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Monomers for preparation of amide linked RNA: synthesis of C3′-homologated nucleoside amino acids from D-xylose

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Amides as neutral and hydrophobic internucleoside linkages in RNA are highly interesting modifications for RNA interference. However, testing amides in siRNAs is hampered by the shortage of efficient methods to synthesize the monomeric building blocks, the nucleoside amino acid equivalents. This paper reports an efficient synthesis of protected ribonucleoside 5′-amino 3′-carboxylic acids from D-xylose in 14 steps 7% overall yield. The key features that ensure efficiency and ease of operations are chemoselective reduction of the ester and minimization of protecting group manipulation.

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1. Introduction

The potential of RNA interference (RNAi) to become a new therapeutic strategy has revitalized the interest in chemical modifications of RNA. To be useful as therapeutic agents short interfering RNAs (siRNAs) need to be chemically modified to optimize their potency, enzymatic stability, cellular uptake, biodistribution, and pharmacokinetics.[1] We have been interested in hydrophobic non-ionic mimics of phosphate backbone, such as formacetals[2] and amides[3] (Fig. 1). Non-ionic phosphate mimics may offer several advantages for siRNAs: (1) the absence of natural phosphate will confer high nuclease resistance, (2) the reduction of charge may facilitate crossing of cellular membranes, and (3) the increased hydrophobicity of siRNAs may improve their biodistribution and pharmacokinetics.

In previous studies we found that replacement of selected phosphates with amide linkages (Fig. 1) did not change the overall conformation and UV melting temperature (thermal stability) of RNA double helix.[3] The amide linkages appeared to be excellent mimics of phosphate backbone in RNA and were expected to be compatible with RNAi machinery. In accord with such expectation, Iwase and co-workers[4] recently reported that siRNA having two amide linkages at the overhanging uridines retained high activity in RNAi assays. These results suggest a hypothesis that siRNAs may tolerate even more extensive amide modification, which may

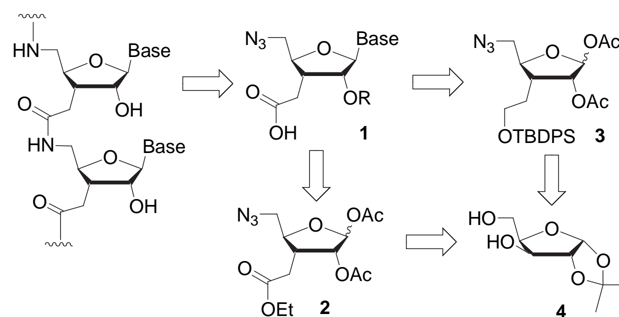

Figure 1. Structure and retrosynthetic analysis of amide linked RNA.

realize the potential advantages of the hydrophobic RNA modifications. The bottleneck of testing the above hypothesis is the shortage of efficient and large scale syntheses of enantiomerically pure C3′-homologated carboxylic acids **1** (Fig. 1), the monomers for introduction of consecutive amide linkages in siRNAs.

In their study of amide-modified siRNAs, Iwase and co-workers[4] used uridine carboxylic acids, which were prepared from uridine following a procedure by Robins and co-workers.[5] The problem with such an approach is that four independent synthetic routes must be pursued to prepare all four nucleoside carboxylic acids, which is time and resources consuming. Robins and co-workers have also developed synthesis of **1** starting from D-glycose or D-xylose.[6] The sugar route diverges at the common intermediate **2** (Fig. 1) on which the desired heterocylces can be installed in

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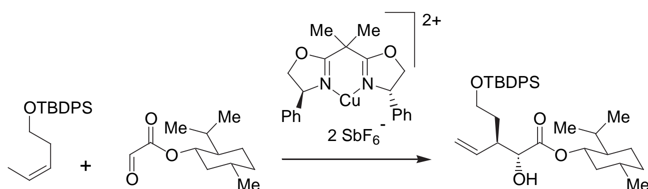
a straightforward manner. However, we found that Robin's route from sugars was complicated at the finals steps by the need to cleave the ester (see **2**) and, consequently, laborious reintroduction of 2′-OH and heterocycle protecting groups, which being base labile, were lost during the ester cleavage.

Recently, we reported an asymmetric de novo synthesis of **1** starting from small molecules and proceeding through the common intermediate **3**.[7] The final oxidation of alcohol led to straightforward and efficient preparation of carboxylic acids **1**. However, we encountered difficulties in scaling up the enantioselective reactions during the starting steps of de novo route. The de novo route started with a double asymmetric ene reaction that could be performed on a 4 g scale (13 mmol) of 1-(*tert*-butyldiphenylsilanoxy)-3-pentene, but required an excess of 28 g (130 mmol) of (1′*S*, 2′*R*, 5′*S*)-menthyl glyoxalate.

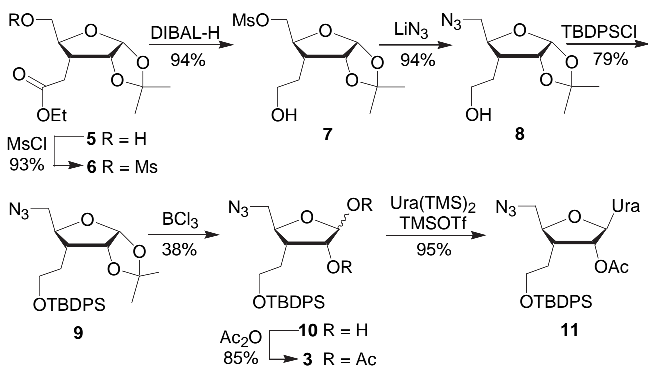


Preparation of pure menthyl glyoxylate[8] involved column chromatography and vacuum distillation and was not practical on scales larger than 28 g. The double asymmetric reaction involving large excess of menthyl glyoxylate was necessary to insure good yields and high enantiomeric purity (>98:2) of the product and it appeared unlikely that this reaction could be scaled up to >50 mmol required to support our planned studies.

Herein we report optimization of our synthetic route[7] by adopting the initial steps from the Robin's synthesis to prepare the key intermediate **3** starting from D-xylose.[6] The key features that ensure efficiency of the new route are chemoselective reduction of the ester and minimization of protecting group manipulation.

2. Results and discussion

Our synthesis (Scheme 1) started with the C3′-homologated ribose derivatives **5** and **6**, which were prepared as described by Robins and co-workers.[6] The plan was to reduce the ester before installation of the azide and then oxidize the alcohol after the nucleoside synthesis as was successfully done in our de novo route.[7] In this way we would avoid the cleavage of ester under basic conditions after the nucleoside synthesis. Direct reduction of **5** would generate two primary alcohols, which would be difficult (if at all possible) to selectively functionalize. To avoid additional protecting groups we decided to use the mesyl group (Ms, Scheme 1) as both differentiating functionality for the 5-OH in **5** and leaving group for



Scheme 1. Synthesis of C3′-homologated uridine.

later nucleophilic substitution with azide.[9] Treatment of alcohol **5** with methanesulfonyl chloride, as described by Robins and co-workers, gave mesylate **6**.[6]

The challenge with such an approach was the selective reduction of the ester in the presence of potentially reactive mesyl group. Of several reducing agents tried (Table 1), the best results were obtained with DIBAL-H at 0 °C.[10] Borane dimethyl sulfide complex[11] also performed well but required elevated temperature (60 °C) and longer reaction time. While $LiAlH_4$ and $Ca(BH_4)_2$ (formed in situ from $NaBH_4$ and $CaCl_2$[12]) gave good yields, $LiBH_4$ with catalytic amounts of 9BBN[13] gave complex reaction mixture containing no target product.

Table 1
Results of selective reduction of ester **6**

	Reagent	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DIBAL-H	CH_2Cl_2, hexane	0	1	94
2	$BH_3 \cdot Me_2S$	THF	60	2	93
3	$LiAlH_4$	Dimethoxyethane	0	2	78
4	$NaBH_4$, $CaCl_2$	THF	25	24	74
5	$LiBH_4$-9BBN	THF, toluene	100	24	0

Importantly, the mesylation and DIBAL-H reduction steps gave products in acceptable purity without the need for column chromatography. Treatment of mesylate **7** with lithium azide gave alcohol **8**, which was purified by silica gel column chromatography. Treatment of **8** with TBDPCl gave **9**, which was used in next step again without chromatographic purification.

The most challenging step in our synthesis was the removal of the 1,2-isopropylydene protecting group. Cleavage of 1,2-acetals in carbohydrates generally requires relatively harsh conditions. In our case, the TBDPS ether, which was relatively close on the same side of the tetrahydrofuran ring (see **9** in Scheme 1), further complicated the reaction. Typical protic acid hydrolysis procedures (Table 2) gave either no reaction (entry 1) or led to concurrent cleavage of the TBDPS group (entries 2–7).

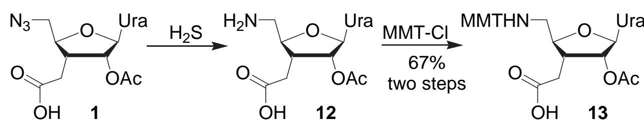
Table 2
Results of cleavage of isopropylydene in **9**

	Reagent	Temp (°C)	Time (h)	Yield (%)
1	Amberlyst-15/MeOH	25	Overnight	NR[a]
2	THF/TFA/H_2O (5:4:1)	25	Overnight	0[b]
3	80% Acetic acid	80	Overnight	0[b]
4	5% Methanesulfonic acid/MeOH	25	Overnight	0[b]
5	0.3% H_2SO_4/MeOH	25	Overnight	0[b]
6	0.5 M HCl/THF	50	Overnight	0[b]
7	H_2SO_4/AcOAc/AcOH (1:2:60)	25	Overnight	29%[c]
8	BBr_3 in hexanes/CH_2Cl_2 (3:40)	−78 to 0	0.5	0[c]
9	BCl_3 in hexanes/CH_2Cl_2 (3:40)	0	0.5	38%[d]

[a] No reaction.
[b] Cleavage of TBDPS.
[c] Decomposition to polar by-products.
[d] Based on recovered starting material.

Acceptable yield of **10** was achieved using BCl_3[14] after recycling of the recovered starting material. Acylation with pyridine/acetic anhydride gave the glycosyl donor **3**, which serves as a common intermediate in synthesis of the modified nucleosides.

Final steps in preparation of all four ribonucleoside 5′-amino 3′-carboxylic acids from the common intermediate **3** have been previously reported by us.[7] Following these procedures we used **3**, prepared from D-xylose, to synthesize uridine derivative **11**. The product obtained was identical to **11** previously synthesized via the de novo route.[7] Following the reported procedures, compound 11 was further converted to the uridine azido acid **1** (Scheme 2). Reduction of azide with hydrogen sulfide was immediately followed by protection of the amino group with methoxytrityl chloride to



Scheme 2. Synthesis of uridine 5′-amino 3′-carboxylic acid.

give the amino acid **13**, suitable for solid phase synthesis of oligoamides.

3. Conclusion

In summary, we have developed a new synthesis of uridine 5′-azido 3′-carboxylic acid **1** from D-xylose in 14 steps 7% overall yield. One step reduction followed by protection of amino group gave the target 5′-amino 3′-carboxyl uridine **13** in 67% yield. Although the yield of the new route is somewhat lower than that of our previous de novo synthesis (nine steps and 19% to **1**),[7] the ability to produce enantiomerically pure material on larger scales is an important advantage for our current studies on solid phase synthesis of oligoamides. While the start of our de novo route was limited to ca. 13 mmol scale in the first step, the new route could be easily started with 200 mmols (30 g) of D-xylose. We envision that the new route should allow future preparation of the target nucleoside 5′-azido 3′-carboxylic acids on a gram scale.

The route presents formal synthesis of all four ribonucleoside 5′-azido 3′-carboxylic acids (**1**) because it makes the common intermediate **3** described in our previous work.[7] The key features that ensure efficiency and ease of operations are chemoselective reduction of the ester, minimization of protecting group manipulation and minimization of silica gel column purification steps. The efficiency may be further increased by optimization of the removal of the 1,2-isopropylydene protecting group. The new route should facilitate synthesis and testing of amide-modified siRNAs, which have shown promising results in initial studies.[4]

4. Experimental section

4.1. 3-Deoxy-3-(2-hydroxyethyl)-1,2-*O*-isopropylidene-5-*O*-(methanesulfonyl)-α-D-ribofuranose (7)

DIBAL-H (46.5 mL, 45.6 mmol, 25% in hexanes) was added slowly to a solution of **6** (7.88 g, 23.2 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C. The solution was stirred at 0 °C for 1 h. The reaction was quenched by extracting with diluted HCl (0.2%, 150 mL), the organic layer was separated, filtered to remove solid particles, and dried over anhydrous Na_2SO_4. Evaporation gave the *title compound* **7** (6.43 g, 94%) as a colorless oil, which could be used in next step without further purification. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.78 (d, *J*=3.6 Hz, 1H), 4.69 (m, 1H), 4.44 and 4.26 (ABX, *J*=2.2, 4.3, 11.5 Hz, 2H), 4.03 (m, 1H), 3.74 (m, 2H), 3.04 (s, 3H), 2.13 (m, 1H), 1.91 (s, 1H), 1.86 (m, 1H), 1.63 (m, 1H), 1.47 (s, 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 111.8, 104.9, 81.0, 79.2, 68.6, 60.6, 41.6, 37.6, 29.6, 27.5, 26.4. MS (ESI) calcd for $2\times C_{11}H_{20}O_7S+Na$ 615.2; found 614.7.

4.2. 5-Azido-3,5-dideoxy-3-(2-hydroxyethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (8)

LiN_3 (4.48 g, 89.5 mmol) was added to a solution of **7** (5.30 g, 17.9 mmol) in anhydrous DMF (50 mL). The solution was heated to 60 °C and stirred at this temperature for 14 h. The solution was concentrated in vacuum, the residue was dissolved in ethyl acetate (40 mL) and washed with brine (30 mL) and water (3×30 mL), the organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuum. The crude product was purified on silica gel column using hexane/ethyl acetate (4:1 v/v) to give the *title compound* (4.11 g, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.81 (d, *J*=3.1 Hz, 1H), 4.67 (m, 1H), 3.98 (m, 1H), 3.75 (m, 2H), 3.62 (dd, *J*=3.0, 13.7 Hz, 1H), 3.23 (dd, *J*=4.7, 13.7 Hz, 1H), 2.12 (m, 1H), 1.84 (m, 1H), 1.58 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 111.7, 104.8, 81.2, 80.4, 60.9, 51.5, 42.5, 27.6, 26.6, 26.3.

4.3. 5-Azido-3,5-dideoxy-3-[2-(*tert*-butyldiphenylsilyoxy)-ethyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (9)

tert-Butyldiphenylsilyl chloride (3.1 mL, 11.8 mmol) was added to a solution of 8 (2.41 g, 9.9 mmol) and imidazole (1.47 g, 21.6 mmol) in anhydrous DMF (20 mL). The solution was stirred at room temperature over night. The reaction was then quenched with water, evaporated in vacuum and the residue was dissolved in EtOAc (20 mL) and washed once with brine (15 mL) then with water (3×15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuum to give the *title compound* **9** (3.75 g, 79%) as a crude colorless oil whose purity was acceptable for the next step. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.71 (m, 4H), 7.44 (m, 6H), 5.77 (d, *J*=3.4 Hz, 1H), 4.42 (m, 1H), 3.98 (m, 1H), 3.82 (m, 2H), 3.61 (dd, *J*=3.0, 13.7 Hz, 1H), 3.20 (dd, *J*=4.8, 13.2 Hz, 1H), 2.17 (m, 1H), 1.84 (m, 1H), 1.55 (m, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 135.6, 129.7, 127.6, 111.6, 104.9, 80.9, 61.9, 51.6, 42.3, 27.6, 26.8, 19.1. MS (ESI) calcd for $C_{26}H_{35}N_3NaO_4Si$ 504.2; found 504.2.

4.4. 5-Azido-3,5-dideoxy-3-[2-(*tert*-butyldiphenylsilyoxy)-ethyl]-α-D-ribofuranose (10)

A solution of **9** (1.505 g, 3.12 mmol) in anhydrous CH_2Cl_2 (40 mL) was cooled to 0 °C and then treated with BCl_3 (3.12 mL, 3.12 mmol, 1 M solution in hexanes) for 30 min. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and brought to room temperature, the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layers were pooled together, dried over Na_2SO_4, filtered, and evaporated in vacuum. The residue was purified on silica gel column using hexane/ethyl acetate (4:1 v/v) to give the *title compound* **10** (0.309 g, 0.718 mmol, 23%) as a colorless oil. After chromatography 0.624 g, 40% of **9** was recovered bringing the yield of **10** to 38% based on the recovered starting material. The spectroscopic data are for mixture of α and β diastereomers. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.70–7.64 (m, 4H), 7.47–7.39 (m, 6H), 5.48 and 5.38 (d, *J*=3.4 Hz, 1H), 4.31–4.25 (m, 1H), 4.10–4.04 (m, 1H), 3.83–3.65 (m, 2H), 3.57–3.48 (m, 1H), 3.31 (dd, *J*=5.5, 13.2 Hz), 3.12 and 3.03 (dd, *J*=4.3, 13.2 Hz), 2.40–2.30 and 2.23–2.14 (m, 1H), 1.97–1.85 (m, 1H), 1.68–1.50 (m, 1H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 135.5, 132.5, 130.0, 127.8, 102.8, 98.2, 82.9, 80.0, 71.8, 63.3, 54.2, 52.4, 42.8, 28.0, 26.7, 18.9.

4.5. 5-Azido-3,5-dideoxy-3-[2-(*tert*-butyldiphenylsilyoxy)-ethyl]-1,2-*O*-diacetyl-α-D-ribofuranose (3)

Compound **10** (0.8 g, 1.81 mmol) was dissolved in pyridine/acetic anhydride (6 mL, 1:1 v/v) and stirred at room temperature for 12 h. The solution was concentrated in vacuum, the residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give the *title compound* **3** (0.809 g, 1.54 mmol, 85%) as colorless oil of purity acceptable for the next step. The spectroscopic data are for mixture of α and β diastereomers. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.69–7.61 (m, 4H), 7.46–7.36 (m, 6H), 6.38 and 6.08 (d, *J*=3.1 Hz, 1H), 5.24–5.16 (m, 1H), 4.24–4.18 and 4.13–4.08 (m, 1H), 3.74–3.58 (m, 3H), 3.27–3.23 and 3.18–3.14 (dd, *J*=4.3, 13.7 Hz, 1H), 2.77–2.68 and

2.55–2.46 (m, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 1.81–1.50 (m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 135.5, 129.7, 127.7, 98.7, 83.8, 82.7, 61.7, 38.0, 29.7, 27.4, 26.8, 20.6.

4.6. 2′-*O*-Acetyl-5′-azido-3′-[2-(*tert*-butyldiphenylsiloxy) ethyl]-3′,5′-dideoxyuridine (11)

The *title compound* **11** was prepared from **3** (0.222 g, 0.412 mmol) as previously described by us[7] in 95% yield (0.226 g). The ^{1}H and ^{13}C NMR matched the reported data.[7] Elemental analysis ($C_{29}H_{35}N_5O_6Si$): calculated C, 60.29; H, 6.11; N, 12.12; found C, 60.44; H, 6.17; N, 11.78.

4.7. 2′-*O*-Acetyl-3′,5′-dideoxy-3′-carboxymethyl-5′-(monomethoxytrityl)amino-uridine triethylammonium salt (13)

Hydrogen sulfide was passed through a solution of **1** (275 mg, 0.78 mmol) in pyridine/water (25 mL, 4:1 v/v) for 1 h at room temperature. The solution was stirred over night and evaporated in vacuum. The residue was dissolved in water (50 mL) and washed with CH_2Cl_2 (4×50 mL). The organic layers were discarded and the water phase was evaporated to give amine **12** (∼230 mg, ∼0.70 mmol, ∼90%), which was used in the next step without further purification. Amine **12** was dissolved in anhydrous pyridine (10 mL) and 4-methoxytrityl chloride (1.08 g, 3.5 mmol) was added. The solution was stirred at room temperature over night. The reaction was quenched with saturated aqueous triethylammonium bicarbonate (1 mL) and evaporated in vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and extracted with saturated aqueous $NaHCO_3$ (3×50 ml). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified on silica gel column eluting with a stepwise gradient of MeOH (0–10%) in CH_2Cl_2 containing 100 ppm of triethylamine to give the *title compound* **13** (362 mg, 0.52 mmol, 67% for two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, J=8.6 Hz, 1H), 7.29 (m, 12H), 6.80 (d, J=9.0 Hz, 2H), 5.81 (s, 1H), 5.60 (d, J=8.1 Hz, 1H), 5.46 (d, J=5.7 Hz, 1H), 4.04 (m, 1H), 3.76 (s, 3H), 2.95 (q, J=7.1 Hz, 6H), 2.72 (m, 2H), 2.26 (m, 3H), 2.06 (s, 3H), 1.17 (t, J=7.14 Hz, 9H). ^{13}C NMR ($CDCl_3$, 72 MHz) δ 175.7, 169.6, 163.7, 158.2, 150.7, 150.1, 146.2, 146.1, 140.4, 137.9, 130.1, 128.7, 128.1, 126.6, 113.5, 102.5, 90.3, 84.3, 78.4, 70.5, 55.4, 45.4, 45.2, 39.6, 31.2, 29.9, 20.8, 8.6. HRMS (ESI) calcd for $C_{33}H_{33}N_3NaO_8$, 622.2165; found, 622.2157.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.110. These data include MOL files and InChiKeys of the most important compounds described in this article.

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