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A novel conversion of *erythro* phospholane epoxides to one-carbon atom homologated allylic alcohols ☆

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Abstract—A novel synthetic approach is described to incorporate one more carbon atom at C-2 position of phospholane oxides as homologated allylic alcohol by treatment of *erythro*-2,3-epoxy-3-methylphospholane 1-oxides with excess of dimethylsulfonium methylide.

The well-established accessibility and versatility of epoxides have made them one of the key intermediates of modern organic synthesis.[1] Alcaraz et al. reported the vinylation of halides, and also *cis*-epoxides to their homologated allylic alcohols using excess of dimethylsulfonium methylide.[2] However, in the latter case, transformation was limited to selective cyclic and acyclic *cis*-epoxides, which are not possessing electron-withdrawing groups adjacent to epoxide moiety. To the best of our knowledge, no method has been described for homologation reactions of epoxides possessing electron-withdrawing groups, particularly for phospholane epoxide rings. Therefore, we first examined the ring opening of phospholane epoxides using dimethylsulfonium methylide. To our delight, our endeavors were successful in the direct conversion of *erythro*-2,3-epoxy-3-methylphospholane 1-oxides to homologated allylic alcohols using excess of dimethylsulfonium methylide.

In our on going research, aimed in developing the synthesis of pentofuranose skeleton of phospha sugar molecules and their nucleoside analogs, exemplified in Figure 1, prompted us at first to investigate the synthetic

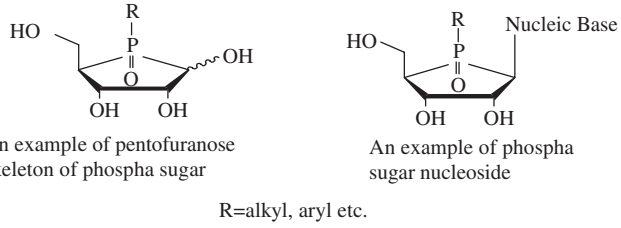

Figure 1.

approaches to incorporate an additional carbon atom either at C-5 or C-2 position. The term 'phospha sugar' belongs to the class of hetero sugars. In recent years, it has been well focused on the synthesis, and bioactivity of hetero sugars, for example, 5-amino-5-deoxy-D-glucose is an antibiotic and 5-deoxy-5-thio-D-glucopyranose is an active substance for increment of blood sugar concentration etc.[3,4] However, phospha sugars, have never been found in nature and information about their expected bioactivity[5] has hitherto been sparse, since the amounts and kinds of phospha sugars obtained were very small. Previous methods, for the preparation of phospha sugars, sugars as starting materials required many and tedious synthetic steps,[6,7] and resulted in low overall yields.

Hence, we wished to develop an efficient protocols and reported the synthesis of various tetrofuranose analogs via simple reaction methods.[8] Nevertheless, several attempts remained unsuccessful or led to obtain very

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low yields during introduction of an additional carbon atom on phospholane ring, for example, direct alkylation using stronger nucleophiles, such as lithium diisopropylamide or *n*-butyllithium upon treatment with phospholene oxide or allylic ketone of phospholene oxide[8d] etc. led to the formation of only 10% alkylated compound and in the latter case allylic O-alkylation was predominant than C-alkylation at C-5 active methylene group of phospholene oxide. Therefore, we now describe our preliminary synthesis of one-carbon homologated allylic alcohols of phospholane oxides from *erythro*-epoxides, in 42–55% isolated yields. The synthesized one-carbon homologated compounds are expected to be good precursors to prepare the target pentofuranose analogs of phospha sugars, and to further their nucleoside derivatives.

In order to obtain one-carbon atom homologated phospholane oxides, first we treated bromophospholane oxide **6** (*threo*-1-phenyl-2-bromo-3-methyl-3-methoxyphospholane 1-oxide) with excess of dimethylsulfonium methylide (which was prepared in situ by treatment of trimethylsulfonium iodide with *n*-butyllithium) according to the reported synthetic procedure (Fig. 2).[2a] However, our attempts remained unsuccessful because it gave 1-phenyl-2-bromo-3-methyl-2-phospholene 1-oxide **7** (by elimination of MeOH) instead of desired homologated compound at C-2 position. We then, understood the precursor is favorite to elimination rather than nucleophilic addition reaction at C-2 position.

Later, we envisaged that epoxide could be a good precursor to prepare the desired compounds. Accordingly, we recently reported an efficient method to prepare *erythro*-epoxides directly from 2-phospholene oxides using sodium peroxide reagent.[8a] But the reagent was found to be inactive toward 3-methyl-2-phospholene 1-oxides (e.g., compound **1** in Scheme 1) to produce epoxides. Therefore, the *erythro*-epoxides **4a**–**f** were prepared by treatment of *threo*-bromohydrin derivatives of phospholane oxides **3a**–**f** with K_2CO_3 in methanol at room temperature for 3–4 h, afforded 85–90% pure *erythro*-epoxides **4a**–**f** [whereas, *erythro*-bromohydrin

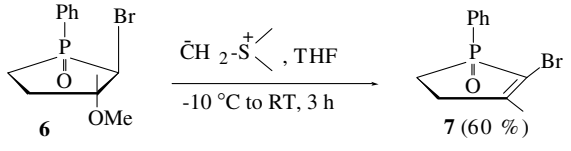
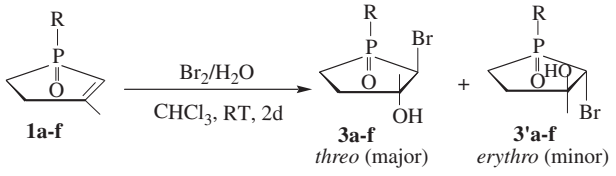


Figure 2.



Scheme 1. Preparation of bromohydrin derivatives.[8c]

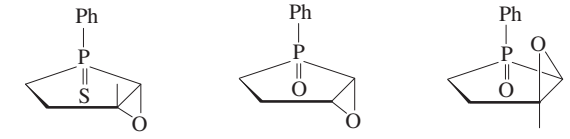
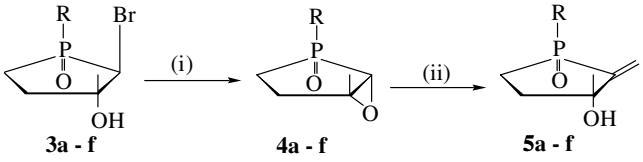


Figure 3.

derivatives (**3′a**–**f**) produced *threo*-epoxides, e.g., compound **9** in Fig. 3].[9]

The bromohydrin derivatives (**3a**–**f**) were prepared according to our reported method as outlined in Scheme 1.[8c] On the other hand, replacement of water (in Scheme 1) by methanol afforded the corresponding methoxy derivatives, for example, compound **6** in Figure 2. The *erythro*-epoxides are good precursors to prepare the desired compounds **5a**–**g**. The *erythro* configuration was ascertained by comparison of $^2J_{PH}$ coupling constants of **4a**–**f** (25.8–29.2 Hz) and H-2, H-3 chemical shift values with our recently reported analogs, prepared using sodium peroxide.[8a]

Further treatment of *erythro*-epoxides **4a**–**g** with excess of dimethylsulfonium methylide gave the desired homologated allylic alcohols in their crude form (Scheme 2), subsequent purification on silica gel flash column chromatography afforded 42–55% pure compounds **5a**–**g** (Table 1) as oily liquids.[10] Initially, we used 3–4 equiv excess of methylide, but the % of conversion was found to be up to 40–45%. Having established that the protocol was viable, we then wished to increase the % of conversion and achieve the optimum reaction conditions. Therefore, increasing the molar ratio of



Scheme 2. Synthesis of C-2 homologated allylic alcohols of phospholane oxides. Reagents and conditions: (i) K_2CO_3, MeOH, rt, 3–4 h; (ii) *n*-BuLi, $(CH_3)_3SI$, dry THF, 3 h, −20 °C to rt.

Table 1. Preparation of homologated allylic alcohols **5a**–**g**

Entry	R	Substrate	Product	Yield (%)[a]
1	Ph	**4a**	**5a**	49
2	Ph–NO_2 (*m*)	**4b**	**5b**	42
3	Ph–OMe (*p*)	**4c**	**5c**	48
4	OMe	**4d**	**5d**	55[b]
5	OEt	**4e**	**5e**	52
6	O*i*-Pr	**4f**	**5f**	49
7	Ph (P=S)	**4g**	**5g** (P=S)	49

[a] Isolated yield.
[b] Comparingly better yield was obtained due to the presence of electron repelling group, and also less steric hindrance exerted by the the substituent on P atom.

sulfur ylide, from 3.0 to 6.0 equiv led to improve the conversion up to 62%. Significantly, using more than 6.0 equiv of ylide leading to the formation of unwanted by-products, which are unable to identify structurally, and also attempts remained unsuccessful to improve the conversion by lowering the initial reaction temperature to −30 °C. The progress of the reaction was monitored by TLC analysis, and it was found that the reaction progress was very slow at below −20 °C, and finally led to obtaining lower conversions. Therefore, the optimal temperature range is −10 to −20 °C.

Therefore, the maximum conversion was found to be ⩽62%, and in all the cases 10–20% of starting epoxides were recovered. The electron densities on carbon atoms of phospholane ring were calculated using MOPAC AM1 calculations. The MOPAC data attributed that the carbon atom adjacent to P=O and linked with epoxide (C-2) is more electrophilic than C-5. Therefore, the reason for the lower conversion is due to epoxide precursors having a stronger electron-withdrawing phosphoryl group caused to develop electrophilic nature on adjacent (C-2) carbon atom (by decreasing the pK_a value on C-2) led to form oxylanyl anion by removal of H^+ at C-2, and the H^+ ion may partially quenched the sulfur ylide and thus ultimately inhibited the nucleophilic attack at C-2, and may also be due to less reactivity of phospholane epoxides toward the dimethylsulfonium methylide. We then, examined the reactivity of sulfur ylide toward different P-substituted *erythro*-epoxides, the product isolated yields were given in Table 1. As can be seen from Table 1, the conversions are slightly affected by the steric factors exerted by the substituents on P atom, and the conversion is slightly enhanced by the presence of electron-donating groups on P atom (**4c**–**f**), which are known to promote such nucleophilic addition reactions,[1b] while electron-withdrawing groups on phenyl ring substituted on P atom (**4b**) had the opposite effect.

In an effort to compare the reactivity between *erythro*-epoxides of phosphoryl (P=O) and its sulfide derivative (P=S) toward the sulfur ylide, we replaced O atom of compound **4a** by S using P_4S_{10} and obtained the precursor **4g** (Fig. 3) in 70% yield.[11] Subsequent treatment of **4g** with dimethylsulfonium methylide under similar reaction conditions of **4a**–**f**, afforded desired compound **5g** in 49% yield. Therefore, the less electronegativity of S atom caused a little increase in the conversion when compared with **4a**.

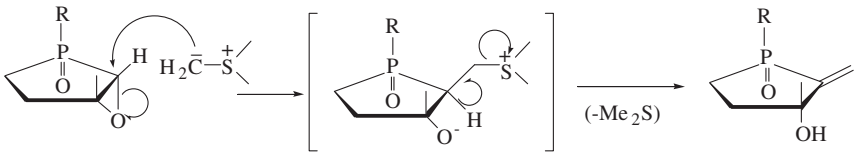
The obtained compounds **5a**–**g** were structurally characterized by spectral analyses.[12] In proton NMR spectra of compounds **5a**–**g**, the allylic methylene group protons resonated as double triplet in between 5.1 and 5.9 ppm due to P–C–H coupling ($^3J_{PH}$) and H–H coupling (J_{HH}). The coupling constant ($^3J_{PH}$) values are in good agreement when compared with the P–C–H coupling of 2-phospholene oxides. More precisely, in ^{13}C NMR spectra of compounds **5a**–**g**, the carbon atoms corresponding to C–OH and C=CH_2 clearly resonated in between 72 and 73 ppm (C–OH), 111–113 (*C*=CH_2) ppm and 143–144.5 ppm (C=*C*H_2), respectively.

The stereochemistry of epoxides, or oxirane ring opening by nucleophiles is broadly discussed in the number of reviews that have appeared over the years.[1b,c] Normally, backside attack of the nucleophile on an epoxide carbon occurs, resulting in Walden inversion at this center.[1b] Therefore, the stereochemistry at C-3 position of **5a**–**g** was explained via S_N2 reaction (often been termed borderline S_N2 with the difference that the leaving group stays attached to the molecule).[1c,d] The sulfur ylide was attacked on C-2 position from the rear side of epoxide ring and led to obtain *R* configuration at C-3 position, and it is also supported by our previous method in the ring opening of *erthro*-phospholane epoxides with amines to prepare N-glycosides.[13] Thus, we proved the dimethylsulfonium methylide is active to produce desired allylic alcohols from the *erythro*-epoxides possessing adjacent electron-withdrawing phosphoryl group located on five-membered heterocyclic ring, for the first time.

However, attempts to prepare the desired compounds from phospholane epoxides, which lack the methyl group at C-3 position, for example, compound **8** and *threo*-epoxides, for example, compound **9** (Fig. 3) were unsuccessful. Thus, it revealed the requirement of electron-donating group at C-3 position and *erythro* configuration for epoxide precursors.

The mechanism as outlined in Scheme 3 is similar to the one reported for related homologations.[2] The reaction proceeds by nucleophilic addition of sulfur ylide, which reacts regioselectively at C-2 due to its electrophilic nature, transferring a methylene group, forms a betaine intermediate **2** and followed by concomitant loss of dimethyl sulfide by β-elimination (via intramolecular process) led to formation of desired allylic alcohol.

In conclusion, we have developed a novel synthetic route to incorporate one more carbon atom at C-2 position of phospholane ring. Further synthesis in the conversion of these homologated alcohols to pentofuranose skeleton of phospha sugar molecules and their nucleosides are



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Scheme 3. Reaction mechanism.

currently under progress and will be reported in our future communications.

Acknowledgements

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9. Preparation of *erythro*-epoxides (**4a**–**g**). Representative compound **4a** (*erythro*-1-phenyl-2,3-epoxy-3-methylphospholane 1-oxide): *threo*-Bromohydrin **3a** (1.2 g, 4.2 mmol) was treated with K_2CO_3 (0.6 g, 4.5 mmol) in methanol (20 mL) for 4 h at room temperature. The reaction mixture was filtered, methanol was removed under vacuum and the residue was dissolved in water (5 mL). The aqueous layer was extracted with $CHCl_3$ (20 mL × 2), the combined extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The resultant crude was purified on silica gel column chromatography (20:1 chloroform–methanol) to get pure epoxide **4a**, colorless solid in 87% yiled. Mp: 95–97 °C. ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 3H, CH_3), 1.73–2.47 (m, 4H, H-4,5), 3.24 (d, 1H, $^2J_{PH} = 25.8$ Hz), 7.27–7.73 (m, 5H, Ph), ^{13}C NMR ($CDCl_3$): δ 19.25 (CH_3), 22.76 (d, $J_{CP} = 71.5$ Hz, C-5), 28.48 (C-4), 34.61 (C-3), 57.77 (d, $J_{CP} = 98.2$ Hz, C-2), 128.92 (d, $^3J_{CP} = 11.36$ Hz, C-3,5 of Ph), 130.03 (d, $J_{CP} = 87.54$, C-1 of Ph), 130.81 (d, $^2J_{CP} = 9.36$ Hz, C-2,6 of Ph), 132.82 (d, $^4J_{CP} = 3.33$ Hz, C-4 of Ph); ^{31}P NMR ($CDCl_3$, H_3PO_4): δ 49.92. MS (m/z): 209.18 (M^++H) for $C_{11}H_{13}PO_2$. IR (KBr): ν (cm^{-1}) 2960 (C–H of epoxide), 1270 and 828 (epoxide), 1194 (P=O).
10. Preparation of allylic alcohols (**5a**–**g**). Representative compound **5a**: To a −20 °C suspension of trimethylsulfonium iodide (1.2 g, 6.0 mmol, 6.1 equiv) in THF (10 mL) was added *n*-BuLi (4.0 mL of 1.6 M hexane solution, 6.4 mmol, 6.5 equiv). After 30–40 min, epoxide **4a** (0.2 g, 0.97 mmol, 1.0 equiv) in THF (5 mL) was introduced and the reaction slowly allowed to warm to 0 °C over 1 h; the reaction mixture was then stirred at ambient temperature for 2 h. The reaction was quenched with water and extracted with chloroform. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residues were purified on silica gel flash column chromatography (20:1 chloroform–methanol) and recycle GPC analysis to give pure allylic alcohol **5a** as oily liquid.
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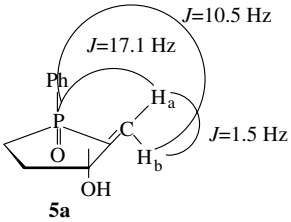
12. All compounds (**5a**–**g**) were structurally characterized by spectral ^{1}H NMR (JEOL JNM-300 at 300.40 MHz), ^{13}C NMR (JEOL JNM-300 at 75.0 MHz), ^{31}P NMR (JEOL JNM EX-90 at 36.18 MHz), mass (Kompact MALDI-TOF MS).



5a

Compound **5a** (1-phenyl-3-hydroxy-2-methylene-3-methylphospholane 1-oxide): ^{1}H NMR ($CDCl_3$): 1.37 (s, 3H, CH_3), 1.95–2.71 (m, 4H, H-4,5), 5.08–5.28 (dt, 2H, =CHH, $^3J_{PH} = 10.5$ & 17.1 Hz and $J_{HH} = 1.5$ Hz), 7.51–7.76 (m, 5H, Ph), OH peak was not observed; ^{13}C NMR ($CDCl_3$): δ 23.86 (d, C-5, $J_{CP} = 51.5$ Hz), 28.12 (CH_3), 33.57 (C-4), 72.19 (C-3), 112.62 (d, $J_{CP} = 15.1$ Hz, C-2), 128.54 (d, $^3J_{CP} = 11.36$ Hz, C-3,5 of Ph), 130.31 (d, $J_{CP} = 87.54$, C-1 of Ph), 130.76 (d, $^2J_{CP} = 9.36$ Hz, C-2,6 of Ph), 131.69 (d, $^4J_{CP} = 3.33$ Hz, C-4 of Ph), 144.05 (=CH_2); ^{31}P NMR ($CDCl_3$, H_3PO_4): δ 35.12. MS (m/z): 222.12 (M^+) for $C_{12}H_{15}PO_2$.
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