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Original article

Synthesis of a novel *C*-branched polyhydroxylated cyclic nitrone

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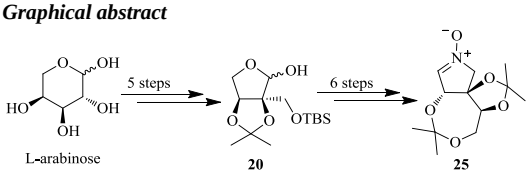
Graphical abstract



A novel *C*-branched polyhydroxylated cyclic nitrone **25**, which could be a valuable intermediate for the synthesis of *C*-branched pyrrolidine iminosugars, was synthesized starting from the commercially available L-arabinose in 29.0% total yield.

ABSTRACT
A novel *C*-branched polyhydroxylated cyclic nitrone **25**, which could be a valuable intermediate for the synthesis of *C*-branched pyrrolidine iminosugars, was synthesized starting from the commercially available L-arabinose in 29.0% total yield.

Keywords:
Cyclic nitrone
Branched chain
Iminosugars
Azasugars
Polyhydroxylated pyrrolidine

1. Introduction

"Nitrogen-in-the-ring" analogues of pyranoses and furanoses, namely iminosugars, azasugars or polyhydroxylated alkaloids, are potent inhibitors of glycosidases and other glycosyl processing enzymes [1, 2]. Therefore, these compounds have great potential in the treatment of type II diabetes, cancers and viral infections, and some of them have already been used as drugs, such as NHE-DNJ (Miglitol) and NB-DNJ (Miglustat) [3-6]. Until now, numerous methods have been developed for the synthesis of natural iminosugars and their non-natural analogs from either carbohydrates or non-sugar chiral-pool compounds [7-12]. Among these approaches to iminosugars, polyhydroxylated or sugar-derived cyclic nitrones (**1**-**7**, Fig. 1) have been proven to be one of the most useful

intermediates due to their capability of undergoing a variety of important transformations, such as 1,3-dipolar cycloaddition, nucleophilic addition, and pinacol-type coupling reaction [13-15]. Based on our general interests in the synthesis and bioactivity study of iminosugars, we became interested in synthesis of a novel *C*-branched polyhydroxylated cyclic nitrone, which is likely to be of significant value as a diverse intermediate for the construction of some *C*-branched pyrrolidine iminosugars with functionalized quaternary centers on the pyrrolidine ring [16-20].

Introduction of *C*-branched chain is a useful method for structural modification of iminosugars in the study of structure-activity relationship, and some of these alkaloids have already been reported (**8**-**16**, Fig. 2). For example, isoDAB (**8**) was a potent but more selective α-glucosidase inhibitor comparing to its parent iminosugar DAB [21]. 4-*C*-Me-DAB (**9**) is a competitive, specific and potent α-glucosidase inhibitior [22]. Compound **10** shows potent inhibition to α-glucosidase from rice (IC_{50} = 5 μmol/L), while L-isoDMDP (**11**) is potent specific competitive inhibitor of gut disaccharidases (K_i = 81 mmol/L for rat intestinal maltase) and is more effective in the suppression of hyperglycaemia in a maltose loading test than Miglitol [23, 24]. Both compound **12** and **13** display moderate inhibitory activity against *Mycobacterium smegmatis* galactan biosynthesis [25]. Compound **14** was a specific potent α-glucosidase inhibitor (IC_{50} = 52 nmol/L, rice α-glucosidase), while DNJ and castanospermine are also inhibitors of β-glucosidase [15]. Azepane **15** displays selective and moderate competitive L-fucosidase inhibition [26]. Early in this year, a new iminosugar **16** [27] had been synthesized from D-glucose by Zhang and coworkers, whose enantiomer could be synthesied from the title cyclic nitrone in one step.

2. Results and discussion

The synthetic route of the title nitrone was shown in Scheme 1. (2*S*, 3*S*)-2-Hydroxymethyl-2,3-*O*-isopropylidene-L-erythrose (**19**) was prepared in 74% yield from commercially available L-arabinose according to the literature reported method [28]. The detail is deposited in Supporting information. Initially, we attempted to obtain the triol **22** by the Grignard addition between compound **19** and vinyl magnesium bromide without supplementing more protecting groups (Scheme 2). Unfortunately, the resulting two diastereomers **22** and **4-*epi*-22** are a pair of inseparable isomers and failed to be separated by flash column chromatography.

Thus, compound **19** was first transformed to silyl ether **20** and then underwent Grignard addition to produce diol **21** (d.r. = 74:26), the C4 configuration of which was confirmed as *R* by the crystal structure of compound **25**. The TBS protecting group of diol **21** was removed by TBAF, and then the C1 and C5 hydroxyl groups were protected by acetonide to give alcohol **23**. The free hydroxyl group in **23** was activated by mesyl chloride to afford methanesulfonate **24**. Compound **24** was then ozonized to give the intermediate aldehyde, which was used directly due to its instability. The aldehyde was then put under routine procedure to give the title nitrone, (2*S*, 3*R*, 4*R*)-1-amino-1,4-anhydro-1,*N*-didehydro-3-(1,2-dihydroxyl)ethyl-2,6:3,5-di-*O*-isopropylidene-L-threose *N*-oxide (**25**). Compound **25** is unstable and would decompose while purified by silica gel column chromatography. However, it was found stable when purified by alkaline aluminum oxide column chromatography [29]. The structure of compound **25** was confirmed unambiguously by spectroscopic data and X-ray crystal structure (Fig. 3). The crystal data is deposited in Supporting information and at the Cambridge Crystallographic Data Centre with number of CCDC 1515829.

3. Conclusion

In summary, a novel *C*-branched polyhydroxylated cyclic nitrone **25** with a quaternary chiral center has been synthesized starting from commercially available L-arabinose in 29.0% total yield, with Grignard addition, ozonization and cyclization as the key steps.

4. Experimental

4.1 General Methods.

NMR spectra was recorded at 300 MHz or 400 MHz (^{1}H NMR) and 75 MHz, 100 MHz (^{13}C NMR) in $CDCl_3$ (with TMS as internal standard). High-resolution mass spectra (HRMS) were performed with a LTQ/FT linear ion trap mass spectrometer. All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Tetrahydrofuran was distilled from sodium and benzophenone. TLC plates were visualized by treatment with a spray of Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O). Polarimetry was determined using a polarimeter with concentrations (*c*) given in gram per 100 mL.

*4.2 Synthesis of (2S, 3S)-2-((tert-butyldimethylsilyl)oxy)methyl-2,3-O-isopropylidene-L-erythrose (**20**)*

TBSCl (10.1 g, 67.1 mmol) and imidazole (6.1 g, 89.4 mmol) were added into a solution of compound **16** (8.5 g, 44.7 mmol) in dichloromethane (150 mL) and the reaction mixture was stirred at room temperature for 6 h. Then water (100 mL) was added, the aqueous and organic phases were separated and the aqueous phase was extracted with dichloromethane (100 mL×3). The organic phases were combined, dried with $MgSO_4$, concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give compound **17** as a light yellow syrup (13.4 g, 99%). Data for **17**:

$[\alpha]_D^{20}$ +11 (*c* 1.05 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33-5.31 (d, 0.5H, *J* = 6.6 Hz), 4.98 – 4.94 (d, 0.5H, *J* = 12 Hz), 4.67 – 4.66 (d, 1H, *J* = 3 Hz), 4.67 – 4.66 (d, 1H, *J* = 3 Hz), 4.38 – 4.36 (d, 0.5H, *J* = 6.6 Hz), 4.08 – 3.94 (m, 2H), 3.86 – 3.74 (m, 2H), 3.56 – 3.51 (m, 0.5H), 1.55 (s, 1.5H), 1.48 (s, 1.5H), 1.43 (s, 1.5H), 1.39 (s, 1.5H), 0.92 (s, 4.5H), 0.90 (s, 4.5H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.50, 113.42, 104.75, 97.72, 92.19, 88.30, 83.34, 82.77, 72.09, 68.03, 64.16, 63.09, 27.48, 27.45, 27.05, 26.77, 25.76, 25.74, 18.14, -5.59, -5.64, -5.68; HRMS(ESI) calcd. for $C_{14}H_{28}O_5SiNa^+$ $[M+Na]^+$ 327.1598, found 327.1593.

*4.3 Synthesis of (2S, 3R, 4R)-2-((tert-butyldimethylsilyl)oxy)methyl-2,3-O-isopropylidene-5-ene-1,4-diol (**21**)*

Compound **20** (100.0 mg, 0.3 mmol) was dissolved in anhydrous THF (10 mL), and vinyl magnesium bromide (1 mol/L, 0.3 mL) was added dropwise at 0 ºC under Ar atmosphere. The reaction mixture was stirred for 1 h, and then saturated aqueous NH_4Cl solution was added dropwise to quench the reaction. Water (10 mL) was added, the organic and the aqueous phases were separated and the aqueous phase was extracted with ethyl acetate (20 mL×3). The organic phases were combined, dried with $MgSO_4$, concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give compound **21** as a light yellow syrup (**21**, 73.1 mg: **4-*epi*-21**, 25.7 mg; 90% total yeild). Data for **21**: $[\alpha]_D^{20}$ +52 (*c* 2.15 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 – 6.10 (m, 1H), 5.56 – 5.28 (m, 2H), 4.41 – 4.37 (m, 1H), 4.30 – 4.27 (m, 1H), 4.09 – 3.94 (m, 3H), 3.77 – 3.75 (m, 1H), 3.63 – 3.60 (m, 1H), 3.34 – 3.30 (m, 1H) 1.45 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.88, 115.87, 108.40, 82.40, 81.42, 73.24, 65.57, 61.06, 28.46, 26.76, 25.78, 18.13, -5.67, -5.83; HRMS(ESI) calcd. for $C_{16}H_{32}O_5SiNa^+$ $[M+Na]^+$ 355.1911, found 355.1906.

*4.4 Synthesis of (2S, 3R, 4R)-2-hydroxymethyl-1,4:2,3-di-O-isopropylidene-5-hexene (**23**)*

Compound **21** (1.0 g, 3.0 mmol) and TBAF (950.0 mg, 3.0 mmol) were dissolved in THF (25 mL), and the reaction mixture was stirred at room temperature for 2 h. Water (10 mL) was added and the aqueous phase was extracted with ethyl acetate (40 mL×7). The organic phases were combined, dried with $MgSO_4$, concentrated under reduced pressure and the crude product was used in the next step without further purification. The crude product, 2,2-dimethyoxypropane (376.4 mg 3.6 mmol) and *p*-TSA (51.6 mg, 0.3 mmol) were dissolved in DMF (10 mL), and the reaction mixture was stirred at r.t. for 10 hours. H_2O (30 mL) was added and the aqueous phase was extracted with ethyl acetate (30 mL×3). The organic phases were combined, dried with $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give compound **23** as a yellow syrup (684.2 mg, 88% for 2 steps). Data for **23**: $[\alpha]_D^{20}$ +79 (*c* 1.75 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 – 5.97 (m, 1H), 5.39 – 5.23 (m, 2H), 4.55 (dd, 1H, *J* = 3.5, 1.9 Hz), 4.14 (s, 1H), 4.00 (d, 2H, *J* = 1.5 Hz), 3.78 – 3.60 (m, 2H), 2.13 – 2.08 (m, 1H), 1.55 (s, 3H), 1.40 (s, 6H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.84, 116.07, 108.01, 101.86, 83.43, 77.45, 77.38, 77.03, 76.60, 71.30, 61.36, 58.95, 28.55, 26.13, 24.27, 23.51; HRMS(ESI) calcd. for $C_{13}H_{22}O_5Na^+$ $[M+Na]^+$ 281.1359, found 281.1360.

*4.5 Synthesis of (2S, 3R, 4R)-2-((mesyloxy)methyl)-1,4:2,3-di-O-isopropylidene-5-hexene (**24**)*

Compound **23** (54.0 mg, 0.21 mmol) and Et_3N (31.7 mg, 0.31 mmol) were dissolved in dichloromethane (25 mL), and mesyl chloride (28.8 mg, 0.25 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 8 h, water (20 mL) was added. The organic and the aqueous were separated and the aqueous phase was extracted with dichloromethane (20 mL×3). The organic phases were combined, dried with $MgSO_4$, concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give compound **24** as a colorless syrup (64.0 mg, 91%). Data for **24**: $[\alpha]_D^{20}$ 79 (*c* 6.60 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 – 5.97 (m, 1H), 5.42 – 5.25 (m, 2H), 4.52 – 4.51 (m, 1H), 4.40 – 4.25 (m, 2H), 4.13 (s, 1H), 3.98 (s, 2H), 3.02 (s, 3H), 1.55 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.86, 116.76, 108.31, 101.92, 82.74, 75.53, 70.38, 66.99, 58.18, 37.41, 28.42, 25.83, 24.26, 23.51; HRMS(ESI) calcd. for $C_{14}H_{24}O_7SNa^+$ $[M+Na]^+$ 359.1135, found 359.1131.

*4.6 Synthesis of (2S, 3R, 4R)-1-amino-1,4-anhydro-1,N-didehydro-3-(1,2-dihydroxyl)ethyl-2,6:3,5-di-O-isopropylidene-L-threose N-oxide (**25**)*

The solution of compound **24** (44.0 g, 0.13 mmol) in CH_3OH (20 mL) was cooled to -60 °C and purged with oxygen, then submitted to the ozonization procedure until TLC showed completion of the reaction. The reaction mixture was purged with Ar and quenched by dimethyl sulfide. The resulting mixture was stirred at room temperature for 2 h, and then concentrated in vacuo. Water (20 mL) was added and the aqueous phase was extracted with ethyl acetate (20 mL×3). The organic phases were combined, dried with $MgSO_4$, concentrated under reduced pressure and the residue was used without further purification. The crude product was dissolved in ethanol (8 mL) and H_2O (2 mL), $NH_2OH{\cdot}HCl$ (27 mg, 0.39 mmol) and $NaHCO_3$ (44 mg, 0.52mmol) were added, and the reaction mixture was stirred at r.t. for 8 h. Then H_2O (20 mL) was added and the aqueous phase was extracted with ethyl acetate (20 mL×3). The organic phases were combined, dried with $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on alkaline aluminum oxide (petroleum ether/EtOAc = 1/1) to give compound **25** as a white solid (25 mg, 75.0% for 2 steps). Data for **25**: mp: 56-57 °C; $[\alpha]_D^{20}$ +56 (*c* 1.80 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (s, 1H), 4,794 – 4.790 (d, 1H, *J* = 1.6 Hz), 4.33 – 4.29 (m, 1H), 4.14 (s, 1H), 4.07 – 4.03 (m, 1H), 3.93 – 3.81 (m, 2H), 1.46 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.25, 109.29, 102.26, 83.94, 78.28, 77.59, 69.94, 57.99, 27.60, 25.28, 24.37, 24.00; HRMS(ESI) calcd. for $C_{12}H_{20}O_5^+$ $[M+H]^+$ 258.1336, found 258.1334.

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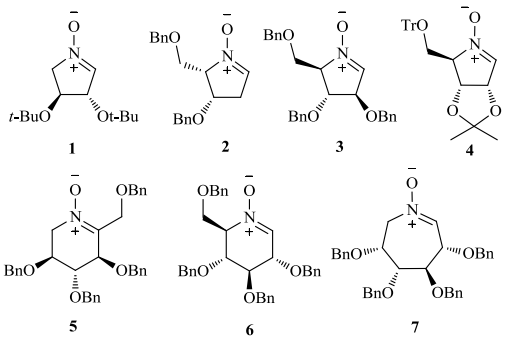


Fig. 1. Examples of some polyhydroxylated cyclic nitrones.

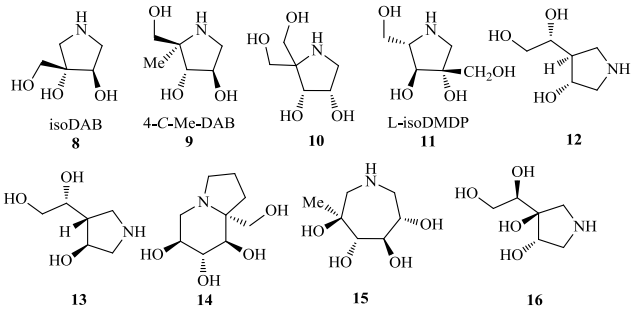


Fig. 2. Structures of some branched iminosugars.

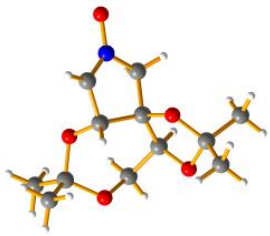
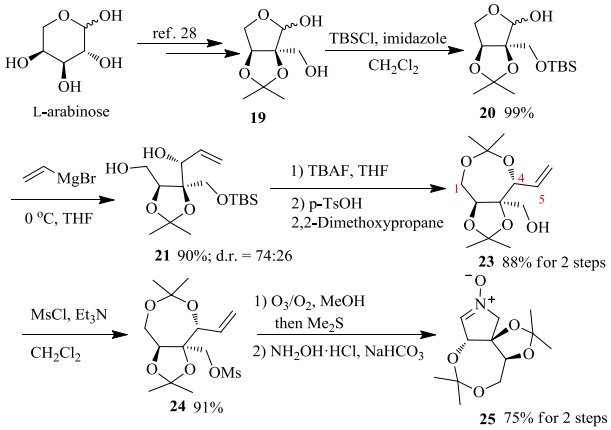
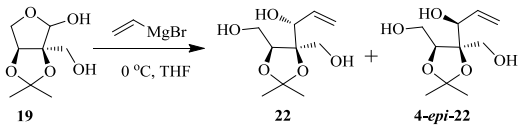


Fig. 3. Crystal structure of compound **25**.



Scheme 1. Synthesis of (2*S*, 3*R*, 4*R*)-1-amino-1,4-anhydro-1,*N*-didehydro-3-(1,2-dihydroxyl)ethyl-2,6:3,5-di-*O*-isopropylidene-l-threose *N*-oxide (**25**).



Scheme 2. Attempt of the synthesis of triol **22.**