Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Stereoselective Synthesis of α-L-Rhamnopyranosyl Phosphonates via α-L-Rhamnopyranosyl Trifluoroacetate

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Published online: 23 Sep 2006.

To cite this article: Zhan-Jiang Li , Zhen-Zi Li & Wen-Kai Li (1995) Stereoselective Synthesis of α-L-Rhamnopyranosyl Phosphonates via α-L-Rhamnopyranosyl Trifluoroacetate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:17, 2545-2551, DOI: 10.1080/00397919508011798

To link to this article: http://dx.doi.org/10.1080/00397919508011798

SYNTHETIC COMMUNICATIONS, 25(17), 2545-2551 (1995)

STEREOSELECTIVE SYNTHESIS OF α-L-RHAMNOPYRANOSYL PHOSPHONATES VIA α-L-RHAMNOPYRANOSYL TRIFLUOROACETATE

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ABSTRACT: α-L-Rhamnopyranosyl phosphates **8a-b~12a-b** were obtained in high yield and high stereoselectivity from α-L-rhamnopyranosyl trifluoroacetate **2a-b** and phosphoric acid diesters in the presence of a Lewis acid.

Glycosyl phosphates are of importance as cell wall materials and as intermediates in biological glycosyl transfer [1]. The preparation of these compounds is usually based on the condensation of haloglycose with phosphoric acid diesters, but , low yields and α,β-selectivities are often observed [2]. Recently, major advances in this field have been made by the use of trichloroacetimidate method [3].

In this paper, we report the synthesis α-L-rhamnopyranosyl phosphate using the trifluoroacetoxyl group as the anomeric leaving group. The method is easy to operate and the reaction proceeds under mild conditions.

2,3,4-Tri-*O*-acetyl or benzyl-α-L-rhamnopyranose **1a-b** was treated with trifluoroacetic anhydride [4-9] to give 1-*O*-trifluoroacetyl-2,3,4-tri-*O*-acetyl or benzyl-α-L-rhamnopyranose **2a-b**. When **2a** or **2b** was reacted with some

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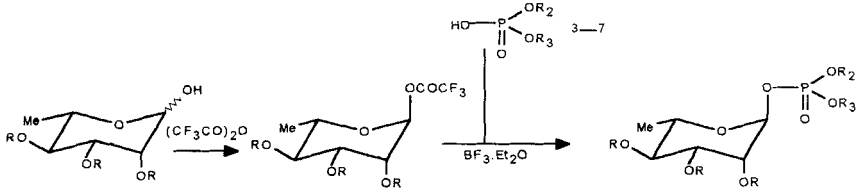
phosphoric acid diesters **3-7** in the presence of boron trifluoride etherate in dichloromethane, the compounds **8a-b~12a-b** were obtained in high yields (84~96%).



1a-b **2a-b** **8a-b~12a-b**

a: R=Acetyl **8:** R_2=R_3=Ethyl **9:** R_2=R_3=Propyl **10:** R_2=R_3=Isopropyl
b: R=Benzyl **11:** R_2=R_3=n-Butyl **12:** R_2=R_3=Benzyl

Scheme 1

EXPERIMENTAL

The NMR spectra were recorded as $CDCl_3$ solutions on a Varian XL 300 spectrometer. Mass spectroscopic analyses were performed with a Perkin-Elmer 240c mass spectrometer. Column chromatography was performed on silica-gel H (Qing Dao Chem. Co.).

Preparation of 1-*O*-trifluoroacetyl-2,3,4-tri-*O*-acetyl or benzyl-α-L-rhamnopyranose 2a-b

2,3,4-Tri-*O*-acetyl or benzyl-α-L-rhamnopyranose **1a-b** (1.0mmoL) was added to trifluoroacetic anhydride (6mL) with stirring at room temperature for 5 mins, then sodium trifluoroacetate (1.0mmoL) was added. The reaction was monitored by TLC ($CHCl_3$: CH_3OH=10 : 1). Dichloromethane (10mL) was added to the mixture after 40 mins. Then the product was subjected to silica gel column chromatography using dichloromethane (20mL) as eluant. The solvent was removed in vacuo to give a syrup, **2a** or **2b**, yields 95% and 98%, respectively.

Preparation of α-L-rhamnopyranosyl phosphates 8a-b~12a-b: General procedure.

A solution of **2a** or **2b** (1mmoL), phosphonic acid diesters **3-7** (1.5mmoL) and boron trifluoride etherate (3 drops) in dichloromethane (5mL) was stirred at room

temperature for 1-3 hrs. When TLC ($CHCl_3$: CH_3OH=10 : 1) showed the absence of substrate and the presence of new product, the solvent was evaporated to give a syrup. Compounds **8a-b~12a-b** were obtained as colorless needles or syrups after silica gel column chromatography. The reaction time, melting point , and yields are indicated in Table 1. The data of spectra and analysis are follows:

8a: ^{1}H NMR: δ 5.97 (d ,1H , $J_{1,2}$=1.3Hz , H-1) ; 5.30-5.10 (m , 3H , H-2 ,3 , and 4) ; 3.90(m ,1H, H-5) ;3.35 (m,4H ,OCH_2-) ;2.20-2.01(3s,9H ,-$COCH_3$) ; 1.22 (d , 3H , $J_{5,6}$=5.8Hz , Rha-CH_3) ; 0.93 (t , 6H , -C-CH_3) . Mass spectrum : m/z 426 (M^+). Anal Calcd for $C_{16}H_{27}O_{11}P$ (426) : C , 45.07 ; H , 6.38. Found : C , 45.09 ; H , 6.40.

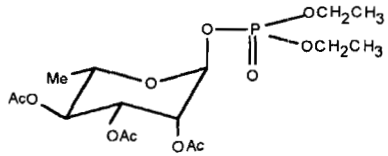
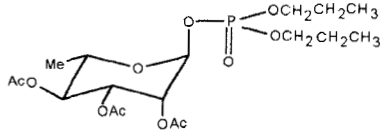
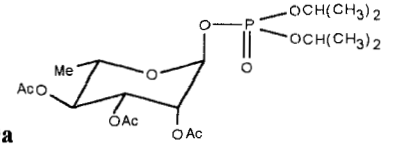
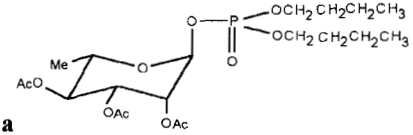
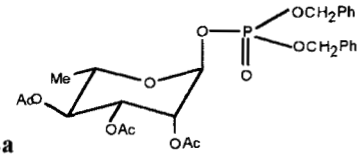
9a: ^{1}H NMR: δ 6.01(d ,1H, $J_{1,2}$=1.0Hz ,H-1) ; 5.35 (dd ,1H, $J_{2,3}$=3.0Hz, H-2) ; 5.20 (dd , 1H , $J_{4,5}$=10Hz, H-4) ;5.10 (dd ,1H, $J_{3,4}$=9.5Hz , H-3) ;3.86 (m ,1H , H-5) ; 3.33 (m , 4H , OCH_2-) ; 2.25-2.01 (3s , 9H , -$COCH_3$) ; 1.25 (d , 3H , $J_{5,6}$=6.0Hz , Rha-CH_3) ;1.10 (m , 4H , -C-CH_2-Me) ; 0.90 (t , 6H ,-C-CH_3) . Mass spectrum : m/z 454 (M^+). Anal Calcd for $C_{18}H_{31}O_{11}P$ (454) : C ,47.57 ; H , 6.88. Found : C , 47.45 ; H , 6.59.

10a: ^{1}H NMR: δ 5.90 (d , 1H , $J_{1,2}$=1.5Hz , H-1) ; 5.34-5.08 (m,3H, H-2 ,3,and 4) ; 3.94 (m ,1H , H-5) ; 3.41(m , 2H ,OCHMe) ; 2.28-2.10 (3s,9H,-$COCH_3$) ; 1.19 (d , 3H , $J_{5,6}$=6.2Hz , Rha-CH_3) ; 0.98 (t , 6H , isopropyl-CH_3) . Mass spectrum : m/z 454 (M^+). Anal Calcd for $C_{18}H_{31}O_{11}P$ (454) : C , 47.57 ; H , 6.88. Found : C , 45.89 ; H , 6.50.

11a: ^{1}H NMR: δ 5.96 (d , 1H , $J_{1,2}$=1.1Hz , H-1) ; 5.38 (dd ,1H , $J_{2,3}$=3.0Hz , H-2) ; 5.20-5.05 (m , 2H , H- 3 and 4) ; 3.99 (m , 1H , H-5) ; 3.54 (m , 4H , OCH_2-) ; 2.23-2.05 (3s , 9H , -$COCH_3$) ; 1.25 (d , 3H, $J_{5,6}$=5.8Hz , Rha-CH_3) ; 1.15 (m , 8H , -C-CH_2-CH_2-Me) ; 0.97 (m , 6H , -C-CH_3) . Mass spectrum : m/z 482 (M^+). Anal Calcd for $C_{20}H_{35}O_{11}P$ (482) : C , 49.79 ; H , 7.31 . Found : C , 49.38 ; H , 6.99.

12a: ^{1}H NMR: δ 7.40–7.20 (m , 10H , Ph-H) ; 6.05 (d,1H , $J_{1,2}$=1.3Hz , H-1) ; 5.35-5.05 (m , 3H , H-2 ,3 ,and 4) ; 4.45 (m , 4H, Ph-CH_2) ; 3.89(m,1H ,H-5) ; 2.20-2.01 (3s , 9H , -$COCH_3$) ; 1.19 (d , 3H , $J_{5,6}$=5.9Hz , Rha-CH_3) . Mass spectrum : m/z 550 (M^+). Anal Calcd for $C_{26}H_{31}O_{11}P$ (550) : C , 56.73 ; H , 5.68. Found : C , 56.25 ; H , 5.48.

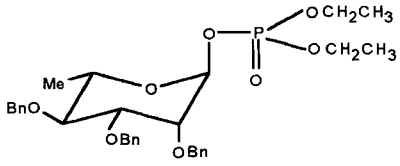
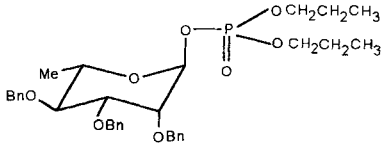
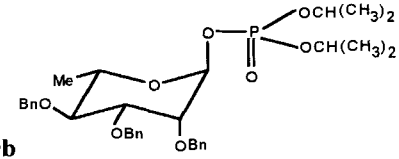
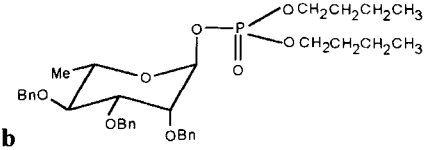
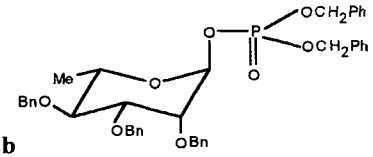
Table 1 Data of reaction conditions , melting points ,and yields of **8a-b~12a-b**

Products	Reaction time[a] (h)	m. p. (C)	Yield[b] (%)
 **8a**	3	104-106	85
 **9a**	3	oil	88
 **10a**	3	84-86	93
 **11a**	3	oil	84
 **12a**	2	oil	92

8b: ^{1}H NMR: δ 7.50–7.20 (m , 15H , Ph-H) ; 5.88 (d ,1H , $J_{1,2}$=1.0Hz , H-1) ; 4.48 (m , 6H , Ph-CH_2) ; 4.20-3.60 (m, 3H , H-2 ,3 ,and 4) ;3.50-3.30 (m ,5H , H-5 and -OCH_2-Me) ;1.29 (d ,3H ,$J_{5,6}$=5.9Hz ,Rha-CH_3) ;1.05 (t,6H ,-C-CH_3). Mass spectrum : m/z 570 (M^+). Anal Calcd for $C_{31}H_{39}O_8P$ (570): C , 65.25 ; H , 6.89. Found : C , 65.09 ; H , 6.54.

9b: ^{1}H NMR: δ 7.55–7.10 (m , 15H , Ph-H) ; 5.85 (d ,1H , $J_{1,2}$=1.0Hz , H-1) ; 4.60-4.45 (m , 6H , Ph-CH_2) ; 4.30-3.60 (m ,3H, H-2 ,3 ,and 4) ;3.45-3.30 (m ,

Table 1. Continued

Products	Reaction time[a] (h)	m. p. (C)	Yield[b] (%)
 **8b**	2	oil	86
 **9b**	2	79-81	93
 **10b**	2	oil	89
 **11b**	2	oil	91
 **12b**	3	oil	96

a : All reactions were carried out in dichloromethane.
b : Isolated yield.

5H , H-5 and -OCH_2-Me) ; 1.25 (d , 3H , $J_{5,6}$=5.9Hz , Rha-CH_3) ;1.10 (m,4H , -C-CH_2-Me) ; 0.90 (t , 6H , -C-CH_3). Mass spectrum : m/z 598 (M^+). Anal Calcd for $C_{33}H_{43}O_8P$ (598) : C , 66.21 ; H , 7.26. Found : C , 66.20 ; H , 7.14.

10b: ^{1}H NMR: δ 7.50–7.10 (m , 15H , Ph-H) ; 5.95 (d ,1H, $J_{1,2}$=1.0Hz , H-1) ; 4.70-4.38 (m , 6H , Ph-CH_2) ; 4.20-3.50 (m, 3H, H-2 ,3 ,and 4) ;3.40-3.20 (m , 3H , H-5 and -OCH-Me) ; 1.20 (d, 3H , $J_{5,6}$=5.9Hz , Rha-CH_3) ;1.00 (m ,12H , isopropyl-CH_3). Mass spectrum : m/z 598 (M^+). Anal Calcd for $C_{33}H_{43}O_8P$ (598) : C , 66.21 ; H , 7.26. Found : C , 66.15 ; H , 7.08.

11b: ^{1}H NMR: δ 7.56–7.10 (m , 15H , Ph-H) ; 5.85 (d,1H , $J_{1,2}$=1.0Hz , H-1) ; 4.58-4.40 (m , 6H , Ph-CH_2) ; 4.25-3.50 (m,3H , H-2 ,3 ,and 4) ;3.40-3.28 (m , 5H , H-5 and -OCH_2-Me) ; 1.20 (d, 3H , $J_{5,6}$=5.9Hz , Rha-CH_3) ;1.10 (m, 8H , -C-CH_2-CH_2-Me) ; 0.94 (m , 6H , -C-CH_3). Mass spectrum : m/z 626 (M^+). Anal Calcd for $C_{35}H_{47}O_8P$ (626) : C , 67.07 ; H , 7.56. Found : C , 67.01 ; H , 7.50.

12b: ^{1}H NMR: δ 7.50–7.18 (m ,15H , Ph-H) ; 5.94 (d ,1H , $J_{1,2}$=1.0Hz , H-1) ; 4.65-4.38 (m ,10H , Ph-CH_2) ; 4.20-3.60 (m ,3H ,H-2 ,3 ,and 4) ; 3.40 (m ,1H , H-5) ; 1.18 (d , 3H , $J_{5,6}$=5.9Hz , Rha-CH_3) . Mass spectrum : m/z 694 (M^+). Anal Calcd for $C_{41}H_{43}O_8P$ (694) : C , 70.88 ; H , 6.24. Found : C , 70.60 ; H , 6.05.

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(Received in the UK 16 November 1994)