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SHORT-STEP SYNTHESIS OF 5-THIO-L-HEXOPYRANOSES FROM D-GLYCONOTHIO-*O*-LACTONES

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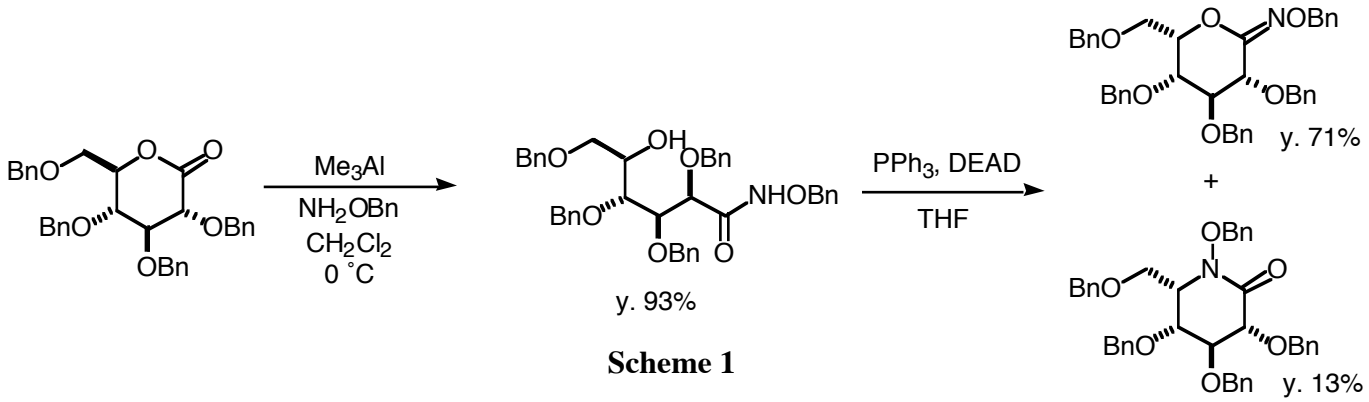
Abstract – We developed a synthetic method for 5-thio-L-hexopyranose from D-glyconothio-*O*-lactone using the initial ring-opening reaction and subsequent recyclization under Mitsunobu conditions. Using this method, only a three-step transformation is required from D-glyconothio-*O*-lactone to 5-thio-L-glyconolactone.

INTRODUCTION

5-Thiohexopyranoses, which replace the ring oxygen atom with a sulfur atom, are biologically interesting hexopyranose analogues, and they might exhibit unique activities which hexopyranoses do not possess.[1] Since 5-thiohexopyranoses are a rare sugar in nature, they should be provided only by chemical syntheses.[2] Most of the syntheses are based on the work by Whistler *et al.*[2b]: they prepared 5-thio-D-glucose from the α-D-glucofuranose derivative[3] by introducing a sulfur group with two-times nucleophilic substitutions. Also, this work made it possible to prepare 5-thio-L-hexopyranoses from α-D-glucofuranoses by a simple nucleophilic substitution with a sulfur group.[2k,l,n] The above syntheses always required hexofuranoses with a free hydroxyl group at the 5-position, and some chemical modifications to distinguish the hydroxyl group from others are necessary. By the way, we have already developed a synthetic method for a L-hexopyranoses from D-glycono-1,5-lactones using the initial ring-opening reaction and the successive recyclization under Mitsunobu conditions (Scheme 1).[4] Applying this method, we accomplished the rather straightforward synthesis of 5-thio-L-hexopyranoses from D-glyconothio-*O*-lactones in very short steps.

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo Universiry.

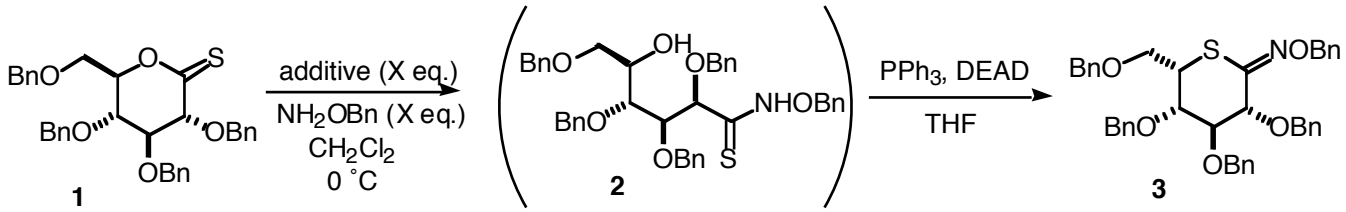


Scheme 1

RESULTS AND DISCUSSION

At first, we investigated the ring-opening reaction using the known D-gluconothio-*O*-lactones (**1**) derived from D-glucono-1,5-lactone (Table 1).[5] The reaction of **1** by the combination of $BnONH_2$ and Me_3Al, afforded the expected product (**2**). However, **2** was chemically unstable and difficult to isolate, so that the crude product of this reaction was subjected to the next Mitsunobu reactions without further purification. Stirred with three equivalents of PPh_3 and three equivalents of diethyl azodicarboxylate (DEAD) in THF, the crude product was transformed to the desired 5-thio-L-hexopyranose (**3**) in 40% yield from **1** (entry 1). After investigation of various reagents, it was found that three equivalents of

Table 1. Synthesis of 5-thio-L-glucopyranose derivative from D-gluconothio-*O*-lactone



entry	additive	X	yield (%), 2 steps
1	Me_3Al	3.9	40
2	Me_2AlCl	3	45*
3	$BF_3{\cdot}Et_2O$	4	10
4	$Ti(OiPr)_4$	4	84
5	$Ti(OiPr)_4$	3	88
6	$Ti(OiPr)_4$	2	82*
7	Y_2O_3	4	8
8	$ZrCl_4$	4	10
9	$La(OTf)_3$	3	50
10	$Yb(OTf)_3$	2	36

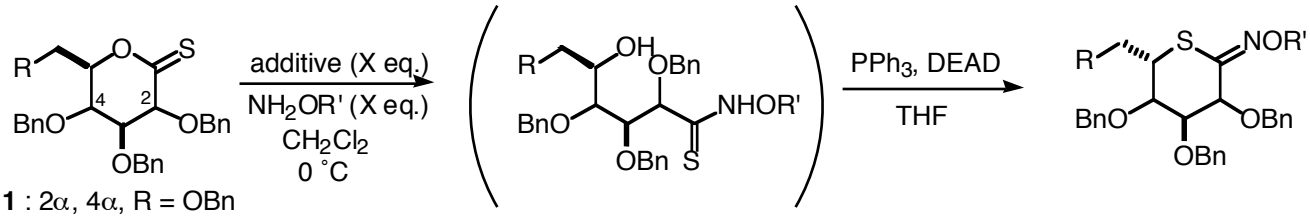
* Reaction was performed at room temperature.

$Ti(OiPr)_4$ was the best reagent and we could obtain **3** in 88% yield (entry 5). In this reaction, the product was exclusively the *S*-cyclic product (spectral data; IR (neat): 1574.1 $_{cm}^{-1}$ (C=N), ^{13}C-NMR (100 MHz,

$CDCl_3$) δ : 148.9 (C=N)), and no *N*-cyclic compound was observed. The stereochemistry in the oxime moiety of **3** was one-sided and could not be determined.

To adapt this method to various 5-thio-L-hexopyranose syntheses, we utilized the reactions of the D-glyconothio-*O*-lactones derived from D-galactose, D-mannose and 6-deoxy-D-glucose as the substrates and $TBSONH_2$ as a hydroxylamine derivative. As shown in Table 2, compound (**1**) and $TBSONH_2$ were reacted in the presence of $Ti(OiPr)_4$; however, they did not afford any desired compound due to the decomposition of $TBSONH_2$ (entry 1). Therefore, we were forced to investigate the reagents and solvents again (Table 2). Fortunately, 5-thio-L-hexopyranose (**7**) was obtained by using $La(OTf)_3$ in 10% yield in CH_2Cl_2 (entry 3), in 30% yield in THF (entry 4) and finally in 77% yield in Et_2O (entry 5). Under the best conditions, the D-glyconothio-*O*-lactones (**4** and **5**) derived from D-galactose and D-mannose were also converted to 5-thio-L-hexopyranoses (**8** and **9**) in 74% and 54% yields, respectively (entries 8, 9). Next, the same conditions were applied to the D-glyconothio-*O*-lactone (**6**) derived from 6-deoxy-D-glucose. However, the desired compound was not observed, and a complex mixture was

Table 2. Synthesis of 5-thio-L-glycopyranose derivatives from D-glyconothio-*O*-lactones



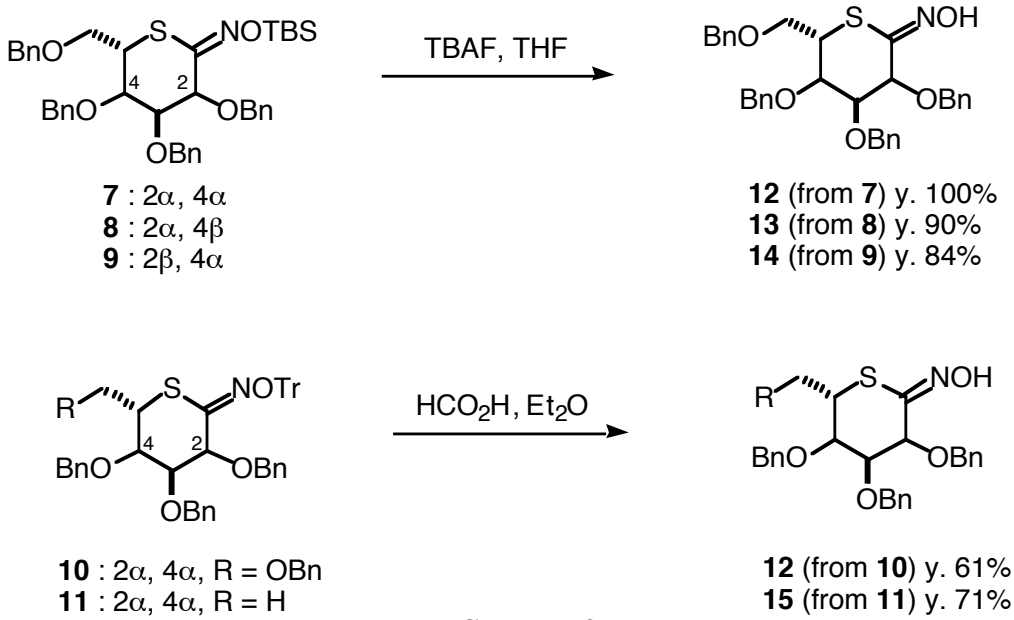
1 : 2α, 4α, R = OBn
4 : 2α, 4β, R = OBn
5 : 2β, 4α, R = OBn
6 : 2α, 4α, R = H

entry	substrate	additive	X	R'	solvent	yield ; %, 2 steps
1	**1**	$Ti(OiPr)_4$	3	TBS	CH_2Cl_2	0
2	**1**	Me_3Al	6	TBS	CH_2Cl_2	0
3	**1**	$La(OTf)_3$	3	TBS	CH_2Cl_2	10 (**7**)
4	**1**	$La(OTf)_3$	3	TBS	THF	30 (**7**)
5	**1**	$La(OTf)_3$	3	TBS	Et_2O	77 (**7**)
6	**1**	$Sm(OTf)_3$	3	TBS	Et_2O	69 (**7**)
7	**1**	$Yb(OTf)_3$	3	TBS	Et_2O	27 (**7**)
8	**4**	$La(OTf)_3$	3	TBS	Et_2O	74 (**8**)
9	**5**	$La(OTf)_3$	3	TBS	Et_2O	54 (**9**)
10	**6**	$La(OTf)_3$	3	TBS	Et_2O	0
11	**1**	$Ti(O\textit{i}Pr)_4$	3	Tr	Et_2O	67 (**10**)
12	**6**	$Ti(O\textit{i}Pr)_4$	3	Tr	Et_2O	81 (**11**)

obtained. So, we changed the reagent for the hydroxylamine derivative from $TBSONH_2$ to $TrONH_2$. The reaction using $TrONH_2$ with $Ti(O\textit{i}Pr)_4$ in Et_2O gave a good result, and compound **6** was transformed

to the desired product (**11**) in 81% yield (entry 12), while **1** was transformed to **10** in 67% yield under these reaction conditions (entry 11). All the reactions shown in Tables 1 and 2 afforded only *S*-cyclic compounds as we expected, and no *N*-cyclic compound was observed. This remarkable selectivity is thought to be attributed to the strong nucleophilicity of the sulfur atom, and the cyclization with a sulfur atom proceeds exclusively.

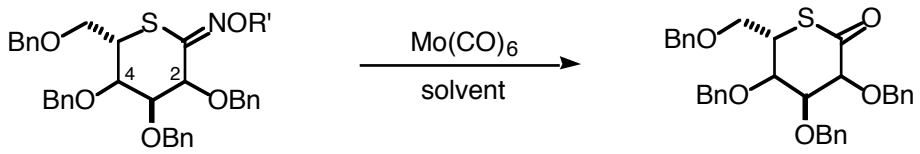
For the biological evaluation of thiosugars, we also tried the further transformation of 5-thio-L-hexopyranoses. The TBS group of compounds (**7**, **8**, **9**) and the Tr group of compounds (**10** and **11**) were effectively removed by TBAF in THF and HCO_2H in Et_2O, respectively (Scheme 3).[2m] Compounds (**11** and **15**) were thought to be useful tools for the 6-deoxy-L-hexopyranose analogues such as L-rhamnose and L-fucose. The next transformation is to prepare 5-thio-L-glyconolactones which would be good precursors of oligosaccharides containing 5-thio-L-hexopyranoses. Unexpectedly, these thiolactone oximes (**7** ~ **14**) are extremely stable to various reaction conditions. Various reactions such as acid hydrolyses, hydride reductions, electron transfer reactions and various metal reductions were examined in vain, to result in the recovery or decomposition of the substrates. Only on using $Mo(CO)_6$, we were able to obtained the desired compound with a carbonyl group at the C-1 position albeit in low yield.[6] After many attempts, adding H_2SO_4 to the reaction was found to be effective, and finally we were able to obtain 5-thio-L-glyconolactones (**16** ~ **18**) as shown in Table 3 with the concomitant removal



Scheme 2

of the protecting groups at oximes in compounds (**7** ~ **10**) (entries 1 ~ 4). In these reactions, each substrate needs different H_2SO_4 conditions, and the yields were low in the case of **7**, **10** and **12** derived from D-glucose.

Table 3. Synthesis of 5-thio-L-glyconolactones from 5-thio-L-glyconolactone oximes



entry	substrate	solvent	yield ; %
1	**7** : 2α, 4α, R' = TBS	4.5M. H_2SO_4 / MeCN (1 / 3)	21 (**16**)
2	**8** : 2α, 4β, R' = TBS	6M. H_2SO_4 / MeCN (1 / 3)	77 (**17**)
3	**9** : 2β, 4α, R' = TBS	3M. H_2SO_4 / MeCN (1 / 6)	62 (**18**)
4	**10** : 2α, 4α, R' = Tr	4.5M. H_2SO_4 / MeCN (1 / 3)	21 (**16**)
5	**12** : 2α, 4α, R' = H	4.5M. H_2SO_4 / MeCN (1 / 3)	30 (**16**)
6	**13** : 2α, 4β, R' = H	6M. H_2SO_4 / MeCN (1 / 3)	67 (**17**)
7	**14** : 2β, 4α, R' = H	3M. H_2SO_4 / MeCN (1 / 6)	53 (**18**)

As above, we have developed a synthetic method for 5-thio-L-hexopyranose from D-glyconothio-*O*-lactone using the initial ring-opening reaction and subsequent recyclization by Mitsunobu reaction. This method was proved to be applicable to various lactones derived from D-glucose, D-galactose, D-mannnose and 6-deoxy-D-glucose, though different reaction conditions were necessary for some substrates. And only three steps are required in the conversion from D-glyconothio-*O*-lactones to 5-thio-L-glyconolactones by the final hydrolysis step using $Mo(CO)_6$. These products would be applicable to the syntheses of various thiosugar derivatives and oligosaccharides containing thiosugars, and would contribute to the thiosugar chemistry.

EXPERIMENTAL

Infrared (IR) spectra were measured on a Jasco FT/IR-8000 Fourier-transform infrared spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a JEOL JNM-GSX400, 600 (400, 600MHz) pulse Fourier transform NMR spectrometer in $CDCl_3$ solution. Low-resolution mass spectra (MS) and high-resolution (HR) mass spectra were obtained with a JEOL JMS-SX102A mass spectrometer. Optical rotations were determined using a Jasco DIP-370 digital polarimeter. Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in ethanol/H_2O followed by heating. Except for special cases as mentioned, column chromatography was performed using SiO_2 (Wakogel C-300, Wako).

1-*N*-(*O*-Benzyl)-2,3,4,6-tetra-*O*-benzyl-5-thio-L-gluconhydroximo-1,5-lactone (3) : The synthetic method is the same as for **8,** to give the product (**3**) (88 %) as oil. $[\alpha]_D^{25}$ = - 14.8° (*c* = 0.5, $CHCl_3$). IR (neat): 1574.1 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.18-7.48 (20H, *m*); 5.24 (2H, s, *J* = 11.72 Hz,

PhCH_2); 4.52-4.60 (4H, m, PhCH_2); 4.48 (1H, *d*, *J* = 10.99 Hz, PhCH_2); 4.47 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.42 (1H, d, *J* = 12.02 Hz, PhCH_2); 4.26 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.22 (1H, *d*, *J* = 3.15 Hz, H2); 3.90 (1H, *dd*, *J* = 5.38, 3.42 Hz, H6a); 3.83 (2H, *m* , H3, H4); 3.80 (1H, *dd*, *J* = 5.38, 3.42 Hz, H6b); 3.63 (1H, *m*, H5). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 148.9 (C=N), 137.9, 137.8, 137.8, 137.7, 137.4, 128.2, 128.2, 128.2, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 80.7, 78.5, 78.3, 76.4, 73.2, 72.4, 71.9, 70.7, 69.4, 41.9. MS (FAB – NBA + NaI): m/z 683 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{41}H_{41}NO_5NaS$ 682.2608, found 682.2593.

1-*N*-(*O-tert*-Butyldimethylsilyl)-2,3,4,6-tetra-*O*-benzyl-5-thio-L-idonhydroximo-1,5-lactone (7) : The synthetic method is the same as for **8,** to give the product (**7**) as oil (77 %). $[\alpha]_D^{19}$ = - 16.8° (*c* = 0.32, $CHCl_3$). IR (neat): 1572.2 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.32-7.18 (20H, *m*); 4.66 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.56 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.52 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.51 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.48-4.43 (3H, *m*); 4.37 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.28 (1H, *d*, *J* = 3.17 Hz, H2); 3.89 (1H, *dd*, *J* = 5.86, 3.67 Hz, H6a); 3.86-3.83 (2H, *m* , H3, H4); 3.78 (1H, *dd*, *J* = 5.86 Hz, 3.17, H6b); 3.57-3.53 (1H, *m*, H5); 0.95 (9H, s); 0.19 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 153.89 (C=N), 137.82, 137.79, 128.27, 128.25, 127.76, 127.71, 127.69, 127.62, 127.58, 127.50, 81.22, 78.91, 78.60, 73.14, 72.38, 71.99, 70.77, 69.53, 41.50, 26.14, 18.32, - 5.00. MS (FAB – NBA + NaI): m/z 707 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{40}H_{49}NO_5NaSSi$ 706.2998, found 706.2985.

1-*N*-(*O-tert*-Butyldimethylsilyl)-2,3,4,6-tetra-*O*-benzyl-5-thio-L-altronhydroximo-1,5-lactone (8) : To a stirred mixture of **4** (29.0 mg, 0.05 mmol) in 2 mL of Et_2O were added $La(OTf)_3$ (92.1 mg, 0.15 mmol) and *O*-(*tert*-butyldimethylsilyl) hydroxylamine (23.0 mg, 0.15 mmol) at 0 °C, then the whole mixture was stirred for 40 min at rt. The reaction was quenched with pH. 7 phosphate buffer, and the product was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The residue was purified roughly by silica gel chromatography (Silica Gel 60 N spherical, neutral, KANTO CHEMICAL, hexane/AcOEt = 1:1). Then, the crude product was carried to the next Mitsunobu conditions. To a stirred mixture of the crude product and in 2 mL of THF, were added PPh_3 (41.2 mg, 0.15 mmol) and diethyl azodicarboxylate (0.025 mL, 0.15 mmol). The reaction mixture was stirred for 3 h at rt. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (hexane/AcOEt = 40:1) to yield (**8**) as oil (26.4 mg, 74 %). $[\alpha]_D^{19}$ = - 53.55° (*c* = 0.245, $CHCl_3$). IR (neat): 1564.5 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.31-7.15 (20H, *m*); 4.59-4.53 (4H, *m*); 4.45 (1H, *d*, *J* = 12.20 Hz, PhCH_2); 4.44 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.38 (1H, *d*, *J* = 11.47 Hz, PhCH_2); 4.31 (1H, *d*, *J*=12.20 Hz, PhCH_2,); 4.28-4.22 (2H, *m*, H2, H4); 3.86 (1H, *dd, J* = 4.51, 1.22 Hz, H4); 3.79-3.65 (3H, *m*, H5, H6a, H6b); 0.94 (9H, s); 0.18 (6H, *d*, *J* = 5.37 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 153.44 (C=N), 137.96, 137.85, 137.77, 137.76, 128.21, 128.18, 128.12, 127.99, 127.65, 127.61, 127.56, 127.45, 127.40, 76.15, 74.81, 74.52, 73.16, 72.12, 69.95, 69.34, 60.33, 40.43, 26.15,

18.33, - 5.06. MS (FAB – NBA + NaI): m/z 707 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{40}H_{49}NO_5NaSSi$ 706.2998, found 706.2993

1-*N*-(*O*-*tert*-Butyldimethylsilyl)-2,3,4,6-tetra-*O*-benzyl-5-thio-L-gulonhydroximo-1,5-lactone (9) : The synthetic method is the same as for **8,** to give the product (**9**) as oil (54 %). $[\alpha]_D^{19}$ = - 61.75° (*c* = 0.16, $CHCl_3$). IR (neat): 1574.1 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.36-7.15 (20H, *m*); 4.67 (1H, *d*, *J* = 12.45 Hz, PhCH_2); 4.60 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.55 (1H, *d*, *J* = 2.93 Hz, H2); 4.47 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.44-4.34 (5H, *m*, PhCH_2, H5); 4.25 (1H, *d*, *J* = 11.47 Hz, PhCH_2); 4.08 (1H, *t*, *J* =3.91 Hz, H4); 3.69 (2H, *m*, H3, H6a); 3.56 (1H, *dd* , *J* = 9.76, 7.57 Hz, H6b); 0.94 (9H, s); 0.17 (6H, *d*, *J* = 4.40 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 156.06 (C=N), 138.04, 137.75, 137.43, 137.22, 128.49, 128.25, 128.11, 127.81, 127.76, 127.73, 127.66, 127.59, 127.54, 127.45, 83.48, 78.47, 73.16, 72.85, 72.43, 70.73, 70.11, 69.02, 42.12, 26.11, 18.27, - 5.07. MS (FAB – NBA + NaI): m/z 707 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{40}H_{49}NO_5NaSSi$ 706.2998, found 706.2987.

1-*N*-(*O*-Triphenylmethyl)-2,3,4,6-tetra-*O*-benzyl-5-thio-L-idonhydroximo-1,5-lactone(10) : The synthetic method is the same as for **11,** to give the product (**10**) as oil (67 %). $[\alpha]_D^{25}$ = - 40.86° (*c* = 0.47, $CHCl_3$). IR (neat): 1591.5 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.41-6.98 (35H, *m*); 4.61 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.55-4.50 (2H, *m*); 4.46-4.43 (2H, *m*); 4.37 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.18 (1H, *d*, *J* = 11.97 Hz, PhCH_2); 4.12 (1H, *d*, *J* = 3.17 Hz, H2); 3.93-3.86 (4H, *m*, PhCH_2, H3, H6a, H6b); 3.75 (1H, *dd*, *J* = 5.74, 3.30 Hz, H4); 3.67-3.63 (1H, *m*, H5). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 148.82 (C=N), 144.23, 137.92, 137.77, 137.69, 137.53, 128.99, 128.95, 128.81, 128.28, 128.25, 128.23, 128.16, 128.12, 128.02, 127.99, 127.70, 127.62, 127.57, 127.53, 127.51, 127.49, 127.44, 127.38, 127.29, 126.94, 91.35, 80.66, 78.39, 78.08, 73.13, 72.16, 71.99, 70.10, 69.41, 41.85. MS (FAB – NBA + NaI): m/z 835 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{53}H_{49}NO_5NaS$ 834.3230, found 834.3217.

1-*N*-(*O*-Triphenylmethyl)-2,3,4-tri-*O*-benzyl-6-deoxy-5-thio-L-idonhydroximo-1,5-lactone (11) : To a stirred mixture of **6** (214.0 mg, 0.48 mmol) and 3 mL of Et_2O were added $Ti(OiPr)_4$ (0.42 mL, 1.44 mmol) at 0 °C, then *O*-tritylhydroxylamine (393.8 mg, 1.44 mmol) was added, then the whole mixture was stirred for 1.5 h at rt. The reaction was quenched with pH. 7 phosphate buffer, and the product was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The residue was purified roughly by silica gel chromatography (Silica Gel 60 N spherical, neutral, KANTO CHEMICAL, hexane/AcOEt = 1:1). Then, the crude product was carried to the next Mitsunobu conditions. To a stirred mixture of the crude product and 2 mL of THF, were added PPh_3 (375.0 mg, 1.44 mmol) and diethyl azodicarboxylate (0.225 mL, 1.44 mmol). The reaction mixture was stirred for 10 h at rt. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (hexane/AcOEt = 40:1) to yield (**11**) as oil (73.6 mg, 81 %). $[\alpha]_D^{25}$ = - 16.15° (*c* = 0.14, $CHCl_3$). IR (neat): 1595.3 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.43-7.00 (30H, *m*); 4.67 (1H, *d*, *J*

= 11.97 Hz, PhCH_2); 4.55 (1H, *d*, *J* = 11.97 Hz, PhCH_2); 4.46 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.38 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.24 (1H, *d*, *J* = 11.97 Hz, PhCH_2); 4.12 (1H, *d*, *J* = 3.54 Hz, H2); 3.92 (1H, *d*, *J* = 11.97 Hz, PhCH_2); 3.84 (1H, *dd*, *J* = 5.43, 3.54 Hz, H3); 3.73. (1H, *dd*, *J* = 5.43, 3.06 Hz, H4); 3.47 (1H, *m*, H5); 1.45 (3H, *d*, *J* = 7.08 Hz, H6). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 149.41 (C=N), 144.32, 137.82, 137.77, 1278.98, 128.27, 128.23, 128.09, 128.02, 127.75, 127.72, 127.62, 127.59, 127.48, 126.96, 91.54, 80.42, 78.07, 72.45, 71.93, 70.33, 65.54, 36.19, 16.79. MS (FAB – NBA + NaI): m/z 728 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{46}H_{43}NO_4NaS$ 728.2810, found 728.2802.

2,3,4,6-Tetra-*O*-benzyl-5-thio-L-idonhydroximo-1,5-lactone(12) : To a stirred mixture of **7** (185.1 mg, 0.32 mmol) and 3 mL of THF were added tetrabutylammonium fluoride solution (0.38 mL of 1.00 M solution in THF, 0.38 mmol) at 0 °C, then the whole mixture was stirred for 5 min at rt. The reaction was quenched with saturated aqueous ammonium chloride, and the product was extracted with AcOEt. The combined organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt = 3:1) to yield **12** as oil (148.3 mg, 100 %). $[\alpha]_D^{25}$ = - 7.00° (*c* = 0.13, $CHCl_3$). IR (neat): 1604.9 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.48-7.20 (20H, *m*); 4.69 (1H, *d*, *J* = 11.96 Hz, PhCH_2); 4.60 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.58 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.48 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.47-4.44 (2H, *m*); 4.40 (1H, *d*, *J* = 11.96 Hz, PhCH_2); 4.38 (1H, *d*, *J* = 11.72 Hz PhCH_2); 4.26 (1H, *d*, *J* = 3.66 Hz, H2); 3.87 (1H, *dd*, *J* = 5.37, 3.66 Hz, H6a); 3.79 (1H, *dd*, *J* = 5.37, 3.66 Hz, H6b); 3.65-3.60 (1H, *m*, H5). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 150.28 (C=N), 137.82, 137.58, 137.55, 137.29, 128.24, 128.16, 128.07, 127.83, 127.81, 127.67, 127.59, 127.55, 127.52, 80.93, 78.95, 78.28, 73.17, 72.56, 71.93, 71.23, 69.40, 41.92. MS (EI): m/z 569 (M^+). HRMS (EI): calcd for $C_{34}H_{35}NO_5S$ 569.2236, found 569.2225.

2,3,4,6-Tetra-*O*-benzyl-5-thio-L-altronhydroximo-1,5-lactone(13) : The synthetic method is the same as for **12,** to give the product (**13**) as oil (90 %). $[\alpha]_D^{25}$ = - 65.08° (*c* = 0.72, $CHCl_3$). IR (neat): 1597.3 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 9.04 (1H, s); 7.33-7.18 (20H, *m*); 4.63-4.39 (7H, *m*, PhCH_2); 4.31-4.27 (3H, *m*, PhCH_2, H2, H4); 3.89-3.77 (3H, *m*, H3, H5, H6a); 3.72 (1H, *dd*, *J* = 10.01, 2.69 Hz, H6b). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 150.45 (C=N), 137.84, 137.64, 137.49, 128.25, 128.20, 127.70, 127.68, 127.60, 127.57, 127.51, 127.49, 127.44, 76.65, 74.68, 74.19, 73.19, 72.22, 72.03, 70.24, 69.16, 60.45, 40.87. MS (EI): m/z 569 (M^+). HRMS (EI): calcd for $C_{34}H_{35}NO_5S$ 569.2236, found 569.2230.

2,3,4,6-Tetra-*O*-benzyl-5-thio-L-gulonhydroximo-1,5-lactone(14) : The synthetic method is the same as for **12,** to give the product (**14**) as oil (84 %). $[\alpha]_D^{25}$ = - 16.92° (*c* = 0.065, $CHCl_3$). IR (neat): 1603.0 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 8.79 (1H, s); 7.39-7.19 (20H, *m*); 4.74 (1H, *d*, *J* = 12.21 Hz, PhCH_2); 4.62 (1H, *d*, *J* = 11.72 Hz, PhCH_2); 4.55 (1H, *d*, *J* = 2.92 Hz, H2); 4.53-4.39 (6H, *m*, PhCH_2, H5); 4.34 (1H, *d*, *J* = 11.72 Hz); 4.13 (1H, *t*, *J* = 3.91 Hz, H4); 3.78-3.73 (2H, *m*, H3, H6a); 3.65 (1H, *dd*,

J = 9.76, 7.57 Hz, H6b). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 152.63 (C=N), 137.85, 137.64, 137.39, 137.08, 128.35, 128.32, 128.30, 128.27, 128.16, 127.86, 127.79, 127.74, 127.72, 127.56, 127.54, 82.52, 77.99, 73.59, 73.21, 72.47, 71.09, 70.66, 68.97, 42.57. MS (EI): m/z 569 (M^+). HRMS (EI): calcd for $C_{34}H_{35}NO_5S$ 569.2236, found 569.2235.

2,3,4-Tri-*O*-benzyl-6-deoxy-5-thio-L-idonhydroximo-1,5-lactone(15) : To a stirred mixture of **11** (11.2 mg, 0.016 mmol) and 1 mL of Et_2O were added formic acid (1 mL), then the whole mixture was stirred for 14 h at rt. The reaction was quenched with saturated aqueous sodium hydrogen carbonate, and the product was extracted with AcOEt. The combined organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt = 5:1) to yield (**15**) as oil (5.2 mg, 71 %). $[\alpha]_D^{25}$ = + 16.60° (*c* = 1.29, $CHCl_3$).IR (neat): 1597.3 $_{cm}^{-1}$ (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.41-7.23 (15H, *m*; 4.79 (1H, *d*, *J* = 11.72 Hz, PhC*H*$_2$); 4.66 (1H, *d*, *J* = 11.96 Hz, PhC*H*$_2$); 4.60 (1H, *d*, *J* = 11.72 Hz, PhC*H*$_2$); 4.53 (1H, *d*, *J* = 11.96 Hz, PhC*H*$_2$); 4.51 (1H, *d*, *J* = 11.72 Hz, PhC*H*$_2$); 4.46 (1H, *d*, *J* = 11.72 Hz, PhC*H*$_2$); 4.29 (1H, *d*, *J* = 4.15 Hz, H2); 3.89 (1H, *t*, *J* = 4.76 Hz, H3); 3.72 (1H, *dd*, *J* = 5.25, 3.05 Hz, H4); 3.48 (1H, *m*, H5); 1.43 (3H, *d*, *J* = 7.08 Hz, H6). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 151.03 (C=N), 137.78, 137.66, 137.48, 128.29, 128.25, 128.11, 127.85, 127.70, 127.67, 127.65, 80.65, 80.36, 78.91, 72.85, 71.89, 71.54, 36.44, 16.69. MS (FAB – NBA + NaI): m/z 486 (M + Na)$^+$. HRMS (FAB – NBA + NaI): calcd for $C_{27}H_{29}NO_4NaS$ 486.1715, found 486.1727.

2,3,4,6-Tetra-*O*-benzyl-5-thio-L-idono-1,5-lactone(16) : The synthetic method is the same as for **17** to give the product (**16**) as oil (21 % from **7**, 30 % from **12**). $[\alpha]_D^{19}$ = - 9.70° (*c* = 0.26, $CHCl_3$). IR (neat): 1691.8 $_{cm}^{-1}$ (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.41-7.19 (20H, *m*); 4.97 (1H, *d*, *J* = 11.23 Hz, PhC*H*$_2$); 4.68 (1H, *d*, *J* = 11.48 Hz, PhC*H*$_2$); 4.60-4.54 (3H, *m*); 4.46 (1H, *d*, *J* = 11.96 Hz, PhC*H*$_2$); 4.42 (1H, *d*, *J* = 11.96 Hz, PhC*H*$_2$); 4.35 (1H, *d*, *J* = 11.96 Hz, PhC*H*$_2$); 4.25 (1H, *d*, *J* = 6.84 Hz, H2); 4.03-3.98 (2H,*m*, H3, H5); 3.89 (1H, *dd*, *J* = 6.59, 2.68 Hz, H4); 3.60 (2H, *d*, *J* = 6.60 Hz, H6a, H6b). ^{13}C-NMR (150 MHz, $CDCl_3$) δ : 197.91 (C=O), 137.64, 137.43, 137.27, 137.24, 128.73, 128.52, 128.49, 128.45, 128.43, 128.41, 128.35, 128.28, 128.05, 127.97, 127.95, 127.84, 127.72, 86.28, 81.57, 76.32, 73.75, 73.29, 73.27, 71.54, 68.64, 44.49. MS (FAB – NBA + NaI): m/z 577 (M + Na)$^+$. HRMS (FAB – NBA + NaI): calcd for $C_{34}H_{34}O_5NaS$ 577.2024, found 577.2034.

2,3,4,6-Tetra-*O*-benzyl-5-thio-L-altrono-1,5-lactone(17) : To a stirred mixture of **8** (15.4 mg, 0.02 mmol), 2.4 mL of MeCN and 0.8 mL of 6.0 M H_2SO_4 were added $Mo(CO)_6$ (8.7 mg, 0.03 mmol), then the whole mixture was stirred at reflux for 35 min. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (hexane/AcOEt = 19:1) to yield (**17**) as oil (77 % from **8**, 67 % from **13**). $[\alpha]_D^{19}$ = + 24.25° (*c* = 0.67, $CHCl_3$). IR (neat): 1662.8 $_{cm}^{-1}$ (C=O). ^{1}H-NMR (400 MHz,

$CDCl_3$) δ : 7.28-7.18 (20H, *m*); 4.77 (1H, *d*, *J* = 11.47 Hz, PhCH_2); 4.58-4.41 (7H, *m*); 4.24 (1H, *d*, *J* = 8.05 Hz, H3); 4.03 (1H, *d*, *J* = 6.10 Hz, H3); 3.91-3.92 (1H, *m*, H5); 3.86 (1H, *d*, *J* = 5.13 Hz, H4); 3.64 (1H, *dd*, *J* = 10.01, 6.11 Hz, H6a); 3.58 (1H, *dd*, *J* = 10.01, 4.64 Hz, H6b). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 198.72 (C=O), 137.61, 137.52, 137.44, 137.11, 128.35, 128.32, 128.30, 128.02, 127.84, 127.73, 127.69, 127.66, 127.57, 81.87, 76.06, 74.13, 73.39, 73.25, 736.03, 72.36, 69.93, 43.56. MS (FAB – NBA + NaI): m/z 577 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{34}H_{34}O_5NaS$ 577.2024, found 577.2004.

2,3,4,6-Tetra-*O*-benzyl-5-thio-L-gulono-1,5-lactone(18) : The synthetic method is the same as for **17** to give the product (**18**) as oil (53 % from **14**, 62 % from **9**). $[\alpha]_D^{19}$ = - 106.51° (*c* = 0.32, $CHCl_3$). IR (neat): 1678.3 $_{cm}^{-1}$ (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.36-7.24 (20H, *m*); 7.02-7.00 (2H, m); 5.02 (1H, *d*, *J* = 12.20 Hz, PhCH_2); 4.83 (1H, *d*, *J* = 11.96 Hz, PhCH_2); 4.56 (1H, *d*, *J* = 11.96 Hz, PhCH_2); 4.53 (1H, *d*, *J* = 12.20 Hz, PhCH_2); 4.47-4.46 (3H, *m*, PhCH_2, H2); 4.36-4.28 (3H, *m*, PhCH_2, H5); 4.00 (1H, *dd*, *J* = 5.37, 2.93 Hz, H6a); 3.95 (1H, *dd*, *J* = 5.37, 2.19 Hz, H6b); 3.73 (1H, *t*, *J* = 8.79 Hz H3); 3.50 (1H, *dd*, *J* = 9.27, 6.59 Hz, H4). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 198.56 (C=O), 137.74, 137.62, 137.45, 137.02, 128.40, 128.38, 128.29, 127.93, 127.87, 127.84, 127.78, 127.73, 127.66, 80.93, 78.63, 74.59, 74.01, 73.50, 73.27, 72.81, 68.40, 45.06. MS (FAB – NBA + NaI): m/z 577 $(M + Na)^+$. HRMS (FAB – NBA + NaI): calcd for $C_{34}H_{34}O_5NaS$ 577.2024, found 577.2004.

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