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Contents

Preface

Carbohydrates, such as starch, are extensively used as feedstocks by the chemical industry; similarly, derivatized carbohydrates are increasingly used by organic chemists as starting materials in the synthesis of chiral heterocyclic compounds. The aim of this book is to review the recent literature dealing with the use of carbohydrates as raw materials in the synthesis of naturally occurring nitrogen heterocycles. Although carbohydrates have been used for the synthesis of other types of heterocycles, we have limited our review to their use in the synthesis of naturally occurring nitrogen heterocycles. This limitation was dictated by the extremely large number of publications that has appeared on the subject during the last two decades and our desire to give the reader as much information as possible in the confines of our book. We have not merely cited references for a given synthesis but instead have given as much detail as was possible on the experimental conditions used. The text contains six main chapters arranged according to the size and complexity of their heterocyclic rings, ranging from five- to seven-membered rings and from single to multiple fused rings. The book gives enough information on the synthesis of the compounds to enable a chemist to design a multistep synthesis. It cites the different approaches to the synthesis of naturally occurring nitrogen heterocycles in a format that enables the reader to make comparisons with other methods and make decisions on whether to use a certain procedure, modify it or devise a new synthetic methodology. In summary, the book is not a mere list of the conversion methods cited in the literature, but rather a rational discussion of these methods. Of course, the large volume of literature cited has dictated that some references be discussed in less detail than some readers would have liked, but we hope that they will understand our difficulty and forgive us. We feel that the added information in our reference book will be of greatest value to chemist in both industry and academia, and to researchers and graduate students in the fields of organic chemistry, medicinal chemistry, heterocyclic chemistry, natural product chemistry and glycochemistry.

We thank Professor N. Rashed (Egypt), Professor H.S. El Khadem (United States), Professor T. Tsuchiya (Japan) and Professor S. Abdo (Egypt) for comments and useful suggestions. In addition, thanks are due to Professor R.R. Schmidt (Germany) for his valuable discussions and for providing library facilities. The AvH and DFG are highly appreciated for their partial supports. Our appreciation goes also to the members of El Ashry group for their help and efforts.

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Author details

El Sayed H. El Ashry was born in 1942 in Elmahal Alkobra, Egypt. He studied chemistry at Alexandria University (BSc 1963, MSc 1966, PhD 1969 and DSc 1997). He has been a visiting professor at Tokyo Institute of Technology, Ohio State University, Michigan Technological University, New York State University, Darmstadt Institute of Organic Chemistry, UmAlqura University and Konstant University. He has given lectures at various universities, institutes, companies and conferences around the world. He is currently a Professor of Organic Chemistry at Alexandria University after being the head of the department for the last four years. He has supervised more than 70 MSc and PhD students and published about 300 publications and review articles in highly renowned journals in the field of carbohydrates and nucleosides, a major area of research in the series 'Heterocycles from Carbohydrate Precursors'. He also edits various international journals. He has received many awards of recognition and distinction: in particular 'Excellence' and '1st class Ribbon of Science and Arts' awards from the President of Egypt.

Ahmed El Nemr was born in 1962 in El Behera, Egypt. He received his bachelor's degree in chemistry in 1984 and his master's degree in organic chemistry from Alexandria University under the supervision of Professor E.S.H. El Ashry, after which he was awarded his PhD in Engineering in Applied Chemistry by Keio University, Yokohama, Japan. He worked for six years as a researcher at the Institute of Bioorganic Chemistry, Kawasaki, Japan, with Professor Tsutomu Tsuchiya. He is now an Associate Professor at the National Institute of Oceanography and Fisheries, Alexandria, Egypt. He is the head of Egyptian National Oceanography Data Centre (ENODC). His research interests involve carbohydrate chemistry, natural products, and organic as well as inorganic pollutants in marine environment.

List of abbreviations and acronyms used in this book

Ac	acetyl
AIBN	azobis(isobutronitrile)
All	allyl
An	anisyl
Ar	aryl
9-BBN	9-borabicyclo[3.3.l]nonane
BMS	borane–dimethyl sulfide complex
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc-L-Val-OH	*tert*-butoxycarbonyl protected L-valine
BOM	benzyloxymethyl
BOP-Cl	*N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxy carbonyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclooctane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCH	dicyclohexano
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPC	diethylphosphorocyanide
DET	diethyl tartrate
DHAP	dihydroxyacetone phosphate
DHP	dihydropyran
DHQ-CLB	Sharpless asymmetric dihydroxylation reagent
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine

DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	2,2-dimethoxypropane
DMPU	N,N'-dimethylpropylene urea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNAP	dinitroaminopyridine
DPPA	diphenylphosphoryl azide
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
FDP	fructose-1,6-diphosphate
FVP	pyrolysis
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBT	1-hydroxybenzotriazole hydrate
IDCP	iodonium dicollidine perchlorate
Im	imidazole
IRA	Amberlite IRA
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
Lev	levulinoyl
LHMDS	lithium hexamethyldisilazide
LPTS	2,6-luidinium *p*-toluenesulfonate
L-Selectride	lithium tri-*sec*-butylborohydride
***m*-CPBA**	*m*-chloroperoxybenzoic acid
MEM	methoxyethoxymethyl
***mm*TrCl**	monomethoxytrityl chloride
MOM	methoxymethyl
MPM	*p*-methoxybenzyl
Ms	mesyl
MS	molecular sieves
Naph	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMDA	*N*-methyl-D-aspartate
NMO	*N*-methylmorpholine *N*-oxide
NSA	2-naphthalenesulfonic acid
PASE	phosphate esters of acid phosphatase

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pf	9-phenyl fluoren-9-yl
Ph	phenyl
Phth	phthalyl
Piv	trimethylacetyl
PM	phenylmenthyl
PMB	*p*-methoxybenzyl
PPL	porcine pancreatic lipase
PPTs	pyridinium *p*-toluenesulfate
Pr	propyl
***p*-TsOH**	*p*-toluenesulfonic acid
Py	pyridine
RAMA	rabbit muscle aldolase, D-fructose-1,6-bisphosphate aldolase
rt	room temperature
TBAF	tetrabutyl ammonium fluoride
TBDPS	*t*-butyl diphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyl dimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-piperidinooxy, free radical
TEOC	*O*-(2-(trimethylsilyl)ethyl)carbamate
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Th	thiazole
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TMSOTf	trimethylsilyltriflate
Tol	tolyl
TPAP	tetra-*n*-propyl ammonium perruthenate
TPS	*t*-butyl diphenylsilyl
Tr	trityl
Ts	tosyl
TSNSO	*N*-sulfinyl-*p*-toluenesulfonamide
Z	benzyloxycarbonyl

Introduction

Carbohydrates are widely distributed in nature and constitute the largest renewable biomasses available. As such, they are considered by many as one of the most promising feedstock for the industrial preparation of many organic chemical compounds. Carbohydrates, resembling the largest class of resources, have attracted the attention to be used as substitutes for the crude oil, natural gas or coal[1–8] in developing materials for trendsetting technologies.[6–8] Moreover, many pharmaceutical agents incorporate nitrogen heterocyclic rings, which has attracted attention toward their synthesis. The use of carbohydrates as starting materials for the synthesis of heterocyclic compounds has long been a subject of interest in our laboratory, where significant efforts were devoted to the exploration of novel routes for the synthesis of nitrogen heterocyclic compounds from nitrogen derivatives of carbohydrates. The skeleton and functionalities in the hydrazones and bishydrazones derived from carbohydrates have been found to be of high synthetic potential, particularly as precursors for acyclic nucleosides[9–11] and heterocyclic compounds.[12–15] Thus, a great deal of work has been done on the transformations of hydrazones and bishydrazones into heterocyclic compounds. Since the subject of the book is naturally occurring nitrogen heterocycles, only a quick information on the role of hydrazones and osazones as precursors for heterocyclic compounds will be given herein, which could be of potential value in using such approaches in the synthesis of naturally occurring nitrogen heterocycles. This can be exemplified by the synthesis of the important starting material, acetonide of L-glyceraldehyde,[16] which has utilized the readily available dehydro-L-ascorbic acid monophenylhydrazone.[17] Much attention has been drawn to the synthesis of pyrazoles[18–74] and pyrazolines [75–97] via various routes.[18] Isoxazolines,[98,99] 1,2,3-triazoles,[100–149] 1,2,4-triazoles,[150–153] oxa- and thia-diazoles as well as dioxalanes,[154–172] tetrazoles,[173,174] pyridazines,[47,175–177] 1,2,4-triazines,[50,53,92,178–187] pyrrolotriazines,[188] triazolotriazinoindoles,[189–193] pyrazolopyrazoles,[194] fused pyridazines,[195] pyrimidines,[196] quinoxalines,[197–221] and pyridopyrazines,[222] as well as condensed triazolo ring systems,[223–233] condensed diazines,[234–244] and condensed quinoxalines[245–247] have been synthesized. Moreover, resulting periodate oxidation of the polyol residues linked to heterocycles followed by using the aldehyde or carboxylic acid functionalities for building heterocycles led to the synthesis of various types of biheterocycles.[248–257]

Rationale and arrangement of the topics

The naturally occurring nitrogen heterocycles possess a wide range of biological and medicinal properties. Consequently, the design of synthetic schemes for naturally occurring heterocycles is highly desirable. Among the useful features of carbohydrates

is the ability of their nitrogen derivatives to incorporate part or all of the nitrogen atoms into the heterocyclic rings they form. Another useful feature is the availability of their multiple chiral centers in nearly all the possible configurations and their ability to retain most of their configuration during conversion to heterocycles. The resulting chirons (optically active synthons) can readily be used as versatile intermediates in the synthesis of naturally occurring heterocycles. Consequently, some monographs and reviews related to the topic became available.[258–262] However, as a result of the tremendous achievement in the field we have found that the topic needs a comprehensive review to help the reader in getting ready information on the topic. The synthetic approaches described in this book are discussed in six chapters arranged according to the size of the heterocyclic rings and the number of heteroatoms in the ring. Accordingly, the chapters are arranged into (1) five-membered nitrogen heterocycles, (2) five-membered heterocycles with two heteroatoms, (3) six-membered nitrogen heterocycles, (4) seven-membered nitrogen heterocycles, (5) fused nitrogen heterocycles and (6) multifused heterocycles. Three- and four-membered nitrogen heterocycles are not treated in separate chapters but are included in the appropriate fused heterocycles.

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1 Five-membered nitrogen heterocycles

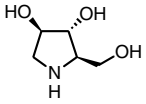
As the title denotes, this chapter deals with the conversion of carbohydrate derivatives into five-membered heterocyclic compounds containing nitrogen. The types of target compounds are (1) hydroxymethylpyrrolidines, (2) carboxypyrrolidines, (3) aralkyl pyrrolidines and (4) aryl pyrrolidines, as well as other heterocycles that are grouped under the title miscellaneous (5). Although many of these naturally occurring compounds and their stereoisomers and analogues have been synthesized from noncarbohydrates, the synthesis of the naturally occurring five-membered nitrogen heterocycles from only carbohydrate will be discussed in this chapter.

1.1 Hydroxymethylpyrrolidines

Because of their 'sugar-like' structure it is not surprising that most syntheses of the naturally occurring hydroxymethylpyrrolidines utilize carbohydrates as starting materials. Pentoses, hexoses and their derivatives are often used; three chiral centers are usually required. Nitrogen is introduced in the synthetic sequence as azide, followed by reduction to the respective amine that can be intramolecularly cyclized. This part contains three groups of compounds: 2-hydroxymethylpyrrolidines, dihydro-2-hydroxymethyl pyrrole (nectrisine) and 2,5-dihydroxymethylpyrrolidines. Each of the first and third groups contains five natural compounds isolated from different sources and characterized by having glycosidase inhibition properties.

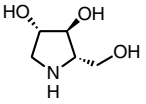
1.1.1 *2-Hydroxymethylpyrrolidines*

1,4-Dideoxy-1,4-imino-D-arabinitol [(2*R*,3*R*,4*R*)-2-hydroxymethyl pyrrolidine-3,4-diol, DAB1, **1**] has been found in both *Arachniodes standishii*[1,2] and *Angylocalyx boutiqueanus*[3] and it is a potent inhibitor of yeast α-glucosidase (50% inhibition at 1.8×10^{-7} M)[4–7] and mouse gut disaccharidases to different degrees.[8] Compound **1** inhibits the hydrolysis of sinigrin and progoitrin from mustard and cabbage aphid *Brevicoryne brassicae*.[9] It also inhibits phloem unloading and/or utilization of sucrose, resulting in insufficient sucrose transport from cotyledons to roots and hypocotyls.[10] The mechanism of insect antifeedant activity of **1** has been studied[11] and it was found that it may be carcinogenic to rodents.[12] The enantiomer 1,4-dideoxy-1,4-imino-L-arabinitol [(2*S*,3*S*,4*S*)-2-hydroxymethyl pyrrolidine-3,4-diol, LAB1, **2**] occurs as a component of bacterial lipopolysaccharides[13,14] but it shows a weaker inhibition of α-glucosidase (50% inhibition at 1.0×10^{-5} M)[15,16] and exhibits several biological activities.[17–20] 1,4-Dideoxy-1,4-imino-D-ribitol [(2*R*,3*R*, 4*S*-2-hydroxymethyl pyrrolidine-3,4-diol, **3**] has been isolated from *Morus* spp.[21,22] 1,4-Dideoxy-1,4-imino-L-xylitol [(2*S*,3*R*,4*R*)-2-hydroxymethyl pyrrolidine-3,4-diol, **4**] was isolated from diatom cell walls[23] and *Amanita vitosa* mushrooms.[24] 2-Hydroxymethyl-3-hydroxypyrrolidine [(2*R*,3*S*)-2-hydroxymethyl pyrrolidin-3-ol, CYB3, **5**] was isolated from legume *Castanospermum australe* and it has no significant biological activity.[25]



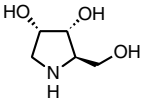
(2*R*,3*R*,4*R*)-2-Hydroxymethyl pyrrolidine-3,4-diol (DAB1)

1



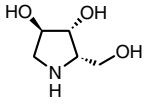
(2*S*,3*S*,4*S*)-2-Hydroxymethyl pyrrolidine-3,4-diol (LAB1)

2



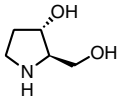
(2*R*,3*R*,4*S*)-2-Hydroxymethyl pyrrolidine-3,4-diol

3



(2*S*,3*R*,4*R*)-2-Hydroxymethyl pyrrolidine-3,4-diol

4



(2*R*,3*S*)-2-Hydroxymethyl pyrrolidin-3-ol (CYB3)

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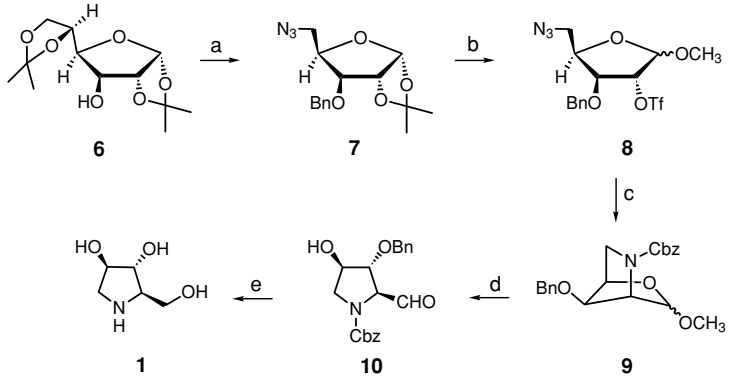
Syntheses of natural polyhydroxypyrrolidines from noncarbohydrate and their unnatural analogues from carbohydrate and noncarbohydrate have been reported.[26–86] Herein, the synthesis of the natural analogues from carbohydrate building blocks will be reviewed.

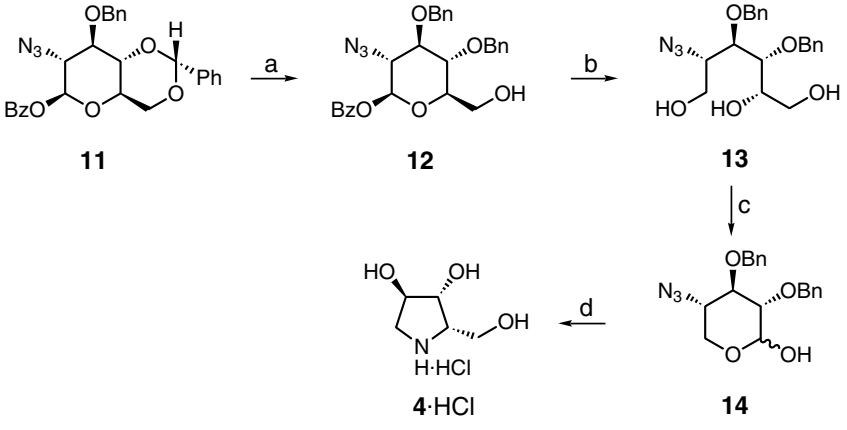
1.1.1.1 *Synthesis from* D*-glucose* A stereoselective synthesis of DAB1 (**1**) from D-glucose has been reported (Scheme 1).[87] Diacetone D-glucose (**6**) was benzylated to give the fully protected furanose, which underwent acid hydrolysis of the terminal isopropylidene group followed by periodate oxidation, sodium borohydride reduction, mesylation and then



Scheme 1 (*a*) 1. THF, NaH, Bu_4NI, 0°C, BnBr, rt to 50°C, 2 h, 97%; 2. CH_3OH–AcOH–H_2O (1:1:1), 50°C, 16 h, 87%; 3. $NaIO_4$, 10% aqueous EtOH, 3 h, CH_2Cl_2; then 20% aqueous EtOH, $NaBH_4$, 8 h at rt, 88%; 4. Py, 0°C, MsCl, rt, 2 h, 94%; 5. NaN_3, DMF, 70°C for 12 h, 97%. (*b*) 1. AcCl, CH_3OH, 0°C, 36 h, α (38%), β (44%); 2. Py, Tf_2O, –50 to −30°C, 1 h, α (92%), β (78%). (*c*) 1. EtOAc, rt, 5%, Pd *on* C, H_2, α (95%), β (92.5%); 2. 3:2 mixture of ether and aqueous $NaHCO_3$, CbzCl, rt, 12 h, α (76%), β (90%). (*d*) 1:1 mixture of TFA and H_2O, 92%. (*e*) 1. EtOH, $NaBH_4$, 15 min, 98%; 2. AcOH, H_2, Pd black, 18 h, 97.6%.

replacement of the mesyloxy group with azide ion to afford the azide **7**. Compound **7** was treated with methanolic hydrogen chloride, followed by triflation of C-2 hydroxyl group to give the corresponding triflate **8**. Hydrogenation of **8** followed by protection of the resulting bicyclic compound with benzyl chloroformate afforded the carbamate **9**. Subsequent hydrolysis with TFA gave the key intermediate **10**. Reduction of **10** with sodium borohydride followed by removal of the carbamate and *O*-benzyl protecting groups by hydrogenolysis in acetic acid gave DAB1 (**1**) in 33% from **6**.

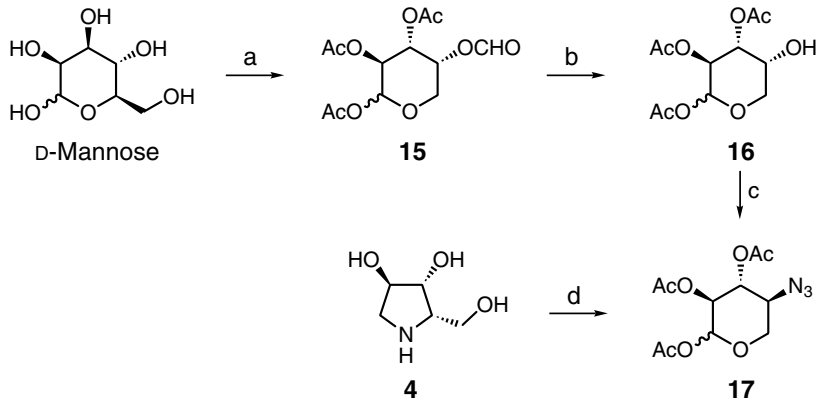
Synthesis of 1,4-dideoxy-1,4-imino-L-xylitol (**4**) has been achieved from D-glucose (Scheme 2).[88] Borane-reductive ring opening of the benzylidene ring in compound **11**, obtained from D-glucose,[89] afforded **12** (90%). Reduction of **12** with sodium borohydride produced the corresponding triol **13** (73%), which was subjected to periodate oxidation to give the cyclic hemiacetal **14** (92%). Hydrogenation of **14** over palladium led to the formation of 3,4-dihydroxypyrrolidine **4**·HCl.



Scheme 2 (*a*) BH_3, THF, 15 mol% V(O)$(OTf)_2$, CH_2Cl_2, rt, 3 h, 90%. (*b*) $NaBH_4$, CH_3OH, 73%. (*c*) $NaIO_4$, CH_3OH, 92%. (*d*) 10% Pd *on* C, H_2, EtOH, 1 N HCl, 94%.

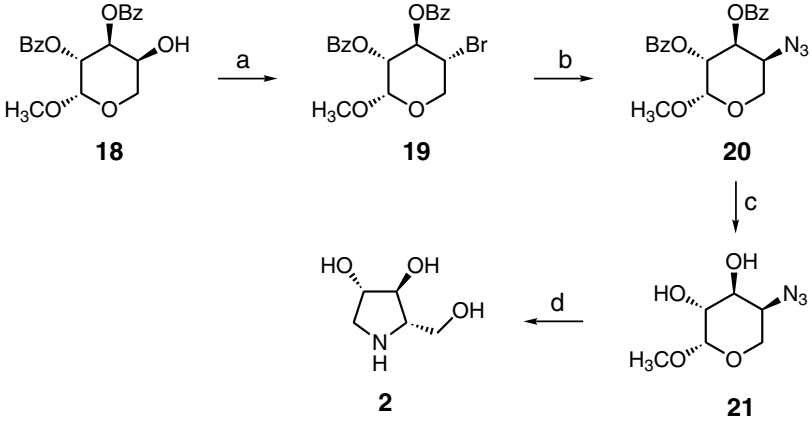
1.1.1.2 *Synthesis from D-mannose* A stereoselective synthesis of 1,4-dideoxy-1,4-imino-L-xylitol (**4**) from D-mannose has been reported (Scheme 3).[90] A pyridine solution of D-mannose containing iron(III) triflate or iron(III) chloride was irradiated with a high-pressure mercury lamp in a Pyrex vessel, while oxygen gas was bubbled through to afford after acetylation the aldopentose derivative **15**, which was treated with aluminum chloride in aqueous methanol to afford 1,2,3-tri-*O*-acetyl-D-arabinopyranose **16** in 24% overall yield from D-mannose. Triflation of **16** followed by treatment with sodium azide gave 1,2,3-tri-*O*-acetyl-4-azido-4-deoxy-L-xylopyranose (**17**) in 55% yield. Deacetylation of **17** with potassium carbonate in methanol followed by catalytic hydrogenation gave **4** in 77% yield.

1.1.1.3 *Synthesis from L-arabinose* Synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (**2**) from methyl β-L-arabinopyranoside has been reported (Scheme 4).[91] The double inversion involving the introduction of the azide function at C-4 has been effected in



Scheme 3 (*a*) Py, $FeTf_3$, *hν*, 8 h, O_2; then Ac_2O, rt, 14 h. (*b*) $AlCl_3$, CH_3OH, H_2O, rt, 36 h, 24% from D-mannose. (*c*) 1. Tf_2O, CH_2Cl_2, Py, 0°C, 1 h; 2. NaN_3, DMF, 15-crown-5, rt, 24 h, 55%. (*d*) 1. 10% aqueous CH_3OH, K_2CO_3, 0°C, 15 min, AcOH; 2. 10% Pd *on* C, H_2, 3 days; then Dowex 50X8-100 (H^+) resin, 77%.

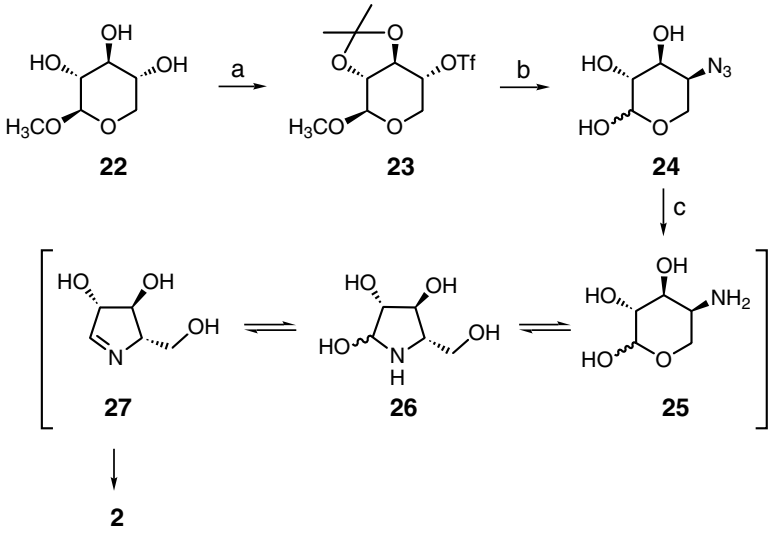
two steps by reacting methyl 2,3-di-*O*-benzoyl-β-L-arabinoside (**18**) with triphenylphosphine and 2,4,5-tribromoimidazole to form methyl 2,3-di-*O*-benzoyl-4-bromo-4-deoxy-α-D-xylopyranoside (**19**). This bromide was reacted with sodium azide to give 4-azido-4-deoxy-L-arabinoside (**20**). Debenzoylation with methanolic sodium methoxide gave methyl 4-azido-4-deoxy-β-L-arabinopyranoside (**21**), whose acid hydrolysis and catalytic hydrogenation gave **2**.



Scheme 4 (*a*) Ph_3P, 2,4,5-tribromoimidazole. (*b*) NaN_3, DMF. (*c*) $NaOCH_3$, CH_3OH. (*d*) 1. H_3O^+; 2. H_2, Pd, Amberlite CG-400 (OH^-) resin.

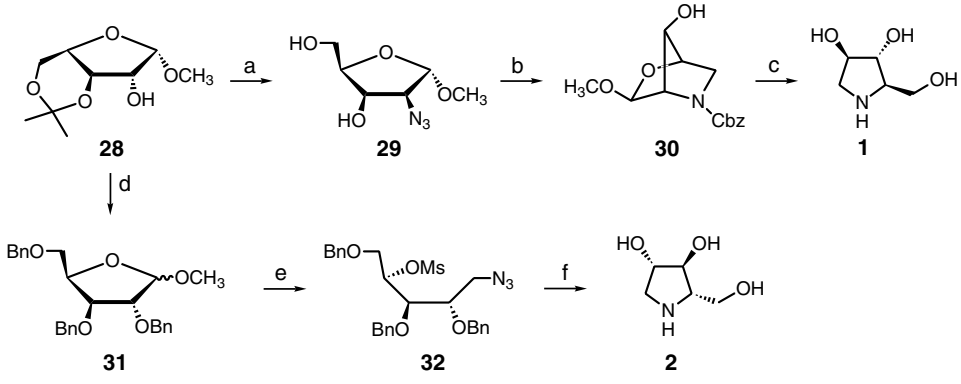
1.1.1.4 *Synthesis from D-xylose* The synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (**2**) can also be achieved from D-xylose (Scheme 5).[92] Thus, methyl β-D-xylopyranoside (**22**) has been treated with 2-methoxypropene followed by triflation with trifluoromethane sulfonic anhydride to afford the triflate **23**. The latter underwent S_N2 displacement with sodium

azide followed by acid hydrolysis to produce the azide **24**. Reduction of **24** afforded **2**, via the intermediates **25–27**, in 21% overall yield from **22**.



Scheme 5 (*a*) 1. DMF, 4 M HCl in CH_3OH, 2-methoxypropene, 60°C, 2 h; then rt, overnight, 72%; 2. CH_2Cl_2, Py, –50°C, Tf_2O, 45 min at –25°C. (*b*) 1. DMF, NaN_3, rt, 2 h, 45% for two steps; 2. AcOH, 2 M H_2SO_4, 95°C, 3 h; then $NaHCO_3$, pH 4, 65%. (*c*) 0.1 M aqueous HCl, 10% Pd *on* C, H_2, rt, 6 h, 100%.

DAB1 (**1**) and LAB1 (**2**) can be alternatively synthesized from D-xylose (Scheme 6).[15] The acetonide **28**,[93] obtained from D-xylose, was triflated, followed by S_N2 displacement with azide ion and subsequent removal of the isopropylidene group to give **29**. Selective

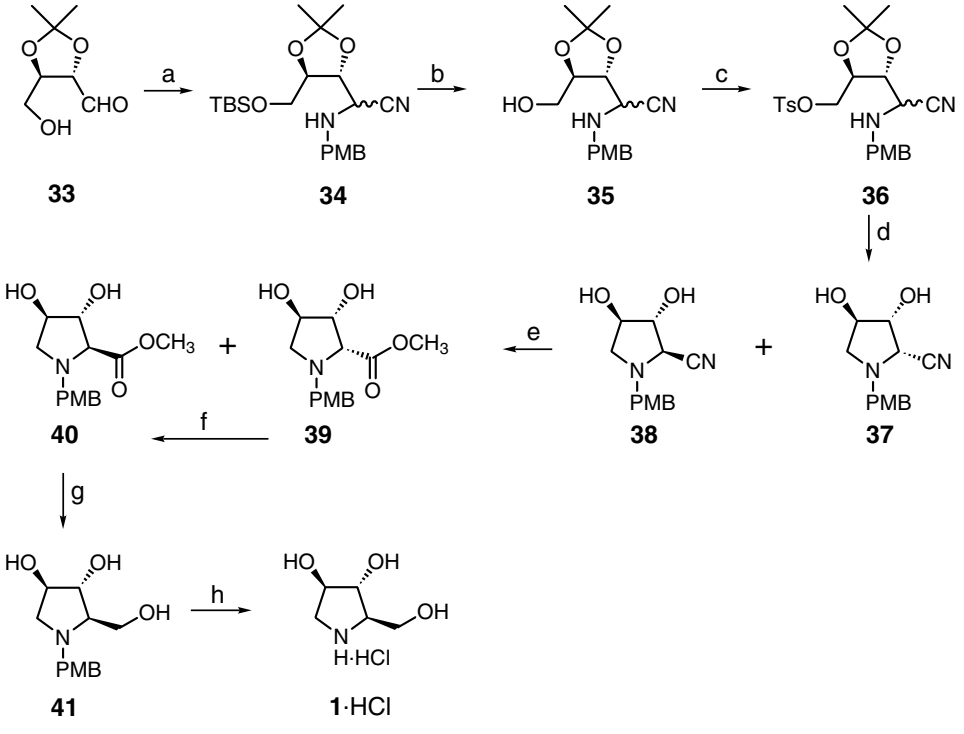


Scheme 6 (*a*) 1. Tf_2O, Py, CH_2Cl_2; 2. NaN_3, DMF, 100°C, 12 h, 76% for two steps; 3. Dowex 50W8X resin, CH_3OH, rt, 4 h, 83%. (*b*) 1. *p*-TsCl, Py, 0°C; 2. H_2, Pd black, EtOH, NaOAc, 50°C; CbzCl, ether, H_2O containing $NaHCO_3$, 36% for three steps. (*c*) 1. TFA–H_2O (4:1); 2. $NaBH_4$, EtOH; 3. H_2, Pd black, AcOH, 65%. (*d*) 1. BnBr, NaH; 2. Dowex 50W8X (H^+) resin; 3. BnBr, NaH, *t*-Bu_4NI, THF, 45% for three steps. (*e*) 1. TFA, H_2O; 2. $NaBH_4$, EtOH, rt, 1 h, 87%; 3. MsCl, Py, 90%; 4. NaN_3, DMF, 66%. (*f*) 1. H_2, Pd black, EtOH; 2. ion-exchange chromatography, 48%.

tosylation of the primary hydroxyl group in **29** followed by azide reduction and subsequent cyclization with sodium acetate and protection with benzyl chloroformate afforded the carbamate **30**. Hydrolysis of **30** by aqueous TFA followed by reduction of the resulting aldehyde, removal of the carbamate protecting group and purification by ion-exchange chromatography gave **1** in 15% overall yield from **28**.

On the other hand, the xylofuranoside **28** was benzylated, followed by removal of the isopropylidene group and subsequent benzylation to give the tribenzylated derivative **31**. Acid hydrolysis of **31** followed by sodium borohydride reduction of the resulting lactol and subsequent mesylation and then selective nucleophilic displacement of the primary mesylate by sodium azide in DMF afforded the azido mesylate **32**. Reduction of the azide was accompanied by cyclization and deprotection to afford **2** in 11% overall yield from **28**.

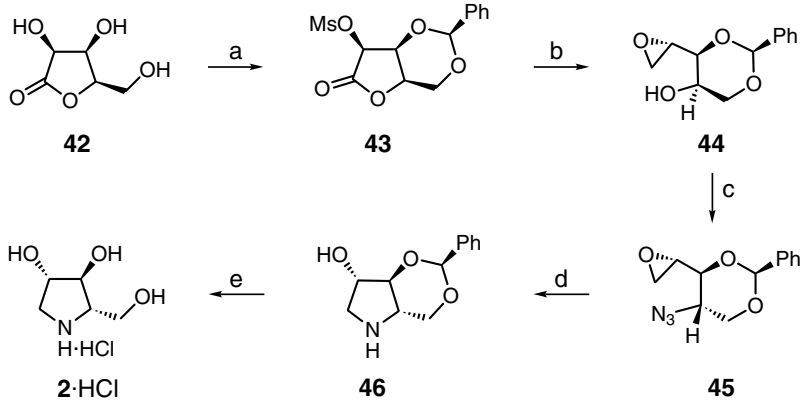
1.1.1.5 *Synthesis from* D*-threose* Synthesis of DAB1 (**1**) has been carried out by conversion of the D-threose derivative **33**,[94] readily available from D-(−)-diethyl tartrate, to the aminonitrile **34** as an inseparable diastereomeric mixture (Scheme 7).[95] Subsequent deprotection with TBAF gave the alcohol **35** (quantitative). Esterification of **35** with *p*-toluenesulfonyl chloride afforded **36** (84%), which was treated with TFA–H_2O–THF



Scheme 7 (*a*) 1. TBSCl, imidazole, CH_2Cl_2; 2. *p*-$(CH_3O)C_6H_4CH_2NH_2$, $(EtO)_2P(O)CN$, THF, 86.7%. (*b*) TBAF, THF, quantitative. (*c*) *p*-TsCl, Py, 84%. (*d*) TFA–H_2O–THF (5:1:1), 70–75°C. (*e*) $NaOCH_3$, CH_3OH; then 2 N HCl, 87%. (*f*) Same as (*e*), 65–70°C, 2 h; then 2 N HCl, 78%. (*g*) $NaBH_4$, EtOH, 89%. (*h*) 1. H_2, 20%, $Pd(OH)_2$ *on* C, HCO_2H, EtOH; 2. conc. HCl, 94%.

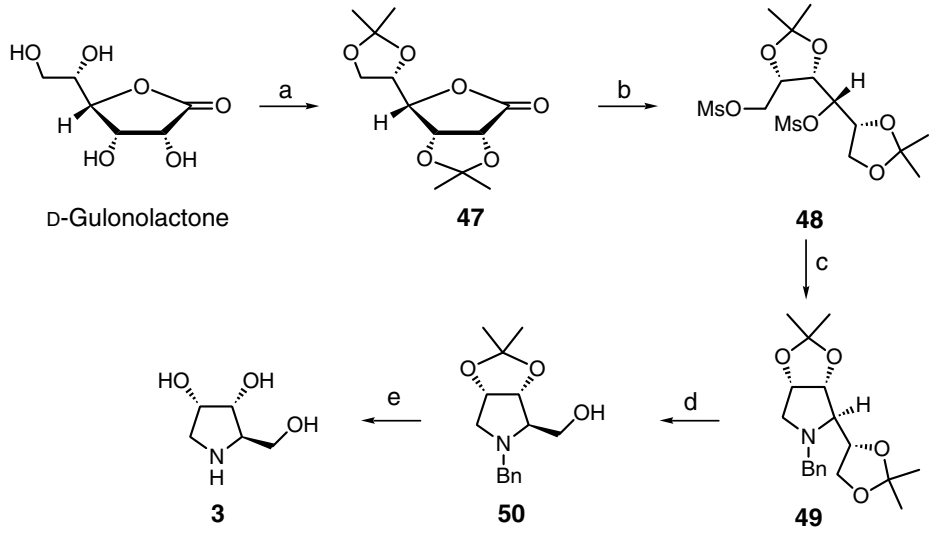
to afford the cyclized isomeric mixture **37** and **38** in a ratio of 4:1 (74%). Subsequent treatment with sodium methoxide in methanol gave a chromatographically separable mixture of the methyl esters **39** (21%) and **40** (28%) in addition to recovery of the starting material (48.7%), which could be recycled. Treatment of **39** with sodium methoxide in methanol afforded a 1:1 mixture of **39** and **40**. Reduction of **40** with sodium borohydride gave the alcohol **41** (89%). Removal of the PMB group from **41** by catalytic hydrogenolysis provided **1**, which was conveniently isolated as its crystalline hydrochloride by treatment with conc. HCl (94%). Its enantiomer LAB1 (**2**) was synthesized from L-(+)-diethyl tartrate following the same set of reactions previously described for **1**.

1.1.1.6 *Synthesis from D-lyxonolactone* A synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (**2**) from D-lyxonolactone (**42**) (Scheme 8)[17] was achieved by benzylidenation, followed by mesylation to afford **43** in 80% yield from **42**. Lithium borohydride reduction of **43** followed by treatment with potassium carbonate afforded the epoxide **44** (72%), which underwent triflation of the free hydroxyl group followed by S_N2 displacement with azide ion to furnish the azidoepoxide **45** (92%). Hydrogenation of **45** followed by ring closure of the resulting amine using tetrabutylammonium iodide, via the intermediate iodoalcohol, afforded the pyrrolidine **46**. Finally, removal of the benzylidene group with H_2SO_4 afforded **2**, which was isolated as the hydrochloride salt in 21% overall yield from **42**.



Scheme 8 (*a*) 1. PhCHO, conc. HCl, 0°C, 3 h, 96%; 2. MsCl, Py, rt, 3 h, 83%. (*b*) 1. $LiBH_4$, THF, –68°C to rt, 16 h, 90%; 2. K_2CO_3, CH_3OH, rt, 24 h, 80%. (*c*) 1. Tf_2O, Py, CH_2Cl_2, –30°C, 2 h, 100%; 2. NaN_3, DMF, 0°C, 2 h, 92%. (*d*) 1. H_2, 5% Pd *on* C, CH_3OH, 30 min, 62%; 2. Bu_4NI, THF, reflux, 72 h, 58%. (*e*) 1. 0.1 N H_2SO_4, 100°C, 3 h, 90%; 2. CH_3OH, 12 M HCl, 10 min, 84%.

1.1.1.7 *Synthesis from D-gulonolactone* Synthesis of 1,4-dideoxy-1,4-imino-D-ribitol (**3**) from D-gulonolactone has been reported (Scheme 9).[96] D-Gulonolactone was treated with DMP to produce diacetone D-gulonolactone (**47**), which underwent $LiAlH_4$ reduction followed by mesylation to furnish **48** in 74% yield from D-gulonolactone. Heating of **48** with benzylamine afforded the protected pyrrolidine **49**. Treatment of **49** with aqueous acetic acid followed by periodate oxidation of the terminal diol and subsequent borohydride reduction afforded the pyrrolidine **50**. Compound **50** was debenzylated and then deacetonated to produce **3** in 29% overall yield from D-gulonolactone.



Scheme 9 (*a*) Acetone, DMP, *p*-TsOH, rt, 2 days; then anhydrous Na_2CO_3, 85%. (*b*) 1. $LiAlH_4$, THF, rt, 30 min, 87%; 2. MsCl, DMAP, Py, rt, 2 h, 100%. (*c*) $BnNH_2$, 60–70°C, 60 h, 77%. (*d*) 1. 80% aqueous AcOH, 50°C, 48 h, 93%; 2. $NaIO_4$, EtOH–H_2O (5:1), rt, 20 min; then $NaBH_4$, 0°C, 30 min, 71%. (*e*) EtOH, H_2, 10% Pd *on* C, rt, 2 h; then 50% aqueous TFA, rt, 24 h, 78%.

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