Tetrahedron Letters 50 (2009) 5364–5366

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient synthesis of new *N*-alkyl-D-ribono-1,5-lactams from D-ribono-1,4-lactone

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ARTICLE INFO

Article history:
Received 26 May 2009
Revised 2 July 2009
Accepted 6 July 2009
Available online 10 July 2009

Keywords:
Azasugars
D-Ribono-1,4-lactone
N-Alkyl-D-ribonamides
N-Alkyl-D-ribono-1,5-lactams

ABSTRACT

D-Ribono-1,4-lactone was treated with ethylamine in DMF to afford *N*-ethyl-D-ribonamide **9a** in quantitative yield. Bromination of amide **9a** by the system $SOBr_2$ in DMF or PPh_3/CBr_4 in pyridine led, after acetylation, to epoxide **7**. However, treatment of amide **9a** with acetyl bromide in dioxane followed by acetylation gave 2,3,4-tri-*O*-acetyl-5-bromo-5-deoxyl-*N*-ethyl-D-ribonamide **10a**. Methanolysis of **10a**, with sodium methoxide, afforded the *N*-ethyl-D-ribonolactam **11a** in 51% overall yields. Using this method, *N*-butyl, *N*-hexyl, *N*-dodecyl, and *N*-benzyl-D-ribonolactams **11b–e** were obtained in good yields (48–53%).

The discovery of the glycosidase inhibitor activity of the natural product nojirimycin **1** initiated the synthesis of various polyhydroxylated pyrrolidine, piperidine, azepane, and lactam derivatives (azasugars).[1] This group of inhibitors is potentially useful for treating metabolic disorders such as diabetes,[2] cancer,[3] and AIDS.[4]

Aldonolactams have been reported to have interesting biological activities such as inhibition of glycosidase activity.[5] For example, compounds **2** and **3** have been reported as potentially useful for treating cancer cell metastasis,[6] and inflammation (Fig. 1).[7]

Earlier we reported the synthesis of 5-amino-5-deoxy-D-pentonolactams from unprotected D-pentono-1,4-lactones in 60–83% overall yields.

Thus, unprotected pentonolactone can be transformed to its azido derivative, whose hydrogenation yields the corresponding 3,4,5-trihydroxylactam by spontaneous lactamization of the aminolactone.[8]

In general, the N-alkylated derivatives were found to be stronger glycosidase inhibitors than the corresponding nonalkylated derivatives.[5,9] For example, the *N*-butyl 1-deoxynojirimycin **4** or miglitol **5** has been shown to possess potent inhibitory activity of glycosidase enzymes.[10]

However, only a few reports have appeared on the synthesis of N-substituted aldonolactams. Except for the work of Diez,[11,12] there have been no reports of the synthesis of these derivatives.

In the continuation of our interest in the synthesis of azasugars, we are now reporting in this preliminary work an efficient strategy for the synthesis of new azasugar analogues namely *N*-alkyl-D-ribonolactams: *N*-ethyl, *N*-butyl, *N*-hexyl, *N*-dodecyl, and *N*-benzyl-D-ribonolactams.

At first, for the synthesis of *N*-ethyl-D-ribonolactam, we tried the strategy given in Scheme 1. We have used D-ribono-1,4-lactone as the starting material via the 5-bromo-5-deoxy-D-ribono-1,4-lactone (**6**) as the intermediate.[13]

The treatment of brominated derivative **6** with ethylamine (1.2 equiv) in DMF at room temperature for 1 h gave after acetylation epoxide **7** as the only product, in quantitative yield. No trace of the intermediate 5-bromo-5-deoxy-*N*-ethyl-D-ribonamide was obtained (Scheme 1). In the literature,[11,12] a similar intermediate was obtained but in two steps: when 5-bromo or 5-iodo-5-deoxy-D-ribono-1,4-lactone was treated by leucine derivatives using Et_3N as

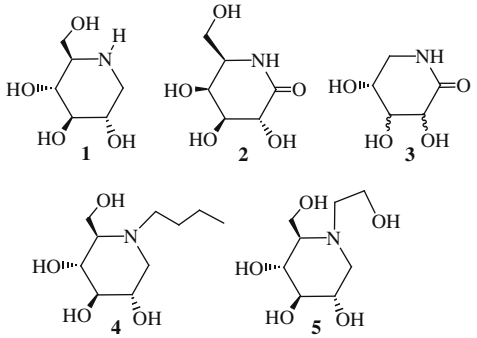

Figure 1. Examples of azasugars.

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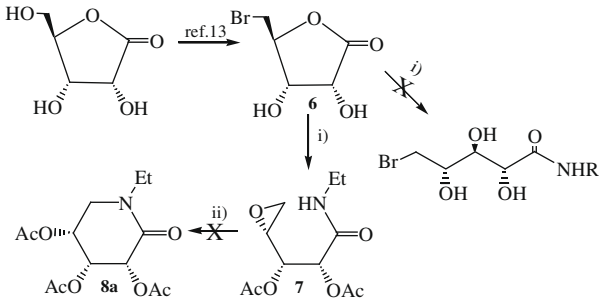
doi:10.1016/j.tetlet.2009.07.026



Scheme 1. Reagents: (i) (a) $EtNH_2$, DMF; (b) Ac_2O, $HClO_4$; (ii) NaH, DMF.

the base the only product obtained was the brominated amide which was converted to epoxide by treatment with K_2CO_3.

Epoxide **7**[14] was then treated with NaH in DMF. Monitoring the reaction by TLC and NMR spectra analysis of the crude product showed that epoxide **7** was present as the only product and no trace of the target 2,3,4-tri-*O*-acetyl-*N*-ethyl-D-ribono-1,5-lactam (**8**) was obtained.

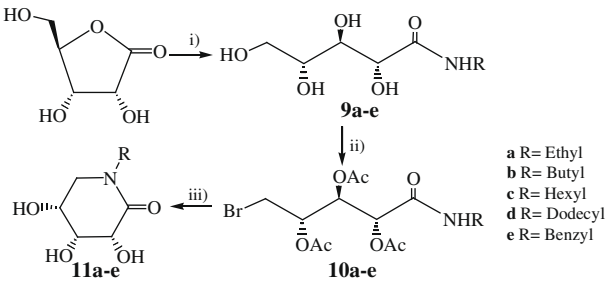
Due to the difficulties in the preparation of 2,3,4-tri-*O*-acetyl-*N*-ethyl-D-ribono-1,5-lactam **8** owing to the formation of epoxide **7** we attempted an alternative strategy.

D-Ribono-1,4-lactone was treated with ethylamine in DMF for 1 h at room temperature to afford the *N*-ethyl-D-ribonamide **9a**[15] in quantitative yield. Treatment of D-ribono-1,4-lactone with butyl, hexyl, dodecyl, and benzylamine gave quantitatively the corresponding *N*-alkyl ribonamides **9b**–**e**. Bromination of amide **9a** by the system $SOBr_2$ in DMF or PPh_3/CBr_4 in pyridine led also, after acetylation, to epoxide **7**.

However, treatment of amide **9a** with acetyl bromide in dioxane for 16 h, at room temperature, followed by acetylation gave the 2,3,4-tri-*O*-acetyl-5-bromo-5-deoxy-*N*-ethyl-D-ribonamide **10a**[16] which was isolated in 51% yield. Bromoamide **10a** was then treated with NaH in DMF, for 1 h, affording 2,3,4-tri-*O*-acetyl-*N*-ethyl-D-ribonolactam. Methanolysis of 2,3,4-tri-*O*-acetyl-*N*-ethyl-D-ribonolactam with sodium methoxide in methanol, led according to NMR spectroscopy, to *N*-ethyl-D-ribonolactam **11a**[17] in quantitative yield. The mass spectrum of compound **11a** showed a diagnostic peak at *m/z* 198 $(M+Na)^+$. The title compound was identified by elemental analysis and NMR spectra which showed, in particular, a signal of a second methylene group at 49.9 ppm corresponding to $-HN-CH_2$ (Scheme 2).

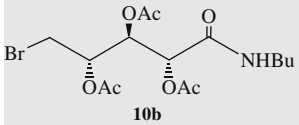
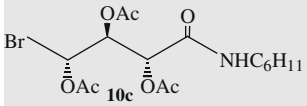
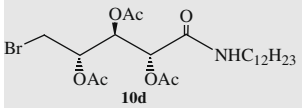
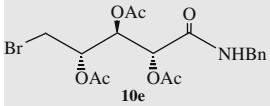
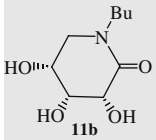
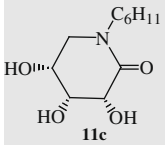
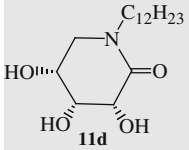
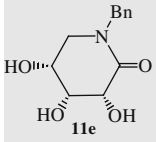
Using this method, *N*-butyl, *N*-hexyl, *N*-dodecyl, and *N*-benzyl-D-ribonolactams (**11b–e**) were obtained in good yields (Table 1).

In summary, we have reported an efficient synthesis of novel *N*-alkyl-D-ribono-1,5-lactams which were synthesized in four steps in 48–53% overall yields from unprotected D-ribono-1,4-lactone.



Scheme 2. Reagents and conditions: (i) RNH_2/DMF, rt; (ii) (a) CH_3COBr/dioxane, rt; (b) Ac_2O/pyridine, rt; (iii) (a) NaH/DMF, rt; (b) MeONa/MeOH, rt.

Table 1
Yields of **10b–e** and **11b–e**

Product	Yield (%)	$[\alpha]_D^{20}$
 **10b**	54	(*c* 0.33; $CHCl_3$) +4
 **10c**	48	(*c* 0.37; $CHCl_3$) +2
 **10d**	40	(*c* 0.23; $CHCl_3$) +6
 **10e**	52	(*c* 0.22; $CHCl_3$) +43
 **11b**	98	(*c* 0.16; H_2O) +7
 **11c**	99	(*c* 0.10; H_2O) +64
 **11d**	99	(*c* 0.10; H_2O) +19
 **11e**	98	(*c* 0.11; H_2O) −10

Acknowledgments

We thank the Ministère de la Recherche, the Conseil Régional de Picardie, and the CNRS for financial support.

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14. *Synthesis procedure and spectral data of 2,3-di-O-acetyl-4,5-anhydro-N-ethyl-D-ribonamide* (**7**): To a stirred solution of 5-bromo-5-deoxy-D-ribono-1,4-lactone (200 mg, 0.95 mmol) in DMF (2 mL) was added ethylamine (1.1 equiv). The solution was kept for 1 h at room temperature. The solvent was removed in vacuo and the residue was treated with acetic anhydride in the presence of perchloric acid for 1 h. After concentration, the residue was diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 extracts were dried, filtered and concentrated. Column chromatography (8:2 EtOAc:cyclohexane) of the residue afforded 2,3-di-*O*-acetyl-4,5-anhydro-*N*-ethyl-D-ribonamide (**7**) (0.233 g, 90%) as a white solid: $[\alpha]_D^{20} - 46$ (*c* 0.22; $CHCl_3$); mp 75–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (t, 1H, *J* = 9.0 Hz), 5.36 (m, 1H, *J* = 6.0 Hz), 4.41 (d, 1H, *J* = 6.1 Hz), 4.23 (dd, 1H, *J* = 3.0 Hz), 3.95 (dd, 1H, *J* = 9.3.0 Hz), 3.31 (q, 2H, *J* = 6.1 Hz), 2.16–2.13 (s, 6H). 1.17 (t, 3H, *J* = 6 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 169.9, 169.6, 79.9, 73.9, 71.0, 70.6.1, 33.8, 20.6, 20.6, 14.7; ESIMS: *m*/*z* $[M+Na]^+$ calcd: 282, found:282. Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.88; H, 6.53; N, 5.32.
15. *Typical synthesis procedure and spectral data of representative compound N-ethyl-D-ribonamide* (**9a**): To a stirred solution of D-ribono-1,4-lactone (200 mg, 1.35 mmol) in DMF (2 mL) was added ethylamine (1.1 equiv). The solution was kept for 1 h at room temperature. The reaction mixture was then concentrated to give quantitatively **9a** (260 mg) as a white solid: $[\alpha]_D^{20} + 41$ (*c* 0.24; H_2O); mp 58–60 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.24 (d, 1H, *J* = 3.1 Hz), 3.87 (m, 2H), 3.71 (dd, 1H, *J* = 3.0 Hz, *J* = 12.0 Hz), 3.58 (dd, 1H, *J* = 6.1 Hz, *J* = 12.0 Hz), 3.16 (q, 2H, *J* = 9.0 Hz). 1.05 (t, 3H, *J* = 9.0 Hz); ^{13}C NMR (75 MHz, D_2O) δ 172.6, 74.3, 73.2, 72.4, 63.6, 33.5, 15.2; ESIMS: *m*/*z* $[M+Na]^+$ calcd: 216, found: 216. Anal. Calcd for $C_7H_{15}NO_5$ C, 43.52; H, 7.83; N, 7.25. Found: C, 43.41.; H, 7.78; N, 7.10.
16. *Typical synthesis procedure and spectral data of representative compound 2,3,4-tri-O-acetyl-5-bromo-5-deoxy-N-ethyl-D-ribonamide* (**10a**): To a stirred solution of *N*-ethyl-D-ribonamide (**9a**) (250 mg, 1.29 mmol) in 1,4-dioxane (3 mL) was added acetyl bromide (105 μL, 1.1 equiv). The solution was kept overnight at room temperature. The solvent was removed in vacuo and the residue was treated with acetic anhydride in pyridine for 1 h. The reaction mixture was then concentrated and the toluene (50 mL) was added to the crude material. After concentration, the residue was diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 extracts were dried, filtered, and concentrated. Column chromatography (7:3 cyclohexane:EtOAc) of the residue afforded 2,3,4-tri-*O*-acetyl-5-bromo-5-deoxy-*N*-ethyl-D-ribonamide **10a** (0.250 g, 51%) as a colorless syrup: $[\alpha]_D^{20} - 3$ (*c* 0.33; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (m, 3H), 3.71 (dd, 1H, *J* = 3.0 Hz; *J* = 6.0 Hz), 3.50 (dd, 1H, *J* = 6.0 Hz, *J* = 12.0 Hz), 3.36 (q, 2H, *J* = 6.0 Hz), 2.13-2.10 (s, 9H). 1.19 (t, 3H, *J* = 6 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 169.6, 169.4, 165.4, 71.9, 71.8, 69.1, 34.3, 31.4, 20.8, 20.7, 20.6, 14.8; ESIMS: *m*/*z* $[M+Na]^+$ calcd: 404, found: 404. Anal. Calcd for $C_{13}H_{20}BrNO_7$: C, 40.85; H, 5.27; Br, 20.91; N, 3.66. Found: C, 40.64; H, 5.30; Br, 20.82; N, 3.53.
17. *Typical synthesis procedure and spectral data of representative compound N-ethyl-D-ribonolactam* (**11a**): To a stirred solution of **10a** (140 mg, 0.367 mmol) in DMF (2.5 mL) was added NaH (1 equiv). The reaction mixture was stirred at room temperature for 1 h and a second portion of NaH (1 equiv) was added. After 1 h, the solvent was removed in vacuo and the residue was chromatographed on silica gel. Elution with (7:3, (AcOEt–cyclohexane) gave 2,3,4-tri-*O*-acetyl-*N*-ethyl-D-ribonolactam. To a solution of the obtained 2,3,4-tri-*O*-acetyl-*N*-ethyl-D-ribonolactam (110 mg, 0.365 mmol) in MeOH (7.5 mL) was added NaOMe (1 M) in MeOH (1.1 mL). The mixture was stirred for 1 h at room temperature. After concentration, the residue was diluted with water and washed with CH_2Cl_2. The water extracts were combined. The acidic resin (Amberlite IR-120 H+) was added and the suspension was stirred for 5 min. The resin was then removed by filtration. The filtrate was concentrated under reduced pressure to give quantitatively the desired *N*-ethyl-D-ribonolactam (**11a**): (65 mg) as a colorless solid; $[\alpha]_D^{20} + 22$ (*c* 0.24; H_2O); mp 143–145 °C; ^{1}H NMR (300 MHz, pyridine-d_5) δ 4.87 (m, 1H), 4.44 (m, 2H), 3.93 (dd, 1H, *J* = 3.6 Hz, *J* = 10.5 Hz), 3.48 (dd, 1H, *J* = 6.3 Hz, *J* = 10.5 Hz), 3.33 (q, 2H, *J* = 7.2 Hz), 1.03 (t, 3H, *J* = 7.2 Hz),. ^{13}C NMR (75 MHz, pyridine-d_5) δ 171.0, 72.1, 70.6, 65.8, 49.9; 41.7, 11.9; ESIMS: *m*/*z* $[M+Na]^+$ calcd: 198, found: 198. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 48.2; H, 7.45; N, 7.89.