Multicarbon Chain Extension of Sugars through Acetylenic Intermediates. A Hexadecitol

R. B. ROY[1] AND W. S. CHILTON*

Department of Chemistry, University of Washington, Seattle, Washington 98105

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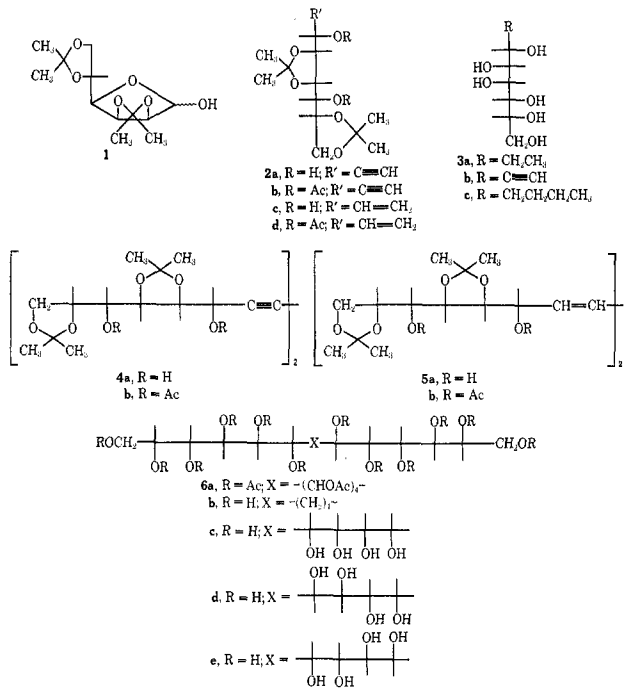
Extension of the carbon chain of sugars is classically carried out one carbon at a time by either the hydrogen cyanide[2] or nitromethane[3] addition route. Recent methods involve introduction of two carbons at a time leading to preparation of previously unknown octoses.[4] The ambitious attempt to prepare a decitol by Kolbe electrolysis of gluconic acid led, instead, to oxidative decarboxylation, a technique for shortening the chain.[5] Over a period of 20 years Fischer's group extended glucose to a nonose by repeated homologation with hydrogen cyanide. In a tour de force Philippe pushed the Fischer homologation on to a decose: "The preliminary treatment destined to transform 12 kg of glucose into seven-, eight-, and nine-carbon derivatives, including 260 g of nonose, required 4 l. of hydrogen cyanide, 300 kg of amalgam, and lasted 3 whole years."[6]

In the course of studying ORD of sugar derivatives,[7] we found the need for higher carbon sugars. We report an example of a preparative technique for obtaining quite long chain alditols while avoiding Philippe's logistic problems. The method involves initial two-carbon chain extension by addition of acetylene Grignard to a suitably protected mannose (**1**) followed by oxidative dimerization of the substituted acetylene (**2a** and **2b**) to yield a C_{16} diyne (**4a** and **4b**). Terminal acetylenes **2a** and **2b** are characterized by acetylenic CH ir absorption and by the presence of an acetylenic proton signal at τ 7.67 coupled to the propargylic hydrogen (J_{13} = 2 Hz). The C_{16} diynes do not show these two spectral characteristics but have the vibrational fine structure uv absorption typical of diynes.

The diyne was reduced to diene **5a** and to the saturated 1,2(*R*),3(*R*),4(*R*),5(*R*),6(*S*),11(*S*),12(*R*),13(*R*),14(*R*),15(*R*),16-dodecahydroxyhexadecane (**6b**.)[8] An attempt to synthesize the 7,8,9,10-tetradeoxyhexadecitol by addition of tetramethylene-1,4-dimagnesium bromide to di-*O*-isopropylidene mannose gave the tetradeoxydecitol **3c** (or its C-6 epimer) arising from hydrolysis of one organomagnesium group in the work-up. Epoxidation of diene **5b** followed by hydrolysis and acetylation yielded the extended acetylated alditol **6a** in 17% overall yield from mannose.

The stereochemistry of the product of addition of ethynylmagnesium bromide to di-*O*-isopropylidene mannose was assigned by reduction of **2a** and **2b** with lithium aluminum hydride to the octene derivative **2c**. Further catalytic reduction gave 7,8-dideoxy-L-*glycero*-D-*manno*-octitol **3a**. Direct addition of ethylmagnesium bromide to di-*O*-isopropylidene mannose gave epimeric 7,8-dideoxy-D-*glycero*-D-*manno*-octitol. Ozonolysis of **2d** followed by oxidative work-up and hydrolysis gave D-*glycero*-D-*galacto*-heptonolactone establishing the configuration at the newly created asymmetric center of **2a** and **2b** as 3(*S*).[10] This also permits assignment of 6(*S*) and 11(*S*) stereochemistry to the hexadecitol acetate **6a**. Stereochemistry at the four centers C-7 through C-10 is unknown and, in fact, the product is likely to be a mixture of several of the six possible diastereomers. That number would be reduced to three diastereomers if diene **5b** is the trans,-trans diene, as seems likely for the product of lithium aluminum hydride reduction of a propargyl alcohol,[11] and if the two epoxides open independently by the normal mechanism. Then C-7 and C-8 would have erythro configuration and C-9 and C-10 would also have erythro configuration. Consequently the hexadecitol could be any of the three diastereomers **6c**, **6d**, **6e**, or a mixture of them.



Experimental Section

Oxidative Dimerization.—Air was bubbled through a stirred mixture of 10.0 g of octyne **2b**[10] and 1 g of freshly prepared cuprous chloride in 10 ml of pyridine and 80 ml of methanol. After passing air through the solution for 3 hr at 30–35°, 100 ml of saturated ammonium chloride solution was added. The mixture was extracted with ether. The ether layer was extracted with dilute sodium carbonate and dried ($MgSO_4$). Ether was removed, and the residue was recrystallized from benzene–petroleum ether (bp 30–60°) to give 9.3 g (93%) of dyne **4b**: mp 147°; ir no acetylenic CH; nmr (CCl_4) τ 7.98 (12, s, $OCOCH_3$), 8.49 (6, s, CCH_3), 8.6–8.7 (18, CCH_3), no acetylenic CH.

Anal. Calcd for $C_{36}H_{50}O_{16}$: C, 58.53; H, 6.82. Found: C, 58.70; H, 6.65.

Reduction to Diene 5b.—A mixture of 9.0 g of diyne **4b** and 2.8 g of lithium aluminum hydride was heated at reflux overnight.

(1) Visiting Professor on leave from B. S. College, Dinapore, Magadh University, Bihar, India.
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Excess hydride was destroyed by treatment with a saturated ammonium chloride solution. Ether was removed and the residue was reacetylated with pyridine and acetic anhydride. The reaction mixture was diluted with water and extracted with ether. The ether was dried and removed. The residue was crystallized from benzene–petroleum ether yielding 5.8 g (85%) of the diene **5b**: mp 160°; nmr ($CDCl_3$) τ 4.7–4.9 (4, complex, vinyl), 7.90 (6, s, $OCOCH_3$), 7.93 (6, s, $OCOCH_3$), 8.50 (6, s, CCH_3), 8.64 (18, s, CCH_3).

Anal. Calcd for $C_{36}H_{54}O_{16}$: C, 58.21; H, 7.33. Found: C, 58.32; H, 7.27.

Hexadeca-*O*-acetylhexadecitol (6a).—A solution of 1.0 g of diene **5b** and 2.5 g of *m*-chlorobenzoic acid in 25 ml of chloroform was kept 2 days at 2°. Then 50 ml of 10% acetic acid was added and the solution was warmed for 0.5 hr. The cooled solution was extracted with ether. Evaporation of water from the aqueous layer gave crude hexadecitol which was acetylated in 30 ml of pyridine and 15 ml of acetic anhydride. The acetylation product was extracted into ether and crystallized from benzene–petroleum ether to give 0.5 g (32%) of hexadeca-*O*-acetylhexadecitol **6a**: mp 110–112°; $[\alpha]^{23}_{589}$ +2.8 ± 1°, $[\alpha]^{23}_{320}$ 15.7° (*c* 0.6, MeOH); nmr ($CDCl_3$) τ 7.9 (unresolved $OCOCH_3$).

Anal. Calcd for $C_{48}H_{66}O_{32}$: C, 49.91; H, 5.71. Found: C, 49.73; H, 5.52.

7,8,9,10-Tetradeoxy-D-*erythro*-L-*gluco*-D-*manno*-hexadecitol (6b).—Catalytic hydrogenation of 450 mg of diene **5a** in ethanol over palladium on charcoal followed by removal of catalyst and solvent gave tetradeoxytetra-*O*-isopropylidenehexadecitol which was recrystallized from benzene–petroleum ether: mp 137–138°; nmr (CCl_4) τ 8.5–8.7 (unresolved CCH_3); *m/e* 561 (M − 17). A mixture of 300 mg of tetradeoxytetra-*O*-isopropylidenehexadecitol and 10 ml of 10% acetic acid was warmed for 15 min until solution was obtained. The cooled solution was extracted with ether, and the aqueous layer was concentrated to yield 230 mg of tetradeoxyhexadecitol **6b**. The tetradeoxyhexadecitol was recrystallized from ethanol: mp 160–163°; $[\alpha]^{25}_{589}$ 11° (*c* 1, water); R_f 0.80 (water–isopropyl alcohol 1:4).

Anal. Calcd for $C_{16}H_{34}O_{12}$: C, 45.93; H, 8.19. Found: C, 45.74; H, 7.95.

7,8,9,10-Tetradeoxydecitol (3c or C-6 Epimer).—A solution of 6.0 g of di-*O*-isopropylidene mannose in 50 ml of ether and 150 ml of 1 *M* tetramethylenedimagnesium bromide in ether (Peninsular ChemResearch) was heated at reflux overnight. The cooled solution was extracted with saturated ammonium chloride solution. The ether layer was dried ($MgSO_4$) and condensed. The 8-g residue was eluted from alumina to give a colorless syrup. The syrup (1.5 g) was hydrolyzed by heating with 50 ml of 10% acetic acid for 40 min. The cooled solution was extracted with ether and the aqueous layer was evaporated. The residue was crystallized from ethanol giving 1.0 g of tetradeoxydecitol: mp 218–220°; $[\alpha]^{23}_{589}$ −2°, $[\alpha]^{23}_{300}$ −11° (*c* 0.6, water); nmr (D_2O) τ 8.6–8.9 (6 complex, CH_2), *ca.* 9.1 (3, virtually coupled CH_3).

Anal. Calcd for $C_{10}H_{22}O_6$: C, 50.80; H, 9.34. Found: C, 50.42; H, 9.24.

1-Octyne-D-*glycero*-D-*galacto*-3,4,5,6,7,8-hexol (3b).—A solution of 800 mg of the octyne derivative **2a** in 30 ml of acetic acid was warmed until a clear solution was obtained. The cooled solution was extracted with ether and the aqueous layer was concentrated. The white residue was crystallized from ethanol to give 450 mg of octynitol **3b**: mp 175°; $[\alpha]^{23}_{589}$ 0°, $[\alpha]^{23}_{250}$ −31° (*c* 0.3, water); R_f 0.47 (water–isopropyl alcohol 1:4); nmr (D_2O) τ 6.0–6.2 (complex, CHOH), 7.00 (1, m, propargyl H), 7.68 (1, broad, acetylenic H).

Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.79. Found: C, 46.49; H, 6.79.

7,8-Dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol.—A solution of 150 ml of 2 *M* ethylmagnesium bromide in ether (Peninsular ChemResearch) and 8.0 g of di-*O*-isopropylidene mannose in 100 ml of ether was heated at reflux 12 hr. The cooled solution was extracted with saturated ammonium chloride solution. The ether layer was dried, and the ether was removed. The residue was crystallized from benzene–petroleum ether giving 3.5 g (40%) of dideoxydiisopropylideneoctitol: mp 78°; $[\alpha]^{23}_{589}$ −17.7°, $[\alpha]^{23}_{300}$ −87° (*c* 3, methanol).

Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.89; H, 9.02. Found: C, 57.83; H, 8.83.

7,8-Dideoxy-D-*glycero*-D-*manno*-octitol.—A mixture of 1.8 g of 7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol and 45 ml of 10% acetic acid was heated until solution occurred. Removal of water and crystallization of the residue from ethanol gave 1.2 g (92%) of dideoxyoctitol: mp 215°; $[\alpha]^{23}_{589}$ −4.7° (*c* 1.3, water); R_f 0.60 (water–isopropyl alcohol 1:4); tri-*O*-isopropylidene derivative mp 71°.

Anal. Calcd for $C_8H_{18}O_6$: C, 45.71; H, 8.63. Found: C, 45.86; H, 8.33.

7,8-Dideoxy-L-*glycero*-D-*manno*-octitol (3a).—Catalytic hydrogenation of 1.0 g of octene **2c** in 50 ml of ethanol over palladium on charcoal followed by concentration of the solution gave 7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene octitol, mp 75–78°. Hydrolysis of this compound in aqueous acetic acid gave crystalline 7,8-dideoxyoctitol: mp 158–159°; $[\alpha]^{23}_{589}$ 0°, $[\alpha]^{23}_{300}$ 11.6° (*c* 0.7, water); R_f 0.65 (water–isopropyl alcohol 1:4).

Anal. Calcd for $C_8H_{18}O_6$: C, 45.92; H, 8.63. Found: C, 45.92; H, 8.27.

Registry No.—**3a**, 31129-32-5; **3b**, 31119-93-4; **3c**, 31119-94-5; **3c** C-6 epimer, 31119-95-6; **4b**, 31081-95-5; **5b**, 31081-96-6; **6a**, 31119-96-7; **6b**, 31119-97-8; 7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol, 31119-98-9; 7,8-dideoxy-D-*glycero*-D-*manno*-octitol, 31119-99-0.

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The Action of Triphenylphosphine Dibromide on Cholest-5-ene-3β,4β-diol, an Unexpected Vilsmeier Reaction

THOR DAHL AND ROBERT STEVENSON*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02154

N. S. BHACCA

Department of Chemistry, Louisiana State University, Louisiana 70803

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Since the introduction by Horner and his colleagues[1] of triphenylphosphine dihalides for the preparation of alkyl and aryl halides from alcohols and phenols, these reagents have been finding increasing use as reagents in organic synthesis. Wiley and coworkers[2] have emphasized advantages of these reagents over phosphorus pentahalides, particularly with alcohols which are readily dehydrated or undergo rearrangement, and have discussed a mechanism.[3] The action of triphenylphosphine dibromide on a variety of steroids,[4] triterpenoids,[5] and norbornanols[6] has also been investigated and the stereochemical consequences of conversion of optically active alcohols to halides have been outlined.[1-7] The phosphine dihalides have also been used to prepare acid halides from carboxylic acids[1,8] and anhydrides,[8]

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