Chinese Chemical Letters Vol. 14, No. 7, pp 685 – 688, 2003
http://www.imm.ac.cn/journal/ccl.html

Convenient and Efficient Synthesis of L-Rhamnopyranosyl Phosphoramidates *via H*-Phosphonate

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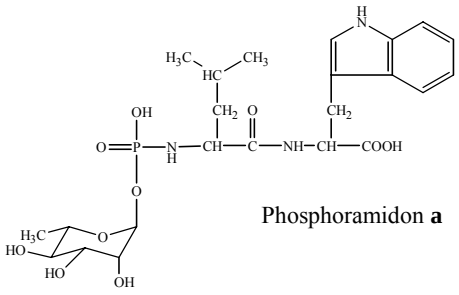
Abstract: The α-L-rhamnopyranosyl phosphomonoesters conjugated with L-amino acid methyl esters were stereoselectively synthesized in a convenient route by utilizing *H*-phosphonate intermediate.

Keywords: *H*-Phosphonate, L-rhamnose, phosphoramidate.

It is known that saccharides linked to proteins *via* a phosphoester hinge can function as immunological determinants. Under regular physiological conditions, it has been suggested that the role of phosphonate group is to direct the protease towards basic substrates[1]. Phosphoramidon **a**, which was isolated from a culture filtrate, is a potent inhibitor of the thermolysin, a metallo-endopeptidase. It is a glycosylated dipeptide, which has a L-rhamnose attached to the N-terminal of Leu-Trp dipeptide *via* a phosphonamide. Its discovery from nature promoted the research on phosphorus-based enzyme inhibitors[2]. However, since only a small number of natural P-linked glycopeptides were found, their functional mechanisms are still not quiet clear. We based on the use of peracetylated-glycosyl *H*-phosphonates to synthesize glycosyl phosphomonoester derivatives of amino acid methyl esters with high stereoselectivity. These glycoconjugate mimetics can provide plentiful information of structures as well as functions.

In this paper, we used peracetyl α-L-rhamnopyranose **1** as starting material for



Phosphoramidon **a**

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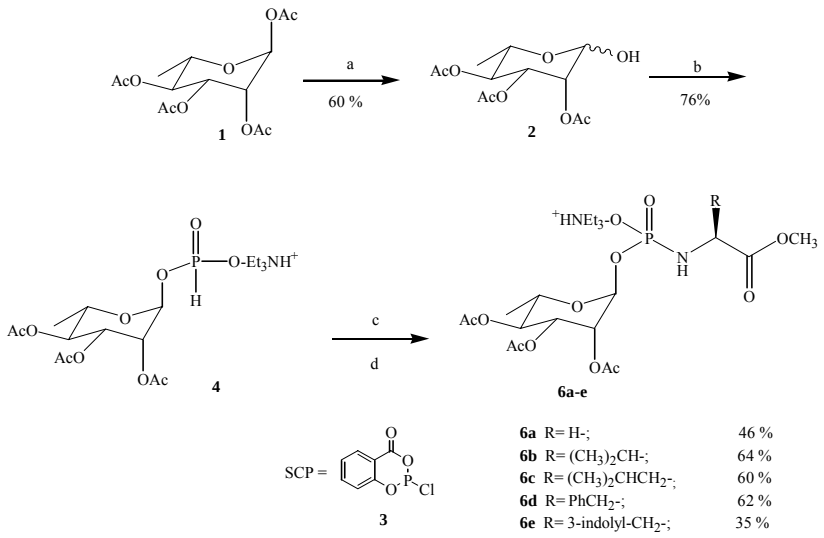
synthesis of phosphomonoester derivatives of L-glycine, L-valine, L-leucine, L-tryptophan and L-phenylalanine methyl esters **6a-e** with hydrophobic side chains. These compounds were prepared for the structure-activity relationships (SAR) investigations.

We found the hydroxyl group at the position 1 of peracetylated α-L- rhamnopyranose **1** was selectively deprotected through a hydrazinolysis reaction, and 2, 3, 4-triacetyl-L-rhamnopyranose **2** was obtained as white cubic crystal after recrystalization from ethyl acetate[3]. Then compound **2** was reacted with salicyl chlorophosphite (SCP) **3** and hydrolyzed immediately. After removing the solvent under reduced pressure, the crude α-2, 3, 4-acetyl-L-rhamnopyranosyl- *H*-phosphonate **4** was given as a yellow solid. The crude **4** was purified on silica gel chromatography with CH_2Cl_2-MeOH-Et_3N (100:10:1) as eluent. The pure compound **4** was obtained as white acicular crystal[4,5]. Its structure was confirmed by ^1H and ^{13}CNMR data as pure α anomer[6].

Scheme 1



Reagents and reaction conditions: (a) 1 equiv. diaminoethane & acetic acid, THF, r.t., 20 hr. (b) i) 1.5 equiv. SCP **3**, dioxane/ pyridine (1:1), r.t., 30min. ii) H_2O, r.t., 5min. (c) i) 3 equiv. TMSCl, pyridine, r.t., 5min, under Ar. ii) 1 equiv. I_2, pyridine, r.t., 5 min. (d) 2 equiv. amino acid methyl ester **5a-e,** 7 equiv. Et_3N, r.t., 30min.

In the following step, *H*-phosphonate monoester **4** was treated with excessive trimethylsilyl chloride in pyridine, and then a solution of over-dosed iodine (I_2) in pyridine was added until the color of the reaction solution changed from yellow to brown. The P-N bonds in compounds **6a-e** were formed with adding excessive amino acid methyl esters **5a-e** and Et_3N. Compounds **6a-e** were purified using silica gel chromatography ($CHCl_3$-MeOH-H_2O, 10:2:0.25, 0.5% Et_3N) followed by Sephadex LH-20 column filtration, and afforded in good yields[7]. The general procedure and yields were described in **Scheme 1**, and the structures of compounds were determined by

^{1}H and ^{13}C NMR[8,9].

Biological activities and chemical properties of these series of compounds are currently under investigations. And extension of this approach to more complex oligosaccharides and oligopeptides are also in progress.

In conclusion, we have presented a convenient and efficient general method for the synthesis of amino acid phosphoramidate monoesters of rhamnose and it could be applied to more complicated compounds with similar basic skeletons.

Acknowledgment

The authors would like to thank the financial supports from the NNSF of China (No. 20172033), the Ministry of Science and Technology, the Ministry of Education and Tsinghua University.

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6. Spectral data of 2, 3, 4 -triacetyl-α-L-rhamnopyranosyl-*H*-phosphonate **4**: ^{31}P NMR (81 MHz, $CDCl_3$, δppm): 1.38. ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 6.98 (d, 1H, J_{P-H}=663.5Hz, P-H), 5.57 (d, H, J=8.5 Hz, H-1), 5.32 (m, 2H, H-2, H-3), 5.09 (dd, 1H, J=9.5Hz, H-4), 4.14 (m, 1H, H-5), 3.14 (m, 6H, $N(CH_2CH_3)_3$), 2.14 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 1.39 (t, 9H, J=7.5 Hz, $N(CH_2CH_3)_3$), 1.21 (d, 3H, J=6.5 Hz, Rha-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δppm): 169.7(3 x CO), 92.7 (C-1), 70.3 (C-4), 69.6 (d, J_{P-C}=7.5 Hz, C-2) , 68.6 (C-3), 67.4 (C-5), 45.7 ($N(CH_2CH_3)_3$) 20.6, 20.5, 20.4, (3 x $COCH_3$), 17.03 (CH_3-6), 8.39 ($N(CH_2CH_3)_3$). ESI-MS (-): *m/z* 353 $(M-H)^-$.
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8. Spectral data of N-(2,3,4,-triacetyl-α-L-rhamnopyranosyl-oxyhydroxyphosphinyl)-L-glycine methyl ester **6a**: ^{31}P NMR (81 MHz, $CDCl_3$, δppm): 3.93. ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 5.45 (d, 1H, J=9 Hz, H-1), 5.32 (m, 2H, H-2, H-3), 5.06 (dd, 1H, J=10.0 Hz, H-4), 4.15 (m, 1H, H-5), 3.76(q, 2H, J_{P-H}=4Hz, J_{H-H}=9.5Hz, CH_2), 3.71(s, 3H, $COOCH_3$), 3.08 (m, 6H, $N(CH_2CH_3)_3$), 2.13 (s, 3H, CH_3CO), 2.04(s, 3H, CH_3CO), 1.96 (s, 3H, CH_3CO), 1.34 (t, 9H, J=7.5 Hz, $N(CH_2CH_3)_3$), 1.18 (d, 3H, J=6 Hz, Rha-CH_3). ESI-MS (-): *m/z* 440 $(M-H)^-$.
Spectral data of N-(2,3,4,-triacetyl-α-L-rhamnopyranosyl-oxyhydroxyphosphinyl)-L-valine methyl ester **6b**: ^{31}P NMR (81 MHz, $CDCl_3$, δppm): 4.13. ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 5.38 (d, 1H, J=8.5 Hz, H-1), 5.33 (m, 2H, H-2, H-3), 5.04 (dd, 1H, J=10.0Hz, H-4), 4.15 (m, 1H, H-5), 3.70(s, 3H, $COOCH_3$), 3.68(m, 1H, CH), 3.10 (m, 6H, $N(CH_2CH_3)_3$), 2.13 (s, 3H, CH_3CO), 2.04(s, 3H, CH_3CO), 1.95 (s, 3H, CH_3CO), 1.34 (t, 9H, J=7.5 Hz, $N(CH_2CH_3)_3$), 1.19 (d, 3H, J=6.0 Hz, Rha-CH_3), 0.95(d, 3H, J=6.5Hz, $CH(CH_3)_2$), 0.91(d, 3H, J=6.5Hz, $CH(CH_3)_2$). ^{13}C NMR (125 MHz, CD_3OD, δppm): 174.6 (COOR), 170.0-169.8 (3 x CO), 93.0 (C-1), 71.0(C-4), 70.2 (d, J_{P-C}=7.5Hz, C-2), 69.2(C-3), 66.7(C-5), 60.1 (NCH), 51.4 (CH), 45.5 ($N(CH_2CH_3)_3$), 32.4 ($COOCH_3$), 20.8, 20.7, 20.6 (3 x $COCH3$), 18.7 (Rha-CH_3), 17.9, 17.3 ($CH(CH_3)_2$), 8.5 ($N(CH_2CH_3)_3$). ESI-MS (-): *m/z* 482 $(M-H)^-$.
Spectral data of N-(2,3,4,-triacetyl-α-L-rhamnopyranosyl-oxyhydroxyphosphinyl)-L-leucine methyl ester **6c:** ^{31}P NMR (81 MHz, $CDCl_3$, δppm): 3.54. ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 5.38 (d, 1H, J=7.5 Hz, H-1), 5.33 (m, 2H, H-2, H-3), 5.04(dd, 1H, J=10.0Hz, H-4), 4.16 (m, 1H, H-5), 3.88(m, 1H, CH), 3.70(s, 3H, $COOCH_3$), 3.06 (m, 6H, $N(CH_2CH_3)_3$), 2.13(s, 3H, CH_3CO), 2.04(s, 3H, CH_3CO), 1.95 (s, 3H, CH_3CO), 1.79 (m, 1H, $CH(CH_3)_2$), 1.49 (m, 2H, J=6.5Hz, $CHCH_2CH$), 1.30 (t, 9H, J=6.5 Hz, $N(CH_2CH_3)_3$), 1.18 (d, 3H, J=6.0

Hz, CH_3), 0.92(d, 6H, J=6.5Hz, CH(CH_3)$_2$). ESI-MS (-): *m/z* 496 (M-H)$^-$.

Spectral data of N-(2,3,4,-triacetyl-α-L-rhamnopyranosyl-oxyhydroxyphosphinyl)-L–phenyl -alanine methyl ester **6d:** ^{31}P NMR (81 MHz, $CDCl_3$, δppm): 3.14. ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 7.25 (m, 3H, H-3', H-4', H-5'), 7.19 (d, 2H, J=6.0Hz, H-2', H-5'), 5.37 (d, 1H, J=7.5 Hz, H-1), 5.34 (m, 2H, H-2, H-3), 5.04 (dd, 1H, J=9.5 Hz, H-4), 4.16 (m, 1H, H-5), 4.15(m, 1H, CH), 3.60(s, 3H, COOCH_3), 3.09(d, 2H, J= 6.0Hz, CHCH_2Ph), 3.03 (m, 6H, N(CH_2CH_3)$_3$), 2.12 (s, 3H, CH_3CO), 2.03(s, 3H, CH_3CO), 1.95 (s, 3H, CH_3CO), 1.79 (m, 1H, CH(CH_3)$_2$), 1.49 (dd, 2H, J=6.5Hz, CHCH_2CH), 1.30 (t, 9H, J=7.5 Hz, N(CH_2CH_3)$_3$), 1.16 (d, 3H, J=6 Hz, Rha-CH_3). ESI-MS (-): *m/z* 530 (M-H)$^-$.

Spectral data of N-(2, 3, 4, -triacetyl- α-L-rhamnopyranosyl- oxyhydroxyphosphinyl)-L-tryptophan methyl ester **6e:** ^{31}P NMR (81 MHz, $CDCl_3$, δppm): 2.95. ^{1}H NMR (500 MHz, $CDCl_3$, δppm): 7.53-7.02 (m, 5H, aromatic protons), 5.43(d, 1H, J=8.0Hz, H-1), 5.34 (m, 2H, H-2, H-3), 5.03 (dd, 1H, J=9.5 Hz, H-4), 4.24 (m, 1H, H-5), 4.13(m, 1H, CH), 3.56 (s, 3H, COOCH_3), 3.20(b, 2H, CH_2), 3.14(b, 2H, CHCH_2Ph), 2.91 (m, 6H, N(CH_2CH$_3$)$_3$), 2.10 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 1.95 (s, 3H, CH_3CO), 1.20 (t, 9H, J=6.5 Hz, N(CH_2CH_3)$_3$), 1.13 (d, 3H, J=6 Hz, Rha-CH_3). ESI-MS (-): *m/z* 569 (M-H)$^-$.

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Received 26 August, 2002