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Facile Diastereoseparation of Glycosyl Sulfoxides by Chiral Stationary Phase

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ABSTRACT Separation of the diastereomers of glycosyl sulfoxides differing in the sulfur chirality has been difficult. This article presents a fast and scalable method for their diastereoseparation using a chiral stationary phase. The usefulness of this method was demonstrated in a 500-mg scale separation within 20 min, and in the separation of trisaccharyl sulfoxide diastereomers. *Chirality 00:000–000, 2016.*

KEY WORDS: chiral HPLC; sulfur chirality; carbohydrate; Kahne glycosidation

Sulfoxide is an important class of molecules used as a blockbuster drug and as essential reagents for a wide range of organic reactions.[1] Among various sulfoxides, the chemistry of glycosyl sulfoxide (Fig. 1) has extensively been studied since Kahne invented its use as a substrate for a glycosidation reaction, now called Kahne glycosidation or sulfoxide glycosidation.[2] This glycosidation has facilitated the synthesis of various natural products and drug candidates including cyclamycin 0, everninomicin, and moenomycin A,[3–6] supported by its advantages such as its ability to react with bulky glycosyl acceptors, high stereoselectivity, and relatively mild reaction condition.[7,8] In Kahne glycosidation, glycosyl sulfoxides are normally used as a mixture of sulfinyl diastereomers that is obtained by oxidation of the corresponding glycosyl sulfides, assuming the reactivity of both diastereomers to be similar.[2] While this assumption may be correct for some cases, Ferrières et al. reported an example where a pair of diastereomers yielded different reaction products.[9] Although whether such a difference can be observed for other pairs is yet to be revealed, further investigation into the difference in their reactivities is needed for a possible improvement of the efficiency of Kahne glycosidation. However, such studies have been hampered by the difficulties in their separation.

In spite of their expected diastereomeric physical differences, their behavior on silica-gel thin-layer chromatography (TLC) is generally quite similar: for example, the differences in the R_f values of various sulfinyl glycosyl diastereomers prepared in a recent study were all within 0.02,[10] and it is not rare to see them described as an inseparable diastereomixture.[11] On the other hand, diastereoselective oxidations are only applicable to limited glycosyl sulfides, especially to those with tailored protective groups or with α-anomeric configuration.[12,13] Development of a fast and scalable method to separate sulfinyl glycosyl diastereomers should facilitate chemical and biological[14,15] studies on their sulfinyl chirality. Previously, our work on brassicanal C, a natural product with a sulfinate functional group, has shown that its racemate was efficiently enantioseparated[16] by using a cellulose-based chiral high-performance liquid chromatography (HPLC).[17,18] This observation, as well as reported successful enantioseparations of chiral sulfoxides by chiral HPLC,[19–21] led us to apply chiral stationary phases to diastereoseparation of glycosyl sulfoxides. Here, through the first systematic application of chiral stationary phase to a variety of glycosyl sulfoxides, we demonstrate the versatility of this method in separating their diastereomers.

MATERIALS AND METHODS

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Varian (Palo Alto, CA) Inova instrument at 25°C. Chemical shift values (δ) are reported in ppm relative to $CDCl_3$ (^{1}H, δ 7.26; ^{13}C, δ 77.00), CD_3OD (^{1}H, δ 4.87; ^{13}C, δ 49.15), or tetramethylsilane, while coupling constant values (J) are in Hz. The following abbreviations were used for signal multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet. Electrospray ionization mass spectrometry was conducted by using a JEOL (Japan) JMS-T100LP spectrometer. Optical rotation was measured on a Jasco (Japan) P-1020 polarimeter at the sodium D-line using a 1-cm optical cell under ambient temperature, and reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). TLC was performed on 0.2 mm silica gel plates (Merck, Darmstadt, Germany; 60 F-254). Normal column chromatography was carried out on silica gel (Kanto 60N, 40–50 μm). Analytical chiral HPLC was conducted on a Jasco PU-2086 Plus pump equipped with a Jasco UV-2075 UV spectrophotomeric detector, using a CHIRALPAK IA, IB, or IC guard column (0.4 cm φ x 1 cm) and its analytical column (0.46 cm φ x 25 cm) from Daicel (Japan).[22] Large-scale chiral HPLC was conducted using a uf-3020SZB2 pump (Denso Sangyo, Japan) equipped with a Shimamura (Japan) YRU-880 midget UV-RI detector, using a CHIRALFLASH IC column (3.0 cm φ x 10 cm) from Daicel.[22]

Crystal data were collected on a Bruker (Billerica, MA) SMART Apex II CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 90 K. The crystal structure was solved by direct methods (SHELXS-97)[23] and refined by full-matrix least-squares methods on F^2 (SHELXL-97)[24] with APEX II software. The sulfur, carbon, and oxygen atoms were refined anisotropically, and the hydrogen atoms were refined isotropically.

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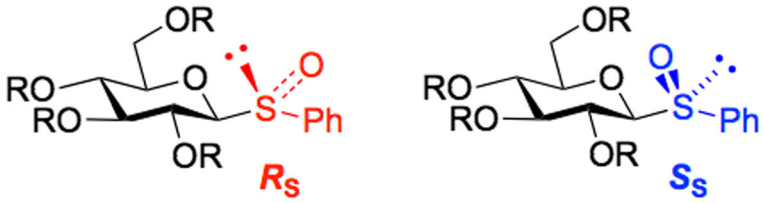


Fig. 1. Structures of aromatic glycosyl sulfoxides and their chirality. As representative structures, sulfoxides of glucose monosaccharide are shown.

Phenyl 2,3,4,6-tetra-O-benzoyl-1-sulfinyl-β-D-glucopyranoside (8)[25]

Phenyl 2,3,4,6-tetra-*O*-bezoyl-1-thio-β-D-glucopyranoside[26] (1.00 g, 1.45 mmol) in CH_2Cl_2 (17 mL) was added Ac_2O (220 μL, 1.6 equiv), silica gel (80 mg), and H_2O_2 (200 μL, 1.2 equiv. from a 34% aqueous solution) and stirred at room temperature for 8 h. The mixture was then diluted with EtOAc, filtered to remove the silica gel, washed with 10% $Na_2S_2O_3$ solution and brine, then dried ($MgSO_4$) and concentrated. Part of the resultant diastereomixture of **8** (ca. 500 mg, dr = 1:1) was directly subjected to a CHIRALFLASH IC column (3.0 cm φ x 10 cm) from Daicel, providing 242 mg of the first-eluted and 236 mg of the second-eluted diastereomers (hexane:EtOAc =1.5:1). Their ^{1}H NMR spectra were consistent with the data reported in Ref. [25]. (R_S)-**8**: ^{1}H NMR ($CDCl_3$) δ 8.00-7.30 (m, 25H, ArH), 6.02 (t, J = 9.3 Hz, 1H, H-3), 5.92 (t, J = 9.6 Hz, 1H, H-2), 5.63 (t, J = 9.8 Hz, 1H, H-4), 4.62 (d, J = 9.8 Hz, 1H, H-1), 4.56 (dd, J = 2.7, 12.3 Hz, 1H, H-6a), 4.45 (dd, J = 6.3, 12.3 Hz, 1H, H-6b), 4.14 (ddd, J = 2.8, 6.4, 10.0 Hz, 1H, H-5); $[\alpha]_D$ + 24.8 (c 1.0, $CHCl_3$).

(S_S)-**8**: ^{1}H NMR ($CDCl_3$) δ 7.95-7.26 (m, 25H, ArH), 5.95 (t, J = 9.3 Hz, 1H, H-3), 5.71 (t, J = 9.5 Hz, 1H, H-2), 5.54 (t, J = 9.7 Hz, 1H, H-4), 4.87 (d, J = 9.8 Hz, 1H, H-1), 4.66 (dd, J = 2.6, 12.5 Hz, 1H, H-6a), 4.42 (dd, J = 4.6, 12.4 Hz, 1H, H-6b), 4.21 (ddd, J = 2.8, 4.5, 10.0 Hz, 1H, H-5); $[\alpha]_D$ − 52.2 (c 1.0, $CHCl_3$).

RESULTS AND DISCUSSION

Synthesis and Diastereoseparation of Monosaccharyl Sulfoxides

First, in order to obtain pairs of monosaccharyl sulfinyl glycosyl diastereomers, several glycosyl sulfides with β-anomeric configuration were prepared. Glycosyl sulfoxide with α-anomeric configuration was not tested because oxidation of the corresponding sulfide is known to proceed with high stereoselectivity to yield mostly one diastereomer.[12] The glycosyl sulfides were oxidized using mCPBA or

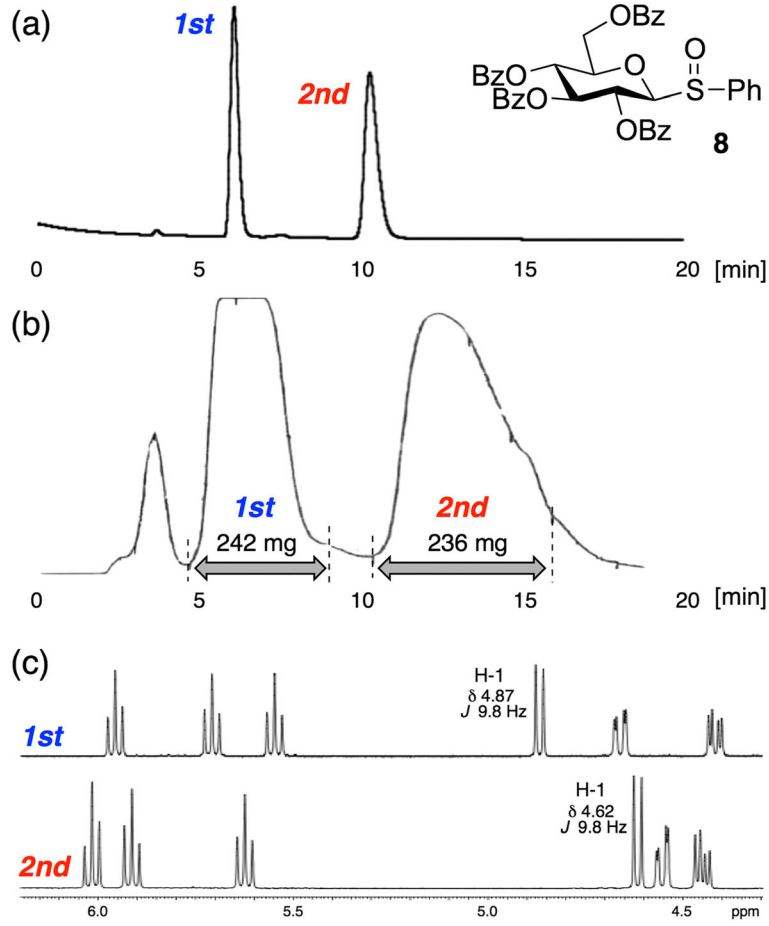
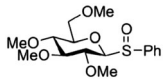
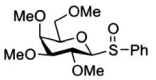
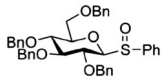
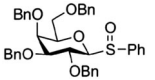
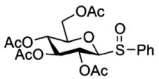
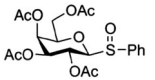
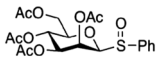
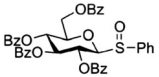
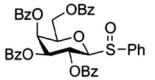
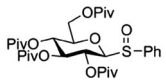
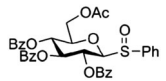


Fig. 2. Separation of the diastereomers of **8** by chiral stationary phase. Chromatograms were obtained using (**a**) CHIRALPAK IC with ~0.1 mg sample loading or (**b**) CHIRALFLASH IC with ~500 mg sample loading, detected at 254 nm. Eluent: hexane-EtOAc 60:40 at the speed of (a) 1 mL/min or (b) 10 mL/min. The UV absorption of the first-eluted diastereomer by CHIRALFLASH IC exceeded the range of the detection limit of the UV detector. (**c**) ^{1}H NMR spectra of the first- and second-eluted diastereomers obtained by CHIRALFLASH IC: 500 MHz, $CDCl_3$.

TABLE 1. Separation of the diastereomers of glycosyl sulfoxides using chiral stationary phase

		CHIRALPAK IA			CHIRALPAK IB			CHIRALPAK IC		
	Condition[a]	t_1 [min][b,c]	t_2 [min][b,c]	α[d]	t_1 [min][b,c]	t_2 [min][b,c]	α[d]	t_1 [min][b,c]	t_2 [min][b,c]	α[a]
1 	A	18.1[M]	26.7[m]	1.6	17.0[M]	17.7[m]	1.1	15.0[m]	17.2[M]	1.2
2 	A	9.5[m]	16.1[M]	2.1	7.9[m]	15.4[M]	2.7	9.4[M]	14.9[m]	1.9
3[e] 	A	10.9 *R*	13.4 *S*	1.3	13.1	14.3	1.1	10.8	12.4	1.2
4 	A	16.3	19.5	1.3	17.3	19.2	1.1	15.5	19.6	1.3
5[f] 	A	17.2 *R*	18.3 *S*	1.1	14.0 *R*	18.4 *S*	1.2	17.8 *S*	19.1 *R*	1.1
	B	7.8 *R*	12.2 *S*	2.0	7.7 *R*	9.4 *S*	1.4	6.2 *S*	7.2 *R*	1.4
6 	B	6.1[m]	14.3[M]	4.3	9.6[m]	11.6[M]	1.3	7.1[m]	10.7[M]	2.0
7 	A	11.6[m]	15.2[M]	1.5	—	—	—	8.2[m]	11.6[M]	1.7
8[f] 	A	18.0 *R*	20.2 *S*	1.2	16.5 *S*	17.5 *R*	1.1	17.8 *S*	18.6 *R*	1.2
	B	7.0 *R*	10.5 *S*	2.0	6.7 *S*	8.0 *R*	1.4	5.8 *S*	9.2 *R*	2.5
	C	7.4 *R*	11.5 *S*	2.1	6.8 *S*	8.1 *R*	1.4	6.1 *S*	10.3 *R*	2.8
9 	A	15.7[m]	20.2[M]	1.4	16 8[m]	17 2[M]	1.0	15.0[m]	16.0[M]	1.1
10[f] 	A	4.5 *R*	6.0 *S*	2.7	—	—	—	10.2 *R*	10.4 *S*	1.0
11[f] 	B	9.1	12.8	1.7	—	—	—	6.2 *S*	10.9 *R*	2.8

(*Continues*)

Table 1. (Continued)

		Condition[a]	CHIRALPAK IA t_1 [min][b,c]	CHIRALPAK IA t_2 [min][b,c]	CHIRALPAK IA α[d]	CHIRALPAK IB t_1 [min][b,c]	CHIRALPAK IB t_2 [min][b,c]	CHIRALPAK IB α[d]	CHIRALPAK IC t_1 [min][b,c]	CHIRALPAK IC t_2 [min][b,c]	CHIRALPAK IC α[a]
12[g]		A	9.8 *S*	10.4 *R*	1.1	—	—	—	9.7 *S*	11.8 *R*	1.3
13		B	9.4[m]	11.6[M]	1.4	—	—	—	16.7[M]	19.3[m]	1.2

[a]Column size: 4.0 mm φ × 10 mm guard column and 4.6 mm φ × 250 mm analytical column. Flow rate: 1.0 mL/min. Gradient conditions for hexane-EtOAc eluent systems: (A) 90:10 to 1:99 over 20 min, then 1:99 until 30 min; (B) 60:40 to 1:99 over 20 min; (C) 60:40.
[b]Elution time for the 1st- or 2nd-eluted diastereomers.
[c](M) major diastereomer obtained by oxidation, (m) minor diastereomer obtained by oxidation, (*R*) R_S diastereomer, (*S*) S_S diastereomer, (unlabeled) two diastereomers were obtained almost equally by oxidation and the chirality was not determined.
[d]Separation factor $(t_2 - t_0)/(t_1 - t_0)$, where t_0 is the time for the solvent front (3.6 min).
[e]The stereochemistry was previously determined in Ref. [11].
[f]The stereochemistry was determined in this study.
[g]The stereochemistry was previously determined in Ref. [33].

$H_2O_2/Ac_2O/SiO_2$,[27] which resulted in 1:1–3:1 mixtures of diastereomers **1–12**. Around 0.1 mg of each mixture was injected into an analytical polysaccharide-based CHIRALPAK IA, IB, or IC column (4.6 mm φ × 250 mm).[18,22] For a quick screening to see whether these diastereomers can be separated, all samples were subjected to a hexane-EtOAc gradient system using conditions A (hexane:EtOAc =90:10 to 1:99 over 20 min) or B (40:60 to 1:99 over 20 min) rather than optimizing the conditions for each sample.[28] Nevertheless, as summarized in Table 1, diastereomers of all monosaccaryl sulfoxides **1–12** were efficiently separated with separation factors of 1.3 or higher when HPLC column and eluent gradient condition are adequate. This separation method is applicable to a wide range of monosaccharides (glucose, galactose, mannose, and glucosamine) and protective groups (methyl, benzyl, acetyl, benzoyl, pivaloyl, N-phthaloyl), which are commonly used in sugar chemistry. A typical chromatogram is shown in Figure 2a. In most cases, CHIRALPAK IA and IC achieved highly efficient diastereoseparation. Separation efficiency can be improved by using a suitable gradient system, as exemplified by the comparison of the outcomes of conditions A and B for compounds **5** and **8**: for **8**, its separation factor was dramatically improved from 1.2 (condition A) to 2.8 (a constant solvent ratio of hexane:EtOAc =60:40, condition C). Although a hexane-EtOAc solvent system is satisfactory, other solvent systems are applicable for their separation (data not shown).

With the above promising results in hand, we then tested the feasibility of a large-scale separation using a CHIRALFLASH IC column (30 mm φ × 100 mm).[22] About 500 mg of a diastereomixture of **8** was loaded onto the column and eluted with a hexane-EtOAc 60:40 solvent system without gradient at a flow speed of 10 mL/min. The resultant chromatogram showed an almost perfect separation of the two diastereomers (Fig. 2b). Only one run of chromatography within 20 min afforded 242 mg of the first-eluted diastereomer and 236 mg of the second-eluted, both of whose purities were confirmed by ^{1}H NMR (Fig. 2c). Thus, this result shows the practicality of the use of a chiral stationary phase for separation of sulfinyl diastereomers of glycosyl sulfoxides even at a preparative scale.[29] Judging from the chromatogram in Figure 2b, this separation method should be applicable to a larger amount of samples and a faster flow speed to further increase its robustness.

Stereochemical Determination

We also conducted a stereochemical determination of the isolated isomers of **8**. Although circular dichroism (CD) and nuclear magnetic resonance (NMR) spectroscopies were proposed to be useful in determining the absolute configuration of glycosyl sulfoxides attached to an alkyl group,[30] their validity to those attached to an aromatic group is yet to be examined. Moreover, the benzoyl groups in **8** may perturb the proposed empirical relationship between CD curve and sulfur chirality. Therefore, the current study employed chemical correlation and X-ray crystallography. While working on several glycosyl sulfoxides, it was found that one diastereomer of a perpivaloylated glucose derivative **10**[2,27] formed a fine crystal suited for X-ray crystallography (Fig. 3a).[31] This established for the first time the stereochemistry of **10** as shown in Figure 3b. In order to chemically correlate the stereochemistries of **8** and **10**, the pivaloyl groups of each diastereomer of **10** were hydrolyzed using NaOH/MeOH/

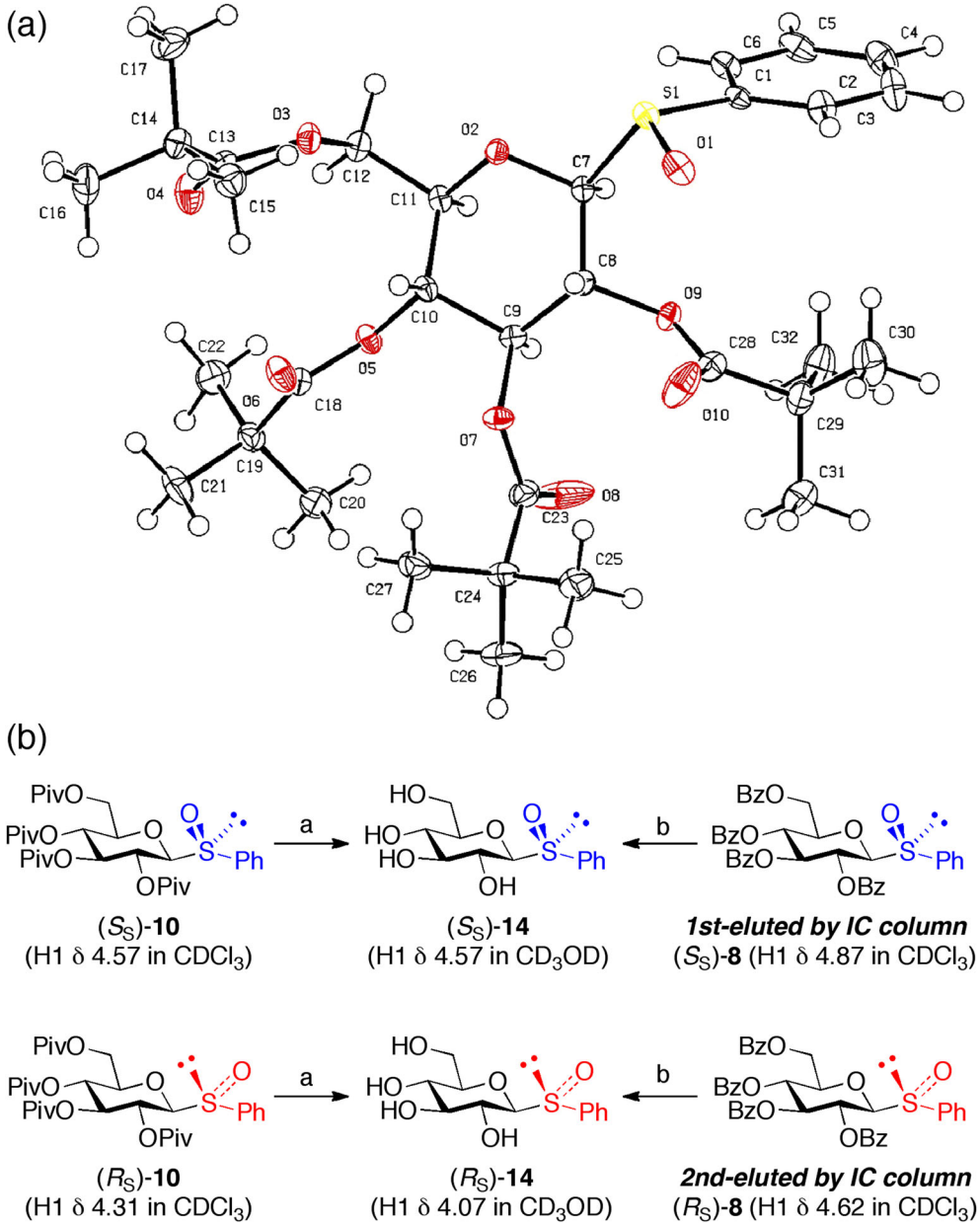


Fig. 3. (**a**) ORTEP drawing of (S_S)-**10**. Thermal ellipsoids are shown at the 50% probability level. (**b**) Stereochemical assignment of **8** through chemical correlation. Reagents and conditions: (a) NaOH, MeOH, H_2O; (b) MeONa, MeOH.

H_2O. The deprotection proceeded without epimerization of the sulfur chirality, and thus the configuration of two isomers of **14**[32] was determined. In a similar manner, separated diastereomers of **8** were converted to **14** using MeONa/MeOH, from which the first and second eluted diastereomers of **8** from the CHIRALFLASH IC column were characterized as S_S and R_S, respectively (Fig. 3b). In a similar manner, the absolute configurations of **5** and **11** were determined, as shown in Table 1. The stereochemistries of **3** and **12** described in Table 1 were previously determined by chemical correlation and X-ray crystallography.[11,33]

Synthesis and Diastereoseparation of Trisaccharyl Sulfoxide

Last, in order to see the efficacy of this separation method to further complex diastereomers, a diastereomixture of a trisaccharyl sulfoxide **13** was prepared and subjected to chiral HPLC. A diastereomixture of **13** was obtained starting with peracetylation of laminaritriose, followed by glycosidation using PhSH, and oxidation using *m*CPBA (dr = 3.5:1). Despite the small structural difference of the diastereomers of **13**, the pair was clearly separated on CHIRALPAK IA with a separation factor of 1.4 (Table 1). This result demonstrated the effectiveness of chiral stationary phase even for sulfinyl diastereomers that would otherwise be difficult to separate.

CONCLUSION

This article presents a new method to separate sulfinyl diastereomers of glycosyl sulfoxides using a chiral stationary phase. This method is fast and scalable: ~500 mg of a diastereomeric mixture was separated within 20 min. Yet the robustness of this method can be expanded even more by further optimizing conditions for solvent system, flow rate,

sample amount, column type, and repetitive sample injections. Furthermore, this work has demonstrated its ability to separate not only various monosaccharyl sulfoxides, but also even oligosaccharyl ones. Although there are cases where diastereomers of glycosyl sulfoxides are separable by a normal SiO_2 column,[8,15] we believe that this approach complements conventional methods and accelerates studies on the effects of the chirality on the properties of glycosyl sulfoxides.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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28. Separation factor α is typically higher for a constant eluent system than for a gradient eluent system. See the results for **8** in Table 1.
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