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# NEW ROUTE TO BRANCHED-CHAIN AMINO SUGARS BY APPLICATION OF MODIFIED WITTIG REACTION TO KETOSES

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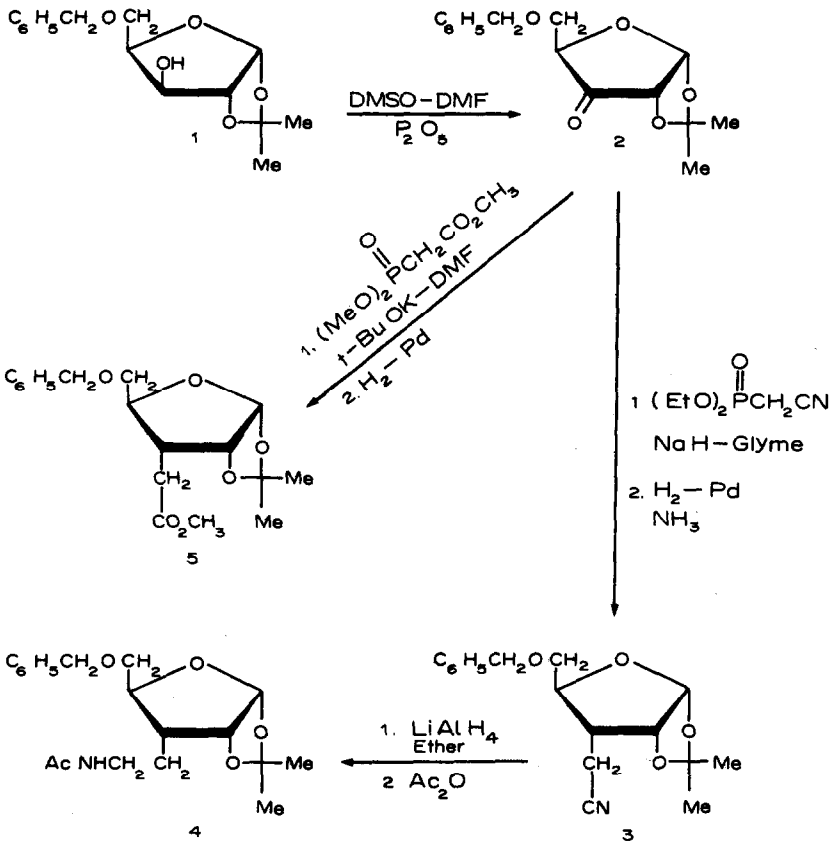
Interest in the general chemistry of the amino sugars (1,2) stems partly from the fact that the amino sugars occur as components of many antibiotics (3-5). An account of the methods of synthesis of amino sugars has already been given (1-3). In addition, the nitromethane method (6) of introducing an amino group into sugars has recently been extended by using nitroethane to afford a new class of branched-chain amino-deoxyhexosides (7).

In this communication we wish to present a new approach to the synthesis of branched-chain amino sugars, namely, the application of a modified Wittig reaction (8) to carbohydrate ketoses to afford in excellent yield novel branched-chain unsaturated carbohydrates containing a nitrile group. The latter compounds are readily reduced to yield branched-chain amino sugars having a terminal primary amino function.

The following is an example of the procedure used at present. An amount of 2.8 g of 5-O-benzyl-1,2-O-isopropylidene-α-D-erythro-pentafuranos-3-ulose 2 (9) was added slowly to a filtered solution of the carbanion from 2.7 g (0.015 M) of diethyl cyanomethylphosphonate and 0.36 g (0.015 M) of sodium hydride in 15 ml of anhydrous 1,2-dimethoxyethane (glyme). The reaction was performed at room temperature in a dry box under a nitrogen atmosphere. After 4 h the reaction mixture was removed from the dry box, diluted with 75 ml water, and extracted thrice with 3 portions of 70 ml of ether. The combined ether extracts were washed twice with 10 ml water and dried over magnesium sulfate. After the ether was removed by evaporation under reduced pressure, the residue (3.0 g) was redissolved in benzene and then decolorized by passage through a column (4.5 x 1.5 cm diam.) of charcoal. An amount of 0.5 g of the purified residue (after evaporation of benzene) was dissolved in a solution of 25 ml ethanol and 25 ml of 15 N ammonium hydroxide and hydrogenated in the presence of 0.25 g of 10% palladium on charcoal for 1 h. The reaction was stopped when 1 mole of gas was absorbed. After the catalyst was removed and the solvent evaporated, 0.5 g of substance 3 (contaminated with traces of three other substances) remained. Careful surveillance of reaction conditions of both the Wittig reaction and the reduction step are


DMSO-DMF
P2O5
1. (MeO)2PCH2CO2CH3
t-BuOK-DMF
2. H2-Pd
1 (EtO)2PCH2CN
NaH-Glyme
2. H2-Pd
NH3
1. LiAlH4
Ether
2 Ac2O
Me
OH
CH2
CO2CH3
CN
NHCH2
Ac
1
2
3
4
5

essential to minimize side reactions, particularly in the reduction stage. Preparative thin layer chromatography (tlc) of part of this product on silica gel G using benzene-methanol (95:5) as developer gave pure 3 in 93% yield. Compound 3 did not crystallize; $[\alpha]_D^{22}$ +60° (c 2, chloroform). [Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.95; N, 4.62. Found: C, 67.45; H, 7.20; N, 4.78]. The 60 MHz, nuclear magnetic resonance spectrum of compound 3 shows the following proton signals: $\tau^{CDCl_3}$ 4.2 (doublet, assigned to H-1, $J_{1,2}$ = 3.6 Hz); 5.34 (triplet, assigned to H-2, $J_{2,3}$ = 3.9 Hz); 5.48 (two proton singlet, assigned to $\underline{CH_2}Ph$), 6.1 (one proton multiplet), 6.35 (two proton doublet), 7.55 (3 proton multiplet, assigned to H-3 and to the two protons on C-1').

The configuration of C-3 of compound 3 was deduced from the following facts. In 1,2-isopropylidene-α-D-xylofuranose there is no coupling between H-2 and H-3, thus leading to a doublet for H-2. In the spectrum of compound 3, the H-2 signal is a triplet showing that H-2 is also coupled to H-3; therefore, the only possible configuration for C-3 is the ribo configuration. Therefore, compound 3 is undoubtedly 3-C-(acetonitrile)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose. Substance 3 was reduced with lithium aluminum hydride in ether, followed by acetylation in acetic anhydride in the presence of methanol to afford 5-O-benzyl-3-deoxy-3-C-(ethyleneacetamide)-1,2-O-isopropylidene-α-D-ribofuranose 4. Compound 4 was purified by tlc on alumina; $\tau^{CDCl_3}$ 4.2 (doublet, assigned to H-1); 4-4.4 (broad signal assigned to NH), 8.1 (3 proton singlet assigned to $\underline{CH_3}\overset{O}{\overset{\|}{C}}\text{-N}$); $[\alpha]_D^{22}$ +39° (c 3, chloroform).

Alternatively, the amide 4 was prepared as follows. The ketose 2 was allowed to react with phosphonoacetic acid trimethyl ester according to a previous procedure (8) to give an unsaturated branched-chain sugar in about 80% yield. This sugar was then reduced over palladium on charcoal to give 5. The reaction muxt be stopped when one mole of gas per mole of sugar was absorbed to prevent hydrogenolysis of the benzyl group. The main product, namely, 5-O-benzyl-3-C-(carbomethoxymethyl)-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose 5, was readily separated from any debenzylated product by column chromatography on alumina using benzene-methanol (99:1) as developer; m.p. 38-39°, $[\alpha]_D^{22}$ +61° (c 2, chloroform). [Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.19]. $\tau^{CDCl_3}$ 4.19 (doublet, assigned to H-1, $J_{1,2}$ = 3.9 Hz), 5.24 (one proton triplet assigned to H-2 and having $J_{2,3}$ = 3.8 Hz). Treatment of the ester 5 with ammonia at 65° followed by lithium aluminum hydride reduction of the amide and acetylation of the amine also gave 4.

Studies of the application of the modified Wittig reaction to methyl 4,6-O-benzylidene-3-deoxy-α-D-erythro-hexopyranosid-2-ulose and to methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose to yield novel dideoxy-branched-chain amino sugars will be reported in a

future communication.

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9. Prepared by oxidizing 5-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose 1 (10) with methyl sulfoxide in the presence of N,N-dimethylformamide and phosphorus pentoxide (11). Compound 2 was a sirup, $[\alpha]_D^{22}$ + 140° (c 2, chloroform), and could not be distilled without decomposition. Its 2,4-dinitrophenylhydrazone derivative had a m.p. of 143-144°.

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