Enantioselective Access to All-*trans* 5-Alkylpiperidine-3,4-diols: Application to the Asymmetric Synthesis of the 1-*N*-Iminosugar (+)-Isofagomine

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Dedicated to the memory of Dr. Christian Marazano

Abstract: Access to 3,4-disubstituted *N*-benzylprolinol derivatives is described that, after optimization of the ring-enlargement reaction conditions, could be efficiently transformed into the corresponding 3-hydroxypiperidines. This approach was applied to the asymmetric synthesis of (+)-isofagomine relying on regio- and stereoselective oxirane opening with the cyanide anion of a pivotal epoxypyrrolidine.

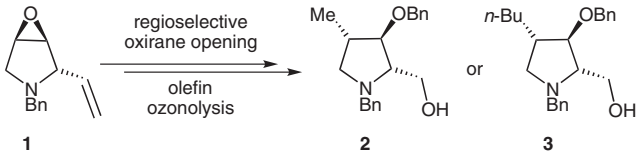
Key words: iminosugar, piperidine, ring enlargement, epoxide opening

Iminosugars represent a large family of naturally occurring polyhydroxylated alkaloids with potent glycosidase inhibitory properties.[1] Due to their wide biological effects, they hold promise for great therapeutic development.[2] Two iminosugar-based drugs have been commercialized[3] and the recent phase II clinical trial for the use of *N*-butyldeoxynojirimycin in the treatment of cystic fibrosis (mucoviscidosis) further illustrates their pharmacological potential.[4] As a consequence, iminosugars have constantly stimulated the synthetic chemistry community.[5]

In the course of our ongoing program aimed at the asymmetric synthesis of iminosugars,[6] we gained access to the high value-added enantioenriched epoxypyrrolidine **1**.[6c] Notably, the regio- and stereoselective oxirane-opening reaction of **1** allowed smooth C4 functionalization of the pyrrolidine ring. We recently reported an in-depth study of this transformation as well as its use in the synthesis of biologically active sphingolipid mimics.[7] We envisioned that the substituted prolinol derivatives used in this former study might also represent suitable precursors of all-*trans* 3,4,5-trisubstituted piperidines by means of ring-enlargement reactions. We already briefly communicated preliminary results along this line and wish to report here a full account of this work.[8]

The stereospecific ring enlargement of 2-(halomethyl)- or 2-(hydroxymethyl)pyrrolidines via an aziridinium intermediate is a well-studied process.[9] In particular, Cossy and co-workers have developed efficient access to enantiopure 3-hydroxypiperidines based on the following sequential procedure: treatment of the starting prolinol with trifluoroacetic anhydride in tetrahydrofuran, prolonged heating in the presence of an excess of triethylamine, and smooth saponification of the ring-expanded trifluoroacetate.[10] The scope of this procedure was illustrated through synthetic work directed toward zamifenacin,[11] pseudoconhydrine,[12] the velbanamine piperidine core,[13] as well as more recently Ro 67-8867[14] and (–)-swainsonine;[15] it was also used in the bicyclic series.[16] Yet, applications of these conditions to N-alkylated 3,4-disubstituted prolinol substrates remain scarce and does not concern all-*trans* substituted pyrrolidines.[9f,10b] The ring enlargement of such a trisubstituted pyrrolidine into the corresponding 3-chloropiperidine, relying on the use of mesyl chloride as an activating agent, was employed in a formal synthesis of paroxetine, which implied a subsequent radical dehalogenation step.[17]

We first selected the prolinol **2** as a representative starting material. The latter was obtained from the key epoxypyrrolidine **1** according to a three-step sequence including the opening of the oxirane by a cuprate reagent and the ozonolytic cleavage of the vinyl moiety (Scheme 1).[7]



Scheme 1 Preparation of the starting prolinol derivatives **2** and **3**

When the trisubstituted pyrrolidine **2** was treated with trifluoroacetic anhydride in tetrahydrofuran and refluxed for 64 hours in the presence of triethylamine, the expected piperidine **4** was isolated, after saponification, in 27% yield along with 38% of the starting pyrrolidine, i.e., 43.5% yield based on recovered starting material (brsm) at 62% conversion (Scheme 2). The steric bulk generated by the flexible benzyloxy group adjacent to the site of nucleophilic attack in the aziridinium intermediate **10** might account for this sluggish reaction (Scheme 3). Indeed, kinetically favored opening of the aziridinium ion at the more accessible secondary position would lead to a nonproductive pathway giving back the starting trifluoroacetate (pathway a vs pathway b, Scheme 3).

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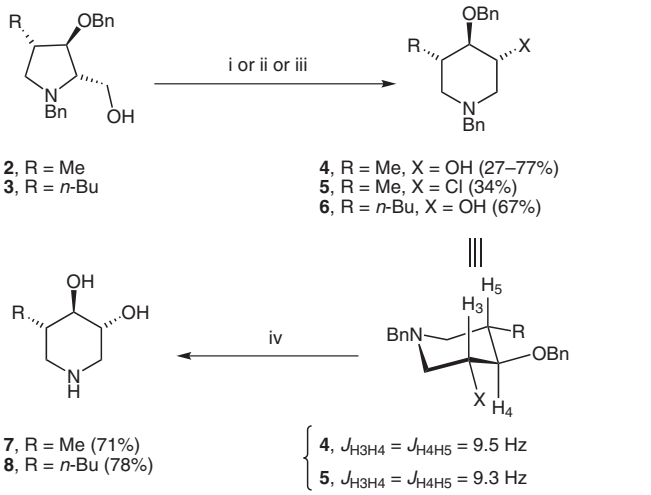
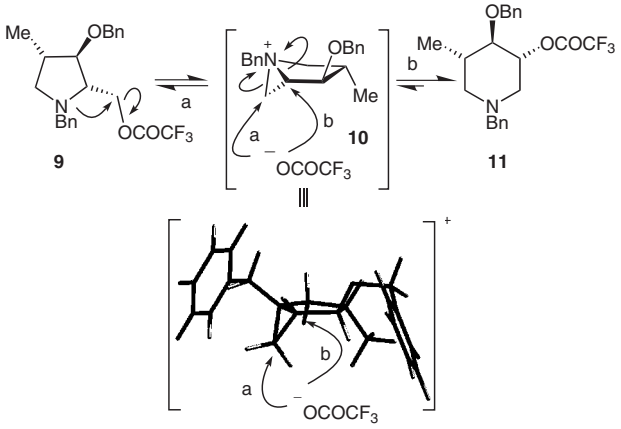


Scheme 2 *Reagents and conditions:* (i) (a) TFAA, THF, –78 °C, (b) Et_3N, THF, reflux, 64 h, (c) aq NaOH, **4**: 27%; (ii) (a) TFAA, DCE, –78 °C, (b) Et_3N, DCE, 70 °C, 72 h, (c) aq NaOH, **4**: 34%, **5**: 34% ; (iii) (a) TFAA, 1,4-dioxane, 10 °C to r.t., (b) Et_3N, 1,4-dioxane, 90 °C, 72 h, (c) aq NaOH, **4**: 77% or **6**: 67%; (iv) H_2, 20% Pd/C, concd HCl, MeOH, **7**: 71%, **8**: 78%.



Scheme 3 Ring enlargement of 3,4-disubstituted prolinol substrates

In an attempt to obtain a better conversion, we briefly explored the use of solvents with a higher boiling point. The transformation was reported not to take place in toluene or hexane.[10] When the reaction was run in 1,2-dichloroethane, heating at 70 °C for 72 hours led to the clean formation of two piperidines, isolated along with the starting material (94% global yield brsm, 73% conversion). The two products were identified as the expected 3-hydroxypiperidine **4** and the corresponding 3-chloro derivative **5**. Participation of chloride anion as a nucleophile has been reported in dichloromethane.[10] In our case, it seemed that this concurrent pathway was somewhat time dependent. Indeed, when *N*-benzylprolinol itself was reacted in 1,2-dichloroethane at 70 °C for only five hours, the expected 3-hydroxypiperidine was the sole product formed (100% yield brsm, 80% conversion). ^{1}H NMR analysis of the chlorinated piperidine **5** was in agreement with an all-*trans* relative configuration ($J_{H3H2} = J_{H3H4} = 9.5$ Hz). Opening of the aziridinium intermediate by the chloride anion would account for such a stereochemical result. Slow dehydrohalogenation of 1,2-dichloroethane under prolonged reflux in basic media [Et_3N (4 equiv)] might be responsible for the liberation of chloride anions. 1,4-Dioxane was then considered as a substitute for tetrahydrofuran. To our satisfaction, an efficient transformation took place at 90 °C after 72 hours, allowing isolation of the piperidine **4** in 91% at 85% conversion. When applied to *N*-benzylprolinol itself, this procedure (Et_3N, 1,4-dioxane, 90 °C, 18 h, 90% yield) gave essentially the same results as the standard reaction protocol (Et_3N, THF, reflux, 20 h, 85% yield).

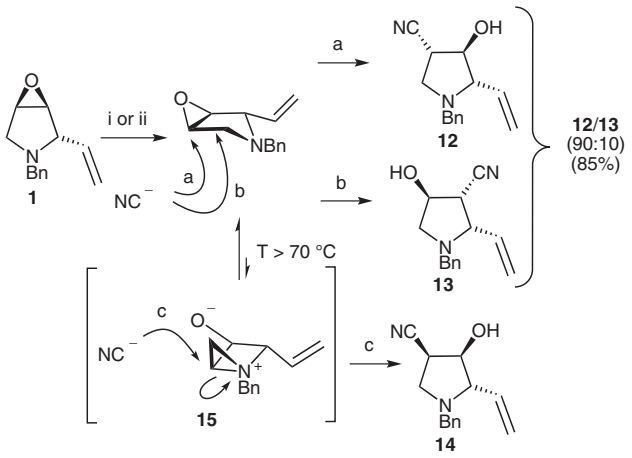
In order to further illustrate the usefulness of these conditions, we looked at other substrates. Our previously described synthetic approach also afforded access to the 4-butylprolinol **3**.[7] The use of 1,4-dioxane as solvent also proved efficient with this substrate, affording the ring-expanded product **6** in 78% yield (brsm, 86% conversion).

The final hydrogenolysis step proceeded uneventfully, delivering the unprotected piperidines in good yields. Our spectral data for 5′-deoxyisofagomine **7**, which was first prepared in 2004, were in agreement with the literature.[18] This reaction sequence also allowed the preparation of the hitherto unknown 5-butylpiperidine-3,4-diol **8**.

We then decided to further illustrate the relevance of the present synthetic route with an asymmetric synthesis of (+)-isofagomine (**21**). This synthetic derivative is the representative member of a class of sugar mimic, referred to as 1-*N*-iminosugars.[19] Defined by the location of the nitrogen atom in place of the anomeric carbon of the parent sugar, 1-*N*-iminosugars were originally proposed as selective β-glycosidases inhibitors.[20] More recently, isofagomine has been the subject of a renewed interest. In particular, it proved an excellent scaffold to elaborate glucocerebrosidase ligands, either as inhibitors[21] or as pharmacological chaperones.[22] Due to its high biological relevance, isofagomine has been the object of intense synthetic efforts.[23]

Our plan was to use a cyano group as a synthetic equivalent of the required hydroxymethyl residue. We thus first studied the oxirane-opening step. The use of Sharpless' conditions [Ti(O*i*-Pr)$_4$, KCN, TBAI, DMSO, r.t.],[24] hypervalent silicate cyanide (TBAF, TMSCN, THF, 65 °C),[25] or in situ generated HCN (KCN, TFA, EtOH, 65 °C)[26] left the starting material unaffected. In contrast, a smooth transformation was obtained due to the use of an excess of freshly prepared lithium cyanide–acetone complex.[27] After heating at 70 °C for 36 hours in tetrahydrofuran, we observed the clean formation of the expected *trans*-cyanohydrins **12** and **13**, isolated as a mixture of isomers (90:10 ratio, based on ^{1}H NMR analysis) in 87% yield (brsm, 97% conversion) (Scheme 4).

The structure of the major product **12** was unambiguously determined by X-ray diffraction analysis of a single crystal obtained from an HPLC-purified sample (Figure 1).[28]



Scheme 4 *Reagents and conditions*: (i) LiCN·acetone, THF, 70 °C, 36 h, 85%, ratio **12/13** (90:10); (ii) LiCN·acetone, THF, reflux, 24 h, 70%, ratio **12/13/14** (88:6:6).

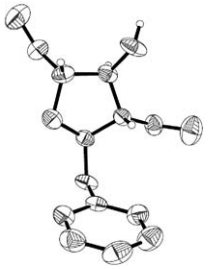
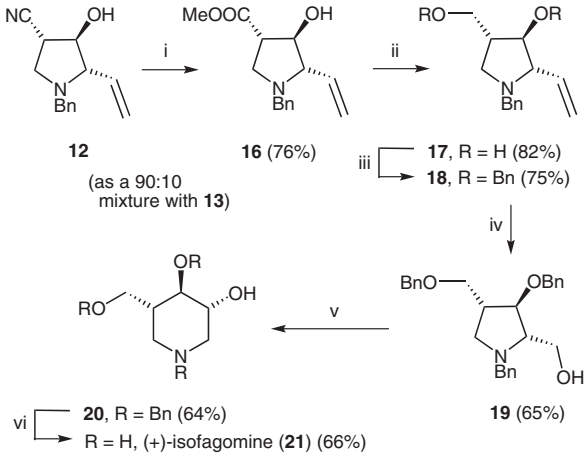


Figure 1 Molecular view of the cyanohydrin **12** in the solid state (thermal ellipsoids at 50% probability); hydrogen atoms are omitted for clarity

This result is in line with our precedent studies showing that the opening of the oxirane at the less hindered 4-position is always the most favorable pathway.[7] The present reaction thus further illustrates the generality of this process. The structure of the C3-opening product **13** was assigned to the minor component of this mixture on the basis of spectral analysis after its separation at the next step of the synthesis (*vide infra*). It is worth noting that refluxing in tetrahydrofuran for 24 hours led to a much less efficient transformation, a mixture of three isomeric opening products (88:6:6 ratio based on HPLC analysis) being in this case isolated in 83% yield (brsm, 84% conversion). The additional reaction product was clearly identified as a diastereoisomeric C4 opening product from mass spectra and 1D and 2D NMR analysis (COSY, HSQC, HMBC experiments). The *cis*-cyanohydrin **14** may indeed arise, upon heating at higher temperature, from a double inversion process involving the intramolecular attack of the oxirane by the tertiary amine and the formation of a bicyclic azetidinium intermediate **15** (Scheme 4). Alternatively **14** may also arise from base-catalyzed epimerization of **12**.

We thus decided to carry on the synthesis with the mixture of *trans*-cyanohydrins **12** and **13**. Clean conversion of the nitrile into an ester functionality was achieved upon treatment with anhydrous hydrogen chloride solution in methanol (Scheme 5). Gratifyingly, not only the two reaction products proved easily separable, but only the major component of the starting mixture was transformed; the minor cyanohydrin **13** was recovered unaffected. This allowed its full characterization as the C3-opening product. The identity of the methyl ester **16** (81% yield based on the recovery of the unreacted minor isomer **13**) was confirmed by means of X-ray crystallographic analysis (Figure 2).[29] The preparation of the prolinol derivative **19**, required for the ring-enlargement step, relied on the oxidative cleavage of the vinyl moiety. This was accomplished as follows: the ester function was first reduced to the primary alcohol by action of lithium aluminum hydride and perbenzylation of the diol **17** led to the vinyl pyrrolidine **18** (62% overall yield). The latter, once acidified with hydrogen chloride in methanol, was quickly reacted with ozone at –78 °C in methanol. Immediate reduction of the highly sensitive aminoaldehyde intermediate with an excess of sodium borohydride allowed isolation of the expected *N*-benzylprolinol **19** in 65% yield.



Scheme 5 *Reagents and conditions*: (i) HCl, MeOH, 76%; (ii) $LiAlH_4$, THF, 0 °C to r.t., 82%, (iii) BnBr, NaI, NaH, DMF, 0 °C to r.t., 75%; (iv) (a) HCl, MeOH (b) O_3, MeOH, –78 °C (c) $NaBH_4$, MeOH, –10 °C, 65%; (v) (a) TFAA, 1,4-dioxane, 10 °C to r.t., (b) Et_3N, 1,4-dioxane, 90 °C, 96 h, (c) aq NaOH, 64%; (vi) H_2, $Pd(OH)_2$, MeOH, 66%.

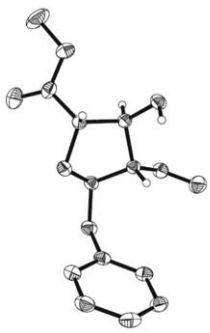


Figure 2 Molecular view of the hydroxy ester **16** in the solid state (thermal ellipsoids at 50% probability); hydrogen atoms are omitted for clarity

The end of the synthesis proved straightforward. Thanks to the use of 1,4-dioxane as solvent, the ring-enlargement reaction delivered the desired piperidine **20** in 75% yield (brsm, 85% conversion) after heating at 90 °C for 96 hours. The targeted (+)-isofagomine (**21**) was finally obtained upon catalytic hydrogenation. Spectral data recorded for **21** were in agreement with that reported in the literature for isofagomine.

In conclusion, thanks to the use of 1,4-dioxane as solvent, we extended the scope of the N-alkylated prolinol ring enlargement to the preparation of all-*trans* 5-alkylpiperidine-3,4-diols. When applied to 2-(hydroxymethyl)pyrrolidines obtained via the regio- and stereoselective oxirane opening of a key epoxypyrrolidine precursor with the cyanide anion, these conditions proved useful for the asymmetric synthesis of 1-*N*-iminosugars such as (+)-isofagomine (**21**).

NMR spectroscopic data were obtained with Bruker Avance 300, ARX 400 and Avance 500 relative to residual solvent peak. IR spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrophotometer. MS data were obtained on a ThermoQuest TSQ 7000 spectrometer. HRMS were performed on a ThermoFinnigan MAT 95 XL spectrometer. For chromatography, petroleum ether = PE. Optical rotations were measured on a Perkin-Elmer model 241 spectrometer. For crystallographic analysis, the selected crystals were mounted on a glass fiber using perfluoropolyether oil and cooled rapidly in a stream of cold N_2. The data were collected on a Bruker-AXS APEX II diffractometer equipped with the Bruker Kryo-Flex cooler device and using a graphite-monochromated MoKα radiation. The structures were solved by direct methods (SHELXS-97)[30] and all non-hydrogen atoms were refined anisotropically using the least-squares method on F^2.[31]

Ring-Enlargement Reaction; General Procedure A

To a 0.1 M soln of the prolinol substrate in anhyd 1,4-dioxane at 10 °C under inert atmosphere was added TFAA (1.2 equiv). The mixture was stirred at r.t. for 1 h and then Et_3N (4.0 equiv) was added. After 15 min, the mixture was heated to 90 °C for 3 to 4 d and then allowed to cool and 2.5 M aq NaOH (9.0 equiv) was added. After 1 h, brine was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness.

(3*R*,4*R*,5*S*)-1-Benzyl-4-(benzyloxy)-5-methylpiperidin-3-ol (4)

Following general procedure A using prolinol **2** (22.6 mg, 72.7 μmol). The crude product was purified by flash column chromatography (silica gel, PE–*i*-PrOH, 95:5 to 85:15 + 0.15% Et_3N) to give **4** (17.5 mg, 77%) as a white amorphous solid along with starting material (3.30 mg, 15% recovery); R_f = 0.24 (PE–*i*-PrOH, 90:10 + 0.15% Et_3N).

$[\alpha]_D^{25}$ –4 (*c* 1.3, $CHCl_3$).

IR (neat): 3434 (O–H), 1604 (C=C), 1266 cm^{-1} (C–O).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, ^3J = 6.5 Hz, 3 H), 1.84 (pseudo t, $^2J \approx {}^3J \approx$ 11.1 Hz, 1 H), 1.89–1.97 (m, 1 H), 2.01 (pseudo t, $^2J \approx {}^3J \approx$ 10.5 Hz, 1 H), 2.15–2.45 (m, 1 H), 2.82 (ddd, ^2J = 11.2 Hz, ^3J = 3.5 Hz, ^4J = 2.0 Hz, 1 H), 2.91 (pseudo t, $^3J \approx {}^3J \approx$ 9.3 Hz, 1 H), 3.08 (ddd, ^2J = 10.6 Hz, ^3J = 4,6 Hz, ^4J = 2.0 Hz, 1 H), 3.58 (AB system, ^2J = 13.2 Hz, δa–δb = 13.4 Hz, 2 H), 3.79–3.85 (m, 1 H), 4.75 (AB system, ^2J = 11.4 Hz, δa–δb = 13.3 Hz, 2 H), 7.27–7.41 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7, 35.4, 58.1, 59.4, 62.2, 71.4, 74.0, 88.4, 127.3, 127.8 (2 peaks), 128.3, 128.5, 129.1, 138.7.

MS (DCI/NH_3): *m*/*z* (%) = 312 (100) $[M + H]^+$.

HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{26}NO_2$: 312.1964; found: 312.1961.

(3*R*,4*R*,5*S*)-1-Benzyl-4-(benzyloxy)-3-chloro-5-methylpiperidine (5)

To a soln of **2** (78.1 mg, 0.25 mmol) in anhyd DCE (2.5 mL) at 0 °C under an inert atmosphere was added TFAA (39.0 μL, 0.28 mmol). The mixture was stirred at this temperature for 3 h and then Et_3N (140 μL, 1.02 mmol) was added. After 15 min, the mixture was heated to 70 °C for 3 d and then allowed to cool and 2.5 M aq NaOH (0.9 mL, 2.25 mmol) was added. After 1 h, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by flash column chromatography (silica gel, PE–*i*-PrOH, 95:5 to 85:15 + 0.15% Et_3N) to give **4** (26.9 mg, 34%) and the chlorinated compound **5** (28.0 mg, 34%) as a colorless oil along with starting material (21.4 mg, 27% recovery); R_f = 0.49 (PE–*i*-PrOH, 90:10 + 0.15% Et_3N).

$[\alpha]_D^{25}$ +16 (*c* 1.1, $CHCl_3$).

IR (neat): 1603 (C=C), 1265 cm^{-1} (C–O).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, ^3J = 6.2 Hz, 3 H), 1.84–2.01 (m, 2 H), 2.30 (pseudo t, $^2J \approx {}^3J \approx$ 11.2 Hz, 1 H), 2.83–2.87 (m, 1 H), 3.04 (pseudo t, $^3J \approx {}^3J \approx$ 9.5 Hz, 1 H), 3.17 (ddd, ^2J = 11.2 Hz, ^3J = 4.7 Hz, ^4J = 2.4 Hz, 1 H), 3.58 (s, 2 H), 4.09 (ddd, ^3J = 11.1 Hz, ^3J = 9.6 Hz, ^3J = 4.7 Hz, 1 H), 4.66 (d, ^2J = 10.5 Hz, 1 H), 4.99 (d, ^2J = 10.5 Hz, 1 H), 7.28–7.46 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 37.6, 59.2, 60.2, 60.7, 61.7, 75.1, 87.9, 127.3, 127.7, 128.1, 128.3, 128.9, 137.5, 138.3.

MS (DCI/NH_3): *m*/*z* (%) = 330 (100) $[M + H]^+$.

HRMS (DCI/NH_3): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{25}ClNO$: 330.1625; found: 330.1626.

(3*R*,4*R*,5*S*)-1-Benzyl-4-(benzyloxy)-5-butylpiperidin-3-ol (6)

Following general procedure A using prolinol **3** (30.0 mg, 85.0 μmol). The crude product was purified by flash column chromatography (silica gel, PE–EtOAc, 70:30 to 60:40 + 0.8% NH_4OH) to give **6** (20.0 mg, 67%) as a yellow amorphous solid along with starting material (4.20 mg, 14% recovery); R_f = 0.22 (PE–EtOAc, 70:30 + 0.8% NH_4OH).

$[\alpha]_D^{25}$ +16 (*c* 1.0, $CHCl_3$).

IR (neat): 3400 (O–H), 1604 (C=C), 1065 cm^{-1} (C–O).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.9 Hz, 3 H), 1.11–1.39 (m, 5 H), 1.70–1.87 (m, 3 H), 1.96 (pseudo t, $^2J \approx {}^3J \approx$ 10.3 Hz, 1 H), 2.01–2.20 (m, 1 H), 2.88–2.98 (m, 1 H), 2.98 (pseudo t, $^3J \approx {}^2J \approx$ 8.7 Hz, 1 H), 3.01 (ddd, ^2J = 10.7 Hz, ^3J = 4.7 Hz, ^4J = 2.1 Hz, 1 H), 3.56 (AB system, ^2J = 13.2 Hz, δa–δb = 45.6 Hz, 2 H), 3.78 (ddd, ^3J = 9.8 Hz, ^3J = 8.5 Hz, ^3J = 4.7 Hz, 1 H), 4.73 (AB system, ^2J = 11.4 Hz, δa–δb = 6.5 Hz, 2 H), 7.25–7.41 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 23.0, 29.1, 29.6, 40.2, 57.3, 57.9, 62.4, 71.6, 73.8, 86.8, 127.1, 127.8 (2 peaks), 128.2, 128.5, 129.0, 137.9, 138.7.

MS (DCI/NH_3) *m*/*z* (%) = 354 (100) $[M + H]^+$.

HRMS (ESI$^+$) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{32}NO_2$: 354.2433; found: 354.2431.

Catalytic Hydrogenation; General Procedure B

To a 0.1 M soln of *N*-benzylpiperidine in MeOH was added successively $Pd(OH)_2$ (20% w/w) and 12 M HCl (1–2 drops). The flask was purged with N_2 and then loaded with H_2 (8–10 bar). The mix-

ture was stirred at r.t. until disappearance of the starting material (24–90 h). The catalyst was then removed by filtration through Celite and the filtrate was evaporated to dryness. The intermediate was taken up in MeOH–H_2O (2:1, 25 mL/mmol) and Dowex 50WX8-200 ion-exchange resin (12 g/mmol) was added. The mixture was stirred for 1 h and the resin was successively filtered and washed with H_2O and MeOH. 3 M NH_4OH was then added (50 mL/mmol) and the resin was stirred for 1 h and then it was filtered and rinsed with 3 M NH_4OH (500 mL/mmol). The resulting soln was evaporated to dryness under reduced pressure.

(3*R*,4*R*,5*S*)-5-Methylpiperidine-3,4-diol (5′-Deoxyisofagomine, 7)

Following general procedure B using *N*-benzylpiperidine **4** (37.5 mg, 0.12 mmol). The crude product was purified by flash column chromatography (silica gel, MeOH–EtOH–NH_4OH–CH_2Cl_2, 12:15:6:67 to 15:20:10:55) to give **7** (11.1 mg, 71%) as a white amorphous solid; R_f = 0.21 (MeOH–EtOH–NH_4OH–CH_2Cl_2, 12:15:6:67).

$[\alpha]_D^{25}$ +8 (*c* 0.75, EtOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 0.98 (d, ^3J = 6.5 Hz, 3 H), 1.45–1.60 (m, 1 H), 2.18–2.27 (m, 1 H), 2.37 (dd, ^2J = 12.2 Hz, ^3J = 10.8 Hz, 1 H), 2.86–2.95 (m, 2 H), 3.08 (ddd, ^2J = 12.2 Hz, ^3J = 5.0 Hz, ^3J = 1.5 Hz, 1 H), 3.36 (ddd, ^3J = 10.8 Hz, ^3J = 8.8 Hz, ^3J = 5.0 Hz, 1 H).

^{1}H NMR (300 MHz, D_2O): d = 0.80 (d, ^3J = 6.5 Hz, 3 H), 1.31–1.48 (m, 1 H), 2.09 (pseudo t, $^2J \approx {}^3J \approx$ 12.2 Hz, 1 H), 2.24 (pseudo t, $^2J \approx {}^3J \approx$ 11.5 Hz, 1 H), 2.76 (dd, ^2J = 13.0 Hz, ^3J = 3.6 Hz, 1 H), 2.90 (pseudo t, $^3J \approx {}^3J \approx$ 9.7 Hz, 1 H), 2.96 (dd, ^2J = 12.2 Hz, ^3J = 4.7 Hz, 1 H), 3.29 (ddd, ^3J = 10.4 Hz, ^3J = 9.7 Hz, ^3J = 5.0 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 15.4, 39.4, 52.2, 52.9, 73.8, 80.7.

^{13}C NMR (75 MHz, D_2O): δ = 13.3, 36.7, 49.0, 49.8, 71.1, 78.1.

MS (DCI/NH_3): *m*/*z* (%) = 132 (50) $[M + H]^+$, 149 (100) $[M + NH_4^+]$.

HRMS (DCI/NH_3): *m*/*z* $[M + H]^+$ calcd for $C_6H_{14}NO_2$: 132.1025; found: 132.1026.

(3*R*,4*R*,5*S*)-5-Butylpiperidine-3,4-diol (8)

Following general procedure B using *N*-benzylpiperidine **6** (39.0 mg, 0.11 mmol). The crude product was purified by flash column chromatography (silica gel, MeOH–NH_4OH–CH_2Cl_2, 10:3:87) to give **8** (14.9 mg, 78%) as a white amorphous solid; R_f = 0.19 (MeOH–NH_4OH–CH_2Cl_2 10:3:87).

$[\alpha]_D^{25}$ +30 (*c* 1.3, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 0.92 (t, ^3J = 6.9 Hz, 3 H), 1.03–1.49 (m, 6 H), 1.76–1.87 (m, 1 H), 2.18 (pseudo t, $^2J \approx {}^3J \approx$ 12.4 Hz, 1 H), 2.34 (dd, ^2J = 12.1 Hz, ^3J = 10.7 Hz, 1 H), 2.97 (dd, ^3J = 10.1 Hz, ^3J = 8.7 Hz, 1 H), 2.99–3.05 (m, 1 H), 3.07 (ddd, ^2J = 12.1 Hz, ^3J = 5.0 Hz, ^4J = 1.5 Hz, 1 H), 3.35 (ddd, ^3J = 10.7 Hz, ^3J = 8.7 Hz, ^3J = 5.0 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 14.4, 24.2, 30.3, 30.4, 44.5, 50.6, 52.2, 74.1, 79.3.

MS (DCI/NH_3): *m*/*z* (%) = 174 (100) $[M + H]^+$, 191 (66) $[M + NH_4^+]$.

HRMS (DCI/NH_3): *m*/*z* $[M + H]^+$ calcd for $C_9H_{20}NO_2$: 174.1494; found: 174.1497.

(3*R*,4*R*,5*S*)-1-Benzyl-4-hydroxy-5-vinylpyrrolidine-3-carbonitrile (12), (2*S*,3*S*,4*S*)-1-Benzyl-3-hydroxy-2-vinylpyrrolidine-4-carbonitrile (13), and (3*S*,4*R*,5*S*)-1-Benzyl-4-hydroxy-5-vinylpyrrolidine-3-carbonitrile (14)

To epoxypyrrolidine **1** (292 mg, 1.45 mmol) in soln in THF (15 mL) was added under an inert atmosphere to freshly prepared LiCN·acetone complex [from acetone cyanohydrin (570 μL, 6.23 mmol) and 1.6 M MeLi in hexane (2.7 mL, 4.32 mmol)].[27] The mixture was gently heated at 70 °C for 36 h and allowed to cool and H_2O (90 mL) was added. The aqueous layer was extracted with Et_2O. The combined organic phases were then dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by flash column chromatography (silica gel, PE–CH_2Cl_2–EtOAc, 50:40:10 to 30:56:14) to give a mixture of isomers **12** and **13** (280 mg, 85%) along with starting material (8.00 mg, 3% recovery). When formed upon prolonged reflux, the minor isomer **14** was isolated by simple flash column chromatography (silica gel, PE–EtOAc, 90:10 to 60:40). An analytically pure sample of the major product **12** was obtained as a white amorphous solid by HPLC purification (XTerra MSC18 5 μm 100 × 19 column, 3 mM Et_3N in H_2O–MeCN, 70:30, 15 mL/min).

(3*R*,4*R*,5*S*)-1-Benzyl-4-hydroxy-5-vinylpyrrolidine-3-carbonitrile (12)

R_f = 0.22 (PE–EtOAc, 70:30).

$[\alpha]_D^{25}$ +88 (*c* 1.2, $CHCl_3$).

IR (neat): 3436 (O–H), 2245 (C≡N), 1666, 1645, 1604 cm^{-1} (C=C, aromatic C=C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (m, 1 H), 2.82–2.91 (m, 2 H), 3.14 (dd, ^2J = 9.8 Hz, ^3J = 2.9 Hz, 1 H), 3.23 (d, ^2J = 13.5 Hz, 1 H), 4.03 (d, ^2J = 13.5 Hz, 1 H), 4.26–4.30 (m, 1 H), 5.40 (dd, ^3J = 10.1 Hz, ^2J = 1.5 Hz, 1 H), 5.47 (br d, ^3J = 17.2 Hz, 1 H), 5.87 (ddd, ^3J = 17.2 Hz, ^3J = 10.1 Hz, ^3J = 8.4 Hz, 1 H), 7.28–7.39 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.1, 53.5, 56.4, 74.5, 79.5, 120.5, 121.3, 127.2, 128.3, 128.5, 136.5, 137.4.

MS (DCI/NH_3): *m*/*z* (%) = 229 (100) $[M + H]^+$.

HRMS (DCI/NH_3): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1341; found: 229.1340.

(2*S*,3*S*,4*S*)-1-Benzyl-3-hydroxy-2-vinylpyrrolidine-4-carbonitrile (13)

R_f = 0.22 (PE–EtOAc, 70:30).

$[\alpha]_D^{25}$ +59 (*c* 0.8, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (dd, ^2J = 10.2 Hz, ^3J = 5.5 Hz, 1 H), 3.03 (dd, ^3J = 7.0 Hz, ^3J = 3.1 Hz, 1 H), 3.25 (d, ^2J = 13.3 Hz, 1 H), 3.35–3.42 (m, 2 H), 4.01 (d, ^2J = 13.3 Hz, 1 H), 4.55–4.60 (m, 1 H), 5.43 (m, 1 H), 5.49 (m, 1 H), 5.96 (ddd, ^3J = 17.6 Hz, ^3J = 9.6 Hz, ^3J = 8.8 Hz, 1 H), 7.24–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.1, 56.3, 59.6, 66.4, 73.2, 119.0, 121.2, 127.2, 128.3, 128.6, 135.1, 137.8.

MS (ESI$^+$): *m*/*z* (%) = 229 (100) $[M + H]^+$.

HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1341; found: 229.1372.

(3*S*,4*R*,5*S*)-1-Benzyl-4-hydroxy-5-vinylpyrrolidine-3-carbonitrile (14)

R_f = 0.13 (PE–EtOAc, 70:30).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (br s, 1 H), 2.52–2.64 (m, 1 H), 2.89–2.94 (m, 1 H), 3.05–3.18 (m, 2 H), 3.20 (d, ^2J = 13.2 Hz, 1 H), 3.91 (d, ^2J = 13.2 Hz, 1 H), 4.04–4.14 (m, 1 H), 5.28 (dd, ^3J = 10.1 Hz, ^2J = 1.1 Hz, 1 H), 5.39 (br d, ^3J = 17.1 Hz, 1 H), 5.68–5.79 (m, 1 H), 7.18–7.28 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.8, 53.8, 57.1, 74.8, 75.0, 117.9, 120.1, 127.5, 128.4, 128.9, 136.2.

MS (DCI/NH_3): *m*/*z* (%) = 229 (100) $[M + H]^+$, 246 (18) $[M + NH_4^+]$

Methyl (3*S*,4*R*,5*S*)-1-Benzyl-4-hydroxy-5-vinylpyrrolidine-3-carboxylate (16)

To a mixture of **12/13** (90:10, 280 mg, 1.23 mmol) in soln in MeOH (3.5 mL) was added 20 wt% methanolic HCl soln (2.6 g, 12 equiv) and the mixture was allowed to stir at r.t. for 3 d. The soln was then neutralized by addition of solid $NaHCO_3$ (1.2 g, 12 equiv) and the MeOH was evaporated under vacuum. The residue was taken up in THF, filtered over Celite, and concentrated to dryness. The resulting crude mixture was purified by flash column chromatography (silica gel, CH_2Cl_2–EtOAc, 80:20) to give the minor starting cyanohydrin **13** (15.2 mg, 0.07 mmol) and the ester **16** (245 mg, 76%) as a white amorphous solid; R_f = 0.34 (CH_2Cl_2–EtOAc, 80:20).

$[\alpha]_D^{25}$ +92 (*c* 1.3, $CHCl_3$).

IR (neat): 3350 (O–H), 1745 (C=O), 1682, 1661, 1623 cm^{-1} (C=C, aromatic C=C).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (br s, 1 H), 2.60 (pseudo t, $^3J \approx {}^3J \approx$ 10.0 Hz, 1 H), 2.80–2.87 (m, 2 H), 3.16 (dd, ^2J = 9.7 Hz, ^3J = 3.9 Hz, 1 H), 3.17 (d, ^2J = 13.5 Hz, 1 H), 3.67 (s, 3 H), 3.94 (d, ^2J = 13.5 Hz, 1 H), 4.22 (pseudo t, $^3J \approx {}^3J \approx$ 7.5 Hz, 1 H), 5.31 (dd, ^3J = 10.1 Hz, ^2J = 1.7 Hz, 1 H), 5.38 (dd, ^3J = 17.2 Hz, ^2J = 1.7 Hz, 1 H), 5.80 (ddd, ^3J = 17.2 Hz, ^3J = 10.1 Hz, ^3J = 8.4 Hz, 1 H), 7.18–7.31 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.4, 52.1, 52.7, 57.2, 74.8, 78.2, 119.9, 126.9, 128.2, 128.7, 137.8, 138.1, 173.9.

MS (ESI^+): *m*/*z* (%) = 262 (100) $[M + H]^+$.

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$: 262.1443; found: 262.1433.

(2*S*,3*R*,4*R*)-1-Benzyl-4-(hydroxymethyl)-2-vinylpyrrolidin-3-ol (17)

To a soln of the ester **16** (213 mg, 0.82 mmol) in anhyd THF (6.0 mL) under an inert atmosphere at 0 °C was added $LiAlH_4$ (47.0 mg, 1.5 equiv). The mixture was allowed to stir at 0 °C for 1 h and at r.t. for 2 h. The reaction was then treated successively with H_2O (50 μL), 15% aq NaOH (50 μL), and H_2O (150 μL). The white precipitate formed was filtered off over Celite and the filtrate concentrated to dryness. The resulting crude mixture was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 92:8 + 0.3% Et_3N) to give diol **17** (156 mg, 82%) as a white amorphous solid; R_f = 0.27 (CH_2Cl_2–MeOH, 98:2 + 0.3% Et_3N).

$[\alpha]_D^{25}$ +106 (*c* 0.7, $CHCl_3$).

IR (neat): 3433 (O–H), 1645, 1604 cm^{-1} (C=C, aromatic C=C).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.06–2.17 (m, 1 H), 2.64 (AB of ABX, $^2J \approx {}^3J \approx$ 9.7 Hz, ^3J = 2.7 Hz, δa–δb = 39.5 Hz, 2 H), 2.67 (br s, 2 H), 2.81 (dd, ^3J = 8.4 Hz, ^3J = 6.6 Hz, 1 H), 3.12 (d, ^2J = 13.2 Hz, 1 H), 3.60–3.70 (m, 2 H), 3.92–4.00 (m, 2 H), 5.31 (dd, ^3J = 10.1 Hz, ^2J = 1.6 Hz, 1 H), 5.39 (dd, ^3J = 17.2 Hz, ^2J = 1.6 Hz, 1 H), 5.85 (ddd, ^3J = 17.2 Hz, ^3J = 10.1 Hz, ^3J = 8.6 Hz, 1 H), 7.22–7.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6, 53.9, 57.4, 65.1, 76.1, 79.1, 119.5, 127.0, 128.2, 128.9, 137.8, 137.9.

MS (ESI^+): *m*/*z* (%) = 234 (100) $[M + H]^+$.

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$: 234.1494; found: 234.1507.

(2*S*,3*R*,4*R*)-1-Benzyl-3-(benzyloxy)-4-[(benzyloxy)methyl]-2-vinylpyrrolidine (18)

To the diol **17** (97.0 mg, 0.42 mmol) in soln in dry DMF (2.9 mL) at 0 °C under an inert atmosphere were successively added 4 Å molecular sieves (29.0 mg, 30% w/w), NaI (5.00 mg, 0.08 equiv), BnBr (170 μL, 2.4 equiv), and NaH (24.0 mg, 2.4 equiv). The mixture was stirred at 0 °C for a further 10 min and at r.t. overnight. The reaction was then quenched by addition of H_2O, the aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by flash column chromatography (silica gel, PE–EtOAc, 95:5 to 80:20) to give **18** (133 mg, 75%) as a colorless oil; R_f = 0.26 (PE–EtOAc, 90:10).

$[\alpha]_D^{25}$ +58 (*c* 1.6, $CHCl_3$).

IR (neat): 1643, 1604 cm^{-1} (C=C, aromatic C=C).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.30–2.39 (m, 1 H), 2.45 (pseudo t, $^3J \approx {}^3J \approx$ 8.7 Hz, 1 H), 2.71 (br d, ^2J = 9.1 Hz, 1 H), 2.94 (pseudo t, $^3J \approx {}^3J \approx$ 7.2 Hz, 1 H), 3.09 (d, ^2J = 13.4 Hz, 2 H), 3.40 (d, ^3J = 7.6 Hz, 1 H), 3.59 (dd, ^3J = 6.0 Hz, ^2J = 3.1 Hz, 1 H), 3.96 (d, ^2J = 13.4 Hz, 1 H), 4.46 (s, 2 H), 4.56 (AB system, ^2J = 12.0 Hz, δa–δb = 14.5 Hz, 2 H), 5.23 (dd, ^3J = 10.1 Hz, ^2J = 1.7 Hz, 1 H), 5.38 (dd, ^3J = 17.2 Hz, ^2J = 1.7 Hz, 1 H), 5.85 (m, 1 H), 7.18–7.33 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.6, 54.1, 57.1, 71.6, 72.3, 73.0, 74.5, 86.5, 118.4, 126.7, 127.4, 127.5, 127.6 (2 peaks), 128.1, 128.2, 128.6, 138.4, 138.5, 139.0, 139.2.

MS (ESI^+): *m*/*z* (%) = 414 (100) $[M + H]^+$.

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{32}NO_2$: 414.2433; found: 414.2426.

{(2*S*,3*R*,4*R*)-1-Benzyl-3-(benzyloxy)-4-[(benzyloxy)methyl]pyrrolidin-2-yl}methanol (19)

To the olefin **18** (78.0 mg, 0.19 mmol) in soln in MeOH (2.4 mL) under inert atmosphere at 0 °C was added 24 wt% methanolic HCl soln (290 mg, 10 equiv). The soln was stirred for 30 min at this temperature and evaporated to dryness. The residue was then dissolved in MeOH (3.2 mL) and cooled to –78 °C. Ozone was bubbled into the soln until it became bluish (3 min). $NaBH_4$ (3 × 7 equiv) was then added portionwise and the mixture was vigorously stirred at –78 °C for 1 h and at –10 °C overnight. The reaction was then quenched by addition of sat. aq NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by flash column chromatography (silica gel, PE–EtOAc, 90:10 + 0.4% NH_4OH to 80:20 + 0.8% NH_4OH) to give **19** (51.5 mg, 65%) as a colorless oil; R_f = 0.21 (PE–EtOAc, 80:20 + 0.8% NH_4OH).

$[\alpha]_D^{25}$ +4 (*c* 0.7, $CHCl_3$).

IR (neat): 3447 (O–H), 1604 (aromatic C=C), 1266 cm^{-1} (C–O).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.30–2.41 (m, 1 H), 2.59–2.74 (m, 2 H), 2.77–2.87 (m, 1 H), 3.29 (d, ^2J = 13.3 Hz, 1 H), 3.36 (d, ^3J = 7.6 Hz, 2 H), 3.64 (AB of ABX, ^2J = 11.5 Hz, ^3J = 3.2 Hz, ^3J = 15 Hz, δa–δb = 36.9 Hz, 2 H), 3.86 (dd, ^3J = 5.3 Hz, ^2J = 2.4 Hz, 1 H), 3.91 (d, ^2J = 13.3 Hz, 1 H), 4.40–4.49 (m, 3 H), 4.56 (d, ^2J = 11.7 Hz, 1 H), 7.21–7.30 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 55.2, 57.9, 59.1, 71.5, 71.8 (2 peaks), 73.2, 83.7, 127.4, 126.6, 127.7, 127.8, 128.4 (2 peaks), 128.5, 128.8, 129.6, 138.3 (2 peaks).

MS (ESI^+): *m*/*z* (%) = 418 (100) $[M + H]^+$.

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{32}NO_3$: 418.2382; found: 418.2416.

(3*R*,4*R*,5*R*)-1-Benzyl-4-(benzyloxy)-5-[(benzyloxy)methyl]piperidin-3-ol (20)

Following general procedure A using prolinol **19** (67.5 mg, 0.16 mmol). The crude product was purified by flash column chromatography (silica gel, PE–EtOAc, 80:20 to 70:30 + 0.8% NH_4OH) to give **20** (43.2 mg, 64%) as a colorless oil along with starting material (10.0 mg, 15% recovery); R_f = 0.16 (PE–EtOAc, 80:20 + 0.8% NH_4OH).

$[\alpha]_D^{25}$ +20 (*c* 0.8, $CHCl_3$).

IR (neat): 3435 (O–H), 1641 (C=C), 1092 cm^{-1} (C–O).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.94 (pseudo t, $^2J \approx {}^3J \approx 10.3$ Hz, 1 H), 1.98–2.06 (m, 1 H), 2.14 (pseudo t, $^2J \approx {}^3J \approx 10.3$ Hz, 1 H), 2.86–2.98 (m, 2 H), 3.23 (pseudo t, $^3J \approx {}^3J \approx 9.1$ Hz, 1 H), 3.50 (AB system, $^2J = 13.0$ Hz, δa–δb = 30.3 Hz, 2 H), 3.51–3.59 (m, 2 H), 3.69–3.76 (m, 1 H), 4.41 (AB system, $^2J = 12.0$ Hz, δa–δb = 16.2 Hz, 2 H), 4.60 (AB system, $^2J = 11.5$ Hz, δa–δb = 15.6 Hz, 2 H), 7.20–7.33 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.4, 55.4, 57.8, 62.3, 69.2, 71.8, 73.0, 73.9, 82.6, 127.1, 127.6 (2 peaks), 127.8 (2 peaks), 128.2, 128.3, 128.5, 129.0, 138.0, 138.2, 138.6.

MS (ESI^+): *m*/*z* (%) = 418 (100) $[M + H]^+$.

HRMS (ESI^+): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{32}NO_3$: 418.2382; found: 418.2414.

(+)-Isofagomine (21)

Following general procedure B using *N*-benzylpiperidine **20** (53.0 mg, 0.13 mmol). The crude product was purified by flash column chromatography (silica gel, *i*-PrOH–H_2O–NH_4OH, 70:20:10) to give **21** (12.7 mg, 66%) as a white amorphous solid. For the sake of NMR data comparison, a sample of **21** was acidified by addition of 1 M aq HCl soln to the free base in soln in MeOH at 0 °C; $R_f = 0.35$ (*i*-PrOH–H_2O–NH_4OH, 70:20:10).

$[\alpha]_D^{25}$ +19 (*c* 1.3, EtOH).

^1H NMR (500 MHz, D_2O) (chlorohydrate): δ = 1.90–1.97 (m, 1 H), 2.85 (t, $^3J = 11.9$ Hz, 1 H), 2.95 (t, $^3J = 12.8$ Hz, 1 H), 3.48–3.52 (m, 3 H), 3.71–3.85 (m, 3 H).

^1H NMR (125 MHz, D_2O) (chlorohydrate): δ = 43.8, 47.6, 49.4, 61.8, 71.3, 73.9.

MS (ESI^+): *m*/*z* (%) = 148 (100) $[M + H]^+$.

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(28) *Crystal data for* **12**: $C_{14}H_{16}N_2O$, M = 228.29, orthorhombic, $P2$ (1)2 (1)2 (1), a = 4.8314 (4) Å, b = 9.9404 (8) Å, c = 25.912 (2) Å, $\alpha = \beta = \gamma = 90°$, V = 1244.44 (18) Å^3, Z = 4, ρ_{calcd} = 1.218 mg/m^3, $F(000)$ = 488, λ = 0.71073 Å, T = 173 (2) K, crystal size 0.70 × 0.10 × 0.10 mm^3, 4458 reflections collected (2407 independent, R_{int} = 0.0408), $R1$ [$I > 2\sigma(I)$] = 0.0510, $wR2$ [all data] = 0.1115, largest diff. peak and hole: 0.202 and –0.164 e·Å^{-3}. CCDC 722378 contains the supplementary crystallographic data for **12**. It can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

(29) *Crystal data for* **16**: $C_{15}H_{19}NO_3$, M = 261.31, monoclinic, $P2$ (1), a = 9.3250 (2) Å, b = 4.80970 (10) Å, c = 15.5678 (4) Å, $\alpha = \gamma = 90°$, β = 102.439 (2)°, V = 681.83 (3) Å^3, Z = 2, ρ_{calcd} = 1.273 mg/m^3, $F(000)$ = 280, λ = 0.71073 Å, T = 173 (2) K, crystal size 0.8 × 0.10 × 0.10 mm^3, 10163 reflections collected (3246 independent, R_{int} = 0.0214), $R1$ [$I > 2\sigma(I)$] = 0.0476, $wR2$ [all data] = 0.1289, largest diff. peak and hole: 0.252 and –0.172 e·Å^{-3}. CCDC 722379 contains the supplementary crystallographic data for **16**. It can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

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