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Biomimetic Chain Elongation of Carbohydrates via Radical Carbon-Carbon Bond Formation

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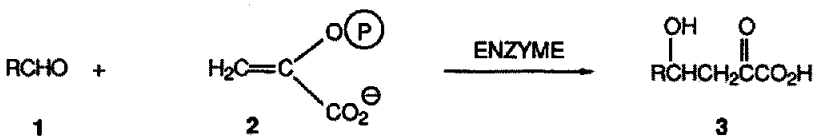
Abstract - Radical bond forming reactions can be used to mimic enzymatic aldol reactions between phosphoenol pyruvate and carbohydrates.

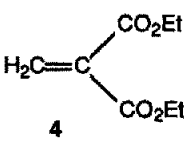
Phosphoenol pyruvate **2** reacts as C-3 unit with aldehyde functions of carbohydrates **1** under enzymatic conditions and yields products **3** of aldol reactions.[1] Depending upon the structure of the carbohydrate this reaction can lead to shikimic acid, KDO or neuraminic acids.



1 **2** **3**

ERYTHROSE ⟶ SHIKIMIC ACID
ARABINOSE ⟶ KDO
AMINOMANNOSE ⟶ NEURAMINIC ACID

Because respective in vitro reactions fail in the absence of enzymes, we have started with biomimetic syntheses using radical methods. In preceding studies it had been demonstrated that glycosyl radicals can be easily generated treating bromides[2] and selenides[3] with tin radicals. This paper now shows that alkenes **4** and **5** are suitable synthons of phosphoenol pyruvate.



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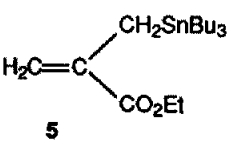
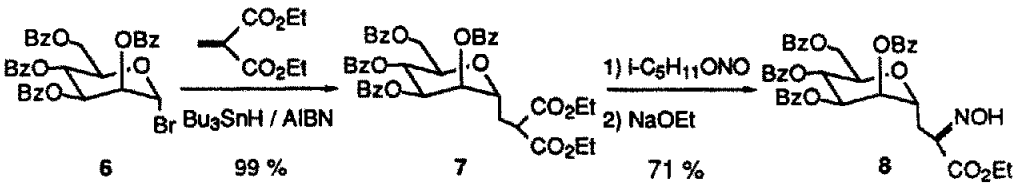


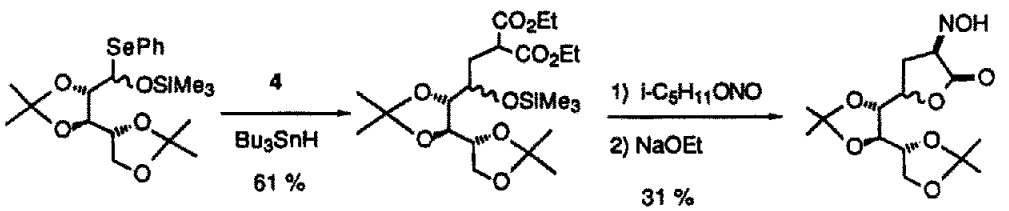
5

The two electron withdrawing ester groups make methylene malonate **4** an efficient trap for the highly nucleophilic glycosyl radicals.[4] Thus the reaction of mannosyl bromide **6**, alkene **4** and Bu_3SnH leads in high diastereoselectivity to addition product **7** in quantitative yield. Nitrosation and basic cleavage[5] of **7** gives oxime **8**.



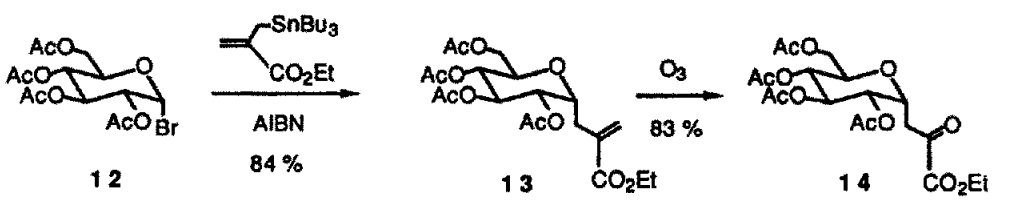
6 99 % **7** 71 % **8**

The same reaction sequence with the acyclic derivative **9** of arabinose yields addition product **10** and oxime **11**.



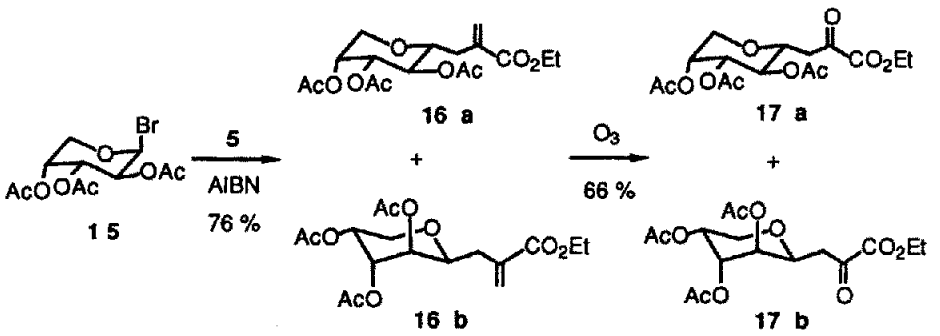
9 **10** **11**

Whereas the reaction with the cyclic system **6** leads exclusively to product **7**, in the acyclic system two diastereomers **10a** and **10b** are formed as a 2:1 mixture. Oximes **8** and **11** are derivatives of the formal aldol reaction products of phosphoenol pyruvate with the respective carbohydrates. But attempts to cleave the oxime function led always to product mixture. This disadvantage was overcome using alkene **5**[6] as synthon for phosphoenol pyruvate. The radical allylation reaction[6] of the glucosyl bromide **12** yields product **13** that undergoes ozonolysis and gives the ketoester **14** in high yields.



12 **13** **14**

In contrast to the high diastereoselectivity of the CC-bond formation with hexosyl radicals the arabinose derivative leads even in the cyclic form **15** to a mixture of diastereomers **16a** and **16b**. Ozonolysis gives keto esters **17a** and **17b**.



The lower stereoselectivity seems to be typical for pentopyranosyl radicals.[7] We have explained this effect by the high flexibility of these systems that could lead to the formation of sugar radicals with different conformations as intermediates of the reaction.[7] Compounds **14** and **17** are the cyclized products of the formal aldol reaction between carbohydrate derivatives and pyruvate. Cleavage of the ester and ether bonds should lead to the free carbohydrates.

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Experimental Part

Ethyl 4,8-anhydro-5,6,7,9-tetra-O-benzoyl-2,3-dideoxy-2-C-ethoxycarbonyl-D-glycero-D-talo-nononate (7):

To a solution of 3.30 g (5.0 mmol) benzobromomannose (6)[8] in 15 ml of toluene was added at 67°C under argon over 1 h a solution of 1.03 g (6.0 mmol) of methylene malonic ester (4)[9] in 8 ml of toluene and a solution of 1.74 g (6.0 mmol) tributylstannane and 100 mg AIBN in 8 ml of toluene. The solution was kept at this temperature for 30 min and then the toluene was distilled off. The residue was dissolved in 40 ml of acetonitrile and extracted five times with 20 ml of pentane. After concentration of the acetonitrile layer and chromatography on silica gel (diethyl ether/pentane = 3:1), compound **7** (3.73 g, 99%) was isolated as a colourless oil. No β-addition product could be detected.

$[\alpha]_D^{20}$ = -56.5(c = 1.0 in chloroform). - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.26, 1.28 (2t, J = 7.0 Hz, 6H, 2x$OCH_2\underline{CH_3}$), 2.39 (ddd, J = 2.9, 7.5, 14.7 Hz, 1H, 3-H'), 2.72 (ddd, J = 6.5, 11.8, 14.7 Hz, 1H, 3-H), 3.65 (dd, J = 6.5, 7.5 Hz, 1H, 2-H), 4.13-4.31 (m, 4H, 2x$O\underline{CH_2}CH_3$), 4.32-4.40 (m, 2H, 4-, 8-H), 4.53 (dd, J = 4.6, 12.2 Hz, 1H, 9-H'), 4.61 (dd, J = 3.0, 12.2 Hz, 1H, 9-H), 5.68 (t, J = 3.0 Hz, 1H, 5-H), 5.80 (dd, J = 3.0, 9.0 Hz, 1H, 6-H), 6.06 (t, J = 9.0 Hz, 1H, 7-H), 7.26-8.13 (m, 20H, OBz).

$C_{42}H_{40}O_{13}$ (752.8) Calcd. C 67.01 H 5.36
Found C 66.99 H 5.28

Ethyl 4,8-anhydro-5,6,7,9-tetra-O-benzoyl-3-deoxy-2-oximino-D-glycero-D-talo-2-nonulosonate (8).

To a solution of 654 mg (0.87 mmol) of **7** in 4 ml ethanol and 5 ml dioxane was added at 0°C over 15 min 0.58 ml (4.3 mmol) of isopentyl nitrite. The mixture was stirred for 15 more min, then it was cooled to -10°C and a solution of 27.6 mg (1.2 mmol) sodium in 0.6 ml of ethanol was added over 15 min. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was distilled off and the residue was dissolved in 7 ml dichloromethane and 5 ml pyridine. To this solution was added slowly at 0°C 7 ml benzoyl chloride and the mixture was then stirred 3d at room temperature.The solution was concentrated in vacuo, coevaporated with toluene, the residue dissolved in dichloromethane, washed with water and with a $NaHCO_3$ solution and dried over Na_2SO_4. Distillation of the solvent and chromatography on silica gel

(diethyl ether/pentane = 3:2) gave 441 mg (71%) of **8** as a colourless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 3.29 (dd, J = 3.6, 13.3 Hz, 1H, 3-H'), 3.70 (dd, J = 11.2, 13.3 Hz, 1H, 3-H), 4.22-4.29 (m, 2H, $O\underline{CH_2}CH_3$), 4.49-4.70 (m, 3H, 8-, 9-H, 9-H'), 4.93 (dt, J = 3.6, 11.2 Hz, 1H, 4-H), 5.79 (dd, J = 3.1, 3.6 Hz, 1H, 5-H), 5.93 (dd, J = 3.1, 8.6 Hz, 1H, 6-H), 6.02 (dd, J = 7.4, 8.6 Hz, 1H, 7-H), 7.24-8.18 (m, 20H, OBz), 10.25 (broad s, 1H, NOH).

$C_{39}H_{35}NO_{12}$ (709.7)	Calcd.	C 66.00 H 4.97 N 1.97
	Found	C 65.90 H 5.04 N 1.83

Ethyl 2,3-dideoxy-2-C-ethoxycarbonyl-5,6:7,8-di-O-isopropylidene-4-O-trimethylsilyl-D-manno-octonate and Ethyl 2,3-dideoxy-2-C-ethoxycarbonyl-5,6:7,8-di-O-isopropylidene-4-O-trimethylsilyl-D-gluco-octonate (10).
To a solution of 1.38 g (3.0 mmol) 2,3:4,5-di-O-isopropylidene-1-phenylseleno-1-O-trimethylsilyl-arabinitol (**9**) in 10 ml of toluene was added at 82°C under argon over 2 h a solution of 620 mg (3.6 mmol) methylene malonic ester (**4**)[9] in 5 ml toluene and a solution of 1.05 g (3.6 mmol) tributylstannane and 60 mg AIBN in 5 ml toluene. The solution was kept at this temperature for 30 min and the toluene distilled off. Chromatography on silica gel (gradient diethyl ether / pentane = 1:9 to 1:5) gave 869 mg (61%) of a 2:1 mixture of the two isomers **10** as a colourless oil. The physical data were measured from the mixture.
^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 0.14 (s, 9H, $Si(CH_3)_3$, major product), 0.15 (s, 9H, $Si(CH_3)_3$, minor product), 1.24-1.30 (m, 6H, $2xOCH_2\underline{CH_3}$, both isomers), 1.34-1.41 (several s, 12H, $C(CH_3)_2$, both isomers), 2.08-2.32 (m, 2H, 3-H, 3-H', both isomers), 3.61 (dd, J = 5.9, 8.7 Hz, 1H, 2-H, both isomers), 3.80-4.30 (m, 10H, $2xO\underline{CH_2}CH_3$, 4-, 5-, 6-, 7-, 8-H, 8-H', both isomers).

$C_{22}H_{40}SiO_9$ (476.6)	Calcd.	C 55.44 H 8.46
	Found	C 55.57 H 8.42

3-Deoxy-5,6:7,8-di-O-isopropylidene-2-oximino-D-manno-2-octulosono-1,4-lactone and 3-Deoxy-5,6:7,8-di-O-isopropylidene-2-oximino-D-gluco-2-octulosono-1,4-lactone (11).
To a solution of 239 mg (0.5 mmol) of a 2:1 mixture of **10** in 1 ml ethanol was added at 0°C over 15 min 117 mg (1.0 mmol) isopentyl nitrite. The mixture was cooled to -5°C and a solution of 23 mg (1.0 mmol) sodium in 0.5 ml ethanol was added over 15 min. After standing at 0°C over night, the solvent was distilled off and the residue was chromatographed on silica gel (gradient diethyl ether/pentane = 1:2 to 2:1). This gave 48 mg (31%) of a 2:1 mixture of lactones **11** as a colourless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.33-1.47 (several s, 12H, $C(CH_3)_2$, both isomers), 3.01-3.14 (m, 2H, 3-H, 3-H', both isomers), 3.95-4.10 (m, 5H, 5-, 6-, 7-, 8-H, 8-H', both isomers), 4.91 (ddd, J = 1.3, 4.7, 8.0 Hz, 1H, 4-H, major product), 4.95 (ddd, J = 2.5, 4.8, 8.5 Hz, 1H, 4-H, minor product), 10.90 (broad s, 1H, NOH, both isomers).

$C_{14}H_{21}NO_7$ (315.3)	Calcd.	C 53.33 H 6.71 N 4.44
	Found	C 54.11 H 7.25 N 4.43

Ethyl 5,6,7,9-tetra-O-acetyl-4,8-anhydro-2,3-dideoxy-2-methylene-D-glycero-D-ido-nononate (13).
To a solution of 2.0 g (5.0 mmol) ethyl α-tributylstannyl methacrylate (**5**)[6] in 10 ml benzene was added over 3 h at 80°C a solution of 2.06 g (5.00 mmol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**12**)[10] and 80 mg (0.5 mmol) AIBN in 30 ml benzene. After one more h at 80°C the solvent was evaporated and the residue dissolved in 50 ml acetonitrile. Extraction (4 times with 50 ml pentane), concentration of the acetonitrile solution and chromatography (pentane/diethyl ether/dichloromethane = 5:4:1) gave 1.86 g (84%) of product **13**.
$[\alpha]_D^{20}$ = + 59.9 (c = 1.1 in chloroform). - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.03, 2.04, 2.06, 2.07 (4s, 12H, OAc), 2.63 (dd, J = 15.2, 3.5 Hz, 1 H, 3-H), 2.76 (dd, J = 15.2, 11.0 Hz, 1H, 3-H'), 3.97 (ddd, J = 9.1, 7.4, 2.6 Hz, 1H, 8-H), 4.02 (dd, J = 14.3, 2.6 Hz, 1H, 9-H), 4.20 (dd, J = 14.3, 7.4 Hz, 1H, 9-H'), 4.22 (q, J = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 4.44 (ddd, J = 11.0, 5.9, 3.5 Hz, 1H, 4-H), 4.99 (t, J = 9.1 Hz, 1H, 7-H), 5.12 (dd, J = 9.5, 5.9 Hz, 1H, 5-H), 5.36 (dd, J = 9.5, 9.1 Hz, 1H, 6-H), 5.68 (s, 1H, $=CH_2$), 6.30 (d, J = 0.7 Hz, 1H, $=CH_2$').

$C_{20}H_{28}O_{11}$(444.4)	Calcd.	C 54.04 H 6.35
	Found	C 54.07 H 6.39

Ethyl 5,6,7,9-tetra-O-acetyl-4,8-anhydro-3-deoxy-D-glycero-D-ido-2-nonulosonate (14).
At -78°C a solution of 1.86 g (4.20 mmol) alkene **13** in 30 ml ethyl acetate was treated for 30 min with ozone. 70 ml water, 20 ml H_2O_2 and 10 ml formic acid was added and the solution was stirred at 20°C for 1 h. The solution was extracted 3 times with 50 ml diethyl ether, washed 2 times with 50 ml of a saturated $NaHCO_3$ solution and 2 times with 50 ml water. Concentration and chromatography (pentane/diethyl ether/dichloromethane = 5:4:1) gave 1.55 g (83%) of product **14**.
$[\alpha]_D^{20}$ = + 28.9 (c = 0.8 in chloroform). - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.03, 2.05, 2.06, 2.07 (4s, 12H, OAc), 3.22 (d, J = 6.9 Hz, 2H, 3-H), 3.95 (ddd, J = 8.9, 5.1, 2.9 Hz, 1H, 8-H), 4.06 (dd, J = 12.2, 2.9 Hz, 1H, 9-H), 4.24 (dd, J = 12.2, 5.1 Hz, 1H, 9-H'), 4.35 (q, J = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 4.81 (dt, J = 6.9, 5.7 Hz, 1H, 4-H), 5.00 (dd, J = 8.9, 8.8 Hz, 1H, 7-H), 5.16 (dd, J = 9.0, 5.7 Hz, 1H, 5-H), 5.30 (dd, J = 9.0, 8.8 Hz, 1H, 6-H).
$C_{19}H_{26}O_{12}$ (446.4) Calcd. C 51.12 H 5.87
Found C 51.62 H 6.42

Ethyl 5,6,7-tri-O-acetyl-4,8-anhydro-2,3-dideoxy-2-methylene-D-manno-(D-gluco)-octonate (**16a** + **16b**):
To a solution of 2.0 g (5.0 mmol) ethyl α-tributylstannyl methacrylate(**5**)[6] in 10 ml benzene was added over 2.5 h at 80°C a solution of 1.7 g (5.0 mmol) 2,3,4-tri-O-acetyl-β-D-arabinopyranosyl bromide (**15**)[11] and 80 mg (0.5 mmol) AIBN in 30 ml benzene. After one more h at 80°C the solvent was evaporated and the residue dissolved in 50 ml acetonitrile. Extraction (4 times with 50 ml pentane), concentration of the acetonitrile solution and chromatography (pentane/diethyl ether/dichloromethane = 5:4:1) gave 1.41 g (76%) of a 1:1 mixture of products **16a** and **16b**.
16a: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.13, 2.15, 2.18 (3 s, 9H, OAc), 2.45-2.53 (m, 1H 3-H), 2.64 (dd, J = 14.5, 3.3 Hz, 1H, 3-H'), 3.56-3.67 (m, 2H, 4-, 8-H), 3.83 (dd, J = 11.0, 5.0 Hz, 1H, 8-H'), 4.21 (q, J = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 5.02 (dd, J = 3.4, 3.5 Hz, 1H, 6-H), 5.08-5.20 (m, 2-H, 5- ,7-H), 5.68 (s, 1H, $=CH_2$), 6.25 (s, 1H, $=CH_2$'). -

16b: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.13, 2.15, 2.18 (3s, 9H, OAc), 2.48 (d, J = 6.6 Hz, 2H, 3-H), 3.56-3.67 (m, 1H, 8-H), 3.96 (dd, J = 13.1, 1.7 Hz, 1H, 8-H'), 4.03 (t, J = 6.6 Hz, 1H, 4-H), 4.21 (q, J = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 4.91 (d, J = 3.3 Hz, 1H, 5-H), 5.26-5.36 (m, 2H, 6-, 7-H), 5.64 (s, 1H, $=CH_2$), 6 .22 (s, 1H, $=CH_2$').
$C_{17}H_{24}O_9$ (372.4) Calcd. C 54.83 H 6.50
Found C 54.73 H 6.54

Ethyl 5,6,7-tri-O-acetyl-4,8-anhydro-3-deoxy-D-manno-(D-gluco)-2-octulosonate (17a + 17b):
At -78°C a solution of 1.41 g (3.79 mmol) of the alkene mixture **16a** + **16b** in 30 ml ethyl acetate was treated for 30 min with ozone. 70 ml water, 20 ml H_2O_2 and 10 ml formic acid was added and the solution was stirred at 20°C for 1 h. The solution was extracted 3 times with 50 ml diethyl ether, washed 2 times with 50 ml of a saturated $NaHCO_3$ solution and 2 times with 50 ml water. Concentration and chromatography (pentane/diethyl ether/dichloromethane = 5:4:1) gave 935 mg (66%) of a 2:1 mixture of products **17a** and **17b**.

17a: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.09, 2.10, 2.11 (3s, 9H, OAc), 2.88 (dd, J = 17.1, 3.5 Hz, 1H, 3-H), 3.25 (dd, J = 17.1, 9.0 Hz, 1H, 3-H'), 3.68 (dd, J = 13.3, 0.9 Hz, 1H, 8-H), 3.95 (dd, J = 13.3, 2.0 Hz, 1H, 8-H'), 3.97 (ddd, J = 9.5, 9.0, 3.5 Hz, 1H, 4-H), 4.33 (q, J = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 5.05 (dd, J = 9.8, 3.5 Hz, 1H, 6-H), 5.17 (dd, J = 9.8, 9.5 Hz, 1H, 5-H), 5.26-5.34 (m, 1H, 7-H).

17b: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.10, 2.11, 2.12 (3s, 9H, OAc), 2.84 (dd, J = 17.7, 4.9 Hz, 1H, 3-H), 3.11 (dd, J = 17.7, 8.2 Hz, 1H, 3-H'), 3.70 (t, J = 10.5 Hz, 1H, 8-H), 3.82 (dd, J = 10.5, 5.5 Hz, 1H, 8-H'), 4.25 (q, J = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 4.39 (ddd, J = 8.2, 4.9, 1.5 Hz, 1H, 4-H), 4.94 (dd, J = 4.5, 1.5 Hz, 1H, 5-H), 5.15 (dd, J = 6.5, 4.5 Hz, 1H, 6-H), 5.26-5.34 (m, 1H, 7-H).
$C_{16}H_{22}O_{10}$ (374.3) Calcd. C 51.34 H 5.92
Found C 51.08 H 6.12

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