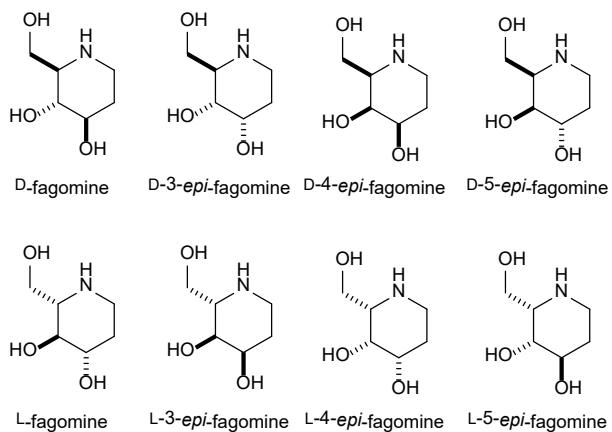


## Asymmetric syntheses of fagomine and its stereoisomers

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*Dedicated to Professor Stephen G. Davies in recognition of his outstanding contributions to the field of organic chemistry.*

### Abstract

D-fagomine (1,2,5-trideoxy-1,5-imino-D-*arabino*-hexitol), a naturally occurring polyhydroxylated piperidine (iminosugar), and its stereoisomers display important biological activities such as glycosidase inhibition. This review delineates both *de novo* asymmetric and enantiospecific syntheses of fagomine and its stereoisomers.

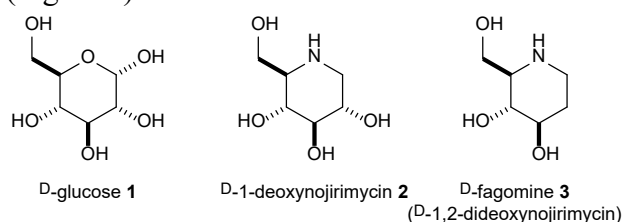
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### 1. Introduction

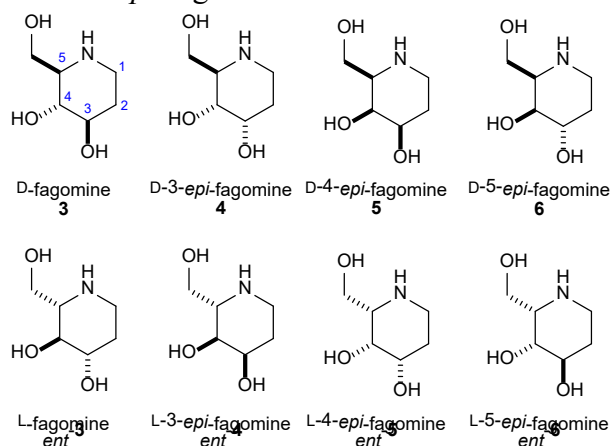
Polyhydroxylated piperidines (iminosugars) are widely known as sugar mimics possessing various biological properties.<sup>1</sup> Among them, arguably the most frequently reported compound in this class is 1-deoxynojirimycin **2**,<sup>2,3</sup> which has the same relative configuration as glucose **1** but the endocyclic oxygen within the pyranose structure is replaced with a nitrogen and the 1-hydroxy group is absent. D-Fagomine **3**

has been reported as a directly related deoxy analogue to 1-deoxynojirimycin **2**, i.e., 1,2-dideoxynojirimycin (Figure 1).



**Figure 1.** D-Glucose **1** and naturally occurring iminosugars **2** and **3**.

D-Fagomine **3** {mp 186–188 °C;  $[\alpha]_D^{11} +23$  ( $c$  1.0 in H<sub>2</sub>O);  $[\alpha]_D^{11} +37$  ( $c$  1.0 in 0.1 M aq HCl)}<sup>4</sup> was first isolated from buckwheat seeds in 1974.<sup>4</sup> Its relative configuration was assigned by NMR analysis and its absolute configuration was established later following the synthesis of an authentic sample { $[\alpha]_D^{20} +21.6$  ( $c$  0.36 in H<sub>2</sub>O)}<sup>5</sup> derived from D-glucose **1**, which was reported by Fleet and co-workers.<sup>5</sup> D-Fagomine **3** and glycosides of D-fagomine have been isolated from various natural sources for example the seeds of *Castanospermum australe* (Leguminosae),<sup>6,7</sup> the seeds of the African legume *Angylocalyx pynaertii*,<sup>8</sup> the seeds of *Xanthocercis zambesiaca*,<sup>9</sup> the leaves of *Morus bombycis*,<sup>2a</sup> the roots of *Lycium Chinese*,<sup>10</sup> the root bark of *Morus alba* L.,<sup>2d</sup> the pods of *Angylocalyx pynaertii*,<sup>11</sup> and from traditional Chinese medicines such as *Faeces bombycis*<sup>12</sup> and mulberry leaf (*Morus alba* L.).<sup>13</sup> D-Fagomine **3** may be considered to be the parent compound in a set of eight stereoisomers **4–6** and *ent-3–ent-6* (Figure 2), which have been systematically named according to carbohydrate nomenclature. Several of these stereoisomers have been isolated from Nature: D-3-*epi*-fagomine **4** was isolated from the roots of *Morus alba*, along with D-fagomine **3**, and its absolute and relative configurations were established by chemical correlation to D-fagomine **3**.<sup>2c,14</sup> Also, D-5-*epi*-fagomine **6** (also known as D-3,4-di-*epi*-fagomine)<sup>15</sup> was isolated along with D-fagomine **3** and D-3-*epi*-fagomine **4** from the leaves and roots of *Xanthocercis zambesiaca*.<sup>16</sup>



**Figure 2.** D-Fagomine **3** and its stereoisomers **4–6** and *ent-3–ent-6*.

Since its first isolation in 1974, many biological studies of D-fagomine **3** and its stereoisomers have been reported.<sup>17–19</sup> For example, D-fagomine **3** has been shown to possess inhibitory activity against mammalian

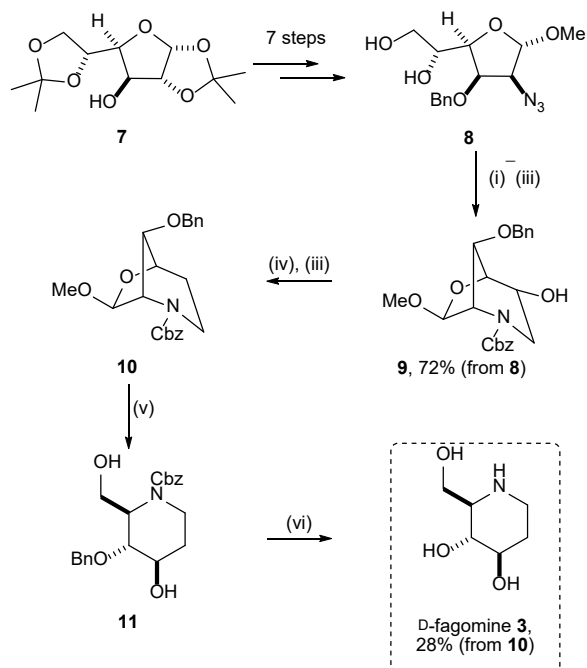
$\alpha$ -glucosidase and  $\beta$ -galactosidase,<sup>16,19</sup> a potent antihyperglycaemic affect in streptozocin-induced diabetic mice, and also a potentiation of glucose-induced insulin secretion.<sup>20,21</sup> D-4-*epi*-Fagomine **5** also displays considerable  $\alpha$ -galactosidase A inhibitory activity and has been reported to inhibit non-lysosomal glucosylceramidase (GABA-2) which is known to be associated with inflammation and diabetes.<sup>18</sup> As glycosidases are involved in several important biological processes *in vivo*, D-fagomine **3** and its stereoisomers have been of great interest as therapeutics such as potential treatments for diabetes, inflammation and HIV.

In this review, methods for the syntheses of D-fagomine **3** and its stereoisomers will be discussed, highlighting the enantio- and diastereodefining steps in particular.

## 2. Chiral pool syntheses of fagomine and its stereoisomers

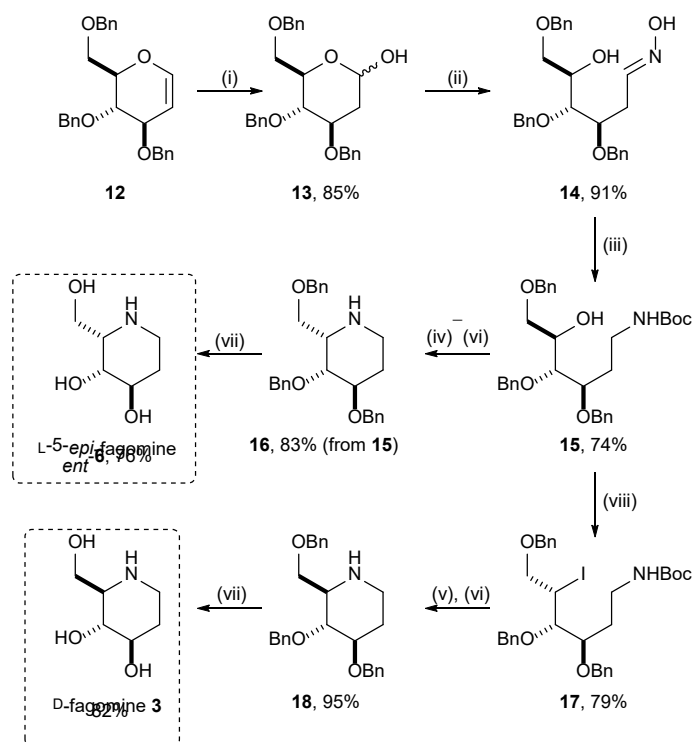
### 2.1. From sugar derivatives

Fleet and co-workers confirmed the absolute configuration of D-fagomine **3** by completing a synthesis starting from the D-glucose derived azidomannofuranoside **8**.<sup>5</sup> Azidodiol **8**, which was derived from diacetone glucose **7**, was realised as a common intermediate for several polyhydroxylated piperidine natural products.<sup>22,23</sup> Selective tosylation of the primary hydroxy group within **8**, followed by hydrogenation in the presence of palladium black gave the corresponding amine intermediate, which was treated with NaOAc in EtOH to promote cyclisation, and subjected to subsequent *N*-protection with CbzCl, which gave the bicyclic product **9** in 72% yield from **8**. Subsequently, **9** was treated with Tf<sub>2</sub>O and the corresponding triflate was removed by reduction with LiBHEt<sub>3</sub> to give **10**.<sup>24</sup> Acid-mediated hydrolysis of **10**, reduction with NaBH<sub>4</sub>, and subsequent global hydrogenolysis of the *N*-Cbz and *O*-Bn protecting groups gave D-fagomine **3** {[ $\alpha$ ]<sub>D</sub><sup>20</sup> +21.6 (*c* 0.36 in H<sub>2</sub>O)} in 28% yield from **10** (Scheme 1). Comparison of the specific rotation of this sample with that of a sample isolated from a natural source established the absolute configuration of D-fagomine **3**.



**Scheme 1.** *Reagents and conditions:* (i) TsCl, pyridine, rt, 6 h; (ii) Pd black, H<sub>2</sub>, EtOH, 30 min then NaOAc, EtOH, 50 °C; (iii) CbzCl, Et<sub>2</sub>O, aq NaHCO<sub>3</sub>; (iv) Tf<sub>2</sub>O, pyridine, -20 °C then LiBHET<sub>3</sub>, THF; (v) CF<sub>3</sub>CO<sub>2</sub>H/H<sub>2</sub>O (1:1), rt, 1 h then NaBH<sub>4</sub>, EtOH, H<sub>2</sub>O; (vi) Pd(OH)<sub>2</sub>/C, H<sub>2</sub>, EtOH.

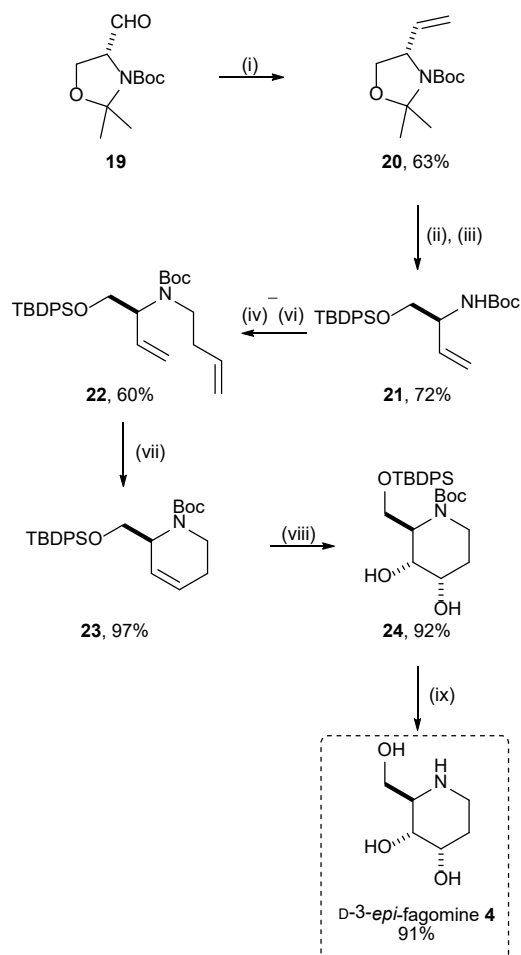
Glycals, which incorporate a double bond between C(1) and C(2) within the sugar scaffold, have also been employed as chiral pool starting materials for syntheses of members of fagomine family.<sup>25-28</sup> For example, very recently, Pratap and co-workers reported the stereoselective syntheses of D-fagomine **3** and L-5-*epi*-fagomine *ent*-**6** from 3,4,6-tri-*O*-benzyl-D-glucal **12**, which is derived from D-glucose.<sup>29</sup> Hydration of the glycal **12** with PPh<sub>3</sub> and HBr in water and THF gave **13** in 85% yield. Treatment of **13** with hydroxylamine and NaOAc in MeOH gave oxime **14** in 91% yield, then reduction of oxime **14** with NaBH<sub>4</sub> and *in situ* *N*-Boc protection gave carbamate **15** in 74% yield. The C(5)-epimeric piperidines **16** and **18** were prepared from the same intermediate **15**: mesylation of the secondary hydroxyl group within **15** followed by acid-mediated N-deprotection and subsequent cyclisation proceeded with inversion of configuration at the C(5) stereogenic centre to give **16** in 83% yield (from **15**). Instead, treatment of **15** under Appel conditions gave iodide **17** in 79% yield, and analogous cyclisation of **17** gave piperidine **18** in 95% yield; in this case double inversion of configuration at C(5) results in overall retention of configuration. Hydrogenolysis of both **16** and **18** gave L-5-*epi*-fagomine *ent*-**6** {[α]<sub>D</sub><sup>25</sup> -10.2 (*c* 0.5 in H<sub>2</sub>O)} and D-fagomine **3** {[α]<sub>D</sub><sup>25</sup> +19.7 (*c* 0.5 in H<sub>2</sub>O)} in 76% and 82% yield, respectively (Scheme 2). Several other total syntheses of fagomine and its stereoisomers from carbohydrate precursors have also been reported.<sup>18,30-33</sup>



**Scheme 2.** Reagents and conditions: (i)  $\text{PPh}_3 \cdot \text{HBr}$ , THF,  $\text{H}_2\text{O}$ , rt, 4 h; (ii)  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , NaOAc, MeOH,  $\text{H}_2\text{O}$ , rt, 3 h; (iii)  $\text{NaBH}_4$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{Boc}_2\text{O}$ , MeOH, 0 °C to rt; (iv)  $\text{MsCl}$ , DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 2 h; (v) 10%  $\text{HCl}$  in  $\text{EtOH}$ , rt, 2 h; (vi)  $\text{K}_2\text{CO}_3$ , MeCN, reflux, 4 h; (vii) 10%  $\text{Pd/C}$ , conc aq  $\text{HCl}$ ,  $\text{H}_2$ , MeOH, rt, 18 h; (viii)  $\text{I}_2$ ,  $\text{PPh}_3$ , imidazole,  $\text{PhMe}$ , reflux, 2 h.

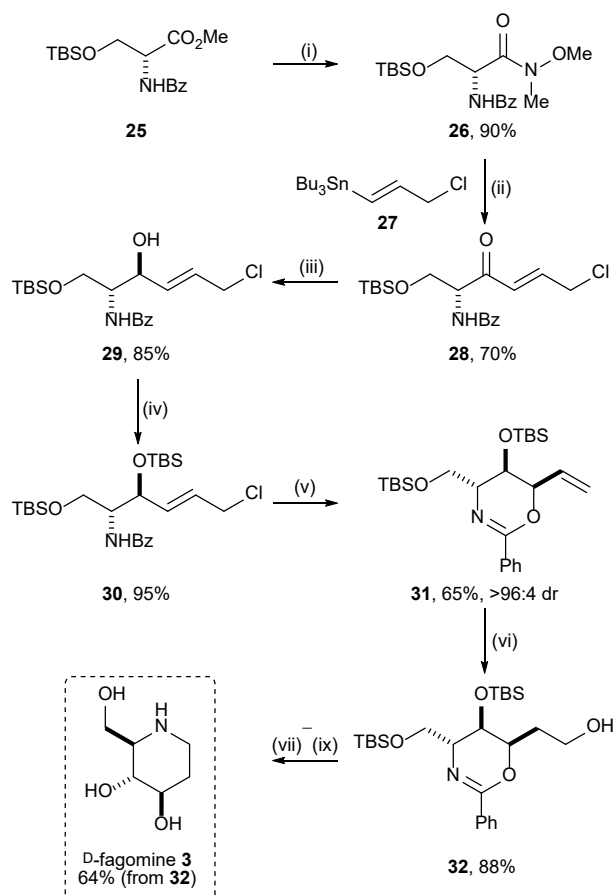
## 2.2. From other chiral pool starting materials

Takahata and co-workers reported the syntheses of fagomine and its stereoisomers from a common building block - Garner's aldehyde **19**, which is derived from D-serine.<sup>34-36</sup> Initially, Wittig olefination of Garner's aldehyde **19** gave **20** in 63% yield. Acid-mediated hydrolysis of **20** followed by treatment with TBDPSCl and imidazole gave **21** in 72% yield. *N*-Alkylation of **21** followed by ring-closing metathesis with Grubbs I catalyst gave the key intermediate **23** in 58% yield (from **21**). Diastereoselective oxidation of **23** under Upjohn conditions ( $\text{OsO}_4$  and NMO) proceeded on the least hindered face which gave diol **24** as a single diastereoisomeric product in 92% yield. Global deprotection of **24** with 10% aq  $\text{HCl}$  gave D-3-*epi*-fagomine **4**  $\{[\alpha]_{\text{D}}^{26} +74.4$  ( $c$  0.95 in  $\text{H}_2\text{O}$ ) $\}$  in 91% yield (Scheme 3).



**Scheme 3.** *Reagents and conditions:* (i)  $[\text{MePh}_3\text{P}]^+[\text{I}]^-$ , NaHMDS, THF,  $-20\text{ }^\circ\text{C}$ , overnight; (ii) TsOH, MeOH, rt, overnight; (iii) TBDPSCl, DMAP, imidazole,  $\text{CH}_2\text{Cl}_2$ , rt, overnight; (iv)  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 1 h; (v) 4-bromo-1-butene,  $\text{K}_2\text{CO}_3$ , MeCN,  $90\text{ }^\circ\text{C}$ , overnight; (vi)  $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, overnight; (vii) Grubbs I catalyst,  $\text{CH}_2\text{Cl}_2$ ; (viii) cat.  $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ , NMO, acetone,  $\text{H}_2\text{O}$ , rt, overnight; (ix) 10% aq HCl, 1,4-dioxane,  $100\text{ }^\circ\text{C}$ , 30 min.

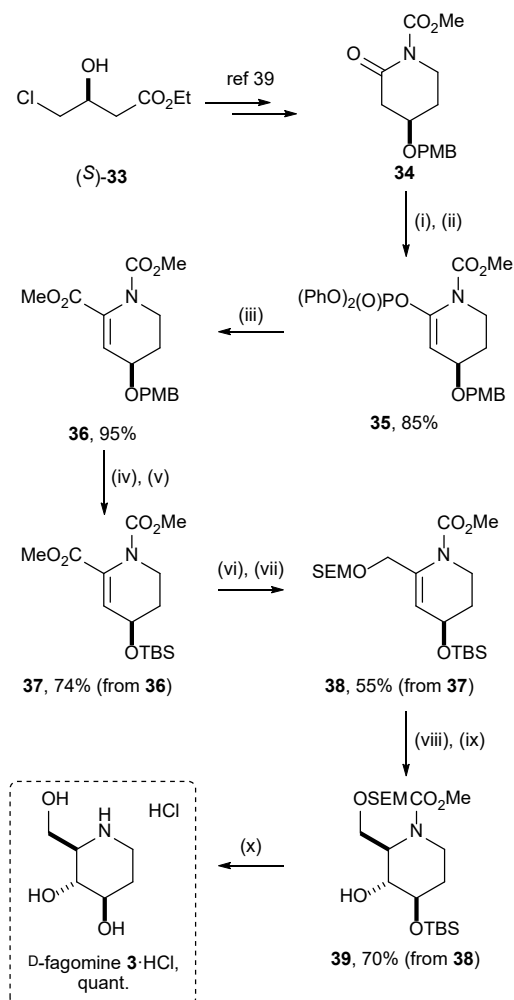
Ham and co-workers employed the Pd(0)-catalysed stereoselective formation of an oxazine ring from a benzamide in their synthesis of D-fagomine **3** starting from the non-natural, (*R*)-serine derived precursor **25**.<sup>37</sup> Protected (*R*)-serine methyl ester was converted to the corresponding Weinreb amide **26** in 90% yield. Treatment of **26** with vinyltin **27** and MeLi followed by diastereoselective reduction with  $\text{LiAlH}(\text{OtBu})_3$  gave **29** in 60% yield (from **26**). In order to achieve better selectivity in the intramolecular oxazine formation step, it was necessary to protect the hydroxyl group within **29** as the corresponding sterically demanding TBS ether. Treatment of **30** with NaH and TBAI in the presence of  $\text{Pd}(\text{PPh})_3$  gave oxazine **31** in 65% yield with high diastereoselectivity. Hydroboration of **31** with 9-BBN followed by oxidation gave primary alcohol **32** in 88% yield. Mesylation of **32** and subsequent hydrogenolysis facilitated cyclisation to form the corresponding piperidine and a global deprotection with 6 N HCl gave D-fagomine **3**  $\{[\alpha]_{\text{D}}^{25} +14.9$  (*c* 0.9 in  $\text{H}_2\text{O}$ ) $\}$  in 64% yield over 3 steps (Scheme 4).



**Scheme 4.** Reagents and conditions: (i)  $\text{NH}(\text{OMe})\text{Me}\cdot\text{HCl}$ ,  $\text{Me}_3\text{Al}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 1 h; (ii) **27**,  $\text{MeLi}$ , THF,  $-78^\circ\text{C}$ , 30 min; (iii)  $\text{LiAlH}(\text{OtBu})_3$ , EtOH,  $-78^\circ\text{C}$ , 2 h; (iv) TBSCl, imidazole, DMF, rt, 2 h; (v)  $\text{Pd}(\text{PPh})_3$ , NaH, TBAI, THF,  $0^\circ\text{C}$ , 5 h; (vi) 9-BBN, THF, rt, 20 h then  $\text{H}_2\text{O}_2$ , NaOH, EtOH, rt, 30 min; (vii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 2 h; (viii)  $\text{Pd}(\text{OH})_2/\text{C}$ ,  $\text{H}_2$  (1 atm), MeOH, rt, overnight; (ix) 6 N HCl aq, rt, 24 h.

Occhiato and co-workers reported a synthesis of D-fagomine **3** using a Pd-catalysed methoxycarbonylation reaction of a lactam derived vinyl phosphate as the key step, starting from commercially available ethyl (*S*)-4-chloro-3-hydroxybutanoate **33**.<sup>38</sup> Initially, enantiopure precursor (*S*)-**33** was converted to the protected lactam **34** over 5 steps.<sup>39</sup> Treatment of **34** with KHMDS followed by the addition of diphenylchlorophosphate gave vinyl phosphate **35** in 85% yield. Pd-catalysed carbonylation of **35** in the presence of MeOH gave methyl ester **36** in 95% yield. Protecting group manipulation then gave **37** in 74% yield (from **36**). Chemoselective reduction of the ester moiety within **37** with DIBAL-H, and subsequent protection of the resultant primary hydroxyl group with SEMCl gave **38** in 55% yield (from **37**). Regio- and diastereoselective hydroboration of **38** followed by oxidation gave **39** in 70% yield with all three stereogenic centres installed. The global deprotection of **39** with HCl gave D-fagomine **3** as the corresponding HCl salt  $\{[\alpha]_{\text{D}}^{23} +12.3$  ( $c$  0.38 in  $\text{H}_2\text{O}$ ) $\}$  in quantitative yield (Scheme 5).



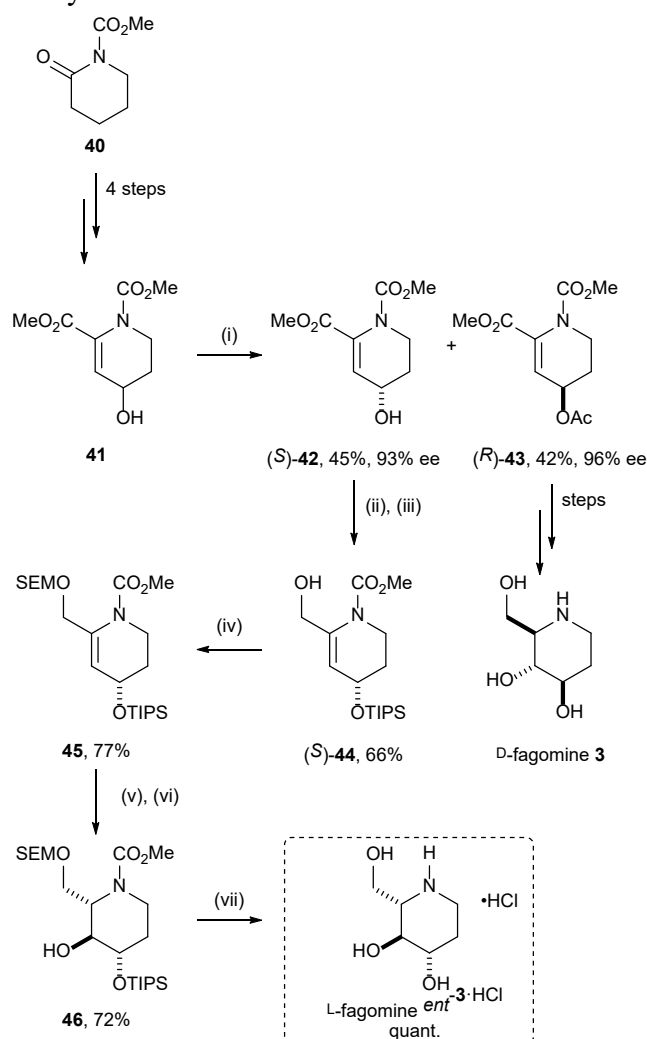


**Scheme 5.** Reagents and conditions: (i) KHMDS, THF,  $-78^{\circ}\text{C}$ ; (ii)  $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$ , THF,  $-78^{\circ}\text{C}$ ; (iii)  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , CO, MeOH,  $\text{Et}_3\text{N}$ , DMF,  $50^{\circ}\text{C}$ ; (iv) DDQ,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  (18:1); (v) TBSCl, imidazole, DMF,  $40^{\circ}\text{C}$ ; (vi) DIBAL-H,  $\text{Et}_2\text{O}$ ,  $-78^{\circ}\text{C}$ ; (vii) SEMCl, DIPEA,  $\text{CH}_2\text{Cl}_2$ ; (viii)  $\text{BH}_3\cdot\text{THF}$ ,  $-78^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ ; (ix)  $\text{Me}_3\text{NO}$ , THF,  $65^{\circ}\text{C}$ ; (x) 2 N HCl, reflux.

### 3. Asymmetric syntheses of fagomine and its stereoisomers via enzymatic approaches

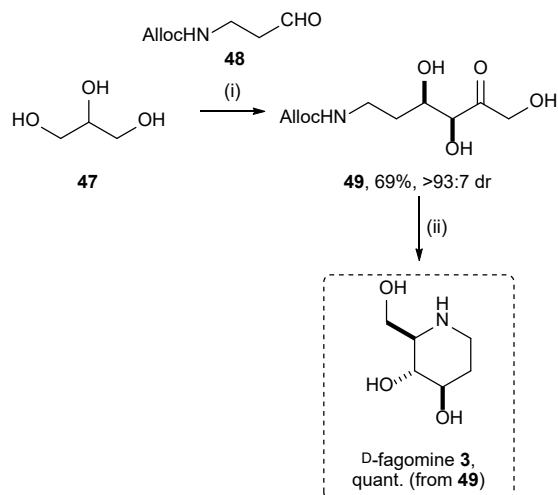
Occhiato and co-workers reported a synthesis of L-fagomine *ent*-3 via enzymatic kinetic resolution using immobilised lipases from *Burkholderia cepacia* (lipase PS Amano IM).<sup>40</sup> Racemic allylic alcohol **41** was prepared from lactam **40** over four steps in 57% yield. Kinetic resolution of **41** under optimised conditions using lipase PS Amano IM and vinyl acetate gave (*S*)-alcohol **42** (93% ee) and acetate (*R*)-**43** (96% ee). After O-protection of **42** with TIPSCl, reduction of the corresponding  $\alpha,\beta$ -unsaturated ester with DIBAL-H gave alcohol **44** in 66% yield. Treatment of **44** with SEMCl gave **45** in 77% yield and diastereoselective hydroboration followed by oxidative work-up gave **46** in 72% yield. Subsequent acid-mediated global hydrolysis gave L-fagomine *ent*-3 as the corresponding HCl salt  $\{[\alpha]_{\text{D}}^{21} -12.0$  (*c* 0.26 in  $\text{H}_2\text{O}$ ) $\}$  in quantitative yield. Similarly, enantioenriched acetate **43** was converted into *ent*-**42** via basic ester hydrolysis in a formal synthesis of D-fagomine **3**<sup>38</sup> (Scheme 6). Takahata also demonstrated preparations of both

enantiomeric series of fagomines and their diastereoisomers from a common building block using the lipase-catalysed transesterification.<sup>41</sup>



**Scheme 6.** Reagents and conditions: (i) Lipase PS "AMANO" IM, vinyl acetate, THF, 30 °C, 9 h; (ii) TIPSCl, imidazole, DMF, 40 °C, 5 h; (iii) DIBAL-H, Et<sub>2</sub>O, -78 °C, 1 h then 0 °C, 30 min; (iv) SEMCl, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 30 °C, 16 h; (v) BH<sub>3</sub>·THF, THF, 0 °C, 20 h; (vi) Me<sub>3</sub>NO, 65 °C, 2 h; (vii) 2 N aq HCl, reflux, 18 h.

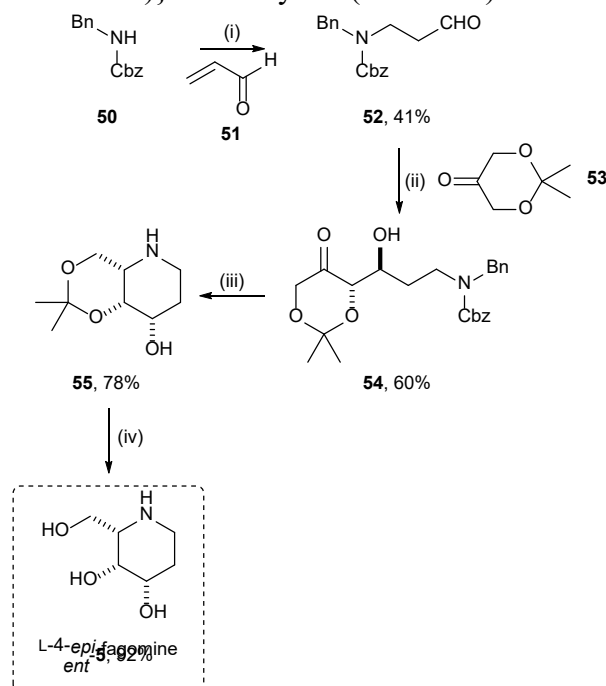
Babich and co-workers developed a one-pot cascade enzymatic reaction for the synthesis of enantio- and diastereoisomerically pure natural and non-natural carbohydrates from glycerol and aldehydes. This four-enzymatic cascade reaction was highlighted in the asymmetric synthesis of D-fagomine **3**.<sup>42</sup> The cascade reaction of glycerol **47** and *N*-Alloc protected aldehyde **48** gave aldol product **49** in 69% yield and >93:7 dr. Treatment of **49** with Pd/C and Et<sub>3</sub>SiH promoted deprotection of the *N*-Alloc group followed by in situ reductive cyclisation to give D-fagomine **3** {[α]<sub>D</sub><sup>20</sup> +6.6 (*c* 0.6 in MeOH)} in quantitative yield (Scheme 7). Several other groups have also reported asymmetric syntheses of fagomine and its stereoisomers via enzymatic approaches (aldolases, in particular, have often been used).<sup>43</sup>



**Scheme 7.** Reagents and conditions: (i) PPI, GPO, catalase, RAMA, PhN-Sf, H<sub>2</sub>O, 20 °C, 12 h; (ii) Et<sub>3</sub>SiH, Pd/C, EtOH, rt, overnight.

#### 4. *de novo* Asymmetric syntheses of fagomine and its stereoisomers

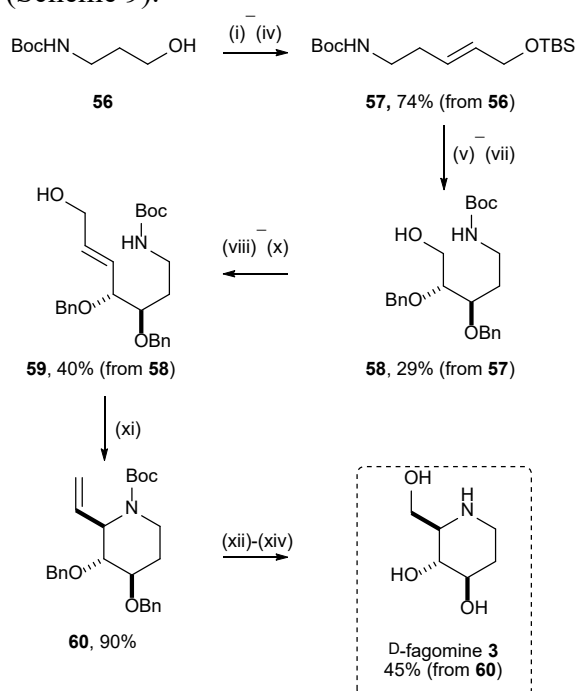
Ferjancic and co-workers reported a short asymmetric synthesis of L-4-*epi*-fagomine *ent*-**5** using an (*S*)-proline catalysed aldol reaction as a key step.<sup>44</sup> Treatment of commercially available protected amine **50** with acrolein **51** gave β-amino aldehyde **52** in 41% yield. The (*S*)-proline catalysed aldol reaction of **54** with dioxanone **53** gave the adduct **54** in 60% yield as a single diastereoisomer. The global *N*-deprotection of **54** followed by diastereoselective reductive cyclisation via hydrogenolysis and hydrogenation afforded piperidine **55** in 78% yield. Acid-mediated hydrolysis of **55** gave L-4-*epi*-fagomine *ent*-**5** {[α]<sub>D</sub><sup>20</sup> −15.5 (*c* 1.0 in H<sub>2</sub>O)} in 92% yield (Scheme 8).



**Scheme 8.** Reagents and conditions: (i) acrolein **51**, (+)-camphorsulfonic acid (CSA), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 3.5 h; (ii) **53**, (*S*)-proline, DMF, 4 °C, 24 h; (iii) H<sub>2</sub> (5 atm), Pd/C, EtOH, 2 h; (iv) 3 M HCl, MeOH, reflux, 4 h.

The vicinal diol unit within fagomine and its epimers may also be installed via Sharpless asymmetric dihydroxylation. Hirai and co-workers reported the asymmetric synthesis of D-fagomine **3** via Sharpless

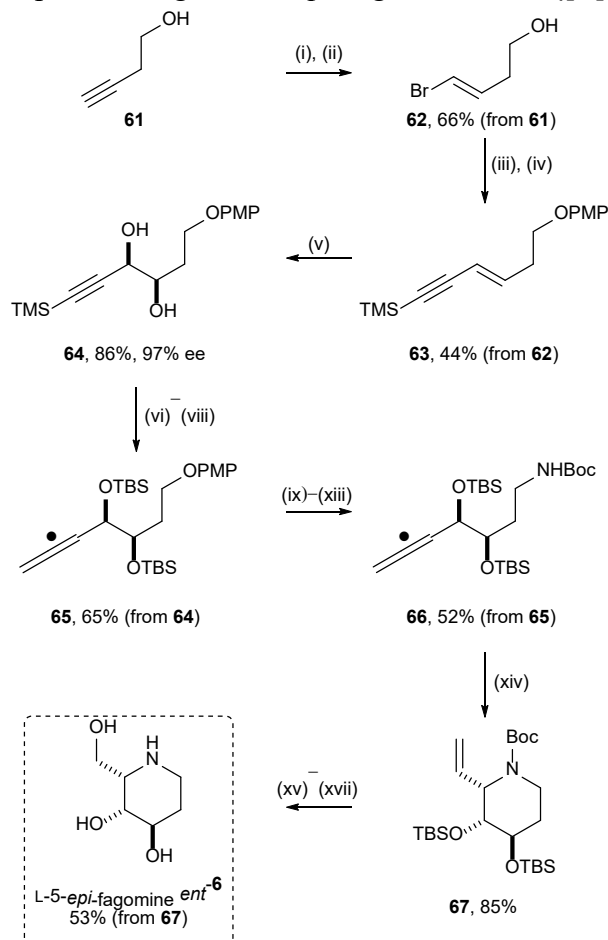
asymmetric dihydroxylation and Pd(II)-catalysed cyclisation to form the piperidine ring.<sup>45</sup> *N*-Boc protected 3-aminopropanol **56** was oxidised under Swern conditions and subsequent Horner-Wadsworth-Emmons reaction of the resultant aldehyde was followed by reduction with DIBAL-H to give the corresponding allylic alcohol, which was *O*-TBS protected to give **57** in 74% yield (from **56**). Sharpless asymmetric dihydroxylation of **57** gave the corresponding *syn*-diol, which was protected as the corresponding bisbenzyl ether. Its acid promoted desilylation gave primary alcohol **58** in 29% yield (from **57**). The same sequential treatment of **58** (i.e., Swern oxidation, Horner-Wadsworth-Emmons reaction and reduction with DIBAL-H) afforded homologated allylic alcohol **59** in 40% yield (from **58**). Treatment of **59** with PdCl<sub>2</sub>(MeCN)<sub>2</sub> facilitated diastereoselective cyclisation to give vinyl piperidine **60** in 90% yield. Ozonolysis of the vinyl group within **60** followed by reductive work-up, acid-mediated deprotection of the *N*-Boc group, and hydrogenolysis gave D-fagomine **3** {[ $\alpha$ ]<sub>D</sub><sup>27</sup> +13.4 (*c* 0.86 in H<sub>2</sub>O)} in 45% yield over 3 steps from **60** (Scheme 9).



**Scheme 9.** Reagents and conditions: (i) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1.5 h; (ii) (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, NaH, THF, -50 °C to rt, 1 h; (iii) DIBAL-H, THF, -78 °C, 2 h; (iv) TBSCl, imidazole, DMF, rt, 3 h; (v) AD-mix- $\beta$ , CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub>, tBuOH/H<sub>2</sub>O (1:1), 0 °C, 20 h; (vi) BnBr, NaH, Bu<sub>4</sub>NI, THF, rt, 4 h; (vii) *p*-TsOH, MeOH, rt, 3 h; (viii) IBX, THF/DMSO (1:1), rt, 4 h; (ix) (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, NaH, THF, rt, 30 min; (x) DIBAL-H, THF, -78 °C to rt, 5 h; (xi) PdCl<sub>2</sub>(MeCN)<sub>2</sub>, THF, rt, 3 h; (xii) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (4:1), -78 °C then NaBH<sub>4</sub>, -78 °C to rt, 2 h; (xiii) aq HCl, MeOH, 70 °C, 5 h; (xiv) H<sub>2</sub> (1atm), Pd/C, AcOH, rt, 2 days.

Bates and co-workers reported the asymmetric synthesis of L-5-*epi*-fagomine *ent*-**6** via asymmetric dihydroxylation to introduce the vicinal diol unit and gold(I)-catalysed allene cyclisation.<sup>46</sup> Alkyne **61** was treated with NBS and AgNO<sub>3</sub> to give the corresponding terminal bromide, which was reduced with AlCl<sub>3</sub> and LiAlH<sub>4</sub> to give (*E*)-vinyl bromide **62** in 66% yield (from **61**). Sonogashira coupling of **62** with trimethylsilylacetylene followed by introduction of the PMP ether via Mitsunobu reaction gave **63** in 44%

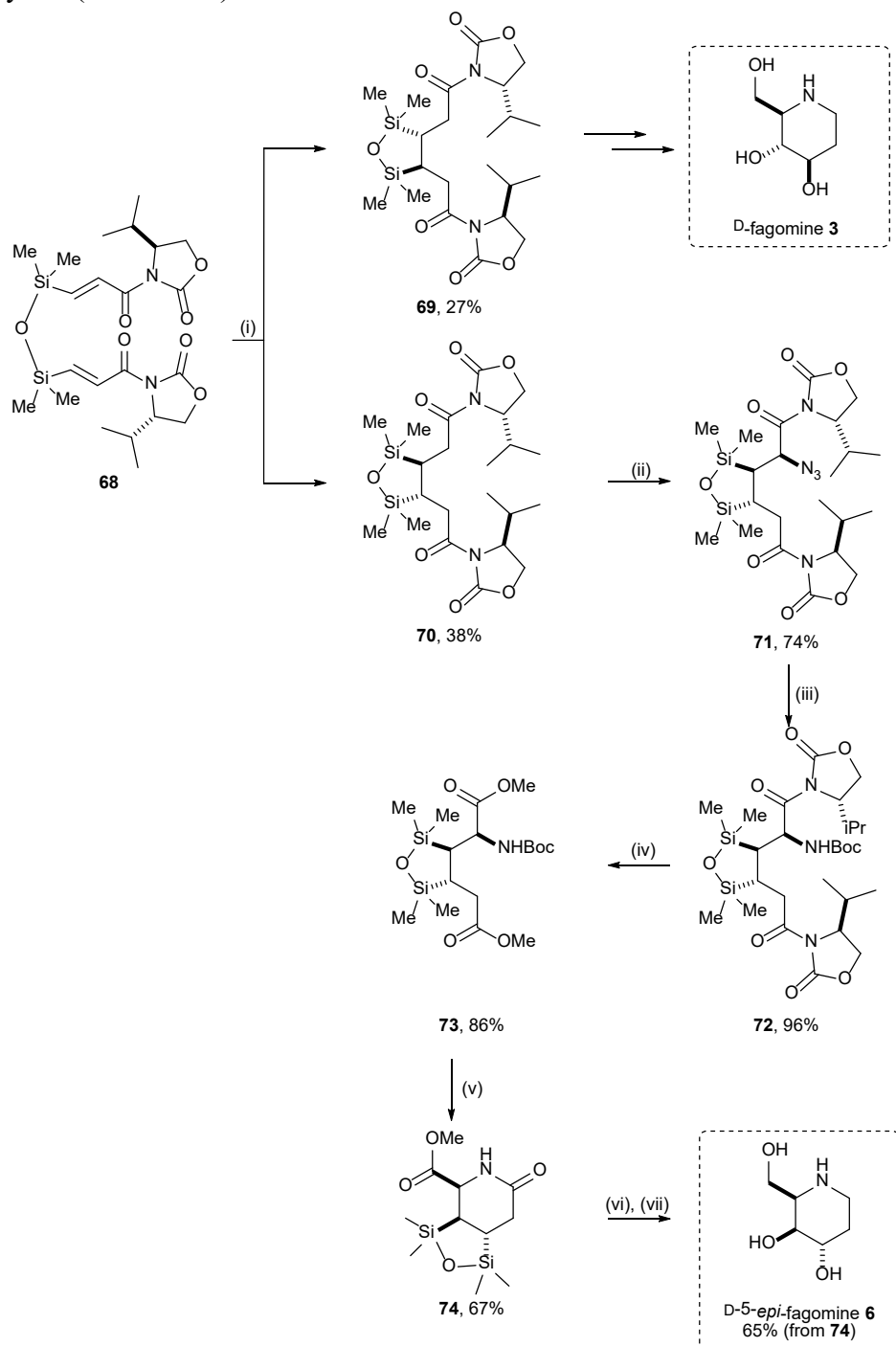
yield (from **62**). Asymmetric dihydroxylation of **63** with AD-mix- $\beta$  afforded *syn*-diol **64** in 86% yield and 97% ee. Treatment of **64** with K<sub>2</sub>CO<sub>3</sub> in MeOH followed by Searles-Crabbé homologation<sup>47</sup> and *O*-silyl protection of the diol unit gave allene **65** in 65% yield (from **64**). The requisite (*N*-Boc protected) amino functionality was installed via five further synthetic transformations to give **66** in 52% overall yield from **65**. Gold (I) catalysed diastereoselective cyclisation of **66** gave piperidine **67** in 85% yield as a single diastereoisomer. Ozonolysis of **67** followed by reductive work-up and subsequent acid mediated global deprotection gave L-5-*epi*-fagomine *ent*-**6** {[ $\alpha$ ]<sub>D</sub><sup>21</sup> –10.6 (*c* 0.32 in H<sub>2</sub>O)} in 53% yield from **67** (Scheme 10).



**Scheme 10.** Reagents and conditions: (i) NBS, AgNO<sub>3</sub>; (ii) AlCl<sub>3</sub>, LiAlH<sub>4</sub>; (iii) HC≡CTMS, (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, CuI, Et<sub>3</sub>N, THF; (iv) *p*-(MeO)C<sub>6</sub>H<sub>4</sub>OH, PPh<sub>3</sub>, DIAD; (v) AD mix- $\beta$ , MeSO<sub>2</sub>NH<sub>2</sub>, aq <sup>t</sup>BuOH; (vi) MeOH, K<sub>2</sub>CO<sub>3</sub>; (vii) (CH<sub>2</sub>O)<sub>n</sub>, Cy<sub>2</sub>NH, CuBr; (viii) TBSOTf, 2,6-lutidine; (ix) CAN, pyridine, aq MeCN; (x) MsCl, Et<sub>3</sub>N; (xi) NaN<sub>3</sub>; (xii) PPh<sub>3</sub>, H<sub>2</sub>O; (xiii) Boc<sub>2</sub>O, <sup>i</sup>Pr<sub>2</sub>NEt; (xiv) Ph<sub>3</sub>PAuCl, AgSbF<sub>6</sub>, CaCO<sub>3</sub>; (xv) O<sub>3</sub>, NaBH<sub>4</sub>; (xvi) HCl, MeOH, dioxane; (xvii) amberlyst A26.

Ghosh and co-workers reported the asymmetric syntheses of D-fagomine **3** and D-5-*epi*-fagomine **6** from C2-symmetric 3,4-bis-silyl substituted adipic acid derivatives (which incorporate the Evans chiral auxiliary) via diastereoselective azidation as the key step.<sup>15</sup> Mg-mediated reductive coupling of silicon-tethered diacrylic acid derivative **68** gave, after exhaustive purifications, **69** and **70** in 27% and 38% yield, respectively as single diastereoisomers.<sup>48</sup> The major diastereoisomer **70** was treated with KHMDS followed by addition of trisyl azide to give **71** in 74% yield as a single diastereoisomer. The stereochemical outcome of this reaction was consistent with the Evans chiral auxiliary being the dominant stereocontrol element in

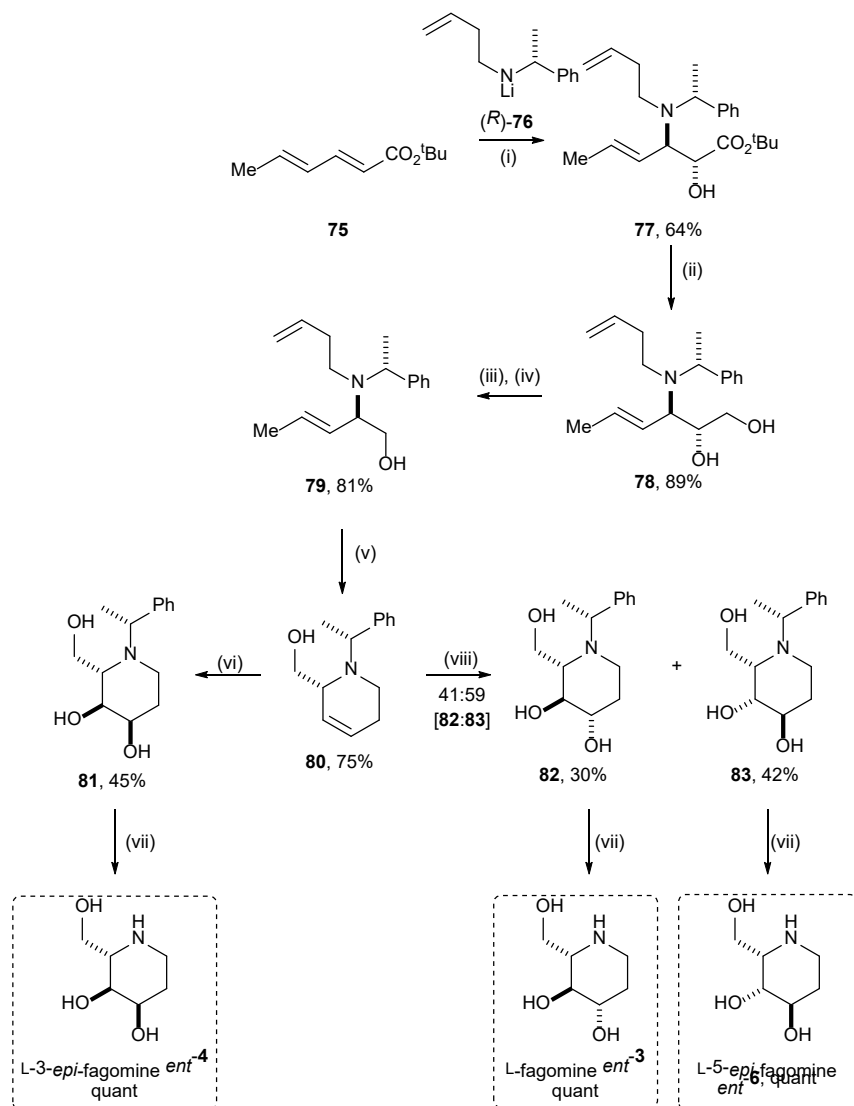
this system. Azide **71** was reduced and protected in situ to give **72** in 96% yield. The oxazolidinones were removed by treatment with  $K_2CO_3$  in MeOH, and treatment of the corresponding dicarboxylic acid with diazomethane gave **73** in 86% yield. Treatment of **73** with  $CF_3CO_2H$  removed the *N*-Boc group and cyclisation gave lactam **74** in 67% yield. Reduction of **74** with  $LiAlH_4$  and Tamao-Fleming oxidation gave D-5-*epi*-fagomine  $\{[\alpha]_D^{24} +12.1$  (*c* 0.33 in  $H_2O$ ) $\}$  in 65% yield (from **74**). The analogous sequential treatment of the other diastereoisomer **69** gave D-fagomine **3**  $\{[\alpha]_D^{22} +18.6$  (*c* 0.43 in  $H_2O$ ) $\}$  in 40% overall yield (Scheme 11).<sup>15</sup>



**Scheme 11.** Reagents and conditions: (i) Mg, TMSCl, DMF, 0 °C to rt, 6 h; (ii) KHMDS, THF, −78 °C, 30 min then trisyl azide, −78 °C, 8 min then AcOH, −78 °C; (iii)  $H_2$  (1 atm), Pd/C, (Boc) $_2$ O, EtOAc, rt, 24 h; (iv)  $K_2CO_3$ , MeOH, 30 °C, 1 h then HCl,

H<sub>2</sub>O, rt then CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O; (v) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, 30 °C, 1 h then aq NaHCO<sub>3</sub>; (vi) LiAlH<sub>4</sub>, Et<sub>2</sub>O, reflux, 4 h; (vii) KHF<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, THF/MeOH (1:1), 60 °C, 15 h.

Davies and co-workers have recently reported a diastereodivergent route to L-fagomine *ent*-**3**, L-3-*epi*-fagomine *ent*-**4** and L-5-*epi*-fagomine *ent*-**6** employing diastereoselective *syn*- and *anti*-dihydroxylations of an enantiopure tetrahydropyridine precursor.<sup>49,50</sup> Conjugate addition of lithium (*R*)-*N*-(but-3-en-1-yl)-*N*-( $\alpha$ -methylbenzyl) amide (*R*)-**76** to dienyl ester **75** (derived from sorbic acid), followed by in situ enolate oxidation with (–)-camphorsulfonyloxaziridine [(–)-CSO] gave  $\alpha$ -hydroxy- $\beta$ -amino ester **77** in 64% yield as a single diastereoisomer. Reduction of **77** with LiAlH<sub>4</sub> gave diol **78** in 89% yield, and subsequent oxidative cleavage of the diol moiety within **78** with NaIO<sub>4</sub> followed by reduction with NaBH<sub>4</sub> gave **79** in 81% yield. Ring-closing metathesis of **79** with Grubbs II catalyst gave tetrahydropyridine **80** in 75% yield. Tetrahydropyridine **80** was next subjected to *syn*- and *anti*-dihydroxylation conditions. *syn*-Dihydroxylation of **80** under Upjohn conditions gave triol **81** in 45% yield and >95:5 dr. After hydrogenolysis of **81**, L-3-*epi*-fagomine *ent*-**4** {[ $\alpha$ ]<sub>D</sub><sup>20</sup> –72.2 (*c* 1.0 in H<sub>2</sub>O)} was isolated in quantitative yield as a single diastereoisomer. Chemoselective olefinic oxidation<sup>51</sup> of **80** with *m*CPBA and aq HBF<sub>4</sub> gave a 41:59 mixture of *anti*-diols **82** and **83**, respectively. After separation hydrogenolytic *N*-deprotection of **82** and **83** gave L-fagomine *ent*-**3** {[ $\alpha$ ]<sub>D</sub><sup>20</sup> –15.0 (*c* 0.5 in H<sub>2</sub>O)} and L-5-*epi*-fagomine *ent*-**6** {[ $\alpha$ ]<sub>D</sub><sup>20</sup> –13.6 (*c* 0.5 in H<sub>2</sub>O)}, respectively, in quantitative yield in each case (Scheme 12).

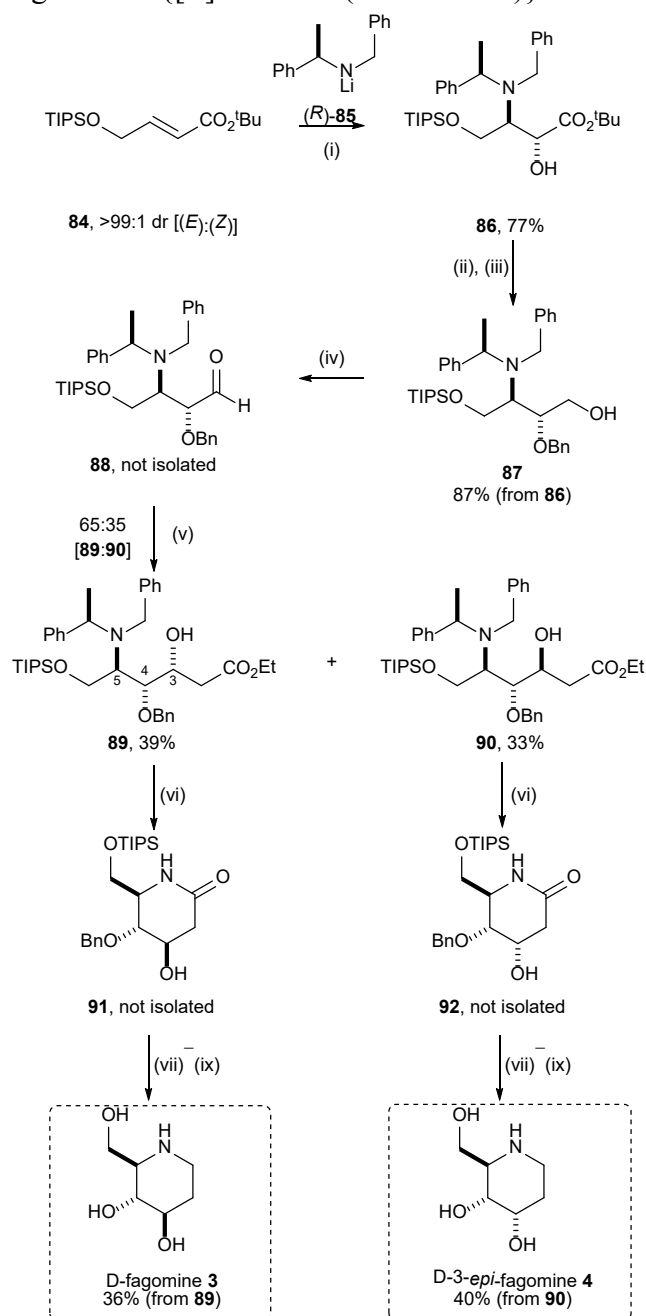


**Scheme 12.** Reagents and conditions: (i) (*R*)-**76**, THF,  $-78\text{ }^{\circ}\text{C}$ , 2 h then (–)-CSO,  $-78\text{ }^{\circ}\text{C}$  to rt, 12 h; (ii)  $\text{LiAlH}_4$ , THF,  $-78\text{ }^{\circ}\text{C}$  to rt, 16 h; (iii)  $\text{NaIO}_4$ , EtOH/ $\text{H}_2\text{O}$  (5:1), rt, 20 min; (iv)  $\text{NaBH}_4$ ,  $0\text{ }^{\circ}\text{C}$  to rt, 12 h; (v) Grubbs II,  $\text{CH}_2\text{Cl}_2$ ,  $35\text{ }^{\circ}\text{C}$ , 48 h; (vi)  $\text{OsO}_4$ , NMO, THF/ $\text{H}_2\text{O}$  (4:1), rt, 12 h; (vii)  $\text{H}_2$  (1 atm),  $\text{Pd}(\text{OH})_2/\text{C}$ , MeOH, rt, 12 h; (viii) *m*CPBA, aq  $\text{HBF}_4$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 48 h.

Davies and co-workers also demonstrated syntheses of D-fagomine **3** and all three other D-configured diastereoisomers **4–6** via diastereoselective aminohydroxylation methodology to install the C(4)*H* and C(5)*H* stereogenic centres and aldol reactions with ethyl acetate to install the C(3)*H* stereogenic centre of the corresponding diastereoisomeric fagomine diastereoisomers.<sup>52</sup> Aminohydroxylation of **84** with (*R*)-**85** and (–)-CSO gave *anti*- $\alpha$ -hydroxy- $\beta$ -amino ester **86** in 77% yield as a single diastereoisomer. The hydroxyl group within **85** was protected as the corresponding benzyl ether, and reduction with DIBAL-H gave primary alcohol **87** in 87% yield (from **86**). Swern oxidation of **87** followed by aldol reaction of the resultant aldehyde **88** with the lithium enolate derived from ethyl acetate gave a 65:35 mixture of **89** and **90**, respectively, which were isolated in 39% and 33% yield. The major diastereoisomeric product **89** was treated with  $\text{H}_2$  in the presence of  $\text{Pd}(\text{OH})_2/\text{C}$  in MeOH to give lactam **91**. Treatment of **91** with Na and naphthalene in DME removed the *O*-benzyl group, subsequent reduction of the lactam with  $\text{BH}_3$ , and acid mediated deprotection of the *O*-silyl group gave D-fagomine **3**  $\{[\alpha]_{\text{D}}^{25} +14.9\text{ (c 1.0 in H}_2\text{O)}\}$  in 36% yield



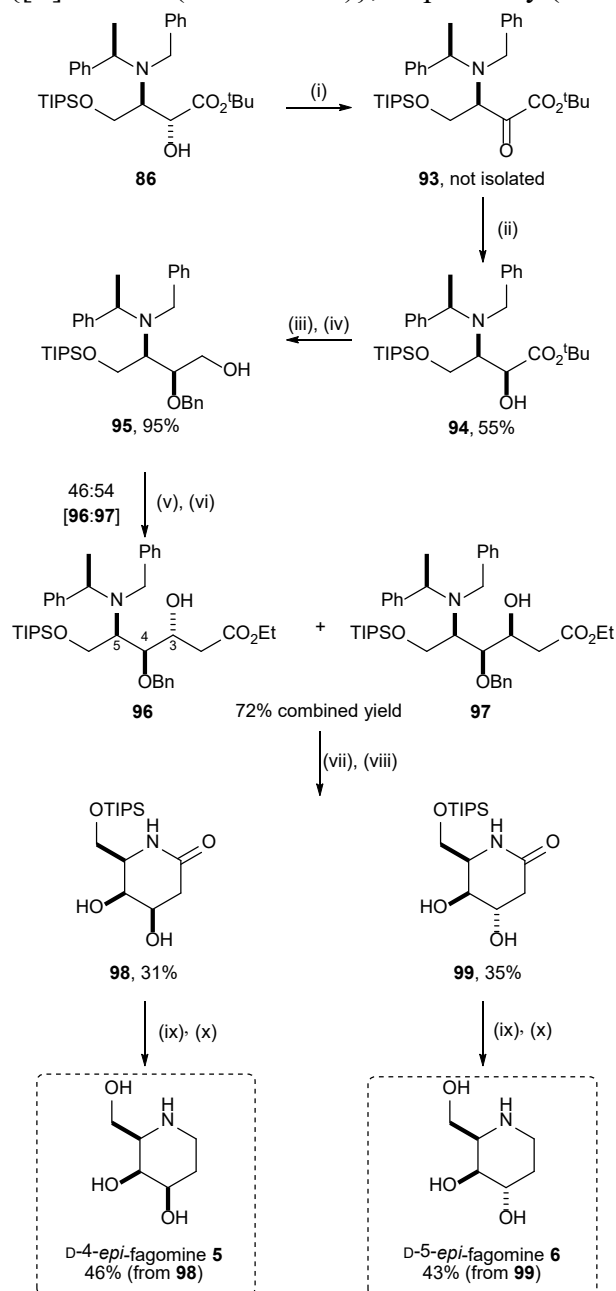
from **89**. Analogous sequential transformation of the minor diastereoisomeric aldol product **90** gave D-3-*epi*-fagomine **4**  $\{[\alpha]_D^{25} +62.8$  ( $c$  1.0 in H<sub>2</sub>O) $\}$  in 40% yield from **90** (Scheme 13).



**Scheme 13.** Reagents and conditions: (i) (*R*)-**85**, THF,  $-78$  °C, 2 h then  $(-)$ -CSO,  $-78$  °C to rt, 18 h; (ii) NaH, THF, BnBr, 0 °C to rt, 18 h; (iii) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>,  $-78$  °C to rt, 2 h; (iv) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>,  $-78$  °C, 1 h; (v) LDA, EtOAc, THF,  $-78$  °C to 0 °C, 3 h; (vi) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, rt, 24 h; (vii) Na, DME, naphthalene,  $-78$  °C to rt, 18 h; (viii) H<sub>3</sub>B·SMe<sub>2</sub>, THF, rt, 2.5 h then H<sub>2</sub>O<sub>2</sub>, NaOH, 85 °C, 1 h; (ix) 6 N aq HCl, rt, 18 h.

The remaining two D-configured diastereoisomers were synthesised upon elaboration of the epimeric precursor **94**, which was prepared by epimerisation of **86**. *anti*- $\alpha$ -Hydroxy- $\beta$ -amino ester **86** was oxidised under Swern condition to give the corresponding ketone **93** and diastereoselective reduction of **93** with NaBH<sub>4</sub> gave the corresponding *syn*- $\alpha$ -hydroxy- $\beta$ -amino ester **94** in 55% yield as a single diastereoisomer. Subsequent Swern oxidation of **94** followed by aldol reaction gave a 46:54 mixture of **96** and **97** in 72% combined yield. Global N-deprotections via hydrogenolysis followed by in situ cyclisation and treatment

with Na and naphthalene in DME gave **98** in 31% yield and **99** in 35% yield, respectively. Analogous elaboration of **98** and **99** gave D-4-*epi*-fagomine **5**  $\{[\alpha]_{\text{D}}^{25} +13.9$  ( $c$  1.0 in  $\text{H}_2\text{O}$ ) $\}$  and D-5-*epi*-fagomine **6**  $\{[\alpha]_{\text{D}}^{25} +8.0$  ( $c$  1.0 in  $\text{H}_2\text{O}$ ) $\}$ , respectively (Scheme 14).



**Scheme 14.** Reagents and conditions: (i)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h; (ii)  $\text{NaBH}_4$ , MeOH,  $-20^\circ\text{C}$ , 2 h; (iii) NaH, THF, BnBr,  $0^\circ\text{C}$  to rt, 18 h; (iv) DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to rt, 2 h; (v)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h; (vi) LDA, EtOAc, THF,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , 3 h; (vii)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$ , MeOH, rt, 24 h; (viii) Na, DME, naphthalene,  $-78^\circ\text{C}$  to rt, 18 h; (ix)  $\text{H}_3\text{B}\cdot\text{SMe}_2$ , THF, rt, 2.5 h then  $\text{H}_2\text{O}_2$ , NaOH,  $85^\circ\text{C}$ , 1 h; (x) 6 N aq HCl, rt, 18 h.

## 5. Conclusion

In conclusion, D-fagomine (1,2,5-trideoxy-1,5-imino-D-*arabino*-hexitol) and its stereoisomers have attracted interest from the biomedical and synthetic communities due to their potent biological activities, despite their relatively simple structures. In this review, the representative methods to access this family of molecules in

enantiopure form were presented, with a range of enantio- and/or diastereoselective synthetic strategies, which enable access to all 8 members of this class of hydroxylated piperidines.

## 6. References and notes

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