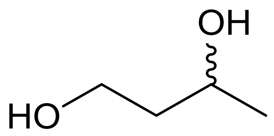
UK BioChem 10 – 7 1,3-Butanediol

Name	1,3-butanediol
Synonyms	1,3-butandiol, 1,3 butylene glycol
CAS Number	107-88-0, (R)6290-03-5, (S) 24621-61-2
Molecular formula	$C_4H_{10}O_2$
MW	90.12 g mol^{-1}
Patents related to synthesis	44



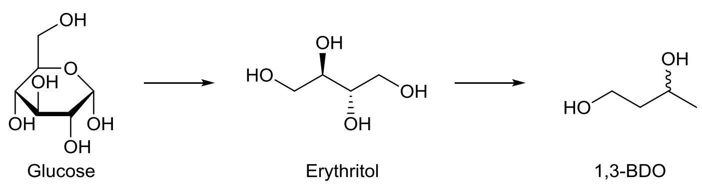
Why is it of interest?

1,3 butanediol (1,3-BDO) is a short chain compound containing both a primary and a secondary alcohol. It has a number of uses and applications, primarily as a humectant in the cosmetic industry and also in the flavour and fragrance industry. Like all diols it can be applied in the synthesis of polyesters where the branching gives rise to differing properties. It is also used as a platform molecule in the production of pharmaceutical relevant compounds, most notably beta lactam antibiotics. The market for 1,3-BDO is small but relatively well established, however the petrochemical route to its production is multi-stepped and relatively expensive. As such a simple bio-derived route is highly attractive.

Feedstocks for 1,3-butanediol

The current industrial route to 1,3-BDO is *via* 4 hydroxy-butanone, using either chemocatalytic reduction to give a racemic product followed by biocatalytic resolution to the optically pure isomer if desired, or by whole cell asymmetric reduction.[1] Bio-derived chemocatalytic pathways require the use of the C4 sugar erythritol which is produced industrially as a sweetener but is very high cost. This route of production has poor selectivity, giving a variety of diols, mainly for use in the production of polyols or olefins.[2] A more promising route is the use of synthetic biology to engineer a route to 1,3-BDO *via* fermentation. This is still very much in the early stages of investigation, with various pathways under analysis but is the most likely to yield an industrially viable process.[3] Finally, a 4 step route starting from the amino acid theronine is also known, but not applicable at scale.[4]

Highlighted routes of production



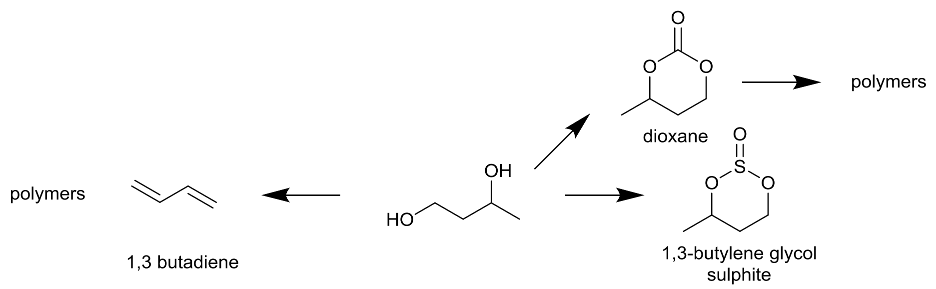
The chemocatalytic route to 1,3-BDO results in the formation of a racemate product. The initial step requires the conversion of glucose to erythritol which is currently subject to a lot of interest and development. This interest is primarily as a food sweetener with a very low calorific content for use in weight loss or in treatment of diabetes. It is already produced at scale *via* fermentation, with best results demonstrated at a 50 ton scale with the yeast *P. tsukubaensis* KN75 (61% yield).[5] This in turn is reacted with a precious metal catalyst, sulphuric acid and hydrogen to give a range of triols and diols via dehydration and hydrogenation. Conversion of erythritol is 65%, with selectivity towards 1,3-BDO at 13.5% (1,4-butanediol being the major product).[2a] This gives an overall yield of 5.4% for 1,3-BDO from glucose (AE 48.9%, RME 2.6%), with a total butanediol yield of 23.1% from glucose (10.4% RME). A route for direct fermentation of optically pure 1,3-BDO does not exist in nature and thus had to be engineered. This was first successfully achieved and reported in 2009 using *E.Coli* to give modest yields of 7% but with high purity towards the more valuable R isomer from glucose.[6] After this initial success, a number of routes to 1,3-BDO were then pursued, with the best reported to date being 44% (AE 50%, RME 22%) in batch trials and 37% (RME 18.5%) in continuous fed batch.

Current applications of 1,3-butanediol

The highest cost current application of BDO is as a precursor to beta-lactams which constitute the most commonly used antibiotics. Although many antibiotics can generally be manufactured bio-catalytically, roughly 75% of penicillin produced is consumed as feedstock in the formation of semi synthetic antibiotics.[7] Many of these class of antibiotics require optically pure (R)-1,3-BDO in their synthesis, specifically penems and carbapenems.[8] The other major use is in the cosmetics industry where a high grade of BDO is required in order to eliminate odorous side products from the industrial route.[9] High purity 1,3-BDO is utilised as a low volatility moisturising agent, as well as helping to disperse hydrophobic and hydrophilic components in cosmetic formulations and imparting antibacterial properties.[10]

Future markets and applications

1,3-BDO is already applied in resins and polymers but its use is limited due to cost. With an increase in supply, this would be expected to expand. One such area is the formation of cyclic carbonates, which have interesting properties in their own right as solvents, and can be used to form a range of polycarbonates.[11] The low toxicity and high biodegradability of this class of polymers results in numerous uses in biomedical electrolytes, binders, thermoplastics, and adhesives.[11] Another route to useful polymers and plastics is the dehydration of any BDO to give 1,3 butadiene, which in turn can be used in the production of the commodity polymer synthetic styrene-butadiene rubber (SBR).[12] In a similar vein, the reaction of BDO with dimethyl sulphate can be used to form the cyclic butylene glycol sulphite. This is a potential polar aprotic solvent, which is an area under much investigation, with one already proven application being its use as an electrolyte in lithium ion batteries.[13]



References: **1.** US5413922A, **2.a** JP5684657, **b** US10071937B2, **3.a** DOI.org/10.1016/j.ymben.2018.04.013, **b** DOI.org/10.1080/09168451.2014.891933, **4.** DOI.org/10.1080/00397919108021588, **5.** DOI.org/10.1007/s00253-009-1871-5, **6.** WO2011052718A1, **7.** doi.org/10.1007/s00253-003-1274-y, **8.** DOI.org/10.1002/9780470054581.eib640, **9.** EP0616992 (A1) **10.** DOI.org/10.11311/jscta1974.26.2, **11.** DOI.org/10.1039/C5RA07290E, **12.** WO2016092063A1, **13.a** EP2648267, **b** CN106749165A

Additional feedstocks

As only glucose has been applied in the production of 1,3-BDO the feedstocks will be limited to primary biomass. Here this class of feedstock has been investigated to determine how much would be required to supply a 10 kton 1,3-BDO plant.

First generation biomass

The crops presented are those that are most intensively farmed in the UK, principally as food crops, although a small percentage of wheat, maize and sugar beet are also utilised in industrial applications. Sugar cane figures are from Brazil.*

crop	ktons needed to supply a 10 kton 1,3-butandiol plant	ktons produced per annum (UK)	% required
wheat	59.1	14837	0.40
barley	59.1	7169	0.82
maize	58.3	3054	1.91
sugar beet	253.7	8325	3.05
potatoes	246.4	5075	4.86
field beans	239.6	965	24.83
oats	65.3	875	7.47
sugar cane*	431.2	666925	0.06