Carbohydrate Research 472 (2019) 103–114

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

A novel and environmental friendly synthetic route for hydroxypyrrolidines using zeolites

A. Fan*, G.K. Chuah, Stephan Jaenicke

Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543, Singapore

ABSTRACT

A critical step in the synthesis of the hydroxypyrrolidines, 1,4-dideoxy-1,4-imino-L-lyxitol and 1,4-dideoxy-1,4-imino-D-lyxitol, from the corresponding D-sugars is the synthesis of *O*-methyl 2,3-*O*-isopropylidenepentofuranoses. Instead of applying homogeneous catalysis process with conventional inorganic acid catalysts like HCl and $HClO_4$, it was found that heterogeneous catalysis using zeolites could be used for the *one-pot* synthesis of *O*-methyl 2,3-*O*-isopropylidenepentofuranoses directly from D-sugars, MeOH and acetone at mild condition. The best catalyst was H-beta zeolite containing a Si/Al molar ratio of 150, where a yield of > 83% was obtained. The overall yields of the five-step procedure to 1,4-dideoxy-1,4-imino-L-lyxitol and 1,4-dideoxy-1,4-imino-D-lyxitol were 57% and 50%, respectively. This synthetic procedure has several advantages such as competitive overall yield, reduced number of steps, and mild reaction conditions. Furthermore, the zeolite catalyst can be easily recovered from the reaction mixture and reused with no loss of activity.

1. Introduction

Iminosugars are carbohydrate analogs in which the ring oxygen has been replaced with nitrogen and are found to be widespread in plants and microorganisms. Due to their structural similarity to native carbohydrates, they are potent inhibitors of many carbohydrate-processing enzymes involved in biological systems. These unique molecules promise a new generation of iminosugar-based medicines for a wide range of diseases such as viral infections, diabetes, tumor metastasis, AIDS and lysosomal storage disorders [1–11].

Hydroxypyrrolidines are structurally identical to five-membered iminosugars, which belong to the general class of azasugars. Hydroxypyrrolidines include the mannosidase inhibitors 1,4-dideoxy-1,4-imino-D-mannitol [12] and its 6-deoxy analog [13], 1,4-dideoxy-1,4-imino-D-xylitol [14], phytotoxin swainsonine [15] whose properties include the inhibition of both lysosomal α-mannosidase [16] and mannosidase II [17], the antibiotic anisomycin [18], broussonetinine A [19] and the potent-galactosidase and α-mannosidase inhibitor, guamylycin [20].

Of the lyxitol pyrrolidines, 1,4-dideoxy-1,4-imino-D-lyxitol (Fig. 1), which has the structure tentatively assigned to a pyrrolidine isolated from the marine sponge raispalia [21], was found to be a potent α-galactosidase inhibitor [14,22], while the enantiomer, 1,4-dideoxy-1,4-imino-L-lyxitol, has not been isolated or assayed [23]. A number of strategies to achieve a total synthesis of lyxitol pyrrolidines have been reported [24–30]. In spite of their elegance and creativity, many of these strategies are lengthy, some show poor diastereoselectivity, and all employ standard protecting group manipulations. Dangerfield et al. [23,31,32] presented a protecting group-free synthetic route to produce lyxitol hydroxypyrrolidines in competitive yield and high stereoselectivity. However, their methodology still has disadvantages, such as producing highly volatile and toxic HCN from the $NaBH_3CN$ used for the reduction of the imine, tedious work-up procedure (especially for the synthesis of the *O*-methyliodoglycosides), and unfavorable economics due to the large amount of ammonium acetate waste (~150 equiv), which when considered in overall, makes the synthetic scheme environmental unfriendly.

As mentioned in our previous work [33], heterogeneous catalysis have unique advantages, e.g., ease of handling, separation from the reaction mixtures and recovery of the catalyst. Moreover, heterogeneous catalysis often perform well under mild conditions and are seldom corrosive. Inventing an environmental friendly synthetic scheme with heterogeneous catalysis process to produce lyxitol hydroxypyrrolidines is highly desired. However, heterogeneous catalysis for the direct transformation of carbohydrates are underexplored [34].

Here, we report an efficient and environmental friendly route to synthesize 1,4-dideoxy-1,4-imino-L-lyxitol **6** from the cheap starting material, D-ribose, through the use of heterogeneous catalysis process and readily available reagents (Scheme 1). The proposed synthetic route from D-ribose to lyxitol hydroxypyrrolidines **6** consists of five reactions: (i) *one-pot* synthesis of *O*-methyl 2,3-*O*-isopropylidene-D-ribofuranoside **2**, (ii) iodination at C5 of **2**, (iii) Vasella reductive amination to produce **4**, (iv) halocyclization/carbonylation of **4** using an iodine-promoted annulation methodology, and (v) hydrolysis of the

* Corresponding author.
E-mail address: fanao2013cn@gmail.com (A. Fan).

https://doi.org/10.1016/j.carres.2018.11.016
Received 5 October 2018; Received in revised form 28 November 2018; Accepted 28 November 2018
Available online 04 December 2018
0008-6215/

1,4-dideoxy-1,4-imino-D-lyxitol 1,4-dideoxy-1,4-imino-L-lyxitol

Fig. 1. Structures of 1,4-dideoxy-1,4-imino-D-lyxitol and 1,4-dideoxy-1,4-imino-L-lyxitol.

carbamate to form the targeted compound **6**. The applicability of the scheme to the synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol **11** starting from D-lyxose was also attempted (Scheme 2).

2. Results and discussion

2.1. Synthesis 1,4-dideoxy-1,4-imino-L-lyxitol 6 from D-ribose

The synthesis of *O*-methyl 2,3-*O*-isopropylidene-D-ribofuranoside from D-ribose can proceed *via* two different pathways: **Route 1** where D-ribose is first reacted with MeOH and subsequently with acetone, or **Route 2** where D-ribose is first reacted with acetone and subsequently with MeOH (Fig. 2). **Route 1** is preferred because the increased electrophilicity of the oxygen atom on C3 and C4 resulting from the methoxylation of the hydroxyl group on C1 will assist in the following electrophilic addition to acetone.

Several homogeneous inorganic acid catalysts such as CH_3COCl [23,31,32], HCl [35,36], H_2SO_4 [37] and $HClO_4$ [38] have been used to catalyze the *O*-glycosylation of pentoses including D-ribose, L-ribose, D-xylose and D-arabinose, with methanol. Amongst them, HCl, and $HClO_4$ were also used to synthesize *O*-methyl 2,3-*O*-isopropylidenepentofuranoses in a *one-pot* transformation. Although the reactions proceed with relatively high yields and under mild reaction conditions, they all involve tedious work-up procedures and the catalysts could not be reused. Zeolite catalysts used in heterogeneous catalysis can serve as an environmental friendly alternative to the traditional synthetic routes. The range of well-defined zeolites available, and their advantages as easily recoverable and reusable materials, have prompted their application in green and sustainable procedures for the conversion of carbohydrates [39]. There are several carbohydrate *O*-glycosylation reactions that employ zeolites as catalysts such as synthesis of *O*-butyl D-glucosides by acetylation of D-glucose with *n*-butanol [40,41], *O*-glycosylation of 1,2-anhydro sugars with cyclohexanol [42], and Fischer-type glycosylation of *N*-acetyl-α-D-galactosamine (GalNAc) with methanol [43]. In view of the good catalytic activity in the glycosylation of D-glucose-based sugars, we decided to investigate use of zeolites for the glycosylation of D-ribose with methanol to *O*-methyl D-ribofuranoside (Fig. 3). Commercially available zeolites of H-ZSM-5, HY and H-Beta with different Si/Al ratio were screened to find the most appropriate one with respect to activity and selectivity.

The catalytic activities of zeolites for the *O*-glycosylation of D-ribose with methanol are shown in Table 1, where the average and standard deviation of three trials are reported. The reaction conditions are 300 mg D-ribose (2 mmol), 6 mL MeOH, and 350 mg catalyst (catalyst/reagent: 117% weight). Within each class of zeolite, there is a similar trend in the relationship between catalytic activity and framework Si/Al ratios: the catalytic activity increased with increasing Si/Al ratios. Zeolites with high Si/Al ratio have fewer acid sites but these acid sites are stronger than in zeolites with low Si/Al. Furthermore, the hydrophobicity increases with increasing Si/Al ratio due to the decrease in the number of hydrophilic charge-compensating ions in the zeolite structure [44]. Glycosylation of D-ribose with methanol liberates one mole of water which can poison the acid sites of the catalysts [45]. The poisoning will be reduced for high Si/Al zeolites despite their smaller density of acid sites. The highest yield of *O*-methyl D-ribofuranoside, 94%, was obtained after 18 h over H-beta zeolite with a very high framework Si/Al-ratio of 150. Additionally, the large pore openings and spacious channel intersections of H-beta zeolite may also contribute to its catalytic activity (Table 5) [46]. Reducing the temperature led to long reaction times and after 18 h, the yield of the *O*-methyl D-ribofuranoside was only 65 and 20%, respectively, when the reaction was conducted at 50 °C and 25 °C.

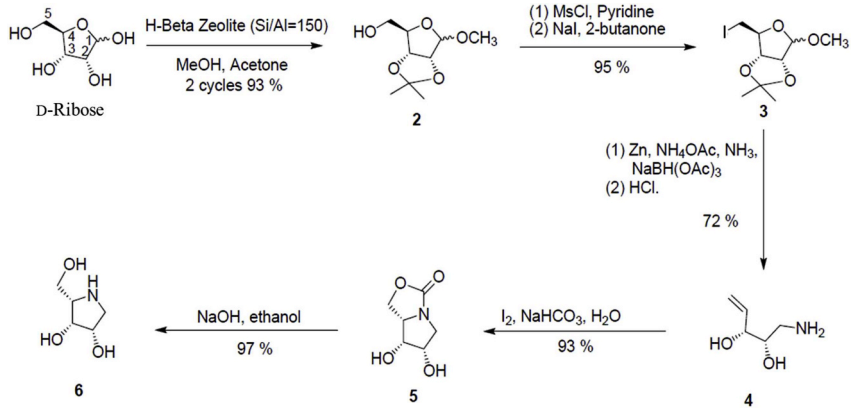
It was reported that the isopropylidenation of D-ribose and *O*-methyl D-ribofuranoside can be catalyzed by HY zeolite and 37–75% yields for di-*O*- and/or mono-*O*-isopropylidene derivatives were achieved [47]. As H-beta (150) catalyzed the methoxylation of D-ribose efficiently, it was interestingly to investigate the reaction from D-ribose to *O*-methyl 2,3-*O*-isopropylidene-D-ribofuranoside in *one-pot* synthesis. The reaction was carried out by the additional presence of acetone. Satisfyingly, an encouraging 76% yield was achieved after 24 h. Moreover, the significant difference in solubility of D-ribose and the 2,3-acetonide **2** allows them to be easily separated with liquid–liquid (ethyl acetate/water) extraction. In turn, it was possible to recover the unreacted D-ribose and carry out further batch reactions to improve the yield. About 93% total yield was achieved after another cycle of the reaction.

The used catalyst was recovered by filtration of the reaction mixture, regenerated and used in new batch reactions. Washing of the used catalyst with water and acetone followed by drying and calcination at 500 °C for 2 h led to almost complete recovery of the initial catalytic activity (Table 2), where the average and standard deviation of yield were based on three trials. In the next step, 2,3-*O*-isopropylidene-5-iodo-D-furanoside **3** was formed by reacting 2,3-acetonide **2** in pyridine with methanesulfonyl chloride (MsCl) followed by reacting with sodium iodide in 2-butanone [35]. After a very simple work-up procedure using liquid–liquid (dichloromethane/water) extraction followed by filtration through a silica gel plug using ethyl acetate/hexane = 1: 3 as eluent, the iodide **3** was recovered in 95% isolated yield.

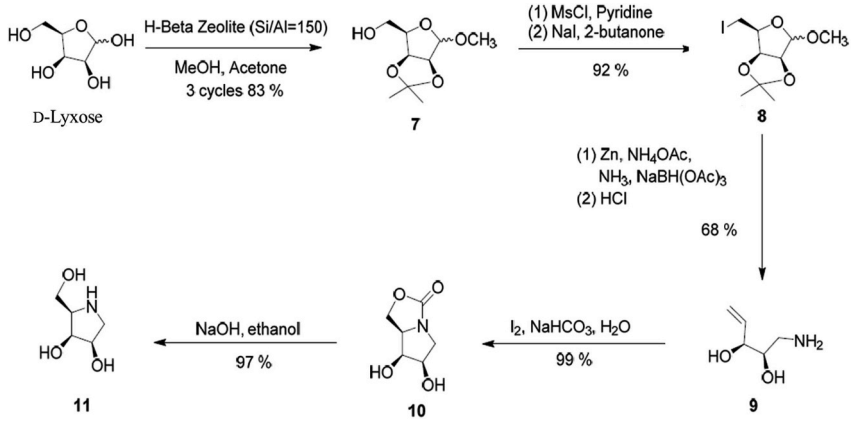
Conversion of iodo-substituted D-furanoside **3** to alkenylamine **4** (Fig. 4) is the next step. The Vasella reaction [48], which involves the formation of aldehydes from halogeno sugars by induction over metals such as indium and zinc, is used to convert **3** to **3c**.

In their studies on the synthesis of lyxitol pyrrolidines, Dangerfield et al. [23,31,32] used $NaBH_3CN$ for the reduction of the intermediate imine to amine with the formation of toxic HCN. We modified this reduction reaction by using *in-situ* molecular H_2 generated from NH_3 solution and Zn dust. The choice of Zn comes from the fact that it is a very good reducing agent [49] and promoter in the preparation of amines from imine [50–52] and oximes [53–56]. It is well known that the use of ammonia or ammonium salts in reductive amination reactions typically results in the formation of amine dimers **3b** (Table 3) due to the lower nucleophilicity of ammonia compared to the primary amine product of the reductive amination [31]. Therefore, the reaction has to proceed under an environment where ammonia or ammonium salts should be largely in excess. Hence, the reaction of converting the iodo-substituted D-furanoside **3** to olefinic amine **4** was carried out by using excess Zn, NH_3 solution and ammonium salts.

Different ammonium salts, $(NH_4)_2SO_4$, NH_4HCO_2, NH_4Cl, $(NH_4)_2CO_3$ and NH_4OAc, were investigated for the reductive amination reaction (Table 3, entries 1–5, the general reaction conditions are iodo-substituted D-furanoside 3 (160 mg, 0.5 mmol), Zn dust (800 mg, ~25 equiv), EtOH (10 mL), 25% NH_3 aqueous solution (8 mL, 100 equiv) and 90 °C for 18 h in autoclave). It was found that after the addition of 20 equivalents of $(NH_4)_2SO_4$ or NH_4HCO_2, only degradation of the starting material occurred, but no product could be detected. Although NH_4Cl and $(NH_4)_2CO_3$ had some activity, both were not satisfactory due to the excessive formation of the dimer **4a**. NH_4OAc showed a promising monomer selectivity, **4**: **4a** of 2: 1, and total amine (**4** + **4a**) yield. Next, taking advantage of the greater solubility of NH_4OAc in EtOH, the concentration of NH_4OAc was increased in an attempt to drive monomer formation. An increase from 20 to 200 equiv NH_4OAc proved beneficial, and the monomer **4** was formed in a 10: 1 ratio



Scheme 1. Synthesis route from D-ribose to 1,4-dideoxy-1,4-imino-*l*-lyxitol 6.



Scheme 2. Synthesis route from d-lyxose to 1,4-dideoxy-1,4-imino- d-lyxitol 11.

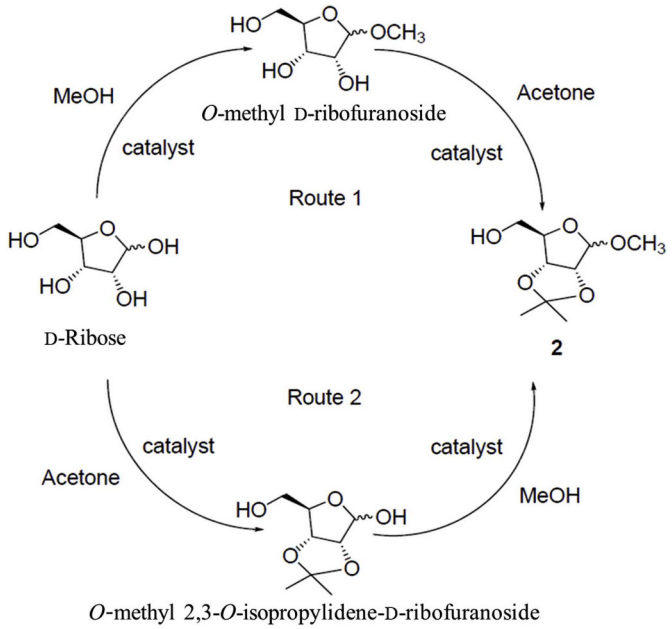


Fig. 2. Different synthesis pathways to O-methyl 2,3-*O*-isopropylidene-D-ribofuranoside from D-ribose.

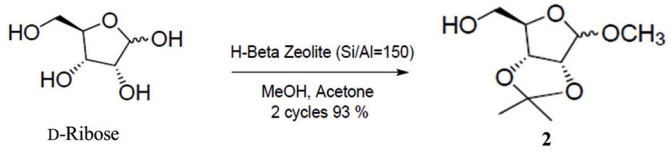


Fig. 3. One-pot synthesis of O-methyl 2,3-*O*-isopropylidene-D-ribofuranoside over H-Beta zeolite.

Table 1
Yield of O-methyl d-ribofuranoside over different catalysis conditions.

Catalyst	Temperature (°C)	Time (h)	Isolated yield (%)	Ratio(α/β)[a]
H-Beta(150)	65	18	94 ± 2.5	2.8
	50	18	65 ± 3.1	2.8
	25	18	20 ± 3.7	2.8
H-Beta(75)	65	18	82 ± 3.1	2.8
HY(15)	65	18	67 ± 2.2	2.6
HY(2.6)	65	18	45 ± 2.6	2.6
ZSM-5(60)	65	18	70 ± 2.4	2.2
ZSM-5(40)	65	18	62 ± 2.2	2.2
ZSM-5(15)	65	18	48 ± 2.5	2.2

[a] Estimated ratio of *O*-methyl β-D-ribofuranoside: *O*-methyl α-D-ribofuranoside based on NMR analyses.

(Table 3, entries 5–7). The ammonia concentration also affected the monomer selectivity significantly as a reduction from 100 to 30 equiv led to a decrease in both yield and selectivity. Surprisingly, when the reaction was proceeded under optimized condition but in an open-air environment, the amine yield dropped from 85 to 25%, although the high monomer selectivity remained the same. To further investigate reaction mechanism, the *one-pot* Vasella-reductive amination was separated into two sequence steps (Scheme 3).

As shown in Scheme 3, the first step is a classic Vasella reaction where an aldehyde intermediate **3c** was obtained. Then, the unreacted

Table 2
Yield of O-methyl 2,3-*O*-isopropylidene-D-ribofuranoside 2 for successive cycles using regenerated H-beta (150) catalyst.

Run	Time (h)	Isolated Yield (%)
No catalyst	24	< 5
1st cycle (*Fresh catalyst)*	24	76 ± 2.6
2th cycle (*catalyst regenerated)*	24	74 ± 2.4
3th cycle (*catalyst regenerated)*	24	73 ± 2.5
4th cycle (*catalyst regenerated)*	24	74 ± 2.3
5th cycle (*catalyst regenerated)*	24	73 ± 2.5

Reaction: D-ribose (500 mg), acetone (6 mL), MeOH (6 mL), 350 mg catalyst (catalyst/reagent: 70% weight) and 65 °C(reflux).

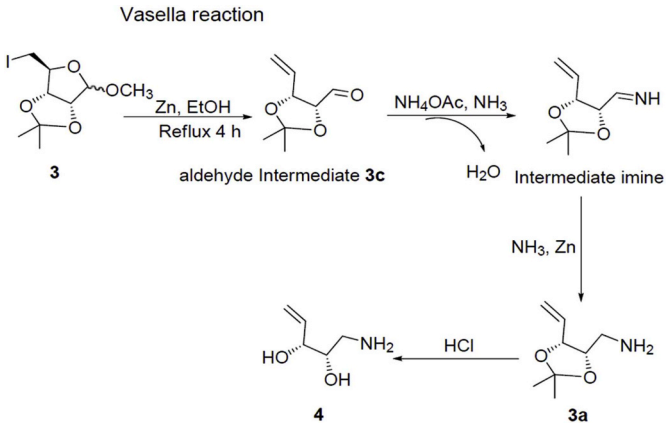


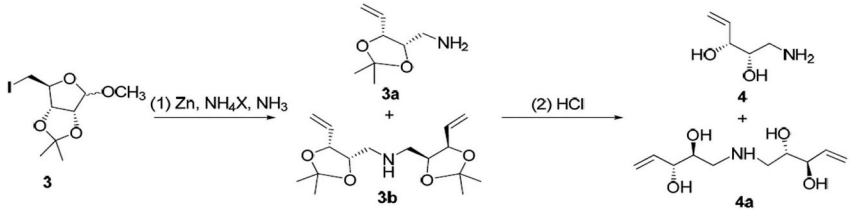
Fig. 4. Reaction mechanism for the formation of 4.

excess Zn dust was removed by filtration before the reaction mixture was subjected to the second step reaction. Surprisingly, no imine product **4b** or **4c** was detected in second reaction (no residue was obtained after work-up procedure as in Experimental 4.6). According to the reaction mechanism (Fig. 4), imine **4b** is produced by the condensation of aldehyde intermediate **3c** with NH_3 to form **3a** followed by the deprotection of isopropylidene with HCl. During the process, one equivalent of water was generated. Removal of the water from the reaction system should push the reaction towards imine formation. However, the large amount of water which is already present in the reaction mixture due to the use of aqueous ammonia solution as ammonia source severely hinders the formation of imine. The absence of imine (**4b**/**4c**) in second reaction indicates that the deprotection of intermediate imine with HCl was not proceeded. So, the only pathway to form targeted compound amine **4** is through amine **3a**, which involves to reduce intermediate imine. The nascent H_2 produced from the Zn dust and ammonia solution is the only reducing agent for the imine reduction, therefore, no intermediate imine was converted to **3a** in the second step because of the absence of the Zn dust. The low amine yield obtained when H_2 produced in round-bottomed flask can easily diffuse away in air, resulting in a lack of reducing agent for the intermediate imine reduction. This problem can be overcome by adding a stable and selective reducing agent. In contrast to $NaBH_3CN$, sodium triacetoxyborohydride ($NaBH(OAc)_3$) is a safe, mild, environmental friendly reducing agent and especially suitable for reductive aminations [57]. By adding 3 equivalents of $NaBH(OAc)_3$ in the second reaction, a satisfactory high amine yield of 81% was achieved (Table 3, Entry 10).

In contrast to amine **4**, amine **3a** is easily dissolved in organic solvents such as CH_2Cl_2 due to the presence of the isopropylidene group that masked the hydroxyl groups at C2 and C3. The significant difference in solubility of amine **3a** and NH_4OAc, which is present in large excess, allows them to be easily separated by liquid–liquid (CH_2Cl_2/water) extraction. The unreacted NH_4OAc can be reused for at least five batches without causing a significant decrease of the monomer selectivity (Fig. 5). Hence, this strategy is favored from perspectives of economics as well as environmental compatibility.

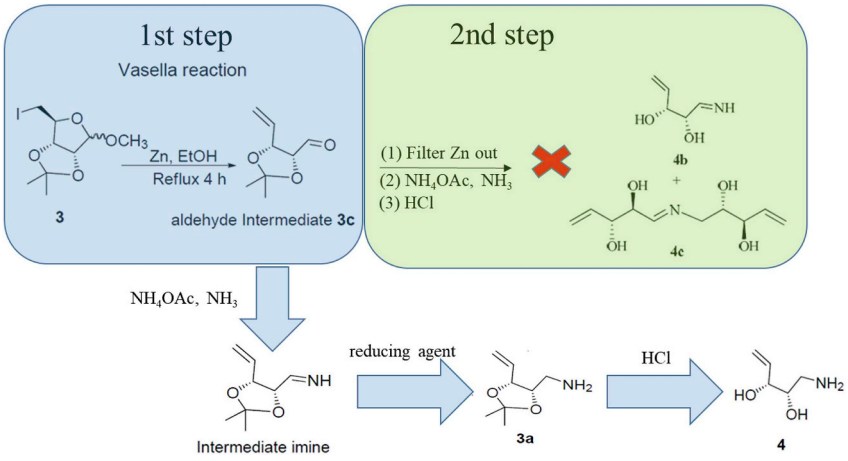
Next, olefinic amine **4** was converted to pyrrolidine ring system via halocyclization [23,31,32]. Subjecting amine **4** to molecular iodine and $NaHCO_3$ in water led to the formation of a single cyclic carbamate product **5** in 93% yield. Then, the formed cyclic carbamate **5** was hydrolyzed with NaOH, and the desired pyrrolidine **6** was obtained in excellent yield (~99%). The overall yield of hydroxypyrrolidine **6** was 57% from D-ribose.

Table 3
Preparation of olefinic amine 4 under different reaction conditions 4.



Entry	Conditions	Ratio (4: 4a)[a]	Yield (%)[b]
1	$(NH_4)_2SO_4$ (20 equiv)	–	–
2	NH_4HCO_2 (20 equiv)	–	–
3	$(NH_4)_2CO_3$ (20 equiv)	1:1	42
4	NH_4Cl (20 equiv)	1:1	53
5	NH_4OAc (20 equiv)	2:1	61
6	NH_4OAc (80 equiv)	4:1	74
7	NH_4OAc (200 equiv)	10:1	85, 72[c]
8	NH_4OAc (20 equiv), NH_3 (30 equiv)	1:2	36
9	NH_4OAc (200 equiv)[d]	10:1	25
10[e]	NH_4OAc (20 equiv), $NaBH(OAc)_3$ (3 equiv)	10:1	81, 66[c]

[a] Estimated ratio is based on NMR analyses.
[b] Combined yield of primary amine **4** and secondary amine **4a**.
[c] Isolated yield for primary amine **4**.
[d] Round bottle flask and open-air environment.
[e] Vasella reaction to form aldehyde intermediate **3c**, followed by addition of NH_4OAc, $NaBH(OAc)_3$. The reaction was stirred at RT for 30 h in an open round-bottomed flask.



Scheme 3. Iodo-substituted D-furanoside 3 to olefinic imine 4b

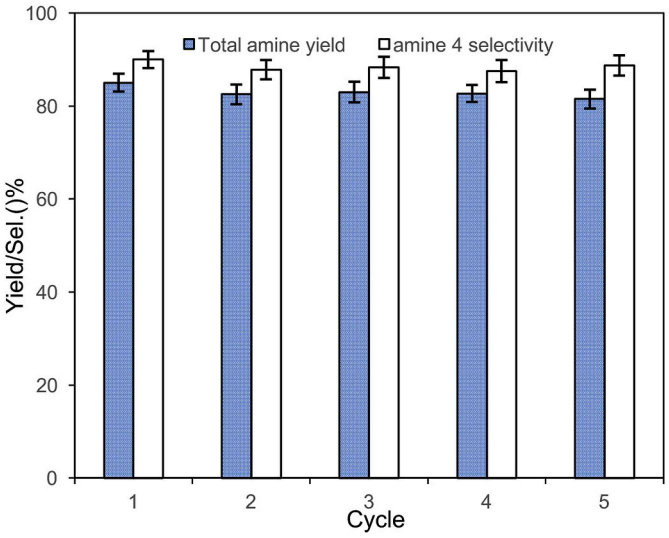


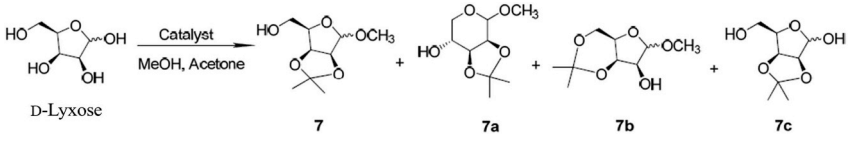
Fig. 5. Yield of amine products with recovered NH4OAc.

2.2. Synthesis 1,4-dideoxy-1,4-imino-D-lyxitol 6 from D-lyxose

The generality of the designed route was tested for the synthesis of D-lyxose to 1,4-dideoxy-1,4-imino-D-lyxitol (Scheme 2). Various zeolite catalysts and reaction conditions were tested for the transformation of D-lyxose to *O*-methyl 2,3-*O*-isopropylidene-D-lyxofuranoside **7** (Table 4). The general reaction conditions are 500 mg D-lyxose (3.3 mmol), 6 mL MeOH, 6 mL acetone, 350 mg catalyst (catalyst/reagent: 70% weight) and 65 °C. The reported yield were based on the average of three trials.

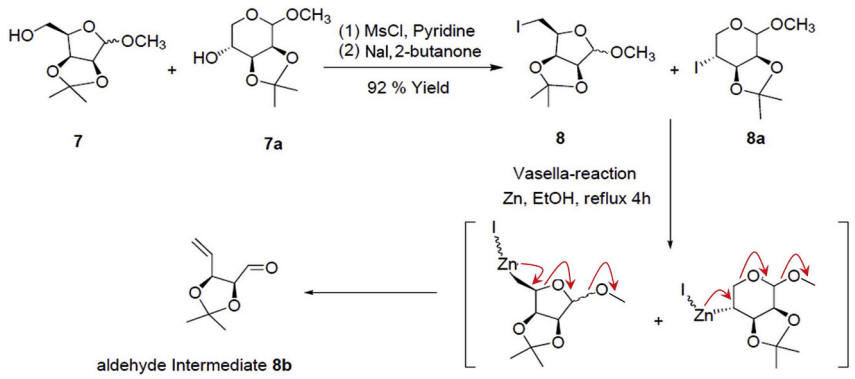
As shown in Table 4, strongly acid zeolites such as H-beta (12.5), HY (2.6) and ZSM-5 (15) did not improve the yield of 2,3-acetonide **7** + **7a** and some unglycosylated 2,3-acetonide **7c** were also detected. The best result was achieved over H-beta (150) and 45% yield of 2,3-acetonide (**7** + **7a**) in one batch reaction. After reaction, the reaction mixture includes unreacted D-lyxose, *O*-methyl D-lyxofuranoside and 2,3-acetonide **7** + **7a**. Although ~45% yield in one batch reaction was relatively low, the significant difference in solubility of the reagents including D-lyxose and *O*-methyl D-lyxofuranoside and products including 2,3-acetonide **7** + **7a** allows them to be easily separated with

Table 4
Yield of *O*-methyl 2,3-*O*-isopropylidene-D-lyxofuranoside 7 over different zeolites.5.



Run	Catalyst	Time (h)	Yield (%)[a]	Ratio[c]
1	H-Beta(12.5)	24	12, 10[b]	> 10
2	HY(2.6)	24	6, 6[b]	–
3	ZSM-5(15)	24	43, 22[b]	4
4	H-Beta(150)	24	45	> 10
5	H-Beta(150) (cycle 2)	24	44	4
6	H-Beta(150) (cycle 3)	24	44	2.5
7	H-Beta(150), MeOH (step 1) Acetone (step 2)	48 24	65	2.5
8	H-Beta (150), 10 equiv 2,2-dimethoxypropane	24	77, 13[b]	> 10 (3:2)[d]

[a] Yield of 7 + 7a + 7b + 7c.
[b] Estimated yield of 7c based on NMR analyses.
[c] Estimated ratio of furanoside product **7** to pyranoside product **7a** based on NMR analyses.
[d] Estimated ratio of 2,3-acetonide (**7** + **7a**) to 3,5-acetonide **7b** based on NMR analyses.



Scheme 4. O-methyl 2,3-*O*-isopropylidene-D-lyxofuranoside to aldehyde intermediate 8b

liquid–liquid (ethyl acetate/water) extraction. Therefore, it was possible to recover those unreacted D-lyxose and *O*-methyl D-lyxofuranoside and carry out further batch reactions to improve the yield. About 82% yield was achieved after three cycles of the reaction. Interestingly, it was found that the ratio of **7a** to **7** increased in the subsequent cycles (see Appendix-1H NMR of *O*-methyl 2,3-*O*-isopropylidene-D-lyxofuranoside **7**). A separate experiment was carried out by allowing the formation of *O*-methyl D-lyxofuranoside before the addition of acetone (Table 4, Run 7). A high molar ratio of **7a** to **7** was obtained with this strategy, which proves that pre-synthesis of the *O*-methyl D-lyxofuranoside led to the preferred formation of the pyranoside product **7a**. Adding 10 equiv 2,2-dimethoxypropane in reaction mixture helps to improve the total yield to 77%, however, it was also observed that the significant amount of 3,5-acetonide **7b** and unglycosylated 2,3-acetonide **7c** by-products were formed (Table 4, Run 8).

Treating the 2,3-acetonide (**7** + **7a**) with methanesulfonyl chloride (MsCl) in pyridine followed by reacting with sodium iodide in 2-butanone led to a mixture of iodo-substituted D-lyxofuranoside **8** and D-lyxopyranoside **8a** (Scheme 4). After a very simple work-up by liquid–liquid (dichloromethane/water) extraction and filtration through a silica gel plug using ethyl acetate/hexane = 1: 3 as eluent), a total 92% isolated yield was achieved. Fortunately, based on the mechanism of Vasella reaction (Scheme 4), it was expected that only a single aldehyde intermediate **8b** would be obtained from the mixture of iodo-substituted D-lyxofuranoside **8** and D-lyxopyranoside **8a**. By applying the optimized reaction condition as in Table 3, Entry 7 for the mixture of D-lyxofuranoside **8** and D-lyxopyranoside **8a**, the monomer olefinic amine **9** was obtained in 68% isolated yield. Finally, halocyclization/carbonylation of olefinic amine **9** to cyclic carbamate **10** and then hydrolysis of the cyclic carbamate **10** afforded the hydroxypyrrolidine **11** in total 50% yield (starting from D-lyxose).

3. Conclusion

The novel and environmental friendly synthetic route for hydroxypyrrolidines, 1,4-dideoxy-1,4-imino-L-lyxitol and 1,4-dideoxy-1,4-imino-D-lyxitol was carried out in a simple 5-steps starting from commercially available D-ribose and D-lyxose, respectively. The *one-pot* synthesis of the *O*-methyl 2,3-*O*-isopropylidenepentofuranoses of the D-pentoses was managed over zeolite solid acid catalysts. The best catalyst was H-beta zeolite containing a Si/Al molar ratio of 150, where a yield of > 83% was obtained. The catalyst could be reused for subsequent batch reactions, with no significant loss of activity and selectivity. The synthetic route resulted in good yields of 1,4-dideoxy-1,4-imino-L-lyxitol and 1,4-dideoxy-1,4-imino-D-lyxitol of 57% and 50%, respectively. The yields are comparable to previously reported yields of 55% and 57% [23,31]. Besides the competitive yield, the reported strategy also employs many principles of Green Chemistry such as avoiding toxic or noxious chemical, and recycling and reusing the reagents.

4. Experimental

4.1. Preparation and characterization of zeolite catalysts

All zeolite catalysts are commercially available and purchased from Zeolite International. The sample is named as zeolite-type (t) where t is the framework Si/Al ratios. The nitrogen adsorption/desorption isotherms of the zeolite samples were measured with a Micromeritics Tristar 3000. Before the measurement, each sample was degassed at 500 °C for 4 h to remove physisorbed water. The surface area was determined using the Brunauer–Emmett–Teller (BET) method. The pore size distribution was calculated from the desorption branch of the isotherm using the Barrett–Joyner–Halenda (BJH) equation. The total pore volume of the sample was taken from the volume of nitrogen adsorbed at the P/P° of 0.99. The crystal structure and phase of the samples were determined with a Siemens D5005 powder x-ray diffractometer equipped with a Cu anode and variable primary and secondary beam slits. The diffractograms were measured from of 5° to 50°, using a step size of 0.02° and a dwell time of 1 s/step. The average crystallite size D was calculated using the Scherrer equation as below:

$$D = \frac{K\lambda}{\beta \cos\theta}, \beta = \sqrt{B^2 - b^2}$$

where, K is a constant taken as 0.9, θ is the angle between the X-ray beam and the normal on the reflecting plane, λ is the wavelength of Cu Kα = 0.15418 nm, β is the peak line width. The peak line width β is corrected for the instrumental broadening, where B is the measured peak width and b is the instrumental broadening. Diffraction data from standard silicon (Si) powder was used to measure the instrumental broadening. The silicon (111) reflection at 2θ ~26.77° was considered and the instrumental broadening b was determined to be 1.413×10^{-3} rad.

The nitrogen adsorption-desorption isotherms of the different zeolite catalysts are given in Fig. 6.

The textural properties of zeolite catalysts were shown in Table 5, where the average and standard deviation of three measurements are reported. The steep increase at low P/P° indicates the presence of micropores. The hysteresis above P/P ° 0.5 in these zeolite samples does not indicate the presence of mesopores but originates from the interparticle space of the sample. The HY (15) sample has the highest surface area of 567 $m^2 g^{-1}$ with ~433 $m^2 g^{-1}$, due to micropores. The surface area and porosity of the samples were lower for zeolites with higher Al content.

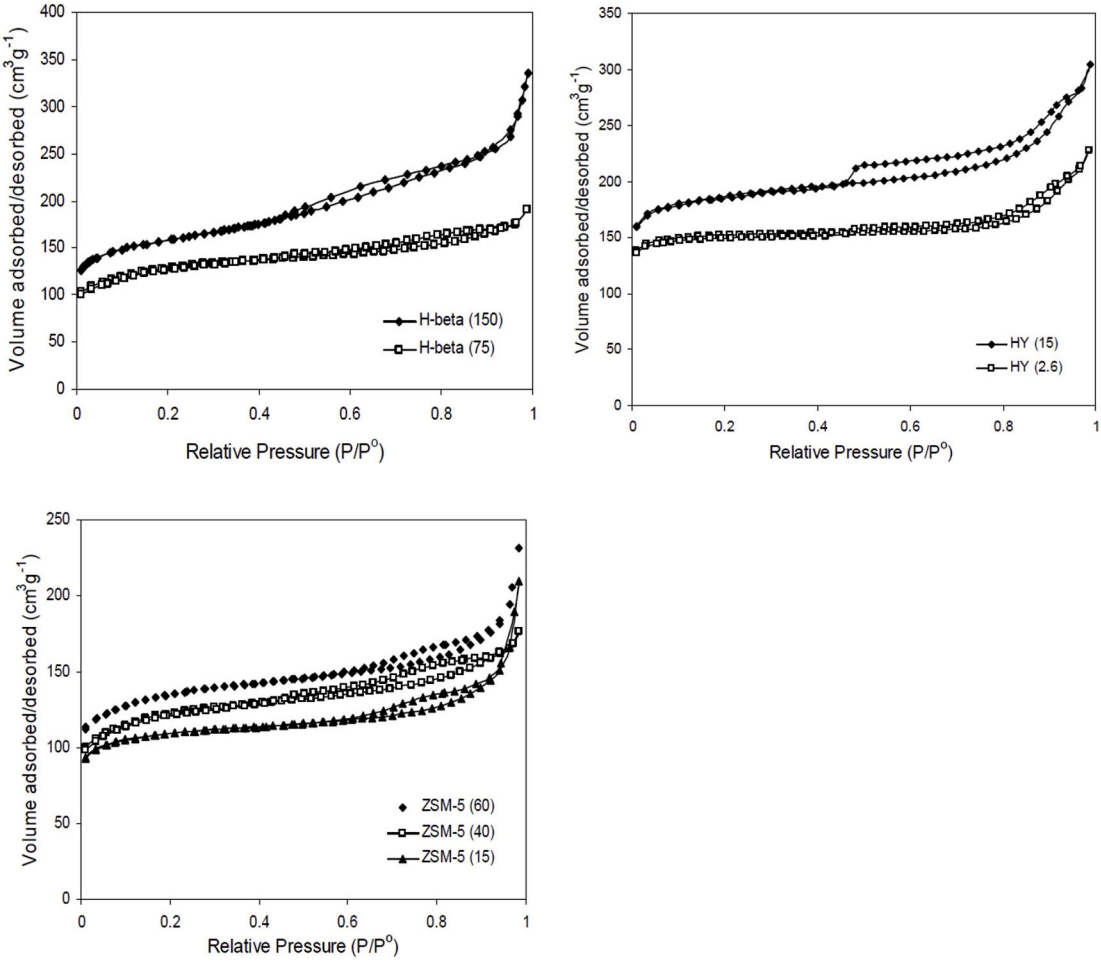


Fig. 6. Adsorption/desorption isotherms of (a) H-beta (b) HY and (c) ZSM-5 zeolites with different Si/Al ratios (in parenthesis).

4.2. Identification of products

^{1}H and ^{13}C NMR spectra were measured at 75, 300 and 400 MHz with a Bruker Avance 300 NMR spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in ppm downfield from TMS. Mass spectrometry (MS) and high resolution-mass spectrometry electron ionization (HR-MS EI)were taken with a Finnigan MAT95XL-T and Micromass VG7035 double focusing mass spectrometer of high resolution, respectively. Optical rotations were measured by a Perkin Elmer 341 polarimeter in a 1 dm cell. Analytical and preparative thin layer chromatography (TLC) were conducted on precoated TLC plates (silica gel 60 F254, Merck). To detect the sugars, thymol (0.5 g)/sulfuric acid (5 mL, *conc.* sulfuric acid in 95 mL ethanol) visualization reagent was used. After spraying, the TLC plate was heated to develop pink spots. No crystal structure data was obtained due to the difficulty in crystal growth for products.

4.3. General procedure for transformation of D-ribose to O-methyl D-ribofuranoside

A 25 mL round-bottomed flask was charged with D-ribose (Carbosynth, 300 mg, 2 mmol) and MeOH (6 mL). The suspension was heated to reflux (65 °C). After that, zeolite catalyst (350 mg, catalyst/reagent: 117 wt %) was added into reaction flask. The mixture was stirred at reflux for 18 h and then cooled to room temperature. The zeolite catalyst was filtered out and the filtrate was evaporated under reduced pressure to give a syrup. The resulting syrup was then purified by column chromatography on silica gel (chloroform/methanol 6: 1) and 310 mg (94% yield) of *O*-methyl D-ribofuranoside was obtained as colourless syrup. For the *O*-glycosylation of other pentoses with methanol, the same experimental procedure was used. All methoxylated products were identified by comparing their proton and carbon NMR spectra with references [23,58–65] and the molar ratios of different

Table 5
Textural properties of Zeolites.

Catalyst	Surf. area ($m^2\ g^{-1}$)	Micropore area($m^2\ g^{-1}$)	Pore vol. ($cm^3\ g^{-1}$)	Micropore vol. ($cm^3\ g^{-1}$)	Crystallite[a] size (nm)
H-Beta(150)	496 ± 12.1	288 ± 8.3	0.52 ± 0.02	0.15 ± 0.01	20.7 ± 0.9
H-Beta(75)	399 ± 10.7	221 ± 7.6	0.30 ± 0.02	0.12 ± 0.01	13.4 ± 0.7
HY(15)	567 ± 12.6	433 ± 11.2	0.47 ± 0.03	0.23 ± 0.02	59.6 ± 1.1
HY(2.6)	451 ± 12.1	406 ± 10.3	0.35 ± 0.02	0.22 ± 0.02	35.6 ± 0.8
ZSM-5(60)	414 ± 8.8	274 ± 6.6	0.36 ± 0.03	0.15 ± 0.01	61.5 ± 1.0
ZSM-5(40)	377 ± 7.5	240 ± 6.1	0.27 ± 0.02	0.13 ± 0.01	84.7 ± 1.2
ZSM-5(15)	331 ± 6.6	245 ± 5.2	0.32 ± 0.01	0.13 ± 0.01	77.1 ± 1.1

[a] Crystallite sizes were obtained by XRD measurements using the Scherrer equation.

isomer products were estimated from the integral values of the corresponding ^{1}H NMR signals.

4.4. General procedure for the one-pot synthesis of O-methyl 2,3-O-isopropylidene-D-ribofuranoside 2 from D-ribose

A 25 mL round-bottomed flask was charged with D-ribose (Carbosynth, 500 mg, 3.3 mmol), acetone (6 mL) and MeOH (6 mL). The suspension was heated to reflux (65 °C). After that, zeolite catalyst (350 mg, catalyst/reagent: 70 wt %) was added into reaction flask. The mixture was stirred at reflux for 24 h and then cooled to room temperature. The zeolite catalyst was filtered out and the filtrate was evaporated under reduced pressure to give crude product. The crude product was dissolved in ethyl acetate (20 mL) and then washed twice with deionized water (10 mL). The organic phase was rotary evaporated to dryness to afford 520 mg (76% yield) of colorless syrup. The aqueous phase was rotary evaporated to dryness followed by adding acetone (3 mL), MeOH (3 mL), zeolite catalyst (100 mg) and stirring at reflux for 24 h. Applied the same work-up procedure as above, a total of 630 mg of pure product **2** was obtained (93% overall yield from D-ribose). $[\alpha]_D^{20}$ − 92.0 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 3H), 1.28 (s, 3H), 3.20 (s, 3H), 3.43 (d, *J* = 4.4 Hz, 2H), 4.16 (t, *J* = 4.1 Hz, 1H), 4.40 (d, *J* = 5.9 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 25.9, 54.7, 63.2, 81.1, 85.1, 87.5, 109.2, 111.7. ESI-MS: *m/z* 227 $[M+Na]^+$.

4.5. General procedure for iodination of O-methyl 2,3-O-isopropylidene-D-ribofuranoside 2 to O-methyl 2, 3-O-isopropylidene-5-iodo-D-ribofuranoside 3

Methanesulfonyl chloride (0.7 mL, 9 mmol) was added dropwise with stirring to an ice-cooled solution of *O*-methyl 2,3-*O*-isopropylidene-D-ribofuranoside (1630 mg, 8.0 mmol) in pyridine (5 mL) and the mixture was kept for 2 h at 0 °C. The reaction was quenched with water (5 mL) and then CH_2C1_2 (20 mL) was added. The resulting solution was washed successively with 10% aq HCl (5 mL) until the organic layer extract became acidic (pH < 3). After added an additional portion of 10% aq HCl (5 mL) followed by saturated aq $NaHCO_3$ (5 mL) to the solution, the organic layer was separated and dried with $MgSO_4$. After filtration, Organic extract was evaporated under reduced pressure to give semisolid mesylate. To the solution of the semisolid mesylate in 2-butanone (10 mL), NaI (1800 mg, 12 mmol) was added and the mixture was stirred and heated at reflux for 24 h. After the mixture was cooled to room temperature, the precipitate of sodium methane sulfonate was filtered out and the filtrate was concentrated. The resulting residue was dissolved in dichloromethane (50 mL) and then washed twice with water (2 × 40 mL). After dried with $MgSO_4$, the resulting solution was filtered and evaporated under reduced pressure to give a syrup. The syrup then was taken up in hexane/EtOAc, 3/1(v/v) and filtered through a silica plug to remove excess NaI to give iodo-substituted D-furanoside **3** in 95% yield (2380 mg). $[\alpha]_D^{20}$ − 67.0 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.41 (s, 3H), 3.12 (t, *J* = 10.0 Hz, 1H), 3.21 (dd, *J* = 9.9, 6.1 Hz, 1H), 3.30 (s, 3H), 4.36 (dd, *J* = 9.9, 3.8 Hz, 1H), 4.57 (d, *J* = 5.9, 1H), 4.70 (d, *J* = 5.9 Hz, 1H), 4.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.61, 24.8, 26.2, 55.0, 82.8, 85.1, 87.2, 109.4, 112.4. ESI-MS: *m/z* 337 $[M+Na]^+$.

4.6. General procedure for synthesis of alkenylamine 4

4.6.1. Method 1

Activated Zn (Sigma-Aldrich, 800 mg, 12.3 mmol), NH_4OAc (7700 mg, 100 mmol) and 25% aqueous NH_3 (8 mL) were added to a solution of iodo-substituted D-furanoside **3** (160 mg, 0.5 mmol) in EtOH (10 mL). The mixture was stirred at 90 °C for 18 h in an autoclave. After cooled to room temperature, the mixture was filtered and rotary evaporated under reduced pressure. The resulting residue was then dissolved in deionized water (20 mL) and extracted twice with CH_2Cl_2 (15 mL × 2). The organic phase was rotary evaporated to dryness to give a syrup. The resulting syrup was dissolved in iPrOH (5 mL) followed by dropwise adding 1000 mg (10 mmol) *conc.* HCl solution. The suspension was stirred for 2 h and then filtered through celite and concentrated under reduced pressure. The residue was re-dissolved in iPrOH (5 mL). The resulting solution was dry loaded onto silica gel and purified by gradient chromatography (DCM/EtOH/MeOH/30% aqueous NH_3, 25/2/2/1 to 5/2/2/1, v/v/v/v) to give the alkenylamine **4** in 72% yield as the HCl salt (55 mg, 0.36 mmol, light yellow powder).

4.6.2. Method 2

To a solution of iodo-substituted D-furanoside **3** (314 mg, 1 mmol) in EtOH (20 mL), activated Zn (Sigma-Aldrich, 650 mg, 10 mmol) was added. The mixture was stirred at reflux for 3 h before cooled down to room temperature. Then, NH_4OAc (15400 mg, 200 mmol), 25% aqueous NH_3 (16 mL) and $NaBH(OAc)_3$ (636 mg, 3 mmol) were added to the reaction mixture. The resulting mixture was stirred at room temperature for 30 h in round-bottomed flask. After that, the mixture was filtered and rotary evaporated under reduced pressure. The resulting residue was dissolved in deionized water (30 mL) and extracted twice with CH_2Cl_2 (20 mL × 2). The organic phase was rotary evaporated to dryness to afford a syrup. The resulting syrup was dissolved in *i*PrOH (10 mL) followed by dropwise adding 2000 mg (20 mmol) *conc.* HCl solution. The suspension was stirred for 2 h and then filtered through celite and concentrated under reduced pressure. The residue was re-dissolved in *i*PrOH (10 mL). The resulting solution was dry loaded on to silica gel and purified by gradient flash chromatography (DCM/EtOH/MeOH/30% aqueous NH_3, 25/2/2/1 to 5/2/2/1, v/v/v/v) to give the alkenylamine **4** in 66% yield as the HCl salt. (102 mg, 0.66 mmol, light yellow powder). $[\alpha]_D^{20}$ 8.0 (*c* 0.1, EtOH). ^{1}H NMR (400 MHz, D_2O): δ 5.82 (ddd, *J* = 16.8, 10.4, 6.5 Hz, 1H), 5.31 (dd, *J* = 16.7, 10.3 Hz, 2H), 4.15 (dd, *J* = 6.5, 5.5 Hz, 1H), 3.81 (ddd, *J* = 9.6, 5.5, 2.8 Hz, 2H), 3.25 (dd, *J* = 13.0, 2.8 Hz, 1H), 2.97 (dd, *J* = 13.1, 9.5 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 135.2, 118.3, 73.9, 69.7, 41.0. HRMS (ESI) *m/z* calcd. for $[C_5H_{11}O_2N + H]^+$: 118.0863, found: 118.0871.

4.7. Synthesis of carbamate 5

To a solution of the alkenylamine hydrochloride **4** (154 mg, 1 mmol) in water (5 mL), $NaHCO_3$ (126 mg, 1.5 mmol) and I_2 (279 mg, 1.1 mmol) were added. The solution was stirred 18 h at room temperature. After that, the mixture was filtered and rotary evaporated under reduced pressure to give crude product. The crude product was purified by silica gel chromatography (EtOAc/MeOH, 99/1, v/v) to afford amorphous white powder carbamate **5** (148 mg, 0.93 mmol, 93%). $[\alpha]_D^{20}$ 32.5 (*c* 0.3, EtOH). ^{1}H NMR (400 MHz, D_2O): δ 4.54–4.73 (m, 3H), 4.18 (ddd, *J* = 10.3, 7.4, 5.4 Hz, 1H), 4.05 (t, *J* = 4.4 Hz, 1H), 3.53 (dd, *J* = 14.5, 10.8 Hz, 1H), 3.17 (dd, *J* = 14.4, 10.3 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 164.2 (C6), 73.3 (C2), 70.7 (C3), 64.4 (C5), 61.6 (C4), 48.7 (C1). HRMS (ESI) *m/z* calcd. For $[C_6H_9O_4N + Na]^+$: 182.0424, found: 182.0429.

4.8. Synthesis of hydroxymethyl-pyrrolidine-3,4-diols 6

To a solution of carbamate **5** (159 mg, 1 mmol) in EtOH (5 mL), NaOH (400 mg, 10 mmol) was added. The mixture was stirred at reflux for 2 h before cooled down to room temperature. Then, Amberlite IR 120H acidic ion exchange resin (1000 mg) was added to the mixture and the suspension was stirred at room temperature for overnight. After filtering out the ion exchange resin, the resin was eluted with 5–15% aqueous NH_3. The resulting eluent was concentrated under reduced pressure. 1, 4-dideoxy-1,4-imino-L-lyxitol **6** was isolated as the HCl salt (165 mg, 0.97 mmol, 97%). $[\alpha]_D^{20}$ − 22.5 (*c* 0.3, H_2O). ^{1}H NMR (400 MHz, D_2O): δ 4.52 (dt, *J* = 7.4, 4.1 Hz, 1H), 4.37 (t, *J* = 4.1 Hz, 1H), 4.00 (dd, *J* = 12.2, 4.9 Hz, 1H), 3.92 (dd, *J* = 12.2, 8.4 Hz, 1H),

3.75 (ddd, J = 13.0, 8.8, 4.8 Hz, 1H), 3.55 (dd, J = 12.2, 7.5 Hz, 1H), 3.23 (dd, J = 12.0, 7.3 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 69.9 (C2), 69.7 (C3), 62.4 (C4), 57.4 (C5), 47.0 (C1). HRMS (ESI) *m/z* calcd. for $[C_5H_{11}O_3N + H]^+$:134.0812, found: 134.0813.

4.9. General procedure for one-pot synthesis O-methyl 2,3-O-isopropylidene-D-lyxofuranoside 7 from D-lyxose

A 25 mL round-bottomed flask was charged with D-lyxose (Carbosynth, 500 mg, 3.3 mmol), acetone (6 mL) and MeOH (6 mL). The suspension was heated to reflux (65 °C). After that, zeolite catalyst (350 mg, catalyst/reagent: 70 wt %) was added into reaction flask. The mixture was stirred at reflux for 24 h and then cooled to room temperature. The zeolite catalyst was filtered out and the filtrate was evaporated under reduced pressure to give crude product. The crude product was dissolved in ethyl acetate (20 mL) and then washed twice with deionized water (10 mL). The organic phase was rotary evaporated to dryness to afford 310 mg (45% yield) of colorless syrup. The aqueous phase was rotary evaporated to dryness followed by adding Acetone (6 mL), MeOH (6 mL) and zeolite catalyst (350 mg). The resulting mixture was stirred at reflux for 24 h. Applied the same work-up procedure as above to give another batch of colorless syrup product. Repeated the same reaction and work-up process for those unreacted D-lyxose and *O*-methyl D-lyxofuranoside in aqueous extract for another 2 cycles, a total of 560 mg of pure product was obtained (82% overall yield from D-lyxose). D-lyxofuranoside product **7**: ^{1}H NMR (300 MHz, $CDCl_3$): (Major) δ 1.28 (s, 3H), 1.42 (s, 3H), 3.30 (s, 3H), 3.85–4.04 (m, 2H), 4.02 (dd, J = 8.6, 2.8 Hz, 1H), 4.55 (d, J = 4.4 Hz, 1H), 4.74 (dd, J = 4.8, 2.7 Hz, 1H), 4.89 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (Major) δ 112.7, 107, 85.1, 80.3, 79.3, 61.0, 54.6, 25.9, 24.5. D-lyxopyranoside product **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): (Minor) δ 1.33 (s, 3H), 1.49 (s, 3H), 3.40 (s, 3H), 3.59–4.0 (m, 2H), 4.0–4.33 (m, 3H), 4.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (Minor) δ 112.7, 99.9, 76.3, 74.4, 63.9, 62.9, 55.8, 27.5, 25.6. ESI-MS: *m/z* 337 $[M + Na]^+$.

4.10. General procedure for iodination of O-methyl 2,3-O-isopropylidene-D-lyxofuranoside 7 to O-methyl 2, 3-O-isopropylidene-5-iodo-D-lyxofuranoside 8

Methanesulfonyl chloride (0.7 mL, 9 mmol) was added dropwise with stirring to an ice-cooled solution of *O*-methyl 2,3-*O*-isopropylidene-D-lyxofuranoside (1630 mg, 8.0 mmol) in pyridine (5 mL) and the mixture was kept for 2 h at 0 °C. The reaction was quenched with water (5 mL) and then CH_2C1_2 (20 mL) was added. The resulting mixture was washed successively with 10% aq HCl (5 mL) until the organic layer extract became acidic (pH < 3). After added an additional portion of 10% aq HCl (5 mL) followed by saturated aq $NaHCO_3$ (5 mL) to the solution, the organic layer was separated and dried with ($MgSO_4$). After filtration, organic extract was concentrated to give semisolid mesylate. To the solution of the mesylate in 2-butanone (20 mL), NaI (12000 mg, 80 mmol) was added. The mixture was stirred and heated at reflux for 36 h. After the mixture was cooled to room temperature, the precipitate of sodium methane sulfonate and unreacted NaI were filtered out and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (50 mL) and washed with water (2 × 40 mL). After dried with $MgSO_4$, the resulting solution was evaporated under reduced pressure to give a syrup. The resulting syrup then was taken up in hexane/EtOAc, 3/1 (v/v) and filtered through a silica plug to remove excess NaI to give iodo-substituted D-lyxofuranoside **8** in 92% yield (2310 mg). $[\alpha]_D^{20}$ 65.0 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): (Major) δ 1.30 (s, 3H), 1.42 (s, 3H), 3.25–3.35 (m, 4H), 4.14–4.19 (m, 1H), 4.57 (d, J = 5.8 Hz, 1H), 4.70–4.74 (m, 1H), 4.88 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (Major) δ 112.6, 107.1, 85.1, 80.4, 79.4, 54.6, 26.0, 24.9, −0.8. ESI-MS: *m/z* 337 $[M + Na]^+$.

4.11. General procedure for synthesis of alkenylamine 9

To a solution of iodo-substituted D-lyxofuranoside **8** (160 mg, 0.5 mmol) in EtOH (10 mL), activated Zn (Sigma-Aldrich, 800 mg, 12.3 mmol), NH_4OAc (7700 g, 100 mmol) and 25% aqueous NH_3 (8 mL) were added. The mixture was stirred at 90 °C for 18 h in an autoclave. After cooled down to room temperature, the mixture was filtered and concentrated under reduced pressure. The residue was dissolved in deionized water (20 mL) and extracted twice with CH_2Cl_2 (15 mL × 2). The organic phase was rotary evaporated to dryness to afford a syrup. The resulting syrup was dissolved in iPrOH (5 mL) followed by adding dropwise 1000 mg (10 mmol) conc. HCl solution. The suspension was stirred for 2 h and then filtered through celite and concentrated under reduced pressure. The residue was re-dissolved in iPrOH (5 mL) and filtered. The solution was dry loaded on to silica gel and purified by gradient flash chromatography (DCM/EtOH/MeOH/30% aqueous NH_3, 25/2/2/1 to 5/2/2/1, v/v/v/v) to give the alkenylamine **9** in 68% yield as the HCl salt (52 mg, 0.34 mmol, light yellow powder). $[\alpha]_D^{20}$ − 8.0 (*c* 0.1, EtOH). ^{1}H NMR (400 MHz, D_2O): δ 5.72–6.08 (m, 1H), 5.15–5.55 (m, 2H), 4.15 (dd, J = 6.5, 5.4 Hz, 1H), 3.81 (ddd, J = 9.5, 5.4, 2.8 Hz, 2H), 3.25 (dd, J = 13.3, 3.0 Hz, 1H), 2.97 (dd, J = 13.2, 9.6 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 135.4, 118.6, 74.2, 69.9, 41.3. HRMS (ESI) *m/z* calcd. for $[C_5H_{11}O_2N + H]^+$: 118.0868, found: 118.0873.

4.12. Synthesis of carbamate 10

To a solution of the alkenylamine hydrochloride **9** (154 mg, 1 mmol) in water (5 mL), $NaHCO_3$ (126 mg, 1.5 mmol) and I_2 (279 mg, 1.1 mmol) were added. The solution was stirred 18 h at room temperature. After that, the mixture was filtered and rotary evaporated under reduced pressure to give crude product. The crude product was purified by silica gel chromatography (EtOAc/MeOH, 99/1, v/v) to afford carbamate **10** (157 mg, 0.99 mmol, 99%) as an amorphous white powder. $[\alpha]_D^{20}$ − 30.2 (*c* 0.3, EtOH). ^{1}H NMR (400 MHz, D_2O): δ 4.54–4.80 (m, 3H), 4.18 (ddd, J = 8.0, 5.2, 2.8 Hz, 1H), 4.05 (t, J = 3.4 Hz, 1H), 3.54 (dd, J = 10.8, 8.0 Hz, 1H), 3.18 (dd, J = 10.8, 8.0 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 164.3 (C6), 73.3 (C2), 70.7 (C3), 64.4 (C5), 61.6 (C4), 48.7 (C1). HRMS (ESI) *m/z* calcd. For $[C_6H_9O_4N + Na]^+$: 182.0429, found: 182.0433.

4.13. Synthesis of hydroxymethyl-pyrrolidine-3,4-diols 11

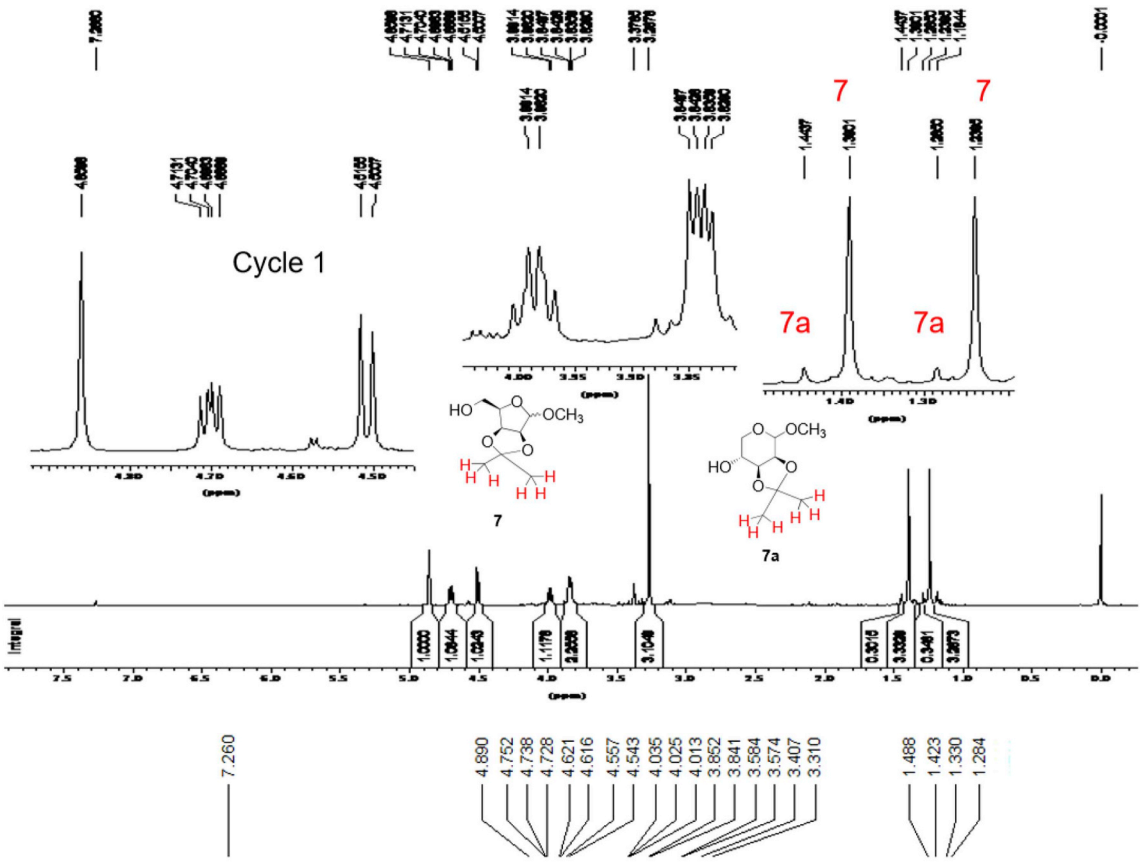
To a solution of carbamate **10** (159 mg, 1 mmol) in EtOH (5 mL), NaOH (400 mg, 10 mmol) was added. The mixture was stirred at reflux for 2 h before cooled down to room temperature. Amberlite IR 120H acidic ion exchange resin (1000 mg) was added to the mixture and the resulting suspension was stirred at room temperature for overnight. After filtering out the ion exchange resin, the resin was eluted with 5–15% aqueous NH_3. The resulting eluent was concentrated under reduced pressure. 1,4-dideoxy-1,4-imino-L-lyxitol **11** was isolated as the HCl salt (166 mg, 97 mmol, 97%). $[\alpha]_D^{20}$ 21.5 (*c* 0.3, H_2O). ^{1}H NMR (400 MHz, D_2O): δ 4.50–4.54 (m, 1H), 4.37 (t, J = 1.6 Hz, 1H), 4.00 (dd, J = 3.3, 1.3 Hz, 1H), 3.96 (dd, J = 5.6, 2.1 Hz, 1H), 3.74–3.80 (m, 1H), 3.55 (dd, J = 13.2, 3.0 Hz, 1H), 3.27 (dd, J = 13.3, 9.5 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 69.3 (C2), 69.1 (C3), 61.4 (C4), 57.1 (C5), 46.5 (C1). HRMS (ESI) *m/z* calcd. for $[C_5H_{11}O_3N + H]^+$:134.0817, found: 134.0815.

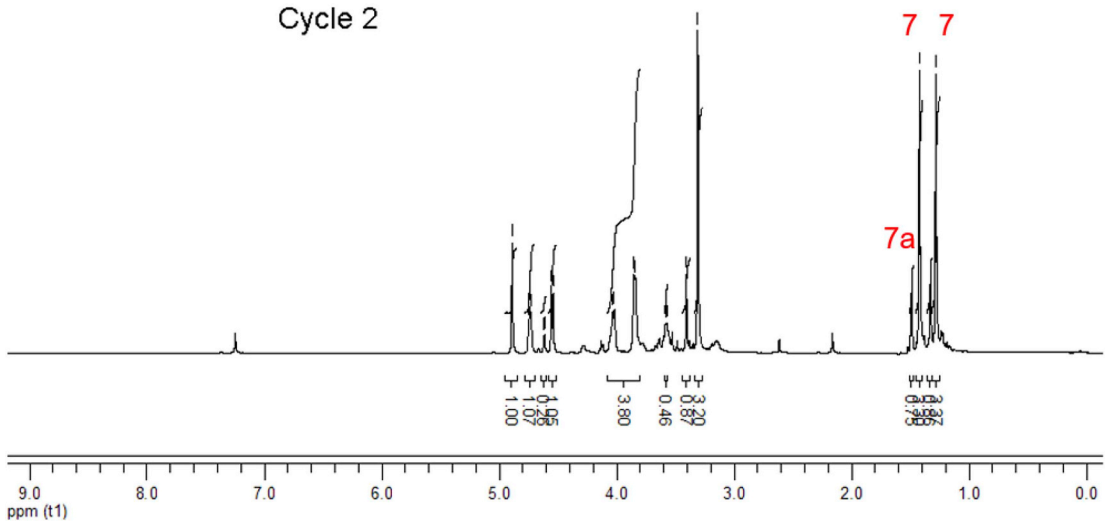
Appendix A. Supplementary data

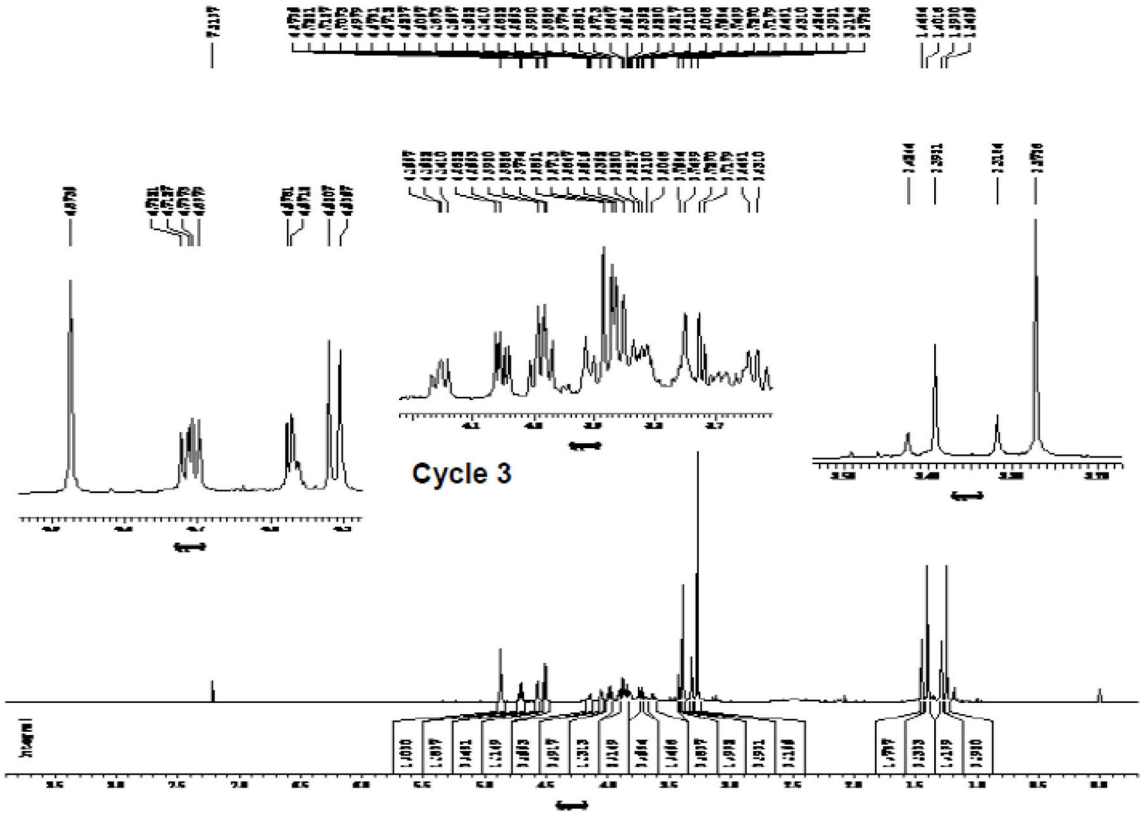
Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2018.11.016.

Appendix

^{1}H NMR (300 MHz, $CDCl_3$) of *O*-methyl 2,3-*O*-isopropylidene-D-lyxofuranoside **7.**







References

[1] P. Compain, O.R. Martin (Eds.), Iminosugars: from Synthesis to Therapeutic Applications, John Wiley & Sons, 2007.
[2] T.D. Butters, R.A. Dwek, F.M. Platt, Curr. Top. Med. Chem. 3 (2003) 561–574.
[3] E.B.D. Melo, A.D.S. Gomes, I. Carvalho, Tetrahedron 62 (2006) 10277–10302.
[4] D. Durantel, C. Alotte, F. Zoulim, Curr. Opin. Invest. Drugs 8 (2007) 125–132.
[5] K. Whitby, D. Taylor, D. Patel, P. Ahmed, A.S. Tyms, Antiviral Chem. Chemother. 15 (2004) 141–151.
[6] A.A. Watson, G.W.J. Fleet, N. Asano, R.J. Molyneux, R.J. Nash, Photochemistry 56 (2001) 265–397.
[7] R.A. Dwek, T.D. Butters, F.M. Platt, N. Zitzmann, Nat. Rev. Drug Discov. 1 (2002) 65–75.
[8] T.D. Butters, R.A. Dwek, F.M. Platt, Glycobiology 15 (2005) 43–53.
[9] P. Greimel, J. Spreitz, A.E. Stutz, T.M. Wrodnigg, Curr. Top. Med. Chem. 3 (2003) 513–523.
[10] M.E.C. Caines, S.M. Hancock, C.A. Tarling, T.M. Wrodnigg, R.V. Stick, A.E. Stutz, A. Vasella, S.G. Withers, N.C.J. Strynadka, Angew. Chem. Int. Ed. 46 (2007) 4474–4476.
[11] T.M. Wrodnigg, A.J. Steiner, B.J. Ueberbacher, Anti Cancer Agents Med. Chem. 8 (2008) 77–85.
[12] M.S. Butler, Nat. Prod. Rep. 25 (2008) 475–516.
[13] M.J. Eis, C.J. Rule, B.A. Würzburg, B. Ganem, Tetrahedron Lett. 26 (1985) 5397–5398.
[14] J.P. Saludes, S.C. Lievens, T.F. Molinski, J. Nat. Prod. 70 (2007) 436–438.
[15] F.P. Guengerich, S.J. DiMari, H.P. Broquist, J. Am. Chem. Soc. 95 (1973) 2055–2056.
[16] Y.F. Liao, A. Lal, K.W. Moreman, J. Biol. Chem. 271 (1996) 28348–28358.
[17] G.P. Kaushal, T. Szumilo, I. Pastuszak, A.D. Elbein, Biochemistry 29 (1990) 2168–2176.
[18] B.A. Sobin, F.W. Tanner Jr., J. Am. Chem. Soc. 76 (1954) 4053.
[19] M. Shibano, S. Kitagawa, S. Nakamura, N. Akazawa, G. Kusano, Chem. Pharm. Bull. 45 (1997) 700–705.
[20] K. Tsuchiya, S. Kobayashi, T. Harada, T. Kurokawa, T. Nakagawa, N. Shimada, K. Kobayashi, J. Antibiot. 48 (1995) 626–642.
[21] G.W.J. Fleet, S.J. Nicholas, P.W. Smith, S.V. Evans, L.E. Fellows, R.J. Nash, Tetrahedron Lett. 26 (1985) 3127–3130.
[22] M.-J. Blanco, F.J. Sardina, J. Org. Chem. 63 (1998) 3411–3414.
[23] E.M. Dangerfield, S.A. Gulab, C.H. Plunkett, M.S.M. Timmer, B.L. Stocker, Carbohydr. Res. 345 (2010) 1360–1365.
[24] B.L. Fera, F. Nicotra, Synthetic methods for the preparation of iminosugars, in: A.E. Stütz (Ed.), Iminosugars as Glycosidase Inhibitors: Norjirimycin and beyond, Wiley-VCH, Weinheim, Germany, 1999, pp. 68–92 (Chapter 4).
[25] P. Merino, I. Delso, T. Tejero, F. Cardona, M. Marradi, E. Faggi, C. Parmeggiani, A. Goti, Eur. J. Org Chem. (2008) 2929–2947.
[26] D. Díez, M.T. Bebéitez, M.J. Gil, R.F. Moro, I.S. Marcos, N.M. Garrido, G.P. Basabe, Synthesis 4 (2005) 565–568.
[27] A.S. Davis, N.J. Gates, K.B. Lindsay, M. Tang, S.G. Pyne, Synlett 1 (2004) 49–52.
[28] L. Espelt, T. Parella, J. Bujons, C. Solans, J. Joglar, A. Delgado, P. Clapés, Chem. Eur J. 9 (2003) 4887–4899.
[29] A.L. Lei, G. Liu, X. Lu, J. Org. Chem. 67 (2002) 974–980.
[30] C.-C. Wang, S.-Y. Luo, C.-R. Shie, S.-C. Hung, Org. Lett. 4 (2002) 847–849.
[31] E.M. Dangerfield, M.S.M. Timmer, B.L. Stocker, Org. Lett. 11 (2009) 535–538.
[32] E.M. Dangerfield, C.H. Plunkett, B.L. Stocker, M.S.M. Timmer, Molecules 14 (2009) 5298–5307.
[33] A. Fan, S. Jaenicke, G.K. Chuah, Org. Biomol. Chem. 9 (2011) 7720–7726.
[34] M.J. Climent, A. Corma, S. Iborra, Green Chem. 13 (2011) 520–540.
[35] L.M. Lerner, Carbohydr. Res. 53 (1977) 177–185.
[36] V. Popsavin, S. Grabež, B. Stojanović, M. Popsavin, V. Pejanović, D. Miljković, Carbohydr. Res. 321 (1999) 110–115.
[37] J.J. Forsman, J. Wärnå, D.Y. Murzin, R. Leino, Eur. J. Org Chem. (2009) 5666–5676.
[38] L.G. Dickson, E. Leroy, J.-L. Reymond, Org. Biomol. Chem. 2 (2004) 1217–1226.
[39] N.M. Xavier, S.D. Lucas, A.P. Rauter, J. Mol. Catal. 305 (2009) 84–89.
[40] A. Corma, S. Iborra, S. Miquel, J. Primo, J. Catal. 161 (1996) 713–719.
[41] J.-F. Chapat, A. Finiels, J. Joffre, C. Moreau, J. Catal. 185 (1999) 445–453.
[42] Y. -i. Matsushita, K. Sugamoto, Y. Kita, T. Matsui, Tetrahedron Lett. 38 (1997) 8709–8712.
[43] B. Helferich, E. Schmitz-Hillebrecht, Chem. Ber. 66B (1933) 378–383.
[44] A. Corma, J. Catal. 216 (2003) 298–312.
[45] S. Namba, Y. Wakushima, T. Shimizu, H. Masumoto, T. Yashima, B. Imelik, C. Naccache, G. Condurier, Y. Ben Taarit (Eds.), Catalysis by Acids and Bases, vol. 20, Elsevier, Amsterdam, 1985, pp. 205–211.
[46] B.S. Balaji, M. Sasidharan, R. Kumar, B. Chanda, Chem. Commun. (1996) 707–708.
[47] A.P. Rauter, F. Ramôa-Ribeiro, A.C. Fernandes, J.A. Figueiredo, Tetrahedron 51 (1995) 6529–6540.
[48] E. Henon, A. Bercier, R. Plantier-Royon, D. Harakat, C. Portella, J. Org. Chem. 72 (2007) 2271–2278.
[49] W. Boland, N. Schroer, C. Sieler, M. Feigel, Helv. Chim. Acta 70 (1987) 1025–1040.
[50] R.A.D. Silva, I.H.S. Estevam, L.W. Bieber, Tetrahedron Lett. 48 (2007) 7680–7682.
[51] R.A.D. Silva, L.W. Bieber, Tetrahedron Lett. 51 (2010) 689–691.
[52] K. Abiraj, B. Dinesh, G.R. Srinivasa, D. Channe Gowda, J. Chem. Res-S. (2006) 534–535.
[53] P. Falus, Z. Boros, G. Hornyánszky, J. Nagy, F. Darvas, L. Ürge, L. Poppe, Tetrahedron Lett. 52 (2011) 1310–1312.
[54] K. Abiraj, D.C. Gowda, J. Chem. Res., Synop. (2003) 332–334.
[55] S. Robin, G. Rousseau, Eur. J. Org Chem. 17 (2000) 3007–3011.

[56] J.C. Jochims, Monatsh. Chem. 94 (1963) 677–680.
[57] A.F. Abdel-Magid, K.G. Carson, B.D. Harris, C.A. Maryanoff, R.D. Shah, J. Org. Chem. 61 (1996) 3849–3862.
[58] N.-S. Li, J. Lu, J.A. Piccirilli, Org. Lett. 9 (2007) 3009–3012.
[59] G. Lopeza, C. Nugier-Chauvina, C. Rémondb, M. O'Donohue, Carbohydr. Res. 342 (2007) 2202–2211.
[60] G.W.J. Fleet, P.W. Smith, Tetrahedron 42 (1986) 5685–5692.
[61] W.V. Dahlhoff, Liebigs Ann. Chem. 11 (1990) 1093–1097.
[62] W.V. Dahlhoff, W. Fenzl, R. Köster, Liebigs Ann. Chem. 8 (1990) 807–810.
[63] K. Paradowska, T. Gubica, A. Temeriusz, M.K. Cyrański, I. Wawer, Carbohydr. Res. 343 (2008) 2299–2307.
[64] P. Prabhakar, S. Rajaram, D.K. Reddy, V. Shekar, Y. Venkateswarlu, Tetrahedron Asymmetry 21 (2010) 216–221.
[65] M. Bennett, G.B. Gill, G. Pattenden, A.J. Shuker, A. Stapleton, J. Chem. Soc. Perkin Trans. 1 (1991) 929–937.