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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of fagomine and its congeners

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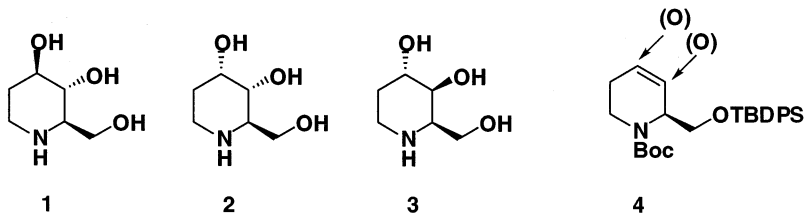
Abstract—The total synthesis of fagomine and its congeners **1**–**3** has been achieved starting from D-serine-derived Garner aldehyde **5** by catalytic ring-closing metathesis (RCM) for the construction of the piperidine ring followed by dihydroxylation.

Azasugar inhibitors of glycosidases and related enzymes are the subject of intense current interest.[1–3] Polyhydroxylated piperidines and their synthetic analogues have attracted a great deal of attention in recent years due to their ability to mimic sugars, and competitively and selectively inhibit glycosidases and glycosyltransferases,[4] the carbohydrate processing enzymes. These attributes make hydroxylated piperidines (azasugars) likely therapeutic agents for the treatment of diseases related to metabolic disorders involving carbohydrates such as diabetes, cancer, AIDS, and viral infections,[5] where glycoprotein processing is crucial. Recently three fagomine isomers **1**–**3** were found from *Xanthocercis zambesiaca* occurring in southern Africa in dry forest.[6] Among them, fagomine **1** and 3-*epi*-fagomine **2** have been shown to have activity against mammalian α-glucosidase and β-galactosidase.[6] More recently **1** was found to have a potent antihyperglycaemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.[7] To date the asymmetric synthesis of **1** has been reported twice,[8] but asymmetric synthesis of **2** and 3,4-di-*epi*-fagomine **3** is not known. In a project devoted to the chiral synthesis of glycosidase inhibitors, we envisaged the preparation of a new common chiral building block, hydroxymethylpiperidene **4**, which seems to be an ideal precursor for the synthesis of dihydroxypiperidinols. Herein, we describe a new entry to the synthesis of fagomine and its congeners by the preparation of **4** in a straightforward and stereoselective manner using Garner aldehyde **5** and catalytic ring-closing metathesis (RCM) for the construction of the piperidine ring.[9]

Our synthesis of **4** began with the Wittig reaction of the D-serine-derived Garner aldehyde **5**.[10] The treatment of **5** with methyltriphenylphosphonium iodide in the presence of sodium bis(trimethylsilyl)amide gave the olefin **6** in 63% yield[11] (Scheme 1). Hydrolysis of **6** with *p*-toluenesulfonic acid in MeOH followed by *O*-silylation then afforded **7** in 72% yield. *N*-Alkylation of **7** with 4-bromo-1-butene under several conditions resulted only in recovery of the starting material **7**.[12] However, use of a three-step sequence (1. deprotection of *N*-Boc group; 2. alkylation; 3. *N*-protection) afforded the butenylated product **8** in 60% yield. RCM of **8** with Grubbs' catalyst, bis(tricyclohexylphosphine)benzylidineruthenium(IV) dichloride under standard conditions afforded the desired intermediate **4** {$[\alpha]_D^{27}$ −150.1 (*c* 1.04, $CHCl_3$)} in 97% yield.



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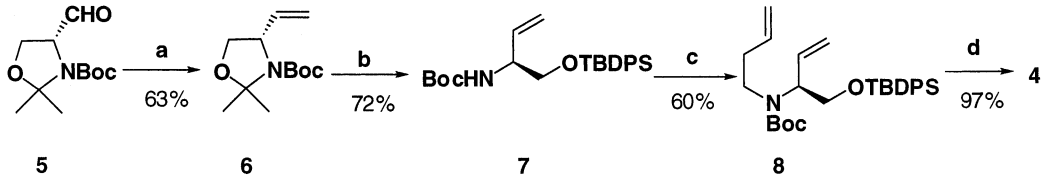
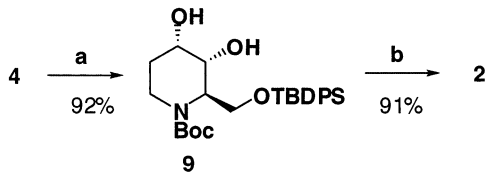


Scheme 1. Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, $NaN(THF)_2$, THF; (b) (i) *p*-TsOH–H_2O, MeOH, (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2; (c) (i) CF_3COOH, CH_2Cl_2, (ii) 4-bromo-1-butene, K_2CO_3, CH_3CN, (iii) $(Boc)_2O$, Et_3N, CH_2Cl_2; (d) Grubbs' catalyst, CH_2Cl_2.

With **4** in hand, the stereoselective dihydroxylation of the double bond could be examined. Under modified Upjohn conditions,[14] treatment of **4** with a catalytic amount of $K_2OsO_4{\cdot}2H_2O$ (5 mol%) and 4-methylmorpholine *N*-oxide (1.5 equiv.) as co-oxidant gave diol **9** as a single diastereoisomer in high 92% yield[15] (Scheme 2). Deprotection of **9** with 10% hydrochloric acid in dioxane followed by treatment with ion-exchange resin (Dowex® 1X2 OH^- form) afforded 3-*epi*-fagomine **2**[16] in 91% yield. It was found that dihydroxylation occurred exclusively at the less hindered *anti*-side to the siloxymethyl substituent.

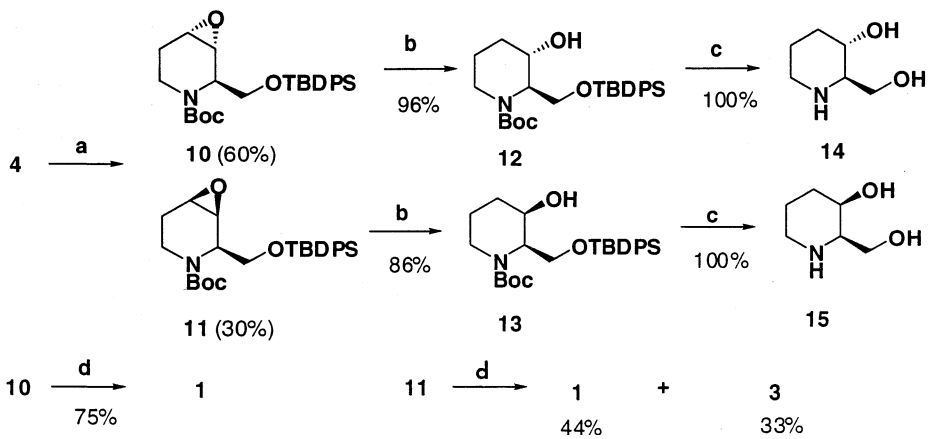
In order to obtain both **1** and **3** containing *trans*-diols at the 3 and 4 positions, we introduced an epoxy functionality into the double bond. The dioxirane generated in situ from oxone® with 1,1,1-trifluoroacetone according to a recent procedure[17] reacted with **4** to give a mixture of stereoisomeric epoxy compounds **10**[13] and **11**[13] which were separated by medium pressure chromatography in high 91% yield though the diastereoselectivity was low (ds: 33%)[18] (Scheme 3). The stereochemistry of the epoxide products was determined by stereoselective cleavage of the epoxy ring using



Scheme 2. Reagents and conditions: (a) cat. $K_2OsO_4{\cdot}2H_2O$, 4-methylmorpholine *N*-oxide, acetone, H_2O; (b) (i) 10% HCl, dioxane, (ii) Dowex 1X2 (OH^-) form.

Super-Hydride®. Treatment of **10** and **11** with Super-Hydride® in THF led to the hydroxy compounds **12** (96%) and **13** (86%), respectively. The complete deprotection of **12** and **13** with hydrochloric acid in methanol followed by treatment with ion-exchange resin of the resulting salts afforded the known (2*R*,3*S*)- and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidines **14**[13,19] and **15**,[13,20] respectively, in quantitative yields. Acidic hydrolysis of the epoxy group of **10** was examined with a mixture of H_2SO_4/dioxane/H_2O in a ratio of 0.2/3/2 mL[21] followed by treatment of the ion-exchange resin to exclusively give fagomine **1**[16] in 75% yield. This high selectivity may be rationalized as follows: attack of H_2O with back-side displacement of the leaving oxygen in the epoxy-substituted ring occurs at the more remote 4 position because nucleophilic attack at the 3 position is *syn*-oriented with respect to the adjacent hydroxymethyl substituent at the 2 position. Similar treatment of **11** afforded a mixture of **1** and **3**[16] in 78% yield and a product ratio of 1.3:1, which were separated by chromatography. In this case, due to the *anti*-relationship between the hydroxymethyl substituent at the 2 position and attack orientation, there is less steric difference between the two possible sites of ring opening and back-side attack of H_2O to the epoxy ring can occur at both the 3 and 4 positions.

In conclusion, we have described a rapid and straightforward asymmetric synthesis of fagomine and its congeners **1**–**3** (the first total synthesis for **2** and **3**) using a common chiral piperidine **4**. The products **1**–**3** and intermediate **4** are expected to be of great utility as chiral building blocks in the synthesis of piperidine-derived alkaloids.[22]



Scheme 3. Reagents and conditions: (a) Oxone®, CF_3COCH_3, $NaHCO_3$, aq. $Na_2{\cdot}EDTA$, CH_3CN; (b) Super-Hydride®, THF; (c) (i) 10% HCl, dioxane, (ii) Dowex 1X2 (OH^- form); (d) H_2SO_4, dioxane, H_2O.

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11. This is a two-step yield from the Garner alcohol.[10]
12. Several conditions: (1. NaH, *N*,*N*-dimethylformamide, 60°C; 2. pulverized KOH, cat. *n*-Bu_4NI, THF, reflux; 3. pulverized KOH, cat. 18-crown-6-ether, THF, reflux).
13. Spectral data: Compound **4**:^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (9 H, s), 1.21–1.50 (9 H, br d), 1.93–2.00 (1 H, br s), 2.18–2.23 (1 H, br s), 2.94 (1 H, br d), 3.72 (2 H, br s), 4.00–4.25 (1 H, br d), 4.45–4.65 (1 H, br d), 5.82 (1 H, br s), 5.98 (1 H, br s), 7.42 (6 H, m), 7.70 (4 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.35, 24.92, 26.92, 28.58, 37.48, 53.81, 65.34, 126.24, 126.88, 127.79, 133.67, 135.74, 154.80. Compound **10**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (9 H, s), 1.41 (9 H, s), 1.90–2.01 (2 H, m), 3.00 (1 H, m), 3.30 (2 H, d, $J=13.7$ Hz), 3.40–3.88 (3 H, m), 4.50 (1 H, br s), 7.42 (6 H, m), 7.65 (4 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.34, 22.86, 26.97, 28.53, 50.53, 51.89, 63.84, 127.95, 127.97, 129.98, 130.03, 133.11, 135.65, 135.73, 155.37. Compound **11**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (9 H, s), 1.38–1.45 (9 H, m), 1.87–2.02 (2 H, m), 2.63–2.68 (1 H, m), 3.35–3.71 (3 H, m), 3.80–3.83 (1 H, m), 4.44–4.46 (0.7 H, m), 4.65–4.70 (0.3 H, m), 7.37–7.42 (6 H, m), 7.69–7.74 (4 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.42, 25.39, 26.93, 28.48, 51.57, 51.69, 51.91, 61.64, 127.88, 129.89, 133.68, 135.64, 135.73, 135.84, 154.36. Compound **14**: ^{13}C NMR (D_2O, 125 MHz, internal standard dioxane δ 67.4) δ 24.12, 32.99, 45.09, 61.93, 63.12, 68.20. **15**: ^{13}C NMR (D_2O, 125 MHz, internal standard dioxane δ 67.4) δ 34.22, 36.80, 43.83, 56.69, 65.54, 68.75.
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15. At this stage, the stereochemistry was unknown.
16. Physical and spectral data of products were identical with the reported values.[6] Compound **1**: ^{13}C NMR (D_2O, 125 MHz, internal standard dioxane δ 67.4) δ 33.56, 43.40, 61.70, 62.50, 74.07, 74.09. Compound **2**: ^{13}C NMR (D_2O, 125 MHz, internal standard dioxane δ 67.4) δ 31.87, 39.15, 56.52, 62.93, 68.71, 70.40. Compound **3**: ^{13}C NMR (D_2O, 125 MHz, internal standard dioxane δ 67.4) δ 28.28, 39.37, 56.07, 61.39, 68.22, 69.19.
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