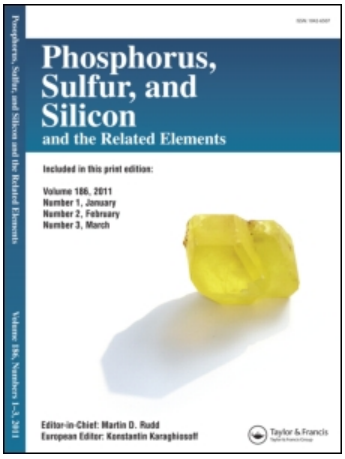

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FACILE SYNTHESIS OF NOVEL PENTOFURANOSE ANALOGS OF PHOSPHA SUGAR DERIVATIVES

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*Novel pentofuranose analogs of phospha sugar derivatives were synthesized starting from 1-phenyl-2-phospholene 1-oxide (**1**). First, the allylic oxidation of 1-phenyl-2-phospholene 1-oxide (**1**) with CrO_3 in Ac_2O-AcOH or 3-hydroxy-1-phenyl-2-phospholene (**2**) with MnO_2 afforded 1-phenyl-4-oxo-2-phospholene 1-oxide (**3**). The C-5 alkylation of **3** in the presence of NaH by using benzyl bromide or methyl iodide as electrophiles afforded the target title compounds.*

Keywords: Allylic oxidation; C-5 alkylation; phenyl-2-phospholene

INTRODUCTION

Heterosugars are inherent and interesting substances because of their wide range of important biological activities in living systems. The potential bioactivity of natural as well as synthetic heterosugar nucleosides prompted many scientists to synthesize several of their analogs and explore the possibility of their use as anti-HIV, anti-cancer, etc., agents.[1–3] In search for finding therapeutically improved inhibitors of HIV, -wide variety of sugar-modified nucleosides were developed and found to possess potential bioactivity. Among them, Ribavirin,[4] AZT,[5] 4′-thio-ddC,[6] Aristeromycin,[7] etc., are the most interesting compounds due to their potent anti-HIV activities. Recent developments in the heterosugar chemistry and structure-activity relationship studies have indicated that functional changes of the sugar moiety can be compatible with potent bioactivity.[8] Replacement of hemiacetal ring oxygen

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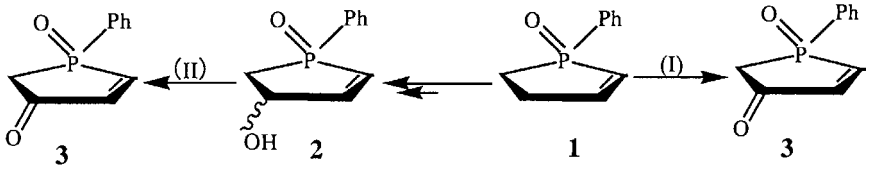
with methylene, nitrogen, sulfur, etc., is one of the most interesting approaches for making functional changes in the nucleoside subunits.[8,9] In order to provide more potent anti-HIV, anti-cancer, etc., agents, several novel classes of heterosugars, such as carbo,[10] aza,[11] thiosugar,[12] nucleosides were developed and extensively studied; however, to provide more potential analogs with enhanced bioactivity, further modification of nucleoside subunits to a variety of derivatives with different bioactive moieties is considered to be desirable. The present work deals with the synthesis of pentofuranose analogs of phospha sugar derivatives.

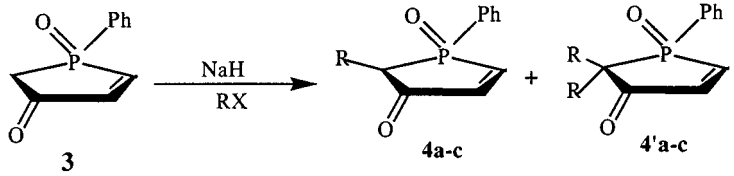
RESULTS AND DISCUSSION

Introduction of one more carbon atom at C-5 position in 2-phospholene ring of compound **1** by using simple base, such as NaH, is a challenging reaction in the phospha sugar chemistry. For the preparation of the desired pentofuranose analog phospha sugar derivatives **4**, we started first to convert allylic methylene group of 2-phospholene **1** into carbonyl by allylic oxidation method, and then alkylation follows in a facile way at activated methylene group in the phospholene ring system. In view of this, our attempts by using specific reported reagents like SeO_2, CrO_3-Pyridine complex, and CrO_3-DMP complex were failed to oxidize **1**-phenyl-2-phospholene-1-oxide. Later we attempted with more acidic oxidizing agent (i.e., CrO_3 in Ac_2O—AcOH[13]) at the reaction conditions (Scheme 1). Oxidation succeeded well, and nearly 60% of the 2-phospholene was oxidized without getting any side products. In another process, product **2** was simply stirred for 6–8 h in $CHCl_3$ with 3 eq. of MnO_2 at room temperature, which produced allylic carbonyl derivative **3**.

The C-5 alkylation of 1-phenyl-4-oxo-2-phospholene 1-oxide (**3**) in the presence of NaH with 1.5 mole of CH_3I for 2–3 hrs at -5° to $0^\circ C$ produced the mixture of alkylation products. From the HPLC and proton NMR data it was revealed that there were 90% of monoalkylation product **4a** and 10% of dialkylation product **5a** being occurred. When, $C_6H_5CH_2Br$ was used as an electrophile we observed predominant formation of monoalkylation product **4c**. The reason for the product selectivity may be due to the steric factors. We observed only formation of dialkylative product **4′b** when we used excess of NaH and methyliodide at room temperature. The synthesized title compounds **4a–c** were confirmed by proton NMR. The further spectral analysis, stereochemistry of the title compounds is under progress.



(I) $5CrO_3$, Ac_2O-AcOH, CH_2Cl_2, 0-10°C, 5 hrs
(II) $3MnO_2$, $CHCl_3$, RT, 6-8 hrs



SCHEME 1

Entry	Number of Moles of NaH	RX	Temp °C	Reaction time	Alkylation total yield (%)	Mono-alkylation yield (%)	Dialkylation yield (%)
4a	1.4	$1.5CH_3I$	−5° to 0°C	2–3 hrs	40	90	10
4b	2.4	$3CH_3I$	RT	6–8 hrs	42	—	100
4c	1.4	$1.5C_6H_5CH_2Br$	0–5°C	4–5 hrs	52	100	—

EXPERIMENTAL

Allylic Oxidation of 1-Phenyl-2-phospholene 1-Oxide (1→3)

The reagent was prepared by addition of CrO_3 5g (50 mmol) in small portions to a mixture of Ac_2O (12.5 ml) and glacial AcOH (25 ml), followed by dilution with CH_2Cl_2 or benzene under ice cooling. Into the solution of the above reagent, 1-phenyl-2-phospholene 1-oxide (1, 10 mmol) in CH_2Cl_2 or benzene (5 ml) was added dropwise with stirring. The reaction mixture was stirred for 5 h at 0–10°C. The reaction mixture was diluted with water, neutralized with sodium hydroxide solution, and extracted with chloroform. After being dried over anhydrous sodium sulfate, the extract was concentrated and purified by flash chromatography and recycled GPC. Yield: 35%; MP: 92–95°C; IR ν (cm^{-1}) 1730 (C=O), 1640 (C=C), 1260 (P=O); m/z 192 ($M^{+\cdot}$); ^{31}P NMR (δ, $CDCl_3$, H_3PO_4): 36.9; ^1H NMR (δ, $CDCl_3$, TMS): 2.8–3.1 (*ddd*, 2H, H-2,2′, $J_{PH} = 15$, 8 Hz and $J_{HH} = 18$ Hz), 6.7 (*d*, 1H, H-4, $J_{PH} = 8.3$ Hz), 7.5 (*d*, 1H, H-5, $J_{PH} = 10.1$ Hz), 7.6 (m, 5H, Ph); ^{13}C NMR (δ, $CDCl_3$, TMS): 36.8 (*d*, $J_{CP} = 75.4$ Hz, C-2), 128.2 (*d*, $^3J_{CP} = 12.1$ Hz,

m-Ph), 130.1(*d*, $^2J_{CP} = 10.1$ Hz, *o*-Ph), 131.3 (*d*, $^4J_{CP} = 2.6$ Hz, *p*-Ph), 133.1 (*d*, $J_{CP} = 97.5$ Hz, x-Ph), 147.2 (*d*, $^2J_{CP} = 8.2$ Hz, C-4), 150.3 (*d*, $J_{CP} = 76.5$ Hz, C-5), 196.5 (*d*, $^2J_{CP} = 21.8$ Hz, C=O).

C-5 Alkylation of 1-Phenyl-4-oxo-2-phospholene 1-Oxide (General Procedure)

To a suspension of NaH (2.8 mmol) in dry THF (2.5 ml) and 1-phenyl-4-oxo-2-phospholene 1-oxide (**3**, 2.0 mmol) in dry THF (2 ml) was added at -5° to 0°C. The reaction mixture was stirred for 1–2 h at this temperature. After changing the reaction mixture color, alkyl halide (1.5 mmol) in dry THF (2 ml) was added at 0°C. When the addition was complete, the reaction mixture was stirred for 1–3 h at 0–10°C. The completion of the reaction was monitored by TLC analysis. The reaction mixture was neutralized with sodium hydroxide solution, followed by extraction with chloroform, dried and evaporated the solvent under reduced pressure afforded alkylation products **4a–c** being purified by flash chromatography and recycled GPC.

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