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A novel synthesis of deoxy phospha sugar–sugar disaccharides ☆

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Abstract—A novel and facile synthetic method is described in the synthesis of several deoxy phospha sugar–sugar disaccharides, analogs of normal sugar disaccharides by treatment of (±)-2-bromo-3-methoxy-1-phenylphospholane 1-oxide with several pentose and hexose sugar acetonides.

The biological importance of carbohydrates and glycosylated natural products[1] has resulted in an increased focus on the development of synthetic methods for the procurement of pure oligosaccharides and glycoconjugates. Thus, preparation of sugar derivatives such as glycosides and nucleosides is an interesting field in the hetero sugar chemistry as in the carbohydrate chemistry.[2] This letter deals with a novel synthesis and structure of phospha sugar–sugar disaccharides.

The term 'phospha sugar' belongs to the class of hetero sugars and denotes the replacement of hemiacetal oxygen of normal sugar by phosphorus moiety. In recent years, phospha sugar molecules have attracted considerable synthetic interest in view of their physicochemical properties as well as potential biological activity.[3] Though several routes are available for the synthesis of carba-, aza-, and thia-sugar disaccharides in racemic or enatiomerically pure form,[4] no method has been described hitherto in the synthesis of phospha sugar–sugar disaccharides.

Moreover, synthesis of phospha sugars was rather difficult due to long reaction sequences and low yields,[5] and preparations generally were normal sugars as starting materials. Therefore, it would be interesting to establish facile synthetic approaches and newer concepts in the synthesis and development of phospha sugar molecules. Hence, we wished to develop efficient protocols and reported the successful synthesis of several tetrofuranose analogs in high yields via simple reaction methods.[6] However, our aim to develop potential bioactive compounds of phospha sugars led us to synthesize phospha sugar–sugar disaccharides. Therefore, we now report our preliminary synthesis and structural analysis of deoxy phospha sugar–sugar disaccharides.

In developing the synthesis of phospha sugar–sugar disaccharides, we first started from the bromohydrin derivatives I, II (Fig. 1), which were prepared from the corresponding 2-phospholene 1-oxides, because introduction of sugar moiety at C-2 position was expected to be relatively easy through its 2-bromophospholane derivative.[7] We previously reported the preparation of *threo*-bromohydrin derivatives I and II obtained via bromohydrination of 1-phenyl-2-phospholene 1-oxides.[8] However, using such bromohydrin derivatives I and II, we obtained epoxides[9] instead of desired disaccharides. To avoid β-elimination reactions, we tried to protect

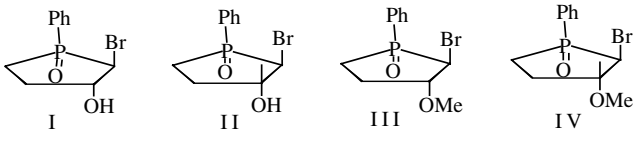

Figure 1. Different type of 2-bromo-3-hydroxy/methoxy-phospholane based glycosyl donors.

Keywords: Phospha sugars; Hetero sugars; Phospha sugar–sugar disaccharides.
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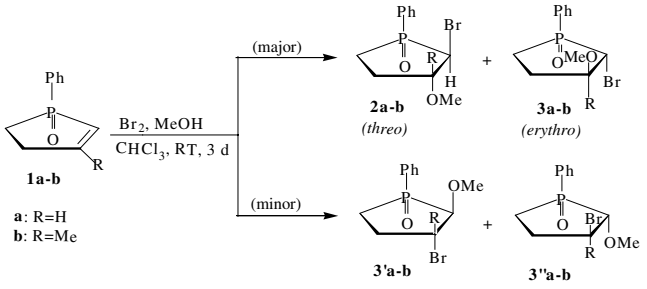


Scheme 1. Preparation of bromomethoxy derivatives from 1-phenyl-2-phospholene 1-oxides (**1a**–**b**).

3-hydroxy group of bromohydrin derivative of I and II via acylation and methylation reactions using mild base K_2CO_3, but the reactions led us to obtain same epoxides instead of –OH group protected compounds. Then we decided to prepare 1-phenyl-2-bromo-3-methoxyphospholane 1-oxides from starting 2-phospholenes using methanol in place of water in bromohydrination (Scheme 1).

Bromination of 1-phenyl-2-phospholene 1-oxides (**1a**–**b**) in methanol, afforded the diastereomeric mixture of (±)-2-bromo-3-methoxyphospholane derivatives, **2a**–**b** (*threo*) and **3a**–**b** (*erythro*) (Scheme 1) as major isomers in addition to the minor regiodiastereomers, **3′a**–**b** and **3″a**–**b**. Preliminary TLC analysis of the reaction mixture showed only two spots, suggesting the formation of two major isomers, **2a**–**b** [(±)-*threo*-1-phenyl-2-bromo-3-methoxy-phospholane 1-oxide (**2a**) and (±)-*threo*-1-phenyl-2-bromo-3-methoxy-3-methylphospholane 1-oxide (**2b**)] and **3a**–**b** [(±)-*erythro*-1-phenyl-2-bromo-3-methoxyphospholane 1-oxide (**3a**) and (±)-*erythro*-1-phenyl-2-bromo-3-methoxy-3-methylphospholane 1-oxide (**3b**)]. However, HPLC analysis revealed that each compound consists of four isomers. The isomers **2a**, **2b** and **3a**, **3b** were separated by column chromatography on silica gel using ethyl acetate, *n*-hexane and methanol (25:10:1) and obtained as liquids.

Table 1. Isomeric ratios and yields of bromomethoxy phospholane oxides

Substrate	Isomeric ratio[a]				Yield (%)[b]	
	2a–**b**	**3a**–**b**	**3′a**–**b**	**3″a**–**b**	**2a**–**b**	**3a**–**b**
1a	6	4	1	1	45	44
1b	6	3	1	1	47	45

[a] Determined by ^{31}P NMR spectroscopy.
[b] Isolated yield.

Furthermore, detailed spectral analysis of compounds **3a**–**b** showed that the presence of minor regiodiastereomers **3′a**–**b** and **3″a**–**b**, attempts to separate **3′a**–**b** and **3″a**–**b** from **3a**–**b** were remained unsuccessful, and hence isomeric ratios were determined by ^{31}P NMR spectroscopy. The isomeric ratios were given in Table 1. All of these compounds were structurally confirmed from their ^{1}H, ^{13}C, and ^{31}P NMR spectral data. The stereochemistry of these compounds was ascertained by comparison of ^{1}H NMR spectral data, that is, the chemical shift values of H-2 and H-4, long range coupling constants of H-2 and H-4 ($^{4}J_{HH}$), and $^{2}J_{PH}$ coupling constant values with the previously reported bromohydrin derivatives.[8] These bromohydrin derivatives are very useful intermediates for the synthesis of disaccharides.

To obtain the desired disaccharides, further reactions were performed on major isomers **2a**–**b** and **3a**–**b**. Treatment of compound **2a** with glucosediacetonide [1,2,5,6-di-*O*-isopropylidene-α-D-(+)-glucofuranose] in dry DMF at room temperature for 3 h using sodium hydride, afforded disaccharide (**4a**) in 42% yield.[10] Among the four major bromomethoxy intermediates obtained, only one compound that is, compound III (**2a**) gave desired product, whereas, the other isomer IV (**2b**) gave β-eliminated compound (**5d**) instead of disaccharide. It is expected due to the presence of electron-donating (+*I*) natured methyl group at C-3 position, which facilitates β-elimination reaction rather than substitution. The other isomers **3a**–**b** were remained unreactive toward sugar diacetonides due to the presence of regiodiastereomers. Later, we tested compound III with different types of hexose and pentose acetonide derivatives in the same reaction conditions. Product structures and yields are given in Figure 2 and Table 2, respectively. However, in case of mannose diacetonide (entry 6), no disaccharide was obtained, because compound III was found to be unreactive toward free anomeric hydroxyl group. All other reactions underwent smoothly in dry DMF. When the reactions were performed in dry THF, yields were very low and in some cases there was no product at all. To control the β-elimination reaction, mild base K_2CO_3 was used instead of NaH but reaction yields were very low. Therefore, the optimized general reaction conditions were given in Scheme 2. It is noteworthy to state that only

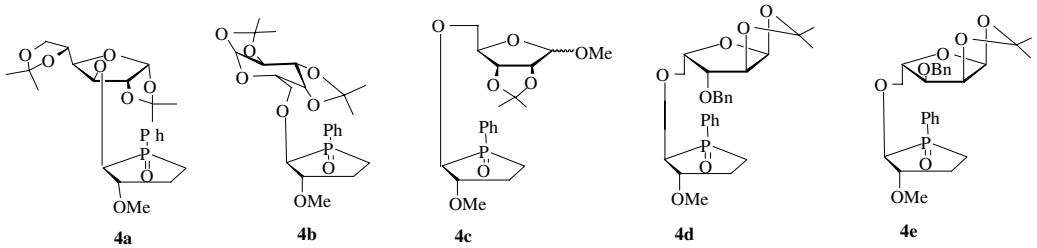
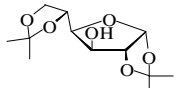
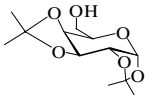
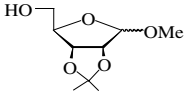
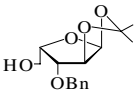
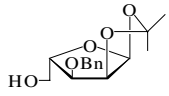
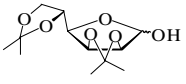
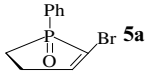
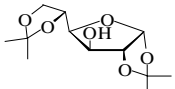
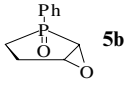
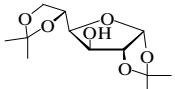
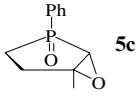
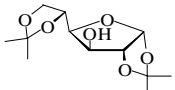
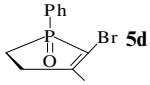


Figure 2. Product structures of **4a**–**e**.

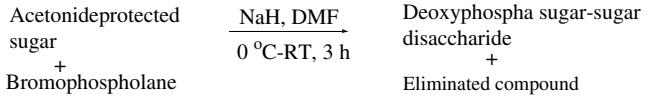
Table 2. Preparation of deoxy phospha sugar–sugar disaccharides

Entry	Donor	Acceptor	Disaccharide	Yield (%)[a]
1	**III**	 D-(+)-Glucosediacetonide	**4a**	42
2	**III**	 D-(+)-Galactosediacetonide	**4b**	44
3	**III**	 D-(-)-Riboseacetonide	**4c**	42
4	**III**	 L-(-)-Xyloseacetonide	**4d**	39
5	**III**	 L-(-)-Arabinoseacetonide	**4e**	41
6	**III**	 D-(+)-Mannosediacetonide	 **5a**	91
7	**I**	 D-(+)-Glucosediacetonide	 **5b**	88
8	**II**	 D-(+)-Glucosediacetonide	 **5c**	92
9	**IV**	 D-(+)-Glucosediacetonide	 **5d**	95

[a] % of yields of **4a**–**e** was calculated after purification by column chromatography and recycle GPC analysis.

bromohydrin III (**2a**) gave desired compounds and the other bromohydrins I, II, and IV gave corresponding eliminated compounds in high yields, given in Table 2.

Purification of compounds **4a**–**e** on silica gel column chromatography and also using recycle GPC analysis afforded in 39–45% yields. Endeavors to improve the reaction yields of disaccharides **4a**–**e** failed due to lack of optical purity in the substrate III (**2a**) [racemate, (±)-*threo*-1-phenyl-2-bromo-3-methoxyphospholane 1-oxide], that means ⩽50% yield should be theoretically achieved. The unreacted sugar diacetonide (~40%) was recovered by column chromatography, whereas, bromophospholane oxide was converted to its β-eliminated compound (i.e., compound **5a**). The structures of products **4a**–**e** were thoroughly investigated by ^{1}H, ^{13}C, and ^{31}P NMR and mass spectral analyses.[11] In ^{31}P NMR spectra of compounds **4a**–**e** showed a single peak, which represents the formation of a single isomer. In proton NMR



Scheme 2. Preparation of deoxy phospha sugar–sugar disaccharides.

Table 3. Chemical shift value of H-2, J_{PH} coupling constant and ^{31}P NMR chemical shift values of **4a–e**

Compound	δ value of H-2 (ppm)	$^2J_{PH}$, $^3J_{HH\,(vic)}$ (Hz)	^{31}P NMR (δ in ppm)
4a	3.52	11.5, 4.1	56.2
4b	3.46	10.7, 4.0	61.7
4c	3.42	11.1, 4.0	52.4
4d	3.57	11.3, 4.2	59.5
4e	3.55	10.8, 4.0	62.7

spectra of compounds **4a–e**, H-2 proton resonated as double doublet (dd) due to P–C–H and H–H (vicinal) coupling. The orientation of the P=O group of phospholane ring in compounds **4a–e** was established from the $^2J_{PH}$ coupling constants (Table 3). The larger $^2J_{PH}$ coupling constant suggests the *cis* (or gauche) relationship of H-2–C-2–P=O.[12] The ^{31}P NMR chemical shift values of **4a–e** were shifted to downfield (by ~5 ppm) from the corresponding bromomethoxyphospholane oxides, it may be due to the replacement of bromine atom by sugar moiety.

On the other hand, the retention of configuration at C-2 was achieved via S_N1 reaction mechanism, which led us formation of a single isomer. The generated secondary carbonium ion intermediate is presumably stabilized by the adjacent partial *−ve* charge on oxygen atom of P=O and thus the nucleophile of sugar molecule is facilitated to attack preferably through opposite side of P=O group, it is assumed due to the electron repulsive interaction between P^+–O^- and attacking nucleophile.[6a] The S_N1 reaction is also supported by the solvent effect, where the reactions were promoted by using higher polar solvent, DMF rather than THF.

Moreover, in our preliminary studies, the configuration at C-2 of compounds **4a–e** was determined by calculation of the heat of formation (ΔH_f) of *R* and *S* forms using MOPAC AM1 analysis data. The calculated data showed that the heat of formation of *S* (for **4a**, $\Delta H_f = -349.41$ kcal) configuration at C-2 is lower than *R* (for **4a**, $\Delta H_f = -347.27$ kcal), and thus the formation of *S* configuration isomer is favored and stable than *R* configuration. Therefore, the resultant configuration obtained at P-1, C-2, and C-3 of **4a–e** is (1S_P,2*S*,3*S*) for the favored formation (Fig. 2).

In conclusions, we established a novel synthetic approach in the synthesis of deoxy phospha sugar–sugar disaccharides. Further synthesis of these compounds, for example, use of optically pure phospholane oxides, determination of optical rotation, phosphate esters of phospholanes as glycosyl donors, and bioactive studies are currently under progress in our laboratory and will be reported in due course.

Acknowledgements

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9. The epoxide structures (**5b**, **5c**) were shown in Table 2, and structurally confirmed from NMR (^1H, and ^{13}C) spectral analyses.
10. (a) The general experimental procedure for the preparation of compounds **4a–e** is as follows: To a 0 °C suspension of sodium hydride (60–72% in oil, 0.036 g, 1.52 mmol) in dry DMF (3 mL) was added the readily prepared solution of protected sugar diacetonide (0.76 mmol) in dry DMF (2 mL) and the resultant reaction mixture was stirred for 40 min at room temperature. After 40 min, reaction mixture was cooled to 0 °C and added the solution of bromomethoxyphospholanes (0.8 mmol) in dry DMF (2 mL) and allowed to stir for additional 2 h at room temperature and then DMF was distilled off under diminished pressure and residue was dissolved in chloroform (20 mL), washed with NH_4Cl solution (5 mL × 2), water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel column chromatography (20:1 chloroform/methanol) and also using recycle GPC analysis to get pure disaccharides **4a–e** as oily liquids.
11. All compounds were structurally characterized by spectral ^1H NMR (JEOL JNM-300 at 300.40 MHz), ^{13}C NMR (JEOL JNM-300 at 75.0 MHz), ^{31}P NMR (JEOL JNM EX-90 at 36.18 MHz), mass (Kompact MALDI-TOF MS using α-cyano-4-hydroxycinnamic acid as a matrix, reflectron flight path and 100 profiles per sample) analyses.
Compound **4a**: ^1H NMR ($CDCl_3$): δ 1.11–1.55 (4s, 12H, $CH_3 \times 4$), 2.00–3.15 (m, 4H, H-4,5), 3.52 (dd, 1H, $^2J_{PH} = 11.5$ Hz and $^3J_{HH\,(vic)} = 4.1$ Hz, H-2), 3.63 (m, 1H, H-3), 3.82 (s, 3H, OMe), 3.95–4.52 (m, 1H, 6H), 4.57 (d,

2H, $J = 3.5$ Hz), 5.93 (d, $J = 3.6$ Hz, 1H), 7.45–7.82 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 23.15, 26.56, 26.68, 26.81, 29.32, 29.34, 57.68, 67.41, 73.25, 74.79, 81.19, 85.15, 89.17, 90.32, 105.21, 109.32, 111.62, 128.38, 128.51, 128.55, 128.66, 130.54, 130.68; ^{31}P NMR ($CDCl_3$, H_3PO_4): δ 56.2. MS (m/z): 468.42 (M^+) for $C_{23}H_{33}O_8P$.

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