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Improved Synthesis of Methyl 4,6-O-Benzylidene-3-cyano-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside and Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-C-formyl-α-D-erythro-hex-2-enopyranoside

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IMPROVED SYNTHESIS OF METHYL 4,6-O-BENZYLIDENE-3-CYANO-2,3-DIDEOXY-α-D-ERYTHRO-HEX-2-ENOPYRANOSIDE AND METHYL 4,6-O-BENZYLIDENE-2,3-DIDEOXY-3-C-FORMYL-α-D-ERYTHRO-HEX-2-ENOPYRANOSIDE

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ABSTRACT. *Simple and efficient route to the title compounds by using diethyl aluminium cyanide in benzene for the epoxide ring opening and the electrophilic assistance of $LiClO_4$ during the isomerization-elimination process.*

Branched alkyl and amino sugars have been subject of considerable synthetic research over the past few years. Furthermore, cyclic α,β unsaturated carbonyl compounds and other types of dienophiles or Michael acceptors, bearing a sugar structure, appear to be unquestionable useful building blocks in organic synthesis.[1,2] There are particularly two reasons for their use: *a.*- they could be obtained in high enantiomeric purity and *b.*- the regio and stereocontrol they could exert on different chemical processes.

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A nitrile is a functional group with much potential and versatility for being transformed into carbonyl or amino species. On the other hand, the oxirane ring opening of a sugar anhydride has been a widely used route of introducing a nucleophile into a carbohydrate framework.

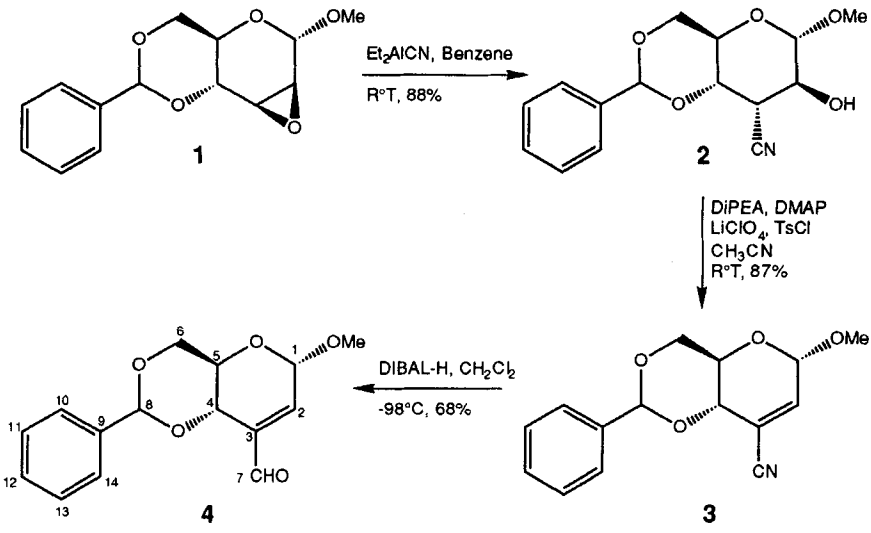
Hitherto, the methyl 2,3-anhydro-4,6-O-benzylidene-α-D-manno-pyranoside (**1**) has been an appealing starting material,[3] although has shown a very inconvenient reluctance to undergo a nucleophilic epoxide ring opening under mild conditions.[4]

Inch and Lewis[5] have studied the reactivity problems of this type of compounds with several Grignard and alkyl (or aryl) lithium reagents under different reaction conditions. Gero and Luckacs[6,7] also developed a procedure to introduce a 1,3 dithianyl residue, but required several reaction days at low temperature, imposing certain operative difficulties.

We have recently reexamined Guthrie's procedure[8] for the introduction of a cyano group into a sugar skeleton and found that treating the epoxide (**1**) with diethyl aluminium cyanide in anhydrous benzene or methylene chloride at room temperature overnight afforded the corresponding cyanohydrin (**2**) in high yield.

In order to obtained the cyano-olefin through an elimination reaction, the hydroxyl on C-2 and the hydrogen on C-3 should adopt an anti-periplanar configuration. Guthrie has observed that the isomerization of the carbon bearing the cyanide group could not be done under normal sulfonylating conditions and required the use of diethylamine or triethylamine at refluxing temperature.[8] Based on that, we decided to investigate the effect of lithium salt on this two steps process.

It is known that the neutral charged lithium perchlorate catalyzes different type of reactions as a result of its Lewis acid character. Lithium cation is responsible for this behavior (perchlorate anion has no effect) and may



Scheme

cause the activation of the nitrile group through a complexation mechanism. The interaction of the free lone pair on nitrogen with the cation enhances the electrophilic nature of this group.[9]

Lithium cation also plays a significant role on E_2 reactions with substrates having poor leaving groups. The accelerating effect produced by lithium perchlorate on this type of reactions may be conceived as an electrophilic assistance. It has been suggested that the oxygen atoms could be responsible for the affinity of the p-toluensulfonyl group to coordinate to small cations, turning it into a better leaving group.[9]

The confluence of these factors prompted us to use lithium perchlorate in conjunction with p-toluenesulfonyl chloride, N,N-diisopropylethylamine and dimethylaminopyridine in order to assist the isomerization-elimination process and make it be possible in one pot reaction.

Fortunately, our expectations became true and the cyano-olefin (**3**) was obtained in high yields from the cyanohydrin (**2**).

The conversion of the nitrile group into the aldehyde (**4**) was done with diisobutylaluminium hydride as the reductive agent and further hydrolisis with ammonium chloride saturated solution. We noticed the efficiency of this reaction was solvent-dependent. After extensive experimentation we found that when using THF or a mixture of ethyl ether-methylene chloride (the compound was not soluble in pure ethyl ether at low temperature) the reaction was not clean, longer reaction time and more equivalents of DIBAL-H were needed and afforded lower yields. However, when the reaction was run in pure methylene chloride with 1.3 equivalent of DIBAL-H at -98°C, it was almost instantaneous furnishing satisfactory yields.

EXPERIMENTAL SECTION

All melting points were taken on a Leitz Wetzlar Microscope Heating Stage Model 350 apparatus and are uncorrected. Infrared spectra were recorded on a Bruker IFS 25 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker AC-200 spectrometer with tetramethylsilane as internal standard and deuterochloroform as solvent. In ^1H NMR descriptions, s = singlet, d = doublet, t = triplet, m = multiplet, and dd = doublet of doublets.

All reactions were monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plates ($60F_{254}$) using UV light and and anisaldehyde-sulfuric acid as developing agent. Flash column chromatography using Merck silica gel 60H, was performed by gradient elution created by mixtures of petroleum ether and increasing amounts of ethyl acetate.

All reactions were carried out under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (1).

See reference 10

Methyl 4,6-O-benzylidene-3-cyano-3-deoxy-α-D-altropyranoside (2)

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside.(528 mg, 2 mmol) was azeotropically dried with benzene under vacuum and dissolved in dry benzene (4 ml) under argon atmosphere. Diethyl aluminium cyanide (1M solution in toluene, 4 ml, 4 mmol) was cautiously added at ambient temperature to the magnetically stirred solution. Stirring was continued during 16 hs at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (20 ml) and poured onto ice-sodium carbonate solution. The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 X 50 ml). The combined organic layers were subsequently washed with NH_4Cl saturated solution (20 ml) and brine (20 ml) and dried (Na_2SO_4). Concentration and purification by flash column chromatography furnished pure **2** (513 mg, 88%) as a white crystalline solid. **2**: mp. = 149.0-150.5°C (benzene-petroleum ether) (Lit[8]: 150-150.5°C); IR (KBr) ν_{max} : 3538, 2938, 2858, 2248 (CN), 1458, 1406, 1216, 1130, 1108, 1044, 956, 760 cm^{-1}; ^{1}H NMR (200 MHz) δ : 7.49 (m, 2H, aromatics), 7.38 (m, 3H, aromatics), 5,59 (s, 1H, benzylic), 4.62 (s, 1H, anomeric), 4.31 (dd, J = 10.0, 4.4 Hz, 1H, CH_2O), 4.13 (m, 3H, CHO), 3.81 (t, J = 9.6 Hz, 1H, CHO), 3.44 (s, 3H, OCH_3), 3.29 (m, 1H, CHCN); ^{13}C NMR (50 MHz) δ : 136.5 (C-9), 129.3 (C-12), 128.3 (2 C-

aromatics), 126.2 (2 C-aromatics), 116.1 (CN), 102.2 (C-8), 100.1 (C-1), 71.5 (C-4), 68.7 (C-6), 68.3 (C-2), 61.0 (C-5), 55.1 (OCH_3), 34.4 (C-3).

Methyl 4,6-O-benzylidene-3-cyano-2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside (3).

Methyl 4,6-O-benzylidene-3-cyano-3-deoxy-α-D-altropyranoside (222 mg, 0.77 mmol) was azeotropically dried with dry benzene under vacuum, dissolved in anhydrous acetonitrile (7.7 ml) and cooled at 0°C under argon atmosphere. N,N-Diisopropylethylamine (0.65 ml, 3.8 mmol), 4-dimethyl-aminopyridine (18 mg, 0.15 mmol), lithium perchlorate (815 mg, 7.7 mmol) and p-toluenesulfonyl chloride (292 mg, 1.54 mmol) were successively added to the stirred solution at 0°C. The cooling bath was then removed and stirring was continued overnight. The reaction mixture was diluted with ethyl ether (50 ml) and poured onto ice-HCl 0.1M solution (10 ml). The aqueous phase was separated and extracted with ethyl ether (3 X 20 ml). The combined organic layers were subsequently washed with Na_2CO_3 10% solution (20 ml) and brine (20 ml) , dried (Na_2SO_4) and concentrated. The crude was purified by flash column chromatography and afforded pure **3** (182 mg, 87%) as a white crystalline solid. **3**: mp.= 214.0-215.0°C (benzene-petroleum ether) (Lit[8]: 214.5-215.5°C); IR (KBr) ν_{max} : 2982, 2918, 2227 (CN), 1453, 1388, 1362, 1186, 1121, 1087, 1058, 988, 763, 697 cm^{-1}; ^1H NMR (200 MHz) δ : 7.53 (m, 2H, aromatics), 7.40 (m, 3H, aromatics), 6.52 (t, J = 2.5 Hz, 1H, vinylic), 5.62(s, 1H, benzylic), 5.00 (dd, J = 2.4, 1.5 Hz, 1H, anomeric), 4.33 (dd, J = 9.2, 3.4 Hz, 1H, CH_2O), 4.18 (m, 1H, CHO), 3.85 (m, 2H, CHO), 3.47 (s, 3H, OCH_3); ^{13}C NMR (50 MHz) δ : 140.6 (C-2), 136.3 (C-9), 129.1 (C-12), 128.1 (2C-aromatics), 126.0 (2C-aromatics), 117.0 (CN), 113.7 (C-3), 101.9 (C-8), 94.7 (C-1), 72.8 (C-4), 68.4 (C-6), 63.6 (C-5), 56.4 (OCH_3).

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-C-formyl-α-D-erythro-hex-2-enopyranoside (4).

Methyl 4,6-O-benzylidene-3-cyano-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (122 mg, 0.44 mmol) was azeotropically dried with dry benzene under vacuum, dissolved in anhydrous CH_2Cl_2 (9 ml) and cooled at -98°C (methanol-liquid nitrogen) under argon atmosphere. Diisobutylaluminium hydride (1M solution in toluene, 0.53 ml, 0.53 mmol) was slowly added to the stirred solution. The reaction mixture was kept at the same temperature during 15 minutes and then quenched with NH_4Cl saturated solution (5 ml) and H_2O (10 ml). Stirring was continued during 30 minutes while the temperature raised to 0°C. The mixture was extracted with CH_2Cl_2 (3 X 20 ml), washed with brine, dried (Na_2SO_4) and concentrated. The crude was purified by flash column chromatography and yielded pure **4** (82 mg, 68%) as a white crystalline solid. **4** : mp.= 156.0-158.0°C (Lit[7]: 155-158°C); IR (KBr) ν_{max} : 2976, 2890, 1690 (carbonyl), 1452, 1388, 1318, 1122, 1084, 964, 756 cm^{-1}; ^1H NMR (200 MHz) δ : 9.67 (s, 1H, carbonyl), 7.50 (m, 2H, aromatics), 7.37 (m, 3H, aromatics), 6.59 (t, $J_{1,2} = J_{2,4} = 2.5$ Hz, 1H, vinylic), 5.69 (s, 1H, benzylic), 5.09 (dd, J = 2.5, 1.3 Hz, 1H, anomeric), 4.50 (m, 1H, CHO), 4.37 (dd, J = 8.2, 2.6, 1H, CH_2O eq.), 3.91 (m, 2H, CHO and CH_2O ax.), 3.51 (s, 3H, OCH_3); ^{13}C NMR (50 MHz) δ : 189.2 (carbonyl), 139.6 (C-3), 138.9 (C-2), 137.0 (C-9), 128.9 (C-12), 128.1 (2C-aromatics), 126.0 (2C-aromatics), 101.8 (C-8), 95.5 (C-1), 74.0 (C-4), 69.0 (C-6), 63.4 (C-5), 56.3 (OCH_3).

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