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A NEW SYNTHESIS OF VITAMIN C

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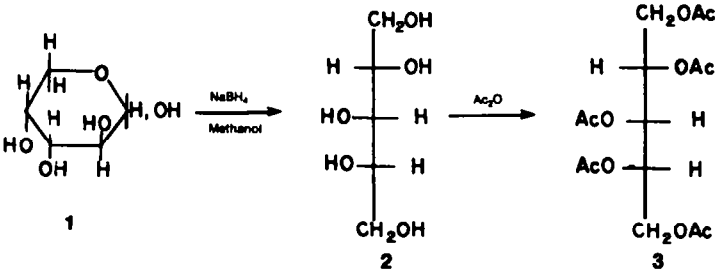
Abstract—L-Arabinose was reduced to L-arabinitol and condensed with formaldehyde to give two bis(di-*O*-methylene-L-arabityloxymethane and two di-*O*-methylene-L-arabinitol derivatives. Cis-fused 1,3:2,4-Di-*O*-methylene-L-arabinitol and trans-fused 2,4:3,5-Di-*O*-methylene-L-arabinitol were also isolated; only the former was affected by the oxidation to give the corresponding aldehyde, which was converted successively to the hydroxy amide, the ethyl hydroxy ester, the corresponding keto ester and vitamin C.

L-Arabinose **1** was converted into L-Arabinitol[1] **2** in almost quantitative yield (90%) according to the Wolfrom and Thompson procedure[2] with a slight modification. Thus, L-arabinose **1** was reduced with sodium borohydride[3] in methanol to give the crude L-arabinitol as crystalline material. Using methanol made the isolation procedure easier than performing the reduction in aqueous solution. L-Arabinitol **2** was isolated in a pure state from the crude mixture by using resin and it was identified as its penta-acetate **3**.



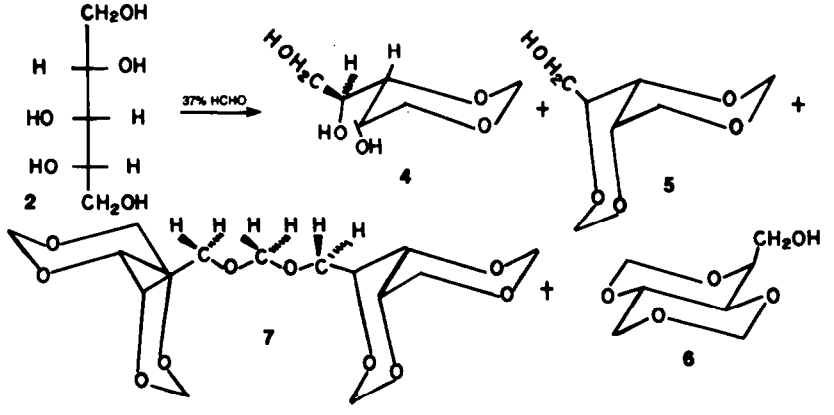
1 **2** **3**

L-Arabinitol was condensed[4] with aqueous formaldehyde (37%) to give a mixture of five compounds. The 1,3:2,4-di-*O*-methylene-L-arabityloxymethane **7** and its isomer which is formed from the condensation of two molecules of **6** with formaldehyde were separated by column chromatography and identified. The third compound was the monomethylene arbinitol **4** was identified as 1,3 - O - methylene - L - arabinitol on the basis of Zissis and Richtmyer's work[5] on the similar condensation of D-arabinitol.

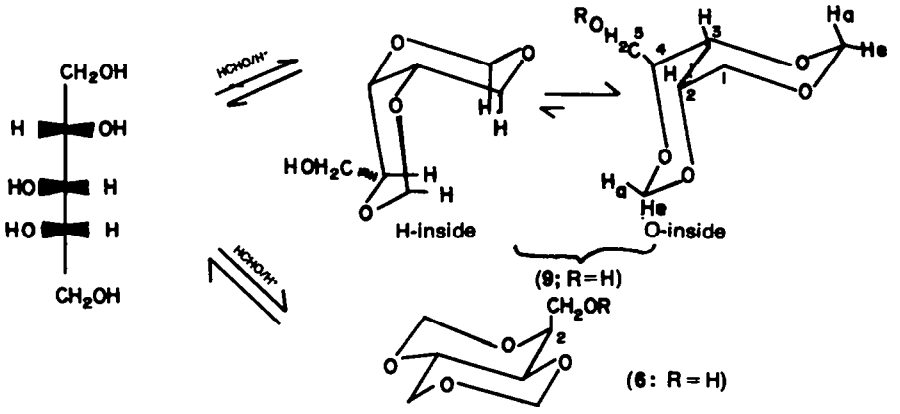
The dimethylene arabinitols were two separable compounds, as expected. Zissis and Richtymer[5] have only reported the formation of the 1,3:2,4 - di - *O* - methylene - D - arabinitol in 49% yield. However, the two dimethylene arabinitols which were successfully separated by careful column chromatography were found to be the 1,3:2,4 - di - *O* - methylene - L - arabinitol **5** in 27% yield and 2,4:3,5 - di - *O* - methylene - L - arabinitol **6** in 39% yield. The assignment of the correct structures to these two isomers was based on an NMR study. The 1,3:2,4 - di - *O* - methylene - L - arabinitol **5** exhibits a *cis*-fused bicyclic system while the 2,4:3,5 - di - *O* - methylene - L - arabinitol exists as a *trans*-fused bicyclic system.

All the physical measurements of the di-*O*-methylene derivatives have been done on the isomer which was concluded to be the *cis*-fused-O-inside **5**.

The *cis*-isomer of dimethylene-D-arabinitol has been isolated by many workers in low yield,[6,7] but no comparative experimental studies were done on the *trans*-



2 **4** **5** **7** **6**

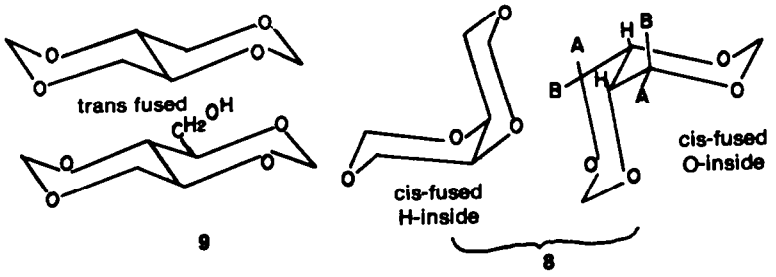


fused isomer, presumably due to the constant absence of the latter.

As would be expected from the general principles of conformational analysis, the bicyclic structures would be most favourable when the axial substituents are H atoms. Mills's survey[8] of the known facts related to the main products formed in the acetylation reactions of carbohydrates led him to the conclusion that the O-inside conformation is inherently more favourable than the H-inside conformation. Although this generalisation is feasible for 1,3:2,4 - di - *O* - methylene - L - threitol **8** when there is an additional CH_2OH, in for example the 1,3:2,4 - di - *O* - methylene ribitol **9**; only 18% yield was formed. This result could not have anticipated on the basis of an inherently unfavourable structure.

The major differences in the NMR spectra of the compounds **5** and **6** are in the chemical shifts and the coupling constants of the bridge-head hydrogens 2 and 3 of the compound **5** and hydrogens 3 and 4 of compound **6** although the bridgehead hydrogens of the threitol derivative (**8**; O inside) are shown as a singlet at 3.62 ppm.[9] The bridgehead hydrogens of (**9**; O inside $R = COCH_3$) were very close (unresolved doublets) at 3.65 ppm. This small splitting of the bridgehead hydrogens of **5** is presumably due to the influence of the additional CH_2OH group which affected the environment of the H-3.

The bridge head hydrogens of the *trans*-fused 2,4:3,5 - di - *O* - Methylene arabinitol (**6**; $R = COCH_3$) appeared as H-3 at 3.4 ppm as a quartet ($J = 9$ c/s) and H-4 at 3.24 as a doublet ($J = 9$ c/s).



The matter of the stereochemistry of the products from the condensation of formaldehyde with tetrols or higher polyhydric alcohols[7,10,11] seemed to be still outstanding. This is presumably due to the fact that the observed products from the condensation always consisted of one isomer of the dimethylene derivatives.[5-7]

Stoddart[7] has shown that although the 2,4:3,5 - di - *O* - methylene - D- or L-arabinitol are predicted by thermodynamical calculations to be 0.7 Kcal $mole^{-1}$ more stable than the 1,3:2,4 - di - *O* - methylene - D- or L-arabinitol, only the latter was isolated in yield 49% after three successive equilibrations of the same reaction. No mention is made of the isolation of the 2,4:3,5 - di - *O* - methylene - D- or L-arabinitol.

The strongest evidence that the structure of the fraction **5** was 1,3:2,4 - di - *O* - methylene - L-arabinitol is that it eventually gave L-*xylo* ascorbic acid **5** since the 2,4:3,5 - di - *O* - methylene - L - arabinitol **6** would lead to L-*arabino* ascorbic acid.

Oxidation of the dimethylene arabinitols has been studied under various oxidising agents. When the 1,3:2,4 - di - *O* - methylene - L - arabinitol was oxidised with chromium trioxide pyridine[12-14] complex prepared according to Poos *et al.*[15] it gave the aldehyde **11** in 50% yield. After being separated from the starting material, the IR spectrum of the product showed no absorption for OH group, instead, an intense absorption at 1710 cm^{-1}

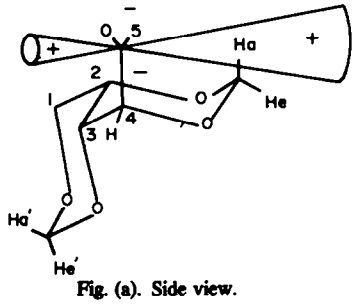


Fig. (a). Side view.

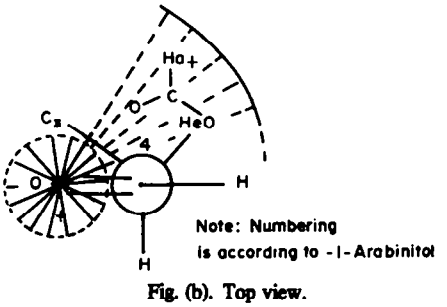
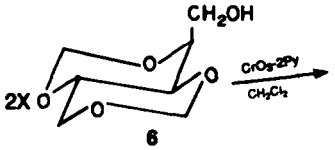


Fig. (b). Top view.

appeared (aldehyde). The NMR spectrum showed the presence of one aldehydic proton at 8.25 ppm as a close doublet of a coupling constant less than 1 c/s. Also, one of the axial methylene-hydrogens was shown at a higher field with respect to the original dimethylene arabinitol. This shift may be explained by the anisotropic effect caused by the aldehyde group shown by the molecular Figs. (A) and (B).

Interestingly, the *trans* isomer 2,4:3,5 - di - *O* - methylene arabinitol **6** has given different results under similar oxidation conditions. The product was an ester which presumably has the structure of **10** deduced from the ester band at 1725 cm^{-1} and elemental analysis. Moreover the NMR spectrum showed no aldehydic hydrogen.



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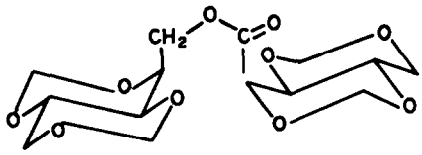

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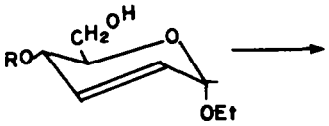
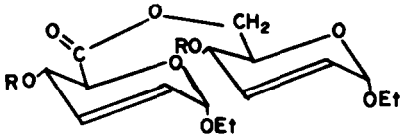
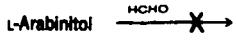
However, such a phenomenon has been reported also by Yanker and Ried[16] on an oxidation of primary alcohol in the carbohydrate field as follows:

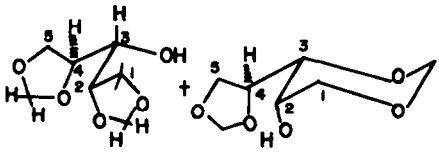




The oxidation with CrO_3·2 py complex was found to be quite dependent on the freshness of the oxidant.[13]

The oxidation of **5** with freshly-prepared lead tetra-acetate–pyridine[17] gave the corresponding aldehyde (12.2%) yield and the acetate derivative (**9**, R = $COCH_3$) in 24.2% yield in addition to the starting material. This finding has excluded the presence of the secondary alcohol in dimethylene arabinitol[18] which might have risen by the following reaction:





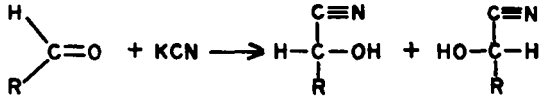
The aldehyde **11** was produced in 41% yield from the oxidation of **5** with dicyclohexyl carbodiimide in dimethyl sulphoxide (DCC/DMSO)[19,20] using dichloroacetic acid as an acidic medium.

The other method of oxidation which was tried on **5** was with N-chlorosuccinimide and dimethyl sulphide[21] to the aldehyde **11** in 20% yield. The trans-fused isomer **6** showed no response to the reagent. Table 1 summarises the yields of the aldehyde **11** produced by the various oxidation methods which showed that CrO_3/pyridine was the best oxidant for giving a higher yield.

Table 1. Reagents used for oxidation of 1,3:2,4 - di - *O* - methylene - L - arbinitol **5**

Oxidant	Percentage yield of **11**
CrO_3/pyridine	50
$Pb(OAc)_4$/pyridine	12.2
Dicyclohexyl carbodimide-dimethyl sulphoxide/$CHCl_2CO_2H$ (DCC-DMSO)	41
N-chlorosuccinimide-dimethyl sulphide (N-CS/DMS)	20

Treatment of the aldehyde **11** with aqueous potassium cyanide solution in a basic medium gave a syrup which showed a strong band in the IR spectrum at 3500 cm^{-1}. The nitrile stretching appeared at 2260 cm^{-1} as a weak band. The CO absorption at 1710 cm^{-1} disappeared. The syrup failed to crystallise after standing for a long time presumably due to the nature of the product which consisted of an epimeric mixture of cyanohydrins.

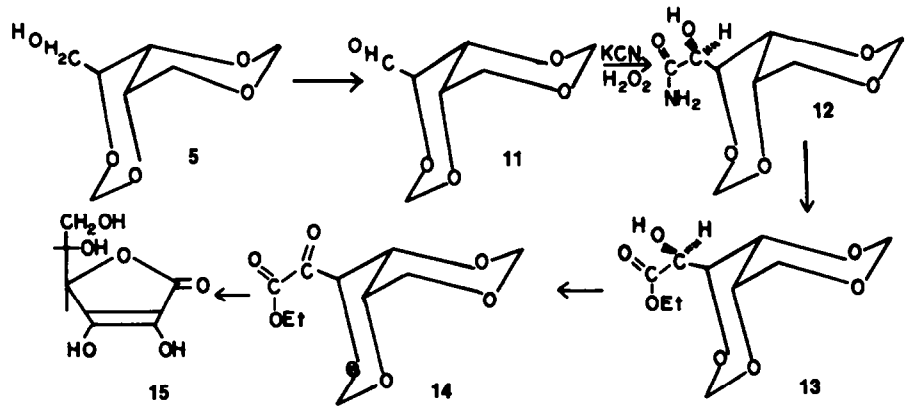


The cyanohydrin syrup resisted oxidation with chromium trioxide/pyridine reagent and was always recovered unchanged even after a prolonged reaction time.

When the Moffat–Kiliani[22] modified procedure was applied on the aldehyde **11**, the α-hydroxy amide epimeric mixture **12** was isolated in 81% yield. The product showed strong IR absorptions at 3429,3350 and 3200 cm^{-1} for unassigned free OH, bonded OH and N-H stretchings. It showed also absorptions at 1710 and 1670 cm^{-1} for amide CO stretchings and 1610 cm^{-1} for N-H bonding. This compound was found to be unstable, and was crystallised by standing at room temperature to give a compound which showed no nitrogen on elemental analysis. The hydroxy amide **12** was treated immediately after isolation with anhydrous ethyl alcohol[22] in the presence of Dowex 50 WX8 to give the bis-hydroxy ester **13** in 74% yield.

The IR spectrum showed the characteristic absorptions for OH and the normal CO groups. The NMR showed the presence of a triplet centered at δ 1.2 ppm for the (CH_3) of the ester group. It is worth mentioning that the hydroxy ester **13** was found to be (contrary to what was expected) more polar than the hydroxy amide **12** as shown by TLC.

Oxidation of the α-hydroxy ester **13** was attempted by two methods. Using dicyclohexyl carbodimide-dimethyl sulphoxide (DCC and DMSO) with dichloro acetic acid[22] as a proton source resulted in the production of the crude



α-keto ester **14** which was difficult to separate from DCC.

A better oxidation was achieved by using freshly activated ruthenium tetroxide[23] in presence of commercial aqueous sodium hypochlorite to give a pure-α-keto ester in a high yield (81%). IR showed no band corresponding to OH stretching. The hydrolysis of the ester **14** was done by boiling in aqueous ethanolic hydrochloric acid for 4h to give vitamin C in quantitative yield.

The product from the hydrolysis was L-*lyxo* rather than L-*xylo*-2-hexulosenic acid, and this difference is of no significance since the difference in the configuration of C-3 in the hydrolysis product will be eliminated by spontaneous enolisation of C-2 and C-3 by the effect of the neighbouring keto group.

The vitamin C produced has the same IR and NMR spectra with an authentic sample. Elemental analysis was consistent with that of structure **15**. Mixing with an authentic sample showed no change in the m.p.

EXPERIMENTAL

M.ps are uncorrected. NMR spectra were measured in deuterochloroform ($CDCl_3$), and TMS as internal standard. The Varian EM-390 90 MHz NMR Spectrometer was operating at 34°. Eluents were used in TLC were (A) Benzene-MeOH (7:3). (B) benzene-MeOH (8:2). (C) benzene-MeOH (6:4). (D) benzene-EtOAc (3:2). (E) benzene-MeOH (2:3), unless otherwise stated.

The general procedure for isolation of the products from the mixture is stated below and will not be detailed throughout the experimental section but only refered to by "as usual":—Several drops of water were added to the mixture to destroy the complex. The mixture was then left to stand for at least 20 min at room temp, and it was then stirred into water. The mixture was extracted with chloroform, and the chloroform layer was washed successively with either aqueous acid or alkali until neutral and finally with water. The chloroform layer was then dried over $MgSO_4$, filtered and evaporated under reduced pressure.

L-*Arabinitol* **2**

The compound was prepared according to the method of Wolfrom and Thompson[2] with modification. L-Arabinose (60 g) was dissolved in MeOH (400 ml) and $NaBH_4$ (12 g) was added in portions (1–2 g) after each production of gas had ceased. The temp of the mixture was not allowed to rise above 50°. At the end of additions the reaction was allowed to stand for an additional 1 hr with continuous stirring.

The reaction was monitored by TLC (solvent A) which showed that all the starting material had been exhausted. The only well-defined component (R_f $E = 0.312$) was attributed to L-arabinitol. BIO-RAD (Dowex 50 WX8) resin was slowly added until the production of gas ceased. The mixture was filtered off and the filtrate was evaporated under reduced pressure to give a pale yellow syrup, which was dissolved again in MeOH and the soln was evaporated under reduced pressure to remove the boric acid in the form of a volatile methyl borate. Crude L-arabinitol (60 g; 98%) was produced as a colourless syrup. The syrup was crystallised from water and EtOH to yield 55 g (90.4%) of L-arabinitol. M.p. 100–105° (reported[2] 102°).

1,2,3,4,5-*Penta*-O-*acetyl*-L-*arabinitol* **3**

L-Arabinitol (2, 0.2 gm) was dissolved in anhydrous pyridine (5 ml) followed by Ac_2O (5 ml). The mixture was set aside at room temp for 2 hr. The mixture was then processed as usual to give a syrup which crystallised by the addition of a small amount of EtOH. Recrystallisation from EtOH gave colourless crystals of penta - O - acetyl - L - arabinitol (0.2 g; 42%); m.p. 74°, similar to that reported.[2] R_f (B) = 0.68, ν_{max}^{Nujol} on absorption band attributed to (–OH) group; 1750 s cm^{-1} (–OAc) group. Calculated for: $C_{15}H_{22}O_{10}$; C 49.72%; H 6.07. Found C 49.71%; H 6.07%.

The condensation of L-*arabinitol with formaldehyde*

L-Arabinitol (500 g) was dissolved in a mixture of 37% aqueous formaldehyde soln (50 ml) and conc HCl (50 ml). The mixture was maintained at 50° for 2 days. The reaction was followed by TLC (solvent(B)), which showed the presence of five components.

The mixture was then cooled to 5° and extracted with chloroform (6 × 50 ml), and processed as usual to give a pale yellow syrup (29.1 g). The aqueous layer, which contained unreacted L-arabinitol, was heated further at 50° for 2 days to give 14 g of syrupy mixture. A third sample was also obtained by the same method (11 g). The overall yield was 54 g. The syrup mixture (38 gm) was absorbed into a column of silica gel, eluted with benzene-MeOH (8:2) to give the following compounds. The less polar component (R_f B = 0.75) which was eluted first was attributed to **7** (5 g; 4.8%) as colourless crystals m.p. 138°, similar to what was reported.[5] ν_{Nujol}^{max}: no absorption band attributed to OH group. Calculated for $C_{15}H_{24}O_{10}$; C, 49.45; H, 6.59. Found C, 50.59; H, 6.27%. The second component was a colourless syrup (5 g) R_f B = 0.6, calculated for $C_{15}H_{24}O_{10}$, C, 49.4, H, 6.59. Found C, 49.18, H, 6.51%. The third component (R_f B = 0.453) was attributed to **6** which was isolated as a colourless syrup (15 g, 39%) which crystalised after standing for one month in the refrigerator to give colourless needles, m.p. 135–136°. ν_{Nujol}^{max} 3460 cm^{-1} (m) (OH) (1170, 1090, 1020, 800) cm^{-1} (s) C–O–C stretching. Calculated for $C_7H_{12}O_5$; C, 47.72, H 6.87. Found: C, 47.57, H, 6.78%. The fourth component (R_f B = 0.4) was attributed to **5** which crystallised immediately to give a cluster of needles, and recrystallised from EtOH/EtOAc (1:1) to give colourless needles, (10 g, 26.5%) m.p. 124°, reported, 124°–125°.[2] ν_{Nujol}^{max} 3460 (m) cm^{-1} (1170, 1090, 1020, 800) (s) cm^{-1} (C–O–C) stretching. Calculated for $C_7H_{12}O_5$, C, 47.72, H 6.87. Found: C 47.39; H 6.81%.

The fifth fraction **4** was the more polar component on TLC (R_f B = 0.26), and it was attributed to the 1,3 - O - methylene - L - arabinitol. Crystallisation from MeOH-ether (1:2) gave white

crystals m.p. 80–85° (0.5 g; 0.17%); reported[5] m.p. 86–87°. ν_{Nujol}^{max} 3500 cm^{-1} (s) OH 1200, 1090 cm^{-1} (s) C–O–C stretching.

Acetylation of 2,4:3,5 - *di* - O - *methylene* - L - *arabinitol* (**6**; *R = Ac*)

Compound **6** (100 mg) was dissolved in anhyd pyridine (10 ml), followed by Ac_2O (10 ml). The mixture was left at room temp for 2 hr, and the reaction was followed by TLC (solvent B), which indicated that most of the starting material was converted to the product. The mixture was then processed as usual to give a colourless syrup which crystallised by addition of few drops of an EtOH. Recrystallisation from EtOH gave white crystals which melted at 126° (40 mg; 32.5%). R_f B = 0.70. ν_{Nujol}^{max} no absorption band characteristic of (OH) group; 1735 (s) cm^{-1} for (OAc) group. NMR data at ppm. (δ): −4.92 (2-protons, doublet, 1-proton, ^{1}He–Ha = 6 c/s, H_2); 4.15 (1-proton, quartet $^1H_{5(e)}$–H_4 = 3 c/s, $H_{5(e)}$; 3.86 (1-proton, quartet, $^1H_{5(a)}H_4$ = 7 c/s, $H_{5(a)}$; 3.7 (2-protons, doublet, H_1–H_2 = 9 c/s, for CH_2–OAc: 3.55 (1-proton unresolved, H-2); 3.4 (1-proton, quartet, H_3–H_4 = 9 c/s, H_3) 3.20 (1-proton, doublet, $^1H_4$–H_3 9 c/s, H-4); 2.075; (3-proton), singlet, CH_3 group of Ac.

Acetylation of 1,3:2,4 - *di* - O - *methylene* - L - *arabinitol* (**5**; *R = Ac*)

Compound **5** (60 mg) was dissolved in anhydrous pyridine (10 ml), followed by Ac_2O (10 ml). The mixture was then left at room temp for 2 hr, and followed by TLC (solvent B). The reaction was processed as usual to give fine needles. Recrystallisation from EtOH gave (30 mg; 24%), m.p. 70–71°, reported[5] m.p. 68–69°. R_f B = 0.58. ν_{Nujol}^{max} no absorption band characteristic of (–OH) group; 1745 (s) cm^{-1} (OAc) group. NMR data at ppm (δ): −5.12 (2-protons, doublet, J_{Ha-He} = 6 c/s for He and He'); 5.0 (1-proton, singlet, Ha); 4.75 (1-proton, doublet $J_{Ha'-He'}$ 6 c/s, Ha'): 4.56–4 (4-protons, unresolved, Ha, H_4 and –CH_2–OAC): 3.87 (1-proton, doublet, $J_{H_1(a)}$–H_2 = 1 c/s; $H_{1(a)}$; 2.1 (3-protons, singlet, Ac group). Calculated for $C_9H_{14}O_6$; C 49.54%; H, 6.42%. Found 49.55%; H, 6.47%.

(2,4:3,5 - *Di* - O - *methylene* - L - *arabinityl*) - 2,4:3,5 - *di* - O - *methylene* - L - *arabinoate* **10**

Chromium trioxide-pyridine complex (9 g) was dissolved in anhydrous CH_2Cl_2 (100 gm) (dried over 10 g P_2O_5). A soln of 2,4:3,5 - DI - *O* - methylene - L - arabinitol (1 g) in anhydrous CH_2Cl_2 (10 ml) was rapidly added with continuous stirring. After reaction the mixture was dried by adding P_2O_5 (5 g). The proceeding of reaction was followed by TLC (solvent B) which showed after ½ hr the presence of a less polar component (R_f B = 0.67) and the starting material (R_f B = 0.45).

Leaving the mixture for 24 hr at room temp did not show any change in the intensities of the spots on TLC. The chromium salts were removed by filtration under vacuum using a sintered glass funnel, and washed thoroughly by CH_2Cl_2. The filtrate was washed with 5% HCL, 5% $NaHCO_3$, then with sat NaCl. The organic layer was dried over $MgSO_4$ and the filtrate was decolorised using activated charcoal. The charcoal was filtered off and the filtrate was evaporated under vacuum to give crude crystals which recrystallised from EtOH giving colourless needles (400 mg; 26.3%) m.p. 200–202°, R_f B = 0.07. ν_{Nujol}^{max} showed no band characteristic of (–OH) group; 1720 (s) cm^{-1} –CO_2R ester group. Calculated for $C_{14}H_{20}O_{10}$; C, 48.27; H, 5.74. Found: C, 48.4; H, 5.74%.

2,4:3,5 - *Di* - O - *methylene* - L - *lyxose* **11**

Chromium trioxide-pyridine complex (9 g) was dissolved in anhydrous CH_2Cl_2 (100 ml). A soln of 1,3:2,4 - di - *O* - methylene - L - arabinitol (11 g) in CH_2Cl_2 (10 ml) was added with continuous stirring. The reaction was followed by TLC (solvent B) which showed after ½ hr the presence of a less polar component and the starting material. No change was observed in the intensities of above spots after 2 days. The mixture was then processed as described in the previous experiment. The syrup produced was absorbed into a column of silica gel (50 gm) using solvent (C) giving a homogeneous aldehyde, which crystallised after the addition of a few drops of EtOH. Recrystallisation from EtOH yielded colourless needles (500 mg; 50%) m.p. 130°–132°; (R_f B = 0.78.). ν_{Nujol}^{max} no absorption band characteristic of (–OH) group, 1710 (s) cm^{-1} (–CHO) group. NMR data at (ppm): 8.25 (1-proton, singlet, CHO); the other protons were present with their expected integrations. Calculated for $C_7H_{10}O_5$; C, 48.27; H, 5.74. Found: C, 48.78; H, 6.18%.

Oxidation of 1,3:2,4 - *di* - O - *methylene* - L - *arabinitol* **5** *with lead tetra-acetate*

1,3:2,4 - Di - *O* - methylene - L - arabinitol (1 g) in pyridine (100 ml) was added to a stirred soln of freshly prepared lead tetra-acetate (3 g) in pyridine (20 ml). The deep red soln became pale yellow after 12 hr. The mixture was followed by TLC (solvent B), which showed the presence the three components: the major component (R_f B = 0.40) was attributed to the starting material, and two minor components (R_f B = 0.78 & 0.58). No change in the products, after 2 days, was observed. Chloroform (100 ml) was added and the mixture was washed successively with water, 10% H_2SO_4 then with sat $NaHCO_3$.

The dried $MgSO_4$ organic layer was evaporated to a syrup (0.6 g). The syrup was fractionated on silica gel (60 g) using solvent (B) to give the first fraction **11** R_f B = 0.78 (0; 122 g, 12.2%) m.p. = 130–131°. The second fraction was the acetylated product of **5** (R_fB = 0.58) m.p. 70° (0.30 gm; 24.23%). The third fraction (0.2 gm) was the unreacted starting material m.p. 124°C.

2,4:3,5 - *Di* - O - *methylene* - L - *lyxose* (*Oxidation of* **5** *with DMS/NCS*)

To a stirred soln of *N*-chlorosuccinimide (NCS; 1.6 g) in toluene (40 ml) was added dimethyl sulphide (DMS; 1.2 ml) at 0°. The mixture was then cooled to −15° and a soln of 1,3:2,4 - di - *O* - methylene - L - arabinitol (1 g) in CH_2Cl_2 (15 ml) was added dropwise. The stirring was continued for 2 hr at −15°. A soln of Et_3N (1.212 g) in toluene (4 ml) was added dropwise. The reaction was followed by TLC using eluent (B) which showed the presence of less polar component (R_fB = 0.78) and a major component (R_fB = 0.40) which was attributed to the starting material.

The cooling bath was removed, and after 5 min the mixture was extracted by $CHCl_3$ (150 ml), the organic layer was washed once with 1% HCl and twice with water (2 × 50 ml). Removal of dried organic solvent produced a syrup that was purified by chromatography into a 2,4:3,5 - di - *O* - methylene - L - arabinitol 130°. ν_{Nujol}^{max} no absorption band characteristic for (–OH) group. 1710 cm^{-1} (–CHO). Calculated for $C_7H_{10}O_5$, C, 48.27; H, 5.74. Found: C, 48.17; H, 5.81%.

2,4:3,5 - *Di* - O - *methylene* - L - *lyxose*

Oxidation by Ph–S–Et/NCS. To a stirred soln of *N*-chlorosuccinimide (1.6 g) in toluene (40 ml) was added at 0° benzyl ethyl sulphide (2 ml). A soln of 1,3:2,4 - di - *O* - methylene - L - arabinitol (1 g) in CH_2Cl_2 (15 ml) was added dropwise. The stirring was continued for 2 hr at 0°, and then a soln of Et_3N (1.212 g) in toluene (4 ml) was added dropwise. The cooling bath was removed. TLC using eluent (B) indicated the presence of a major component (R_fB = 0.40). The mixture was extracted by $CHCl_3$ (150 ml), the organic layer was washed once with 1% HCl aq and twice with water (2 × 50 ml). The organic layer was dried over $MgSO_4$, filtered by passing through a column of silica gel (75 g) using eluent (B) to give (600 mg; 61%) of the crude aldehyde which showed the same R_f values of the aldehyde prepared in the previous experiment, using 2,4-dinitrophenyl hydrazine as a developing spray. ν_{Nujol}^{max} no absorption band characteristic for (–OH) group; 1710 cm^{-1} (s) (–CHO) group. NMR spectrum was identical with that of **11**.

2,4:3,5 - *Di* - O - *methylene* - L - *lyxose oxidation by DMSO/DCC*

Dichloroacetic acid (0.1 ml) was added to a soln of 1,3:2,4 - di - *O* - methylene - L - arabinitol (500 g), and pyridine (0.4 ml), dicyclochexylcarbodimide (DCC) (4 g) in dimethyl sulphoxide (15 ml). The reaction mixture was kept at 20–25° for 2 hr. *N,N*-Dicyclohexylurea began to crystallise after a few minutes. The reaction was followed by TLC which indicated the presence of three components. The less polar compound was attributed to the *N,N*-Dicylohexylurea, R_f B = 0.9. The second was attributed to

the 2,4:3,5 - di - *O* - methylene - L - lyxose ($R_f B = 0.78$), the more polar component ($R_f B = 0.40$) was attributed to the starting material. The reaction mixture was diluted with EtOAc (100 ml) and a soln of oxalic acid dihydrate (1.5 g) in MeOH (5 ml) was added. The mixture was poured into NaCl (50 ml), and *N,N*-Dicyclohexylurea was removed by filtration. The filtrate was separated into two phases, and the aqueous phase was extracted with EtOAc (100 ml). The combined organic phases were washed successively with $NaHCO_3$ (50 ml), and iced water (50 × 2 ml).

The organic layer was dried with $MgSO_4$ and evaporated to dryness under diminished pressure. The residue was disolved in EtOAc (10 ml), filtered to remove the *N,N*-Dicyclohexylurea, the filtrate was concentrated to pale yellow syrup (0.9 g) which seemed to contain more crystalline *N,N*-Dicyclohexylurea. The mixture was dissolved again in EtOAc and filtered off. The filtrate was concentrated and the syrup was absorbed into a silica gel to give a pure aldehyde R_f B = 0.78 (200 gm; 40.5%). IR and NMR spectra were identical with that of the aldehyde prepared earlier.

2,4 - Dinitrophenyl hydrazone of 2,4:3,5 - *di* - O - *methylene* - L - *lyxose*

A soln of 2,4-dinitrophenyl hydrazine (0.250 g) in MeOH (5 ml) containing conc H_2SO_4 (0.5 ml) was added to the soln of 2,4:3,5 - di - *O* - methylene - L - lyxose in MeOH (50 ml). The crystals (2,4:3,5 - di - *O* - methylene - L - lyxose - 2,4 - dinitrophenyl-hydrazone) which formed immediately had m.p. 115°, R_f D = 0.75.

Reaction of aldehyde 11 *with aqueous potassium cyanide*

To a cooled soln (10°) of the aldehyde (11; 300 mg) in water (10 ml), was added a soln of KCN (0.1 g/ml; 10 ml). H_2SO_4 (10%; 2 ml) was added. The reaction mixture was stirred at room temperature for 5 min. TLC showed the development of a well-defined spot R_f B = 0.35 as the only product. The reaction mixture was extracted by $CHCl_3$ and processed as usual to give a syrup product (290 mg). ν^{max}_{Nujol} 2410 (b) cm^{-1} (OH group); 2260 cm^{-1} (s) (C≡N).

3,5:4,6 - *Di* - O - *methylene* - L - *galactonamide or* - L - *talonamide* 12

To a cooled soln (10°) of the 2,4:3,4 - di - *O* - methylene - L - lyxose (300 mg) in diaxane (10 ml) was added a soln of NaCN (1 g), and was stirred at room H_2O_2 (4 ml) was added.

TLC using solvent (B) showed the presence of a well-defined spot R_f B = 0.25, and a faint spot R_f (B) = 0.3 which was attributed to the optical isomer of the produced amide. After 1 hr the reaction mixture was concentrated to 10 ml under reduced pressure. The mixture was extracted with $CHCl_3$ (3 × 25 ml). Evaporation of the dried $MgSO_4$ and solvent gave a pale yellow syrup, which was purified by a column of silica gel to give a colourless syrup. (300 mg; 81%) ν^{max}_{Nujol} 3350 cm^{-1} (b) –NH_2. 3200–3420 cm^{-1} (b) (bonded OH) 1670 cm^{-1} (s; –CO·NH_2) group. Calculated for: $C_8H_{13}O_6N$; C, 43.83, H, 5.9; N, 6.3%; Found: C, 41.04; H, 6.12; N, 5.9%.

Ethyl 3,5:4,6 - *di* - O - *methylene* - L - *galactonate or* L - *talonate* 13

3,5:4,6 - Di - *O* - methylene - L - galactonamide or L-talonamide (300 mg) in dry EtOH (20 ml) was stirred under reflux with (Dowex 50 WX8; H^+) resin (2.5 g) overnight. The reaction mixture was monitored by TLC using solvent (B) which showed the presence of a polar component spot on the base line of the TLC. The resin was removed by filtration and washed with EtOH. Evaporation of the solvent left a syrup (250 mg; 73.79%) which was attributed to 13, ν^{max}_{Nujol} 3380 cm^{-1} (m) (OH group), 1750 cm^{-1} (s) (CO) group and (ppm): -1,2 (3-protons, t, CH_3); the other protons were present with their expected integrations, Calculated $C_{10}H_{16}O_7$: C, 48.38%; H, 6.45%: Found: C, 48.50; H, 6.51%.

Ethyl - 3,5:4,6 - *di* - O - *methylene* - L - *lyxo* - 2 - *hexulosenate* (*ethyl* - *α* - *keto* - 3,5:4,6 - *di* - O - *methylene* - L - *galactonate*, 14

A soln of bis - ethyl - 3,5:4,6 - di - *O* - methylene - L - galactonate (250 mg) in $CHCl_3$ (30 ml) (purified by passing through a column of alumina) was stirred vigorously by a magnetic stirrer and active RuO_2 (10 mg) was added. A soln of commercial NaOCl (50 ml) was added dropwise with continuous stirring until the $CHCl_3$ layer became clear yellow. The progress of the oxidation was followed by TLC which showed the presence of a less polar component with (R_f B = 0.7). The reaction was completed after 2 hr, and $(CH_3)_2CHOH$ (2 ml) was added to reduce the residual RuO_4. The mixture was set aside for 10 min at room temp. The $CHCl_3$ layer was separated and the aqueous layer was washed with $CHCl_3$ (2 × 25 ml).

The combined organic layers were dried and evaporated to give a syrupy product (200 mg, 80.65% 14). ν^{max}_{Nujol} no absorption band attributed for (OH) group; 1749 cm^{-1} (s) (ester group); 1720 cm^{-1} (s) (CO) group. Calculated for $C_{10}H_{14}O_7$: C, 48.78; H, 5.69. Found: C, 48.76; H, 5.65%.

L-*Ascorbic acid* (*Vitamin C*)

Ethyl - *α* - keto - 3,5:4,6 - di - *O* - methylene - L - galactonate (250 mg) was dissolved in 20% EtOH (50 ml), and HCl (5 ml) was added. The mixture was heated under reflux for 4 hr when TLC indicated that all the starting material was hydrolysed to give a well-defined spot on the base line (solvent B). The reaction mixture was processed as usual, and the residue was crystallised and washed with ether. Recrystallisation from MeOH gave a white crystalline material (145 mg; 81.09%) m.p. 185–190°; reported m.p. 190–192°. Mixed m.p. with an authentic sample 185–190°. ν^{max}_{Nujol} 3520, 3400, 3310 (s) cm^{-1} for (OH groups) 1750 cm^{-1} (m) (CO) group. 1665 cm^{-1} (s) (enolic form). Calculated for $C_6H_8O_6$: C, 40.90; H, 4.54%. Found: C, 40.88; H, 4.52%.

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