A Platinum Open Access Journal
for Organic Chemistry

Review

Free to Authors and Readers

DOAJ Seal

Arkivoc **2022**, part vi, 0-0
to be inserted by editorial office

A review on synthetic methods for 2-Deoxy-D-glucose

Raman Singh[a], Vidushi Gupta[b], and Kuldeep Singh[c,*]

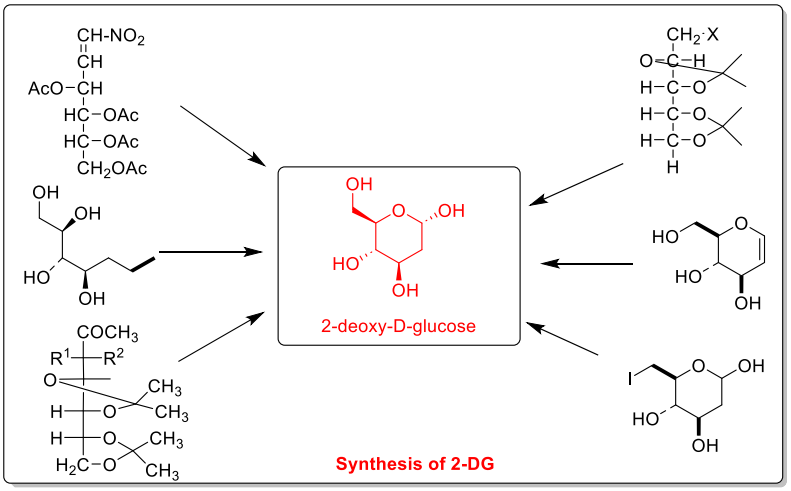
[a]*Division Chemistry and Toxicology, WTL-Clean and Renewable Energy Pvt Ltd, New Delhi*
[b]*Department of Chemistry, Indian Institute of Science Education and Research, Mohali, Punjab-India*
[c]*Department of Applied Chemistry, Amity University Madhya Pradesh, Gwalior, M.P. – 474005, India*
Email: singh@orgsyn.in

Dedicated to Prof. S. Kotha on his 65th Birthday

Received 12-11-2022 **Accepted** 03-09-2023 **Published on line** 03-19-2023

Abstract

2-Deoxy-D-glucose (2-DG) is a non-metabolizable glucose analog that has shown promising pharmacological activities and has been used to study the role of glucose in cancer cells. 2-DG is an inhibitor of glycolysis, potential Energy Restriction Mimetic agent and inhibits pathogen-associated molecular patterns. Its radioisotope derivatives have application as tracers. Recently, 2-DG has been used as an anti-COVID-19 drug lowering the need for supplemental oxygen. In this review, different synthetic strategies for preparation of 2-DG including enzymatic synthesis have been discussed. The understanding of these methods would help in developing therapeutics or diagnostic agents aimed at exploring therapeutic targets related with energy metabolism.



Keywords: 2-DG, aerobic glycolysis, Warburg effect, COVID-19.

Table of Contents

1. Introduction

Energy is an essential requirement for sustaining life in all living organisms. From primitive life to multicellular organized living organisms, glucose is the primary source of the energy. Diseases such as cancer, viral infections and COVID-19 are found to do rewiring in cell metabolism such that the cell start using primarily glycolysis (Warburg effect)[1] to fulfill high energy demand required for high rate of proliferation of diseased cell or virus. In principle, these infected or diseased cells can be targeted by interfering with glycolysis,[2] as the normal cells can rely on fatty acid and keto bodies such as β-hydroxybutyrate metabolism to get essential energy. Lipid metabolism produces acetyl CoA that enters in to citric acid cycle and oxidative phosphorylation.[3]

2-Deoxy-D-glucose (2-DG, 2-deoxy-D-*arabino*-hexopyranose, **1**) was realized as non-metabolizable glucose analog and a competitive inhibitor of glycolysis[4] in which the 2-hydroxyl group of glucose is replaced by hydrogen.[5] Researchers has exploited its application in diagnostics,[6–8] potential in different biological activities including herbicidal activity,[9] as an adjunct to chemotherapy and radiotherapy in the treatment of solid tumors,[10] as an antiviral treatment in herpes simplex patients, and as an antiepileptic in temporal lobe epilepsy patients (Figure 1). Recently, 2-DG has attracted attention due to its application in COVID-19 treatment to lower the need for supplemental oxygen.[2,11,12]

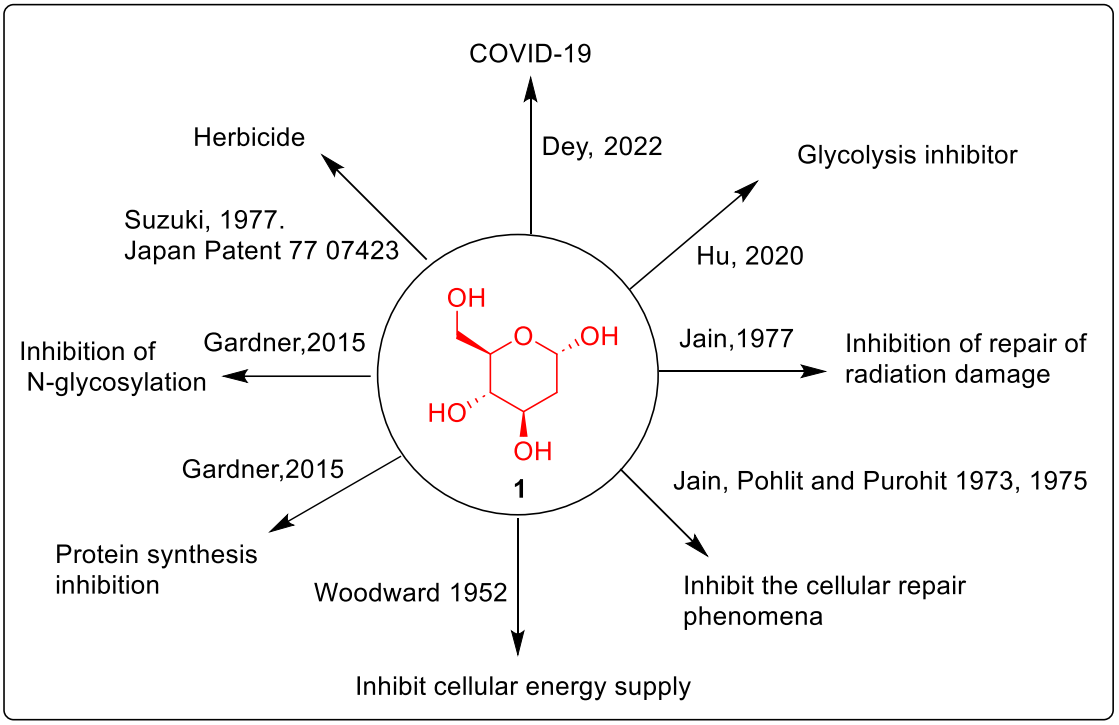


Figure 1. Different Pharmacological Activities of 2-DG.

This review discusses structure, druggability, analysis, estimation, toxicology, handling and preparation of 2-DG. We have focusses on various synthetic strategies for synthesis of 2-DG and isotopic 2-DG. Derivatives of 2-DG have not been considered in this review article.

2. Structure, Physical Properties and Characterization of 2-DG

Structure of 2-DG has been depicted in Figure 2, and it has been assigned CAS number: 154-17-6. Its synonyms are 2-deoxy-D-Glucose, 2-Deoxy-D-*arabino*-hexose; D-*Arabino*-2-deoxyhexose. 2-DG is a crystalline white to off-white solid with a melting point at 146 °C.[13] Recrystallized 2-DG from methanol as colorless needles has mp at 151-154° and $[\alpha]_D^{15}$ +43.0° (c=1.0, H_2O).[14] Other values of specific rotation at different conditions is $[\alpha]_D^{23}$ +48.8° (c 0.13, water).[15] The α-pyranose form of the reducing aldose 2-deoxy-D-*arabino*-hexose (2-Deoxy-D-*arabino*-hexopyranose) adopts a $^4C_1$ conformation, with the anomeric hydroxy group in axial and the other substituents in equatorial positions. A three-dimensional hydrogen-bonded network is created in the crystal as a result of the four hydroxy groups each serving as an intermolecular hydrogen-bond donor function.[16]

2-DG is found in nature.[14,17] 2-deoxy-α-D-*arabino*-hexopyranose, and 2-deoxy-β-D-*arabino*-hexopyranose have been isolated from the carbohydrate portion of the solid-state fermentation extract of *Actinosynnema pretiosum* ssp. auranticum ATCC 31565.[17]

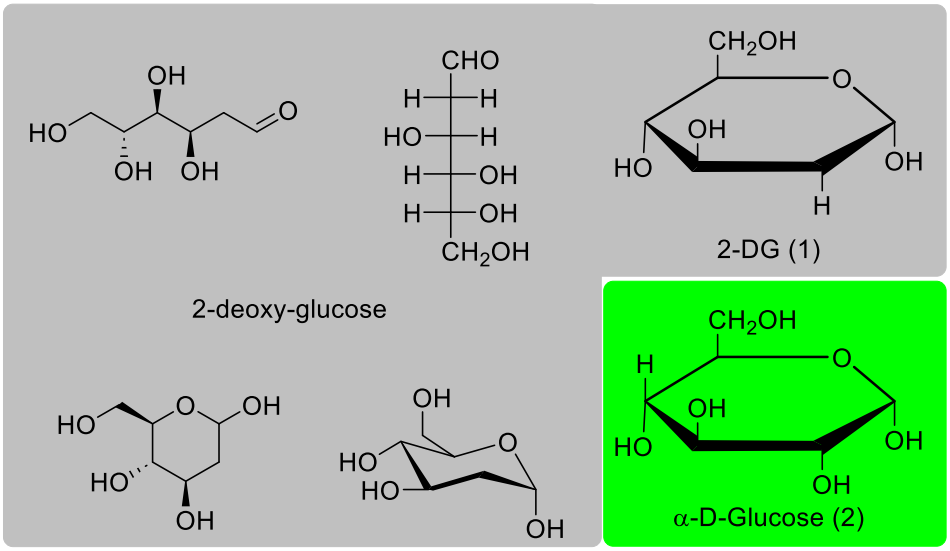


Figure 2. Structure of 2-deoxy-D-Glucose (CAS: 154-17-6), Synonyms: 2-DG; 2-Deoxy-D-*arabino*-hexose; 2-Deoxy-D-*arabino*-hexopyranose.

IR spectrum of 2-DG shows Carbonyl band at 1722 cm^{-1} and Enediol band at 1658 cm^{-1}.[18] ^{1}H-NMR peaks have been listed in Table 1, and ^{13}C NMR shows signals at δ 39.53, 41.77 (C-2), 63.02, 63.27, 70.26, 72.77, 73.17, 73.50, 74.31, 78.31 (C-3,4,5,6), 93.61, and 95.73 (C-1).[19] Recently ^{1}H and data for 2-deoxy- β-D-glucose has been recorded in C_5D_5N using 600 MHz instrument (Table 1).[20]

Table 1. NMR Data of 2-DG

	^{1}H NMR			^{13}C NMR
	α -pyranose	β -pyranose	β -pyranose	β -pyranose
Solvent	D_2O[19]	D_2O[19]	C_5D_5N (600 MHz)[20]	C_5D_5N, 2D HSQC, 150 MHz[20]
H-1	5.39 (broad d, J 3.6 Hz)	4.94 (dd, *J* 9.7 Hz, 1.1Hz)	5.41, dd (*J* 9.7, 1.9 Hz)	95.4
H-2a		1.29-1.87 m	2.79, ddd (*J* 12.4, 4.9, 1.9 Hz)	43
H-2e		2.03-2.40 m	2.30, td (*J* 12.0, 9.7 Hz)	
H-3			4.25, ddd (11.8, 8.6, 4.9 Hz)	72.9
H-4			4.09, t (8.9 Hz)	73.8
H-5		3.26-4.12 m	3.92, ddd (9.4, 5.6, 2.7 Hz)	78.7
H-6a			4.59, dd (11.6, 2.7)	63.4
H-6e			4.42, dd (11.6, 5.6)	

3. Analysis of 2-Deoxy-D-glucose

2-DG reduces Fehling's solution and gives a positive Keller-Kiliani reaction.[14] 2-Deoxy-D-glucose (2-DG) concentration and purity can be measured in a sample of crystalline or liquid by HPLC with accuracy and precision suitable for analysis of active pharmaceutical ingredients and drug products.[21]

The method is suitable for the standardization and quality control of the APIs and drugs.[21] UV-HPLC (195 nm) has been used to detect and quantify 2-DG using µBondapak 10 µm NH_2 column and a Varian Micropak 10 µm NH_2 column. The retention time is usually four minutes with eluent 85% MeCN/H_2O.[22] Polymer-based amino column (HILICpak VG-50 4E column) and Shodex SUGAR SC1011 columns have also been used in the separation of 2-DG and glucose. Pharmacokinetic studies of 2-DG involves estimation of 2-Deoxyglucose in the plasma. [23] For this purpose, precolumn fluorescent derivatization was achieved by reductive amination of 2-DG using sodium cyanoborohydride and 2-aminobenzoic acid.[23]

4. Druggability of 2-DG

2-DG blocks the activity of different enzymes involved in glycolysis, leading to cell death. 2-DG has a molecular weight of 164.158 Da, logP of-1.525, five Hydrogen Bond Acceptors (HBA), and four Hydrogen Bond donors (HBD). Thus, there are four matching Lipinski Rules. The polar Surface Area (PSA) of 2-DG was 90.15, and it consisted of one Rotatable Bond (RotB). Thus, two matching Veber Rules exist. Approval[11] of 2-DG for emergency uses in hospitals to treat COVID-19 patients requiring supplemental oxygen in India highlighted 2-DG, and also a new hope is evolved for development of safe drug to end current pandemic. Mutation in the virus is of much concern, which results in deactivation of available drugs and monoclonal vaccines. Thus, a target which is not directly affected via mutation has its own value. Targeting glycolysis in energy hungry infected cells will stop the multiplication of virus.[24–27] Different studies has used variable amount of 2-DG, however maximum tolerable dose reported is 250 mg/kg body weight (BW).[28]

5. Toxicology and Handling of 2-DG

2-Deoxyglucose (2-DG) is a toxic glucose analog. 2-DG has a pleiotropic mechanism of action.[29–31] 2-DG contains a structural resemblance with glucose and mannose. Due to this resemblance with mannose, 2-DG strongly interferes in the N-linked glycosylation process,[29] resulted to halt protein synthesis and cause endoplasmic reticulum (ER) stress.[29,32] 2-DG stimulates autophagy, enhances oxidative stress, and suppresses N-linked glycosylation.[33] Ketogenic Diet increases tolerance against glycolysis inhibitors.[3] 2-DG should be handled with hand protection and mask. Exposure to moisture should be avoided.

6. Methods for Synthesis of 2-DG

A good number of methods are reported in the literature for the synthesis of 2-DG. These methods suffer from different operational problems, such as low yield, tedious workup or purification, low purity of the product due to formation of diastereomeric mixture or racemic mixture.

As D-Glucose and D-mannose are epimers at C-2, the deoxygenation at C-2 gives one identical product, i.e., 2-DG (Figure 3).[34]

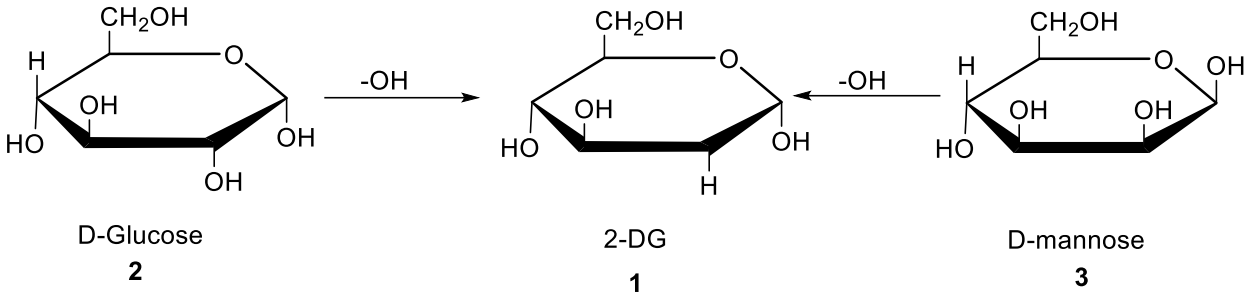


Figure 3. DG from D-Glucose and D-Mannose.

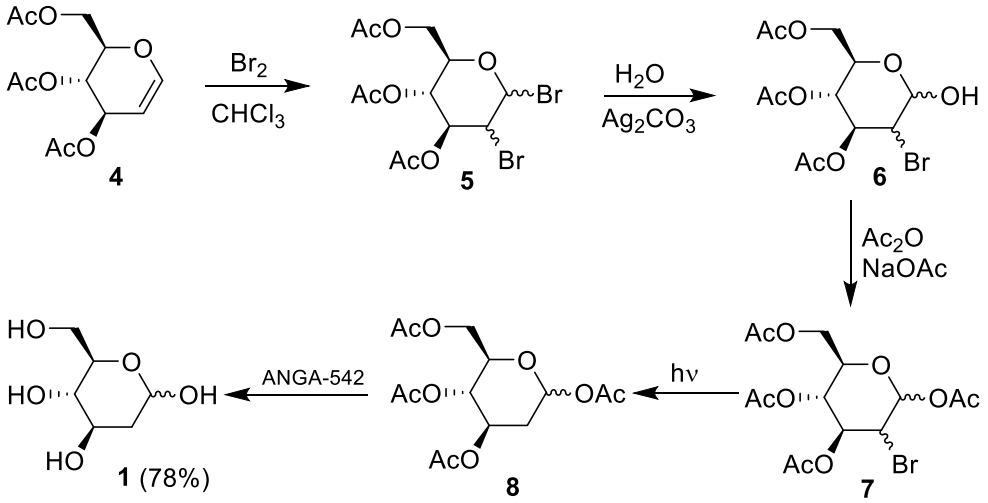
6.1. From Glucal and its derivatives

Glucal is the glycal formed from glucose and is one of the common starting materials for the synthesis of 2-DG. A general conversion involves bromination (or halogenation) of Glycal at C-2 followed by the replacement of bromine with hydrogen. Bromination takes place in nucleophilic solvent using molecular bromine. A number of reagents have been used to replace bromine attached to C-2 with hydrogen are shown in Table 2.

Table 2. Reagents used to replace bromine attached to C-2 with a hydrogen

S.No.	Catalyst/Reagent or Condition	Reference
1.	Photolysis	Binkley and Bankaitis, 1982 [35]
2.	Raney nickel/ H_2	Monneret, 1983 [36]
3.	Pd/C	Mereyala and Mamidyala, 2004 [37]
4.	Zn/NaH_2PO_4	Xu et al., 2017 [38]

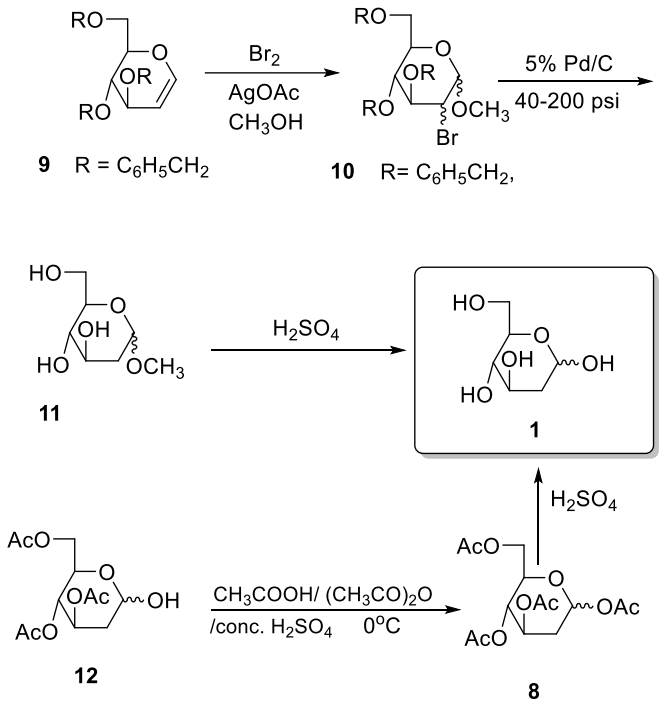
Binkley et. al. reported photolysis of α and β anomers of **7** to yield α and β anomers of **8**. Treatment of **8** with Baker ion exchange resin ANGA-542 in methanol produced 2-DG in 78% yield.[35] The compound **7** was synthesized by nucleophilic bromination of **4** followed by hydrolysis and acetylation (Scheme 1).[35]



Scheme 1. Preparation of 2-DG by photolysis of α and β anomers of **7.**

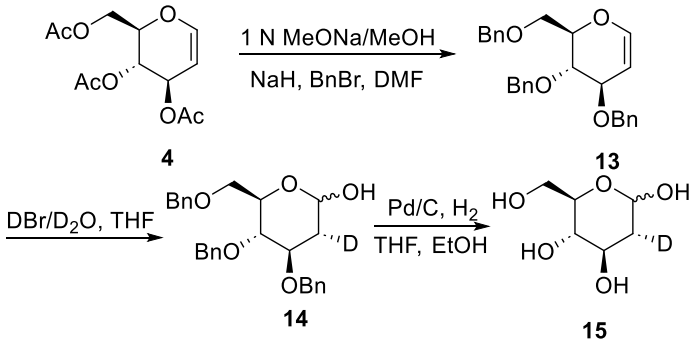
Monneret and his co-workers reported 95% yield in the synthesis of 2-DG from 3,4,6-tri-O-acetyl-l,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol.[36] The method uses N-bromosuccinimide for bromination and hydrogen (1 bar)/Raney Ni for debromination.

Mereyala and coworkers reported an economical and high-yielding process for the synthesis of 2-DG with high purity. (R)-D-Glycal is used as a starting material (Scheme 2).[37]



Scheme 2. Synthesis of 2-DG from D-glucal.

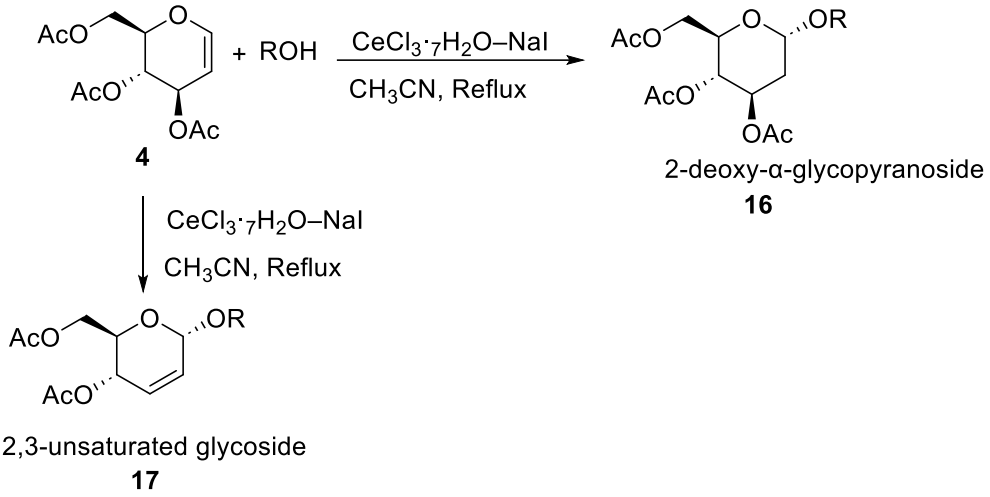
Synthesis of 2-deoxy-D-glucose involves hydrolyses of alkyl 2-deoxy-α/β-D-glucopyranoside. The latter was prepared by haloalkoxylation of R-D-Glucal (R = H, 3,4,6-tri-O-benzyl) to yield alkyl 2-deoxy-2-halo-R-α/β-D-gluco/mannopyranoside and reducing alkyl 2-deoxy-2-halo-R-α/β-D-gluco/mannopyranoside.[37] Fokt et al reported synthesis of 2-deutero-2-DG **15** in 42% yield by debenzylation of **14** (Scheme 3).[29]



Scheme 3. Synthesis of 2-deoxy-2-deutero-D-glucose.

Interestingly, Yadav and co-workers have reported highly stereoselective addition of alcohol to **4** in presence of $CeCl_3 \cdot 7H_2O$–NaI reagent system in refluxing acetonitrile under neutral conditions to afford the

corresponding 2-deoxy-α-glycopyranosides in high yields.[39] In absence of NaI, the glycals underwent Ferrier rearrangement to give 2,3-unsaturated glycosides (Scheme 4). However this methodology has not been extended to produce 2-DG. Although this methodology could be very straight forward way to produce 2-DG, it has not been extended to produce 2-DG (Scheme 4). However, deprotection of C-1 alcohol could be carried out by different literature procedures.[40–43] 2-deoxy-α-glycopyranosides can be reduced to give 2-DG.[37]

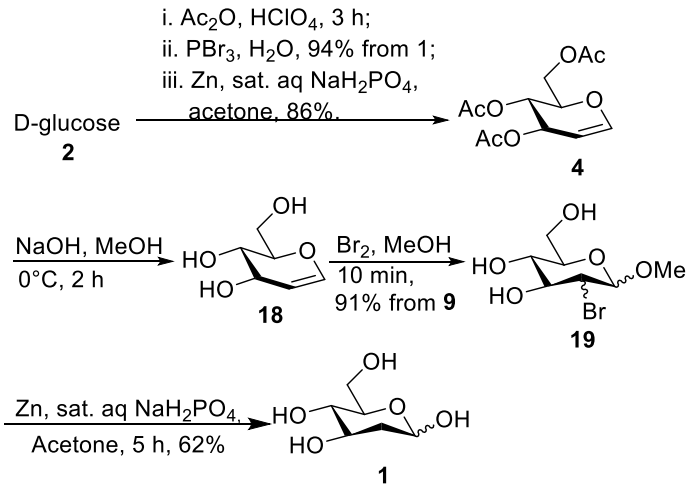


Scheme 4. Synthesis of 2-deoxy-α-glycopyranoside.

Reaction of *N*-iodosuccinimide (NIS) with 3,4,6-tri-*O*-benzyl-D-glucal or 3,4-di-*O*-benzyl-6-*O*-TIPS-D-glucal forms a stereoisomeric mixture of 2-deoxy-2-iodoglucopyranose. Reduction of later with $Na_2S_2O_4$ followed by debenzylation generates 2-deoxyglucopyranose.[44]

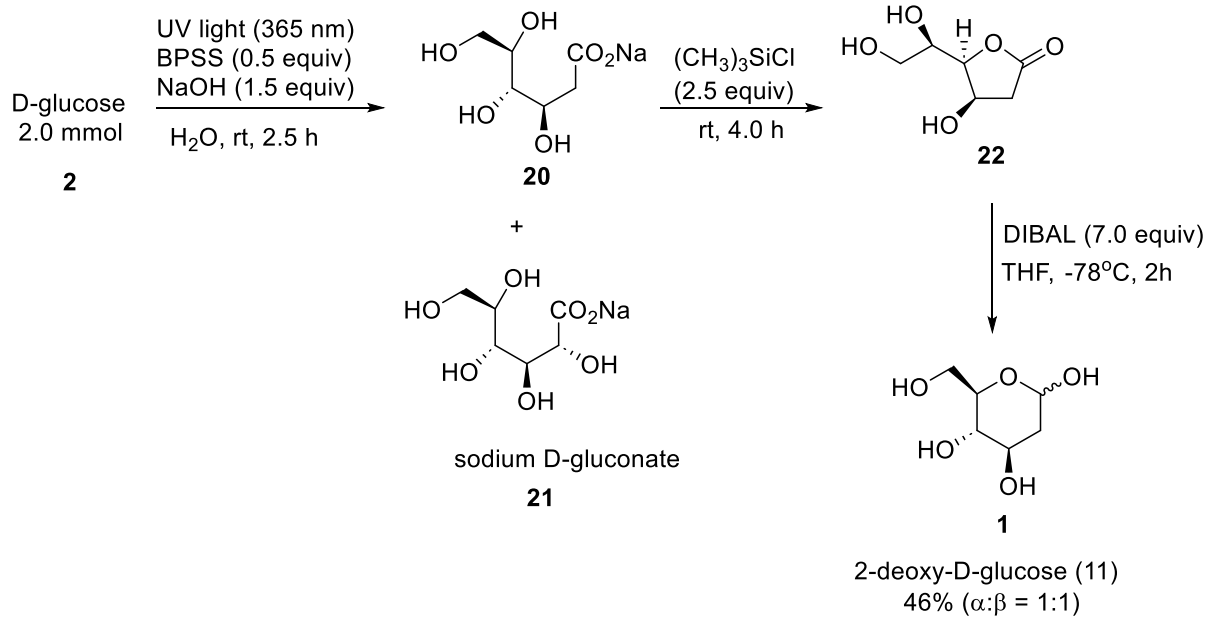
6.2. Preparation of 2-DG from D-glucose

Xu and coworkers reported preparation of 2-DG from D-glucose. 2-DG was obtained in 62% yield (Scheme 5).[38]



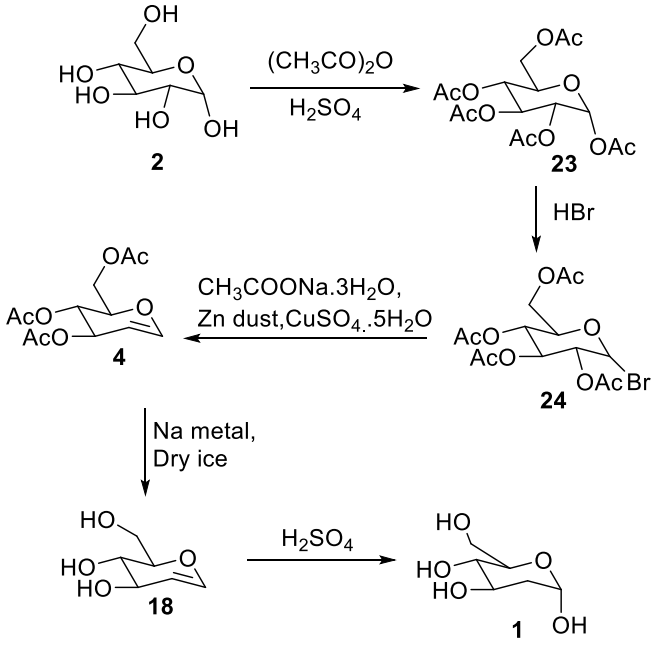
Scheme 5. Synthesis of 2-DG from D-glucose.

Masuda and coworkers reported 2-DG from D-glucose. 2-Deoxy-D-glucose was prepared in three steps from natural D-glucose dispensing with any protection/deprotection procedure and was obtained in 48% yield (Scheme 6).[45]



Scheme 6. Synthesis of 2-deoxy-D-glucose (1).

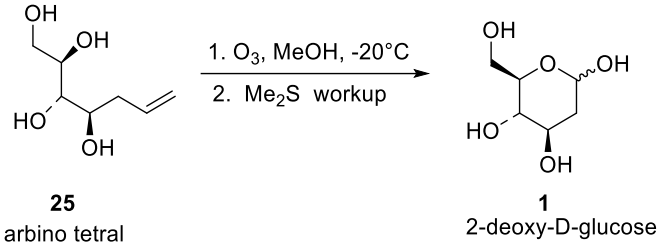
Cramer prepared 2-DG from **2**. Low yields and impurity in the product are major disadvantage of this process (Scheme 7).[46,47]



Scheme 7. Synthesis of 2-DG from D-Glucose.

6.3. Synthesis of 2-DG by ozonolysis of Tetrols

Roush and coworker synthesized 2-DG by ozonolysis of Tetrols **25**. Tetrols **25** was generated by methanolysis of the corresponding tetraacetates (Scheme 8).[48]

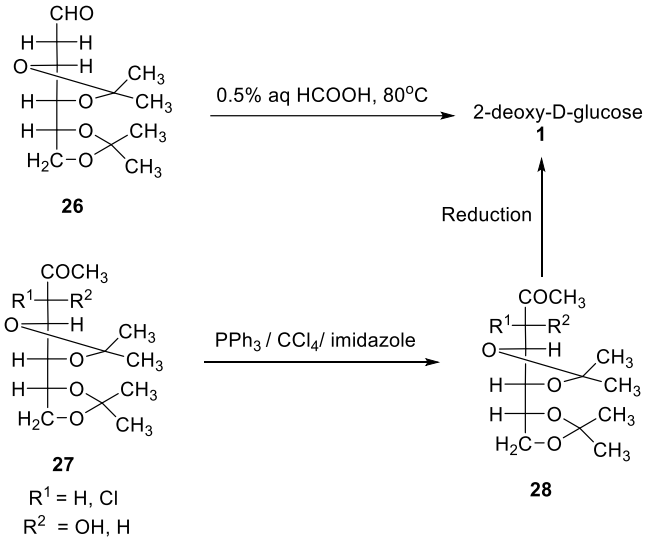


25
arbino tetral

1
2-deoxy-D-glucose

Scheme 8. Synthesis of 2-DG by ozonolysis of Tetrols **25.**

Regeling et al. synthesized 2-deoxy-D-glucose from **30** (Scheme 9).[49]



26

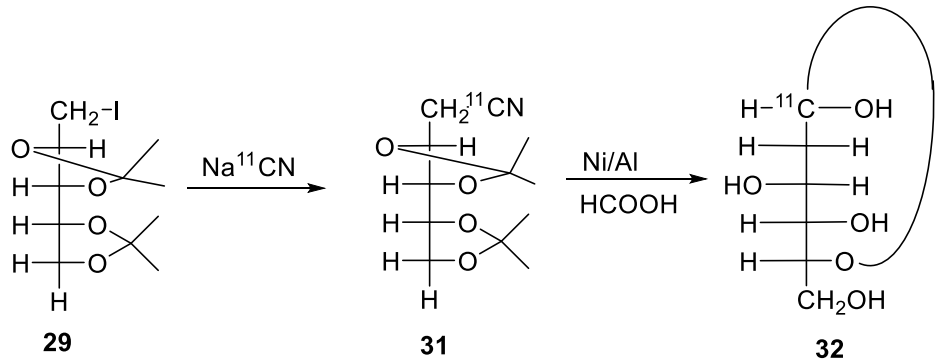
27
R^1 = H, Cl
R^2 = OH, H

28

Scheme 9. Synthesis of 2-deoxy-D-glucose.

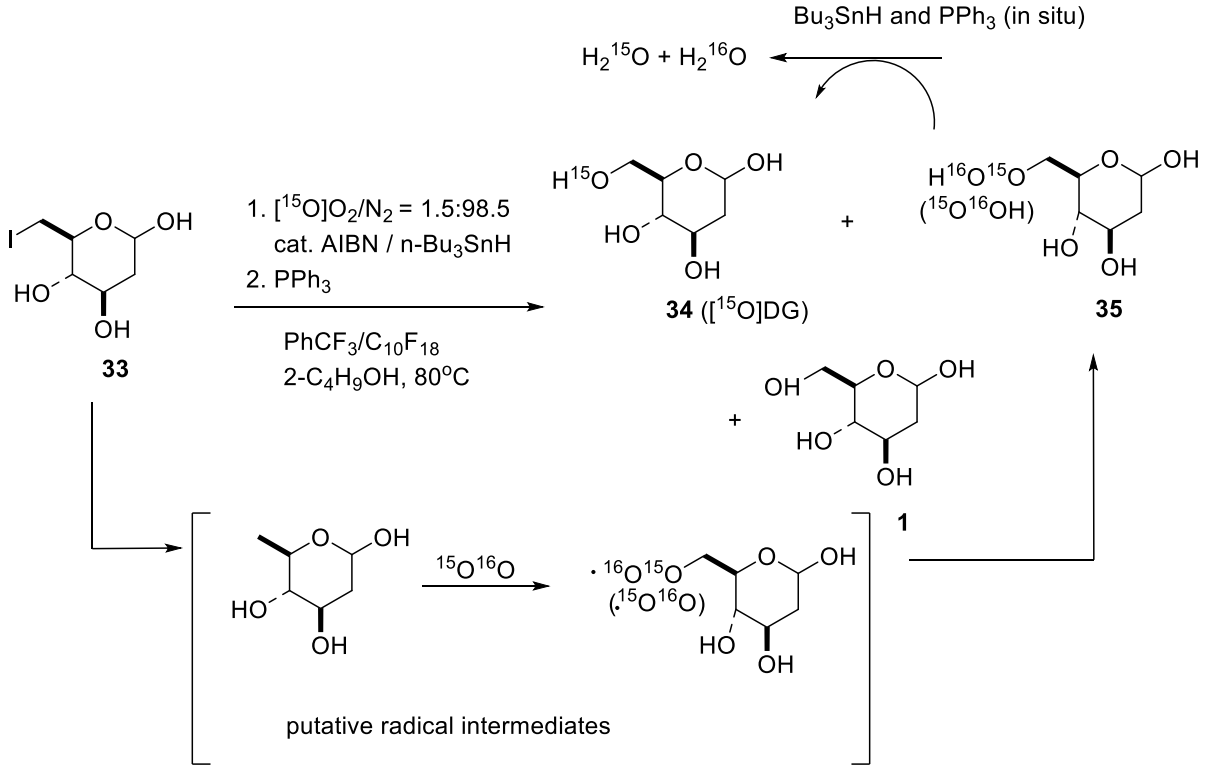
6.4. Synthesis of labelled 2-DG

Van Haver and co-workers reported 2-deoxy-D-[1-^{11}C] glucose. Purification of the intermediate was done before reduction by HPLC (Scheme 10).[50]



Scheme 10. Synthetic route to 2-deoxy-D- [1-^{11}C] glucose.

Yorimitsu et al. synthesized 6-[^{15}O]-2-DG from **33**. Computer-controlled, fully automated synthesis equipment was used for synthesis and purification (Scheme 11).[51]

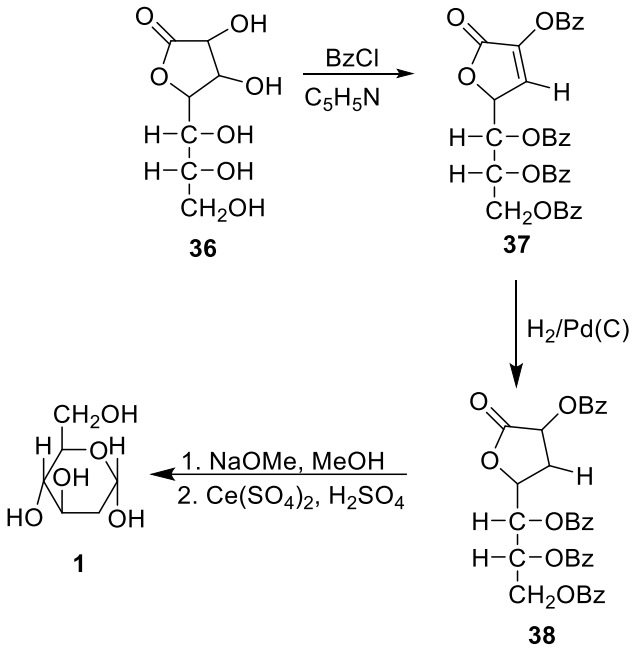


Scheme 11. Rapid synthesis of 6-[^{15}O]-2-deoxy-D-glucose.

2-DG-derived platinum (II) conjugates were synthesized from acetylated 2-deoxyglucose derivatives by platination reaction with 1*R*,2*R*-diaminocyclohexaneplatinumsulfate (Pt(DACH)SO_4) in the presence of barium hydroxide in water.[52]

6.5. Preparation of 2-deoxyglucoses from γ-lactones

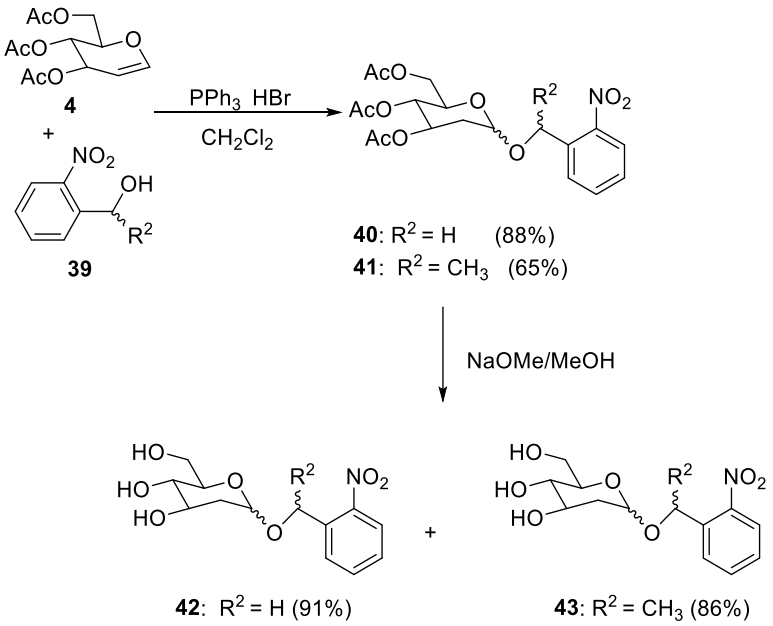
Sala and coworkers reported the synthesis of 2-DG using **36** as starting material (Scheme 12).[53]



Scheme 12. Synthesis of 2-DG from γ-lactone **36.**

6.6. Preparation of caged-2-deoxyglucoses

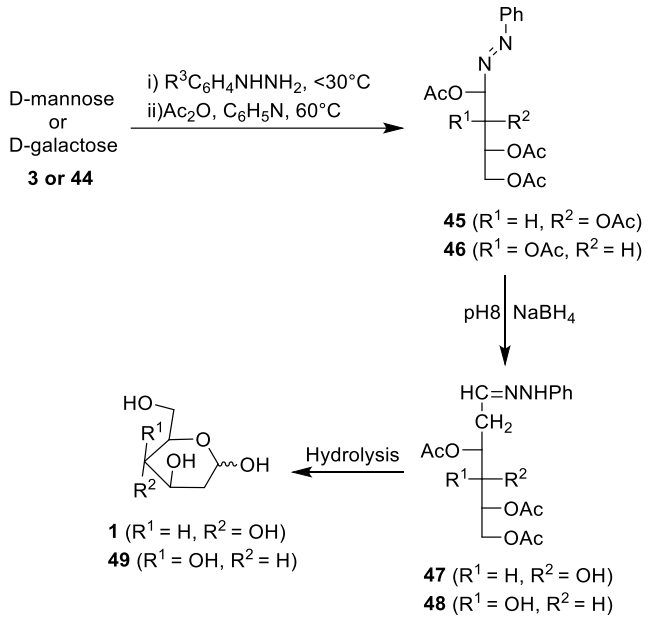
Watanabe and colleagues reported synthesis of caged-2-deoxyglucoses **42** and **43** from **4** with moderate to good yields with α/β ratio of 7/3 and 4/1 respectively (Scheme 13).[54]



Scheme 13. Synthesis of caged-2-deoxyglucoses **42** and **43** from **4.**

6.7. Preparation of 2-DG from phenylhydrazone

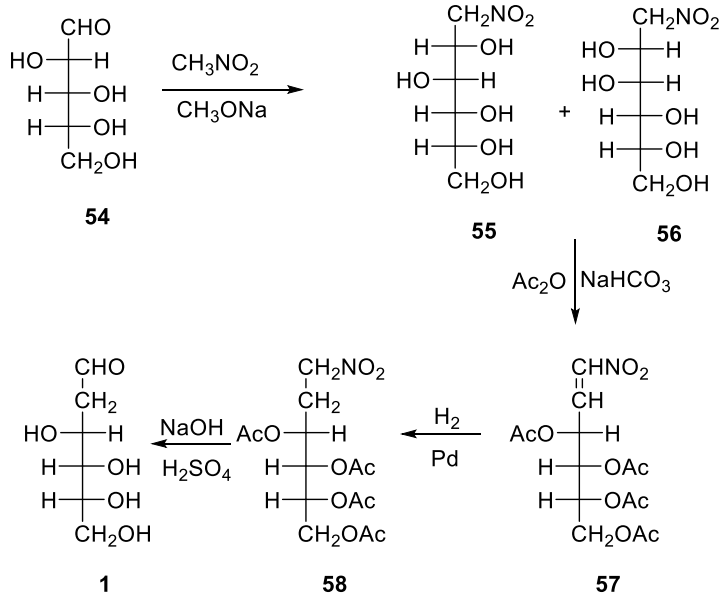
Jogersen and his co-workers synthesized 2-DG and its epimer **49** in 13:7 ratio from phenylhydrazone of D-mannose (Scheme 14).[55]



Scheme 14. Synthesis of 2-DG from D-mannose.

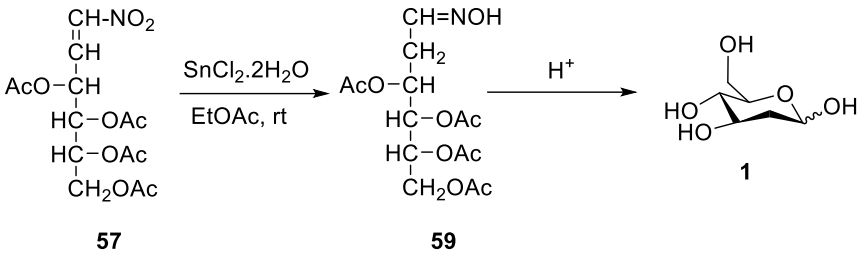
6.9. Preparation of 2-DG from D-*arabino*se

Sowden and his co-workers reported the synthesis of D-arabo-2-desoxyhexose from ribose (Scheme 16).[56]



Scheme 16. Synthesis of 2-desoxy-D-*arabino*-hexose from D-*arabino*se.

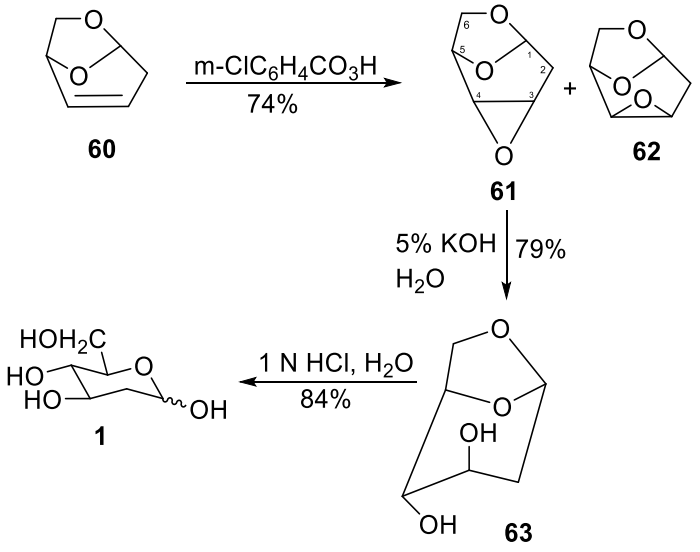
Koos and coworker reported synthesis of 2-DG from tetraacetoxy-D-*arabino*-1-nitro-1-hexene **57** (Scheme 17) in 73% yield as diastereomeric mixture using $SnCl_2$.[57] The reaction occur at room temperature. The starting material **57** is required to be prepared.



Scheme 17. synthesis of 2-DG from tetraacetoxy-D-*arabino*-1-nitro-1-hexene.

6.10. Preparation of 2-DG from 6,8-Dioxabicyclo[3.2.1]oct-2-ene

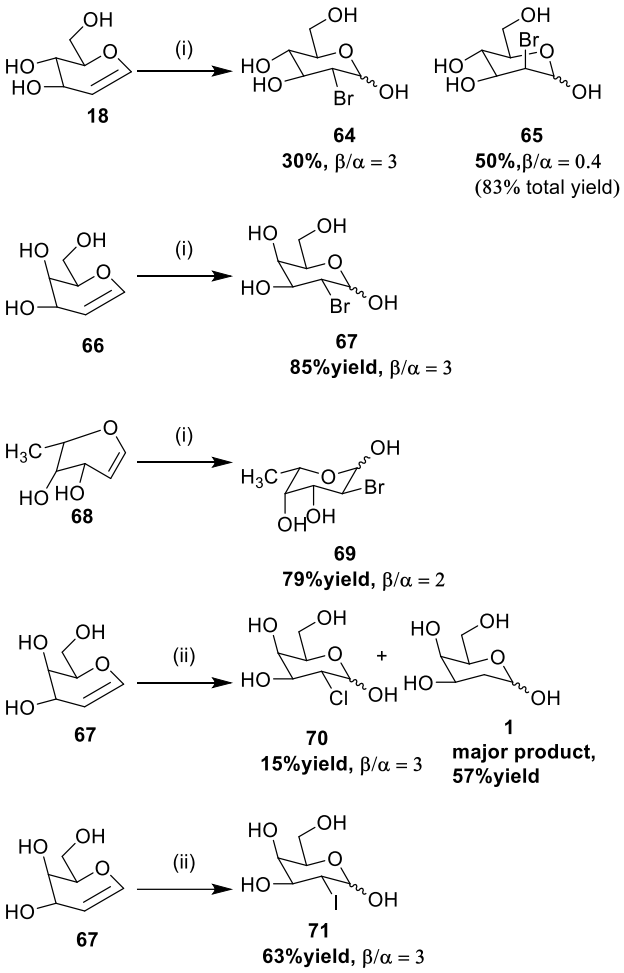
Murray and his co-workers reported conversion of **60** into 1,6-anhydro-2-deoxy-β-DL-*arabino*-hexopyranose using m-CPBA and subsequent alkaline hydrolysis. The bicyclic compound **63** hydrolyzed in presence of acid to yield **1** (Scheme 18)**.**[58] The drawback of this method is multistep synthesis of **60**.[59]



Scheme 18. Synthesis of 2-DG by hydrolysis of bicyclic compound **63.**

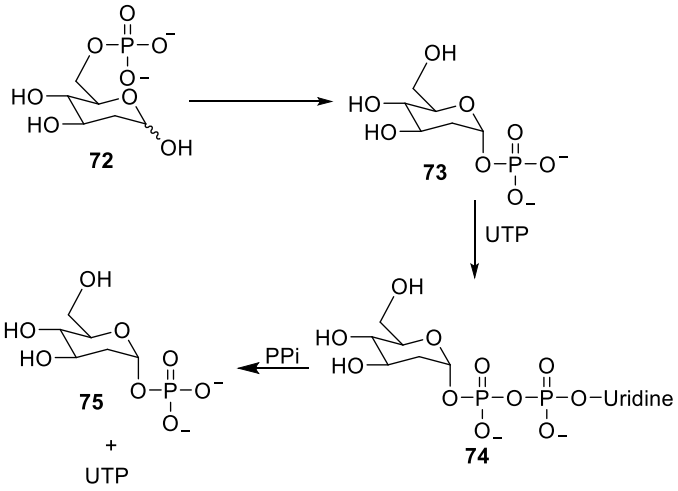
6.11. Enzymatic Syntheses of 2-DG

Lee and coworkers have reported the synthesis of 2-DG containing maltooligosaccharides (2-DG-Mos) from pre-warmed substrate mixture (Tris–HCl buffer (pH 7.0), 2-DG, and sucrose) taken at different interval of time at 35 ^{o}C and purified recombinant AS. The enzymatic reaction was terminated with the boiling water bath.[60] Enzymatic halohydrations of D-galactal, D-glucal, and L-fucal has been reported by Liu and his co-workers. 2-halo-2-deoxy sugars were prepared by Chloroperoxidase-catalyzed Bromohydration and iodohydration reactions of three glycals in good yields (Scheme – 19).[61]



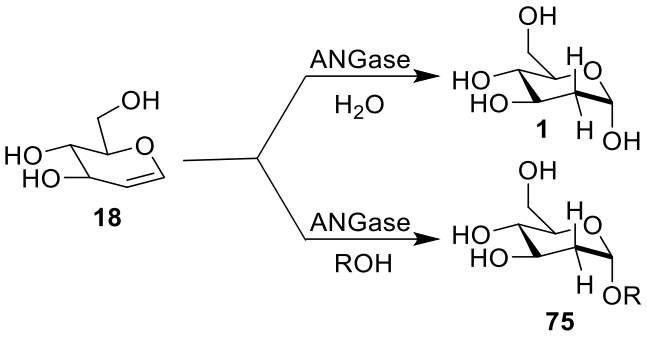
Scheme 19. Reagent and reaction conditions: (i) Chloroperoxidase, KBr, H_2O_2, pH 3 buffer solution, 2 hr; (ii) Chloroperoxidase, H_2O_2, KCl, pH 3, 3 days; (iii) H_2O_2, KCl, pH 3, 30 min, with or without chloroperoxidase.

Percival and his co-workers synthesized **75** from **72** forming an intermediate **74** through the enzymatic process (Scheme 20).[62]



Scheme 20. Synthesis of 2-deoxy-alpha-D-glucopyranosyl phosphate.

Kim and coworkers (Scheme 21) synthesized 2-DG and alkyl α-D-2-deoxyglucosides (A2DGs) by using *Aspergillus niger* α-glucosidase (ANGase).[63]



R: $-CH_3$, $-(CH_2)_nCH_3$ [n = 1–7], cyclohexyl, benzyl, $-CH(CH_3)CH_3$, $-CH_2CH(CH_3)CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH{=}CH_2$,CH_2,

Scheme 21. Synthesis of alkyl α-D-2-deoxyglucosides by using *Aspergillus niger* α-glucosidase.

2-DG was produced in 95% yield by using multistep procedure using Rabbit muscle aldolase (RAMA, D-fructose-1,6-diphosphate aldolase). RAMA catalyzed reaction of 1,3-dioxane-2-acetaldehyde with DHAP followed by dephosphorylation with AP produced a ketone. The $NaHB(OAC)_3$ mediated reduction of the ketone gave a mixture of diastereomers in a 2:1 ratio in 75% yield. The 5S isomer was resolved to give acetal in 55% yield. The deprotection of the acetal with aqueous 1.0 M HCl/THF (1:1) yielded 2-deoxy-D-*arabino*-hexose (95%).[64]

7. Conclusions

The molecule 2-DG follows the Lipinski rule of five and has several activities such as antagonist of glucose metabolism, inhibition of sugar uptake, antiviral uses, antiinflammation activity, and anticancer activity. It is used as a metabolite inhibitor and tracer. 2-DG is a dual D-glucose and D-mannose mimetic. Recent interest due to its use in COVID-19 has again risen. As the present synthetic methods are tedious, and expensive, there is scope for developing a new economical process using more mild conditions to synthesize 2-deoxy-D-glucose with good yield and purity. It will open up development of new antiviral drugs and treatment for hyperglycemic patients.

Acknowledgements

Authors acknowledges infrastructural support from their respective institutions.

References

1. Zhang, X. D.; Deslandes, E.; Villedieu, M.; Poulain, L.; Duval, M.; Gauduchon, P.; Schwartz, L.; Icard, P.

Anticancer Res. **2006**, *26*, 3561.
2. Dey, S.; Murmu, N.; Mondal, T.; Saha, I.; Chatterjee, S.; Manna, R.; Haldar, S.; Dash, S. K.; Sarkar, T. R.; Giri, B. *Biomed. Pharmacother.* **2022**, *156*, 113801. https://doi.org/10.1016/j.biopha.2022.113801
3. Voss, M.; Lorenz, N.; Luger, A.-L.; Steinbach, J.; Rieger, J.; Ronellenfitsch, M. *Int. J. Mol. Sci.* **2018**, *19*, 2462. https://doi.org/10.3390/ijms19082462
4. Zhu, G.; Guo, N.; Yong, Y.; Xiong, Y.; Tong, Q. *Bioprocess Biosyst. Eng.* **2019**, *0*, 0. https://doi.org/10.3390/ijms19082462
5. Xi, H.; Kurtoglu, M.; Lampidis, T. J. *IUBMB Life* **2014**, *66*, 110. https://doi.org/10.1002/iub.1251
6. Zanello, M.; Bozier, E.; Pallud, J. *World Neurosurg.* **2022**, *159*, 144. https://doi.org/10.1016/j.wneu.2022.01.003
7. Eibschutz, L. S.; Rabiee, B.; Asadollahi, S.; Gupta, A.; Assadi, M.; Alavi, A.; Gholamrezanezhad, A. *Semin. Nucl. Med.* **2022**, *52*, 61. https://doi.org/10.1053/j.semnuclmed.2021.06.017
8. Ferreira, M.; Lovinfosse, P.; Hermesse, J.; Decuypere, M.; Rousseau, C.; Lucia, F.; Schick, U.; Reinhold, C.; Robin, P.; Hatt, M.; Visvikis, D.; Bernard, C.; Leijenaar, R. T. H.; Kridelka, F.; Lambin, P.; Meyer, P. E.; Hustinx, R. *Eur. J. Nucl. Med. Mol. Imaging* **2021**, *48*, 3432. https://doi.org/10.1007/s00259-021-05303-5
9. Suzuki, Y. 77 07423 01/20/77, **1977**. https://doi.org/10.1093/comjnl/20.1.77
10. Fadaka, A.; Ajiboye, B.; Ojo, O.; Adewale, O.; Olayide, I.; Emuowhochere, R. *J. Oncol. Sci.* **2017**, *3*, 45. https://doi.org/10.1016/j.jons.2017.06.002
11. Aiestaran-Zelaia, I.; Sánchez-Guisado, M. J.; Villar-Fernandez, M.; Azkargorta, M.; Fadon-Padilla, L.; Fernandez-Pelayo, U.; Perez-Rodriguez, D.; Ramos-Cabrer, P.; Spinazzola, A.; Elortza, F.; Ruíz-Cabello, J.; Holt, I. J. *Sci. Rep.* **2022**, *12*. https://doi.org/10.1038/s41598-022-10168-1
12. Goel, A.; Shah, S. *J. Fam. Med. Prim. Care* **2021**, *10*, 583. https://doi.org/10.4103/jfmpc.jfmpc_2117_20
13. Overend, W. G.; Stacey, M.; Staněk, J. *J. Chem. Soc.* **1949**, 2841. https://doi.org/10.1039/JR9490002841
14. Murakami, T.; Tanaka, N.; Tezuka, T.; Chen, C. *Chem. Pharm. Bull.* **1975**, *23*, 1634. https://doi.org/10.1248/cpb.23.1634
15. Yaylayan, V. A.; Ismail, A. A. *Carbohydr. Res.* **1995**, *276*, 253. https://doi.org/10.1016/0008-6215(95)00188-Y
16. Hess, D.; Klüfers, P. *Acta Crystallogr. Sect. E Struct. Reports Online* **2011**, *67*, o2615. https://doi.org/10.1107/S1600536811035264
17. Lu, C.; Bai, L.; Shen, Y. *Chem. Nat. Compd.* **2008**, *44*, 594. https://doi.org/10.1007/s10600-008-9140-x
18. Parker, F. S.; Ans, R. *Appl. Spectrosc.* **1966**, *20*, 384. https://doi.org/10.1366/000370266774386542
19. Wong, M. Y. H.; Gray, G. R. *Carbohydr. Res.* **1980**, *80*, 87. https://doi.org/10.1016/S0008-6215(00)85317-3
20. Pieri, V.; Schwaiger, S.; Ellmerer, E. P.; Stuppner, H. *J. Nat. Prod.* **2009**, *72*, 1798.

https://doi.org/10.1021/np900373u
21. Li, M. WO2006002323A1, **2005**.
22. Hughes, D. E. *J. Chromatogr. A* **1985**, *331*, 183. https://doi.org/10.1016/0021-9673(85)80020-0
23. Gounder, M. K.; Lin, H.; Stein, M.; Goodin, S.; Bertino, J. R.; Kong, A.-N. T.; DiPaola, R. S. *Biomed. Chromatogr.* **2012**, *26*, 650. https://doi.org/10.1002/bmc.1710
24. Bhatt, A. N.; Shenoy, S.; Munjal, S.; Chinnadurai, V.; Agarwal, A.; Vinoth Kumar, A.; Shanavas, A.; Kanwar, R.; Chandna, S. *BMC Infect. Dis.* **2022**, *22*. https://doi.org/10.1186/s12879-022-07642-6
25. Codo, A. C.; Davanzo, G. G.; Monteiro, L. de B.; de Souza, G. F.; Muraro, S. P.; Virgilio-da-Silva, J. V.; Prodonoff, J. S.; Carregari, V. C.; de Biagi Junior, C. A. O.; Crunfli, F.; Jimenez Restrepo, J. L.; Vendramini, P. H.; Reis-de-Oliveira, G.; Bispo dos Santos, K.; Toledo-Teixeira, D. A.; Parise, P. L.; Martini, M. C.; Marques, R. E.; Carmo, H. R.; Borin, A.; Coimbra, L. D.; Boldrini, V. O.; Brunetti, N. S.; Vieira, A. S.; Mansour, E.; Ulaf, R. G.; Bernardes, A. F.; Nunes, T. A.; Ribeiro, L. C.; Palma, A. C.; Agrela, M. V.; Moretti, M. L.; Sposito, A. C.; Pereira, F. B.; Velloso, L. A.; Vinolo, M. A. R.; Damasio, A.; Proença-Módena, J. L.; Carvalho, R. F.; Mori, M. A.; Martins-de-Souza, D.; Nakaya, H. I.; Farias, A. S.; Moraes-Vieira, P. M. *Cell Metab.* **2020**, *32*, 498. https://doi.org/10.1016/j.cmet.2020.07.015
26. Zhu, J.-Y.; Wang, G.; Huang, X.; Lee, H.; Lee, J.-G.; Yang, P.; van de Leemput, J.; Huang, W.; Kane, M. A.; Yang, P.; Han, Z. *Commun. Biol.* **2022**, *5*. https://doi.org/10.1038/s42003-022-03986-6
27. Chavda, V. P.; Pandya, R.; Apostolopoulos, V. *Expert Rev. Vaccines* **2021**, *20*, 1549. https://doi.org/10.1080/14760584.2021.1987223
28. Singh, D.; Banerji, A. K.; Dwarakanath, B. S.; Tripathi, R. P.; Gupta, J. P.; Mathew, T. L.; Ravindranath, T.; Jain, V. *Strahlentherapie und Onkol.* **2005**, *181*, 507. https://doi.org/10.1007/s00066-005-1320-z
29. Fokt, I.; Skora, S.; Conrad, C.; Madden, T.; Emmett, M.; Priebe, W. *Carbohydr. Res.* **2013**, *368*, 111. https://doi.org/10.1016/j.carres.2012.11.021
30. Budikhina, A. S.; Pashenkov, M. V. *Immunologiya* **2021**, *42*, 5. https://doi.org/10.33029/0206-4952-2021-42-1-5-20
31. Reiter, R. J.; Sharma, R.; Rosales-Corral, S. *Int. J. Mol. Sci.* **2021**, *22*, 764. https://doi.org/10.3390/ijms22020764
32. Zhang, J.; Yang, J.; Lin, C.; Liu, W.; Huo, Y.; Yang, M.; Jiang, S.-H.; Sun, Y.; Hua, R. *Theranostics* **2020**, *10*, 8400. https://doi.org/10.7150/thno.45124
33. Zhang, D.; Li, J.; Wang, F.; Hu, J.; Wang, S.; Sun, Y. *Cancer Lett.* **2014**, *355*, 176. https://doi.org/10.1016/j.canlet.2014.09.003
34. Pająk, B.; Zieliński, R.; Manning, J. T.; Matejin, S.; Paessler, S.; Fokt, I.; Emmett, M. R.; Priebe, W. *Molecules* **2022**, *27*, 5928. https://doi.org/10.3390/molecules27185928
35. Binkley, R. w.; Bankaitis, D. *J. Carbohydr. Chem.* **1982**, *1*, 1. https://doi.org/10.1080/07328308208085074
36. Monneret, C.; Choay, P. *Carbohydr. Res.* **1981**, *96*, 299. https://doi.org/10.1016/S0008-6215(00)81880-7

37. Mereyala, H. B.; Mamidyala, S. K. IN193296B, **2004**.
38. Xu, W.; Yang, H.; Liu, Y.; Hua, Y.; He, B.; Ning, X.; Qin, Z.; Liu, H. M.; Liu, F. W. *Synth.* **2017**, *49*, 3686. https://doi.org/10.1055/s-0036-1589501
39. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Satyanarayana, M. *Tetrahedron Lett.* **2002**, *43*, 7009. https://doi.org/10.1016/S0040-4039(02)01584-8
40. Chen, H.; Zhao, Z.; Hallis, T. M.; Guo, Z.; Liu, H. *Angew. Chemie Int. Ed.* **2001**, *40*, 607. https://doi.org/10.1002/1521-3773(20010202)40:3<607::AID-ANIE607>3.0.CO;2-8
41. Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603. https://doi.org/10.1016/S0040-4039(01)82992-0
42. Zhang, J.; Fu, J.; Si, W.; Wang, X.; Wang, Z.; Tang, J. *Carbohydr. Res.* **2011**, *346*, 2290. https://doi.org/10.1016/j.carres.2011.08.007
43. Sridhar, P. R.; Anjaneyulu, B.; Rao, B. U. *European J. Org. Chem.* **2021**, *2021*, 5665. https://doi.org/10.1002/ejoc.202101033
44. Costantino, V.; Imperatore, C.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **2000**, *41*, 9177. https://doi.org/10.1016/S0040-4039(00)01643-9
45. Masuda, Y.; Tsuda, H.; Murakami, M. *Angew. Chemie Int. Ed.* **2020**, *59*, 2755. https://doi.org/10.1002/anie.201914242
46. Cramer, F. B.; Woodward, G. E. *J. Franklin Inst.* **1952**, *253*, 354. https://doi.org/10.1016/0016-0032(52)90852-1
47. Cramer, F. B. *J. Franklin Inst.* **1954**, *257*, 69. https://doi.org/10.1016/0016-0032(54)91056-X
48. Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636. https://doi.org/10.1021/jo00004a053
49. Regeling, H.; Chittenden, G. J. F. *Recl. des Trav. Chim. des Pays-Bas* **2010**, *108*, 330. https://doi.org/10.1002/recl.19891081003
50. van Haver, D.; Rabi, N. A.; Vandewalle, M.; Goethals, P.; Vandecasteele, C. *J. Label. Compd. Radiopharm.* **1985**, *22*, 657. https://doi.org/10.1002/jlcr.2580220704
51. Yorimitsu, H.; Murakami, Y.; Takamatsu, H.; Nishimura, S.; Nakamura, E. *Angew. Chemie - Int. Ed.* **2005**, *44*, 2708. https://doi.org/10.1002/anie.200500044
52. Mi, Q.; Ma, Y.; Gao, X.; Liu, R.; Liu, P.; Mi, Y.; Fu, X.; Gao, Q. *J. Biomol. Struct. Dyn.* **2016**, *34*, 2339. https://doi.org/10.1080/07391102.2015.1114972
53. Sala, L. F.; Fernández Cirelli, A.; de Lederkremer, R. M. *Carbohydr. Res.* **1980**, *78*, 61. https://doi.org/10.1016/S0008-6215(00)83660-5
54. Watanabe, S.; Hirokawa, R.; Iwamura, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3375. https://doi.org/10.1016/S0960-894X(98)00623-4
55. Jørgensen, C.; Pedersen, C. *Carbohydr. Res.* **1997**, *299*, 307. https://doi.org/10.1016/S0008-6215(97)00022-0
56. Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1947**, *69*, 1048. https://doi.org/10.1021/ja01197a022
57. Koóš, M. *Tetrahedron Lett.* **2000**, *41*, 5403. DOI:10.1016/S0040-4039(00)00863-7. https://doi.org/10.1016/S0040-4039(00)00863-7
58. Murray, T. P.; Singh, U. P.; Brown, R. K. *Can. J. Chem.* **1971**, *49*, 2132.

https://doi.org/10.1139/v71-345
59. Berberich, S. M.; Cherney, R. J.; Colucci, J.; Courillon, C.; Geraci, L. S.; Kirkland, T. A.; Marx, M. A.; Schneider, M. F.; Martin, S. F. *Tetrahedron* **2003**, *59*, 6819. https://doi.org/10.1016/S0040-4020(03)00370-3
60. Lee, B.-H.; Koh, D.-W.; Territo, P. R.; Park, C.-S.; Hamaker, B. R.; Yoo, S.-H. *Carbohydr. Polym.* **2015**, *132*, 41. https://doi.org/10.1016/j.carbpol.2015.06.012
61. Liu, K. K. C.; Wong, C. H. *J. Org. Chem.* **1992**, *57*, 3748. https://doi.org/10.1021/jo00039a050
62. Percival, M. D.; Withers, S. G. *Can. J. Chem.* **1988**, *66*, 1970. https://doi.org/10.1139/v88-317
63. Kim, Y.-M.; Okuyama, M.; Mori, H.; Nakai, H.; Saburi, W.; Chiba, S.; Kimura, A. *Tetrahedron: Asymmetry* **2005**, *16*, 403. https://doi.org/10.1016/j.tetasy.2004.11.046
64. Borysenko, C. W.; Spaltenstein, A.; Straub, J. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 9275. https://doi.org/10.1021/ja00208a046

Authors' Biographies

Dr. **Raman Singh** is a senior research scientist at C and RE Pvt Ltd New Delhi and Vice President (International), Graduate Women in Science, USA. She graduated her PhD in organic chemistry from Jiwaji University, Gwalior. Her research field icludes organic and medicinal chemistry, plant metabolites, toxicity, and antimicrobial resistance. She is member of the Association of chemistry Teachers, Indian Science Congress Association, and the Indian Society of Analytical Scientists.

Ms. **Vidushi Gupta** graduated with BSc (Medical) in 2018 and MSc in 2020 from Maharishi Markandeshwar (Deemed to be University) Mullana, Haryana, India. She worked as a research fellow under the supervision of Professor Kuldeep Singh before joining as JRF/inspire fellow at IISER, Mohali. Her research interests include organic synthesis, metal-organic frameworks, and chemical biology.

Kuldeep Singh is a professor at Amity University Madhya Pradesh, Gwalior, India. He obtained his Ph.D. in 2007 under the supervision of Professor Sambasivarao Kotha at the Indian Institute of Technology Bombay, Mumbai (India). In 2007, he worked as a postdoctoral scientist with Dr. Stéphane MEUNIER in Laboratoire de Synthèse Bioorganique, at Illkrich (France). In 2009, he joined Sai Advantium Pharma Ltd, Pune as a research Scientist. His research focuses on (i) the development of new synthetic methodologies using metathesis, coupling reaction, click chemistry, and C–H activation; (ii) the design and synthesis of new molecules against antibacterial drug resistance. (iii) natural products and their application in medicinal chemistry. He is a member of the Chemical Research Society of India and the Royal Society of Chemistry.