$(CH_3)_3C$). Anal. Calcd for $C_{22}H_{29}NO_7S_2$: C, 54.65; H, 6.04; N, 2.90. Found: C, 54.33; H, 6.23; N, 3.11.

***N*-(*tert*-Butyloxycarbonyl)aspartic Acid α-(1,3-Dithian-2-ylmethyl) Ester (10).** A mixture of the β-phenacyl ester **9** (9 g, 18.6 mmol), sodium thiophenolate (5 g, 37.3 mmol), and 100 mL of dimethylformamide was stirred for 18 h at room temperature. The solvent was removed under reduced pressure, the residue taken up in 150 mL of methylene chloride, and the solution was extracted three times with 50 mL of 2 N $NaHCO_3$ solution. After adjusting the pH of the aqueous layer to 1, it was extracted three times with ether. The combined ethereal solutions were washed five times with brine, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from methylene chloride/petroleum ether yielded 3.5 g (56%) of α ester **10**: mp 97 °C; $[\alpha]^{22}_D$ 19.9° (*c* 1, $cH_3OH$); IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1700 (COOH); 60-MHz $^1H$ NMR ($CDCl_3$) δ 10.8 (s, 1 H, NH), 4.7–4.3 (m, 3 H, $OCH_2CH$), 4.15 (m, 1 H, α-CH), 3.0–2.6 (m, 4 H, $CH_2CH_2CH_2$), 2.2–1.8 (m, 2 H, $CH_2CH_2CH_2$), 1.45 (s, 9 H, $(CH_3)_3C$). Anal. Calcd for $C_{14}H_{23}NO_6S_2$: C, 46.01; H, 6.34; N, 3.83. Found: C, 46.05; H, 6.74; N, 4.08.

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparagine 1,3-Dithian-2-ylmethyl Ester (12).** Aspartic acid α ester **10** (0.5 g, 1.36 mmol) and 0.56 g (1.6 mmol) of glucosylamine **11** were dissolved in 10 mL of methylene chloride. EEDQ (0.47 g, 1.9 mmol) was added and the mixture was stirred for 18 h at ambient temperature. After diluting with methylene chloride, it was extracted three times with 10 mL of HCl, 10 mL of 1 N $NaHCO_3$, and 10 mL of $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from methylene chloride/petroleum ether: yield 0.7 g (74%); mp 146–148 °C; $[\alpha]^{22}_D$ + 6.6° (*c* 1, $CH_3OH$); IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1660; 90-MHz $^1H$ NMR ($CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 1 H, NH), 6.6 (d, *J* = 8.8 Hz, 1 H, NH), 5.7 (d, *J* = 8.7 Hz, 1 H, NH, urethane), 3.0–2.7 (m, 6 H, $CH_2CH_2CH_2$ and β-$CH_2$Asn), 2.09, 2.06 and 2.04 (3 s, 9 H, 3 $CH_3COO$), 1.98 (s, 3 H, $CH_3CONH$), 1.43 (s, 9 H, $(CH_3)_3C$); 22.63-MHz $^{13}C$ NMR (DMSO-$d_6$) δ 171.3–169.3 (C=O), 155.1 (C=O, urethane), 78.5 ($(CH_3)_3C$), 78.1 (C1); 73.3 (C3), 72.3 (C5), 68.5 (C4), 65.0 ($OCH_2CH$), 61.8 (C6), 50.0 (α-CHAsn), 41.8 ($OCH_2CH$), 28.5 ($(CH_3)_3C$), 22.5 ($CH_3CONH$), 20.4 and 20.3 ($CH_3COO$). Anal. Calcd for $C_{28}H_{43}N_3O_{13}S_2$: C, 48.47; H, 6.25; N, 6.06. Found: C, 48.58; H, 6.28; N, 6.24.

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparagine (14).** To a mixture of 1 g (1.44 mmol) of Dim ester **12** were added 15 mL of acetone and 3 mL of a 0.05 M solution of ammonium molybdate, and 5.8 mL of a 33% aqueous $H_2O_2$ solution at 0 °C. After stirring to room temperature for 4 h the acetone was distilled off under reduced pressure (caution: the heating bath temperature should not exceed 20 °C). The pH was adjusted to 1 and the aqueous solution was extracted three times with 20 mL of methylene chloride. The combined organic layers were washed twice with brine and once with water, dried over $MgSO_4$, and concentrated in vacuo: yield 0.5 g (63%); mp 194 °C (lit.[5] mp 194–195 °C); $[\alpha]^{22}_D$ +11.5° (*c* 1, $CH_3OH$) (lit.[5] 11.7° (*c* 1, $CH_3OH$).

**N-Glycodipeptide 1,3-Dithian-2-ylmethyl Esters 15. General Procedure.** The acid **14** (0.6 g (1 mmol)), 0.1 g (1 mmol) of triethylamine, and 1 mmol of dithianyl ester **4** or **7** were dissolved in 10 mL of methylene chloride and 0.4 g (1.6 mmol) of EEDQ was added. After being stirred for 72 h the solution was extracted three times with 10 mL each of 2 N HCl, 1 N $NaHCO_3$, and water, dried over $MgSO_4$, and evaporated to dryness (if the product crystallizes from the reaction mixture it is isolated by filtration and washed with methylene chloride and the filtrates are treated as described above). The remaining residue is recrystallized from methylene chloride/petroleum ether. Yields, physical data, and elemental analyses are given in Table II. By this procedure the following glycopeptides were obtained.

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparaginylphenylalanine 1,3-dithian-2-ylmethyl ester (15a)**: IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1660 (amide I); 90-MHz $^1H$ NMR ($CDCl_3$) δ 7.3 (m, 6 H, NH and phenyl), 6.0 (d, *J* = 8.5 Hz, 1 H, NH), 3.1 (dd, 2 H, β-$CH_2$Asn), 2.9–2.6 (m, 4 H, $CH_2CH_2CH_2$), 2.08, 2.06, and 2.04 (3 s, 9 H, 3 $CH_3COO$), 1.98 (s, 3 H, $CH_3CONH$), 1.4 (s, 9 H, $(CH_3)_3C$); 22.63-MHz $^{13}C$ NMR (DMSO-$d_6$/$CD_3OD$ 1:1) δ 172–170.3 (C=O), 155.9 (C=O, urethane), 137.5 (ipso C), 80.2 ($(CH_3)_3C$), 74.1 (C3), 73.6 (C5), 28.4 ($(CH_3)_3C$), 27.4 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 22.7 ($CH_3CONH$), 20.5 and 20.3 ($CH_3COO$).

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparaginylisoleucine 1,3-dithian-2-ylmethyl ester (15b)**: IR (KBr) $\bar{\nu}$ 1755 (C=O, ester), 1665 (amide I); 90-MHz $^1H$ NMR (DMSO-$d_6$) δ 7.4 (d, *J* = 7.6 Hz, 1 H, NH), 6.3 (d, *J* = 7.9 Hz, 1 H, NH), 6.1 (d, *J* = 7.9 Hz, 1 H, NH), 2.8–2.6 (m, 6 H, β-$CH_2$Asn and $CH_2CH_2CH_2$), 2.08, 2.07, 2.04, and 2.01 (4 s, 12 H, 4 $CH_3CO$), 1.44 (s, 9 H, $(CH_3)_3C$), 0.97–0.82 (m, 6 H, 2 $CH_3$Ile); 22.63-MHz $^{13}C$ NMR (DMSO-$d_6$) δ 171.6–169.2 (C=O), 155.2 (C=O, urethane), 78.3 ($(CH_3)_3C$), 78.0 (C1), 73.2 (C3), 72.2 (C5), 68.4 (C4), 64.8 ($OCH_2CH$), 61.8 (C6), 56.1 (α-CHIle), 52.1 (C2), 50.6 (α-CHAsn), 28.0 ($(CH_3)_3C$), 26.4 ($CH_2CH_2CH_2$), 25.1 ($CH_2CH_2CH_2$), 24.3 (γ-$CH_2$Ile), 22.7 ($CH_3CONH$), 20.5 and 20.3 ($CH_3COO$), 15.3 (γ-$CH_2$Ile), 11.1 (δ-$CH_3$Ile).

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparaginylserine 1,3-dithian-2-ylmethyl ester (15c)**: IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1660 (amide I); 90-MHz $^1H$ NMR (DMSO-$d_6$) δ 8.5 (d, *J* = 8.9 Hz, 1 H, NH), 8.0–7.8 (m, 2 H, 2 NH), 6.8 (d, *J* = 7.8 Hz, 1 H, NH), 3.0–2.8 (m, 4 H, $CH_2CH_2CH_2$), 2.0, 1.96, 1.92, and 1.78 (4 s, 12 H, 4 $CH_3CO$), 1.38 (s, 9 H, $(CH_3)_3C$); 22.63-MHz $^{13}C$ NMR (DMSO-$d_6$) δ 172.2–169.8 (C=O), 155.8 (C=O, urethane), 79.4 ($(CH_3)_3C$), 78.3 (C1), 73.6 (C3), 72.7 (C5), 68.3 (C4), 65.6 ($OCH_2CH$), 28.5 ($(CH_3)_3C$), 27.0 ($CH_2CH_2CH_2$), 25.5 ($CH_2CH_2CH_2$), 22.9 ($CH_3CONH$), 20.7 ($CH_3COO$).

# Fructose 1,6-Diphosphate Aldolase Catalyzed Stereoselective Synthesis of *C*-Alkyl and N-Containing Sugars: Thermodynamically Controlled C–C Bond Formations[1]

John R. Durrwachter and Chi-Huey Wong*

*Department of Chemistry, Texas A&M University, College Station, Texas 77843*

*Received March 14, 1988*

Fructose 1,6-diphosphate aldolase catalyzed aldol condensations have been used in syntheses of several new N-containing and *C*-alkyl sugars on 4–20-mmol scales. The enzyme is highly specific for dihydroxyacetone phosphate as donor but accepts a number of achiral and chiral aldehydes (both D and L isomers) as acceptors. Due to the reversible nature of the aldol reaction, a thermodynamically controlled approach was employed for the syntheses in which racemic aldehydes were used as substrates and thermodynamically more stable products were preferentially produced.

Enzymatic transformations have been increasingly used as alternative methods in enantioselective synthesis.[2] Many useful reactions, particularly those based on the use of hydrolases and oxidoreductases have been demon-

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**Table I. Details of the Crystallographic Experiment and Computations for 16**

| | |
|---|---|
| molecular formula | $C_9H_{16}O_5 \cdot {}^1/_2CH_2Cl_2$ |
| crystal system | monoclinic |
| space group | $P21$ |
| lattice constants | |
| $a$, Å | 9.5164 |
| $b$, Å | 11.3542 |
| $c$, Å | 10.6435 |
| $\alpha$, deg | 90 |
| $\beta$, deg | 91.147 |
| $\gamma$, deg | 90 |
| $V$, Å$^3$ | 1149.81 |
| temperature, °C | −100 |
| $Z$ | 4 |
| $F(000)$ | 524 |
| $p$ (calculated, g cm$^{-3}$) | 0.96 |
| crystal dimensions, mm | 0.2 × 0.3 × 0.4 |
| radiation | Mo K$\alpha$ ($\lambda$ = 0.7107 Å) |
| monocromator | graphite |
| $\mu$, cm$^{-1}$ | 2.36 |
| scan type | $P$ |
| geometry | bisecting |
| scan speed, deg min$^{-1}$ | 2–30 |
| $2\theta$ range, deg | 4–50 |
| index restrictions | monoclinic |
| total no. of reflections | 2214 |
| no. of unique, obsd reflections | 2214 |
| observed reflection criterion | $F > 2.5\Delta F$ |
| no. of least-squares parameters | 295 |
| data/parameter ratio | |
| $R$ | 0.1102 |
| $R_w$ | 0.1074 |
| GOF | 2.3171 |
| $g$ | 0.001 |

**Table II. Selected Bond Angles (deg) and Bond Lengths (Å) for 16**

| | | | |
|---|---|---|---|
| C(5)–O(4)–C(1) | 113.5 (8) | | |
| O(4)–C(1)–O(3) | 110.8 (8) | | |
| C(2)–C(1)–O(4) | 108.5 (9) | | |
| C(6)–C(1)–O(4) | 106.0 (8) | | |
| C(1)–C(2)–O(2) | 111.5 (9) | | |
| C(3)–C(2)–C(1) | 110.4 (9) | | |
| C(4)–C(3)–O(1) | 111.7 (9) | | |
| C(5)–C(4)–C(3) | 109.0 (9) | | |
| C(7)–C(4)–C(5) | 111.2 (9) | | |
| C(1)–C(6)–O(5) | 112.7 (9) | | |
| C(9)–C(8)–C(7) | 122.8 (13) | | |
| C(2)–C(1)–O(3) | 109.4 (9) | | |
| C(6)–C(1)–O(3) | 111.3 (9) | | |
| C(6)–C(1)–C(2) | 110.8 (8) | | |
| C(3)–C(2)–O(2) | 110.7 (8) | | |
| C(2)–C(3)–O(1) | 110.6 (10) | | |
| C(4)–C(3)–C(2) | 109.2 (8) | | |
| C(7)–C(4)–C(3) | 111.6 (9) | | |
| C(4)–C(5)–O(4) | 111.7 (9) | | |
| C(8)–C(7)–C(4) | 112.0 (10) | | |
| O(1)–C(3) | 1.434 (14) | O(2)–C(2) | 1.458 (12) |
| O(3)–C(1) | 1.417 (13) | O(4)–C(1) | 1.445 (13) |
| O(4)–C(5) | 1.431 (13) | O(5)–C(6) | 1.409 (14) |
| C(1)–C(2) | 1.519 (14) | C(1)–C(6) | 1.528 (15) |
| C(2)–C(3) | 1.532 (16) | C(3)–C(4) | 1.514 (15) |
| C(4)–C(5) | 1.515 (16) | C(4)–C(7) | 1.549 (16) |
| C(7)–C(8) | 1.514 (15) | C(8)–C(9) | 1.339 (21) |

strated. Enzyme-catalyzed aldol condensations have also been shown synthetically useful.[3-9] The reactions are normally carried out in aqueous solution under mild conditions and with no protection of functional groups.

More than 15 aldolases have been isolated, each of which catalyzes a distinct type of aldol reaction.[5] The enzyme fructose 1,6-diphosphate (FDP) aldolase has been used for synthesis of a number of common and uncommon sugars including deoxyhexoses,[3-5] fluoro sugars,[4] $^{13}$C-labeled sugars,[3] and many high-carbon sugars.[6] The enzyme is specific for dihydroxyacetone phosphate (DHAP, 1) as the aldol donor, but will accept a variety of aldehydes as acceptors. The stereochemistry of the new C–C bond formed is the same in all aldol reactions studied so far; the chiral environment in the aldehyde acceptors does not affect the stereochemistry of the C–C bond formation.

The major obstacle encountered in the enzymatic aldol condensations is that preparation of aldehyde acceptors is not trivial, particularly if an enantiomerically pure aldehyde is required. Another potential problem is that many interesting $\alpha$-substituted chiral aldehydes are not stable in aqueous solution, prohibiting the preparation of many interesting uncommon sugars.

We report here a thermodynamically controlled synthesis of several enantiomerically pure N-containing and C-alkyl sugars on 4–20–mmol scales with racemic aldehydes as substrates. Because of the reversible nature of the aldol reactions and the favorable equilibrium position in the condensation direction, thermodynamically more stable products (i.e. with 1–2 kcal/mol less energy than the other diastereomer) can be selectively obtained.

## Results and Discussion

The five aldehydes shown in Scheme I are substrates for the enzyme. Rates for the condensations are about one-tenth the rate of the natural substrate D-glyceraldehyde 3-phosphate. When an excess of racemic aldehydes (3–4 equiv) was used, a mixture of diastereomeric products was formed initially according to NMR and HPLC analyses. However, the thermodynamically more stable product was accumulated preferentially at equilibrium, allowing the preparation of a single product in high yield.

**N-Containing Sugars.** Sugars with nitrogen in the ring have been prepared by several workers, notably Paulsen and Hanessian.[10] These sugars are interesting because of their natural rarity, their potent biological effects (antibiotics, glycosidase inhibitors), and their synthetic challenge. These sugars as well as aminoaldehydes are not

(1) Supported by the National Science Foundation (Grant CHE 8318217 and the PYI program, Grant CHE 8552620). Portions of the work were presented at the ACS National Meeting at New Orleans, September 1, 1987.

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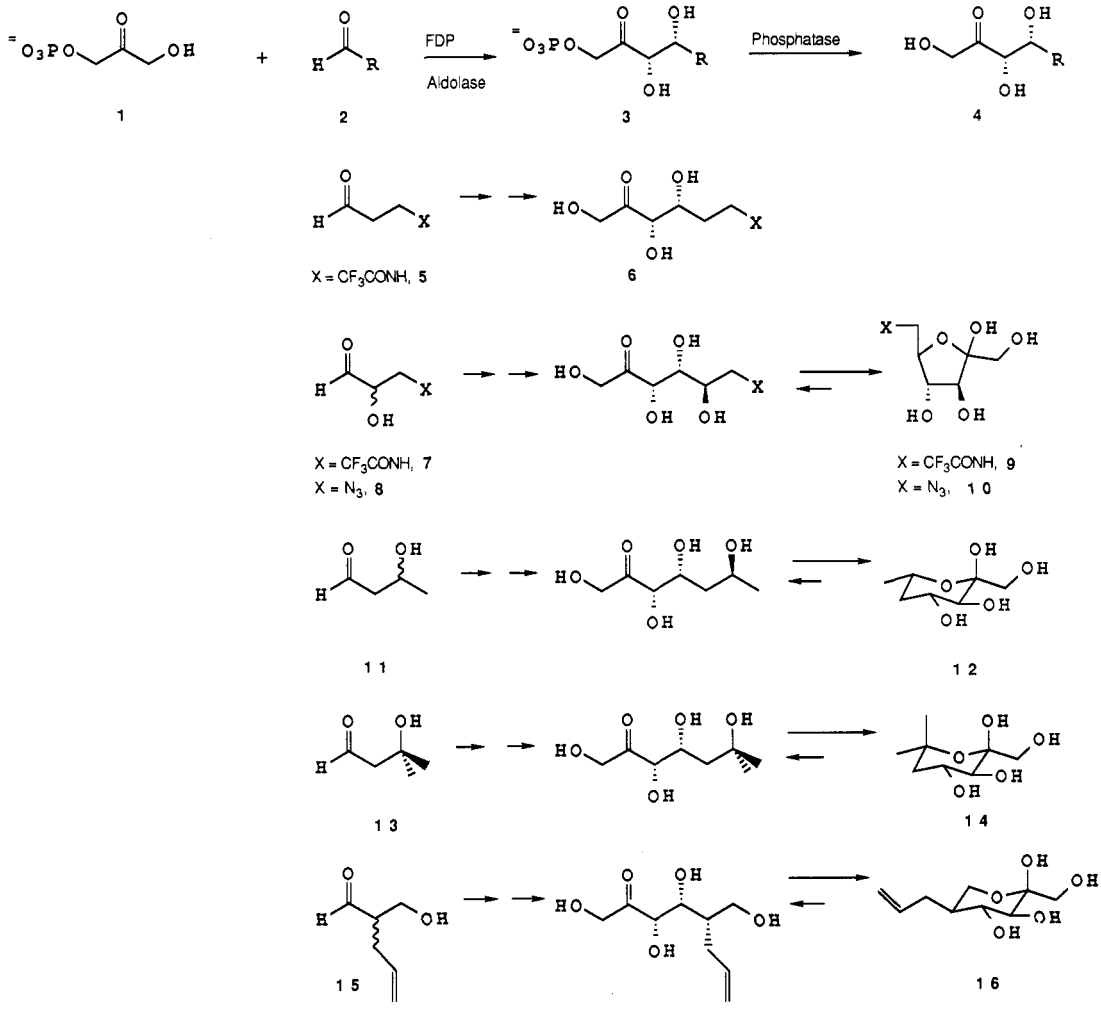
**Scheme I. FDP Aldolase Catalyzed Syntheses of N-Containing and *C*-Alkyl Sugars**




stable and must be prepared in some derivatized form.

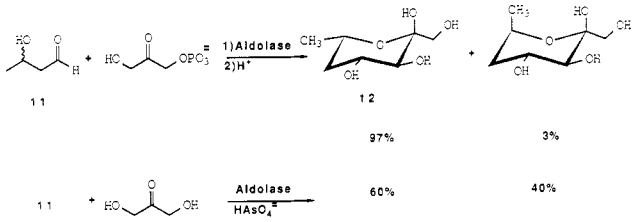
To prepare 5,6-dideoxy-6-(trifluoroacetamido)-D-*threo*-hexulose (**6**), the aldehyde **5** was synthesized from 3-chloropropionaldehyde diethyl acetal, which was first converted to the 3-azido derivative followed by hydrogenation to give 3-aminopropanal diethyl acetal. Trifluoroacetylation was done by stirring the amine with several equivalents of ethyl trifluoroacetate; the reaction was instantaneous. The acetal group was selectively hydrolyzed at pH 1.5, and the product was used for aldol condensation at pH 6.5. The resulting ketose phosphate was hydrolyzed directly to give the desired product **6**. Surprisingly, the sugar remains in the open chain form. In an attempt to prepare the piperidinose with N in the ring, compound **6** was treated with base to remove the trifluoroacetyl group. $^{13}C$ NMR spectroscopy was used to monitor the reaction. At pH 7.5, very little hydrolysis had occurred after 24 h, although the solution had darkened considerably. At a pH of about 10, rapid hydrolysis occurred and new $^{13}C$ peaks, including some in the hemiacetal region, were detected, but the solution turned brown. No further workup was performed.

The second amino sugar of interest is 6-deoxy-6-(trifluoroacetamido)-D-*arabino*-hexulose (**9**). This sugar was prepared by the condensation of **1** with D,L-2-hydroxy-3-(trifluoroacetamido)propanal (**7**). The aldehyde **7** was prepared from glycidaldehyde diethyl acetal. The epoxide was opened with azide to yield D,L-3-azido-2-hydroxypropanal diethyl acetal (**8a**), which upon reduction to D,L-3-amino-2-hydroxypropanal diethyl acetal with hydrogen and palladium was acylated in excess ethyl trifluoroacetate to yield D,L-2-hydroxy-3-(trifluoroacetamido)propanal diethyl acetal (**7a**). Selective deprotection of this compound was done in warm aqueous acid to afford the desired aldehyde **7**. The aldol condensation was done at pH 6. Unfortunately, the sugar product was rather unstable and did not survive the workup.

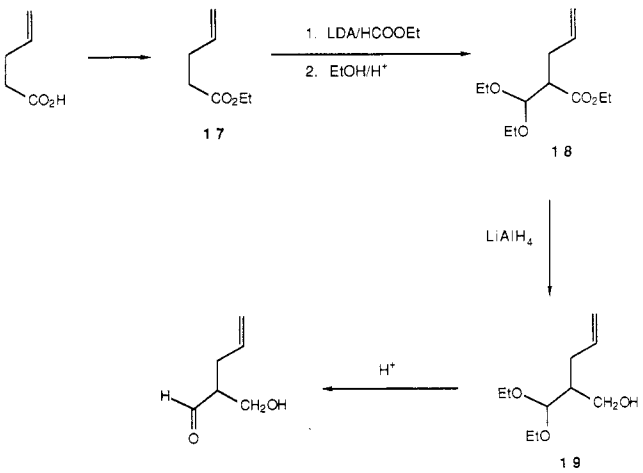
The final N-containing sugar was 6-azido-6-deoxy-D-*arabino*-hexulose (**10**). The aldehyde required for this reaction, D,L-3-azido-2-hydroxypropanal (**8**), was obtained from the intermediate acetal **8a** prepared during the synthesis of **7**. The acetal was hydrolyzed in warm aqueous acid to give the desired acceptor **8**. The aldol condensation was done at pH 6.5. $^{13}C$ NMR analysis of the reaction mixture indicated only one major product. To determine the configuration at carbon 5, compound **10** was allowed to react with glucose isomerase, which was known to accept only D sugars.[4] The reaction of **10** with glucose isomerase indicated a sugar of the D and fructo configuration was formed in the aldol reaction. It was not clear why compound **10** was selectively formed. Preliminary results indicated that (*R*)-**8** reacted faster than the enantiomer.

***C*-Alkyl Sugars.** Three C-alkylated deoxy sugars (**12**, **14**, **16**) were synthesized with FDP aldolase. Potential uses as artificial sweeteners were envisioned for the sugars **12** (5,7-dideoxy-L-*xylo*-heptulose) and **14** (5-deoxy-6,6-dimethyl-D-*threo*-hexulose). The allyl linkage in **16** (5-allyl-5-deoxy-L-*xylo*-hexulose) was seen as a convenient way to link this sugar to some polymeric matrix or to synthesize a polysugar,[11] both could be useful for processes associated

**Scheme II. Thermodynamic (Top) vs Kinetic (Bottom) Products Obtained in FDP Aldolase Catalyzed Synthesis of 12 and the 6 Epimer**




**Scheme III. Syntheses of the Aldol Acceptor D,L-2-(Hydroxymethyl)-4-pentenal (15)**




with chiral recognition. In the synthesis of **12**, two compounds were initially formed at a 1:1 ratio, one of which gradually disappeared during the progress of the reaction. The byproduct was believed to be the 6 epimer, which is about 2 kcal/mol[12] less stable than the 1-phosphate of **12**. The major product (97%) obtained was identical with the product prepared from (*S*)-**11**, thus confirming the configuration of **12** at C6. When a mixture of dihydroxyacetone and inorganic arsenate[13] was used to replace **1** in reaction with **11**, the ratio of **12** to the 6 epimer obtained was 6/4, indicating that the reverse aldol reaction was extremely slow, i.e., reformation of the ketose-1-arsenate of **12** to undergo the retroaldol reaction is unlikely; therefore, the product distribution is kinetic in nature. These reactions are illustrated in Scheme II.

This thermodynamic effect was noted again in the case of **16**. The aldehyde D,L-2-(hydroxymethyl)-4-pentenal **15** is synthesized as shown in Scheme III. Commercially available 4-pentenoic acid is esterified and $\alpha$-formylated, and the aldehyde is protected to yield D,L-ethyl-2-(diethoxymethyl)-4-pentenoate. Reduction with lithium aluminum hydride (LAH) gives D,L-2-(hydroxymethyl)-4-pentenal diethyl acetal, the convenient precursor to **15**. Hydrolysis of this compound gave **15**, which was used in the aldol condensation in 25% dimethyl sulfoxide (DMSO) at room temperature.[14] The aldehyde was not completely soluble at 0.2 M, but the reaction proceeds to give only one product, **16**. The energy difference between axial and equatorial allyl is on the order of 0.9 kcal/mol.[12]

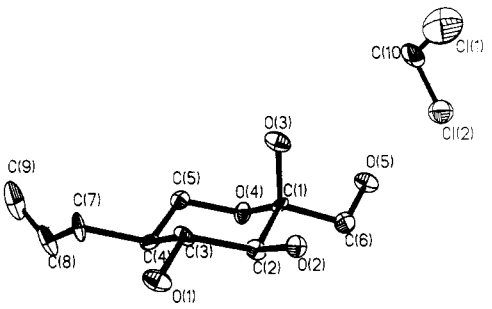



**Figure 1.** X-ray crystal structure of **16**. Hydrogen atoms are omitted. For detailed information, see Tables I and II.

The third alkylated sugar is **14**. The aldehyde acceptor **13**, 3-hydroxy-3-methylbutanal, is synthesized via treatment of acetoacetaldehyde diacetal with methylmagnesium iodide. Condensation of **13** with **1** was successfully carried out on a 20-mmol scale.

The stereochemistry of the C3–C4 bond formation was determined by looking at the coupling constant of the proton on C3. This is a doublet and is relatively easy to discern in the $^1$H NMR spectrum. For **12** that constant is 9.6 Hz, indicative of an axial–axial coupling and of the expected 3(*S*),4(*R*) configuration. For **14** this value is 9.8 Hz. For **16** the coupling could not be easily located. However, the X-ray structure analysis (Figure 1)[15] clearly shows that the allyl substituent is in the equatorial position and that the stereochemistry is consistent with that indicated in **16**.

In summary, this work illustrates the additional use of FDP aldolase as a catalyst for the syntheses of some N-containing and *C*-alkyl sugars, which are difficult to prepare otherwise.

## Experimental Section

The FDP aldolase (EC 4.1.2.13) from rabbit muscle and other enzymes and biochemicals were from Sigma. Solvents and chemicals were of reagent grade. Dihydroxyacetone phosphate was generated in situ from FDP-$Na_3$ in the presence of FDP aldolase and triose phosphate isomerase (TPI) according the procedure described previously.[4] Optical rotations were measured on a Perkin-Elmer 240 polarimeter. Proton, $^{13}$C, and fluorine NMR spectra were obtained on Varian XL-200 or XL-400 spectrometers operating at 200 and 400 MHz, respectively. All chemical shifts were reported in ppm with tetramethylsilane as internal standard unless otherwise indicated. UV spectra were taken with a Beckman DU-70 instrument. HPLC analyses were done on a Gilson chromatography system including a Model 302 pump, Model 131 refractive index detector, and a Rheodyne injector. GC analyses were performed on a Hewlett-Packard 5890 instrument. Nicolet R3m/v X-ray diffractometer and ShelXTL (version 5) software were used in the single-crystal X-ray structure determination.

**3-Aminopropanal Diethyl Acetal.** To 500 mL of dimethylformamide (DMF) containing $NaN_3$ (26.0 g, 400 mmol) was added 3-chloropropionaldehyde diethyl acetal (33.3 g, 200 mmol). The solution was warmed to 60 °C, and the reaction was monitored by GC (50 °C, 1 min to 250 °C at 15 °C/min, DB5-15 m. Retention time ($t_R$) of starting material 5.1 min, product 6.5 min). The reaction mixture was diluted with 1 L of ice water and extracted with ether (3 × 500 mL). The combined ether extracts were washed with water (2 × 500 mL) and then dried over $MgSO_4$.

(11) These sugars have the required functional groups as D-fructopyranose to be recognized by the taste receptor model: Schallenberger, R. S.; Acree, T. E. *Nature (London)* **1977**, *216*, 480. The *C*-alkyl group introduced could enhance the hydrophobic interaction with the receptor. The allyl derivative could be polymerized to a polysugar with a complete carbon backbone.

(12) Calculated according to the procedure reported: Angyal, S. J. *Aust. J. Chem.* **1968**, *21*, 2731.

(13) For the arsenate-mediated reactions, see ref 4 and the references cited therein. The mechanism is believed to proceed through a transient dihydroxyacetone arsenate ester, which is a mimic of DHAP. The detailed mechanism will be published elsewhere.

(14) The aldolase can tolerate up to 20% DMF or DMSO without loss of activity in 1 day at room temperature.

(15) Selected X-ray data are included in Tables I and II.

(16) Becke, F. German Patent 845348, 1952; *Chem. Abstr.* **1952**, *47*, 5426.

Removal of solvent afforded a crude product, which was dissolved in 500 mL of ethanol containing Pd/C (10%, 2.03 g, 2 mmol). The suspension was degassed, saturated with $H_2$, and stirred under a $H_2$ balloon for 4 days, at which time GC analysis of the product amine ($t_R$ 5.4 min) indicated a complete reaction. The solution was degassed and filtered through Celite 545, and the solvent was removed under reduced pressure. The residue was diluted with 25 mL of 12 N KOH and extracted with ether (2 × 50 mL). The ether layer was filtered through glass wool/$Na_2CO_3$ and dried over $Na_2CO_3$. The solvent was removed under water aspirator vacuum, and the residue was distilled to yield the title compound (18.6 g, 126 mmol, 63%): $bp_{17}$ 80–81.5 °C (lit.[16] $bp_{20}$ 68–70 °C); $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.21 (t, 6 H, $CH_3$), 1.58 (s, 2 H, $NH_2$), 1.78 (q, 2 H $CH_2$), 2.81 (t, 2 H, $NCH_2$), 3.53 and 3.66 (m, 4 H, $OCH_2$), 4.62 (t, 1 H, CH). Anal. Calcd for $C_7H_{17}NO_2$: C, 57.1; H, 11.6. Found: C, 57.1; H, 11.5.

**3-(Trifluoroacetamido)propanal Diethyl Acetal (5a).** To 15 mL of ethyl trifluoroacetate (127 mmol) was added the above product (4.8 g, 33 mmol). The reaction was over immediately as shown by GC analysis ($t_R$ 7.9 min, same conditions as above). The solvent was removed under reduced pressure to yield **5** (5.2 g, 21 mmol, 65% yield): $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.23 (t, $J$ = 7.0 Hz, 6 H, $CH_3$), 1.90 (m, 2 H, $CH_2$), 3.50 (m, 2 H, $CH_2N$), 3.52, 3.73 (dq, $J$ = 9.2 Hz, $J$ = 7.0 Hz, 4 H, $CH_2O$), 4.63 (t, $J$ = 4.6 Hz, 1 H, CH). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 14.72 ($CH_3$), 31.69 ($CH_2$), 35.38 ($CH_2N$), 62.25 ($CH_2O$), 102.13 (CH), 115.73 (q, $J$ = 287 Hz, $CF_3$), 156.69 (q, $J$ = 36.5 Hz, C=O); $^{19}F$ NMR (376 MHz, $CDCl_3$) δ −13.99 (s, $CF_3$).

**5,6-Dideoxy-6-(trifluoroacetamido)-D-*threo*-hexulose (6).** Into 5 mL of water containing 50 μL of $CH_3SO_2OH$ was introduced **5a** (1.08 g, 4.5 mmol). The solution was stirred at room temperature and monitored by GC under the same condition as above ($t_R$ of **5** 7.9 min). After completion of hydrolysis, FDP-$Na_3$ (825.6 mg, 1.50 mmol) in 10 mL $H_2O$ was added, and the pH was adjusted to 6.5 with NaOH. After degassing with argon, aldolase (300 units) and triose phosphate isomerase (TPI, 500 units) were added. After 24 h, the reaction was stopped by the addition of a solution of $BaCl_2 \cdot 2H_2O$ (1.485 g, 6.1 mmol). The pH was adjusted to 7.8 with NaOH and diluted with 20 mL of acetone. The precipitate was isolated by centrifugation and washed with acetone (2 × 25 mL). The white solid was suspended in 25 mL of water, and HCl was added to a pH of 1. A solution of $Na_2SO_4$ (850 g, 6 mmol) was added, and the pH was adjusted to 6.5 with NaOH. The suspension was filtered through Celite 545 to remove barium sulfate. The pH of the filtrate was adjusted to 4.9 with acetic acid, and acid phosphatase (100 units) was added. After 12 h, the reaction was complete and TLC (silica gel, ethyl acetate–methanol–$H_2O$, 12:6:2, $R_f$ of **6** 0.76, fructose 0.35) indicated only a trace of fructose (undetectable by NMR). The solution was neutralized and then freeze-dried. The residue was triturated with ethanol to yield, after removal of solvent, a relatively clean sample of **6**. Purification by chromatography (silica gel, water saturated ethyl acetate) yielded **6** as a reddish oil (320 mg, 1.23 mmol, 41% yield): $[\alpha]^{28}_D$ +4.1° (*c* 3.2, ethanol); $^1H$ NMR (200 MHz, $D_2O$) δ 1.5–1.8 (m, 2 H, $CH_2$), 3.20–4.55, a complex series of peaks of 6 H, 3.31 (t), 3.40–3.65 (low multiplets), 3.71 (dt), 3.89 (dt), 4.14 (2 d), 4.25 (d), 4.37 (2 d), 4.50 (d), 5.04 (t); $^{13}C$ NMR (50 MHz, $D_2O$) δ 33.83 (C5), 39.21 (C6), 68.71, 72.04, 80.22 (CHOD), 118.50 (q, $J$ = 286 Hz, $CF_3$), 161.50 (q, $J$ = 37.2 Hz); $^{19}F$ NMR (376 MHz, $D_2O$) δ −10.94, −10.91, −10.66 (s). Anal. Calcd for $C_8H_{12}O_5NF_3$: C, 37.21; H, 4.65; N, 5.43. Found C, 37.11; H, 4.58; N, 5.44. The pH of the $^{13}C$ sample was adjusted to 7.5 with $K_2CO_3$. After 24 h very little hydrolysis of the trifluoroacetate was observed. Upon adjusting the pH to ~10, the hydrolysis proceeded much faster. In either case, new peaks appear that would imply the piperidinose sugar. The sample, however, degraded, resulting in the rapid coloration and the decreased signal to noise ratio.

**D,L-3-Azido-2-hydroxypropanal Diethyl Acetal (8a).** Into a three-neck flask fitted with a stirring bar and pH probe was placed glycidaldehyde diethyl acetal (17.59 g, 102 mmol, 85% pure), 50% ethanol in water (250 mL), and $NaN_3$ (13.35 g, 205 mmol). The pH was adjusted to and maintained at 7.5 with aqueous $H_2SO_4$. The solution was warmed to 50 °C for 12 h. GC analysis (40 °C, 5 min to 250 °C at 15 °C/min, DB-5, $t_R$ of epoxide 5.65 min, product 10.0 min) indicated complete reaction. The ethanol was removed under reduced pressure, and the aqueous solution was saturated with $Na_2SO_4$. This solution was extracted with ethyl acetate (3 × 80 mL), and the combined extracts were dried over $Na_2SO_4$. Removal of solvent by evaporation followed by distillation of residue yielded **8a** (17.8 g, 86.7 mmol, 85% yield) $bp_{2.8}$ 96–97 °C; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.23 and 1.26 (t, $J$ = 7.1 Hz, 6 H, $CH_3$), 2.47 (d, $J$ = 6 Hz, OH), 3.35 (dd, $J$ = 6 Hz, $J$ = 12.8 Hz, 1 H, $CH_2N_3$), 3.51 (dd, $J$ = 3.6 Hz, $J$ = 12.8 Hz, 1 H, $CH_2N_3$), 3.60 (m, 1 H, CHOH), 3.77 (m, 4 H, $OCH_2$), 4.47 (d, $J$ = 6.2 Hz, 1 H, CH) $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 15.69, 15.73 ($CH_3$), 52.8 ($CH_2N_3$), 64.1, 64.5 ($CH_2O$), 71.9 (CHOH), 103.2 (CHOEt).

**D,L-3-Amino-2-hydroxypropanal Diethyl Acetal.** To a suspension of Pd/C (10%, 0.5 g, 0.5 mmol) in 150 mL of ethanol was added **8a** (8.04 g, 39 mmol). The mixture was degassed and hydrogenated under a hydrogen balloon for 24 h. The reaction was monitored by GC (50 °C, 1 min to 250 °C at 15 °C/min, DB-5; $t_R$ of **8a** 7.4 min, amine 6.4 min). The ethanol was removed under reduced pressure, and the residue was distilled to yield the title compound (5.3 g, 33 mmol, 83%; $bp_{0.03}$ 59 °C; solidified upon cooling, mp 45 °C): $^1H$ NMR (200 MHz, DMSO) δ 1.08, 1.10 (t, $J$ = 7.0 Hz, 6 H, $CH_3$), 2.41 (dd, $J$ = 7.4 Hz, $J$ = 13.0 Hz, 1 H, CHN), 2.62 (dd, $J$ = 3.8 Hz, $J$ = 13.0 Hz, 1 H, CHN), 3.27 (ddd, $J$ = 3.8 Hz, $J$ = 7.4 Hz, $J$ = 6.0 Hz, 1 H, CHO), 3.35–3.69 (m, 4 H, $CH_2O$), 4.21 (d, $J$ = 6.0 Hz, 1 H, CH); $^{13}C$ NMR (50 MHz, DMSO) δ 15.32, 15.39 ($CH_3$), 43.63 ($CH_2NH_2$), 61.72, 62.48 ($CH_2O$), 72.51 (CHO), 103.83 (CH).

**D,L-2-Hydroxy-3-(trifluoroacetamido)propanal Diethyl Acetal (7a).** To 30 mL of ethyl trifluoroacetate (250 mmol) was added the above compound (4.25 g, 26 mmol). The reaction was over immediately as determined by GC (same condition as above, $t_R$ of **7a** 8.1 min). The solvent was removed under reduced pressure, and the residue was distilled to yield **7a** (5.1 g, 19.7 mmol, 76% $bp_{0.05}$ 62 °C). The sample solidified upon cooling, mp 42 °C: $^1H$ NMR (200 MHz, DMSO) δ 1.10, 1.11 (t, $J$ = 7.0, 6 H, $CH_3$), 3.14 (ddd, $J$ = 13.3 Hz, $J$ = 8.6 Hz, $J$ = 6.0 Hz, 1 H, CHN), 3.33 (ddd, $J$ = 13.3 Hz, $J$ = 3.5 Hz, $J$ = 6.0 Hz, 1 H, CHN), 3.40–3.72 (m, 5 H, $CH_2O$, CHO), 4.25 (d, $J$ = 4.5 Hz, 1 H, CH), 5.05 (d, $J$ = 5.6 Hz, 1 H, OH), 9.22 (t, $J$ = 6.0 Hz, 1 H, NH); $^{13}C$ NMR (50 MHz, DMSO) 15.22, 15.31 ($CH_3$), 41.59 ($CH_2N$), 62.12, 63.02 ($CH_2O$), 68.87 (CHO), 103.67 (CH), 116.03 (q, $J$ = 288 Hz, $CF_3$), 156.4 (q, $J$ = 36 Hz, C=O). Anal. Calcd for $C_9H_{16}NO_4F_3$: C, 41.7; H, 6.2; N, 5.4. Found C, 41.72; H, 6.23; N, 5.70.

**6-Azido-6-deoxy-D-*arabino*-hexulose (10).** Into 10 mL of $H_2O$ containing 150 μL of concentrated HCl was added **8a** (836 mg, 4 mmol). The solution was warmed to 45 °C and monitored by GC (50 °C, 1 min to 250 °C at 15 °C/min, DB-5, $t_R$ of **8a** 7.4 min). After 12 h the reaction was complete. FDP-$Na_3$ (570 mg, 1.04 mmol) was added, and the pH was adjusted to 6.5 with NaOH. Aldolase (300 units) and TPI (500 units) were added, and the solution was degassed with argon. After 24 h, the solution was treated as before to remove the phosphate moiety. The resulting solid was triturated with methanol (3 × 50 mL). The solvent was removed under reduced pressure, and the residue was chromatographed (Dowex 50, $Ba^{2+}$, 2 × 50 cm, ethanol–$H_2O$, 1:1, v/v) to yield **10** (290 mg, 1.4 mmol, 71%): $[\alpha]^{26}_D$ +22.2° (*c* 2.9, $H_2O$); $^1H$ NMR (200 MHz, $D_2O$) δ 3.18–3.56 (m), 3.66–3.86 (m), 3.89–4.06 (m), 4.11–4.29 (m), 4.36–4.45 (m); $^{13}C$ NMR (50 MHz, $D_2O$) δ 52.47 ($CH_2N_3$), 62.49, 74.92, 75.03, 78.97 (CHOH, $CH_2OH$), 101.80 ($C_2$). Anal. Calcd for $C_6H_{11}O_5N_3$: C, 35.11; H, 5.43; N, 20.5. Found: C, 35.22; H, 5.60; N, 20.66.

**6-Azido-6-deoxy-D-glucose.** In 1 mL of water was combined **10** (100 mg, 0.5 mmol), TAKASWEET (0.4 g, from Miles; this is the enzyme glucose isomerase), 10 μL each of 0.1 M $Co(NO_3)_2$, 0.1 M $MgCl_2$, and 1 M phosphate buffer (pH 7.0), and 5 μL of 0.1 M $MnCl_2$. The solution was warmed to 50 °C for 24 h. Filtration, purification through Dowex 50-$Ba^{2+}$, followed by lyophilization yielded a sample that gave a $^1H$ NMR and a $^{13}C$ NMR spectrum completely different from **10**. The $^1H$ NMR spectrum matched that of 6-deoxy-6-azido-D-glucose, indicating characteristic shifts of the aldose C1-H at 5.22 ppm ($J$ = 2 Hz) for the α-anomer and 4.47 ppm ($J$ = 10 Hz) for the β-isomer: $^{13}C$ NMR (200 MHz, $D_2O$) δ 50.8, 50.9 ($CH_2N_3$), 70.1, 70.2, 70.4, 704, 72.5, 74.0, 74.4, 75.5 (CHOD), 92.1, 95.9 (C2). Anal. Calcd for $C_6H_{11}O_5N_3$: C, 35.11; H, 5.43. Found: C, 35.30; H, 5.50.

**6-Deoxy-6-(trifluoroacetamido)-D-*arabino*-hexulose (9).** Into a solution of 15 mL of $H_2O$ and 200 μL of HCl was dissolved

**7a** (1.036 g, 4 mmol). The solution was warmed to 38 °C. After complete hydrolysis of the acetal (15 h, by GC), FDP-$Na_3$ (593 mg, 1.08 mmol) was added and the pH was adjusted to 6.8 with NaOH. The solution was degassed with argon, and aldolase (300 units) and TPI (500 units) were added. Twenty hours later, the reaction was complete and the mixture was treated as before to remove the phosphate moiety. Further purification by chromatography on Dowex 50-$Ba^{2+}$ resulted in a complete loss of product.

**D,L-3-Hydroxybutanal Dimethyl Acetal.** Freshly distilled acetylacetaldehyde dimethyl acetal (3.3 g, 25 mmol) in 200 mL of ethanol was treated with $NaBH_4$ (0.56 g, 15 mmol) in 5 mL of $H_2O$. The solution darkened and was stirred for 2 h at room temperature. The reaction was monitored by TLC (silica gel, ether–hexane, 3:1, v/v, $R_f$ starting material 0.49, product 0.39). After completion, most of the solvent was removed under water aspirator vacuum and diluted with 40 mL of $H_2O$. This solution was extracted with ethyl acetate (3 × 30 mL), and the combined organics were dried over $Na_2SO_4$. The solvent was removed under reduced pressure to yield the acetal (2.78 g, 21 mmol, 84%): $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.20 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 1.75 (m, 2 H, $CH_2$), 3.08 (s, 1 H, OH), 3.35, 3.38 (s, 6 H, $OCH_3$), 3.98 (m, 1 H, CHOH), 4.58 (t, $J$ = 5.7 Hz, 1 H, CH); $^{13}C$ NMR (50 MHZ, $CDCl_3$) δ 23.36 ($CH_3$), 40.98 ($CH_2$), 52.78, 53.58 ($OCH_3$), 64.45 (CHOH), 103.74 (CH).

**5,7-Dideoxy-L-*xylo*-heptulose (12).** A solution containing the above acetal (0.51 g, 3.8 mmol), 1 mL of 0.5 N HCl, and 9 mL of $H_2O$ was stirred for 3 h at room temperature until the hydrolysis was complete (TLC on silica gel, ether, $R_f$ acetal 0.42, **11** 0.23). FDP-$Na_3$ (440 mg, 0.8 mmol) was added, and the solution was adjusted to pH 7.0 with NaOH and aldolase (125 units) and TPI (100 units) were added. After 15 h, $BaCl_2 \cdot H_2O$ (0.933 g, 3.8 mmol) was added with stirring, and the pH was adjusted to 7.3. Acetone (50 mL, 2 volumes) was added, and the solution was chilled. Centrifugation followed by washing (acetone, 2 × 50 mL) yielded the Ba salt of the product. The solid was suspended in 25 mL of $H_2O$ with Dowex 50 ($H^+$, 4.2 g), stirred for 30 min, neutralized with NaOH, and filtered. The pH was adjusted to 4.8 with HOAc, and acid phosphatase (60 U) was added. After 4 days, the solution was neutralized and freeze-dried. The residue was chromatographed on a Dowex 50 ($Ba^{2+}$) column (ethanol–$H_2O$, 1:1, v/v) to yield 292 mg (1.6 mmol, 97%): $[\alpha]^{25}_D$ −20.6 ($c$ 1.73, $H_2O$); $^1H$ NMR (200 MHz, $D_2O$) δ 1.09 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 1.27 (m, $J$ = 1.20 Hz, $J$ = 12.8 Hz, $J$ = 11.6 Hz, 1 H, C5-$H_{ax}$), 1.94 (m, $J$ = 2.1 Hz, $J$ = 5.0 Hz, $J$ = 12.8 Hz, 1H, C5-$H_{eq}$), 3.33 (d, $J$ = 9.6 Hz, 1 H, C3-H), 3.39, 3.58 (C1-H, C1-H′), 3.83 (m, $J$ = 5.0 Hz, $J$ = 12.0 Hz, 1 H, C6-H); $^{13}C$ NMR (50 MHz, $D_2O$) δ 20.29 (C7), 40.20 (C5), 64.10, 65.35, 68.28, 72.19 (C1, 3, 4, 6) 98.03 (C2). Anal. Calcd for $C_7H_{14}O_5$: C, 47.2; H, 7.90. Found: C, 47.51; H, 7.86.

**Aldolase Reaction of 11 with Dihydroxyacetone in the Presence of Arsenate.** To an aqueous solution of **11** (3 mL, 3 mmol, pH 8.6) was added a solution of sodium arsenate (3 mL, 1.0 M, pH 7.6). Dihydroxyacetone (0.27 g, 3 mmol) and aldolase (400 units) were added, and the solution was stirred slowly at room temperature. The reaction was monitored by HPLC with a Waters carbohydrate column with 85% aqueous acetonitrile as the mobile phase with a flow rate of 1.2 mL/min. After 24 h, HPLC showed only a trace of **11** ($t_R$ 2.3 min) and dihydroxyacetone ($t_R$ 3.9 min) with two major new peaks ($t_R$ 4.4 and 5.9 min). Methanol was added to precipitate arsenate, and the suspension was filtered. The filtrate was applied to a Dowex 50 ($Ba^{2+}$) column (100–200 mesh, 3 × 75 cm) and eluted with 50% ethanol. Fractions (8 mL) were collected and analyzed by HPLC. The product with $t_R$ 4.4 min eluted first [(retention volume 240–400 mL); $^{13}C$ NMR δ 20.10 (C7), 40.18 (C5), 64.10, 65.33, 68.26, 71.01. Anal. Calcd for $C_7H_{14}O_5$: C, 47.20; H, 7.90. Found: C, 47.11; H, 7.70)] followed by the other product (retention volume 400–800 mL). The slow-moving product was evaporated and lyophilized to give 0.19 g, which had the same NMR data as **12** prepared from **1** and **11**. When (*S*)-**11**[17] was used as a substrate, only **12** was produced, and the product with $t_R$ 4.4 was not observed.

**3-Hydroxy-3-methylbutanal Dimethyl Acetal.** $CH_3I$ (18.5 mL, 297 mmol) in 50 mL of ether was added slowly, to maintain reflux, to a suspension of Mg (6.0 g, 250 mmol) in 50 mL of ether. The solution was vigorously stirred during the addition. After the magnesium was consumed, the solution was chilled with an ice bath to ≃5 °C. Acetylacetaldehyde dimethyl acetal (16.5 mL, 124 mmol) in 50 mL of ether was added very slowly, over a period of 2 h. After the addition was complete, the reaction was stirred for an additional hour while warming to room temperature. The reaction was quenched with 1 mL of saturated $(NH_4)_2SO_4$(aq) and filtered. The residue was washed with ether (2 × 50 mL). The combined filtrates were dried over $Na_2SO_4$, and the solvent was removed under water aspirator vacuum (8.3 g, 67 mmol, 54% yield). Distillation of the residue yielded 9.9 g of 3-hydroxy-3-methylbutanal dimethyl acetal, $bp_{4.2}$ 53–56 °C (lit.[18] $bp_{10}$ 60–65 °C, $bp_{14}$ 72–79 °C); $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.24 (s, 6 H, $CH_3$), 1.80 (d, $J$ = 5.9 Hz, 2 H, $CH_2$), 3.36 (s, 6 H, $CH_3O$), 3.41 (s, 1 H, OH), 4.66 (t, $J$ = 5.9 Hz, 1 H, CH); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 29.46 ($CH_3$), 43.85 ($CH_2$), 52.61 ($CH_3O$), 68.63 (COH), 102.51 (CH).

**5-Deoxy-6,6-dimethyl-D-*threo*-hexulose, 14.** 3-Methyl-3-hydroxybutanal dimethyl acetal (640 mg, 4.3 mmol) was hydrolyzed in 19 mL of $H_2O$ with $CH_3SO_2OH$ (100 μL). After 4 h, the hydrolysis was complete as determined by GC (50 °C, 1 min to 250 °C at 15 °C/min, DB-U; $t_R$ of acetal 4.2 min, aldehyde 2.0 min). FDP-$Na_3$ (573 mg, 1.04 mmol) was added to the solution, and the pH was adjusted to 6.5. FDP aldolase (400 units) and TPI (100 units) were added and allowed to react for 16 h. Following the same workup procedure for **6** to remove the phosphate group, the crude sugar was extracted by vigorously stirring the residue with methanol and filtering (3 × 50 mL). The methanol was removed under water aspirator vacuum, and the residue was chromatographed (silica gel, water saturated ethyl acetate), yield 0.20 g (1.04 mmol, 50%): $[\alpha]^{25}_D$ −21.8 °C ($c$ 0.40, $H_2O$); $^1H$ NMR (200 MHz, $D_2O$) δ 1.03, 1.20 (s, 6 H, $CH_3$), 1.37 (dd, $J$ = 13 Hz, $J$ = 11.8 Hz, 1 H, axial H at C5), 1.83 (dd, $J$ = 13 Hz, $J$ = 4.7 Hz, 1 H, equatorial H at C5), 3.15, 3.42 (d, $J$ = 11.8 Hz, 2 H, $CH_2OD$), 3.27 (d, $J$ = 9.8 Hz, 1 H, C3), 3.91 (ddd, $J$ = 9.8 Hz, $J$ = 11.8 Hz, $J$ = 4.7 Hz, 1 H, C4); $^{13}C$ NMR (50 MHz, $D_2O$) δ 27.14, 31.11 ($CH_3$), 43.66 (C5), 64.21, 65.82, 72.06, 75.08 (C1, 3, 4, 6), 98.92 (C2). Anal. Calcd for $C_8H_{16}O_5$: C, 50.04; H, 8.4. Found: C, 50.2; H, 8.4.

**Ethyl 4-Pentenoate (17).** To a solution containing 4-pentenoic acid (20.73 g, 207 mmol) in ethanol (100 mL) and benzene (200 mL) was added $H_2SO_4$ (250 μL). The solution was refluxed and monitored by GC (50 °C, 1 min to 250 °C at 10 °C/min; DB-5; $t_R$ of acid 4.4 min, ester 3.8 min). After 15 h, the reaction was complete; about $^1/_2$ of the solvent was removed under reduced pressure and diluted with 150 mL ether. This was extracted with $H_2O$ (1 × 150 mL), saturated $NaHCO_3$ (2 × 150 mL), $H_2O$ (1 × 150 mL), and brine (1 × 100 mL). The organic layer was dried over $K_2CO_3$, the solvent was removed under water aspirator vacuum, and the residue was distilled to yield **17** (20.79 g, 162 mmol, 78%; $bp_{760}$ 144 °C): $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.25 (t, $J$ = 7.2 Hz, 3 H, $CH_3$), 2.36 (m, 4 H, $CH_2CH_2$), 4.14 (q, $J$ = 7.2 Hz, 2 H, $OCH_2$), 4.95–5.13 (m, 2 H, $H_2C$=), 5.81 (m 1 H, =CH); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 14.2 ($CH_3$), 28.6, 33.5 ($CH_2CH_2$), 115.3 ($H_2C$=), 136.5 (=CH), 172.8 (C=O).

**D,L-Ethyl 2-(Diethoxymethyl)-4-pentenoate (18).** To 575 mL of a chilled (−78 °C) THF/hexane (500 mL of THF/75 mL of hexane) of lithium diisopropylamide (LDA, 112.5 mmol, obtained commercially as 75 mL of 1.5 M LDA in hexane) was slowly added **17** (12.86 g, 100 mmol) in 20 mL of THF. After the addition was complete, ethyl formate (9.1 mL, 112 mmol) was added via a syringe. The reaction mixture was allowed to warm to room temperature and quenched with 15 mL of ethanol. The solution was poured into a large beaker containing ice-cold 2 N $H_2SO_4$ (500 mL) and ether (500 mL). The contents were transferred to a 2-L separatory funnel, shaken, and separated. The ether layer was subsequently washed with 2 N $H_2SO_4$ (1 × 500 mL), $H_2O$ (1 × 500 mL), and brine (1 × 250 mL). The ether layer was dried over $Na_2SO_4$, and the solvent was removed under water aspirator vacuum to yield 40.2 g of a crude product, which was dissolved in 1 L of ethanol containing $CH_3SO_2OH$ (0.5 mL) and warmed to 50 °C for 15 h. The reaction was monitored by GC (same

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condition as for **17**, $t_R$ of intermediate 6.6 min, of **18** 11.2 min). After the reaction was complete, most of the ethanol was removed under reduced pressure and the residue was diluted with a mixture of 250 mL of $H_2O$ and 500 mL of ether. The ether layer was washed with saturated $NaHCO_3$ (2 × 250 mL), water (1 × 250 mL), and brine (1 × 250 mL). The ether layer was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The residue was distilled to yield **18** (13.98 g, 60.7 mmol, 61%): $bp_{2.5}$ 81-84 °C; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.15, 1.22, 1.25 (3 t, $J$ = 7.0-7.4 Hz, 9 H, $CH_3$), 2.30-2.45 (m, 2 H, $CH_2C{=}C$), 2.78 (dt, 1 H, CHC=O), 3.45-3.80 (m, 4 H, $OCH_2$), 4.15 (q, $J$ = 7.4 Hz, 2 H, $OCH_2$), 4.65 (d, 1 H, CH), 4.9-5.15 (m, 2 H, $H_2C{=}$), 5.75 (m, 1 H, =CH); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 14.42, 15.29, 15.36 ($CH_3$), 32.84 ($CH_2$), 49.98 (CH) 60.44, 61.71, 62.74 ($CH_2O$), 102.96 (CH), 116.81 ($=CH_2$), 135.05 (=CH), 172.60 (C=O).

**D,L-2-(Hydroxymethyl)-4-pentenal Diethyl Acetal (19).** To a cold (0-5 °C) suspension of $LiAlH_4$ (12.25 g, 61 mmol) in 500 mL of ether was added dropwise **18** (13.98 g, 61 nmol) in 50 mL of ether. During the addition the temperature did not exceed 5 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature. GC analysis indicated the reaction was complete (same conditions as for **17**, $t_R$ of **19** 9.6 min). Brine was added to quench the reaction. The ether was washed with $H_2O$ (1 × 500 mL), 2 N $H_2SO_4$ (1 × 500 mL), saturated $NaHCO_3$ (1 × 500 mL), and brine (1 × 500 mL). The ether layer was dried over $Na_2SO_4$, and the solvent was removed under water aspirator vacuum to yield **19** (12.89 g, quantitative yield). This was used without further purification: $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.23, 1.24 (2 t, $J$ = 7.0 Hz, 6 H, $CH_3$), 1.85-2.33 (m, 3 H, $HCCH_2C{=}C$), 2.90 (br s, 1 H, OH), 3.45-3.89 (m, 6 H, $CH_2O$), 4.47 (d, $J$ = 5.4 Hz, 1 H, CH), 5.00-5.13 (m, 2 H, $H_2C{=}$), 5.70-5.91 (m, 1 H, =CH); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 15.25, 15.32 ($CH_3$), 31.55 ($CH_2$), 43.19 (CH), 62.19, 62.37, 64.00 ($CH_2O$), 106.02 (CH), 116.54 ($C{=}CH_2$), 136.20 (=CH). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.82; H, 10.71. Found: C, 63.50; H, 10.51.

**5-Allyl-5-deoxy-L-*xylo*-hexulose (16).** A solution containing **19** (0.75 g, 4 mmol), water (8 mL), DMSO (2 mL), and $CH_3SO_2OH$ (100 μL) was stirred for 15 h at room temperature. The reaction was monitored by GC (same as **17**, $t_R$ of **19** 9.5 min, **15** 5.1 min). FDP-$Na_3$ (0.560 g, 1.2 mmol) was added along with 5 mL of 20% DMSO in $H_2O$. The solution was adjusted to pH 6.8. Aldolase (350 units) and TPI (500 units) were added. The reaction was stopped after 48 h. The solution was extracted with ether (1 × 15 mL), and the aqueous layer was treated as before to remove the phosphate group. TLC (silica gel, ethyl acetate-methanol-$H_2O$, 12:6:2, $R_f$ of the product 0.80) indicated no fructose ($R_f$ 0.45). The solution was neutralized and freeze-dried. Trituration with ethanol, followed by removing solvent under reduced pressure, yielded a clean sample of **16**. Further purification was done (silica gel 20:4:1 ethyl acetate-methanol-water) to yield **16** (210 mg, 1.0 mmol, 50%). Residue was crystallized from $CH_2Cl_2$-ether: mp 112-3 °C; $[\alpha]^{26}_D$ -46.5° (*c* 0.37, water); $^1H$ NMR (200 MHz, $D_2O$) δ 1.56 (m, 1 H, CH), 1.74 (m, 1 H, C=CCH), 2.19 (m, 1 H, C=CCH), 3.20-3.90 (m, 6 H, CHOD), 4.87 (m, 2 H, $=CH_2$), 5.66 (m, 1 H, =CH); $^{13}C$ NMR (50 MHz, $D_2O$) δ 31.68 (C5), 41.63 (C7), 62.53, 63.69, 71.80, 71.99 (CHOD), 98.11 (C2), 116.81 ($=CH_2$), 135.70 (=CH). Anal. Calcd for $C_9H_{16}O_5$: C, 52.91; H, 7.92. Found: C, 52.82; H, 7.71. For X-ray structure, see Figure 1.

# Vinylation-Electrophilic Cyclization of Aldopentoses: Easy and Stereoselective Access to *C*-Glycopyranosides of Rare Sugars

Anna Boschetti, Francesco Nicotra,* Luigi Panza, and Giovanni Russo

*Dipartimento di Chimica Organica e Industriale dell'Università and Centro di Studio per le Sostanze Organiche Naturali del CNR Via Venezian 21, 20133 Milano, Italy*

*Received February 16, 1988*

A new C-glycosylation procedure, which involves vinylation of a properly protected aldopentose and mercuriocyclization of the obtained glycoenitol, is described; it allows *C*-glycopyranosides of rare sugars to be obtained from easily available pentoses. 2,3,5-Tri-*O*-benzyl-D-arabinose (**1a**) reacted with vinylmagnesium bromide to afford a mixture of D-gluco and D-manno 1,2-dideoxy-4,5,7-tri-*O*-benzyl-1-heptenitols **2a** and **2b** and with divinylzinc to afford only **2a**. 2,3,5-Tri-*O*-benzyl-D-ribose (**1b**) afforded mainly 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*altro*-1-heptenitol (**2c**) with both vinylmetallic reagents, whereas 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribose (**1e**) afforded 1,2-dideoxy-7-*O*-trityl-4,5-*O*-isopropylidene-D-*allo*-1-heptenitol (**2h**). Vinylation of 2,3,5-tri-*O*-benzyl-D-xylose (**1c**) afforded a mixture of D-iodo and D-gulo 1,2-dideoxy-4,5,7-tri-*O*-benzyl-1-heptenitols **2d** and **2e**, the first one being largely predominant when divinylzinc was employed. 2,3,5-Tri-*O*-benzyl-D-lyxose (**1d**) reacted only with vinylmagnesium bromide to afford a mixture of D-talo and D-galacto 1,2-dideoxy-4,5,7-tri-*O*-benzyl-1-heptenitols **2f** and **2g**. The enitols **2a-h** where cyclized with mercuric acetate and then processed with potassium chloride to afford the corresponding (D-glycopyranosylmethyl)mercurium chlorides **3a-h**. The cyclization was stereoselective except for **2e**, and in all cases, except **3d**, the anomeric substituent of the *C*-glycopyranoside was cis related with the alkoxy substituent at the adjacent carbon atom. So α-gluco, α-manno, β-altro, β-ido, α- and β-gulo, β-talo, α-galacto, and α-allo *C*-glycopyranosides were obtained.

The synthesis of *C*-glycosyl compounds has become an area of increasing interest as these compounds are useful chiral syntons[1] and potential inhibitors of metabolic processes.[2]

The C-glycosylation procedures reported until now generally involve the attack of a carbon nucleophile at the anomeric center of the parent sugar[3] or, more recently, the reaction of a glycosyl radical[4] or a glycosyl carbanion[5] with

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