 mmol) were added to a solution of compound **15a**[14a] (800 mg, 1.87 mmol) in MeCN (20 mL). After stirring at rt for 0.5 h, the volatiles were evaporated to afford a residue, which was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to give **12a** (1043 mg, 95%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 9H), 3.59 (dd, J = 10.8, 4.0 Hz, 1H), 3.73 (dd, J = 10.8, 3.6 Hz, 1H), 4.03 (dd, J = 6.4, 5.2 Hz, 1H), 4.26 (dd, J = 4.8, 4.4 Hz, 1H), 4.30–4.35 (m, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 5.27 (d, J = 4.0 Hz, 1H), 5.98 (d, J = 10.4 Hz, 1H), 6.07 (d, J = 10.4 Hz, 1H), 7.25–7.36 (m, 15H), 7.73 (s, 1H) ppm; ^{13}C-NMR (CD_3OD): δ 26.8, 38.7, 69.5, 69.7, 72.0, 73.4, 76.9, 80.8, 80.8, 123.9, 127.7, 127.7, 127.8, 127.8, 127.9, 128.1, 128.3, 128.3, 128.4, 137.7, 137.8, 138.1, 148.1, 177.4 ppm; HRMS (FABMS: NBA): calcd for $C_{34}H_{40}N_3O_6$ [$(M+H)^+$] 586.2917, found 586.2917.

[4-(β-D-Ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (6a)

A mixture of **12a** (585 mg, 1.0 mmol), 20% $Pd(OH)_2$/C (360 mg), and cyclohexene (3.0 mL, 30.0 mmol) in EtOH (7 mL) was exposed to MW irradiation at 80 °C for 1 h.[6] After filtration through Celite, the filtrates were evaporated to give a residue, which was purified by column chromatography on silica gel (AcOEt) to give **6a** (302 mg, 96 %) as an oil.

[4-(3,5-*O*-DTBS-β-D-ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (19a)

Triol **6a** (150 mg, 0.48 mmol) was co-evaporated three times with pyridine (1 mL) and then redissolved in pyridine (2 mL). DTBS-bis-trifluoromethanesulfonate (0.16 mL, 0.48 mmol) was added dropwise to the solution, and the resulting mixture was stirred at rt for 10 min, followed by evaporation. The residual oil was purified by column chromatography (AcOEt/hexane = 2:8) to give **19a** (124 mg, 57%) as an amorphous solid.

^{1}H-NMR ($CDCl_3$): δ 1.05 (s, 9H), 1.07 (s, 9H), 1.19 (s, 9H), 2.78 (brs, 1H), 3.98 (t-like, J = 8.8 Hz, 1H), 4.08 (ddd, J = 10.4, 9.2, 4.8 Hz, 1H), 4.16 (dd, J = 9.2, 4.8 Hz, 1H), 4.45 (dd, J = 8.8, 4.4 Hz, 1H), 4.54 (d, J = 4.8 Hz, 1H), 5.14 (s, 1H), 6.20 (d, J = 14.4 Hz, 1H), 6.23 (d, J = 14.4 Hz, 1H), 7.76 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ 20.3, 22.6, 26.7, 27.2, 27.3, 38.7, 67.9, 69.5, 74.3, 74.4, 77.5, 80.2, 123.2, 147.0, 177.7 ppm; HRMS (FABMS: NBA): calcd for $C_{21}H_{38}N_3O_6Si$ [$(M+H)^+$] 456.2530, found 456.2531.

[4-(3,5-*O*-DTBS-2-*O*-TBDMS-β-D-ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (20a)

Imidazole (92 mg, 1.35 mmol) and TBDMSCl (122 mg, 0.81 mmol) were added to a solution of **19a** (121 mg, 0.27 mmol) in DMF (3 mL). The mixture was stirred at 50 ºC for 3 h, and then AcOEt (100 mL) was added to the mixture, which was subsequently washed with H_2O (10 mL × 5), dried over Na_2SO_4, and filtrated off. The volatiles were then evaporated. The residual oil was purified by column chromatography (AcOEt/hexane = 10:90) to give **20a** (133 mg, 86%) as an amorphous solid.

^{1}H-NMR ($CDCl_3$): δ 0.13 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 1.04 (s, 18H), 1.18 (s, 9H), 3.90 (dd, J = 10.4, 9.2 Hz, 1H), 3.97 (dd, J = 9.6, 4.4 Hz, 1H), 4.13 (ddd, J = 10.4, 9.6, 5.2 Hz, 1H), 4.45 (dd, J = 9.2, 5.2 Hz, 1H), 4.52 (d, J = 4.4 Hz, 1H), 5.02 (s, 1H), 6.20 (d, J = 13.2 Hz, 1H), 6.22 (d, J = 13.2 Hz, 1H), 7.68 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ -5.0, -4.3, 18.3, 20.3, 22.7, 26.0, 26.8, 27.1, 27.4, 38.7, 68.4, 69.5, 74.0, 76.0, 77.3, 82.3, 122.8, 148.1, 177.7 ppm; HRMS (FABMS: NBA): calcd for $C_{27}H_{52}N_3O_6Si_2$ [$(M+H)^+$] 570.3395, found 570.3399.

[4-(2-*O*-TBDMS-β-D-ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (21a)

A solution of 65% HF·pyridine (30 μL) in pyridine (0.6 mL) was added dropwise over 5 min to a solution of **20a** (125 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) at 0 ºC. The mixture was stirred at 0 ºC for 4 h and then diluted with CH_2Cl_2. The resulting mixture was washed with saturated aq. $NaHCO_3$, dried over Na_2SO_4, and filtrated off. The volatiles were then evaporated. The residue was purified by column chromatography (AcOEt/hexane = 10:90 to 70:30) to give **21a** (94 mg, quant) as an oil.

^{1}H-NMR (CD_3OD): δ -0.10 (s, 3H), -0.01 (s, 3H), 0.85 (s, 9H), 1.17 (s, 9H), 3.66 (dd, J = 12.0, 4.0 Hz, 1H), 3.78 (dd, J = 12.0, 3.6 Hz, 1H), 3.98 (q-like, J = 4.0 Hz, 1H), 4.08 (t-like, J = 5.6 Hz, 1H), 4.31 (dd, J = 6.8, 5.6 Hz, 1H), 4.88 (d, J = 6.8 Hz, 1H), 6.29 (d, J = 10.8 Hz, 1H), 6.32 (d, J = 10.8 Hz, 1H), 8.18 (s, 1H) ppm; ^{13}C-NMR (CD_3OD): δ -4.7, -4.7, 19.0, 26.3, 27.2, 39.7, 63.3, 71.2, 72.9, 78.1, 79.1, 87.1, 126.1, 148.2, 178.4 ppm; HRMS (FABMS: NBA): calcd for $C_{19}H_{36}N_3O_6Si$ [$(M+H)^+$] 430.2373, found 430.2373.

[4-(5-*O*-DMT-2-*O*-TBDMS-β-D-ribofuranosyl)triazol-1-yl]methyl 2,2-dimethylpropionate (22a)

Compound **21a** (90 mg, 0.21 mmol) was co-evaporated three times with pyridine (1 mL) and redissolved in dry pyridine (3 mL). DMTCl (108 mg, 0.32 mmol), Et_3N (44 μL, 0.32 mmol) and DMAP (2 mg, 0.02 mmol) were added to the pyridine solution, and the mixture was stirred at rt for 2 h. MeOH (1 mL) was added to the mixture and the volatiles were evaporated to give a residue, which was then subjected to chromatography on a silica gel column (AcOEt/hexane = 20:80 to 30:70) to give **22a** (141 mg, 92%) as an amorphous solid.

^{1}H-NMR ($CDCl_3$): δ -0.01 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.15 (s, 9H), 2.70 (d, J = 4.8 Hz, 1H), 3.24 (dd, J = 10.0, 4.0 Hz, 1H), 3.42 (dd, J = 10.0, 2.8 Hz, 1H), 3.79 (s, 6H), 4.10–4.14 (m, 2H), 4.58 (t-like, J = 5.6 Hz, 1H), 5.00 (d, J = 5.6 Hz, 1H), 6.12 (d, J = 11.6 Hz, 1H), 6.14 (d, J = 11.6 Hz, 1H), 6.81–6.84

(m, 4H), 7.18–7.29 (m, 3H), 7.33–7.38 (m, 4H), 7.45–7.48 (m, 2H), 7.80 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$) δ -5.2, -4.7, 17.9, 25.7, 26.7, 38.7, 55.1, 63.8, 69.6, 72.4, 77.1, 83.7, 86.1, 113.1, 123.8, 126.7, 127.7, 128.2, 130.1, 135.9, 135.9, 144.8, 147.4, 158.4, 177.4 ppm; IR (film, cm^{-1}) 1740, 3280–3560; HRMS (FABMS: TEOA+NaCl): calcd for $C_{40}H_{53}N_3O_8Si$+Na [$(M+Na)^+$] 754.3500, found 754.3497.

[4-{5-*O*-DMT-2-*O*-TBDMS-3-*O*-(2-cyanoethoxy-*N,N*-diisopropylaminophosphino)-β-D-ribofuranosyl}-triazol-1-yl]methyl 2,2-dimethylpropionate (3a)

Compound **22a** (141 mg, 0.19 mmol) was dissolved in dry CH_2Cl_2 (4 mL), to which 4,5-DCI (27 mg, 0.23 mmol) and 2-cyanoethyl-*N,N,N',N'*-tetraisopropylphosphordiamidite (120 μL, 0.38 mmol) were added. The resulting mixture was stirred at 40 ºC for 30 min, after which the volatiles were evaporated. The residual oil was subjected to chromatography on NH-silica gel (AcOEt/hexane = 20:80) to give PA **3a** (165 mg, 93%) as an amorphous solid. The ca. 1:1 mixture of diastereomers of **3a** could be partially isolated.

3a (less polar: R_f = 0.34, AcOEt/hexane = 20:80)

^{1}H-NMR ($CDCl_3$): δ -0.07 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 1.13–1.16 (m, 21H), 2.25–2.29 (m, 2H), 3.14 (dd, J = 10.4, 4.0 Hz, 1H), 3.49 (dd, J = 10.4, 2.8 Hz, 1H), 3.53–3.67 (m, 4H), 3.79 (s, 6H), 4.21–4.25 (m, 1H), 4.29–4.32 (m, 1H), 4.55 (dd, J = 6.0, 4.8 Hz, 1H), 5.03 (d, J = 6.0 Hz, 1H), 6.10 (d, J = 10.8 Hz, 1H), 6.15 (d, J = 10.8 Hz, 1H), 6.82–6.85 (m, 4H), 7.19–7.30 (m, 3H), 7.35–7.40 (m, 4H), 7.47–7.49 (m, 2H), 7.82 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ -4.9, -4.6, -4.6, 18.0, 19.9, 20.0, 24.6, 24.6, 24.7, 24.7, 25.8, 26.8, 38.7, 43.2, 43.3, 55.2, 57.5, 57.7, 63.5, 69.8, 74.1, 74.2, 77.2, 83.3, 86.1, 110.0, 113.1, 113.1, 117.3, 123.8, 126.7, 127.8, 128.3, 130.2, 130.2, 136.0, 136.1, 144.9, 147.9, 158.4, 177.5 ppm; ^{31}P-NMR ($CDCl_3$): δ 150.7 ppm; IR (film, cm^{-1}) 1740, 2240; HRMS (FABMS: TEOA+NaCl): calcd for $C_{49}H_{70}N_5O_9PSi$+Na [$(M+Na)^+$] 954.4578, found 954.4574.

3a' (more polar: R_f = 0.33, AcOEt/hexane = 20:80)

^{1}H-NMR ($CDCl_3$): δ -0.07 (s, 3H), -0.01 (s, 3H), 0.84 (s, 9H), 0.99 (d, J = 6.8 Hz, 6H), 1.13–1.16 (m, 15H), 2.55–2.71 (m, 2H), 3.16 (dd, J = 10.0, 2.8 Hz, 1H), 3.43 (dd, J = 10.0, 2.8 Hz, 1H), 3.51–3.62 (m, 2H), 3.73–3.97 (m, 8H), 4.23–4.29 (m, 2H), 4.57 (dd, J = 6.8, 4.4 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 6.09 (d, J = 10.8 Hz, 1H), 6.15 (d, J = 10.8 Hz, 1H), 6.81–6.85 (m, 4H), 7.18–7.29 (m, 3H), 7.34–7.38 (m, 4H), 7.46–7.48 (m, 2H), 7.82 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ -4.9, -4.6, -4.6, 18.1, 20.4, 20.4, 24.5, 24.5, 24.6, 24.6, 25.7, 25.8, 26.8, 38.7, 42.8, 42.9, 55.2, 58.5, 58.7, 63.5, 69.8, 73.5, 73.6, 76.8, 77.2, 83.1, 83.1, 86.2, 110.0, 113.1, 113.1, 117.7, 123.9, 126.7, 127.8, 128.2, 130.1, 130.2, 135.8, 135.9, 144.8, 147.7, 158.4, 177.4 ppm; ^{31}P-NMR ($CDCl_3$): δ 148.9 ppm; IR (film, cm^{-1}): 1740, 2240; HRMS (FABMS: TEOA+NaCl): calcd for $C_{49}H_{70}N_5O_9PSi$+Na [$(M+Na)^+$] 954.4578, found 954.4584.

{4-[(2,3,5-*O*-Tribenzyl-β-D-ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (12b)

$POMN_3$ **5** (0.27 mL, 1.79 mmol), CuI (566 mg, 2.98 mmol), and DIPEA (0.76 mL, 4.47 mmol) were

added to a solution of compound **15b**[14a] (800 mg, 1.87 mmol) in MeCN (20 mL). After stirred at rt for 0.5 h, the volatiles were evaporated. The obtained residue was purified by column chromatography on silica gel using AcOEt/hexane (1:4) to give **12b** (749 mg, 82%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H), 2.95 (dd, J = 15.6, 6.8 Hz, 1H), 3.08 (dd, J = 15.6, 4.8 Hz, 1H), 3.46 (dd, J = 10.4, 4.0 Hz, 1H), 3.51 (dd, J = 10.4, 4.0 Hz, 1H), 3.70 (t, J = 5.6 Hz, 1H), 3.78 (t, J = 5.2 Hz, 1H), 4.18 (dd, J = 8.8, 4.0 Hz, 1H), 4.25–4.31 (m, 1H), 4.45–4.58 (m, 6H), 5.96 (d, J = 10.8 Hz, 1H), 6.04 (d, J = 10.8 Hz, 1H), 7.24–7.36 (m, 15H), 7.60 (s, 1H) ppm; ^{13}C-NMR (CD_3OD): δ 26.8, 29.7, 38.7, 69.5, 70.1, 71.9, 72.0, 73.3, 77.1, 77.2, 79.7, 79.9, 81.2, 123.8, 127.5, 127.6, 127.8, 128.0, 128.1, 128.3, 128.3, 128.4, 137.8, 138.1, 144.5, 177.5 ppm; HRMS (FABMS: NBA): calcd for $C_{35}H_{42}N_3O_6$ [$(M+H)^+$] 600.3074, found 600.3073.

{4-[(*β*-D-Ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (6b)

A mixture of **12b** (749 mg, 1.22 mmol), 20% $Pd(OH)_2$/C (450 mg), and cyclohexene (3.7 mL, 30.0 mmol) in EtOH (6 mL) was exposed to MW irradiation at 100 ºC for 1 h. After filtration through Celite, the filtrate volatiles were evaporated to give a residue, which was then purified by column chromatography on silica gel using AcOEt to give **6b** (351 mg, 87 %) as an oil.

^{1}H-NMR (300 MHz, CD_3OD): δ 1.17 (s, 9H), 2.91 (dd, J = 15.3, 7.5 Hz, 1H), 3.07 (dd, J = 15.3, 4.5 Hz, 1H), 3.52 (dd, J = 12.0, 5.1 Hz, 1H), 3.63 (dd, J = 12.0, 3.3 Hz, 1H), 3.72–3.86 (m, 3H), 3.92–4.00 (m, 1H), 6.27 (s, 1H), 7.97 (s, 1H) ppm; ^{13}C-NMR (75.5 MHz, CD_3OD): δ 27.2, 30.2, 39.7, 63.4, 71.1, 72.6, 75.5, 82.9, 85.6, 125.7, 146.0, 178.5 ppm; HRMS (FABMS: NBA): calcd for $C_{14}H_{24}N_3O_6$ [$(M+H)^+$] 330.1665, found 330.1667.

{4-[(3,5-*O*-DTBS-*β*-D-ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (19b)

Triol **6b** (112 mg, 0.34 mmol) was co-evaporated three times with pyridine (1 mL) and then redissolved in pyridine (5 mL). DTBS-bis-trifluoromethanesulfonate (0.11 mL, 0.34 mmol) was added dropwise to the pyridine solution. The reaction mixture was stirred at rt for 10 min, after which the volatiles were evaporated. The residual oil was purified by column chromatography (AcOEt/hexane = 40:60) to give **19b** (160 mg, quant) as an oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.06 (s, 9H), 1.91 (s, 9H), 3.04 (d, J = 6.6 Hz, 2H), 3.61 (dd, J = 8.7, 5.4 Hz, 1H), 3.79–3.94 (m, 2H), 4.15 (d, J = 4.5 Hz, 1H), 4.25 (t, J = 6.6 Hz, 1H), 4.39 (q, J = 3.9 Hz, 1H), 6.20 (s, 2H), 7.67 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.8, 20.3, 22.7, 26.8, 27.2, 27.3, 30.3, 38.8, 68.0, 69.6, 72.9, 74.3, 85.2, 123.5, 144.3, 177.8 ppm; HRMS (FABMS: NBA): calcd for $C_{22}H_{40}N_3O_6Si$ [$(M+H)^+$] 470.2687, found 470.2686.

{4-[(3,5-*O*-DTBS-2-*O*-TBDMS-*β*-D-ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (20b)

Imidazole (279 mg, 4.10 mmol) and TBDMSCl (370 mg, 2.46 mmol) were added to a solution of **19b**

(386 mg, 0.82 mmol) in DMF (6 mL). The mixture was stirred at 50 ºC for 3 h. AcOEt (100 mL) was added to the mixture, which was subsequently washed with H_2O (10 mL × 5), dried over Na_2SO_4, and filtrated off. The volatiles were then evaporated. The residual oil was purified by column chromatography (AcOEt/hexane = 10:90) to give **20b** (478 mg, 89%) as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.02 (s, 9H), 1.03 (s, 9H), 1.22 (s, 9H), 2.92–3.04 (m, 2H), 3.50–3.54 (m, 1H), 3.78 (d, J = 9.6 Hz, 1H), 3.92–4.02 (m, 1H), 4.12–4.18 (m, 2H), 4.38–4.42 (m, 1H), 6.20 (s, 2H), 7.66 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ -5.2, -4.2, 18.2, 20.3, 22.7, 25.6, 25.8, 26.8, 27.0, 27.2, 27.4, 30.7, 38.8, 68.5, 69.7, 73.9, 74.2, 76.6, 87.0, 123.7, 144.4, 177.8 ppm; HRMS (FABMS: NBA): calcd for $C_{28}H_{54}N_3O_6Si_2$ [$(M+H)^+$] 584.3551, found 584.3559.

{4-[(2-*O*-TBDMS-*β*-D-ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (21b)

A solution of 65% HF·pyridine (1 mL) in pyridine (10 mL) was added dropwise over 15 min to a solution of **20b** (423 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h and then diluted with CH_2Cl_2. The resulting mixture was washed with saturated aq. $NaHCO_3$, dried over Na_2SO_4, and filtered off, after which the volatiles were evaporated. The obtained residue was purified by column chromatography (AcOEt/hexane = 1:1) to give **21b** (325 mg, quant) as an oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.19 (s, 9H), 2.93 (dd, J = 15.3, 6.6 Hz, 1H), 3.11 (dd, J = 15.3, 4.2 Hz, 1H), 3.63 (dd, J = 12.0, 2.7 Hz, 1H), 3.83 (dd, J = 12.0, 2.4 Hz, 1H), 3.388–4.12 (m, 4H), 6.20 (s, 2H), 7.74 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ -4.9, -4.6, 17.9, 25.7, 26.8, 28.4, 38.8, 62.4, 69.6, 71.5, 74.9, 81.4, 84.6, 123.9, 144.2, 177.9 ppm; HRMS (FABMS: NBA): calcd for $C_{20}H_{38}N_3O_6Si$ [$(M+H)^+$] 444.2530, found 444.2526.

{4-[(5-*O*-DMT-2-*O*-TBDMS-*β*-D-ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (22b)

Compound **21b** (186 mg, 0.42 mmol) was co-evaporated three times with pyridine (1 mL) and redissolved in dry pyridine (5 mL). DMTCl (223 mg, 0.63 mmol), Et_3N (87 μL, 0.63 mmol), and DMAP (5 mg, 0.04 mmol) were added to the pyridine solution, and the mixture was stirred at rt for 17 h. MeOH (1 mL) was added to the mixture and the volatiles were then evaporated. The obtained residue was subjected to silica gel column chromatography (AcOEt/hexane = 5:95 to 20:80) to give **22b** (232 mg, 74%) as an amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.13 (s, 3H), 0.16 (s, 3H), 0.93 (s, 9H), 1.16 (s, 9H), 2.65 (d, J = 4.0 Hz, 1H), 3.01 (dd, J = 15.2, 7.6 Hz, 1H), 3.09 (dd, J = 10.4, 3.6 Hz, 1H), 3.18 (dd, J = 15.2, 3.6 Hz, 1H), 3.34 (dd, J = 10.4, 3.2 Hz, 1H), 3.79 (s, 6H), 3.89–3.94 (m, 1H), 3.98–4.16 (m, 3H), 6.03 (d, J = 10.4 Hz, 1H), 6.08 (d, J = 10.4 Hz, 1H), 6.79–6.84 (m, 4H), 7.18–7.34 (m, 7H), 7.40–7.44 (m, 2H), 7.74 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ -4.8, -4.6, 18.0, 25.7, 26.8, 29.4, 38.7, 55.2. 64.0, 69.6, 72.5, 75.6, 80.7, 83.7, 86.0, 113.0, 113.1, 123.9, 126.7, 127.8, 128.1, 130.0, 130.1, 135.9, 136.1, 144.8, 144.9, 158.4, 177.6

ppm; HRMS (FABMS: NBA+NaCl): calcd for $C_{41}H_{55}N_3O_8Si$ [$(M+Na)^+$] 768.3656, found 768.3663.

{4-[(5-*O*-DMT-2-*O*-TBDMS-3-*O*-[(2-cyanoethoxy)-(*N*,*N*-diisopropylamino)phosphoramidyl]-β-D-ribofuranosyl)methyl]triazol-1-yl}methyl 2,2-dimethylpropionate (3b)

Compound **22b** (200 mg, 0.27 mmol) was dissolved in dry CH_2Cl_2 (5 mL), to which 4,5-DCI (38 mg, 0.32 mmol) and 2-cyanoethyl-*N,N,N',N'*-tetraisopropylphosphordiamidite (170 μL, 0.54 mmol) were added. The resulting mixture was stirred at 40 ºC for 30 min, after which the volatiles were evaporated. The residual oil was subjected to chromatography on silica gel (AcOEt/hexane = 20:80) to give PA **3b** (213 mg, 84%) as an amorphous.

^{1}H-NMR ($CDCl_3$): δ 010 (s, 1.5H), 0.11 (s, 1.5H), 0.12 (s, 1.5H), 0.13 (s, 1.5H), 0.92 (s, 4.5H), 0.93 (s, 4.5H), 0.96 (d, J = 6.8 Hz, 3H), 1.11–1.16 (m, 9H), 1.17 (s, 4.5H), 1.18 (s, 43.5H), 2.14–2.28 (m, 1H), 2.53–2.68 (m, 1H), 2.90–3.02 (m, 1H), 3.20–3.42 (m, 2H), 3.46–3.62 (m, 3H), 3.77–3.97 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.04–4.20 (m, 4H), 6.05–6.16 (m, 2H), 6.78–6.86 (m, 4H), 7.17–7.36 (m, 7H), 7.42–7.46 (m, 2H), 7.75 (s, 0.5H), 7.77 (s, 0.5H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ -4.8, -4.7, -4.2, -4.2, -4.1, -4.1, 18.1, 18.2, 19.9, 20.0, 20.4, 20.4, 24.4, 24.5, 24.6, 24.7, 25.9, 26.0, 26.8, 26.8, 29.8, 30.0, 38.7, 42.7, 42.8, 43.3, 43.4, 55.2, 55.2, 57.2, 57.4, 58.5, 58.7, 63.7, 63.8, 69.7, 73.8, 73.9, 74.7, 74.8, 75.6, 75.7, 76.2, 76.2, 77.2, 80.1, 80.3, 83.2, 83.2, 83.8, 85.9, 86.1, 113.1, 113.1, 117.3, 117.7, 123.7, 123.8, 126.7, 126.8, 127.8, 128.1, 128.2, 130.0, 130.1, 130.1, 135.8, 135.9, 136.0, 136.2, 144.8, 144.9, 145.4, 145.5, 158.4, 158.4, 177.6, 177.6 ppm; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 147.9, 150.6 ppm; HRMS (FABMS: TEOA+NaCl): calcd for $C_{50}H_{72}N_5O_9PSi$+Na [$(M+Na)^+$] 968.4735, found 968.4736.

{4-[(2,3,5-*O*-Tribenzyl-β-D-ribofuranosyl)ethyl]triazole-1-yl}methyl 2,2-dimethylpropionate (12c)

$POMN_3$ **5** (0.22 mL, 1.44 mmol), CuI (456 mg, 2.40 mmol), and DIPEA (0.61 mL, 3.60 mmol) were added to a solution of compound **15c**[14a] (550 mg, 1.20 mmol) in MeCN (12 mL). After stirred at rt for 0.5 h, the volatiles were evaporated. The obtained residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:4) to give **12c** (740 mg, quant) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 9H), 1.76–1.86 (m, 1H), 1.96–2.06 (m, 1H), 2.74–2.90 (m, 2H), 3.48 (dd, J = 10.4, 4.4 Hz, 1H), 3.51 (dd, J = 10.4, 4.4 Hz, 1H), 3.61 (dd, J = 6.4, 5.6 Hz, 1H), 3.90 (dd, J = 5.6, 4.4 Hz, 1H), 3.99–4.05 (m, 1H), 4.19 (q, J = 4.4 Hz, 1H), 4.44–4.60 (m, 6H), 6.16 (s, 2H), 7.25–7.36 (m, 15H), 7.48 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.8, 26.8, 33.2, 38.8, 69.6, 70.5, 71.8, 72.0, 73.4, 77.4, 79.9, 80.8, 81.3, 122.2, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 137.8, 137.8, 138.1, 148.2, 177.8 ppm; HRMS (FABMS: NBA): calcd for $C_{36}H_{44}N_3O_6$ [$(M+H)^+$] 614.3230, found 614.3229.

{4-[(β-D-Ribofuranosyl)ethyl]triazol-1-yl}methyl 2,2-dimethylpropionate (6c)

A mixture of **12c** (613 mg, 1.0 mmol), 20% $Pd(OH)_2$/C (360 mg), and cyclohexene (3.0 mL, 30.0 mmol) in EtOH was exposed to MW irradiation at 80 ºC for 1 h.[6] After filtration through Celite, the filtrate volatiles were evaporated to give a residue, which was then purified by column chromatography on silica

gel using AcOEt to give **6c** (329 mg, 96 %) as an oil.

{4-[(3,5-*O*-DTBS-β-D-ribofuranosyl)ethyl]triazol-1-yl}methyl 2,2-dimethylpropionate (19c)

Triol **6c** (281 mg, 0.82 mmol) was co-evaporated three times with pyridine (1 mL) and then redissolved in pyridine (5 mL). DTBS-bis-trifluoromethanesulfonate (0.27 mL, 0.82 mmol) was added dropwise to the pyridine solution. The reaction mixture was stirred at rt for 10 min, after which the volatiles were evaporated. The residual oil was purified by column chromatography (AcOEt/Hexane = 2:8) to give **19c** (402 mg, quant) as an oil.

^{1}H-NMR ($CDCl_3$): δ 1.02 (s, 9H), 1.06 (s, 9H), 1.19 (s, 9H), 1.87–2.07 (m, 2H), 2.75–2.91 (m, 2H), 3.79–3.93 (m, 3H), 3.95–4.00 (m, 2H), 4.36–4.45 (m, 1H), 6.20 (s, 2H), 7.58 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ 20.3, 21.7, 22.6, 26.8, 27.2, 27.3, 33.6, 38.8, 68.1, 69.5, 73.6, 74.1, 77.5, 85.8, 122.4, 147.6, 177.9 ppm; HRMS (FABMS: NBA): calcd for $C_{23}H_{42}N_3O_6Si$ [$(M+H)^+$] 484.2843, found 484.2836.

{4-[(3,5-*O*-DTBS-2-*O*-TBDMS-*β*-D-ribofuranosyl)ethyl]triazol-1-yl}methyl 2,2-dimethylpropionate (20c)

Imidazole (279 mg, 4.10 mmol) and TBDMSCl (370 mg, 2.46 mmol) were added to a solution of **19c** (396 mg, 0.82 mmol) in DMF (6 mL). The mixture was stirred at 50 ºC for 3 h. AcOEt (100 mL) was added to the mixture, which was subsequently washed with H_2O (10 mL × 5), dried over Na_2SO_4, and filtered off. The volatiles were then evaporated and the obtained residual oil was purified by column chromatography (AcOEt/hexane = 10:90) to give **20c** (450 mg, 92%) as an oil.

^{1}H-NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.01 (s, 9H), 1.05 (s, 9H), 1.19 (s, 9H), 1.77–1.87 (m, 1H), 1.95–2.05 (m, 1H), 2.70–2.79 (m, 1H), 2.81–2.90 (m, 1H), 3.71 (dd, J = 9.2, 5.2 Hz, 1H), 3.80–4.00 (m, 4H), 4.40 (dd, J = 9.2, 5.2 Hz, 1H), 6.19 (s, 2H), 7.56 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ -5.0, -4.2, 18.3, 20.3, 21.9, 22.7, 25.9, 26.8, 27.1, 27.5, 34.2, 38.8, 68.5, 69.5, 73.7, 75.2, 77.7, 87.3, 122.3, 147.8, 177.9 ppm; HRMS (FABMS: NBA): calcd for $C_{29}H_{56}N_3O_6Si_2$ [$(M+H)^+$] 598.3708, found 598.3698.

{4-[(2-*O*-TBDMS-β-D-ribofuranosyl)ethyl]triazol-1-yl}methyl 2,2-dimethylpropionate (21c)

A solution of 65% HF·pyridine (0.1 mL) in pyridine (2 mL) was added dropwise over 15 min to a solution of **20c** (450 mg, 0.75 mmol) in CH_2Cl_2 (4 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h and then diluted with CH_2Cl_2. The resulting mixture was washed with saturated aq. $NaHCO_3$, dried over Na_2SO_4, and filtered off. The volatiles were then evaporated and the obtained residue was purified by column chromatography (AcOEt/hexane = 1:1) to give **21c** (249 mg, 73%) as an oil.

^{1}H-NMR ($CDCl_3$): δ 0.13 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.19 (s, 9H), 1.80–1.90 (m, 1H), 2.00–2.10 (m, 1H), 2.45 (brm, 1H), 2.64 (d, J = 5.6 Hz, 1H), 2.79–2.95 (m, 2H), 3.64–3.69 (brm, 1H), 3.76–3.88 (m, 4H), 3.98 (dd, J = 9.4, 5.6 Hz, 1H), 6.20 (s, 2H) ppm; ^{13}C-NMR ($CDCl_3$): δ -4.8, -4.6, 18.0, 21.8, 25.7, 26.8, 32.4, 38.8, 62.6, 69.6, 71.7, 76.0, 77.2, 82.1, 84.3, 122.3, 148.0, 177.9 ppm; HRMS (FABMS:

NBA): calcd for $C_{21}H_{40}N_3O_6Si$ [$(M+H)^+$] 458.2687, found 458.2688.

{4-[(5-*O*-DMT-2-*O*-TBDMS-β-D-ribofuranosyl)ethyl]triazol-1-yl}methyl 2,2-dimethylpropionate (22c)

Compound **21c** (249 mg, 0.54 mmol) was co-evaporated three times with pyridine (1 mL) and redissolved in dry pyridine (5 mL). DMTCl (274 mg, 0.81 mmol), Et_3N (112 μL, 0.81 mmol) and DMAP (6 mg, 0.05 mmol) were added to the pyridine solution, and the mixture was stirred at rt for 2 h. MeOH (1 mL) was added to the mixture, after which the volatiles were evaporated. The obtained residue was subjected to chromatography on silica gel column (AcOEt/hexane = 10:90 to 20:80) to give **22c** (382 mg, 93%) as an amorphous solid.

^{1}H-NMR ($CDCl_3$): δ 0.13 (s, 6H), 0.92 (s, 9H), 1.17 (s, 9H), 1.85–1.95 (m, 1H), 2.05–2.15 (m, 1H), 2.62 (d, J = 3.6 Hz, 1H), 2.85–2.95 (m, 1H), 2.96–3.06 (m, 1H), 3.10 (dd, J = 10.4, 3.6 Hz, 1H), 3.33 (dd, J = 10.4, 2.8 Hz, 1H), 3.79 (s, 6H), 3.79–3.83 (m, 1H), 3.96–4.03 (m, 3H), 6.17 (d, J = 10.8 Hz, 1H), 6.19 (d, J = 10.8 Hz, 1H), 6.79–6.84 (m, 4H), 7.17–7.22 (m, 1H), 7.24–7.30 (m, 2H), 7.31–7.38 (m, 4H), 7.44–7.48 (m, 2H), 7.54 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$): δ -4.8, -4.5, 18.0, 22.1, 25.7, 26.8, 33.0, 38.7, 55.2. 64.3, 69.6, 72.7, 76.5, 77.2, 81.0, 83.4, 85.9, 113.0, 122.2, 126.7, 127.7, 128.2, 130.1, 130.1, 136.0, 136.1, 145.0, 148.1, 158.4, 177.7 ppm; HRMS (FABMS: NBA): calcd for $C_{42}H_{57}N_3O_8Si$ [$(M+H)^+$] 759.3915, found 759.3908.

{4-[(5-*O*-DMT-2-*O*-TBDMS-3-*O*-[(2-cyanoethoxy)-(*N*,*N*-diisopropylamino)phosphoramidyl]-β-D-ribofuranosyl)ethyl]triazol-1-yl}methyl 2,2-dimethylpropionate (3c)

Compound **22c** (76 mg, 0.10 mmol) was dissolved in dry CH_2Cl_2 (2 mL), to which 4,5-DCI (14 mg, 0.20 mmol) and 2-cyanoethyl-*N,N,N',N'*-tetraisopropylphosphordiamidite (63 μL, 0.38 mmol) were added. The resulting mixture was stirred at 40 °C for 30 min and then the volatiles were evaporated. The residual oil was subjected to chromatography on silica gel (AcOEt/hexane = 20:80) to give PA **3c** (88 mg, 92%) as an amorphous solid.

^{1}H-NMR ($CDCl_3$): δ 0.10 (s, 2.4H), 0.12 (s, 0.18H), 0.13 (s, 1.8H), 0.90 (s, 3.6H), 0.92 (s, 5.4H), 0.98 (d, J = 6.8 Hz, 4.8H), 1.13 (d, J = 6.8 Hz, 3.6H), 1.14 (d, J = 6.8 Hz, 3.6H), 1.17 (s, 3.6H), 1.17 (s, 5.4H), 1.81–1.93 (m, 1H), 2.07–2.17 (m, 1H), 2.23 (td, J = 6.4, 2.4 Hz, 0.8H), 2.57 (dd, J = 16.4, 6.4 Hz, 0.6H), 2.63 (dd, J = 16.4, 6.4 Hz, 0.6H), 2.85–2.95 (m, 1H), 2.98–3.10 (m, 2H), 3.29 (dd, J = 10.0, 2.8 Hz, 0.6H), 3.38 (dd, J = 10.0, 2.8 Hz, 0.4H), 2.48–3.66 (m, 2.6H), 3.78 (s, 3.6H), 3.79 (s, 2.4H), 3.74–3.94 (m, 2.4H), 3.98 (dd, J = 10.8, 4.4 Hz, 0.4H), 4.03 (dd, J = 10.8, 4.4 Hz, 0.6H), 4.10–4.24 (m, 2H), 6.15 (d, J = 10.8 Hz, 0.4H), 6.16 (d, J = 10.8 Hz, 0.6H), 6.18 (d, J = 10.8 Hz, 0.4H), 6.19 (d, J = 10.8 Hz, 0.6H), 6.79–6.84 (m, 4H), 7.17–7.23 (m, 1H), 7.24–7.30 (m, 2H), 7.31–7.39 (m, 4H), 7.44–7.50 (m, 2H), 7.53 (s, 0.6H), 7.53 (s, 0.4H) ppm; ^{13}C-NMR ($CDCl_3$): δ -4.8, -4.7, -4.2, 18.1, 19.9, 19.9, 20.3, 22.3, 24.4, 24.4, 24.5, 24.5, 24.6, 25.9, 25.9, 26.7, 33.1, 38.7, 42.7, 42.8, 43.2, 43.3, 55.1, 57.3, 57.5, 58.4, 58.6, 63.8, 64.0, 69.6,

73.9, 74.0, 74.6, 74.7, 76.1, 76.4, 77.2, 80.6, 81.0, 82.7, 83.1, 85.8, 86.0, 113.0, 117.3, 117.7, 122.0, 122.1, 126.6, 127.7, 128.1, 128.2, 130.0, 135.8, 136.0, 136.1, 144.9, 144.9, 148.3, 148.5, 158.3, 177.6 ppm; ^{31}P-NMR ($CDCl_3$): δ 148.4, 150.6 ppm; HRMS (FABMS: TEOA+NaCl): calcd for $C_{51}H_{74}N_5O_9PSi$+Na [$(M+Na)^+$] 982.4892, found 982.4893.

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