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Syntheses of Novel Optically Active Bicyclic Lactams from an Acidic Saccharide

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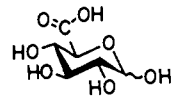
New optically active lactams having a bicyclo[3.2.1]-octene or -octane skeleton were synthesized from D-glucuronic acid. The key step is an intramolecular cyclization of N-(p-methoxybenzyl)-1,2,3,4-tetra-O-acetyl-D-glucuronamide with simultaneous elimination of acetic acid molecules.

D-Glucuronic acid (**1**) is an acidic monosaccharide contained as an important constituent in heteropolysaccharides such as chondroitin sulfate, hyaluronic acid, and glucuronoxylan. Therefore **1** is expected to be an attractive starting material for synthesis of potentially biodegradable or biomedical polymers. The present communication describes the syntheses of new optically active bicyclic lactams, (1S,4S,5R)-4-benzyloxy-8-oxa-6-azabicyclo[3.2.1]oct-2-en-7-one (**2**) and (1S,4S,5R)-4-benzyloxy-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3**), from D-glucofuranurono-6,3-lactone (**4**), which is commercially derived from **1**.[1] The synthetic route is shown in Scheme 1. The characteristic points in the present route are the temporary introduction of p-methoxybenzyl group to the amide nitrogen atom in 1,2,3,4-tetra-O-acetyl-D-glucopyranuronamide in advance of its intramolecular cyclization (see compound **7**), and the elimination of the p-methoxybenzyl group in the final step, as described later.



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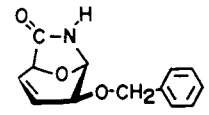

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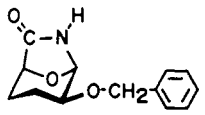

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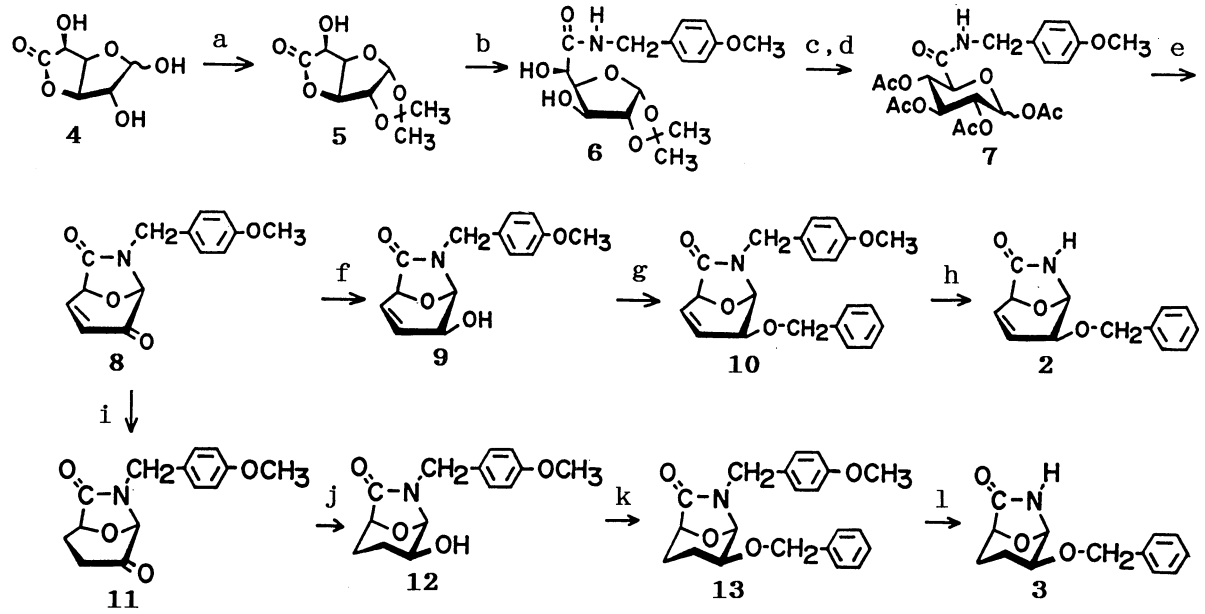
First, the anomeric hydroxyl group in **4** was protected with isopropylidene group according to the literature.[2] The reaction of 1,2-O-isopropylidene-D-glucofuranurono-6,3-lactone (**5**) with small excess of p-methoxybenzylamine proceeded without catalyst in tetrahydrofuran (THF) at room temperature for 4 hour to yield N-(p-methoxybenzyl)-1,2-O-isopropylidene-D-glucofuranuronamide (**6**) (yield after reprecipitation with n-hexane, 94%). Then the isopropylidene group in **6** was removed by hydrolysis, and the resulting colorless solid, N-(p-methoxybenzyl)-D-glucopyran-



a) reference 2, 87%. b) p-methoxybenzylamine, THF, r.t., 94%.
c) CF_3COOH + H_2O (2:1 v/v), r.t., 85%. d) $(CH_3CO)_2O$ + pyridine, r.t., 66%. e) Table 1. f) $NaBH_4$, CH_3OH, 7 °C, 99%.
g) benzyl bromide + NaH, r.t., ≈100%. h) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, r.t., 70%. i) H_2 on 5%Pd/C, CH_3OH, r.t., ≈100%. j) $NaBH_4$, CH_3OH, 30 °C, 96%. k) benzyl bromide + NaH, r.t., ≈100%.
l) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, r.t., 57%.

Scheme 1.

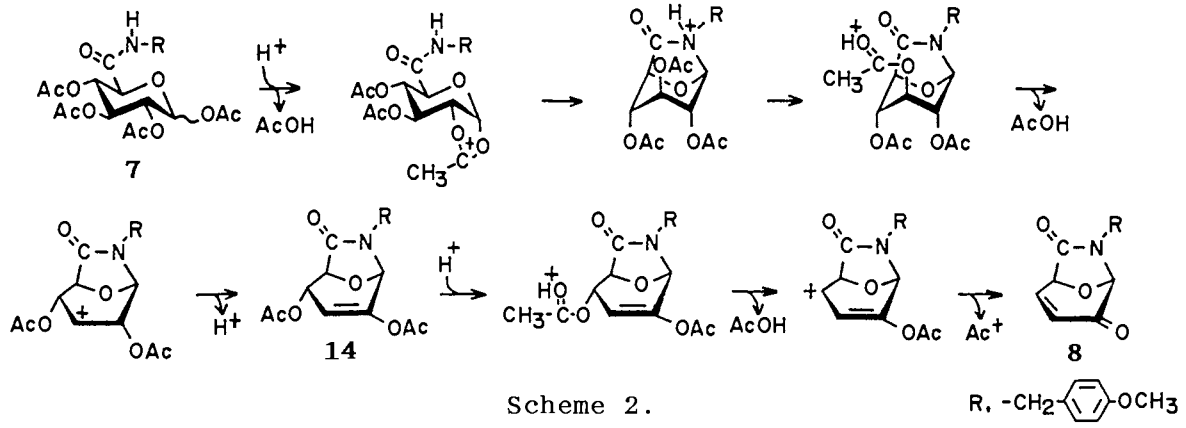
uronamide, was acetylated with excess acetic anhydride and pyridine at room temperature to give a mixture of α- and β-anomers of N-(p-methoxybenzyl)-1,2,3,4-tetra-O-acetyl-D-glucopyranuronamide (**7**).

As shown in Table 1, the acid-catalyzed intramolecular cyclization of the N-substituted glucuronamide **7** was tried under various conditions and monitored by thin layer chromatography. The cyclization needed the reflux of the reaction mixture at higher temperature, by which a significant amount of **7** was forced to resinify. When **7** was refluxed in the presence of a strong acid such as trifluoromethanesulfonic acid in dilute chlorobenzene solution for 30 min, a bicyclic lactam having an unsaturated ketone group, (1S,5R)-N-(p-methoxybenzyl)-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4,7-dione (**8**) was isolated in relatively high yield.[3] Another bicyclic lactam, (1S,2S,5R)-2,4-diacetoxy-N-(p-methoxybenzyl)-8-oxa-6-azabicyclo[3.2.1]oct-3-en-7-one (**14**), was also obtained in the reaction of **7** in the presence of p-toluenesulfonic acid (p-TSA) or methanesulfonic acid.[4] The mole ratio of **8** to **14** and their total yield in the presence of the latter acids increased with the reaction time until the times shown in Table 1. However the excess reflux caused the reduction of their yields because of their resinification. The elimination of acetyl groups during the intramolecular cyclization of **7** was speculated to proceed through the

Table 1. Intramolecular cyclization of **7** with elimination under various conditions[a)]

Catalyst		Solvent	Temp	Time	Yield/%	
	mol%		°C		**8**	**14**
p-TSA	20	Benzene	80	3 d	0	0
p-TSA	20	Toluene	110	3 d	4	7
p-TSA	20	Nitroethane	114	5 d	Trace	0
p-TSA	10	Chlorobenzene	132	8 h	7	24
CH_3SO_3H	20	Chlorobenzene	132	10 h	13	17
CF_3SO_3H	10	Chlorobenzene	132	0.5 h	38	0

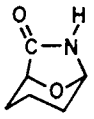
a) **7**, 0.6-4.8 g; solvent, 43-83 L/mol of **7**.



Scheme 2.

intermediate **14** as shown in Scheme 2. The N-unsubstituted analogue of **7**, 1,2,3,4-tetra-O-acetyl-D-glucopyranuronamide, was also refluxed under a similar condition, but the yield of the corresponding bicyclic lactam was found to be less than 1%. Therefore, the N-substitution of **7** is inferred to be of great advantage to its intramolecular cyclization.

After the carbonyl group in **8** was reduced with sodium borohydride, the hydroxyl group in the resulting (1S,4S,5R)-4-hydroxy-N-(p-methoxybenzyl)-8-oxa-6-azabicyclo[3.2.1]oct-2-en-7-one (**9**) was converted to a benzyl ether group, and finally the p-methoxybenzyl group was removed with ceric ammonium nitrate (the yield of (1S,4S,5R)-4-benzyloxy-8-oxa-6-azabicyclo[3.2.1]oct-2-en-7-one (**2**) from **10**, 70%).[5)] Another bicyclic lactam, (1S,4S,5R)-4-benzyloxy-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3**), was also prepared by the same method after reduction of **8** with hydrogen on 5% Pd/C.[6)] The overall yields of **2** and **3** based on **4** were 12% and 9.5%, respectively. Their structures were ascertained by X-ray crystallographic analyses, too.[7)] These are the first N-unsubstituted polymerizable bicyclic lactams prepared from **1**, although a N-(diacetylamino) analogue was previously synthesized through a different route.[8)] The new bicyclic lactam **2** was found to polymerize under mild conditions,[9)] as a similar bicyclic lactam **15** did.[10)]



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References

1) In the present letter, bicyclic oxalactams prepared from D-glucuronic acid are named according to the IUPAC nomenclature but their precursors are named as derivatives of D-glucuronic acid for convenience.
2) L.N. Owen, S. Peat, and W.J.G. Jones, J. Chem. Soc., **1941**, 339.
3) Mp 92.5-93.5 °C; $[\alpha]_D^{25}$, -733 ° ($CHCl_3$, c 1). Anal. Found: C, 64 83; H, 5.00; N, 5.36%. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40%. Parent peak in mass spectrum, m/e=259. ^1H NMR ($CDCl_3$) δ 7.36 (dd, J= 9.9 Hz and J=4.6 Hz, 1H, ^2CH), 7.18 (d, J=8.6 Hz, 2H, ortho), 6.87 (d, J=8.6 Hz, 2H, meta), 6.00 (dd, J=9.9 Hz and J=1.7 Hz, 1H, ^3CH), 5.00 (d, J=1.7 Hz, 1H, ^5CH), 4.77 (d, J=4.6 Hz, 1H, ^1CH), 4.69 and 3.99 (d, J=15.2 Hz, 1H, one of gem CH_2), 3.79 (s, 3H, CH_3O) ppm. ^{13}C NMR ($CDCl_3$) δ 185.8, 169.9, 159.3, 145.6, 129.6, 126.6, 126.1, 114.1, 89.8, 74.4, 55.2, 43.5 ppm.
4) Parent peak in mass spectrum, m/e=361. ^1H NMR ($CDCl_3$) δ 7.16 (d, J= 8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 5.65 (ddd, J=4.4 Hz, J=1.7 Hz and J=1.6 Hz, 1H), 5.34 (dd, J=4.4 Hz and J=0.7 Hz, 1H), 5.03 (d, J=1.7 Hz, 1H), 4.72 and 4.12 (d, J=15.2 Hz, 1H), 4.67 (dd, J=1.6 Hz and J=0.7 Hz, 1H), 3.81 (s, 3H), 2.12 and 2.08 (s, 3H) ppm.
5) Mp 145-146 °C; $[\alpha]_D^{25}$, -297 ° ($CHCl_3$, c 1). Anal. Found: C, 67.43; H, 5.56; N, 6.15%. Calcd for $C_{13}H_{13}NO_3$: C, 67.50; H, 5.67; N, 6.06%. Parent peak in mass spectrum, m/e=231. IR (KBr disk) 3170 (ν_{N-H}), 1725 ($\nu_{C=O}$), 1689 ($\nu_{C=O}$) cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, phenyl), 6.70 (broad s, 1H, lactam NH), 6.28 (ddd, J=10.0 Hz, J=4.2 Hz and J= 1.7 Hz, 1H, ^2CH), 5.87 (ddd, J=10.0 Hz, J=2.2 Hz and J=2.2 Hz, 1H, ^3CH), 5.32 (dd, J= 3.2Hz and J=2.2 Hz, 1H, ^5CH), 4.70 and 4.53 (d, J= 12.0 Hz, 1H, one of gem CH_2), 4.29 (d, J=4.2 Hz, 1H, ^1CH), 4.22 (m, 1H, ^4CH) ppm.
6) Mp 127-128 °C; $[\alpha]_D^{25}$, -138 ° ($CHCl_3$, c 1). Anal. Found: C, 66.76; H, 6.48; N, 6.00%. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%. Parent peak in mass spectrum, m/e=233. IR (KBr disk) 3193(ν_{N-H}), 1725 ($\nu_{C=O}$), 1691 ($\nu_{C=O}$) cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31 (m, 5H), 7.11 (broad s, 1H), 5.16 (s, 1H), 4.59 and 4.48 (d, J=11.7 Hz, 1H), 4.16 (s, 1H), 3.66 (m, 1H), 2.14 (m, 1H), 1.75 (m, 3H) ppm.
7) T. Yamane, E. Matsueda, T. Ashida, K. Hashimoto, and M. Okada, Bull. Chem. Soc. Jpn., to be submitted.
8) Y. Takeda, T. Akimoto, and Y. Kyogoku, Carbohydr. Res., **106**, 175 (1982).
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