Tetrahedron 70 (2014) 7207–7220

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and reduction reactions of pyridones and 5-acyl-2-methoxypyridines

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ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 9 June 2014
Accepted 13 June 2014
Available online 19 June 2014

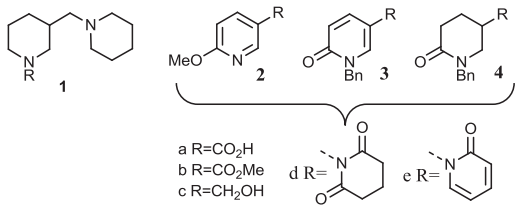
Keywords:
Asymmetric synthesis
Heterocycle reduction
Pyridone
Methoxypyridine
N-containing heterocycles
Ketone reduction

ABSTRACT

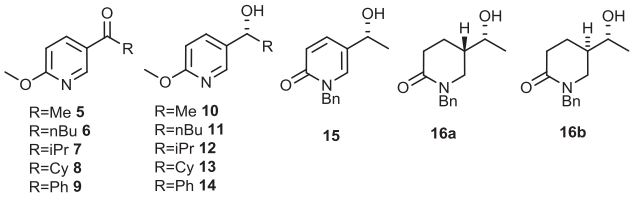
The synthesis of a series of pyridones, from their 2-hydroxypyridine or 2-methoxypyridine precursors, is described, along with studies into their reductions to saturated heterocycles. A number of 5-acylpyridones were prepared and were evaluated as substrates for asymmetric transfer hydrogenation prior to conversion to saturated heterocycles. The enantioselective reduction of 5-acetyl-1-benzylpyrimidine-2,4(1*H*,3*H*)-dione is also described.

1. Introduction

The full or partial reduction of heterocyclic substrates provides a route to numerous target molecules, several of which are represented in pharmaceuticals, fine chemicals and materials. In this paper we describe the development of routes to a series of substituted N-containing heterocycles, including alkoxypyridines, *N*-benzyl pyridines and acyl pyridines, together with a racemic and asymmetric reduction of the latter.



As part of an ongoing project, we were interested in developing routes to *bis*-piperidine (general structure **1**) and close derivatives.[1] We envisaged that these could be prepared from 2-methoxypyridines **2a**–**e**, via **3a**–**e**, to the saturated products **4a**–**e**. In addition, the conversion of 5-acyl-2-methoxypyridines **5**–**9** to alcohols **10**–**14** by asymmetric transfer hydrogenation (ATH) was investigated. The subsequent formation of **15** and **16a**/**b** serves to illustrate the synthetic value of the latter transformation.



2. Results and discussion

We initially studied the reductions of a number of 5-substituted pyridones. Acid **3a** was prepared by the reaction of 6-hydroxynicotinic acid with benzyl bromide in the presence of KOH in methanol. Esterification of **2a** with H_2SO_4 and methanol (72% yield, Scheme 1) gave **2b**, which underwent reaction with benzyl bromide in the presence of K_2CO_3 to give methyl *N*-benzylpyridone-5-carboxylate **3b** in 29% yield.[2]

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http://dx.doi.org/10.1016/j.tet.2014.06.046
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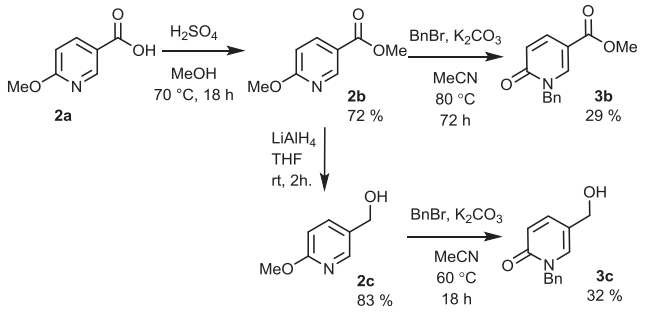
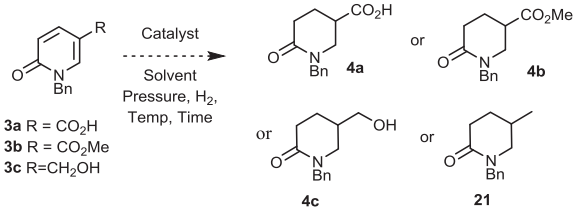


Scheme 1. Synthesis of pyridones **3b** and **3c**.

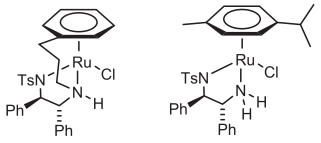
Pyridone **3c** was prepared via reduction of ester **2b** with $LiAlH_4$ to give pyridine **2c** followed by reaction with benzyl bromide (Scheme 1).[2] The reduction reactions are summarised in Table 1. Pyridone **3a** was reduced with Pd/C under forcing conditions

Table 1
Reduction of pyridones **3c**, **3a** and **3b**



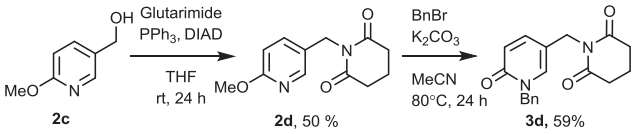
Entry	Pyridone[a]	Cat.	mol %	T/°C)	t/h	P/bar	Conv./%
1	**3a**	Pd/C	10	30	20	25	99
2	**3a**	(*R*)-**17**	5	30	20	20	0
3	**3a**	(*R*,*R*)-**18**	5	30	20	20	0
4	**3a**[b]	(*R*,*R*)-**19**	2	30	72	N/A	0
5	**3b**	Pd/C	10	40	24	1	29[c]
6	**3b**	(*R*,*R*)-**18**	3	40	120	40	75
7	**3c**	$Pd/BaSO_4$	10	rt	18	5	71
8	**3c**	PtO_2	10	rt	18	5	65

[a] Reactions with **3a**: 30 mg scale. Reactions with **3b**: 40 mg scale.
[b] 50 mg scale.
[c] Isolated yield.



(25 bar hydrogen) to give lactam **4a** in near quantitative yield (entry 1). No reduction was observed with the catalysts (*R*)-[Ru(BINAP)$(OAc)_2$][3] (*R*)-**17** or [Rh(I)((*R*,*R*)-EtDuPhos)][4] (*R*,*R*)-**18** under a variety of conditions. Transfer hydrogenation catalyst (*R*,*R*)-**19** (a catalyst related to the Noyori catalyst **20**)[5] was tested but with no success (entry 4). Pyridone **3b** was readily reduced with Pd/C under a balloon of hydrogen to give lactam **4b** (entry 5). The use of (*R*,*R*)-**18** resulted in 75% conversion to racemic **4b** (entry 6). When Pd/$BaSO_4$ was used to reduce **3c**, the fully hydrogenated and C–O cleaved product **21** was obtained in 71% yield (entry 7). The hydrogenation of the pyridone group was achieved with PdO_2 however, resulting in formation of the desired lactam **4c** in 65% yield (entry 8). An asymmetric synthesis of a compound related to **4c** (95% ee) has been reported by Park et al., via the phase transfer organo-catalytic mono-alkylation of a malonamide.[6]

An approach to the natural product cytisine[7] was envisaged through the asymmetric hydrogenation of pyridone **3d**, since the product, lactam **4d**, may be converted to the cytisine precursor lactam **4e**[8] through the three step method detailed by Sivaguru et al.[9] Imide **3d** was prepared via the pyridine **2d**, formed by the coupling of pyridine **2c** with glutarimide under Mitsunobu conditions[10] (Scheme 2). Pyridine **2d** was then converted to **3d** upon treatment with benzyl bromide in 59% yield as a colourless powder. An X-ray crystallographic analysis confirmed the structure (Fig. 1), and that alkylation had occurred exclusively on *N*(8).[11]



Scheme 2. Synthesis of **3d**.

The hydrogenation of pyridone **3d** was carried out using a range of homogeneous and heterogeneous catalysts (Table 2). Using platinum oxide in ethanol for 6 h at room temperature, the desired lactam **4d** was formed in 100% conversion (entry 1).

Conducting the reduction at an elevated pressure of 5 bar at room temperature for 18 h was reproducibly found to give the desired product **4d** in high yield (entry 2). Asymmetric hydrogenation of pyridines is generally known to be challenging,[12,13] however some attempts were made. Partial conversion to lactam **4d** was observed using (*R*,*R*)-**18** following a prolonged reaction time of 72 h at 40 °C under 30 bar of hydrogen (entry 3) however the product was racemic. (*R*)-**17** was remarkably active, resulting in 100% conversion to **4d** after 6 h at 30 °C (50 bar hydrogen) however again the sample was found to be racemic. The absence of any enantioselectivity may be due to the tautomeric forms of the structure.[14] With lactam (±)-**4d** in hand, a racemic formal synthesis of cytisine was completed (Scheme 3).[9] Treatment of (±)-**4d** with sodium borohydride and cerium chloride gave α-hydroxylactam **22** in 70% yield as an inseparable mixture of diastereomers, which were not purified.

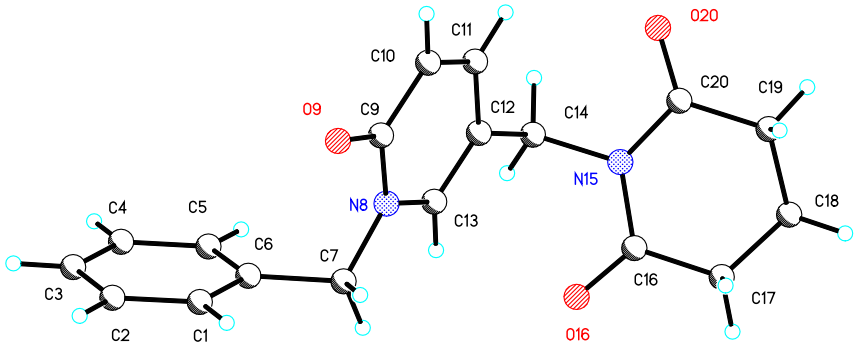
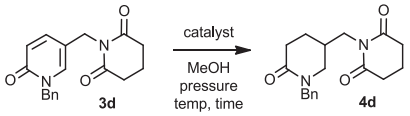


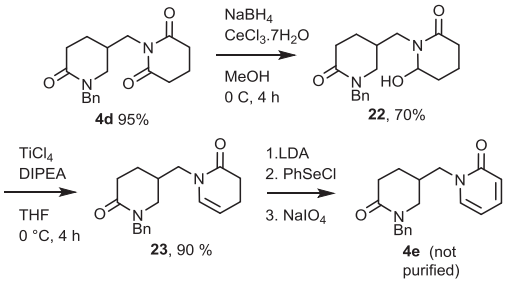
Fig. 1. X-ray crystal structure of **3d**.

Table 2
Asymmetric hydrogenation of pyridone **3d**



Entry	Cat.	Scale/mg	mol %	*T*/°C	*t*/h	*P*/bar	Conv./%
1[a]	PtO_2	40	10	30	6	1[b]	100
2[a]	PtO_2	1140	5	rt	18	5	95[c]
3	(*R*,*R*)-**18**	30	5	40	72	30	54[d]
4	(*R*)-**17**	20	5	30	6	50	100[d]

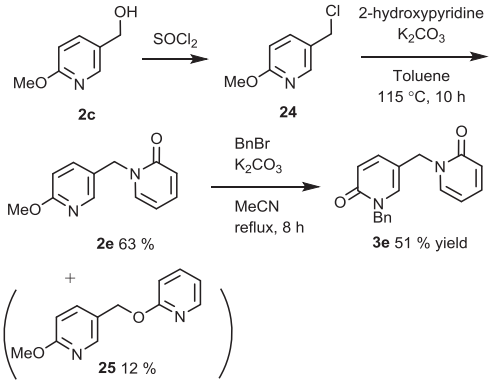
[a] EtOH as solvent.
[b] Under a balloon of hydrogen.
[c] Isolated yield.
[d] The product was racemic.



Scheme 3. Conversion of **3d** to cytisine precursor **4e**.

Treatment of α-hydroxylactam **22** with titanium chloride and DIPEA mediated the formation of the enamide **23**.[15] Oxidation was achieved by treatment of the lithium enolate of **23** (formed with LDA) with PhSeCl at −78 °C followed by oxidation with $NaIO_4$ in a solution of THF:MeOH:H_2O (18:6:2), resulting in formation of a sample containing a mixture of the desired pyridone **4e** and an unidentified product.

Reaction of chloride **24** (formed from **2c** using thionyl chloride) with 2-hydroxypyridine and K_2CO_3 in toluene at 115 °C for 10 h, successfully gave methoxypyridine **2e** in 63% yield as the major isomer, alongside the *O*-substituted isomer, **25**, which was isolated in 12% yield (Scheme 4). Longer reaction times (18 h) resulted in formation of only traces of **25**.



Scheme 4. Synthesis of **3e**.

Methoxypyridine **2e**, readily underwent alkylation with benzyl bromide and K_2CO_3 in acetonitrile at 80 °C for 8 h to give pyridone **3e** in 51% yield as a colourless powder, following recrystallisation from ethanol (Scheme 4). An X-ray diffraction solution served to confirm the structure (Fig. 2).[11]

Pyridone **3e** was reduced with Pd/C under a balloon of hydrogen at 30 °C to give lactam **26** in 90% conversion after 17 h (Table 3, entry 1). Preferably (due to ease of subsequent purification) reduction was achieved with PtO_2 under a balloon of hydrogen at 30 °C. At a larger scale of 644 mg, 90% conversion of the starting material was achieved (as determined by ^{1}H NMR) after 20 h, providing pure lactam **26** in 75% yield following silica gel chromatography (entry 2). Treatment of **22** with Et_3SiH also resulted in its conversion to lactam **26**. Pyridone **3e** underwent partial conversion to lactam **26** with (*R*,*R*)-**18** following a reaction time of 18 h at room temperature under 20 bar hydrogen (entry 3), however the product was racemic.

The racemic synthesis of *bis*-piperidine was completed by treatment of **26** with $LiAlH_4$ in THF (0 °C to rt) to give **1** (R=Bn) in 37% yield following careful purification. Alternatively, reduction with $Ru_3(CO)_{12}$ (2 mol %) and Et_3SiH (7 equiv) in toluene at 100 °C for 18 h resulted a clean crude reaction (^{1}H NMR),[16] to give product **1** (R=Bn) in 57% yield. Debenzylation of *bis*-piperidine **1** (R=Bn) was achieved with $Pd(OH)_2$ under an atmosphere of hydrogen. A sample containing the free amine was isolated through the use of an Isolute-XL SCX amine scavenger thiol resin. The crude reaction mixture was conveniently passed through the resin, which was then washed with solvent to remove non basic impurities. A sample containing the amine **1** (R=H) was obtained showing only a trace of the starting material by ^{1}H NMR.

The asymmetric transfer hydrogenation (ATH) of pyridyl methyl ketone **5**, to **10**, followed by conversion to the corresponding pyridone, **15** and then hydrogenation would be predicted to lead to the formation of two enantiomerically enriched diastereomers, **16a** and **16b**,[17] (Scheme 5) An alternative approach to **15** would be through the formation of **27** followed by reduction.

In principle, lactams **16a**/**b** may be subsequently converted to methylated derivatives of the cytisine precursor (lactam **4e**) through substitution with 2-hydroxypyridine.[7] However, optically pure 5-substituted lactams are in themselves potentially useful in other applications.[1,18] The synthesis of ketones **5** and **27** was achieved via the alkylation of Weinreb amide **28**,[19] which was obtained in 68% yield from the ester **2b**. Direct alkylation with methyl magnesium chloride gave the pyridyl methyl ketone **5** in 61% yield. The synthesis of pyridone methyl ketone **27** was achieved via treatment of **5** with benzyl bromide in acetonitrile at 80 °C (Scheme 6).

The ATH of pyridyl ketones, similar in structure to **5**, has been reported.[20,21] Ikariya described the reduction of a range of pyridyl alkyl ketones in high enantioselectivity with (*S*,*S*)-Ru(TsDPEN), (*S*,*S*)-**20**. Pyridyl alcohols (*S*)-**29**, (*S*)-**30** and (*S*)-**31** were obtained in 93%, 98% and 92% ee, respectively (Fig. 3).[21] Enantioface selection during these reductions was comparable to the reduction of aromatic ketones.

The ATH of ketones **5** and **27** was carried out with the catalyst (*R*,*R*)**19**. Neat formic acid/triethylamine (FA/TEA) was used as solvent at a substrate concentration of 1 M in all cases (Table 4).

Pyridyl methyl ketone **5** underwent complete conversion to alcohol, (*S*)-**10** in 82% ee (entry 1). The ee was slightly lower (75% ee) when run in methanol at room temperature (entry 2). Pyridone methyl ketone **27** underwent complete conversion to (*R*)-**15** in only 42% ee (entry 3). The absolute configuration of the alcohol product obtained from reduction of ketone **5** with (*S*,*S*)-**19** is in accordance with what would be expected through the standard reduction mechanism of aryl methyl ketones, such as acetophenone.[5] Pyridone ketone **27** appeared to also follow this trend; the use of the (*R*,*R*) catalyst resulted in formation of the (*R*) alcohol.

A further series of alkyl derivatives **6**–**9** was studied; each was directly obtained via alkylation of Weinreb amide **28**.[19] Neat FA/TEA was used as solvent at a concentration of 2 M for these ATH studies, together with **5** (Table 5).

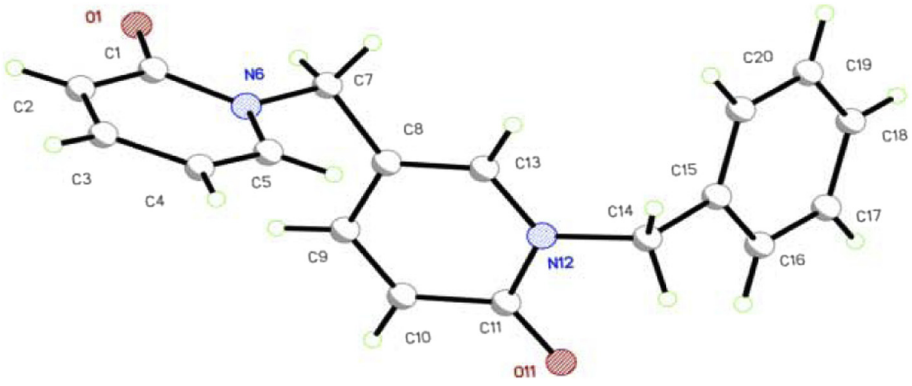
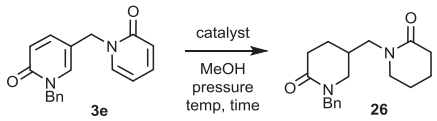


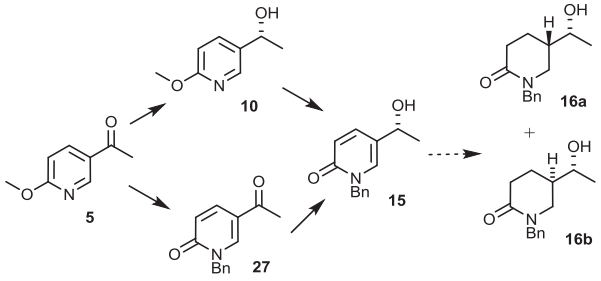
Fig. 2. X-ray crystallographic structure of **3e**.

Table 3
Asymmetric hydrogenation of pyridone **3e**

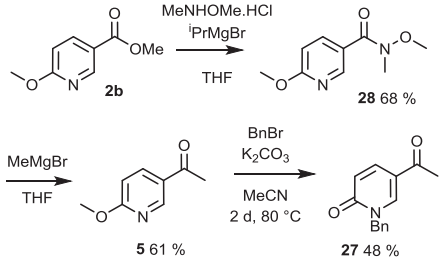


Entry	Cat.	Scale/mg	mol %	*T*/°C	*t*/h	*P*/bar	Conv./%
1	Pd/C	110	5	30	17	1[b]	90
2[a]	PtO_2	644	5	30	20	1[b]	90 (75[c])
3	(*R*,*R*)-**73**	30	5	rt	18	20	40[c]

[a] DCM used as solvent.
[b] Run under a balloon of hydrogen.
[c] The sample was racemic.



Scheme 5. Synthesis of diastereomers **16a** and **16b**.



Scheme 6. Synthesis of ketones **5** and **27**.

The *n*-alkyl derivatives, methyl ketone **5** and *n*-butyl ketone **6** were reduced in highest enantioselectivity; 83% and 76% ee, respectively (entries 1 and 2). The secondary alkyl ketones, isopropyl ketone **7** and cyclohexyl ketone **8** were reduced in 53% and 35% ee, respectively (entries 3 and 4). In each case the products were

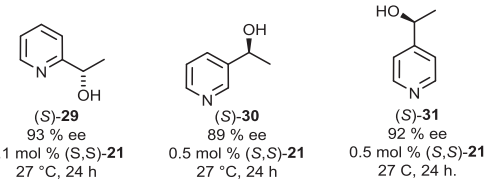
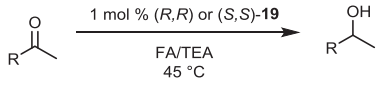


Fig. 3. Optically pure pyridyl alcohols obtained by ATH with (*S*,*S*)-**21**.[21]

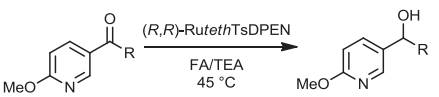
Table 4
ATH of ketones **5** and **27** with (*R*,*R*)-**19**



Entry	Ketone[a]	Cat.	*t*/h	Conv./%[d]	Prod.	ee/%
1	**5**	(*S*,*S*)	21	100	(*S*)-**10**[e]	82[b]
2	**5**	(*S*,*S*)	18	100	(*S*)-**10**	75[b,f]
3	**27**	(*R*,*R*)	20	100	(*R*)-**15**[e]	42[c]

[a] [SM]=1 M.
[b] Determined by chiral GC.
[c] Determined by chiral HPLC.
[d] Determined by ^{1}H NMR.
[e] Config. assigned by comparison of $[\alpha]_D$ values of an authentic sample.
[f] Reaction run at rt and in methanol, [SM]=0.16 M.

Table 5
ATH of ketones **5**–**9**

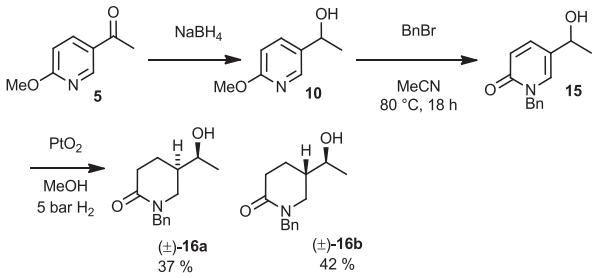


Entry	Ketone[a]	R	*t*/h[g]	Prod.	ee/%
1	**5**[b]	Methyl	21	(*R*)-**10**[h]	83[d]
2	**6**	*n*-Butyl	20	(*R*)-**11**[i]	76[d]
3	**7**	*i*-Propyl	22	(*R*)-**12**[i]	53[c]
4	**8**	Cyclohexyl	24	(*R*)-**13**[i]	35[f]
5	**9**	Phenyl	24	(−)-**14**	48[e]

[a] [SM]=2 M in FA/TEA.
[b] [SM]=1 M in FA/TEA.
[c] Determined by chiral GC.
[d] Determined by chiral GC of the acetate derivative.
[e] Determined by chiral HPLC.
[f] Determined by chiral HPLC of the acetate derivative.
[g] Completion of reaction confirmed by ^{1}H NMR.
[h] Config. confirmed by lit. optical rotation reference.
[i] Config. assigned by analogy.

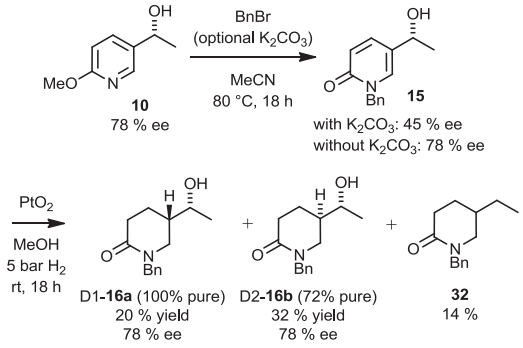
assigned the *R* configuration, in analogy with related compounds. The reduction of pyridyl phenyl ketone **9** resulted in formation of **14**[22] in 48% ee.

Following the ketone ATH results, pyridyl methyl ketone **5** was chosen for the large scale synthesis of diastereomers **16a** and **16b**, due to its relatively higher enantioselectivity during ATH. A racemic reduction of **5** was achieved with $NaBH_4$, resulting in formation of alcohol **10** in quantitative yield (Scheme 7). Alcohol **10** readily underwent alkylation with benzyl bromide and K_2CO_3 in acetonitrile at 80 °C for 24 h to give the racemic pyridone **15** in 63% yield. The hydrogenation of pyridone **15** was carried out with PtO_2 in methanol under 5 bar of hydrogen (Scheme 7) and diastereomers (in order of elution) (±)-**16a** and (±)-**16b** were obtained.



Scheme 7. Synthesis of diastereomers **16a** and **16b**.

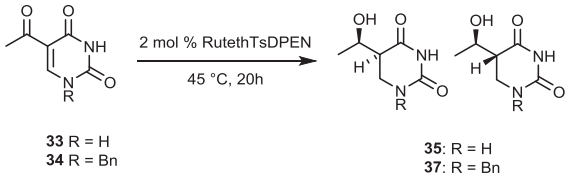
Conveniently, (±)-**16a** provided crystals, which were analysed by X-ray diffraction to confirm its structure (Fig. 4),[11] which may be described as *syn* with respect to the relative positions of the two adjacent hydrogen atoms. Hence, (±)-**16b** may be assigned as the *anti* isomer.



Scheme 8. Asymmetric synthesis of **16a** and **16b**.

and **16b** were isolated in 20% and 32% yield respectfully, alongside lactam **32**. The diastereopurities were 100% for **16a**; and 72% for **16b**, respectively and the ee of both products was 78%.

In a related investigation, the ATH of 5-acetyluracil **33** and *N*-benzyl 5-acetyluracil **34** was investigated to enable comparison with the heterocyclic methyl ketones described above. 5-Acetyluracil was benzylated by treatment with NaH in DMF.



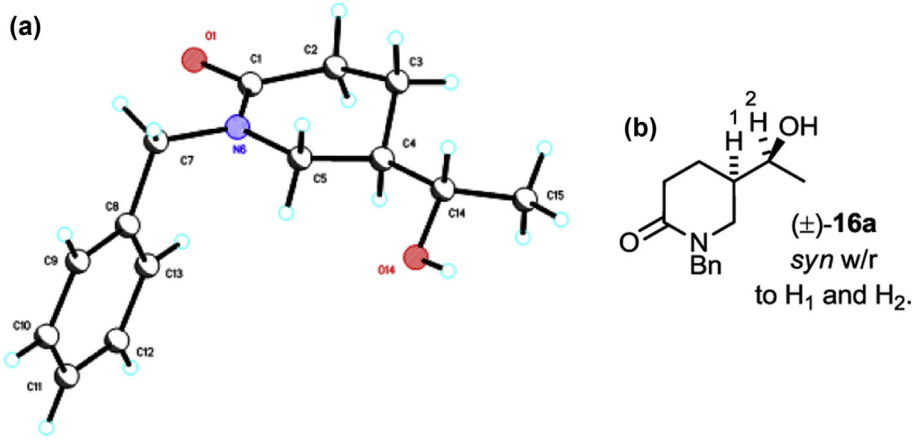


Fig. 4. a. X-ray structure of **16a**; b. corresponding schematic structure of (±)-**16a**.

The ATH of ketone **5** on a larger scale (1.0 g) gave pyridine (*R*)-**10** in 95% yield and 78% ee. Pyridine (*R*)-**10** readily underwent alkylation with benzyl bromide and K_2CO_3 in acetonitrile at 80 °C for 24 h to give the pyridone (*R*)-**15** in 71% yield (Scheme 8) however the sample suffered from loss of enantiopurity, and the ee was determined to be 45%. Repeating the experiment in the absence of K_2CO_3 resulted in formation of (*R*)-**15** in 63% yield. The ee of this sample was not directly determined, but following reduction in the next step it was found to be unchanged at 78% ee.

Hydrogenation of pyridine **15** with PtO_2 resulted in formation of alcohols **16a** and **16b**, however a relatively higher level of hydrogenolysis occurred (Scheme 8). Following purification, **16a**

Following recrystallisation from methanol, *N*-benzyl-5-acetyluracil, **34** was obtained in 39% yield as crystalline white needles; an X-ray diffraction study confirmed that alkylation had occurred exclusively on *N* (7A) (Fig. 5).[11]

The ATH of **33** was carried out with the catalyst (*R*,*R*)-**19** (Table 6). Following a reaction time of 17 h at room temperature, **34** underwent 100% conversion to inseparable diastereomers **35** in a ratio of 3.1:1 (entry 1; relative/absolute configurations and ees were not determined).

The ATH of the benzylated derivative **34** was carried out with (*R*,*R*)- and (*S*,*S*)-**19**, (*R*,*R*)-**20** and racemic TH catalyst, [(*p*-cymene) $Ru(TsCH_2CH_2NH)Cl$] **36**, the latter being used at a higher loading

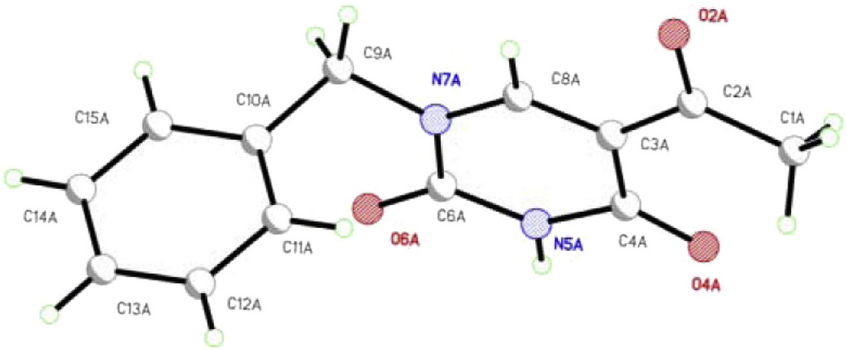
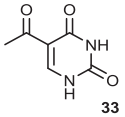
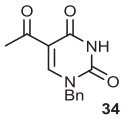


Fig. 5. X-ray crystal structure of **34**.

Table 6
ATH of **33** and **34**



33

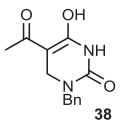


34

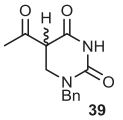
Entry	Ketone[a]	Cat.	mol %	Conv./%[b]	d.r.[b]	ee a/%[c]	ee b/%[c]
1	**33**	(*R*,*R*)-**19**	2	100	3.1:1	N/D	N/D
2	**34**	**36**	6	100	1:1	N/A	N/A
3	**34**	(*R*,*R*)-**20**	6	100	1.3:1[d]	55	36
4	**34**	(*R*,*R*)-**19**	0.8	100	4:1[d]	92	33
5	**34**	(*S*,*S*)-**19**	0.8	100	4:1[d]	86	49

N/D: not determined; N/A: not applicable.
[a] [SM]=2 M.
[b] Determined by ^{1}H NMR (the configurations were not determined and has been included for illustration purposes only).
[c] Determined by chiral HPLC.
[d] The same major diastereomer was identified by ^{1}H NMR in these reactions.

(6 mol %) to achieve full conversion within 20 h. As the diastereoisomeric ratio was determined in each case by ^{1}H NMR, it was possible to assign the chiral HPLC peaks to the correct pairs of enantiomers. This enabled the ee of each diastereoisomer of **37** to be determined. The use of catalyst (*R*,*R*)-**19** resulted in the formation of **37** in a 4:1 diastereoisomeric ratio in 92% and 33% ee, respectively (entry 4) whilst the use of catalyst (*S*,*S*)-**19** gave similar results (entry 5). The relative configuration of the diastereoisomers of **37** was not determined. The catalyst-dependent ee in each reduction suggests that conjugate reduction occurs first, resulting in formation of enol intermediate **38**, which would tautomerise to give racemic ketone **39**. The subsequent ketone reduction of ketone **39** may then proceed via a (dynamic)kinetic resolution.[23]



38



39

In conclusion, in this paper a series of pyridine-based heterocycles have been prepared and their selective reductions examined with a range of catalysts. The new methodology provides access to potentially valuable building blocks for the synthesis of saturated heterocyclic targets.

3. Experimental section

3.1. General information

All reactions unless otherwise stated were run under an atmosphere of nitrogen in glassware (round bottomed flasks or Schlenk tubes). Room temperature refers to ambient room temperature (20–22 °C), and 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminium backed silica gel 60 (F_{254}) plates, visualised using $UV_{254\ nm}$ and PMA, potassium permanganate and ninhydrin dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Fluorochem). NMR spectra were recorded on Bruker DPX-300 (300 MHz), DPX-400 (400 MHz), DRX-500 (500 MHz), AV III-600 (600 MHz) and AV II-700 (700 MHz) instruments. Chemical shifts are reported in δ units, parts per million. ^{1}H NMR spectra run in $CDCl_3$ are downfield from TMS; ^{1}H NMR spectra run in solvents other than $CDCl_3$, and all ^{13}C NMR spectra are referenced to the solvent signal. Coupling constants (*J*) are measured in Hertz. IR spectra were recorded on a Nicolet Model Avatar 320 FTIR fitted with a Specac golden gate single reflection diamond attenuated total reflection top plate. Mass spectra were recorded on a Bruker Esquire2000 (ESI) mass spectrometer. Determinations of ee were measured by HPLC or GC using Chiralcel columns supplied by Daicel. Optical rotations were measured on an AA-1000 polarimeter. Hydrogen gas (99.995% minimum) was supplied by BOC. Hydrogenations were carried out in a Parr bench-top hydrogenator (0.3 L).

3.1.1. 1-Benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, ***3a****.*[24] Under nitrogen, a solution of 6-hydroxynicotinic acid (2.10 g, 15.07 mmol) and potassium hydroxide (2.96 g, 52.74 mmol) in water (3.59 mL) and methanol (17.94 mL) was stirred at 70 °C for 5 min before benzyl bromide (3.58 mL, 5.15 g, 30.13 mmol) was added. The mixture was stirred at 70 °C for 90 min before the reaction was cooled to room temperature concentrated under reduced pressure. The resulting residue was diluted with water (10 mL) and washed diethyl ether (2×10 mL). The aqueous phase was acidified to pH 1 with HCl (2 M) and the resulting white precipitate was washed with water and dried under reduced pressure to give the crude product (2.68 g) as a white solid. A portion of the crude product (0.290 g) was purified by preparative reverse phase HPLC (Phenomenex Gemini-NX axia Prep C_{18} OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Following concentration under reduced pressure, product, **3a** (0.210 g, 0.916 mmol) was obtained as a white powder; Mp 210–214 °C; (found (ESI): M^++H, 230.0807. $C_{13}H_{12}NO_3$ requires M, 230.0812); ν_{max} 3325, 1708, 1638, 1568, 1539, 1497, 727, 692 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.86 (1H, br s, O*H*), 8.56 (1H, d, *J* 2.5, H_3), 7.80 (1H, dd, *J* 9.5, 2.5, H_2), 7.39–7.24 (5H, m, Ar*H*), 6.46 (1H, d, *J* 9.5, H_1), 5.20 (2H, s, CH_2); δ_C (101 MHz, DMSO) 165.2, 161.5, 149.3, 138.9, 136.8, 128.6, 127.7, 127.7, 118.9, 109.6, 51.5; *m*/*z* (ESI) 229.9 (M^+−1).

3.1.2. Methyl 6-methoxynicotinate, ***2b****.*[25] A suspension of 6-methoxynicotinic acid **2a** (2.90 g, 18.94 mmol) in methanol

(28.0 mL) and sulfuric acid (16 M, 1.1 mL, 20.64 mmol) was stirred at 80 °C for 16 h before the mixture was allowed to cool. The mixture was neutralised by careful addition of sodium bicarbonate. Following concentration under reduced pressure, water (20 mL) and aqueous sodium bicarbonate (10 mL) were added. Following extraction with DCM (3×50 mL), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the product **2b** (2.480 g, 14.84 mmol, 72%) as a white powder; (Found: C, 57.11; H, 5.36; N, 8.30. $C_8H_9NO_3$ requires C, 57.48; H, 5.43; N, 8.38%); ν_{max} 2954, 1720, 1603, 1568, 1604, 1496, 783, 730 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.83 (1H, s, H_3), 8.14 (1H, d, *J* 8.7, H_2), 6.76 (1H, d, *J* 8.7, H_1), 4.00 (3H, s, CH_3), 3.91 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 167.0, 150.2, 143.4, 139.9, 119.8, 110.8, 54.1, 52.2; δ_C (101 MHz, DMSO) 162.1, 141.3, 132.5, 119.7, 118.9, 59.7 (two peaks); *m*/*z* (ESI) 168.1 (M^++1).

3.1.3. Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate, ***3b***.[26] A mixture of benzyl bromide (4.40 mL, 6.34 g, 37.05 mmol), methyl 6-methoxynicotinate **2b** (3.00 g, 17.96 mmol) and potassium carbonate (4.96 g, 35.89 mmol) in dry acetonitrile (72 mL) was stirred at 80 °C for 48 h. The mixture was filtered and concentrated under reduced pressure and purified by column chromatography (ethyl acetate–hexane 1:1) to give product **3b** (1.25 g, 5.14 mmol, 29% yield) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 8.18 (1H, d, *J* 2.4, H_3), 7.83 (1H, dd, *J* 9.6, 2.4, H_2), 7.40–7.29 (5H, m, Ar*H*), 6.58 (1H, d, *J* 9.6, H_1), 5.17 (2H, s, CH_2), 3.83 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) 164.6, 162.3, 142.6, 138.4, 135.5, 129.0, 128.3, 128.1, 119.9, 109.9, 52.7, 52.0.

3.1.4. (6-Methoxypyridin-3-yl)methanol, ***2c***.[27] Under nitrogen, a suspension of lithium aluminium hydride solution in THF (1 M, 6.58 mL, 6.58 mmol) in THF (3.39 mL) was stirred at 0 °C for 5 min. Methyl 6-methoxynicotinate **2b** (1.0 g, 5.98 mmol) was added portionwise and the mixture was stirred for 10 m. The suspension was allowed to warm to room temperature and stirred for 2 h before the solution was cooled to 0 °C. The suspension was carefully quenched with water (0.04 mL), 15% NaOH (0.04 mL) followed by water (0.12 mL). The resulting precipitate was filtered with Celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give product **2c** (0.690 g, 4.96 mmol, 83% yield) as a yellow oil; (found (ESI): M^++H, 140.0711. $C_7H_{10}NO_2$ requires M, 140.0706); ν_{max} 3298, 2945, 1608, 1573, 1492 cm^{-1}; δ_H (400 MHz, DMSO) 8.07 (1H, s, H_3), 7.64 (1H, d, *J* 8.5, H_2), 6.77 (1H, d, *J* 8.5, H_1), 5.11 (1H, t, *J* 5.6, O*H*), 4.43 (2H, d, *J* 5.6, H_4), 3.83 (3H, s, CH_3); δ_C (101 MHz, DMSO) 162.7, 144.00, 138.3, 130.6, 109.9, 60.2, 52.9; *m*/*z* (ESI) 139.8 (M^++1).

3.1.5. 1-Benzyl-5-(hydroxymethyl)pyridin-2(1H)-one, ***3c***.[28] A mixture of benzyl bromide (0.56 mL, 0.81 g, 4.71 mmol), 6-methoxypyridin-3-yl)methanol **2c** (1.00 g, 7.19 mmol) and potassium carbonate (1.30 g, 9.40 mmol) in dry acetonitrile (17 mL) was stirred at 60 °C for 18 h. The mixture was filtered, concentrated under reduced pressure and purified by column chromatography (methanol–ethyl acetate 5:95), to give product **3c** (0.500 g, 2.32 mmol, 32% yield) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 7.38–7.18 (7H, m, Ar*H*, H_3, H_1), 6.50 (1H, d, *J* 9.2, H_2), 5.03 (2H, s, PhCH_2), 4.33 (2H, d, *J* 5.5, H_4), 4.00–3.94 (1H, m, O*H*); δ_C (75 MHz, $CDCl_3$) 162.3, 140.1, 136.1, 135.1, 128.8, 128.0, 127.9, 120.6, 120.1, 61.3, 52.0. The *O*-benzylation product was not isolated from the reaction mixture. An NOE ^1H NMR experiment supported the structural assignment: irradiation of the CH_2Ph protons (5.03 ppm) resulted in the excitation of proton H_3 only.

3.1.6. General procedure A—alkene hydrogenation with hydrogen balloons. Under nitrogen, the alkene (1.00 mmol) was loaded into a round bottomed flask containing a magnetic stirrer and the specified solvent was added. The heterogeneous catalyst (at the specified catalytic loading) was carefully added before the flask was evacuated with hydrogen and a balloon of hydrogen was attached. The solution was stirred vigorously for the specified time and temperature before the catalyst was removed by filtration with Celite. Following solvent removal under reduced pressure the product was obtained, following purified by column chromatography (where applicable).

3.1.7. General procedure B—alkene hydrogenation in a hydrogenator. The alkene (1 mmol) and catalyst (at the specified catalytic loading) were added to a small glass hydrogenation vial. A suba seal was attached and the contents were flushed with nitrogen for 10 min before the dry solvent (as specified) was added. The suba seal was removed and the vial was quickly placed into the hydrogenation apparatus. The hydrogenator was filled with hydrogen to the appropriate pressure before the pressure was nearly completely released. The hydrogenator was then filled again with hydrogen and the pressure was released. This fill release cycle carried out for a total of three times to ensure the vessel was sufficiently charged with hydrogen at the stated pressure. A magnetic stirrer box was placed under the hydrogenator to enable stirring for the specified time before the hydrogen was carefully released and the apparatus was disassembled. Following concentration under reduced pressure, the product was obtained, following purified by column chromatography (where applicable).

3.1.8. General procedure for the ATH of ketones. Under nitrogen, FA/TEA (5:2, concentration w/r to ketone as specified) was added to a mixture of the ketone (1 mmol) and [Ru(*teth*-TsDPEN)Cl] **19** (1 mol %). The solution was left stirring at 45 °C for the specified time before the product was obtained, following removal of the catalyst (the reaction mixture directly through a plug of silica gel using ethyl acetate–petroleum ether (1:1) as eluent). Conversion was primarily determined by ^1H NMR. Ee was determined by chiral GC or HPLC via direct analysis, or alternatively indirectly via acetate derivatisation of the product.

3.1.9. General procedure for the preparation of acetate derivatives. Where required, acetate derivatives of alcohols were prepared using the following general procedure; a solution of acetic anhydride (1 drop), alcohol (10 mg) and DMAP (1 mg) in DCM (1 mL) was stirred at room temperature for 18 h. Following concentration under reduced pressure, the product was obtained following purification by column chromatography and used directly in GC or HPLC analysis.

3.1.10. General procedure for the formation of racemic standards: reduction of ketones with $NaBH_4$. Racemic standards were prepared (unless otherwise specified) via reduction with $NaBH_4$, using the following procedure: Under nitrogen, $NaBH_4$ (1.1 mmol) was added to a solution of the ketone (1 mmol) in methanol and the solution was stirred at room temperature until the reaction reached completion. Saturated aqueous hydrogen carbonate was then added. Following extraction with DCM (3×5 mL) the organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (ethyl acetate–petroleum ether 1:1), to give the product. The sample was directly used as a racemic standard for chiral GC or HPLC analysis. In some cases this was not appropriate. Instead, two samples of the alcohol formed from opposite isomers of the catalyst were combined.

3.1.11. 1-Benzyl-6-oxopiperidine-3-carboxylic acid, (±)- ***4a***.[29] This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, **3a** (30 mg, 0.131 mmol) and palladium on carbon

(10% w/w, 13 mg, 1.22×10^{-2} mmol) in methanol (1 mL), following a reaction time of 20 h, at room temperature and 25 bar. Following concentration under reduced pressure, (±)-**4a** (30 mg, 0.129 mmol, 99% yield) was obtained as a colourless oil. δ_H (400 MHz, $CDCl_3$) 10.40 (1H, br s, O*H*), 7.28–7.10 (5H, m, Ar*H*), 4.68 (1H, d, *J* 14.7, CH_2), 4.36 (1H, d, *J* 14.7, CH_2), 3.47–3.25 (2H, m, H_4), 2.75–2.62 (1H, m, H_3), 2.56 (1H, dt, *J* 17.9, 4.5, H_{1A}), 2.42 (1H, dt, *J* 17.9, 6.5, H_{1B}), 2.11–1.99 (1H, m, H_{2A}), 1.98–1.82 (1H, m, H_{2B}); δ_C (101 MHz, $CDCl_3$) 176.9, 170.4, 136.1, 128.6, 128.1, 127.6, 50.6, 48.0, 38.8, 31.5, 25.5.

*3.1.12. Methyl 1-benzyl-6-oxopiperidine-3-carboxylate, (±)-**4b**.*[29] This compound was prepared following the general procedure for alkene hydrogenation, using methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate, **3b** (100 mg, 0.411 mmol) and palladium on carbon (5% w/w, 88 mg, 4.13×10^{-2} mmol) in methanol (1 mL) following a reaction time of 1 d, at 40 °C under a balloon of hydrogen. Following solvent removal and purification by column chromatography (ethyl acetate–hexane 9:1), the product (±)-**4b** (30 mg, 0.121 mmol, 29% yield) was obtained as colourless oil; δ_H (400 MHz, $CDCl_3$) 7.30–7.14 (5H, m, Ar*H*), 4.62 (1H, d, *J* 14.6, CH_2), 4.46 (1H, d, *J* 14.6, CH_2), 3.59 (3H, s, CH_3), 3.42–3.28 (2H, m, H_4), 2.78–2.65 (1H, m, H_3), 2.54 (1H, dt, *J* 17.8, 5.3, H_{1A}), 2.47–2.35 (1H, m, H_{1B}), 2.13–2.02 (1H, m, H_{2A}), 2.00–1.89 (1H, m, H_{2B}); δ_C (75 MHz, $CDCl_3$) 172.5, 168.8, 136.7, 128.5, 128.0, 127.4, 52.1, 50.1, 47.9, 39.0, 30.7, 23.9; Enantiomeric separation was achieved by HPLC analysis (Chiralpak IA, 4.6 mm×250 mm, hexane:IPA 85:15, 1 mL/min, *T*=30 °C, 13.3 min, 14.9 min).

*3.1.13. 1-Benzyl-3-hydroxymethyl 6-oxopiperidine, (±)-**4c**.*[30] This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-5-(hydroxymethyl)pyridin-2(1*H*)-one **3c** (30 mg, 0.139 mmol) and platinum oxide (3 mg, 1.32×10^{-2} mmol) in methanol (1 mL), following a reaction time of 18 h at room temperature under 5 bar of hydrogen. Following concentration under reduced pressure, (±)-**4c** (20 mg, 0.091 mmol, 66% yield) was obtained as an oil; δ_H (400 MHz, $CDCl_3$) 7.37–7.19 (5H, m, Ar*H*), 4.60 (2H, s, CH_2Ph), 3.64–3.54 (1H, m, H_{4A}), 3.53–3.45 (1H, m, H_{4B}), 3.32 (1H, ddd, *J* 12.1, 5.1, 1.8, H_{5A}), 3.02 (1H, dd, *J* 12.1, 10.0, H_{5B}), 2.57 (1H, ddd, *J* 17.8, 6.3, 3.5, H_{1A}), 2.44 (1H, ddd, *J* 17.8, 11.1, 6.5, H_{1B}), 2.11–1.97 (1H, m, H_3), 1.94–1.85 (1H, m, H_{2A}), 1.53 (1H, dtd, *J* 13.1, 11.1, 6.3, H_{2B}). A signal attributable to O*H* was not observed; δ_C (75 MHz, $CDCl_3$) 170.0, 136.9, 128.5, 127.9, 127.3, 64.3, 50.3, 49.78, 36.3, 31.2, 23.8.

*3.1.14. 1-Benzyl-5-methylpiperidin-2-one, (±)-**21**.* This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-5-(hydroxymethyl)pyridin-2(1*H*)-one **3c** (30 mg, 0.139 mmol) and palladium on barium sulfate (5% w/w, 30 mg, 1.41×10^{-2} mmol) in methanol (1 mL), following a reaction time of 18 h at room temperature and 5 bar of hydrogen. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate–hexane 8:2), (±)-**21** (20 mg, 0.098 mmol, 71% yield) was obtained as an oil; (found (ESI): M^++Na, 226.1203. $C_{13}H_{17}NNaO$ requires M, 226.1202); ν_{max} 2955, 2926, 1619, 1493 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.36 (5H, m, Ar*H*), 4.67 (1H, d, *J* 14.6, CH_2), 4.50 (1H, d, *J* 14.6, CH_2), 3.16 (1H, ddd, *J* 12.0, 5.1, 2.0, H_{4A}), 2.83 (1H, dd, *J* 12.0, 10.4, H_{4B}), 2.55 (1H, ddd, *J* 17.7, 6.0, 3.0, H_{1A}), 2.44 (1H, ddd, *J* 17.7, 11.5, 6.3, H_{1B}), 1.88–1.99 (1H, m, H_3), 1.84 (1H, dddd, *J* 13.2, 6.3, 3.0, 2.0, H_{2A}), 1.47 (1H, dtd, *J* 13.2, 11.5, 6.0, H_{2B}), 0.95 (3H, d, *J* 6.5, H_5) δ_C (100 MHz, $CDCl_3$) 169.8, 137.3, 129.0, 128.6, 127.3, 60.3, 54.2, 31.7, 29.5, 29.0, 18.6; *m*/*z* (ESI) 203.8 (M^++1).

*3.1.15. 1-((6-Methoxypyridin-3-yl)methyl)piperidine-2,6-dione, **2d**.* Under nitrogen, a solution of triphenylphosphine (6.73 g, 25.66 mmol), (6-methoxypyridin-3-yl)methanol **2c** (3.50 g, 25.17 mmol) and glutarimide (2.90 g, 25.64 mmol) in THF (75 mL) was stirred at 0 °C for 5 min. A solution of diisopropyl azodicarboxylate (4.99 mL, 5.19 g, 25.66 mmol) in THF (50 mL) was added dropwise over 1 h at 0 °C and the solution was allowed to warm to room temperature and stirred for 18 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate–hexane 1:1), product **2d** (3.03 g, 12.94 mmol, 50% yield) was obtained as a colourless oil; (found (ESI): M^++H, 235.10750. $C_{12}H_{15}N_2O_3$ requires M, 235.10772); ν_{max} 2966, 1716, 1666, 1607, 1572, 1491, 1171 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.22 (1H, d, *J* 2.5, H_3), 7.63 (1H, dd, *J* 8.5, 2.5, H_2), 6.67 (1H, d, *J* 8.5, H_1), 4.87 (2H, s, H_4), 3.90 (3H, s, CH_3), 2.65 (4H, t, *J* 6.7, H_5), 1.92 (2H, quin, *J* 6.7, H_6); δ_C (101 MHz, DMSO) 172.7, 162.7, 146.2, 139.0, 126.2, 110.0, 53.00, 52.9, 32.0, 16.4; *m*/*z* (ESI) 234.97 (M^++1).

*3.1.16. 1-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]piperidine-2,6-dione, **3d**.* Under nitrogen, a mixture of benzyl bromide (1.02 mL, 1.47 g, 8.59 mmol), 1-((6-methoxypyridin-3-yl)methyl) piperidine-2,6-dione, **2d** (1.82 g, 7.77 mmol) and potassium carbonate (2.15 g, 15.56 mmol) in dry acetonitrile (31 mL) was stirred at 80 °C for 24 h before the solution was filtered. The resulting filtrate was concentrated under reduced pressure followed by recrystallisation (ethanol), to give product **3d** (1.42 g, 4.58 mmol, 59% yield) as a white powder; Mp 154–156 °C; (found (ESI): M^++Na, 333.1205. $C_{18}H_{18}N_2NaO_3$ requires M, 333.1210); ν_{max} 2926, 1722, 1666, 1601, 1537, 1496, 1134, 730, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.49–7.41 (2H, m, H_2, H_3), 7.37–7.25 (5H, m, Ar*H*), 6.52 (1H, d, *J* 9.3, H_1), 5.10 (2H, s, CH_2), 4.62 (2H, s, CH_2), 2.64 (4H, t, *J* 6.4, H_5), 1.93 (2H, quin, *J* 6.4, H_6); δ_C (101 MHz, $CDCl_3$) 172.4, 161.9, 141.5, 138.6, 136.2, 128.7, 128.1, 127.9, 120.6, 115.4, 52.0, 39.2, 32.6, 16.9; *m*/*z* (ESI) 333.1 (M^++23). Further recrystallisation (EtOH) provided crystals of sufficient quality for X-diffraction, enabling confirmation of the structure.[11]

*3.1.17. 1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]piperidine-2,6-dione, (±)-**4d**.* This compound was prepared following the general procedure for alkene hydrogenation, using 1-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-methyl]-piperidine-2,6-dione, **3d** (1.14 g, 3.68 mmol) and platinum oxide (42 mg, 0.185 mmol) following a reaction time of 20 h, at 30 °C. Following concentration under reduced pressure, product (±)-**4d** (1.10 g, 3.50 mmol, 95% yield) was obtained as colourless oil, following column chromatography (methanol–ethyl acetate 2:8); (found (ESI): M^++Na, 337.1522. $C_{18}H_{22}N_2NaO_3$ requires M, 337.1523); ν_{max} 2929, 1722, 1668, 1634, 1492, 1134 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.19 (5H, m, Ar*H*), 4.73 (1H, d, *J* 14.6, CH_2), 4.42 (1H, d, *J* 14.6, CH_2), 3.77 (1H, dd, *J* 12.4, 7.3, H_{5A}), 3.68 (1H, dd, *J* 12.4, 7.5, H_{5B}), 3.11 (1H, ddd, *J* 11.0, 5.0, 1.3, H_{4A}), 2.98 (1H, t, *J* 11.0, H_{4B}), 2.63 (4H, t, *J* 6.6, H_6), 2.58 (1H, ddd, *J* 18.0, 5.8, 3, H_{1A}), 2.39 (1H, ddd, *J* 18.0, 11.5, 6.2, H_{1B}), 2.20–2.07 (1H, m, H_3), 1.89 (2H, quin, *J* 6.6, H_7), 1.53 (2H, dtd, *J* 13.1, 11.5, 6.2, H_2); δ_C (101 MHz, $CDCl_3$) 172.3, 169.0, 136.5, 128.1, 127.5, 126.9, 50.1, 49.7, 41.1, 32.8, 32.3, 30.7, 24.8, 16.57; *m*/*z* (ESI) 337.1 (M^++Na). Enantiomeric separation was achieved by HPLC analysis (Chiralpak IB, 4.6 mm×250 mm, hexane:IPA 80:20, 1.0 mL/min, *T*=30 °C, 38.1 min, 41.0 min).

*3.1.18. 1-Benzyl-5-[(2-hydroxy-6-oxopiperidin-1-yl)methyl]piperidin-2-one, (±)-**22**.* Under nitrogen, a solution of cerium chloride heptahydrate (574 mg, 1.54 mmol) and 1-[(1-benzyl-6-oxopiperidin-3-yl)methyl]piperidine-2,6-dione, (±)-**4d** (484 mg, 1.54 mmol) in dry methanol (3.85 mL) was stirred at 0 °C for 5 min. Sodium borohydride (118 mg, 3.12 mmol) was added and the mixture was stirred at 0 °C for 4 h before saturated aqueous sodium hydrocarbonate (5 mL) was added. Following extraction with DCM (3×10 mL), the organic extracts were dried ($MgSO_4$), concentrated

under reduced pressure and purified by column chromatography (methanol–ethyl acetate 5:95), to give an impure sample containing what was characterised to be the inseparable diastereomers (±)-**22** (343 mg, 1.08 mmol, 70% yield). Data obtained for the mixture of diastereomers is as follows: (found (ESI): M^++Na, 339.1683. $C_{18}H_{24}N_2NaO_3$ requires M, 339.1679); ν_{max} 3303, 2926, 1613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38–7.15 (5H, m, Ar*H*), 4.79–4.33 (3H, m, CH_2, H_6), 3.65–3.43 (1H, m, H_{5A}), 3.29–3.04 (2H, m, H_{5B}, H_{4A}), 3.03–2.87 (1H, m, H_{4B}), 2.61–2.10 (5H, m, H_1, H_9, H_3), 2.10–1.42 (6H, m, H_2, H_8, H_7); δ_C (101 MHz, $CDCl_3$) 171.0, 170.9, 169.8, 169.8, 141.56, 137.2, 136.5, 136.4, 128.6, 128.4, 128.4, 127.8, 127.7, 127.6, 127.6, 127.3, 127.2, 119.9, 79.9, 79.8, 78.8, 61.4, 50.5, 50.5, 50.1, 50.1, 46.6, 41.4, 32.8, 32.7, 32.1, 31.6, 30.8, 30.7, 30.6, 25.0, 24.8, 15.5, 15.5; *m*/*z* (ESI) 339.1 (M^++Na).

*3.1.19. 1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]-3,4-dihydropyridin-2(1H)-one, (±)-**23**.* Under nitrogen, a solution of 1-benzyl-5-[(2-hydroxy-6-oxopiperidin-1-yl)methyl]piperidin-2-one, (±)-**22** (240 mg, 0.759 mmol) in dry DCM (19 mL) was stirred at −10 °C for 10 min. Titanium chloride (92 μL, 159 mg, 0.839 mmol) was added and the solution was stirred at −10 °C for 10 min before DIPEA (147 μL, 109 mg, 0.844 mmol) was added. The solution was allowed to warm to 0 °C and left stirring for 4 h before saturated aqueous ammonium chloride (5 mL) was added. Following extraction with DCM (3×10 mL), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give product (±)-**23** (203 mg, 0.681 mmol, 90% yield) as an oil; (found (ESI): M^++H, 299.1743. $C_{18}H_{23}N_2O_2$ requires M, 299.1754); ν_{max} 2926, 1616, 1494, 734, 701 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.21–7.36 (5H, m, Ar*H*), 5.85 (1H, d, *J* 7.7, H_9), 5.10 (1H, dt, *J* 7.7, 4.1, H_8), 4.67 (1H, d, *J* 14.7, CH_2), 4.49 (1H, d, *J* 14.7, CH_2), 3.37 (2H, m, H_4), 3.18 (1H, ddd, *J* 12.0, 4.9, 1.5, H_{5A}), 2.95 (1H, dd, *J* 12.0, 9.8, H_{5B}), 2.58 (1H, ddd, *J* 18.0, 6.0, 3.8, H_{1A}), 2.47 (2H, t, *J* 7.9, H_6), 2.43 (1H, ddd, *J* 18.0, 11.3, 6.8, H_{1B}), 2.23–2.28 (2H, m, H_7), 2.13–2.21 (1H, m, H_3), 1.85–1.90 (1H, m, H_{2A}), 1.50–1.58 (1H, m, H_{2B}); δ_C (151 MHz, $CDCl_3$) 169.6, 169.4, 137.0, 130.0, 128.6, 128.1, 127.4, 106.5, 50.2, 50.1, 48.7, 31.3, 31.0, 30.9, 25.1, 20.2; *m*/*z* (ESI) 299.2 (M^++1).

*3.1.20. The selenoxide oxidation–elimination of enamide (±)-**23**, yielding (±)-1-((1-benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one, (±)-**4e**.*[7,8] Under nitrogen, LDA (1.5 M solution in THF, 70 μL, 0.105 mmol) was added to a solution of 1-[(1-benzyl-6-oxopiperidin-3-yl)methyl]-3,4-dihydropyridin-2(1H)-one, (±)-**23** (15 mg, 0.050 mmol) in freshly distilled THF (0.7 mL) and the solution was stirred at −78 °C for 1 h. A solution of phenyl selenyl chloride (9.6 mg, 0.050 mmol) in freshly distilled THF (1.0 mL) was added and the solution was stirred at −78 °C for 45 min before saturated ammonium chloride was added and the solution was allowed to warm to room temperature. Following extraction with ethyl acetate (3×5 mL), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the intermediate product (25 mg). A solution of the intermediate product (25 mg) in THF:methanol:H_2O 18:6:2 (1 mL) and $NaIO_4$ (37 mg, 0.173 mmol) was stirred at room temperature for 24 h before water was added and the solution was concentrated under reduced pressure. Following extraction with ethyl acetate (3×5 mL), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a sample containing an inseparable mixture of the product (±)-**4e**, and a side product (10 mg, yield not calculated due to mixture) as a colourless oil, as determined by ^{1}H NMR and an unidentified product. This data was in accordance with the characterisation data for **4e**, which has previously been reported.[7,8]

*3.1.21. 5-Chloromethyl-2-methoxypyridine, **24**.*[31] Under nitrogen, thionyl chloride (2.05 mL, 3.34 g, 28.09 mmol) was added to a solution of (6-methoxy-pyridin-3-yl)methanol **2c** (3.56 g, 25.60 mmol) in dry toluene (10.6 mL) and the solution was stirred at room temperature for 1 h before NaOH (2 M, 10 mL) was added. The solution was stirred for 10 min before extraction with toluene (2×20 mL). The organic extracts were washed water and concentrated under reduced pressure to give the product **24** (3.85 g, 24.52 mmol, 96% yield) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 8.15 (1H, d, *J* 2.7, H_3), 7.62 (1H, dd, *J* 8.5, 2.7, H_2), 6.75 (1H, d, *J* 8.5, H_1), 4.55 (2H, s, H_4), 3.94 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 163.6, 146.7, 139.2, 126.1, 111.3, 53.6, 43.3.

*3.1.22. 1-((6-Methoxypyridin-3-yl)methyl)pyridin-2(1H)-one **2e** and 2-methoxy-5-((pyridin-2-yloxy)methyl)pyridine, **25**.* Under nitrogen, a mixture of 5-chloromethyl-2-methoxypyridine **24** (0.342 g, 2.18 mmol), 2-hydroxypyridine (0.413 g, 4.34 mmol) and potassium carbonate (0.601 g, 4.35 mmol) in toluene (22 mL) was stirred at 115 °C for 1 d, before the solution was allowed to cool. Following filtration, the filtrate was concentrated under reduced pressure and purified by column chromatography (ethyl acetate), to give the *O*-substituted product **25** (58 mg, 0.268 mmol, 12% yield) as a colourless oil; (found (ESI): M^++H, 216.0891. $C_{12}H_{12}N_2O_2$ requires M, 216.0899); ν_{max} 2946, 1610, 1596, 1571, 1495, 1285, 1025, 829, 780 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.27 (1H, d, *J* 2.3, H_5), 8.17 (1H, d, *J* 7.8, H_3), 7.70 (1H, dd, *J* 8.5, 2.5, H_2), 7.55–7.60 (1H, m, H_7), 6.88 (1H, t, *J* 6.0, H_6), 6.76 (2H, m, H_1, H_8), 5.31 (2H, s, H_4), 3.94 (3H, s, CH_3); δ_C (176 MHz, $CDCl_3$) 164.0, 163.4, 147.0, 146.6, 139.2, 138.6, 125.6, 117.3, 111.4, 111.0, 65.0, 53.6; *m*/*z* (ESI) 215.97 (M^++1). Increasing the polarity of the eluent (methanol–ethyl acetate 5:95) gave the *N*-substituted product, **2e** (0.299 g, 1.384 mmol, 63% yield) as a colourless oil; (found (ESI): M^+, 216.0887. $C_{12}H_{12}N_2O_2$ requires M, 216.0899); ν_{max} 3018, 2976, 2943, 2852, 1657, 1587, 1568, 1490 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.14 (1H, d, *J* 2.5, H_3), 7.63 (1H, dd, *J* 8.7, 2.5, H_1), 7.34–7.25 (2H, m, H_6, H_8), 6.72 (1H, d, *J* 8.7, H_2), 6.60 (1H, dd, *J* 9.2, 1.2, H_5), 6.15 (1H, td, *J* 6.8, 1.5, H_7), 5.06 (2H, s, H_4), 3.92 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 164.0, 163.4, 147.0, 146.6, 139.2, 138.6, 125.6, 117.3, 111.4, 111.0, 65.0, 53.6; δ_C (101 MHz, DMSO-d_6) 163.1, 161.4, 146.7, 140.1, 139.2, 138.8, 126.1, 119.8, 110.4, 105.6, 53.1, 48.4; *m*/*z* (ESI) 215.97 (M^++1).

*3.1.23. 1-Benzyl-5-[(2-oxopyridin-1(2H)-yl)methyl]pyridin-2(1H)-one, **3e**.* Under nitrogen, a mixture of benzyl bromide (1.60 mL, 2.30 mL, 13.53 mmol), 1-((6-methoxypyridin-3-yl)methyl)pyridin-2(1H)-one, **2e** (1.45 g, 6.71 mmol) and potassium carbonate (1.85 g, 13.39 mmol) in dry acetonitrile (27 mL) was stirred 80 °C for 24 h before the solution was allowed to cool. Following filtration, the resulting filtrate was concentrated under reduced pressure and recrystallised (ethanol), to give product **3e** (1.00 g, 3.42 mmol, 51% yield) as a white powder; 140–142 °C; (found (ESI): M^++Na, 315.1102. $C_{18}H_{16}N_2NaO_2$ requires M, 315.1104); ν_{max} 3034, 2972, 1714 (CO), 1666, 1649, 1595, 1568, 1493, 788, 723, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45 (1H, d, *J* 2.5, H_3), 7.37–7.27 (7H, m, Ar*H*, H_6, H_2), 7.23 (1H, dd, *J* 6.8, 2.0, H_8), 6.58 (2H, d, *J* 9.3, H_1, H_5), 6.16 (1H, td, *J* 6.8, 1.4, H_7), 5.12 (2H, s, CH_2), 4.78 (2H, s, CH_2); δ_C (101 MHz, $CDCl_3$) 162.4, 161.8, 146.3, 139.9, 139.7, 137.5, 136.6, 135.9, 128.7, 127.9, 121.2, 121.1, 114.5, 106.6, 52.0, 49.2; *m*/*z* (ESI) 293.1 (M^++1), 315.1 (M^++23). Further recrystallisation (EtOH) provided crystals of sufficient quality for X-diffraction, enabling confirmation of the structure.[11]

*3.1.24. 1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one, (±)-**26**.*[8] It was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-5-[(2-oxopyridin-1(2*H*)-yl)methyl]pyridin-2(1*H*)-one, **3e** (0.644 g, 2.20 mmol) and platinum oxide (25 mg, 0.110 mmol) following a reaction time of 20 h, at 30 °C. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate–methanol

95:5), product (±)-**26** (497 mg, 1.66 mmol, 75% yield) was obtained as an oil. The data matched that previously reported.[8]

*3.1.25. Synthesis of (1-benzyl-3-(piperidin-1-ylmethyl)piperidine) **1** (R=Bn), 1-benzyl-3-(piperidin-1-ylmethyl)piperidine, (±)-**1** (R=Bn).* Under nitrogen, triethylsilane (1.41 mL, 8.79 mmol) was added to a solution of 1-((1-benzyl-6-oxopiperidin-3-yl)methyl) piperidin-2-one, (±)-**26** (377 mg, 1.256 mmol) and triruthenium dodecacarbonyl (16 mg, 2.50×10^{-2} mmol) in dry toluene (2.5 mL) and the mixture was stirred at 100 °C for 18 h. The solution was concentrated under reduced pressure and purified by column chromatography (ethyl acetate–hexane–triethylamine 10:90:1) to give product (±)-**1** (R=Bn) (194 mg, 0.713 mmol, 57% yield) as a colourless oil; (found (ESI): M^++H, 273.2323. $C_{18}H_{29}N_2$ requires M, 273.2325); ν_{max} 2928, 2849, 2793, 2754, 1493, 1153, 1098 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.33–7.20 (5H, m, Ar*H*), 3.57 (1H, d, *J* 13.2, CH_2), 3.40 (1H, d, *J* 13.2, CH_2), 2.90 (1H, d, *J* 10.1, H_{5A}), 2.76 (1H, d, *J* 10.5, H_{1A}), 2.37–2.21 (4H, m, H_7), 2.13–2.06 (2H, m, H_6), 1.89 (1H, m, H_{1B}), 1.87–1.81 (1H, m, H_4), 1.74 (1H, dq, *J* 13.0, 3.4, H_{3A}), 1.71–1.65 (1H, m, H_{5B}), 1.62 (1H, dquin, *J* 13.0, 3.4, H_{2A}), 1.58–1.48 (5H, m, H_8, H_{2B}), 1.43–1.36 (2H, m, H_9), 0.89 (1H, qd, *J* 13.0, 3.4, H_{3B}); δ_C (75 MHz, $CDCl_3$) 136.6, 129.2, 128.1, 126.8, 63.8, 63.6, 59.4, 55.1, 54.1, 33.6, 29.8, 25.9, 25.1, 24.5; *m*/*z* (ESI) 273.0 (M^++1). The assignments of these proton signals were supported by ^{13}C HMQC and COSY correlation NMR experiments.

*3.1.26. 1-(Piperidin-3-ylmethyl)piperidine, (±)-**1** (R=H).* This compound was prepared following the general procedure for alkene hydrogenation, using 1-benzyl-3-(piperidin-1-ylmethyl)piperidine (±)-**1** (R=Bn) (22 mg, 0.081 mmol) and palladium hydroxide on carbon (20% w/w, 6 mg, 8.55×10^{-3} mmol) following a reaction time of 18 h, at room temperature. Following filtration with Celite, the resulting filtrate was passed through an Isolute-XL SCX amine scavenger resin and the resin was washed with DCM (3×1 mL). The free amine was liberated by passing a solution of approx. 2% NH_4OH in methanol through the resin, followed by washing with DCM (3×1 mL). Following concentration under reduced pressure, product (±)-**1** (R=H) (20 mg, contains solvent) was obtained as colourless oil; (found (ESI): M^++H, 183.1857. $C_{11}H_{23}N_2$ requires M, 183.1856); ν_{max} 3400, 2927, 2848, 2795, 2758, 1546, 1116, 778 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 3.14 (1H, dd, *J* 11.9, 1.5, H_{1A}), 3.01 (1H, d, *J* 11.9, H_{5A}), 2.54 (1H, td, *J* 11.8, 2.8, H_{5B}), 2.19–2.43 (5H, m, H_7, H_{1B}), 2.09 (1H, dd, *J* 12.3, 8.1, H_{6A}), 2.05 (1H, dd, *J* 12.3, 6.2, H_{6B}), 1.81 (1H, dq, *J* 12.7, 3.5, H_{3A}), 1.67–1.73 (1H, m, H_4), 1.64 (1H, dquin, *J* 12.8, 3.5, H_{2A}), 1.54 (4H, quin, *J* 6.4, H_8), 1.46 (1H, qt, *J* 12.8, 3.5, H_{2B}), 1.42–1.37 (2H, m, H_9), 1.01 (1H, qd, *J* 12.8, 3.5, H_{3B}); δ_C (101 MHz, $CDCl_3$) 63.9, 55.2, 52.0, 47.2, 34.6, 30.3, 26.4, 26.0, 24.6; *m*/*z* (ESI) 182.9 (M^++1).

*3.1.27. N,6-Dimethoxy-N-methylpyridine-3-carboxamide, **28**.* Under nitrogen, a solution of methyl 6-methoxynicotinate **2b** (3.00 g, 17.96 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (5.36 g, 54.95 mmol) in THF (40 mL) was stirred at −40 °C for 10 min. Isopropyl magnesium chloride (2 M solution in THF, 26 mL, 52.00 mmol) was added dropwise over 15 min and the reaction was stirred at −40 °C for 90 min before aqueous acetic acid (20%, 20 mL) was added. This solution was extracted with diethyl ether (3×20 mL) and the organic extracts were set aside. The remaining aqueous phase was then basified with saturated aqueous sodium hydrocarbonate and extracted with DCM (2×10 mL). The combined organic extracts were dried ($MgSO_4$) followed by concentration under reduced pressure and purified by column chromatography (petroleum ether–ethylacetate 9:1), to give the product **28** (2.38 g, 12.14 mmol, 68% yield) as a colourless oil; (found (ESI): M+Na, 219.0740. $C_9H_{12}N_2NaO_3$ requires M, 219.0740); ν_{max} 3501, 2971, 1635, 1600, 1566, 1495, 1092 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.65 (1H, d, *J* 2.5, H_3), 7.99 (1H, dd, *J* 8.7, 2.5, H_2), 6.76 (1H, d, *J* 8.7, H_1), 3.99 (3H, s, CH_3), 3.58 (3H, s, CH_3), 3.38 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.3, 165.3, 148.2, 139.3, 122.7, 110.1, 61.0, 53.7, 33.3; *m*/*z* (ESI) 196.8 (M^++1).

*3.1.28. 1-(6-Methoxypyridin-3-yl)ethanone, **5**.*[32] Under nitrogen, a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide **28** (3.66 g, 18.67 mmol) in THF (64 mL) was stirred at 0 °C for 15 m. Methyl magnesium bromide (3 M solution in THF, 6.42 mL, 19.26 mmol) was added dropwise over 5 min and the solution was stirred at 0 °C for 1 h. The solution was allowed to warm to room temperature and stirred for 1 d before the solution was concentrated under reduced pressure and HCl (2 M, 10 mL) was added. Following extraction with diethyl ether (3×30 mL), the organic extracts were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (petroleum ether–ethyl acetate 2:8), to give product **5** (1.73 g, 11.48 mmol, 61% yield) as a colourless solid; Mp 60–64 °C; (found (ESI): M^++Na, 174.0525. $C_8H_9NNaO_2$ requires M, 174.0525); ν_{max} 3068, 2990, 2958, 2861, 1671, 1597, 1562, 1494, 1292, 1277, 1259, 1142 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.78 (1H, dd, *J* 2.5, 0.6, H_3), 8.14 (1H, dd, *J* 8.8, 2.5, H_2), 6.79 (1H, dd, *J* 8.8, 0.6, H_1), 4.01 (3H, s, H_5), 2.71–2.55 (3H, m, H_4); δ_C (101 MHz, $CDCl_3$) 195.6, 166.8, 149.4, 138.1, 127.0, 111.1, 54.0, 26.3; *m*/*z* (ESI) 152.1 (M^++1).

*3.1.29. 5-Acetyl-1-benzylpyridin-2(1H)-one, **27**.*[33] A mixture of benzyl bromide (0.43 mL, 0.62 g, 3.62 mmol), 1-(6-methoxy pyridin-3-yl)ethanone **5** (0.500 g, 3.31 mmol) and potassium carbonate (0.914 g, 6.61 mmol) in dry acetonitrile (17 mL) was stirred at 80 °C for 2 d before the mixture was allowed to cool to room temperature. Following filtration, concentrated under reduced pressure and purification by column chromatography (ethyl acetate–hexane 8:2), the product **27** (0.395 g, 1.74 mmol, 48% yield) was obtained as a colourless oil; (found (ESI): M^++Na, 250.0837. $C_{14}H_{13}NNaO_2$ requires M, 250.0838); ν_{max} 3063, 1640, 1542, 1496, 732, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.10 (1H, d, *J* 2.5, H_3), 7.85 (1H, dd, *J* 9.6, 2.5, H_2), 7.42–7.25 (5H, m, Ar*H*), 6.60 (1H, d, *J* 9.6, H_1), 5.19 (2H, s, CH_2), 2.39 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 193.0, 162.3, 142.1, 137.6, 135.3, 129.1, 128.5128.1, 120.1, 118.0, 52.7, 25.7; *m*/*z* (ESI) 227.8 (M^++1), 249.8 (M^++23).

*3.1.30. 1-(4-Methoxyphenyl)pentan-1-one, **6**.* Under nitrogen, n-butyl magnesium bromide (2 M solution in THF, 0.77 mL, 1.54 mmol) was added to a solution of *N*,6-Dimethoxy-*N*-methylpyridine-3-carboxamide, **27** (200 mg, 1.02 mmol) in THF (1.15 mL) and the solution was stirred at room temperature for 18 h before HCl (2 M, 3 mL) was added. Following extraction with DCM (3×5 mL), the organic extracts were washed with brine (5 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (petroleum ether–ethyl acetate 1:9), to give product **6** (107 mg, 0.554 mmol, 54% yield) as a colourless oil; (found (ESI): M^++H, 194.1172. $C_{11}H_{16}NO_2$ requires M, 194.1176); ν_{max} 2955, 2872, 1678, 1593, 1562, 1493, 1291, 1261, 1014, 837 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.79 (1H, d, *J* 2.4, H_3), 8.14 (1H, dd, *J* 8.7, 2.4, H_1), 6.79 (1H, d, *J* 8.7, H_2), 4.00 (3H, s, H_8), 2.91 (2H, t, *J* 7.7, H_4), 1.72 (2H, quin, *J* 7.7, H_5), 1.40 (2H, sxt, *J* 7.7, H_6), 0.96 (3H, t, *J* 7.7, H_7); δ_C (101 MHz, $CDCl_3$) 198.2, 166.6, 148.9, 138.1, 126.7, 111.1, 54.0, 38.2, 26.5, 22.4, 13.8; *m*/*z* (ESI) 193.9 (M^++1).

*3.1.31. 1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-one, **7**.* Under nitrogen, isopropyl magnesium bromide (2 M solution in THF, 0.77 mL, 1.54 mmol) was added to a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **28** (200 mg, 1.02 mmol) in THF (1.53 mL) and the solution was stirred at room temperature for 18 h before the solution was concentrated under reduced pressure and HCl (2 M, 5 mL) was added. Following extraction with DCM (5×10 mL), the organic extracts were washed with brine (5 mL),

dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (petroleum ether–ethyl acetate 15:85), to give ketone **7** (30 mg, 0.168 mmol, 16% yield) as an oil; (found (ESI): M^++H, 180.1017. $C_{10}H_{14}NO_2$ requires M, 180.1019); ν_{max} 2973, 2944, 1679, 1601, 1562, 1493, 1295, 1232, 1024, 841 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.80 (1H, d, *J* 2.5, H_3), 8.15 (1H, dd, *J* 8.8, 2.5, H_1), 6.80 (1H, d, *J* 8.8, H_2), 4.02 (3H, s, H_6), 3.46 (1H, spt, *J* 7.0, H_4), 1.22 (6H, d, *J* 7.0, H_5); δ_C (75 MHz, $CDCl_3$) 202.2, 166.6, 149.0, 138.6, 125.7, 111.2, 54.0, 35.4, 19.1; *m*/*z* (ESI) 180.1 (M^++1).

3.1.32. Cyclohexyl(6-methoxypyridin-3-yl)methanone, ***8****.* Under nitrogen, cyclohexyl magnesium bromide (1 M solution in Et_2O, 1.5 mL, 1.5 mmol) was added to a solution of *N*,6-Dimethoxy-*N*-methylpyridine-3-carboxamide, **27** (200 mg, 1.02 mmol) in THF (1.9 mL) and the solution was stirred at room temperature for 5 m. The solution was stirred at 70 °C for 2.5 h, before the solution was concentrated under reduced pressure and HCl (2 M, 5 mL) was added. Following extraction with DCM (5×10 mL), the organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure and purified by column chromatography (petroleum ether–ethyl acetate 1:9), to give product **8** (51 mg, 0.233 mmol, 23% yield) as an oil; (found (ESI): M^++H, 220.1331. $C_{13}H_{18}NO_2$ requires M, 220.1332); ν_{max} 2926, 2853, 1677, 1600, 1565, 1494, 1294, 1252, 1021, 838 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.79 (1H, d, *J* 2.2, H_3), 8.14 (1H, dd, *J* 8.8, 2.2, H_2), 6.79 (1H, d, *J* 8.8, H_1), 4.01 (3H, s, CH_3), 3.16 (1H, tt, *J* 11.3, 3.3, H_4), 1.94–1.79 (4H, m, H_5), 1.60–1.18 (6H, m, H_{6-7}); δ_C (101 MHz, $CDCl_3$) 201.5, 166.5, 148.9, 138.5, 125.7, 111.1, 53.9, 45.7, 33.3, 29.3, 25.9; *m*/*z* (ESI) 219.9 (M^++1).

3.1.33. (6-Methoxypyridin-3-yl)(phenyl)methanone, ***9****.*[34] Under nitrogen, a solution of *N*,6-dimethoxy-*N*-methylpyridine-3-carboxamide, **28** (100 mg, 0.510 mmol) in THF (0.96 cm^3) was cooled to 0 °C and left stirring for 5 min. Phenyl magnesium bromide (1 M solution in THF, 0.79 mL, 0.79 mmol) was added dropwise over 5 min and the solution was stirred at 0 °C for the 3 h before the solution was concentrated under reduced pressure and HCl (2 M, 5 mL) was added. Following extraction with DCM (3×5 mL), the organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purification by column chromatography (petroleum ether–ethyl acetate 9:1), to give product **9** (60 mg, 0.282 mmol, 55% yield) as a brown oil; (found (ESI): M^++H, 214.0860. $C_{13}H_{12}NO_2$ requires M, 214.0863); ν_{max} 2948, 1651, 1592, 1492, 1276, 760, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.62 (1H, d, *J* 2.4, H_3), 8.10 (1H, dd, *J* 8.9, 2.4, H_2), 7.83–7.73 (2H, m, H_4), 7.63–7.56 (1H, m, H_6), 7.54–7.43 (2H, m, H_5), 6.85 (1H, d, *J* 8.9, H_1), 4.03 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 193.6, 166.5, 150.8, 140.0, 137.5, 132.5, 129.7, 128.4, 126.9, 126.5, 111.0, 54.0; *m*/*z* (ESI) 214.1 (M^++1).

*3.1.34. (S)-1-(6-Methoxypyridin-3-yl)ethanol, (S)-****10****.*[35] This compound was prepared following the general procedure for ketone transfer hydrogenation, using 1-(6-methoxypyridin-3-yl)ethanone, **5** (30 mg, 0.199 mmol) and Ru(*S*,*S*)*teth*-TsDPEN (1.2 mg, 1.93×10^{-3} mmol) in FA/TEA (199 μL, 1 M), following a reaction time of 22 h. Following concentrated under reduced pressure purification by column chromatography (ethyl acetate–hexane 1:1), product (*S*)-**10** (21 mg, 0.137 mmol, 69% yield) was obtained as colourless oil; $[\alpha]_D^{15}$ 42.4 (*c*1.05 in $CHCl_3$) 82% ee. Lit.[35] $[\alpha]_D^{23}$ +33.7 (*c* 2.70, $CHCl_3$) 98.0% ee (*R*)); (found (ESI): M^++H, 154.0861. $C_8H_{12}NO_2$ requires M, 154.0863); ν_{max} 3300, 2972, 1607, 1574, 1492, 1281, 1024, 761, 724 cm^{-1}; δ_H (400 MHz, DMSO) 8.09 (1H, d, *J* 2.5, H_3), 7.66 (1H, dd, *J* 8.5, 2.5, H_2), 6.76 (1H, d, *J* 8.5, H_1), 5.12 (1H, d, *J* 4.5, O*H*), 4.76–4.65 (1H, qd, *J* 6.5, 4.5, H_4), 3.82 (3H, s, CH_3), 1.32 (3H, d, *J* 6.5, H_5); δ_C (101 MHz, DMSO) 162.6, 143.7, 136.6, 135.3, 109.8, 65.6, 52.9, 25.4; *m*/*z* (ESI) 154.0 (M^++1), 176.0 (M^++23). Enantiomeric separation was determined by GC analysis of the acetate derivative: (CP-ChiraSil-DEX CB 25 m×0.25 mm×0.25 μm, gas: He, *T*=170 °C, *P*=18 psi He, det=250 °C, inj=220 °C, *S* (major) isomer 3.82 min, *R* (minor) isomer 3.95 min) 82% ee (*S*). The configuration was primarily assigned by comparison the reported optical rotation. This was also in agreement with that expected from the theoretical model.

*3.1.35. (R)-1-(6-Methoxypyridin-3-yl)pentan-1-ol, (R)-****11****.* This compound was prepared following the general procedure for ketone transfer hydrogenation, using 1-(4-methoxyphenyl)pentan-1-one, **6** (30 mg, 0.155 mmol) and Ru(*R*,*R*)*teth*-TsDPEN (1.0 mg, 1.61×10^{-3} mmol) in FA/TEA (78 μL, 2 M), following a reaction time of 20 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate–hexane 1:1), product (*R*)-**11** (15 mg, 0.077 mmol, 50% yield) was obtained as colourless oil; $[\alpha]_D^{22}$ +28.5 (*c* 0.61, $CHCl_3$) 76% ee; (found (ESI): M^++H, 196.1329. $C_{11}H_{18}NO_2$ requires M, 196.1332); ν_{max} 3339, 2931, 2859, 1607, 1573, 1491, 1460, 1283, 1026, 831, 762 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.09 (1H, d, *J* 2.3, H_3), 7.61 (1H, dd, *J* 8.7, 2.3, H_2), 6.75 (1H, d, *J* 8.7, H_1), 4.64 (1H, td, *J* 6.7, 3.2, H_4), 3.93 (3H, s, CH_3), 1.90–1.76 (2H, m, H_{5A}, O*H*), 1.78–1.63 (2H, m, H_{5B}), 1.47–1.17 (4H, m, H_{6-7}), 0.93–0.85 (3H, m, H_8); δ_C (101 MHz, $CDCl_3$) 163.8, 144.7, 136.6, 132.8, 110.9, 72.1, 53.4, 38.4, 27.9, 22.5, 13.9; *m*/*z* (ESI) 195.9 (M^++1). Enantiomeric separation was determined by GC analysis for the acetate derivative: (CP-ChiraSil-DEX CB 25 m×0.25 mm×0.25 μm, gas: He, *T*=140 °C, *P*=18 psi He, det=220 °C, inj=220 °C, major isomer 21.30 min, minor isomer 22.33 min) 76% ee (*R*). The absolute configuration was assigned by analogy with the expected outcome of the theoretical model.

*3.1.36. (R)-1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-ol, (R)-****12****.* This compound was prepared following the general procedure for ketone transfer hydrogenation, using 1-(6-methoxypyridin-3-yl)-2-methylpropan-1-one, **7** (11.3 mg, 6.31×10^{-2} mmol), Ru(*R*,*R*)*teth*-TsDPEN (0.4 mg, 6.45×10^{-4} mmol) in FA/TEA (32 μL, 2 M), following a reaction time of 22 h. Following concentrated under reduced pressure and purification by column chromatography (ethyl acetate–hexane 1:1), product (*R*)-**12** (6.9 mg, 0.038 mmol, 60% yield) was obtained as colourless oil; $[\alpha]_D^{21}$ +23.2 (*c* 0.35, $CHCl_3$) 53% ee; (found (ESI): M^++H, 182.1176. $C_{10}H_{16}NO_2$ requires M, 182.1176); ν_{max} 3398, 2961, 1609, 1575, 1493, 1128, 1027 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* 2.4, H_3), 7.57 (1H, dd, *J* 8.6, 2.4, H_2), 6.74 (1H, d, *J* 8.6, H_1), 4.34 (1H, d, *J* 6.9, H_4), 3.93 (3H, s, H_8), 1.94 (1H, oct, *J* 6.9, H_5), 1.02 (3H, d, *J* 6.9, H_6), 0.79 (3H, d, *J* 6.9, H_7); δ_C (126 MHz, $CDCl_3$) 163.9, 150.2, 145.2, 137.00, 110.5, 77.7, 53.4, 35.2, 18.7, 18.4; *m*/*z* (ESI) 181.9 (M^++1); Enantiomeric separation was determined by GC analysis (CP-ChiraSil-DEX CB 25 m×0.25 mm×0.25 μm, gas: He, *T*=140 °C, *P*=18 psi He, det=220 °C, inj=220 °C, major isomer 21.54 min, minor isomer 22.56 min) 53% ee (*R*). The absolute configuration was assigned by analogy with the expected outcome of the theoretical model.

*3.1.37. (R)-Cyclohexyl(6-methoxypyridin-3-yl)methanol, (R)-****13****.* This compound was prepared following the general procedure for ketone transfer hydrogenation, using cyclohexyl(6-methoxy pyridin-3-yl)methanone **8** (26 mg, 0.119 mmol) and Ru(*R*,*R*)*teth*-TsDPEN (0.7 mg, 1.13×10^{-3} mmol) in FA/TEA (58 μL, 2 M), following a reaction time of 24 h. Following concentrated under reduced pressure and purification by column chromatography (ethyl acetate–hexane 1:1), product (*R*)-**13** (27 mg, 0.122 mmol) was obtained as colourless oil; $[\alpha]_D^{21}$ +18.2 (*c* 0.70, $CHCl_3$) 35% ee; (found (ESI): M^++H, 220.1490. $C_{13}H_{20}NO_2$ requires M, 220.1489); ν_{max} 3335, 2922, 2850, 1606, 1573, 1492, 1448, 1284, 1024, 832, 731 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* 2.4, H_3), 7.56 (1H, dd, *J* 8.5, 2.4, H_2), 6.74 (1H, d, *J* 8.5, H_1), 4.34 (1H, dd, *J* 7.3, 3.0, H_4), 3.93 (3H, s, CH_3), 1.87 (1H, br s, O*H*), 1.83–1.73 (1H, m, H_5), 1.73–1.53 (4H,

m, H_6), 1.32–0.82 (6H, m, H_{7-8}); δ_C (101 MHz, $CDCl_3$) 163.7, 145.2, 137.1, 131.6, 110.6, 76.7, 53.4, 44.7, 29.0, 26.3, 25.9; *m*/*z* (ESI) 220.1 (M^++1). Enantiomeric separation was determined by HPLC analysis of the acetate derivative: (Chiralpak IA, 4.6 mm×250 mm, hexane:IPA 98:2, 0.5 mL/min, *T*=28 °C, 13.0 min, 17.2 min) 35% ee (*R*). The absolute configuration was assigned by analogy with the expected outcome of the theoretical model.

*3.1.38. (6-Methoxypyridin-3-yl)(phenyl)methanol, (−)-**14**.*[22] This compound was prepared following the general procedure for ketone transfer hydrogenation, using (6-methoxypyridin-3-yl)(phenyl)methanone, **9** (15 mg, 0.070 mmol) and Ru(*R*,*R*)*teth*-TsDPEN (0.4 mg, 6.45×10^{-4} mmol) in FA/TEA (58 μL, 2 M), following a reaction time of 24 h. Following concentrated under reduced pressure and purification by column chromatography (ethyl acetate–petroleum ether 1:1), product (−)-**14** (10 mg, 0.046 mmol, 66% yield) was obtained as colourless oil; $[\alpha]_D^{20}$ 9.8 (*c* 0.365, $CHCl_3$) 48% ee (lit.[22] $[\alpha]_D^{22}$ −26.2 (*c* 0.26, $CHCl_3$) 96.0% ee); (found (ESI): M^++H, 216.1019. $C_{13}H_{14}NO_2$ requires M, 216.1019); ν_{max} 3340, 2987, 2901, 1607, 1573, 1491, 1452, 1285, 1026, 733, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.13 (1H, d, *J* 2.5, H_3), 7.54 (1H, dd, *J* 8.3, 2.5, H_2), 7.32–7.38 (3H, m, Ar*H*), 7.26–7.30 (2H, m, Ar*H*), 6.70 (1H, d, *J* 8.3, H_1), 5.81 (1H, d, *J* 3.3, H_4), 3.91 (3H, s, CH_3), 2.47 (1H, d, *J* 3.5, O*H*); δ_C (75 MHz, $CDCl_3$) 158.6, 145.1, 143.2, 137.4, 132.1, 128.6, 127.8, 126.3, 110.9, 73.8, 53.5; *m*/*z* (ESI) 216.1 (M^++1), 238.1 (M^++23). Enantiomeric separation was achieved by HPLC analysis (Chiralpak IC, 4.6 mm×250 mm, hexane:IPA 90:10, 1 mL/min, *T*=30 °C, minor isomer 12.2 min, major isomer 14.9 min) 48% ee.

*3.1.39. 1-Benzyl-5-(1-hydroxyethyl)piperidin-2-one, (R)-**15**.* This compound was prepared following the general procedure (C) for ketone transfer hydrogenation, using 5-acetyl-1-benzylpyridin-2(1H)-one, **27** (45 mg, 0.198 mmol) and Ru(*R*,*R*)*teth*-TsDPEN (1.2 mg, 1.93×10^{-3} mmol) in FA/TEA (198 μL, 1 M), following a reaction time of 20 h. Following concentrated under reduced pressure and purification by column chromatography (ethyl acetate–hexane 9:1), product (*R*)-**15** (17 mg, 0.074 mmol, 37%) was obtained as colourless oil; $[\alpha]_D^{22}$ +3.6 (*c* 0.35, $CHCl_3$) 42% ee; (found (ESI): M^++Na, 252.0995. $C_{14}H_{15}NNaO_2$ requires M, 252.0995); ν_{max} 3356, 2970, 1661, 1578, 1542, 1497, 1042, 837, 698 cm^{-1}; δ_H (400 MHz) 7.41–7.22 (7H, m, Ar*H*, H_2, H_3), 6.60 (1H, d, *J* 9.5, H_1), 5.05–5.17 (2H, s, CH_2), 4.63 (1H, q, *J* 6.2, H_4), 2.02–2.11 (1H, br s, O*H*), 1.40 (3H, d, *J* 6.2, H_5); δ_C (101 MHz, $CDCl_3$) 162.4, 138.3, 136.2, 133.7, 128.8, 128.0, 127.9, 124.3, 120.9, 66.8, 52.1, 24.1; *m*/*z* (ESI) 229.8 (M^++1). Enantiomeric separation was determined by HPLC analysis of the acetate derivative: (Chiralpak IC, 4.6 mm×250 mm, hexane:IPA 80:20, 1.0 mL/min, *T*=30 °C, *S* (minor) isomer 41.0 min, *R* (major) isomer 44.3 min) 42% ee. The configuration was determined by comparison of the optical rotation of a sample of (*R*)-**15**, formed from (*R*)-**5.**

*3.1.40. (R)-1-(6-Methoxypyridin-3-yl)ethanol, (R)-**10**.*[35] This procedure was used for the large scale asymmetric reduction of 1-(6-methoxypyridin-3-yl)ethanone **5**. Under nitrogen, FA/TEA (5:2, 9.93 mL, 1 M) was added to 1-(6-methoxypyridin-3-yl)ethanone, **5** (1.00 g, 6.62 mmol). Dissolution was aided by gently heating the mixture at 45 °C. The mixture was then allowed to cool to room temperature for 30 min. Ru(*R*,*R*)*teth*-TsDPEN (41.0 mg, 6.61×10^{-2} mmol) was added and the solution was left stirring at room temperature for 5 min. The mixture was heated to 45 °C and stirred for 24 h before saturated aqueous sodium hydrocarbonate (20 mL) was added. Following extraction with DCM (3×20 mL), the solution was concentrated under reduced pressure and purified by column chromatography (petroleum ether–ethyl acetate 1:1), to give the product (*R*)-**10** (0.960 g, 6.27 mmol, 95% yield) as a light red oil; $[\alpha]_D^{15}$ +27.8 (*c* 0.60, $CHCl_3$) 78% ee (lit.[35] $[\alpha]_D$ +33.7 (*c* 2.70, $CHCl_3$) 98.0% ee (*R*)); Enantiomeric separation was determined by GC analysis of the acetate derivative: (CP-ChiraSil-DEX CB 25 m×0.25 mm×0.25 μm, gas: He, *T*=180 °C, *P*=18 psi He, det=250 °C, inj=220 °C, *S* (minor) isomer 3.23 min, *R* (major) isomer 3.30 min) 78% ee. Full characterisation data was given in the previous section.

*3.1.41. 1-Benzyl-5-(1-hydroxyethyl)pyridin-2(1H)-one, (R)-**15**.* A solution of benzyl bromide (0.77 mL, 1.12 g, 6.47 mmol) and (*R*)-1-(6-methoxypyridin-3-yl)ethanone **10** (78% ee, 0.910 g, 5.94 mmol) in dry acetonitrile (14 mL) was stirred at 80 °C for 16 d before the mixture was concentrated under reduced pressure and purified by column chromatography (ethyl acetate–petroleum ether 1:1 to 1:0), to give product (*R*)-**15** (0.852 g, 3.72 mmol, 63% yield) as a colourless oil; $[\alpha]_D^{20}$ +15.4 (*c* 1.40, $CHCl_3$) 78% ee (*R*).

*3.1.42. (5R)-1-Benzyl-5-[(1R)-1-hydroxyethyl]piperidin-2-one (R,R)-**16b** and (5S)-1-benzyl-5-[(1R)-1-hydroxyethyl]piperidin-2-one, (S,R)-**16a**.* These compounds were prepared following the general procedure for alkene hydrogenation, using *syn*-1-benzyl-5-(1-hydroxyethyl)pyridin-2(1*H*)-one, (*R*)-**15** (78% ee, 0.810 g, 3.54 mmol) and platinum oxide (40 mg, 0.176 mmol) following a reaction time of 18 h, at room temperature and 5 bar of hydrogen. Following concentrated under reduced pressure and purification by column chromatography (1–3 % methanol–DCM, slow gravity elution), two diastereomerically enriched samples of the isomers (*R*,*R*)-**16b** and (*S*,*R*)-**16a** were obtained: (*S*,*R*)-**16a** (100% *syn* as determined by GC) (165 mg, 0.708 mmol, 20% yield) was obtained as a colourless oil, which solidified upon standing; 110–112 °C; $[\alpha]_D^{22}$ 30.1 (*c* 0.75, $CHCl_3$) 78% ee; (found (ESI): M^++Na, 256.1306. $C_{14}H_{19}NNaO_2$ requires M, 256.1308); ν_{max} 3354, 2955, 1614, 1496, 1244, 731, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.20 (5H, m, Ar*H*), 4.60 (1H, d, *J* 14.6, CH_2), 4.56 (1H, d, *J* 14.6, CH_2), 3.61 (1H, quin, *J* 6.4, H_5), 3.40 (1H, ddd, *J* 12.2, 5.1, 1.8, H_{4A}), 3.10 (1H, dd, *J* 12.2, 10.2, H_{4B}), 2.54 (1H, ddd, *J* 18.1, 5.5, 3.0, H_{1A}), 2.41 (1H, ddd, *J* 18.1, 11.5, 6.0, H_{1B}), 1.98 (1H, br s, O*H*), 1.87–1.71 (2H, m, H_2), 1.60–1.47 (1H, m, H_3), 1.20 (3H, d, *J* 6.4, H_6); δ_C (101 MHz, $CDCl_3$) 169.9, 136.9, 128.4, 127.8, 127.2, 68.9, 50.3, 49.4, 41.1, 31.3, 23.8, 21.1; *m*/*z* (ESI) 234.1 (M^++1), 256.1 (M^++23). Enantiomeric separation was determined by GC analysis: (CP-ChiraSil-DEX CB 25 m×0.25 mm×0.25 μm, gas: H, *T*=185 °C, *P*=18 psi H, det=250 °C, inj=220 °C, (*S*,*R*) (major) isomer 18.61 min, (*R*,*S*) (minor) isomer 19.24 min) 78% ee. A racemic sample of the diastereomer **16a** was used as a racemic standard during chiral GC analysis. Recrystallisation of a racemic sample of **16a** (DCM-hexane) provided crystals of sufficient quality to undergo X-ray diffraction.[11] (*R*,*R*)-**16b** (72% *anti*, as determined by GC) (266 mg, 1.14 mmol, 32% yield) was obtained as a colourless oil; $[\alpha]_D^{22}$ +11.0 (*c* 1.00, $CHCl_3$) 78% ee; (found (ESI): M^++Na, 256.1306. $C_{14}H_{19}NNaO_2$ requires M, 256.1308); ν_{max} 3368, 2967, 2927, 1612, 1496, 1260, 736, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37–7.22 (5H, m, Ar*H*), 4.64 (1H, d, *J* 14.7, CH_2), 4.55 (1H, d, *J* 14.7, CH_2), 3.68 (1H, quin, *J* 5.8, H_5), 3.17 (1H, ddd, *J* 11.5, 5.8, 1.5, H_{4A}), 3.07 (1H, t, *J* 11.5, H_{4B}), 2.61 (1H, ddd, *J* 17.9, 5.5, 3.0, H_{1A}), 2.42 (1H, ddd, *J* 17.9, 11.8, 6.0, H_{1B}), 1.79 (1H, dqd, *J* 11.5, 5.8, 3.1, H_3), 1.66–1.53 (2H, m, H_2), 1.15 (3H, d, *J* 5.8, H_6); δ_C (101 MHz, $CDCl_3$) 169.9, 137.1, 128.6, 128.0, 127.4, 68.6, 50.3, 49.2, 40.9, 31.5, 22.4, 21.0; *m*/*z* (ESI) 234.1 (M^++1), 256.1 (M^++23). Enantiomeric separation was determined by GC analysis: (CP-ChiraSil-DEX CB 25 m×0.25 mm×0.25 μm, gas: He, *T*=200 °C, *P*=18 psi He, det=250 °C, inj=220 °C, (*S*,*R*) (minor) isomer 24.70 min, (*R*,*S*) (major) isomer 25.25 min, (*S*,*S*) (minor) isomer 25.54 min, (*R*,*R*) (major) isomer 26.09 min) 78% ee. De was determined by GC analysis of the crude reaction mixture with the chiral GC method stated above: 31% de.

The hydrogenolysis product 1-benzyl-5-ethylpiperidin-2-one, **32** was also isolated from this reaction in variable yields. For the case of this experiment, 1-benzyl-5-ethylpiperidin-2-one (110 mg, 0.507 mmol, 14% yield) was obtained as a colourless oil; (found

(ESI): M^++Na, 240.1357. $C_{14}H_{19}NNaO$ requires M, 240.1359); ν_{max} 2959, 2923, 2874, 1636, 1492, 737, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.22 (5H, m, Ar*H*), 4.63 (1H, d, *J* 14.2, CH_2), 4.55 (1H, d, *J* 14.2, CH_2), 3.20 (1H, ddd, *J* 12.0, 5.1, 1.8, H_{4A}), 2.85 (1H, dd, *J* 12.0, 10.3, H_{4B}), 2.56 (1H, ddd, *J* 17.8, 5.8, 3.3, H_{1A}), 2.42 (1H, ddd, *J* 17.8, 11.4, 6.5, H_{1B}), 1.97–1.87 (1H, m, H_{2A}), 1.75–1.61 (1H, m, H_3), 1.43 (1H, dtd, *J* 13.1, 11.4, 5.8, H_{2B}), 1.34–1.25 (2H, m, H_5), 0.87 (3H, t, *J* 7.5, H_6); δ_C (101 MHz, $CDCl_3$) 137.2, 128.5, 127.9, 127.3, 52.5, 50.2, 35.5, 31.6, 26.0, 11.3; *m*/*z* (ESI) 240.0 (M^++1).

3.1.43. 5-Acetyl-1-benzylpyrimidine-2,4(1H,3H)-dione, ***34****.*[36] Under nitrogen, a suspension of 5-acetyluracil (200 mg, 1.298 mmol) and NaH (60% in oil, 52 mg, 1.300 mmol) in DMF (6.5 mL) was stirred at room temperature for 90 m. A solution of benzyl bromide (200.6 mg, 1.173 mmol) in DMF (6.5 mL) was added dropwise over 30 min and the mixture was stirred at room temperature for 3 d. Following concentration under reduced pressure, purification by column chromatography (ethyl acetate–petroleum ether 1:1) and recrystallisation (methanol), product **34** (123 mg, 0.504 mmol, 39% yield) was obtained as colourless needles; Mp 196–198 °C; (found (ESI): M^++Na, 267.0740. $C_{13}H_{12}N_2NaO_3$ requires M, 267.0740); ν_{max} 3486, 3408, 1724, 1640, 1599, 1554, 1510, 1450, cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.63 (1H, br s, N*H*), 8.26 (1H, s, C*H*), 7.44–7.30 (5H, m, Ar*H*), 4.99 (2H, s, CH_2), 2.59 (3H, s, CH_3); δ_C (151 MHz, DMSO-d_6) 193.5, 161.7, 151.5, 150.4, 136.2, 128.7, 127.9, 127.7, 111.8, 51.0, 30.3; *m*/*z* (ESI) 267.1 (M^++Na). The crystals obtained were of sufficient quality for X-diffraction, enabling confirmation of the structure.[11]

3.1.44. 5-(1-Hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione, ***35****.* This compound was prepared following the general procedure for ketone transfer hydrogenation, using 5-acetyluracil (100 mg, 0.641 mmol) and Ru(*R*,*R*)*teth*-TsDPEN (8.1 mg, 1.31×10^{-2} mmol) in neat FA/TEA (700 μL, 2 M). Following a reaction time of 17 h, DCM (2 mL) was added and the resulting suspension was cooled and filtered. The resulting powder was dried to give an inseparable mixture of the diastereomers (3.1:1, as determined by ^{1}H NMR) **35** (denoted here as **a** and **b**) (80 mg, 0.506 mmol, 79% yield) as a dull yellow powder; (Found (ESI): M^++Na, 181.0588. $C_6H_{10}N_2NaO_3$ requires M, 181.0584); Mp 226–230 °C; ν_{max} 3400, 3219, 3085, 1708, 1674, 1497 cm^{-1}; **35a**: δ_H (600 MHz, DMSO-d_6) 9.90 (1H, br s, N*H*), 7.42 (1H, br s, N*H*), 4.82 (1H, d, *J* 6.0, O*H*), 4.03 (1H, sxt, *J* 6.0, H_2), 3.32–3.15 (2H, m, H_4), 2.31 (1H, q, 6.0, H_3), 1.13 (3H, d, *J* 6.0, H_1); δ_C (151 MHz, DMSO-d_6) 171.8, 153.5, 62.7, 46.8, 36.0, 21.8; **35b**: δ_H (600 MHz, DMSO-d_6) 9.93 (1H, br s, N*H*), 7.43 (1H, br s, N*H*), 4.84–4.83 (1H, m, O*H*), 4.10–4.09 (1H, m, H_2), 3.32–3.15 (2H, m, H_4), 2.57 (1H, dt, *J* 7.2, 6.0, H_3), 1.06 (3H, d, *J* 6.4, H_1); δ_C (151 MHz, DMSO-d_6) 171.8, 153.5, 64.8, 45.8, 36.0, 19.2; *m*/*z* (ESI) 159.0 (M^+–H).

3.1.45. 1-Benzyl-5-(1-hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione, ***37****.* This compound was prepared following the general procedure (C) for ketone transfer hydrogenation, using 5-acetyl-1-benzylpyrimidine-2,4(1*H*,3*H*)-dione **34** (30 mg, 0.123 mmol) and Ru(*R*,*R*)*teth*-TsDPEN (0.6 mg, 9.67×10^{-4} mmol) following a reaction time of 20 h. Following concentration under reduced pressure and purification by column chromatography (ethyl acetate–petroleum ether 9:1), an inseparable mixture of diastereomers **37** (denoted here as **a** and **b**) (3.48:1, as determined by ^{1}H NMR) (23 mg, 0.093 mmol, 75% yield) was obtained as a colourless oil; (found (ESI): M^++Na, 271.1049. $C_{13}H_{16}N_2NaO_3$ requires M, 271.1053); ν_{max} 3400, 3199, 3066, 2974, 1670, 1491 cm^{-1}; *m*/*z* (ESI) 270.8 (M^++23); **37a**: δ_H (400 MHz, $CDCl_3$) 8.22 (1H, br s, N*H*), 7.41–7.25 (5H, m, Ar*H*), 4.67 (1H, d, *J* 14.8, CH_2), 4.58 (1H, d, *J* 14.8, CH_2), 4.33 (1H, sxt, *J* 6.3, H_2), 3.48 (1H, dd, *J* 12.6, 10.8, H_{4A}), 3.28 (1H, dd, *J* 12.6, 6.1, H_{4B}), 2.66–2.59 (1H, m, H_3), 1.20 (3H, d, *J* 6.3, H_1); A resonance attributable to O*H* was not observed; δ_C (101 MHz, $CDCl_3$) 171.6, 152.7, 136.0, 128.8, 127.9, 128.0, 63.9, 50.6, 46.7, 41.7, 19.9. Enantiomeric separation was achieved by HPLC analysis (Chiralpak IA, 4.6 mm×250 mm, hexane:IPA 90:10, 1 mL/min, *T*=30 °C, minor isomer 72.6 min, major isomer 41.8 min) 69% ee; **37b**: δ_H (400 MHz, $CDCl_3$) 8.26 (1H, br s, N*H*), 7.40–7.27 (5H, m, Ar*H*), 4.92 (1H, d, *J* 1.8, O*H*), 4.68 (1H, d, *J* 14.8, CH_2), 4.57 (1H, d, *J* 14.8, CH_2), 4.01 (1H, quind, *J* 6.6, 1.8, H_2), 3.25–3.15 (2H, m, H_4), 2.66–2.59 (1H, m, H_3), 1.14 (3H, d, *J* 6.6, H_1); A resonance attributable to O*H* was not observed; δ_C (101 MHz, $CDCl_3$) 172.7, 152.6, 135.8, 128.9, 128.1, 127.9, 66.2, 50.5, 46.4, 43.4, 20.0; Enantiomeric separation was achieved by HPLC analysis (Chiralpak IA, 4.6 mm×250 mm, hexane:IPA 90:10, 1 mL/min, *T*=30 °C, minor isomer 46.0 min, major isomer 51.9 min) 19% ee.

Acknowledgements

We thank the EPSRC and AstraZeneca for funding (to A.A.B.) and the National Crystallographic Service (Southampton University) for collecting the diffraction data for compound **34**.[37] The data for the other structures (**3d**, **3e** and **16a**) was collected on an Oxford Diffraction Gemini instrument obtained through the Science City Project with support from Advantage West Midlands and part funded by the European Regional Development Fund. Johnson Matthey are thanked for supplying samples of commercially-available catalyst **19** used in this project. We thank Dr. Reddys for the donation of a sample of the Ru(EtDuPHOS) complex **18**. Dr. Peter Quayle (University of Manchester) is thanked for useful discussions.

Supplementary data

NMR spectra and chiral GC/HPLC spectra. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.046.

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