Tetrahedron Letters, Vol.32, No.33, pp 4111-4114, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF SHIKIMIC ACID AND ITS PHOSPHONATE ANALOGUE VIA KNOEVENAGEL CONDENSATION

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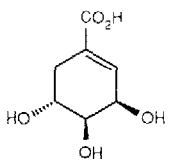
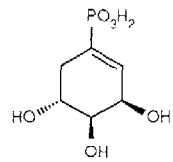
Abstract: *The Knoevenagel condensation and intramolecular olefination have been successfully exploited in a novel synthesis of shikimic acid* ***1*** *and its phosphonate analogue* ***2*** *from D-lyxose 5-aldehyde* ***7****.*

The importance of shikimic acid (1) as a biosynthetic intermediate is well recognized as the shikimate pathway is the major metabolic route leading to the formation of aromatic compounds in plants and microorganisms [1], [2]. Many synthetic studies have been prompted [3], not only by the challenge of stereospecific and chiral synthesis of this trihydroxycarboxylic acid, but also because of the possibility of preparing structural variants as potential regulators of a range of biological processes in plants and bacteria.



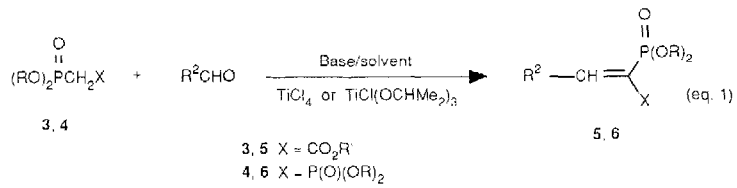
1



2

The anions of phosphorylacetates such as **3** are generally used for Horner-Wittig olefination [4], their condensation with aldehydes in the presence of base/$TiCl_4$ or $TiCl(OCHMe_2)_3$ is known to yield Knoevenagel products **5** [5], [6]. Tetraalkyl methylenediphosphonates **4** react under identical conditions in the same way giving **6** [5] (eq. 1).

Scheme 1.



3, **4**

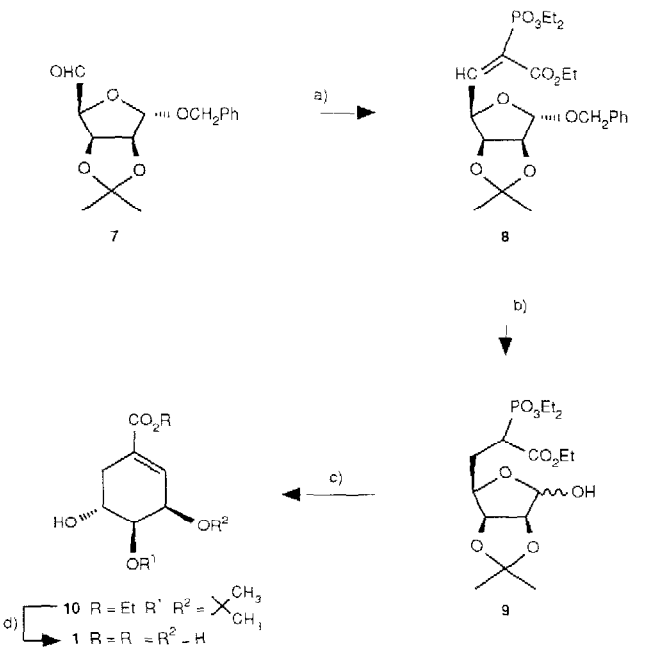
3, **5** X = CO_2R
4, **6** X = $P(O)(OR)_2$

5, **6**

The synthesis of **1** based on this approach is illustrated in Scheme 2. Thus, the condensation of the suitably protected D-lyxose 5-aldehyde **7** [7] with triethyl phosphonoacetic acid, in the presence of N-methylmorpholine, $TiCl_4$, CCl_4/THF afforded E/Z mixture of esters **8** (79%) [8]. This mixture was hydrogenated (H_2, 10% Pd-C, EtOH) to give the hemiacetals **9** which underwent intramolecular olefination (NaOEt/EtOH) [3] furnishing the protected carbocycle **10** in 60% overall yield from **8**.

Finally, saponification (NaOH/EtOH) followed by deacetonation (Dowex 50WX4, H_2O) led to shikimic acid **1** (87% from **10**) [9]

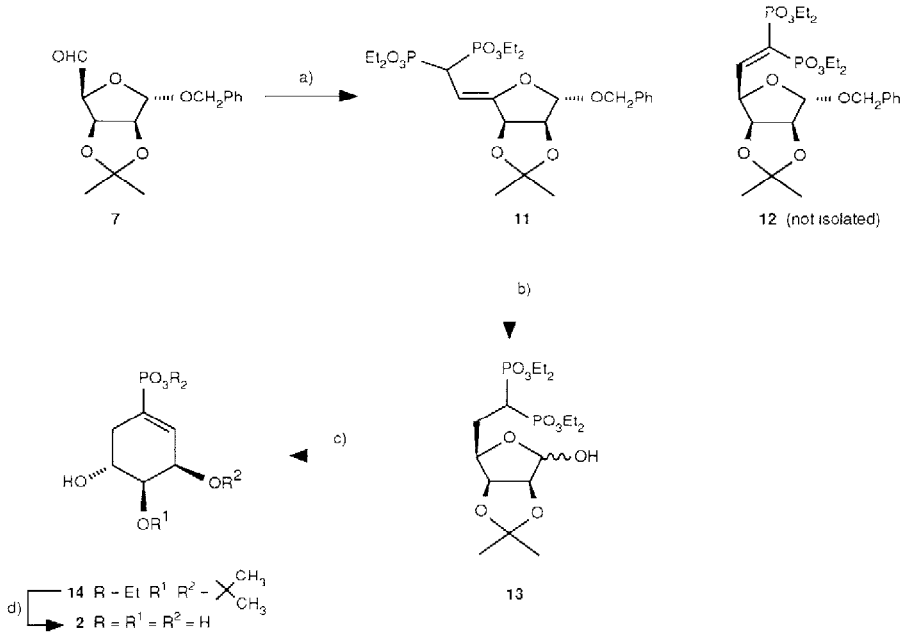
Scheme 2.



a) $(EtO)_2P(O)CH_2CO_2Et$, N-methylmorpholine, $TiCl_4$, CCl_4, THF (79%), b) H_2, 10% Pd-C, EtOH, c) NaOEt, EtOH (60%), d) 1N NaOH, EtOH then Dowex 50 WX4, H_2O (87%)

D-lyxose 5-aldehyde **7** was further used in the synthesis of the phophonate analogue **2** as outlined in *Scheme* 3. Condensation (N-methylmorpholine, $TiCl_4$, CCl_4/THF) of **7** with tetraethyl methylenediphosphonate furnished the tetrahydrofurylidene derivative **11** (64%) [10] instead of the expected intermediate **12**. But this was of little consequence since **11** was hydrogenated (H_2, 10% Pd-C, EtOH) stereoselectively to the hemiacetals **13**, which underwent intramolecular olefination (NaOEt/EtOH) to generate the carbocyclic precursor **14** (42% from **11**) [11]. Finally, **14** was subjected to hydrolysis of the phosphonate ester and cleavage of the acetonide (Me_3SiBr, $CHCl_3$ then H_2O) to afford the trihydroxy phosphonate **2** in 93% yield [12].

Scheme 3.



a) $[(EtO)_2P]_2CH_2$,N-methylmorpholine, $TiCl_4$, CCl_4, THF (64%), b) H_2 10% Pd-C, EtOH, c) NaOEt, EtOH (42%), d) Me_3SiBr, $CHCl_3$ then H_2O (93%)

In conclusion, Knoevenagel condensation of sugar aldehydes opens up possibilities for an easy excess to highly functionalized carbocycles

Acknowledgement We thank Dr T Winkler for helpful discussions

References and notes

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[8] The ratio (E/Z = 2:1) Both isomers were easily separated by flash chromatography [Z-**8** $[\alpha]^{20}_D$ = - 7 8 (c=1, $CHCl_3$); IR($CHCl_3$) 1715, 1620 cm^{-1}, ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7 54 (1H, dd, J = 7, J (P,H) = 45, vinylic H), ^{31}P-NMR (100 MHz, $CDCl_3$ ppm downfield from H_3PO_4) δ 10 82]. [E-**8** $[\alpha]^{20}_D$ = -24 9 (c=1, $CHCl_3$), IR($CHCl_3$) 1715, 1628 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7 13 (1H, dd, J = 6, J (P,H)=23, vinylic H), ^{31}P-NMR (100 MHz, $CDCl_3$) δ 12.49].

[9] Identical with an authetic sample (Fluka AG, Buchs).

[10] Data of **11**: $[\alpha]^{20}_D$ = -17 7 (c=1, $CHCl_3$), IR($CHCl_3$) 1690 cm ^{1}, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3 79 (1H, dt J = 11, J(P,H)=23), 4 90 (1H, dt, J = 11, J(P,H) = 5.5), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.70 (dt, J(P,C) = 135 8), 93 16 (sx.asymmetric t, J(P,C) = 10 4, 10 1), 157 77 (dx.asymmetric t, J(P,C) = 12.6, 11.9), ^{31}P-NMR (100 MHz, $CDCl_3$) δ 18 86 (d, J(P,P) = 3 5, 1P), 19 38 (d, J(P,P) = 3 5, 1P)

[11] Data of **14** $[\alpha]^{20}_D$= -46 5 (c=0.8, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.73 (1H, md, J(P,H) = 21 vinylic H)

[12] Compound **2** ^{1}H-NMR (300 MHz, D_2O) δ 2 04 (1H, m), 2 55 (1H, dt, J = 17, 6 3), 3.56 (1H, dd, J = 9, 4 5), 3.82 (1H, m), 4 22 (1H, m), 6 20 (1H, md, J(P,H) = 20, vinylic H), ^{31}P-NMR (100 MHz, D_2O) δ 11 66.

Bis-sodium salt of **2** $[\alpha]^{25}_D$ = -76 7 (c=1 1, H_2O), ^{1}H-NMR (300 MHz, D_2O) δ 6 15 (1H, md, J(P,H)=20, vinylic H).

Bis-isopropylamine salt of **2** ^{1}H-NMR (300 MHz, D_2O) δ 1 1 (12H, d, J=7), 3.32 (2H, m, $W_{\frac{1}{2}}$ = 7), 6 14 (1H, md, J(P,H) = 20, vinylic H)

(Received in Germany 2 May 1991)