Tetrahedron Letters 53 (2012) 6987–6989

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of 1-deoxy-1-ethynyl-β-D-ribofuranose as a versatile scaffold

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ARTICLE INFO

Article history:
Received 7 September 2012
Revised 9 October 2012
Accepted 12 October 2012
Available online 23 October 2012

Keywords:
C-Nucleoside
Alkynes
Stereoselective synthesis
Huisgen cycloaddition
Click chemistry

ABSTRACT

We have developed an efficient stereoselective synthesis of 1-deoxy-1-ethynyl-β-D-ribofuranose (R^E), via the β-selective cyanation of the anomeric position of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose. Under conditions for copper(I)-catalyzed alkyne–azide 1,3-dipolar cycloaddition, the cycloaddition of R^E with 4-fluorobenzylazide was accomplished within 5 min, to afford the corresponding triazole ribonucleoside in quantitative yield.

C-Nucleosides have attracted considerable interest in medicinal chemistry and chemical biology for their biological properties, which include anticancer and antiviral activities.[1] In particular, β-C-nucleosides functionalized at the 1-position of ribose are useful chiral building blocks for constructing natural products and pharmaceuticals.

In the course of this study, several types of nucleoside analogues bearing one or more ethynyl groups have been developed (Fig. 1).[2] 1-Deoxy-1-ethynyl-β-D-ribofuranose **1** (R^E, Fig. 2) is the simplest acetylenic β-C-nucleoside, yet an efficient synthetic method for R^E has not been reported. Buchanan and co-workers have reported nonstereoselective syntheses of R^E utilizing 2,3,5-tri-*O*-benzyl-D-ribose or D-ribose diethyl dithioacetal as a key intermediate.[2a,c] The direct attachment of a trimethylsilyl (TMS)-alkynyl group, which can be easily converted into an ethynyl group by desilylation, has been achieved at the anomeric position of ribose. Lubin-Germain and Uziel et al. used an alkynylindium reagent, which was generated in situ from indium(0) and TMS-alkynyl iodide, to introduce the TMS-alkynyl group to 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-ribofuranose.[3] Botta and co-workers demonstrated that 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose reacted with trimethylsilylacetylene in the presence of $EtAlCl_2$ to afford 1-deoxy-1-trimethylsilylalkynyl-D-ribofuranose.[4] However, both protocols gave the corresponding C-ribonucleosides as anomeric mixtures, which can be difficult to separate.

Here we report the stereoselective synthesis of R^E (**1**) using 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) as starting material. Moreover, R^E rapidly reacted with 4-fluorobenzylazide[5] to produce the corresponding triazole ribonucleoside, under conditions for Cu(I)-catalyzed alkyne-azide 1,3-dipolar cycloaddition (CuAAC).

The synthesis of **1** was achieved as shown in Scheme 1. First, **3**[6] was prepared by anchimeric assisted stereoselective nucleophilic addition of cyanide via TMSCN to the oxocarbenium ion intermediate generated in situ from commercially available **2**. Treatment of **3** with sodium methoxide and subsequent hydrolysis of the resulting imidate in situ with HCl gave the fully deprotected methyl ester in 70% yield. After selective introduction of a TBDPS group at the 5-OH, the secondary hydroxyl groups of **4** were subjected to isopropylidenation. Fully protected methyl ester **5** was advanced to the corresponding ethynyl riboside **6** by a one-pot protocol using DIBAL-H and Bestmann-Ohira reagent.[7] Finally, removal of the TBDPS and isopropylidene groups by acidic hydrolysis afforded **1** in 79% yield. The structures and stereochemistry of compounds **1** and **3**–**6** were determined by spectroscopic analysis, including the extensive use of 2D NMR techniques.

We next examined the application of **1** in positron emission tomography (PET) labeling using rapid CuAAC. We have recently reported a rapid ligand-free CuAAC protocol for PET labeling of RNA oligomers.[8] Under the reaction conditions [copper sulfate pentahydrate (100 equiv) and sodium ascorbate (100 equiv) in 0.1 M phosphate buffer (pH 7.0)/DMSO/MeCN at rt], R^E (**1**) smoothly reacted with 10 equiv of 4-fluorobenzylazide within

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http://dx.doi.org/10.1016/j.tetlet.2012.10.053

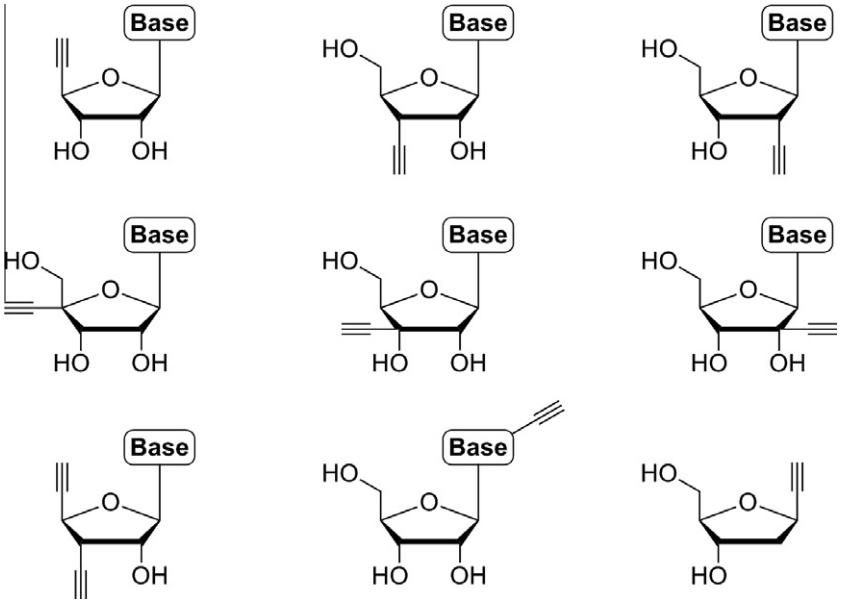


Figure 1. Nucleoside analogues bearing one or more ethynyl groups.

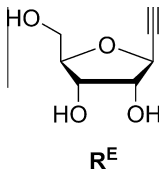
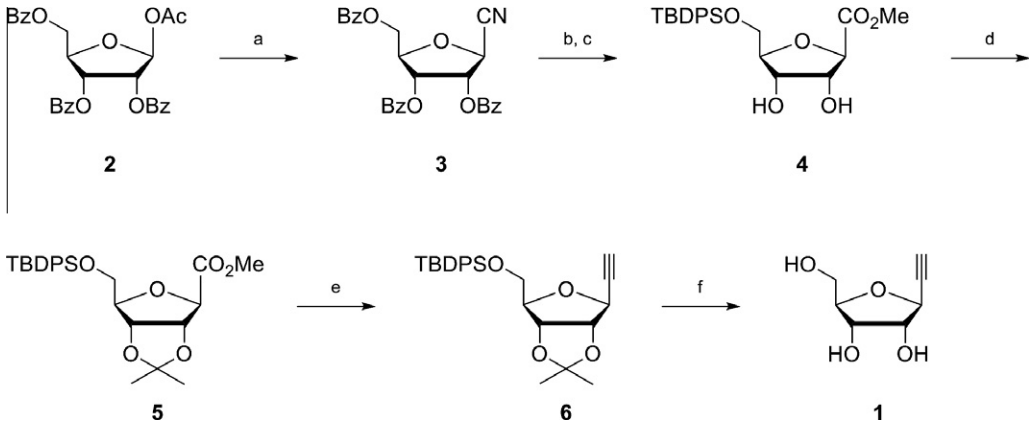


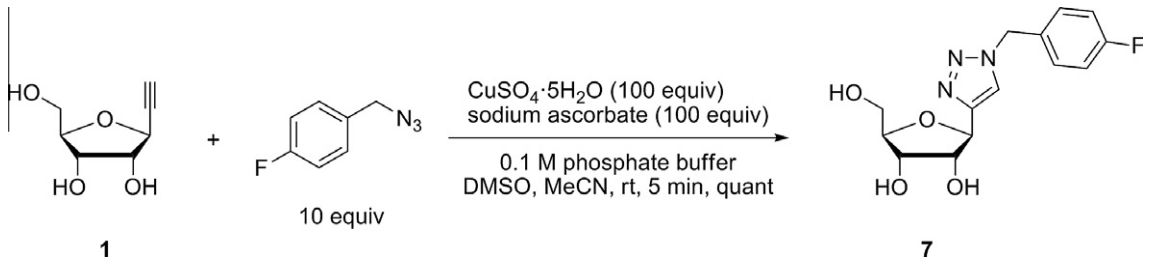
Figure 2. 1-Deoxy-1-ethynyl-β-D-ribofuranose (R^E; **1**).

5 min to give the desired triazole ribonucleoside **7** in quantitative yield (Scheme 2).

In conclusion, the efficient stereoselective synthesis of R^E was developed. Furthermore, we demonstrated that R^E rapidly reacted with azide compounds to give the corresponding C-triazole ribonucleosides. These results will contribute to the design of molecular imaging tools for developing nucleic acid drugs.



Scheme 1. Synthesis of **1**. Reagents and conditions: (a) TMSCN, TMSOTf, CH_2Cl_2, rt, quant; (b) (i) NaOMe, MeOH, rt; (ii) HCl, rt, 70%; (c) TBDPSCl, pyridine, rt, 79%; (d) 2,2-dimethoxypropane, *p*-TsOH, acetone, 94%; (e) (i) DIBAL-H, CH_2Cl_2, −78 °C; (ii) Bestmann-Ohira reagent, K_2CO_3, MeOH, rt, 67%; (f) CF_3CO_2H, H_2O, rt, 79%.



Scheme 2. CuAAC reaction of R^E (**1**) with 4-fluorobenzylazide.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

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Physical and spectral data of synthetic compounds.1-deoxy-1-cyano-2,3,5-tri-*O*-benzoyl-*β*-d-ribofuranose **3**[6]: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15–8.12 (m, 2H, H-Ph), 7.98–7.92 (m, 4H, H-Ph), 7.61–7.54 (m, 3H, H-Ph), 7.47–7.36 (m, 6H, H-Ph), 6.01 (dd, *J* = 5.3 Hz, 4.4 Hz, 1H, H-2), 5.86 (t, *J* = 5.3 Hz, 1H, H-3), 4.99 (d, *J* = 4.4 Hz, 1H, H-1), 4.75–4.71 (m, 2H, H-4, H-5$_\alpha$), 4.62 (dd, *J* = 13.2 Hz, 4.9 Hz, 1H, H-5$_\beta$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1, 165.0, 164.8, 134.0, 133.8, 133.4, 129.8, 129.8, 129.7, 129.2, 128.6, 128.5, 128.4, 128.1, 115.7, 80.9, 74.4, 71.8, 69.4, 63.1; MS (DRAT) m/z 472 $[M+H]^+$, HRMS (DART) Calcd for $C_{27}H_{22}NO_7$ $[M+H]^+$: 472.1396. Found: 472.1360.

1-deoxy-1-methoxycarbonyl-5-*O*-*tert*-butyldiphenylsilyl-*β*-d-ribofuranose **4**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72–7.66 (m, 4H, H-Ph), 7.45–7.36 (m, 6H, H-Ph), 4.42–4.38 (m, 2H, H-1, H-2), 4.27 (t, *J* = 4.0 Hz, 1H, H-3), 4.08 (q, *J* = 4.0 Hz, 1H, H-4), 3.82 (d, *J* = 4.0 Hz, 2H, H-5), 3.75 (s, 3H, CO_2CH_3), 1.05 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.5, 135.6, 135.5, 133.0, 132.8, 129.8, 129.8, 127.8, 127.7, 84.8, 81.1, 74.2, 72.7, 64.1, 52.3, 26.7, 19.1; MS (DRAT) m/z 431 $[M+H]^+$, HRMS (DART) Calcd for $C_{23}H_{31}O_6Si$ $[M+H]^+$: 431.1890. Found: 431.1890; Anal. Calcd for $C_{23}H_{30}O_6Si{\cdot}1/3H_2O$: C, 64.16; H, 7.02. Found: C, 63.28; H, 7.08.

1-deoxy-1-methoxycarbonyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropyridene-*β*-d-ribofuranose **5**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.66 (m, 4H, H-Ph), 7.45–7.39 (m, 6H, H-Ph), 4.93 (dd, *J* = 6.2 Hz, 3.9 Hz, 1H, H-2), 4.75 (dd, *J* = 6.2 Hz, 2.0 Hz, 1H, H-3), 4.51(d, *J* = 3.9 Hz, 1H, H-1), 4.28 (dd, *J* = 4.6 Hz, 2.0 Hz, 1H, H-4), 3.76–3.74 (m, 2H, H-5), 3.70 (s, 3H, CO_2CH_3), 1.56 (s, 3H, CH_3 of isopropylidene), 1.37 (s, 3H, CH_3 of isopropylidene), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8, 135.6 135.6, 132.9, 132.9, 129.8, 129.7, 127.8, 127.7, 113.7, 85.7, 84.0, 83.4, 82.3, 64.1, 52.2, 27.2, 26.8, 25.3, 19.1; MS (DRAT) m/z 471 $[M+H]^+$, HRMS (DART) Calcd for $C_{26}H_{35}O_6Si$ $[M+H]^+$: 471.2203. Found: 471.2154; Anal. Calcd for $C_{26}H_{34}O_6Si$: C, 66.35; H, 7.28. Found: C, 66.08; H, 7.24.

1-deoxy-1-ethynyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropyridene-*β*-d-ribofuranose **6**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.68 (m, 4H, H-Ph), 7.46–7.37 (m, 6H, H-Ph), 4.81 (dd, *J* = 6.2 Hz, 2.0 Hz, 1H, H-3), 4.76 (dd, *J* = 6.2 Hz, 2.9 Hz, 1H, H-2), 4.63 (dd, *J* = 2.9 Hz, 2.4 Hz, 1H, H-1), 4.22 (dt, *J* = 5.8 Hz, 2.0 Hz, 1H, H-4), 3.86–3.78 (m, 2H, H-5), 2.42 (d, *J* = 2.4 Hz, 1H, C≡C*H*), 1.53 (s, 3H, CH_3 of isopropylidene), 1.35 (s, 3H, CH_3 of isopropylidene), 1.09 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 135.6, 133.2, 133.2, 129.7, 129.7, 127.7, 127.7, 113.6, 86.2, 86.0, 82.7, 81.6, 74.9, 74.4, 63.6, 27.0, 26.9, 25.3, 19.2; MS (DRAT) m/z 437 $[M+H]^+$, HRMS (DART) Calcd for $C_{26}H_{33}O_4Si$ $[M+H]^+$: 437.2148. Found: 437.2187; Anal. Calcd for $C_{26}H_{32}O_4Si$: C, 71.52; H, 7.39. Found: C, 71.34; H, 7.39.

1-deoxy-1-ethynyl-*β*-d-ribofuranose **1**[2a]: colorless oil; ^{1}H NMR (400 MHz, acetone-d_6) δ = 4.32 (dd, *J* = 5.2 Hz, 2.1 Hz, 1H, H-1), 4.11 (q, *J* = 5.2 Hz, 1H, H-3), 4.08 (q, *J* = 5.2 Hz, 1H, H-2), 3.83–3.79 (m, 1H, H-4), 3.78–3.58 (m, 2H, H-5), 3.00 (d, *J* = 2.1 Hz, 1H, C≡C*H*); ^{13}C NMR (100 MHz, acetone-d_6): δ = 85.8, 82.9, 77.5, 75.5, 73.3, 72.3, 63.1; MS (DRAT) m/z 159 $[M+H]^+$, HRMS (DART) Calcd for $C_7H_{11}O_4$ $[M+H]^+$: 159.0657. Found: 159.0663.

1-[1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]-1-deoxy-*β*-d-ribofuranose **7**: colorless oil; ^{1}H NMR (400 MHz, acetone-d_6) δ = 7.99 (s, 1H, C*H* of triazole), 7.44 (dd, *J* = 8.8 Hz, 5.3 Hz, 2H, C*H* of 4-F-Ph), 7.15 (t, *J* = 8.8 Hz, 2H, C*H* of 4-F-Ph), 5.62 (s, 1H, NCH_2(4-F-Ph)), 4.88 (d, *J* = 5.1 Hz, 1H, H-1), 4.25 (q, *J* = 5.1 Hz, 1H, H-2), 4.19 (q, *J* = 5.1 Hz, 1H, H-3), 3.93 (dd, *J* = 8.2 Hz, 3.8 Hz, 1H, H-4), 3.73 (dd, *J* = 11.9 Hz, 8.2 Hz, 1H, H-5$_\alpha$), 3.60 (dd, *J* = 11.9 Hz, 3.8 Hz, 1H, H-5$_\beta$); ^{13}C NMR (100 MHz, acetone-d_6): δ = 163.4 (d, *J* = 244.1 Hz), 148.8, 133.1, 131.2 (d, *J* = 8.6 Hz), 123.3, 116.4 (d, *J* = 21.9 Hz), 85.8, 78.6, 77.2, 72.4, 63.2, 53.4; MS (DRAT) m/z 310 $[M+H]^+$, HRMS (DART) Calcd for $C_{14}H_{17}FN_3O_4$ $[M+H]^+$: 310.1203. Found: 310.1188; Anal. Calcd for $C_{14}H_{16}FN_3O_4{\cdot}7/6H_2O$: C, 50.91; H, 5.59; N, 12.72. Found: C, 50.95; H, 5.39; N, 12.53.