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L-Fucose from Vitamin C with Only Acetonide Protection

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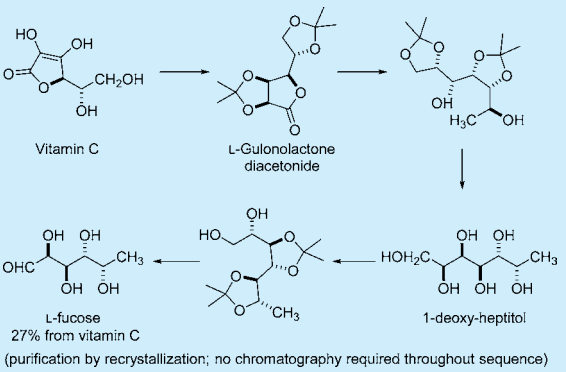
Supporting Information

ABSTRACT: Addition of human milk oligosaccharides (HMO) to baby foods may protect infants from disease. As many simple HMOs are fucosylated this is likely to increase the demand for L-fucose as a synthetic building block. Any chemical synthesis must be cheap to compete with a biotechnological process. Acetonide is the only protecting group we have used in this new synthesis of L-fucose from vitamin C in 27% overall yield (purification by recrystallization; no chromatography required in the entire sequence).



L-Fucose **1** is a monosaccharide that is a common component of many glycolipids, and *N*- and *O*-linked glycans in mammalian cells; fucosylated glycans have many functions and are often regulated during ontogeny and cellular differentiation.[1] Alterations in the expression of fucosylated oligosaccharides are found in several pathological processes, including cancer and atherosclerosis.[2] Fucosylated human milk oligosaccharides (HMO) protect infants from disease[3] and are important in the development and protection of newborn infants.[4] Addition of HMOs as a baby food supplement would sharply increase the demand for fucose. There is thus considerable interest in the biotechnological[5] and chemical[6] synthesis of HMOs; all such syntheses involve the use of fucose as a starting material. At present, almost all fucose is produced by acid hydrolysis or microbial fermentation of sulfated polysaccharides such as fucoidans.[7] For a chemical synthesis to compete, it is necessary that the starting material and reagents are cheap and the process involves minimum purification. This paper describes the synthesis of fucose from vitamin C **2**, a bulk chemical which costs $3−$4 per kg [for 1000 kg].[8]

Palladium-catalyzed hydrogenation of vitamin C **2** formed L-gulonolactone **3**[9] (99%) which on treatment with acetone and *p*-toluenesulfonic acid (*p*TSA) gave the diacetonide **4** in 93% yield[10] [Scheme 1]. The diacetonide **4** and its enantiomer[11] have been used in several scalable syntheses.[12]

Addition of methyl lithium to lactone **4** afforded the lactols **5** in 96% yield; although **5** can be easily crystallized as the α-anomer,[13] the crude residue was used in the next step. Reduction of **5** by sodium borohydride in methanol afforded a mixture of the two 1-deoxyheptitols **6** and **7** in a ratio of 93:7 (95% yield); diastereoselectivity in similar systems has been rationalized by a Felkin−Ahn controlled addition of hydride.[14] The methyl signals in **6** and **7** allow accurate measurements of the ratio by ^{1}H NMR. Hydrolysis of the mixture of **6** and **7** by Dowex (50W X8, H^+) in methanol/water gave the 1-deoxyheptitols **8** and **9** in a ratio of 93:7 as shown by both NMR and HPLC.

Crystallization of the mixture from water/methanol/acetonitrile gave the deoxyheptitols **8** and **9** in a ratio of 98:2 (81% yield; 74% from the diacetonide **4**). The mother liquor from the crystallization contained **8** and **9** in a ratio of ∼4:3 and allowed pure samples of the two heptitols to be isolated by HPLC. The deoxyheptitol **8** was easily crystallized,[15] whereas **9** was an oil.[16] Cleavage of the terminal diol in **8** by periodate would give fucose **1**; cleavage of terminal diols is usually more rapid than other diol oxidations.[17] Similar oxidation of **9** would give the C5 epimer of fucose, 6-deoxy-D-altrose.[18] However, ^{1}H NMR studies of the direct oxidation of **8** by aqueous periodate did not indicate formation of any fucose, so protection of the heptitol **8** was necessary.

Treatment of **8** with acetone in the presence of *p*-toluenesulfonic acid gave the kinetic triacetonide **10** (83%). Although **10** is also the most stable triacetonide derived from **8**, longer reaction times and alternative reaction conditions gave small amounts of other acetonides. Accordingly, the reaction was stopped when other products began to appear; pure

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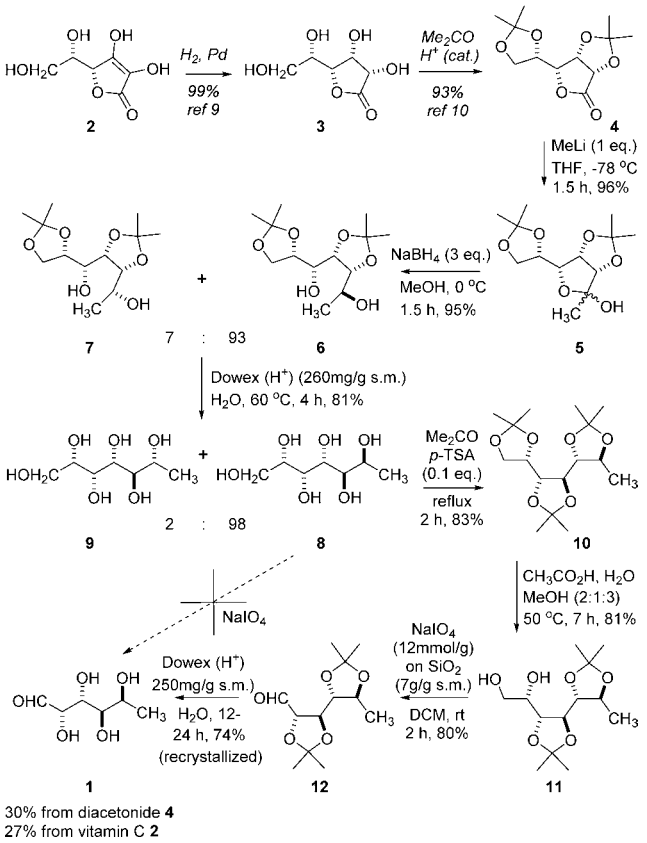
Scheme 1. Synthesis of L-Fucose 1



crystalline **10** was isolated by extraction of the crude residue with cyclohexane. The residue was subjected to the same reaction conditions to give **10** in 83% yield. Kinetic hydrolysis of the terminal acetonide in **10** by acetic acid in aqueous methanol gave the diol **11** in 81% yield. The most efficient procedure involved following the reaction by TLC; initially only **11** was formed. When other products began to appear, the reaction was quenched with $NaHCO_3$ (aq, sat). Unreacted triacetonide **10** and the diacetonide **11** were efficiently recovered by sequential extraction with cyclohexane and ethyl acetate. Both the triacetonide **10** and the diacetonide **11** are crystalline materials; no chromatography is necessary at any stage during the synthesis. Treatment of the diol **11** with sodium periodate adsorbed on silica gel[19] afforded the aldehyde **12** (80%) from which the acetonides were removed by Dowex (50W X8, H^+) in water to give a 100% yield of fucose **1** with a purity, as established by HPLC, of 95.9%. A single crystallization of fucose from ethanol increased the purity to 99.3% in a yield of 74% [see Supporting Information]. The overall yield of crystalline fucose **1** from the diacetonide **4** is 30% (27% from vitamin C **2**). No chromatography was involved in the entire sequence; crystallizations of both the heptitol **8** and fucose **1** were efficient. The residue from the mother liquor of crystallization of fucose contained ~50% fucose; on an industrial scale, there are well-established chromatographic procedures[20] for the purification of fucose so that the overall yield would be higher.

The preparation of fucose by periodate cleavage of a deoxyheptitol, derived from addition of methyl lithium to diacetone mannose, was previously described; a different protecting group strategy was employed.[17] Fucose has been prepared from other monosaccharides,[1] most commonly by adjusting the oxidation levels at C1 and C6 of derivatives of D-galactose, L-galactose, and D-galacturonic acid.[21] Acetonides have been recognized as the optimum protecting group since the dawn of monosaccharide chemistry.[22] As in an approach to L-glucose,[23] the solubility of the seven carbon sugar triacetonide **11** in cyclohexane is crucial for the success of this multi gram synthesis of fucose. The biotechnology of Izumoring[24] allows the conversion of L-rhamnose, the only cheap deoxyhexose, into many other 6- and 1-deoxyhexoses;[25] however, the isomerization of rhamnose to fucose is not efficient.

Although fucose is the 6-deoxyhexose with a well-established demand, there is considerable interest in the synthesis of other deoxyhexoses, particularly as building blocks for their incorporation into oligosaccharides.[26] The strategy of addition of methyl lithium to sugar lactones gives a 1-deoxy-ketose which may be stereoselectively reduced to 1,2-*syn* diols (as in this paper) or under chelation controlled conditions[27] to 1,2-*anti*-diols. Elaboration of each epimeric 1-deoxyheptitol through the triacetonides will generate two 6-deoxyhexoses. Since some six hexonolactones [the enantiomers of *glucono-*, *gulono-*, and *galactono-* lactones] are easily available, some 12 of the 16 6-deoxyhexoses may be accessed by this strategy.

Almost all sugars that are available on industrial scale are made by biotechnology;[28] even the Reichstein process involving chemistry for 80 years[29] for the synthesis of vitamin C **2** has been mostly superseded by a fermentation process developed in China.[30] However, this scalable synthesis of fucose from vitamin C may be competitive with the present biotechnological procedures.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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