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A short and concise synthesis of isofagomine, homoisofagomine, and 5′-deoxyisofagomine

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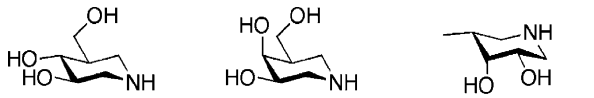
Abstract—A short and concise synthesis of isofagomine derivatives via the epoxidation of chiral *N*-Boc-5-hydroxy-3-piperidene, followed by regioselective epoxide ring opening is described. This constitutes the first reported synthesis of homoisofagomine and the 5′-deoxyisofagomine.

Based on their structural analogy to sugars, polyhydroxylated nitrogen heterocycles (azasugars) competitively and selectively inhibit glycosidases, carbohydrate processing enzymes.[1] Thus glycosidase inhibitors may be potential agents for the treatment of diseases related to metabolic disorders of carbohydrates such as diabetes, cancer, AIDS, hepatitis, Gaucher's disease, and influenza.[2] A particularly effective route to enzyme inhibitors is the design of transition state analogues. In the case of the enzymatic hydrolysis of glycosides, the putative transition state has considerable oxocarbenium-ion characteristics in which the anomeric carbon acquires sp^2 hybridization and a partial positive charge develops at the anomeric carbon and the endocyclic oxygen.[3] A new class of sugar mimic inhibitor having a nitrogen atom at the anomeric position are 1-azasugars. These compounds are highly potent inhibitors of β-glycosidases, whose substrates they mimic.[4] Among them, isofagomine (**1**),[4a] isogalactofagomine,[4c] and isofucofagomine[4d,g] have been found to be particularly potent and selective inhibitors of β-glycosidases (Fig. 1).



isofagomine (**1**) isogalactofagomine isofucofagomine

Figure 1.

Therefore, isofagomine (**1**) and analogues have been the target of a number of recent syntheses.[5] In recent years, the synthesis and evaluation of homoazasugars and 6-deoxyazasugars, such as 1-deoxyhomonojirimycin[6] and 1,6-dideoxynojirimycin,[7] have received considerable attention. However, to our knowledge, no homoazasugars and 6-deoxyazasugars with a D-glucose-type configuration with a nitrogen in place of the anomeric carbon, namely homoisofagomine (**2**) and 5′-deoxyisofagomine (**3**), has been prepared to date. Herein, we describe a new route to the concise synthesis of isofagomine derivatives **1**–**3** through the nucleophilic opening of the epoxide **7** starting from the chiral *N*-Boc-5-hydroxy-3-piperidene (Fig. 2).

Racemic *N*-Boc-5-hydroxy-3-piperidene (**4**), which is readily obtained via the reaction of 1,3-butadiene monoepoxide with allylamine and subsequent catalytic ring-closing metathesis,[8] served as the starting material. Ogasawara and co-workers reported[9] on the lipase catalyzed enantioselective transesterification of a *N*-Cbz-5-hydroxy-3-piperidene with vinyl acetate. We applied this

1-deoxynojirimycin (R = CH_2OH) **1** (R′ = CH_2OH)
1-deoxyhomonojirimycin (R = CH_2CH_2OH) **2** (R′ = CH_2CH_2OH)
1,6-dideoxynojirimycin (R = CH_3) **3** (R′ = CH_3)

Figure 2.

Keywords: Isofagomine; 5-Hydroxy-3-piperidene; Epoxidation; Epoxide ring opening; Homoisofagomine; 5′-Deoxyisofagomine.
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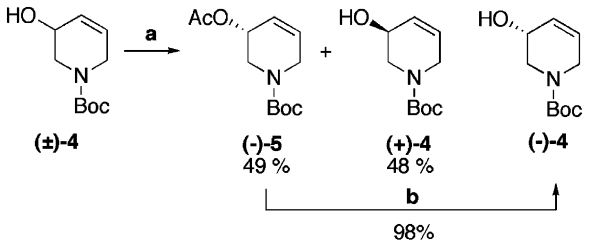


Scheme 1. Reagents and conditions: (a) vinyl acetate, lipase *PS* (immobilized on ceramic particles)/*t*-BuOMe, 40 °C, 18 h; (b) lipase *PS* (immobilized on ceramic particles)/0.1 M phosphate buffer (pH 7), acetone, 40 °C, 18 h.

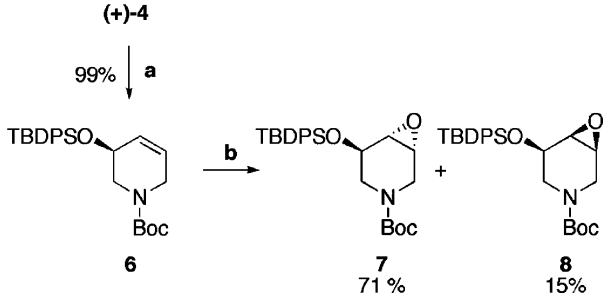
method to **4** using lipase and vinyl acetate. The resolution was best achieved using lipase *PS* (*Pseudomonas cepacia*), immobilized on ceramic particles, in *tert*-butyl methyl ether at 40 °C to give the acetate (−)-**5** in 49% yield, along with the unreacted alcohol (+)-**4**, in 48% yield. Enzymatic hydrolysis of the acetate (−)-**5** using the same lipase in 0.1 M phosphate buffer afforded the enantiomeric alcohol (−)-**4** in 98% yield. The enantiomeric purities of (+)- and (−)-**4** were >99% ee, as determined by chiral HPLC analysis (Chiralcel OD column, 9:1 hexane/2-propanol, 0.5 mL min^{-1}) after replacing the *N*-protecting group with Cbz (Scheme 1).

Alcohol (+)-**4** was initially converted into the TBDPS derivative **6**, thus avoiding the possible assistance of the hydroxyl group in the favored approach of the oxidant. Treatment of (+)-**4** with *tert*-butyldiphenylsilyl chloride under basic conditions gave the TBDPS derivative **6** in 99% yield. Oxidation of **6** with *m*-CPBA gave the *anti* epoxide **7** and the *syn* epoxide **8** in 41% and 23% yields, respectively. However, the diastereoselectivity was low. The use of (trifluoromethyl)methyldioxirane instead of *m*-CPBA as an oxidizing agent improved both the yield and the diastereoselectivity. Thus, the dioxirane, generated in situ[10] from Oxone® with 1,1,1-trifluoroacetone was reacted with **6** to give the *anti* epoxide **7** and the *syn* epoxide **8** in 71% and 15% yields, respectively (Scheme 2).

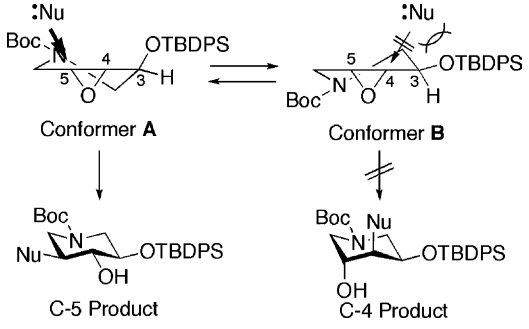
The epoxidation is primarily governed by steric influence of the substituents.[11] An attack at the *syn*-side of the OTBDPS group is highly hindered by the pseudoaxial OTBDPS group. On the other hand, an attack at the *syn*-side would lead to *syn* epoxide **8** as a minor product due to the somewhat less steric hindrance of the pseudoequatorial OTBDPS group. Therefore, it appears that an attack on the dioxirane preferably occurred at the less hindered *anti*-side to the large OTBDPS group.

The nucleophilic opening of the *anti* epoxide **7** with 'higher order' cuprates[12] free halide ions in the presence of boron trifluoride etherate as the activating species was carried out as follows: treatment of **7** with $(CH_2{=}CH)_2CuCNLi_2$ in the presence of BF_3OEt_2 at −78 °C for 2 h, gave **9** as the sole product in 74% yield. Analogously, the reaction of **7** with $Me_2CuCNLi_2$ afforded only **10** in 71% yield. An attempt to employ Grignard reagents in the presence of cuprous bromide[13] resulted in no reaction. Although the rationale for this high selectivity remains unclear, the following mechanism is consistent with the results. The regiochemistry of the nucleophilic opening of the epoxide on a six-membered ring is mainly controlled by *trans* diaxial opening (Fürst–Plattner rule).[14] Consequently, a high regioselectivity could result, if the opening proceeded through only one of the two possible half chair conformations (**A** and **B**). Thus, the exclusive attack of the nucleophile at C-5 through conformer **A** would occur with *trans* diaxial opening. On the other hand, an attack of the nucleophile at C-4 of **7** through conformer **B** would be subject to steric hindrance by the pseudoequatorial OTBDPS group at the C-3. Therefore, a *trans* diaxial opening through one of the half chair conformers, namely conformer **A** would take place. A similar regioselectivity has been reported in ring-opening reactions of *trans*-3-(benzyloxy)-1,2-epoxycyclohexane derivatives[15] (Scheme 3).

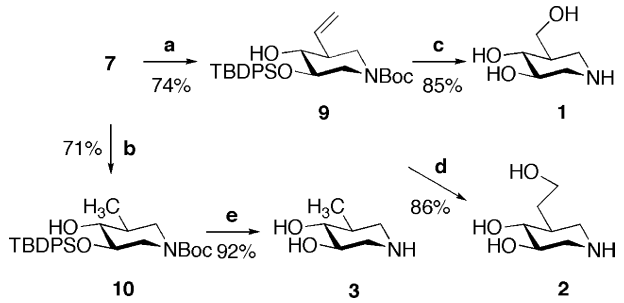
With the vinyl product **9** in hand, our interest was directed to its conversion to isofagomine (**1**) and homoisofagomine (**2**). Oxidative cleavage of the vinyl group of **9** using OsO_4 and $NaIO_4$ afforded the aldehyde, which without purification, and after reduction with $NaBH_4$ followed by deprotection, afforded **1**[16] in 85% combined yield. Next, the hydroboration of the vinyl group of **9** using 9-BBN followed by treatment with hydrogen peroxide gave the corresponding primary alcohol. Deprotection of the alcohol with 10% HCl in 1,4-dioxane afforded **2**[16,17] in 86% combined yield. Conversion of **10** to 5′-deoxyisofagomine (**3**) was accomplished by deprotection. The complete deprotection of **10** by treatment with 10% HCl in 1,4-dioxane afforded **3**[16,18] in 92%



Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, cat. DMAP/CH_2Cl_2, rt, 3 h; (b) Oxone®, aq Na_2EDTA, $NaHCO_3$, CF_3COCH_3/CH_3CN, 0 °C, overnight.



Scheme 3. Regiochemistry of the nucleophilic opening of the epoxide **7**.



Scheme 4. Reagents and conditions: (a) $(CH_2{=}CH)_2CuCNLi_2$ (5 equiv), $BF_3{\cdot}OEt_2$ (2 equiv)/Et_2O, −78 °C, 2 h; (b) $Me_2CuCNLi_2$ (5 equiv), $BF_3{\cdot}OEt_2$ (2 equiv)/Et_2O, −78 °C; (c) (i) cat. OsO_4, $NaIO_4$/50% EtOH, rt, overnight; (ii) $NaBH_4$/50% EtOH, rt, 1 h; (iii) 10% HCl/dioxane, reflux, 1 h; (d) (i) 9-BBN/THF, rt, 6 h; (ii) H_2O_2, 3 mol/L NaOH/THF, rt, 1 h; (iii) 10% HCl/dioxane, reflux, 1 h; (e) 10% HCl/dioxane, reflux, 1 h.

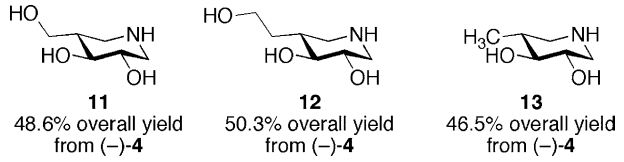


Figure 3.

yield. Thus the first synthesis of **2** and **3** was performed (Scheme 4).

Enantiomers **11**–**13** of **1**–**3** were also prepared starting from (−)-**4**, following the same procedure as above (Fig. 3).

In summary, an efficient synthesis of isofagomine (**1**), homoisofagomine (**2**), 5′-deoxyisofagomine (**3**), and enantiomers **11**–**13** was achieved in 44–50% overall yields from readily obtainable chiral *N*-Boc-5-hydroxy-3-piperidene (**4**). The reaction employed epoxidation into a double bond and a regioselective epoxide ring opening reaction with 'higher order' cuprates. To our knowledge our route to isofagomine (**1**) is shorter and more efficient than the other reported syntheses.[5] This synthetic route permits the preparation of substantional amounts of 1-azasugars having a glucose configuration and would be suitable for further studies of such compounds as glycosidase inhibitors.

Acknowledgements

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16. Compounds **1**–**3** were purified by flash column chromatography on silica gel (MeOH–10% NH_4OH 50:1).
17. Compound **2**: ^{1}H NMR (270 MHz, D_2O) δ 1.18–1.45 (m, 2H), 1.72–1.85 (m, 1H), 2.10 (dd, J = 12.8, 11.4 Hz, 1H), 2.22 (dd, J = 12.0, 10.9 Hz, 1H), 2.87 (dd, J = 12.9, 4.2 Hz, 1H), 2.92–3.02 (m, 2H), 3.24–3.34 (m, 1H), 3.43–3.58 (m, 2H); ^{13}C NMR (67.8 MHz, D_2O): δ 76.5, 71.3, 58.8, 48.8, 47.6, 39.1, 30.7; MS (EI): *m*/*z* 161 (M^+); HRMS (EI): calcd for $C_7H_{15}NO_3$161.0152. Found 161.1088; $[\alpha]_D$ +17.70 (*c* 1.10, EtOH).
18. Compound **3**: ^{1}H NMR (270 MHz, D_2O) δ 0.82 (d, J = 5.6 Hz, 3H), 1.39 (br s, 1H), 2.08 (t, J = 12.1 Hz, 1H), 2.23 (t, J = 11.4 Hz, 1H), 2.75 (d, J = 11.9 Hz, 1H), 2.83–3.03 (m, 2H), 3.29 (br s, 1H); ^{13}C NMR (67.8 MHz, D_2O): δ 78.1, 71.2, 49.7, 49.0, 36.8, 13.1; MS (EI): *m*/*z* 131 (M^+); HRMS (EI): calcd for $C_6H_{13}NO_2$ 131.0946. Found 131.0984; $[\alpha]_D$ +3.93 (*c* 1.12, EtOH).