HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1197-1203. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 4th September, 2016, Accepted, 14th November, 2016, Published online, 24th January, 2017
DOI: 10.3987/COM-16-S(S)69

SYNTHESIS OF CYCLIC NIGEROSYLNIGEROSE (CNN) BIS-IMIDAZOLIUM SALTS

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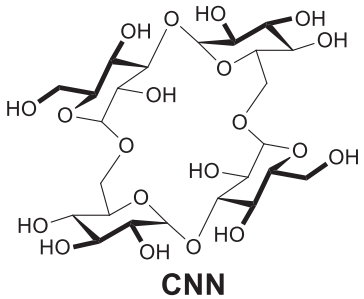
Abstract – Cyclic nigerosyl-(1→6)-nigerose (CNN) monotosylate **1** and CNN ditosylate **2** were prepared and characterized by MALDI-TOF mass and NMR Spectroscopies. CNN bis-imidazolium salts **3** were also obtained by nucleophilic displacement reaction of **2** with imidazoles.

Cyclic nigerosyl-(1→6)-nigerose (CNN; *cyclo*-{→6}-α-D-Glc*p*-(1→3)-α-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→3)-α-D-Glc*p*-(1→)) is a cyclic tetrasaccharide composed of four glucose units. This oligosaccharide is produced from alternan and starch by their degrading enzymes.[1-3] The X-ray crystal structural analysis revealed that CNN has a shallow round bowl-like shape with a small concavity at the center.[4] It is known that CNN traps a water molecule[5] and forms complexes with some optically active amino acid esters as a guest molecule.[6]

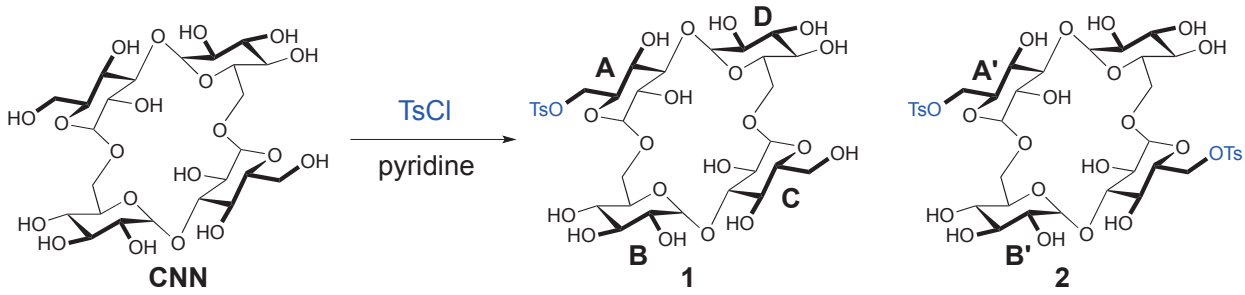


Scheme 1. Structure of CNN

This unique molecular structure of CNN attracts much attention by its molecular recognizing ability and/or as a chiral source. In 2003 as a pioneering work, Dunlap and co-workers synthesized a CNN

dicarboxylic acid derivative by selective oxidation of the primary hydroxyl groups of CNN and its metal complexes including Fe and Pb.[7] Recently, Inoue's group reported enantiodifferentiating photoisomerization of cyclooctene by use of CNN-based sensitizers and diastereodifferentiating photocyclodimerization of 2-anthracenecarboxylates carrying a CNN auxiliary.[8-11] Aiming at the synthetic application of CNN to transition metal chemistry as a chiral source and/or a chiral scaffold of ligands, we intended to functionalize CNN at its primary alcohol carbons and prepared new CNN derivatives possessing tosyl and imidazolium functional groups.

Table 1. Preparation of tosylates **1** and **2**



Entry	TsCl (equiv.)	temperature (°C)	reaction time (h)	yield (%)[a]	
				mono-tosylate **1**[b]	di-tosylate **2**[b]
1	3	rt	17	27(10)[c]	2
2	3	40	10	12	2
3	6	rt	3	40(27)[c]	19
4	7	rt	10	26	30(13)[c]
5	10	rt	10	trace	3
6	10	rt	1	3	13(13)[c]
7	10	rt	0.5	9	25(25)[c]
8	10	rt	0.1	11	38(23)[c]

[a]Isolated yield. [b]A mixture of primary and secondary tosylates. Structures of only primary tosylates were depicted. [c]The number in parentheses is the isolated yield of **1** or **2**.

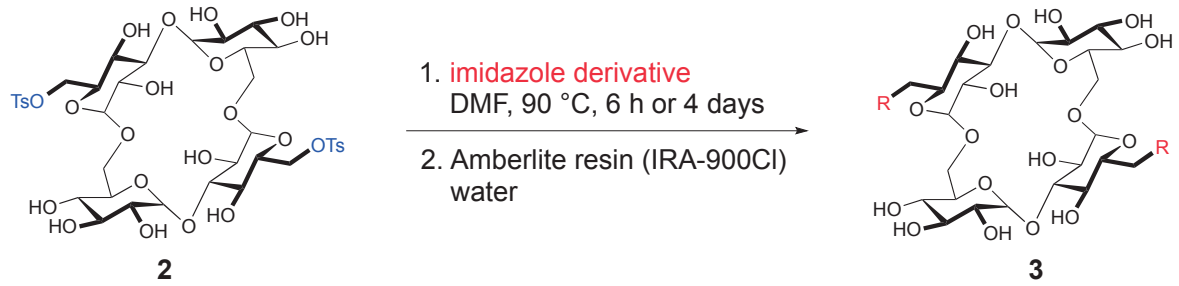
We firstly optimized the tosylation reaction of CNN by changing the amount of tosyl chloride, temperature and reaction time in order to achieve selective tosylation at the primary alcohol units employing the reaction conditions[12] that enabled selective tosylation of cyclodextrins on their primary alcohol unit to afford 6-O-mono-tosyl-cyclodextrins. Under the conditions using three equivalents of tosyl chloride at room temperature in entry 1 of Table 1, a CNN monotosylate mixture, tosylated at either primary or secondary hydroxyl group, was obtained in 27% yield after a silica gel column chromatography. Although it was reported that primary hydroxyl group is preferentially tosylated than secondary hydroxyl group,[13] NMR analysis suggested that the obtained monotosylate mixture contained a

CNN derivative(s) tosylated at a secondary alcohol unit in about 15%. The desired primary tosylate **1** was isolated in pure form after the second silica gel column chromatography albeit in only 10% yield because the primary and secondary tosylates have similar retention factors. The monotosylate was characterized by mass spectroscopy (MALDI-TOF) and NMR spectroscopies. ^{1}H NMR spectrum of **1** was complicated due to the four non-equivalent glucopyranose units represented by **A**-**D** in Table 1. When the reaction was carried out at a higher temperature of 40 °C, a complex mixture of multi-tosylates was obtained (entry 2, Table 1). The yield of **1** was largely increased by using six equivalents of tosyl chloride with a short reaction time (3 h) at rt (entry 3, Table 1). Primary tosylate **1** was isolated in 27% yield in pure form by subjecting the mixture to column chromatography (two times). The secondary tosylates were not isolated nor characterized, so that the position of the tosyl group on the CNN derivatives is not yet clear.

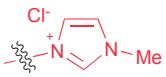
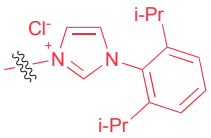
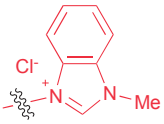
Next, the reaction conditions were optimized for preparation of CNN ditosylate **2**. In entry 4 of Table 1, a CNN ditosylate mixture was obtained in 30% yield by using seven equivalents of tosyl chloride at room temperature for 10 h. The ^{1}H NMR spectrum of the mixture indicated that the bis-primary tosylate **2**, a CNN derivative tosylated at both primary hydroxyl sites, was formed as the major product along with a small amount of ditosylates having a secondary tosyl group(s). These minor ditosylates were not yet isolated nor characterized. The desired ditosylate **2** was isolated in 13% yield by column chromatography. The ^{1}H NMR spectrum of the isolated ditosylate **2** indicated that the CNN derivative has C_2 symmetrical structure with two pairs of non-equivalent glucopyranose units **A'** and **B'** as shown in Table 1. Since a monotosylate mixture was also formed in 26% yield in entry 4, we performed tosylation of CNN using ten equivalents of tosyl chloride at room temperature (entry 5, Table 1). However, unfortunately, the yield of compound **2** was not improved due probably to further reaction of ditosylates with the excess tosyl chloride. When the reaction time was shortened (entries 6-8, Table 1), the yield of desired ditosylate **2** was improved with suppression of monotosylate formation. Especially, in entries 7 and 8, the compound **2** was easily isolated from the crude mixture after a single column chromatography in 25% and 23% respectively. Under these entries, multitosylates such as tri-, tetra-, and pentatosylates were also formed.

We then treated the ditosylate **2** with *N*-substituted imidazoles and subjected the mixture to ion-exchange process using Amberlite resin (IRA-900Cl) to prepare the corresponding bis-imidazolium salts **3a**-**3c**. Both substitution reaction and subsequent ion-exchange reaction efficiently proceeded and the target compounds **3a**-**3c** were obtained in good yields (71-84%) only by precipitation without any further purification. The bis-imidazolium salts **3** were characterized by mass spectroscopies (FAB MS) and NMR spectroscopies. The ^{1}H NMR spectra of these imidazolium salts showed that the CNN derivatives has C_2 symmetry with two pairs of non-equivalent glucopyranose units as in the case of **2**.

Table 2. Preparation of bis-imidazolium salts **3**



2 **3**

	3a	**3b**	**3c**
R =			
isolated yield (%)	71% (6 h)	84% (4 days)	71% (4 days)

In conclusion, we have prepared monotosylate **1** and ditosylate **2** as the key intermediates for further modification of CNN on their primary alcohol units. These tosylates were characterized by mass and NMR spectroscopies. Thus formed ditosylate **2** was efficiently converted to bis-imidazolium salts **3a**-**3c**. Further studies for synthesis of metal complexes employing **3** as the NHC (*N*-heterocyclic carbene) ligand precursors are ongoing.

EXPERIMENTAL

Melting points were measured with a Stanford Research Systems MPA100 apparatus. Optical rotations were recorded by a Jasco P-2000 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded by a JEOL JNM-Alice 400 (for 400 MHz and 100 MHz, respectively) spectrometer and a Bruker DRX-600 (for 600 MHz and 150 MHz, respectively) spectrometer. Matrix assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra were obtained with 2,5-dihydroxy benzoic acid as a matrix on a BRUKER autoflex III. FAB mass spectroscopies (HR-MS) were carried out by using a JEOL JMS-700 with polyethleneglycol as a matrix. Elemental analyses were performed on Perkin Elmer 240C apparatus in the Instrumental Analysis Center of the Faculty of Engineering, Osaka University.

Materials. Cyclic nigerosylnigerose (CNN) was supplied by Hayashibara Co., Ltd. Other reagents were purchased from commercial sources and used without further purification.

Typical procedure for the preparation of CNN tosylates.

Under nitrogen, CNN (3.0 mmol) was dissolved in pyridine (40 mL). To the solution, tosyl chloride (21 mmol) was added at once, the resulting reaction mixture was stirred at room temperature. After 10 h, pyridine was removed in vacuo. To the residue, Et_2O was added, and then the mixture was vigorously

stirred. After standing, the top clear layer was removed. The precipitate was washed another three times with Et_2O by the same decantation process. The residue was dried in vacuo to give a pale yellow solid. The crude was purified with column chromatography (ODS; KP-C18-HS 60 g (Biotage), water/EtOH = 100/0 → 40/60) to obtain a ditosylate mixture. The mixture was purified again with column chromatography (ODS; KP-C18-HS 120 g (Biotage), water/EtOH = 75/25 → 65/35) to acquire the desired CNN ditosylate **2** as a white solid.

CNN ditosylate (2): a white solid; mp 169-172 °C, accompanied by decomposition; $[\alpha]_D^{20}$ +113.0 (c 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.42 (s, 6H), 2.83 (m, 2H), 3.19 (m, 4H), 3.44-3.25 (m, overlapped with HOD), 3.54 (m, 2H), 3.75 (t, *J* = 9.3 Hz, 2H), 4.06 (dd, *J* = 5.9, 10.7 Hz, 2H), 4.22 (m, 2H), 4.30 (d, *J* = 8.9 Hz, 2H), 4.40 (d, *J* = 6.6 Hz, 2H), 4.45 (m, 2H), 4.53 (d, *J* = 3.6 Hz, 2H), 4.77 (d, *J* = 4.7 Hz, 2H), 5.00 (d, *J* = 4.7 Hz, 2H), 5.28 (d, *J* = 4.0 Hz, 2H), 5.41 (d, *J* = 7.4 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 4H), 7.77 (d, *J* = 8.2 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 21.2, 69.2, 69.4, 69.8, 70.0, 70.6, 71.0, 72.2, 73.4, 75.3, 97.6, 100.0, 127.7, 130.2, 132.4, 145.0; MALDI-TOF-MS: (*m/z*) 979.200 ($[M+Na]^+$, $C_{38}H_{52}NaO_{24}S_2$, calacd. 979.219); Anal. Calcd for $C_{38}H_{52}O_{24}S_2 \cdot H_2O$: C, 46.81; H, 5.58; S, 6.58. Found: C, 46.55; H, 5.71; S, 6.36.

CNN monotosylate (1): a white solid; mp 166-169 °C, accompanied by decomposition; $[\alpha]_D^{20}$ +167.6 (c 1.0, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 2.42 (s, 3H), 2.85-2.87 (m, 2H), 3.17-3.60 (m, overlapped with HOD), 3.78-3.81 (m, 2H), 4.07 (dd, *J* = 6.1, 10.8 Hz, 1H), 4.19 (d, *J* = 9.2 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.32-4.37 (m, 3H), 4.45-4.49 (m, 3H), 4.55 (d, *J* = 3.7 Hz, 1H), 4.59 (d, *J* = 3.8 Hz, 1H), 4.73-4.75 (m, 2H), 4.97-4.99 (m, 2H), 5.09 (d, *J* = 5.5 Hz, 1H), 5.29 (d, *J* = 4.3 Hz, 1H), 5.35 (d, *J* = 3.9 Hz, 1H), 5.39 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 21.6, 61.0, 69.3, 69.7, 69.8, 70.1, 70.2, 70.5, 70.5, 70.9, 71.0, 71.5, 71.6, 72.6, 72.7, 72.9, 73.9, 75.7, 76.1, 97.9, 98.0, 100.4, 128.1, 130.6, 132.9, 145.4; MALDI-TOF-MS: (*m/z*) 825.199 ($[M+Na]^+$, $C_{31}H_{46}NaO_{22}S$, calacd. 825.210); Anal. Calcd for $C_{31}H_{46}O_{22}S \cdot 2H_2O$: C, 44.39; H, 6.01; S, 3.82. Found: C, 44.17; H, 6.20; S, 3.74.

Typical procedure for preparation of CNN imidazolium salt (3a).

Under nitrogen, CNN ditosylate **2** (0.39 mmol) was dissolved to 1-methylimidazole (7.8 mmol) at 90 °C. The mixture was stirred at 90 °C for 6 h. Acetone was added at once to the reaction mixture, and then the resulting precipitate was filtered. The filter residue was washed with another acetone and dried in vacuo. The residue was dissolved in water, and then Amberlite IRA-900 (Cl) resin was added to the solution. After overnight standing, the mixture was filtered, and then the filtrate was concentrated under reduced pressure and dried in vacuo to obtain the desired bis-imidazolium salt **3** as a white solid (71% yield in 2 steps).

CNN bis-*N*-methylimidazolium salt (3a): a white solid; mp 221-223 °C; $[\alpha]_D^{20}$ +141.9 (c 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.79 (m, 2H), 3.12-3.27 (m, 8H), 3.41 (m, 2H), 3.47 (d, *J* = 9.1 Hz, 2H), 3.71 (m, 2H), 3.82 (t, *J* = 9.3 Hz, 2H), 3.87 (s, 6H), 4.35-4.50 (m, 10H), 4.64 (d, *J* = 3.7 Hz, 2H), 4.85 (d, *J* = 4.5 Hz, 2H), 5.03 (d, *J* = 4.8 Hz, 2H), 5.34 (d, *J* = 3.9 Hz, 2H), 5.68 (m, 2H), 7.71 (d, *J* = 1.7, 2H), 7.74 (d, *J* = 1.7 Hz, 2H), 9.09 (s, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 35.8, 49.5, 69.0, 69.3, 69.6, 70.0, 71.0, 71.3, 72.2, 73.4, 75.0, 97.2, 99.9, 123.3, 123.4, 137.5; HR-MS (FAB): (*m/z*) 813.2823 ($[M-Cl]^+$, $C_{32}H_{50}ClN_4O_{18}$, calacd. 813.2803); Anal. Calcd for $C_{32}H_{50}Cl_2N_4O_{18}\cdot H_2O$: C, 44.30; H, 6.04; N, 6.46. Found: C, 44.15; H, 6.33; N, 6.55.

CNN bis-*N*-diisopropylphenylimidazolium salt (3b): a pale yellow solid; mp 229-234 °C, accompanied by decomposition; $[\alpha]_D^{20}$ +108.1 (c 1.0, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 1.16 (m, 24H), 2.24 (m, 4H), 2.79 (m, 2H), 3.19-3.30 (m, 8H), 3.46 (m, 4H), 3.77 (m, 2H), 3.86 (t, *J* = 9.1 Hz, 2H), 4.35 (dd, *J* = 8.1, 14.2 Hz, 2H), 4.43 (d, *J* = 8.9 Hz, 2H), 4.47-4.51 (m, 4H), 4.65 (d, *J* = 3.6 Hz, 2H), 4.69 (d, *J* = 12.0 Hz, 2H), 4.87 (d, *J* = 4.6 Hz, 2H), 4.95 (d, *J* = 4.5 Hz, 2H), 5.41 (d, *J* = 3.9 Hz, 2H), 5.83 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 4H), 7.63 (t, *J* = 7.8 Hz, 2H), 8.10 (d, *J* = 1.7 Hz, 2H), 8.14 (d, *J* = 1.7 Hz, 2H), 9.58 (s, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 23.7, 28.1, 50.4, 64.9, 69.7, 69.8, 70.2, 71.1, 72.0, 72.2, 73.4, 74.8, 97.4, 100.5, 124.1, 124.4 (two peaks overlapped), 124.9, 130.5, 131.5, 138.8, 145.0, 145.2; HR-MS (FAB): (*m/z*) 1105.5006 ($[M-Cl]^+$, $C_{54}H_{78}ClN_4O_{18}$, calacd. 1105.4994); Anal. Calcd for $C_{54}H_{78}Cl_2N_4O_{18}\cdot 6H_2O$: C, 51.88; H, 7.26; N, 4.48. Found: C, 51.88; H, 7.02; N, 4.33.

CNN bis-*N*-methylbenzimidazolium salt (3c): a white solid; mp 227-232 °C, accompanied by decomposition; $[\alpha]_D^{20}$ +182.5 (c 1.0, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 2.88 (t, *J* = 10.0 Hz, 2H), 3.02 (m, 2H), 3.19-3.56 (m, overlapped with HOD), 3.78 (t, *J* = 9.3 Hz, 2H), 3.92 (m, 2H), 4.12 (s, 3H), 4.27 (m, 4H), 4.44 (d, *J* = 6.4 Hz, 2H), 4.58 (d, *J* = 3.6 Hz, 2H), 4.64 (dd, *J* = 7.2, 14.8 Hz, 2H), 4.76 (d, *J* = 4.8 Hz, 2H), 4.80 (dd, *J* = 2.3, 14.8 Hz, 2H), 4.89 (d, *J* = 5.0 Hz, 2H), 5.21 (d, *J* = 3.9 Hz, 2H), 5.71 (d, *J* = 7.6 Hz, 2H), 7.71 (m, 4H), 7.98 (m, 2H), 8.03 (m, 2H), 9.67 (s, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 33.3, 47.5, 68.2, 68.9, 69.2, 70.0, 71.0, 71.8, 72.1, 73.2, 74.7, 96.7, 99.1, 113.4, 114.2, 126.5, 126.6, 131.4, 131.6, 143.5; HR-MS (FAB): (*m/z*) 913.3128 ($[M-Cl]^+$, $C_{40}H_{54}ClN_4O_{18}$, calacd. 913.3116); Anal. Calcd for $C_{40}H_{54}Cl_2N_4O_{18}\cdot 5H_2O$: C, 46.20; H, 6.20; N, 5.39. Found: C, 45.93; H, 6.13; N, 5.41.

ACKNOWLEDGEMENT

We thank Hayashibara Co., Ltd. for suppling of Cyclic nigerosylnigerose (CNN) samples.

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