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Preliminary communication

Stereoselective total synthesis of 6-deoxy-L-hexose derivatives from L-alanine without a resolution step

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For the total synthesis of optically active monosaccharides and related compounds starting from non-carbohydrate precursors, resolution is usually required at some stage of the synthetic route[1]. By choice of a suitable, optically active, starting material, however, an optically active product can be obtained without resolution, as in the stereoselective synthesis of various D-pentoses from L-glutamic acid[2]. The present paper describes a new stereoselective synthesis of 6-deoxy-L-hexose derivatives from L-alanine.

Nitrous acid deamination of L-alanine (**1**) in acetic acid afforded 2-acetoxypropionic acid (**2**) in 47% yield, $[\alpha]_D^{22}$ −47.3° (chloroform), with 96% retention of configuration[3,4]. Treatment of **2** with thionyl chloride gave 2-acetoxypropionyl chloride (**3**) in 83.5% yield. Treatment of **3** with the Grignard reagent (**4**) obtained from propiolaldehyde dimethyl acetal and ethylmagnesium bromide, in the presence of cuprous chloride, afforded the acetylene **5**, b.p. 115–125°/4 torr, $[\alpha]_D^{20}$ −19.5° (chloroform), in 67% yield. Partial hydrogenation of **5** in ethyl acetate with 5% palladium on barium sulfate in the presence of quinoline afforded a good yield of the *cis*-alkene **6**, b.p. 117–119°/4 torr, $[\alpha]_D^{20}$ −30.0° (chloroform) n.m.r. (carbon tetrachloride) $J_{1,2}$ 7 Hz, $J_{2,3}$ 12 Hz. Treatment of **6** with an equimolar amount of sodium hydroxide in aqueous 1,4-dioxane for 1 min gave the deacetylated product **7**, which was heated in carbon tetrachloride in the presence of phosphoric acid to afford methyl 2,3,6-trideoxy-α-L- and β-L-hex-2-enopyranosid-4-uloses (**8** and **9**) of b.p. 78–85°/14 torr in about 60% yield from **5**. The n.m.r. spectra of racemic **8** and **9** have already been reported[6], and the anomeric mixture obtained in the present synthesis was found to be composed of **8** and **9** in the ratio of about 2:1, based on n.m.r. analysis. Resolution of this mixture by column chromatography on silica gel with 20:1 petroleum ether–ethyl acetate followed by recrystallization from hexane afforded the optically pure α-anomer (**8**) as colorless needles, m.p. 50–52°, $[\alpha]_D^{24}$ −16.6° (chloroform), in 30% yield from **5**.

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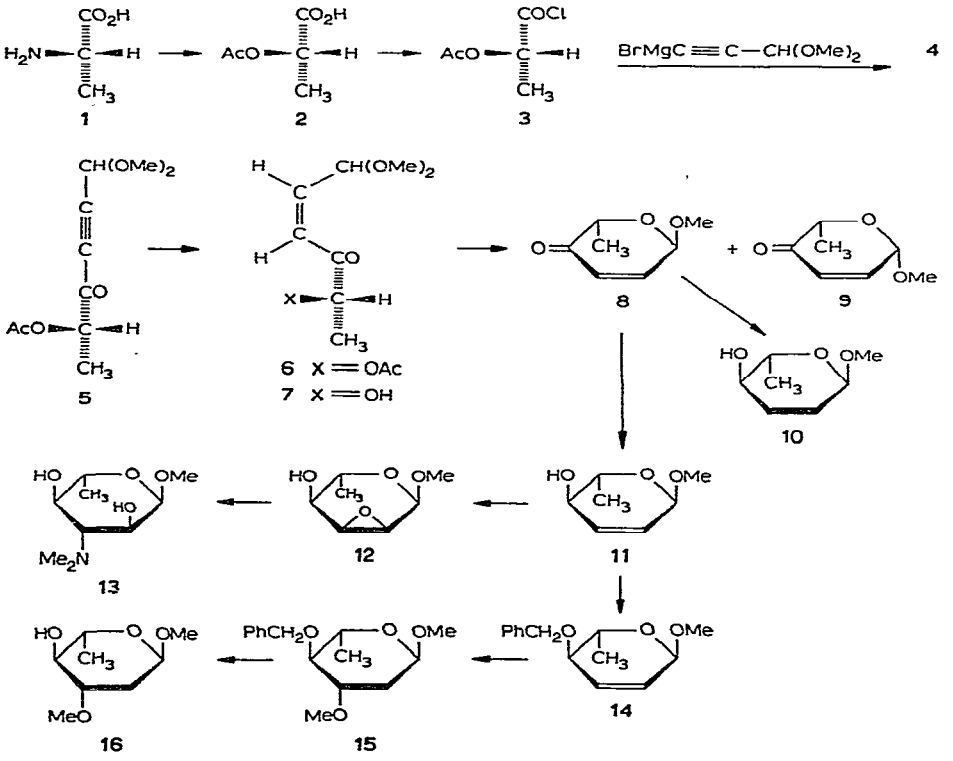

Catalytic hydrogenation of **8** in methanol with 10% palladium-on-charcoal, followed by reduction[6] of the product with lithium aluminum hydride afforded a syrup that was chromatographed on silica gel with 2:3 petroleum ether–ethyl acetate to give methyl α-L-amicetoside (**10**) as a colorless liquid b.p. 110° (bath)/10 torr, $[\alpha]_D^{20}$ −147° (water) [lit.[7] $[\alpha]_D^{20}$ + 142 ±1° (water) for the D-enantiomorph], in 57% yield. Compound **10** was further characterized as its 3,5-dinitrobenzoate, m.p. 97.5–99.5°, $[\alpha]_D^{22}$ −134° (chloroform) [lit.[7] m.p. 100–101°, $[\alpha]_D^{20}$ + 134 ±1° (chloroform) for the D-enantiomorph]. Reduction of **8** with lithium aluminum hydride in ether afforded an unsaturated alcohol **11** as a liquid, $[\alpha]_D^{24}$ −103° (chloroform) [lit.[8] $[\alpha]_D$ −94° (chloroform)], in 74% yield. Benzoylation of **11** gave the corresponding 4-benzoate as colorless needles, m.p. 56–57°, $[\alpha]_D^{20}$ −219° (chloroform) [lit. m.p.[8] 53–54.5°, m.p.[9] 43–45°, $[\alpha]_D$ −225° (ref. 8) $[\alpha]_D^{23}$ −215° (chloroform)]. The conversion of racemic **11** into methyl α-DL-mycaminoside[10] and methyl α-DL-oleandroside[11] has already been reported. The reaction of **11** with *m*-chloroperoxybenzoic acid in benzene afforded the epoxide **12**, m.p. 98–99.5°, $[\alpha]_D$ −165° (chloroform), in 77% yield. Treatment of **12** with saturated aqueous dimethylamine for 8 h at 80° afforded methyl α-L-mycaminoside (**13**), m.p. 83.5–86°, $[\alpha]_D^{22}$ −125° (water) [lit.[12] m.p. 81–82°, $[\alpha]_D$ +123° (water) for the D-enantiomorph], in 67% yield. N.m.r. spectral data for **12** and **13** agreed well with those reported for the corresponding racemates[10]. Treatment of **11** with benzyl chloride in the presence of sodium

hydroxide gave the benzyl ether **14**, $[\alpha]_D^{22}$ −170° (chloroform) [lit.[13] $[\alpha]_D^{23}$ −168° (chloroform)], in 80% yield. Heating **14** in methanol in the presence of *p*-toluenesulfonic acid, followed by separation of the adducts by preparative t.l.c. (silica gel, 20:3 hexane–ethyl acetate), afforded **15** as a syrup $[\alpha]_D^{23}$ −100° (chloroform), in 49% yield. Hydrogenolysis of **15** in the presence of palladium on charcoal gave methyl α-L-oleandroside (**16**) as a syrup, $[\alpha]_D^{24}$ −105° (chloroform), in 71% yield. The n.m.r. spectrum of **16** was in good agreement with that reported for the corresponding racemate[11]. Compound **16** was further characterized as its 3,5-dinitrobenzoate, m.p. 122–123°, $[\alpha]_D^{20}$ −63.5° (chloroform).

The foregoing results show that optically active enones (**8** and **9**) are readily accessible and serve as potential intermediates for the synthesis of various kinds of optically active 6-deoxyhexose derivatives that are abundant in Nature[14] especially as component sugars of antibiotics[15].

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