Tetrahedron 65 (2009) 4671–4680

Contents lists available at ScienceDirect

Tetrahedron

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

Synthetic evaluation of an enantiopure tetrahydropyridine *N*-oxide. Synthesis of (+)-febrifugine

Amir Ashoorzadeh, Glenn Archibald, Vittorio Caprio *

Department of Chemistry, University of Auckland, 23 Symonds Street, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 12 December 2008
Received in revised form 24 March 2009
Accepted 9 April 2009
Available online 17 April 2009

ABSTRACT

A study into the synthesis and synthetic utility of (*S*)-3-benzyloxy-3,4,5,6-tetrahydropyridine *N*-oxide is described. This nitrone is readily accessed from L-glutamic acid and the regio- and stereoselectivity of cycloaddition of this compound with a range of alkenes has been probed. Reductive cleavage of the major cycloadducts provides access to a diverse range of *trans*-2,3-disubstituted piperidines. The synthetic scope of this nitrone is further illustrated by the use of this compound as a key intermediate in a concise synthesis of the anti-malarial agent (+)-febrifugine.

1. Introduction

trans-2-Substituted-3-hydroxypiperidines form the core structure of a diverse range of alkaloids of biological interest, such as the anti-malarial alkaloid (+)-febrifugine **1**[1] and the analogue of baclofen **2**[2] (Fig. 1). Furthermore, this moiety also exists as a central structural subunit in the antibiotic and anaesthetic prosopis alkaloids prosopinine **3** and prosophylline **4**,[3] and also the α-mannosidase inhibitor swainsonine **5**.[4]

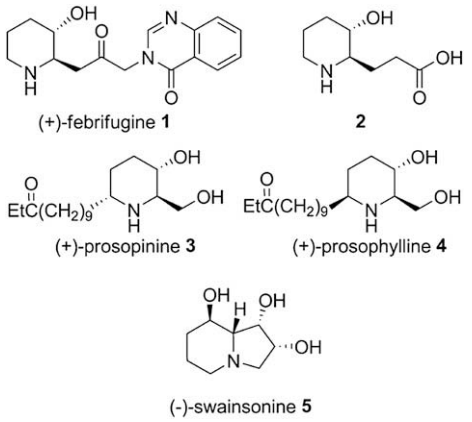


Figure 1.

While a number of synthetic routes to *trans*-2-substituted-3-piperidinols have been developed, few are sufficiently flexible for the synthesis of a diverse range of targets.[5] We envisioned that an enantiomerically pure 3-hydroxy-3,4,5,6-tetrahydropyridine *N*-oxide would function as a useful synthon in this regard. Nitrones are known to exhibit a diverse reactivity profile, undergoing 1,3-dipolar cycloaddition with a variety of electron rich and electron deficient alkenes and also addition with nucleophiles at C-2.[6] While derivatives of 3-hydroxy-1-pyrroline *N*-oxide **6** (Fig. 2) have seen wide application in the stereoselective syntheses of pyrrolidine-based alkaloids,[7] and polyhydroxylated six-membered ring nitrones are also known,[8] there is only one report of the in situ generation/1,3-dipolar cycloaddition of a 3-hydroxytetrahydropyridine *N*-oxide in synthesis,[9] and the chemistry and synthetic scope of these compounds remains to be studied.

To this end, we recently reported the development of a concise synthetic route to (*S*)-3-benzyloxy-3,4,5,6-tetrahydropyridine *N*-oxide **7** from L-glutamic acid and demonstrated the utility of this nitrone in a convergent synthesis of (+)-febrifugine.[10] Full details of this synthesis are reported herein, along with the results of a study aimed at more fully probing the reactivity of nitrone **7** with a range of dipolarophiles.

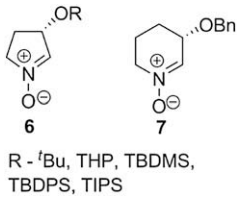
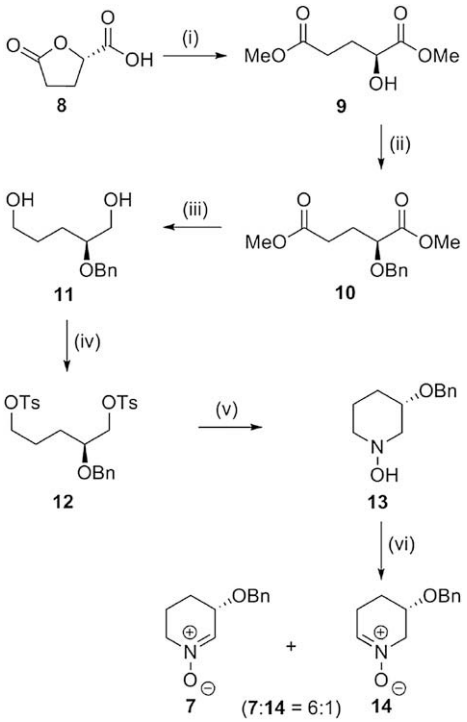


Figure 2.

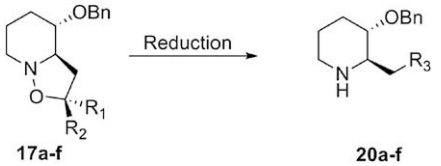
* Corresponding author. Tel.: +64 9 373 7599; fax: +69 9 373 7422.
E-mail address: v.caprio@auckland.ac.nz (V. Caprio).

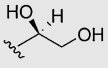
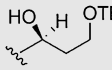
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.04.044



Scheme 1. Reagents and conditions: (i) $HCl_{(concd)}$, MeOH, reflux, 12 h, 93%; (ii) BnBr, Ag_2O, EtOAc, rt, 48 h, 79%; (iii) $LiAlH_4$, Et_2O, 24 h, 88%; (iv) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 12 h, 86%; (v) $NH_2OH{\cdot}HCl$, Et_3N, reflux, 4 h, 74%; (vi) MnO_2, CH_2Cl_2, 0 °C, 12 h, **7** 51%, **14** 9%.

Table 2
Reductive cleavage of isoxazolidines **17a–f**



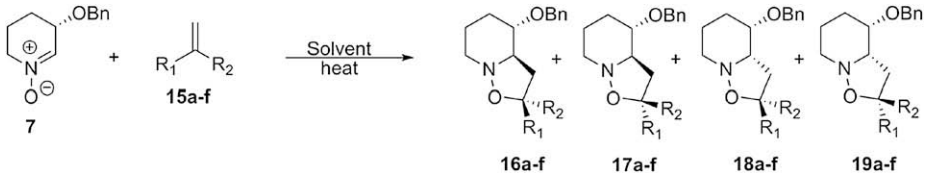
Entry	R_1	R_2	Isoxazolidine **17**	Conditions[a]	Piperidine **20**	R_3	Yield (%)[b]
1	Ph	H	**17a**	A	**20a**		77
2	OEt	H	**17b**	A/B	**20b**		—
3	$OSiMe_3$	Me	**17c**	A	**20c**		68
4	CO_2Et	H	**17d**	A	**20d**		—
5	CH_2OH	H	**17e**	B	**20e**		45
6	$(CH_2)_2OTBS$	H	**17f**	B	**20f**		53

[a] Conditions A: 5.6 equiv Zn, 7 mol % $Cu(OAc)_2$, AcOH, reflux, 1 h. Conditions B: 2.0 equiv Zn, 10 mol % In, EtOH/$NH_4Cl_{(aq)}$ (2:1) reflux, 12 h.
[b] Isolated and chromatographically pure products.

2. Results and discussion

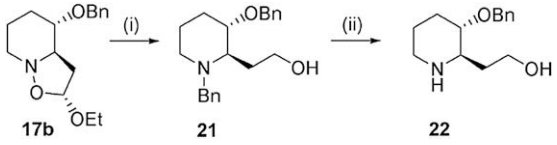
Enantiopure, *O*-protected 3-hydroxypyrroline *N*-oxides are conveniently accessed by regioselective oxidation of the corresponding *N*-hydroxypyrrolidine, obtained from L-malic acid.[7k] We adopted a similar, chiral-pool based strategy for the synthesis of nitrone **7**, utilising (*S*)-acid lactone **8**, derived from L-glutamic acid, as starting material (Scheme 1). Acid-catalysed esterification of lactone **8** in methanol gave hydroxydiester **9**.[11] Protection of **9**, and subsequent elaboration, was initially problematic. We originally desired to access a silyl-protected derivative of nitrone **7**. While protection of alcohol **9** as the *tert*-butyl dimethylsilyl ether proceeded with high yield, subsequent reduction using lithium aluminium hydride gave an inseparable mixture of reduction products, thought to arise from partial migration of the silyl group. Reduction using lithium borohydride in THF also resulted in the isolation of mono-protected triols, and attempts to suppress migration using a mixture of sodium borohydride and cerium trichloride, according to the method of Fleet and co-workers was unsuccessful.[12] Consequently, we opted to protect the hydroxyl moiety in **9** as a benzyl ether. Attempted benzylation, using benzyl bromide/sodium hydride or benzyl trichloroacetimidate/TFA,[12] led to the isolation of **10** in only low yield. Optimum yields of **10** were obtained using benzyl bromide in combination with freshly prepared silver oxide.[13] Reduction of **10**, proceeded cleanly, using lithium aluminium hydride, to give the diol **11** in high yield. Subsequent ditosylation, followed by cyclisation in the presence of hydroxylamine hydrochloride, also proceeded uneventfully to give *N*-hydroxy-3-benzyloxypiperidine **13**. Mercury(II) chloride is commonly used to oxidise cyclic and acyclic *N*-hydroxylamines to nitrones.[14] However, in an effort to

Table 1
1,3-Dipolar cycloaddition of nitrone **7** with dipolarophiles **15a–f**

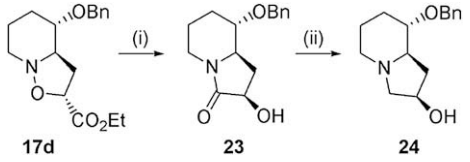


Entry	Alkene	R_1	R_2	Solvent	Temp (°C)	Time (h)	Yield (%) of isomers[a]				Overall yield/[b](%)
							16	**17**	**18**	**19**	
1	**15a**	Ph	H	$CHCl_3$	60	20	—	64	34	—	98
2	**15b**	OEt	H	PhMe	45	3	—	53	27	—	80
3	**15c**	$OSiMe_3$	Me	PhMe	110	48	12	27	16	—	55
4	**15d**	CO_2Et	H	CH_2Cl_2	25	3	8	55	24	—	87
5	**15e**	CH_2OH	H	PhMe	110	24	7	40	10	—	57
6	**15f**	$(CH_2)_2OTBS$	H	PhMe	80	12	—	52	20	—	72

[a] Stereochemistry determined by 2D-NOESY studies.
[b] Isolated and chromatographically pure products.



Scheme 2. Reagents and conditions: (i) (a) BnBr, CH_2Cl_2, rt, 12 h; (b) $LiAlH_4$, THF, reflux, 3 h, 59%; (ii) H_2, Pd/C, MeOH, rt, quant.



Scheme 3. Reagents and conditions: (i) 5.6 equiv Zn, 7 mol % $Cu(OAc)_2$, AcOH, reflux, 1 h, 94%; (ii) (a) $BH_3{\cdot}SMe_2$, THF, −15 to 66 °C, 4 h; (b) Pd/C, H_2, MeOH, rt, 5 h, 89%.

avoid large scale use of this toxic reagent, we effected oxidation of **13** to a regioisomeric mixture of nitrones **7** and **14** in ratios ranging from 7:1 to 6:1, using freshly prepared manganese dioxide.[15]

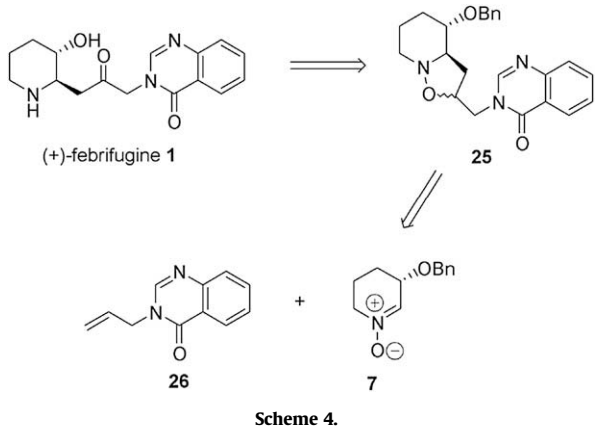
The origin of regioselectivity in the oxidation step is intriguing, and we are yet to conduct detailed studies in this area. This process is thought to be a two-step reaction, proceeding via oxidation of the *N*-hydroxyl moiety to give a nitrosonium ion, followed by rate-determining hydrogen abstraction from the α-carbon.[7k,16] Cicchi and co-workers have investigated the oxidation of 3-substituted *N*-hydroxypyrrolidines to give nitrones of type **6**. These studies reveal that regioselectivity arises from polarisation of a C–H bond at C-2, by the electronegative C-3 substituent, leading to selective deprotonation at the 2-position.[7k,17]

The regio- and stereochemistry of cycloaddition of nitrone **7** with a diverse range of alkenes **15a**–**f** was then probed, and the results of this study are presented in Table 1. The reaction conditions specified for the cycloadditions are those giving optimum yields of products. Nitrone **7** undergoes 1,3-dipolar cycloaddition, in moderate to good yield with styrene **15a**, electron rich alkenes **15b**,**c** and an electron poor alkene **15d**. Good yields are also obtained in the cycloaddition with allyl alcohol **15e** and silyloxybutene **15f**, giving cycloadducts of potential in the synthesis of indolizidines and quinolizidines, respectively.[6f,h,j] Excellent regioselectivity is observed giving 2-substituted isoxazolidines as the sole products. High *exo*/*endo* selectivity is also observed. However, the cis/trans selectivity across the C2–C3 bond is only modestly in favour of the *trans*-cycloadduct.

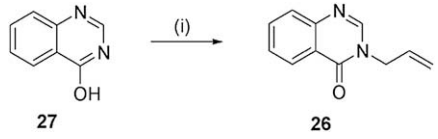
The synthetic utility of nitrone **7** was further illustrated by the ease of reductive ring opening of cycloadducts **17a**,**c** and **17e**,**f** to give access to a range of 2,3-*trans*-disubstituted piperidines, in moderate to good yield, using either zinc in acetic acid,[18] or zinc and catalytic indium[19] as the reductants (Table 2). Isoxazolidine **17b** was not converted to the expected aldehyde **20b** under either set of reduction conditions. However, reductive cleavage of **17b**, to *N*-benzyl protected (2-hydroxyethyl)piperidine **21**, was achieved by conversion to the *N*-benzyl salt followed by addition of lithium aluminium hydride (Scheme 2). Selective deprotection, at nitrogen, to give piperidine **22**, was achieved, quantitatively, by hydrogenolysis in the presence of palladium on carbon.

Reductive ring opening of cycloadduct **17d** also did not proceed as expected. Ring cleavage in the presence of zinc/acetic acid was followed by lactamization to give indolizidinone **23**. Further reduction using borane-dimethylsulfide gave *O*-protected dihydroxyindolizidine **24**. The free diol derived from **24** has been previously reported and shown to exhibit glycosidase activity (Scheme 3).[20]

With the general synthetic utility of this intermediate probed, our attention turned to evaluating the use of this compound in the synthesis of a suitable natural product target. (+)-Febrifugine **1**,



Scheme 4.

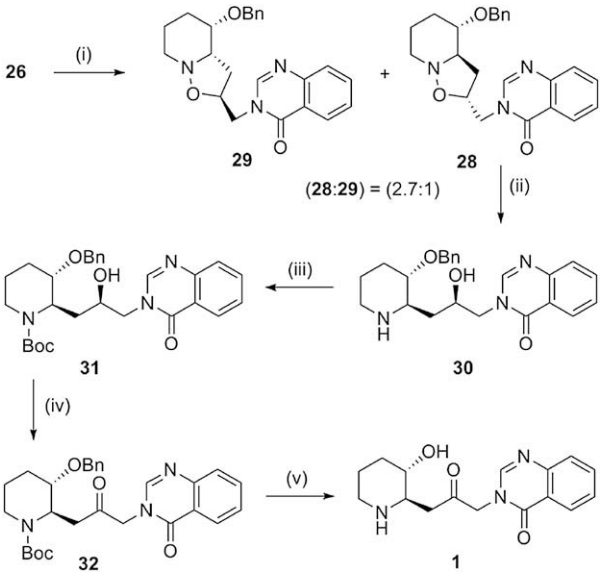


Scheme 5. Reagents and conditions: (i) Allyl bromide, NaOMe/MeOH, rt, 12 h, 78%.

isolated from the roots of *Dichroa febrifugia*,[1] exhibits potent anti-malarial activity[21] and, as no parasite resistance to **1** has been reported,[22] this compound is an important lead in the search for new anti-malarial drugs.[5b,d,i,9,23] Moreover, the presence of a *trans*-2-substituted 3-hydroxypiperidine, as a key subunit of this target, made it an ideal candidate for the synthetic evaluation of synthon **7**. Our highly convergent approach to this molecule, outlined in Scheme 4, centres on the reductive cleavage of isoxazolidine **25**, accessed by 1,3-dipolar cycloaddition of **7** with readily available *N*-allylquinazoline **26**.

Dipolarophile **26** was prepared, in good yield, by reaction of commercially available 4-hydroxyquinazoline **27** with allyl bromide in the presence of sodium methoxide in methanol (Scheme 5).[24]

The key cycloaddition of **26** with nitrone **7** was readily achieved, in toluene under reflux, to give the desired *trans*-adduct **28** as the



Scheme 6. Reagents and conditions: (i) **7**, PhMe, reflux, 24 h, **28** 48%, **29** 18%; (ii) Zn, HOAc, reflux, 5 h, 53%; (iii) BOC_2O, Et_3N, CH_2Cl_2, 20 h, 80%; (iv) Dess–Martin periodinane, pyridine, CH_2Cl_2, 2 h, quant.; (v) 6 M $HCl_{(aq)}$, reflux, 40 min, 67%.

exo-isomer as the major product (Scheme 6). Closer inspection of the reaction mixture revealed the presence of the corresponding *cis*-adduct **29**, as a minor, readily separable component. The trans/cis ratio of 2.7:1 obtained in this key step is comparable to the selectivities observed during the model studies described in Table 1. All stereochemical assignments were made using 2D-NOESY studies recorded in DMSO-d_6 at elevated temperature.[10]

With the desired isoxazolidine **28** in hand, the target molecule **1** was accessed in four further steps (Scheme 6). Reductive cleavage of the N–O bond, using zinc powder in acetic acid, followed by Boc-protection of the resulting hydroxyketone, gave alcohol **31**, in moderate overall yield. Dess–Martin periodinane mediated oxidation gave *N*,*O*-protected febrifugine **32**, previously prepared by Kobayashi and co-workers, in quantitative yield. Global deprotection, using boiling aqueous HCl, under Kobayashi's conditions then gave (+)-febrifugine **1**, that exhibits physical data ($[\alpha]_D^{24}$ +26.4 (*c* 0.30, EtOH) mp 139–141 °C) in close agreement with that obtained by Kobayashi and co-workers ($[\alpha]_D^{27}$ +26.6 (*c* 0.10, EtOH) mp 138–140 °C)[23j] and for the isolated natural product ($[\alpha]_D^{25}$ +28.0 (*c* 0.30, EtOH) mp 139–140 °C).[1b]

3. Conclusion

Nitrone **7** has been shown to have utility as a chiral, non-racemic building block in the synthesis of piperidine alkaloids. The 1,3-dipolar cycloadditions of this compound proceed with moderate facial selectivity. However, good to high yields of cycloadducts are obtained with a range of alkenes, providing ready access to a diverse set of *trans*-2-disubstituted-3-hydroxypiperidines and indolizidines. Our use of **7** as a key intermediate in a concise and convergent synthesis of (+)-febrifugine further underlines the synthetic potential of this compound. Future work, directed towards further probing the reactivity of nitrones of this family and their applications in total synthesis will be reported in due course.

4. Experimental section

4.1. General methods

All reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried by distillation from calcium hydride (CH_2Cl_2, DMF) or sodium-benzophenone (THF and diethyl ether). Flash chromatography was performed using Scharlau 60 (230–400 mesh ASTM) silica gel and reversed phase (C_{18}) chromatography was performed using Merck Lichroprep RP-18 40–63 μm. Thin layer chromatography was performed on Merck silica gel 60 F_{254} plates. Melting points were measured by a Reicher–Kofler block and are uncorrected. Optical rotations were measured using a Perkin–Elmer 341 polarimeter at 589 nm (sodium—D line). IR spectra were recorded using a Perkin–Elmer Spectrum 1000 Fourier-Transform IR spectrometer. NMR spectra were recorded using a Bruker Avance 300 Spectrometer or a Bruker DRX 400 Spectrometer. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak (δ 0.00 ppm). ^{1}H NMR values are reported as chemical shift δ, relative integral, multiplicity, (s, singlet; d, doublet; t, triplet; q, quartet; quintet; m, multiplet), coupling constant (J)$_2$ and assignment. Coupling constants were taken directly from the spectra. Assignments were made with the aid of DEPT, COSY, HSQC, HMBC and NOESY experiments. Low resolution and accurate mass data were recorded on a VG70SE spectrometer operating at a nominal accelerating voltage of 70 eV. Ionisation was effected using electron impact (EI^+), chemical ionisation (CI^+) using ammonia as a carrier gas, or fast atom bombardment (FAB^+) using 3-nitrobenzylalcohol as the matrix. Major and significant fragments are quoted in the form *x* (*y*), where *x* is the mass to charge ratio (*m*/*z*) and *y* is the percentage abundance relative to the base peak (100%).

4.2. Synthesis of nitrone 7

4.2.1. (2S)-Dimethyl 2-hydroxypentanedioate (**9**)

Four drops of $HCl_{(concd)}$ were added to a stirred solution of acid lactone **8** (6.0 g, 46.1 mmol) in MeOH (57 mL). The reaction mixture was then stirred under reflux for 12 h, cooled to room temperature and solid $NaHCO_3$ (1.0 g, 12 mmol) was added. The reaction mixture was stirred for a further 10 min, filtered and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (1:4) to give the *title compound* as a colourless oil (7.6 g, 93%). R_f (50% EtOAc/hexane) 0.31; $[\alpha]_D^{20}$ −2.5 (*c* 0.9, EtOH); ν_{max} (film) 3480, 1737, 1215 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.25 (1H, dd, *J* 7.9, 4.2, H-2), 3.80 (3H, s, C1-OMe), 3.68 (3H, s, C5-OMe), 2.95 (1H, br s, O*H*), 2.58–2.24 (2H, m, H-4), 2.22–2.14 (1H, m, H_a,H_b-3), 2.00–1.91 (1H, m, H_a,H_b-3); δ_C (75 MHz; $CDCl_3$) 174.9, 173.5, 69.4, 52.5, 51.6, 29.3, 29.1; *m*/*z* (EI) 176 (0.8, M^+), 159 (3), 145 (8), 117 (18), 85 (100), 59 (5), 57 (10%). HRMS (EI): M^+, found 176.0682. $C_7H_{12}O_5$ requires 176.0685.

4.2.2. (2S)-Dimethyl 2-(benzyloxy)pentanedioate (**10**)

A solution of hydroxydiester **9** (4.77 g, 27.1 mmol) in EtOAc (23 mL) was added dropwise to a suspension of freshly prepared Ag_2O (9.29 g, 40.1 mmol) in EtOAc (23 mL) at room temperature. The mixture was stirred for 10 min then benzyl bromide (4.74 mL, 40.1 mmol) was added. The reaction mixture was stirred at this temperature for 48 h then filtered through Celite®. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to give the *title compound* as a colourless oil (5.69 g, 79%). R_f (40% EtOAc/hexane) 0.8; $[\alpha]_D^{20}$ −71.6 (*c* 1.0, EtOH); ν_{max} (film) 3055, 2953, 1735, 1437, 1206 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.38–7.27 (5H, m, Ar–H), 4.72 (1H, d, *J* 11.6, OC*H*$_a$,H$_b$Ph), 4.40 (1H, d, *J* 11.6, OCH$_a$,*H*$_b$OPh), 4.01 (1H, dd, *J* 8.2, 4.5, H-2), 3.76 (3H, s, C5-OMe), 3.63 (3H, s, C1-OMe), 2.46 (2H, t, *J* 7.4, H-4), 2.18–2.06 (2H, m, H-3); δ_C (75 MHz; $CDCl_3$) 173.3, 172.7, 137.2, 128.4, 128.1, 127.9, 76.5, 72.4, 52.0, 51.6, 29.6, 27.9; *m*/*z* (CI, NH_3) 267 (93, MH^+), 235 (20), 198 (2), 181 (10), 176 (2), 160 (18), 145 (7), 108 (27), 91 (100%). HRMS (CI, NH_3): MH^+, found 267.1235. $C_{14}H_{19}O_5$ requires 267.1233.

4.2.3. (2S)-2-(Benzyloxy)pentane-1,5-diol (**11**)

A solution of diester **10** (13.5 g, 50.7 mmol) in Et_2O (270 mL) was added dropwise to a stirred solution of $LiAlH_4$ (3.86 g, 101.7 mmol) in Et_2O (270 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h then quenched by careful addition of EtOAc (270 mL) then H_2O (24 mL) and 4 M $NaOH_{(aq)}$ (6 mL). The mixture was extracted with Et_2O (3×200 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (1:2) to give the *title compound* as a colourless oil (9.44 g, 88%). R_f (66% EtOAc/hexane) 0.14; $[\alpha]_D^{20}$ −19.7 (*c* 1.1, EtOH); ν_{max} (film) 3369, 2942, 1454, 1062 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.36–7.29 (5H, m, Ar–H), 4.62 (1H, d, *J* 11.5, OC*H*$_a$,H$_b$Ph), 4.57 (1H, d, *J* 11.5, OCH$_a$,*H*$_b$Ph), 3.73–3.69 (1H, m, H-2), 3.64–3.52 (4H, m, H-1, H-5), 1.96 (2H, br s, O*H*), 1.72–1.59, (4H, m, H-3, H-4); δ_C (75 MHz; $CDCl_3$) 138.2, 128.5, 127.8 (2C), 79.4, 71.6, 64.0, 62.7, 28.4, 27.3; *m*/*z* (CI, NH_3) 211 (100, MH^+), 193 (6), 108 (19), 101 (19), 91 (87), 85 (9), 71 (23%). HRMS (CI, NH_3): MH^+, found 211.1337. $C_{12}H_{19}O_3$ requires 211.1334.

4.2.4. (2S)-(2-Benzyloxy)-1,5-bis(para-toluenesulfonyloxy)-pentane (**12**)

A solution of TsCl (7.60 g, 39.9 mmol), in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of diol **11** (2.76 g, 13.1 mmol),

Et_3N (5.3 mL, 38 mmol) and DMAP (0.32 g, 2.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h and then concentrated under reduced pressure. The residue was diluted with a saturated brine solution and extracted with EtOAc (3×200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give the *title compound* as a white solid (5.83 g, 86%). Mp 52.1–54.0 °C; R_f (40% EtOAc/hexane) 0.71; $[\alpha]_D^{20}$ −16.0 (*c* 0.9, $CHCl_3$); ν_{max} (solid) 3032, 2924, 1597, 1453, 1357, 1175 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.78–7.74 (4H, m, Ar–H), 7.34–7.32 (4H, m, Ar–H), 7.32–7.28 (3H, m, Ar–H), 7.22–7.20 (2H, m, Ar–H), 4.52 (1H, d, *J* 11.6, OC*H*$_a$,H$_b$Ph), 4.39 (1H, d, *J* 11.6, OCH$_a$,*H*$_b$Ph), 3.98–3.97 (2H, m, H-1), 3.96–3.92 (2H, m, H-5), 3.54 (1H, qd, *J* 7.8, 4.9, H-2), 2.44 (6H, s, Ar–Me), 1.72–1.60 (2H, m, H-4), 1.54–1.46 (2H, m, H-3); δ_C (75 MHz; $CDCl_3$) 145.0, 144.8, 137.7, 133.1, 132.8, 129.9 (2C), 128.4, 127.9, 127.8 (3C), 75.4, 72.2, 70.8, 70.0, 27.5, 24.6, 21.6 (2C); *m*/*z* (FAB$^+$, *m*-nitrobenzylalcohol) 519 (5, MH^+), 391 (2), 347 (3), 341 (1), 257 (20), 219 (4), 165 (6), 91 (100), 85 (20%). HRMS (FAB$^+$): MH^+, found 519.1517. $C_{26}H_{31}O_7S_2$ requires 519.1511.

4.2.5. (3S)-3-(Benzyloxy)-N-hydroxypiperidine (**13**)

The ditosylate **12** (3.40 g, 6.56 mmol) was added to a stirred suspension of $NH_2OH{\cdot}HCl$ (1.97 g, 28.3 mmol) in Et_3N (18.6 mL) at room temperature. The reaction mixture was then stirred under reflux for 4 h, cooled to room temperature and filtered through Celite®. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with CH_2Cl_2/MeOH (24:1) to give the *title compound* as a colourless oil (1.0 g, 74%). R_f (5% MeOH/CH_2Cl_2) 0.34; $[\alpha]_D^{20}$ −9.6 (*c* 0.96, EtOH); ν_{max} (film) 3201, 3054, 2951, 1454 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.36–7.21 (5H, m, Ar–H), 4.54 (2H, s, OC*H*$_2$Ph), 3.63–3.52 (1H, m, H-3), 3.22–3.11 (1H, m, C*H*$_a$,H$_b$-2), 2.94–2.83 (1H, m, C*H*$_a$,H$_b$-6), 2.53–2.42 (2H, m, CH$_a$,*H*$_b$-2, CH$_a$,*H*$_b$-6), 1.89–1.78 (1H, m, C*H*$_a$,H$_b$-4), 1.76–1.64 (1H, m, C*H*$_a$,H$_b$-5), 1.57–1.40 (1H, m, CH$_a$,*H*$_b$-5), 1.33–1.17 (1H, m, CH$_a$,*H*$_b$-4); δ_C (75 MHz; DMSO-d_6, 353 K) 138.6, 127.5, 126.7, 126.5, 73.2, 69.1, 62.3, 57.5, 28.7, 20.3; *m*/*z* (EI) 207 (2, M^+), 190 (1), 116 (16), 101 (3), 91 (100), 71 (22%). HRMS (EI): M^+, found 207.1261. $C_{12}H_{17}NO_2$ requires 207.1259.

4.2.6. (3S)-3-Benzyloxy-3,4,5,6-tetrahydropyridine N-oxide (**7**) and (5S)-5-benzyloxy-3,4,5,6-tetrahydropyridine N-oxide (**14**)

A solution of *N*-hydroxypiperidine **13** (0.89 g, 4.3 mmol) in CH_2Cl_2 (10 mL) was added to a stirred suspension of MnO_2 (1.49 g, 17.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h then filtered through Celite®. The filtrate was concentrated under reduced pressure to give a yellow oil composed of a mixture of nitrones **7** and **14**. These regioisomers were separated by flash column chromatography eluting with CH_2Cl_2/MeOH (24:1) to give 0.45 g (51%) of nitrone **7** and 0.076 g (9%) of nitrone **14**. Data for **7**: R_f (5% MeOH/CH_2Cl_2) 0.17; $[\alpha]_D^{20}$ −72.0 (*c* 1.2, EtOH); ν_{max} (film) 3031, 2949, 1454 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.36–7.31 (5H, m, Ar–H), 7.22 (1H, d, *J* 3.7, H-2), 4.60 (2H, s, OCH_2Ph), 4.18–4.15 (1H, m, H-3), 3.83–3.74 (2H, m, H-6), 2.21–2.16 (1H, m, C*H*$_a$,H$_b$-5), 1.93–1.82 (3H, m, H-4, CH$_a$,*H*$_b$-5); δ_C (75 MHz; $CDCl_3$) 137.4, 135.1, 128.5, 128.0, 127.6, 71.0, 70.3, 58.7, 24.4, 19.0; *m*/*z* (CI, NH_3) 206 (6, MH^+), 192 (14), 190 (100), 188 (15), 174 (6), 100 (16), 98 (32), 91 (9), 84 (13%). HRMS (CI, NH_3): MH^+, found 206.1182. $C_{12}H_{16}NO_2$ requires 206.1181. Data for **14**: R_f (5% MeOH/CH_2Cl_2) 0.11; $[\alpha]_D^{20}$ +21.1 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3053, 2985, 1422 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.36–7.28 (5H, m, Ar–H), 7.27–7.16 (1H, m, H-2), 4.61 (1H, d, *J* 12.0, OC*H*$_a$,H$_b$Ph), 4.56 (1H, d, *J* 12.0, OCH$_a$,*H*$_b$Ph), 3.99–3.94 (1H, m, H-5), 3.90 (2H, br s, H-6), 2.61–2.60 (1H, m, C*H*$_a$,H$_b$-3), 2.41–2.39 (1H, m, CH$_a$,*H*$_b$-3), 2.05–1.95 (1H, m, C*H*$_a$,H$_b$-4), 1.83–1.75 (1H, m, CH$_a$,*H*$_b$-4); δ_C (75 MHz; $CDCl_3$) 137.5, 136.0, 128.5, 127.9, 127.5, 70.6, 70.3, 61.2, 22.2, 21.5; *m*/*z* (EI) 205 (3, M^+), 188 (3), 114 (3), 99 (10), 91 (100), 83 (9%). HRMS (EI): M^+, found 205.1098. $C_{12}H_{15}NO_2$ requires 205.1103.

4.3. General procedure for the synthesis of cycloadducts

A solution of dipolarophile **15** in the solvent given in Table 1 was added to a stirred solution of nitrone **7** in the same solvent at room temperature. The reaction mixture was then stirred at the temperature and time specified in Table 1, cooled to room temperature, then concentrated under reduced pressure and the residue purified by flash chromatography.

4.3.1. Synthesis of (2R,3aR,4S)-2-phenyl-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**17a**) and (2S,3aS,4S)-2-phenyl-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**18a**)

Following the general procedure, a solution of styrene **15a** (0.051 g, 0.49 mmol) in $CHCl_3$ (2 mL) was added to nitrone **7** (0.033 g, 0.16 mmol) in $CHCl_3$ (2 mL) and the mixture stirred at 60 °C for 20 h. Purification of the residue by flash chromatography eluting with hexanes/EtOAc (4:1) gave compound **17a** (0.032 g, 64%) as a yellow oil and **18a** (0.017 g, 34%) as a yellow solid. Data for **17a**: R_f; (20% EtOAc/hexanes) 0.29; $[\alpha]_D^{22}$ +27.3 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3053, 2949, 1453; δ_H (400 MHz; DMSO-d_6, 393 K) 7.39–7.25 (10H, m, Ar–H), 5.04 (1H, dd, *J* 9.2, 4.8, H-2), 4.63 (1H, d, *J* 12.0, OC*H*$_a$,H$_b$Ph), 4.55 (1H, d, *J* 12.0, OCH$_a$,*H*$_b$Ph), 3.52 (1H, ddd, *J* 4.3, 8.0, 9.1, H-4), 3.26 (1H, dt, *J* 4.1, 9.4, C*H*$_a$,H$_b$-7), 2.81–2.76 (1H, m, H-3a), 2.67 (1H, td, *J* 9.4, 3.3, CH$_a$*H*$_b$-7), 2.61–2.53 (1H, m, C*H*$_a$,H$_b$-3), 2.20–2.26 (1H, m, CH$_a$*H*$_b$-3), 2.10–2.04 (1H, m, C*H*$_a$,H$_b$-5), 1.85–1.78 (1H, m, C*H*$_a$,H$_b$-6), 1.67–1.56 (1H, m, CH$_a$*H*$_b$-6), 1.40–1.29 (1H, m, CH$_a$*H*$_b$-5); δ_C (100 MHz; DMSO-d_6, 393.2 K) 141.7, 138.3, 127.4, 127.3, 126.6, 126.5, 126.4, 125.6, 76.6, 76.3, 69.5, 67.9, 51.5, 40.4, 27.5, 20.1; *m*/*z* (EI) 309 (5, M^+), 292 (25), 218 (23), 203 (7), 186 (6), 148 (10), 105 (25), 97 (16), 91 (100), 77 (19), 71 (84%). HRMS (EI): M^+, found 309.1725. $C_{20}H_{23}NO_2$ requires 309.1729. Data for **18a**: mp 61.5–64.5 °C; R_f (20% EtOAc/hexanes) 0.16; $[\alpha]_D^{20}$ −3.5 (*c* 0.98, $CHCl_3$); ν_{max} (solid) 3019, 2953, 1422, 1216 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.35–7.23 (10H, m, Ar–H), 5.22 (1H, dd, *J* 4.3, 9.6, H-2), 4.61 (1H, d, *J* 12.1, OC*H*$_a$,H$_b$Ph), 4.52 (1H, d, *J* 12.1, OCH$_a$,*H*$_b$Ph), 3.96–3.90 (1H, m, H-4), 3.50 (1H, br s, H-3a), 2.96 (1H, td, *J* 9.5, 3.0, C*H*$_a$,H$_b$-7), 2.86–2.81 (1H, m, CH$_a$*H*$_b$-7), 2.81–2.73 (1H, m, C*H*$_a$,H$_b$-3), 1.97–1.89 (1H, m, CH$_a$*H*$_b$-3), 1.84–1.74 (1H, m, C*H*$_a$,H$_b$-6), 1.72–1.56 (2H, m, H-5), 1.52–1.40 (1H, m, CH$_a$*H*$_b$-6); δ_C (75 MHz; DMSO-d_6, 373 K) 141.8, 138.3, 124.4 (2C), 126.6, 126.5 (2C), 125.7, 76.4, 73.8, 69.8, 64.6, 49.9, 35.4, 24.4, 19.5; *m*/*z* (EI) 309 (15, M^+), 292 (28), 218 (23), 203 (12), 186 (8), 148 (10), 105 (18), 97 (18), 96 (14), 91 (100), 77 (15), 71 (85%). HRMS (EI): M^+, found 309.1725. $C_{20}H_{23}NO_2$ requires 309.1729.

4.3.2. (2R,3aR,4S)-2-Ethoxy-4-(benzyloxy)-hexahydroisoxazolo-[2,3-a]pyridine (**17b**)+(2S,3aS,4S)-2-ethoxy-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**18b**)

Following the general procedure, a solution of ethyl vinyl ether **15b** (0.18 g, 2.4 mmol) in toluene (2 mL) was added to a solution of nitrone **7** (0.05 g, 0.24 mmol) in toluene (2 mL) and the mixture stirred at 45 °C for 3 h. Purification of the residue by flash column chromatography eluting with hexanes/EtOAc (17:3) gave the *title compounds* **17b** (0.036 g, 53%) and **18b** (0.018 g, 27%) as yellow oils. Data for **17b**: R_f (50% EtOAc/hexanes) 0.54; $[\alpha]_D^{20}$ −29.2 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2938, 2864, 1454, 1084, 989, 735, 697 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.39–7.23 (5H, m, Ar–H), 5.10 (1H, dd, *J* 2.3, 6.1, H-2), 4.60 (1H, d, *J* 12.0, OC*H*$_a$,H$_b$Ph), 4.48 (1H, d, *J* 12.0, OCH$_a$,*H*$_b$Ph), 3.62 (1H, dq, *J* 9.9, 7.0, OC*H*$_a$,H$_b$CH$_3$), 3.44 (1H, dq, *J* 9.9, 7.0, OCH$_a$,*H*$_b$CH$_3$), 3.35 (1H, ddd, *J* 4.3, 8.1, 9.7, H-4), 3.21–3.12 (1H, m, C*H*$_a$,H$_b$-7), 2.92–2.80 (1H, m, 3a-H), 2.80–2.67 (1H, m, CH$_a$,*H*$_b$-7), 2.34–2.22 (1H, m, C*H*$_a$,H$_b$-3), 2.12 (1H, ddd, *J* 2.3, 6.1, 12.7, CH$_a$,*H*$_b$-3), 2.08–1.99 (1H, m, C*H*$_a$,H$_b$-5), 1.67–1.56 (2H, m, 6-H), 1.35–1.22 (1H,

m, CH_aH_b-5), 1.12 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (75 MHz; DMSO-d_6, 373 K) 138.4, 127.5, 126.9, 126.7, 100.0, 75.6, 69.5, 64.3, 61.9, 50.9, 39.2, 27.6, 19.6, 14.5; *m*/*z* (EI) 277 (21, M^+), 260 (65), 186 (38), 171 (6), 116 (10), 91 (100), 71 (57), 65 (6), 43 (14%). HRMS (EI): M^+, found 277.1683. $C_{16}H_{23}NO_3$ requires 277.1678. Data for **18b**: R_f (50% EtOAc/hexanes) 0.37; $[\alpha]_D^{20}$ +55.2 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2926, 2868, 1454, 1108, 1078, 735, 696 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 353 K) 7.38–7.22 (5H, m, Ar–H), 5.29 (1H, dd, *J* 1.2, 6.0, H-2), 4.58 (1H, d, *J* 12.1, COH_aH_bPh), 4.49 (1H, d, *J* 12.1, COH_aH_bPh), 3.82 (1H, ddd, *J* 4.3, 4.3, 8.5, H-4), 3.61 (1H, dq, *J* 9.9, 7.0, $OCH_aH_bCH_3$), 3.49 (1H, br s, 3a-H), 3.45 (1H, dq, *J* 9.9, 7.0, $OCH_aH_bCH_3$), 2.91–2.81 (1H, m, CH_aH_b-7), 2.79–2.67 (1H, m, CH_aH_b-7), 2.42 (1H, ddd, *J* 6.0, 10.9, 12.7, CH_aH_b-3), 1.89 (1H, ddd, *J* 1.2, 6.0, 12.7, CH_aH_b-3), 1.77–1.61 (2H, m, CH_aH_b-5, CH_aH_b-6), 1.61–1.48 (1H, m, CH_aH_b-5), 1.41–1.28 (1H, m, CH_aH_b-6), 1.12 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (75 MHz; DMSO-d_6, 353 K) 138.3, 127.5, 126.7 (2C), 101.4, 73.6, 69.8, 61.8, 51.2, 33.8, 27.9, 24.3, 19.0, 14.5; *m*/*z* (EI) 277 (13, M^+), 260 (49), 186 (31), 171 (7), 116 (10), 91 (100), 71 (54), 65 (9), 43 (13%). HRMS (EI): M^+, found 277.1677. $C_{16}H_{23}NO_3$ requires 277.1678.

4.3.3. Synthesis of (2R,3aR,4S)-4-(benzyloxy)-2-methyl-2-(trimethylsilyloxy)-hexahydro-2H-isoxazolo[2,3-a]pyridine (**16c**), (2S,3aR,4S)-4-(benzyloxy)-2-methyl-2-(trimethylsilyloxy)-hexahydro-2H-isoxazolo[2,3-a]pyridine (**17c**) and (2R,3aS,4S)-4-(benzyloxy)-2-methyl-2-(trimethylsilyloxy)-hexahydro-2H-isoxazolo[2,3-a]pyridine (**18c**)

Following the general procedure, a solution of 2-(trimethylsilyloxy)propene **15c** (0.21 mL, 1.26 mmol) in toluene (12 mL) was added to nitrone **7** (0.14 g, 0.68 mmol) in toluene (12 mL) and the mixture stirred under reflux for 48 h. Purification of the residue by flash chromatography eluting with hexanes/EtOAc (6:1) gave the *title compounds* **16c** (0.027 g, 12%), **17c** (0.062 g, 27%) and **18c** (0.037 g, 16%) as colourless oils. Data for **16c**: R_f (20% EtOAc/hexanes) 0.69; $[\alpha]_D^{20}$ +36.8 (*c* 0.82, $CHCl_3$); ν_{max} (film) 3031, 2929, 1454, 1248, 841 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.37–7.26 (5H, m, Ar–H), 4.61 (1H, d, *J* 11.8, OCH_aH_bPh), 4.50 (1H, d, *J* 11.8, OCH_aH_bPh), 3.47–3.39 (1H, m, H-4), 3.28 (1H, dt, *J* 8.9, 3.3, CH_aH_b-7), 2.54 (1H, dd, *J* 5.4, 11.4, CH_aH_b-3), 2.40–2.30 (2H, m, H-3a, CH_aH_b-7), 2.26–2.19 (1H, m, CH_aH_b-3), 2.16–2.06 (1H, m, CH_aH_b-5), 1.86–1.78 (1H, m, CH_aH_b-6), 1.70–1.63 (1H, m, CH_aH_b-6), 1.46 (3H, s, C2-CH_3), 1.23–1.11 (1H, m, CH_aH_b-5), 0.15 (9H, s, Me_3-Si); δ_C (75 MHz; $CDCl_3$) 138.5, 128.4, 127.7, 127.6, 103.8, 78.2, 72.2, 71.1, 53.8, 49.4, 30.1, 28.7, 21.7, 1.8; *m*/*z* (EI) 335 (14, M^+), 318 (68), 244 (53), 91 (100), 75 (20), 73 (29), 71 (40%). HRMS (EI): M^+, found 335.1916. $C_{18}H_{29}NO_3Si$ requires 335.1917. Data for **17c**: R_f (20% EtOAc/hexane) 0.51; $[\alpha]_D^{20}$ −3.09 (*c* 0.81, $CHCl_3$); ν_{max} (film) 3030, 2951, 1454, 1248, 841 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 353 K) 7.39–7.24 (5H, m, Ar–H), 4.59 (1H, d, *J* 12.1, OCH_aH_bPh), 4.47 (1H, d, *J* 12.1, OCH_aH_bPh), 3.37 (1H, ddd, *J* 4.2, 8.3, 9.7, H-4), 3.15 (1H, dt, *J* 11.2, 3.8, CH_aH_b-7), 2.94–2.87 (1H, m, H-3a), 2.72 (1H, td, *J* 11.2, 3.6, CH_aH_b-7), 2.29 (1H, dd, *J* 12.3, 5.9, CH_aH_b-3), 2.13–2.01 (2H, m, CH_aH_b-5, CH_aH_b-3), 1.72–1.62 (1H, m, CH_aH_b-6), 1.60–1.47 (1H, m, CH_aH_b-6), 1.41 (3H, s, C2-Me), 1.33–1.19 (1H, m, CH_aH_b-5), 0.12 (9H, s, Me_3-Si); δ_C (75 MHz; DMSO-d_6, 353 K) 138.3, 127.5, 127.0, 126.7, 103.2, 75.5, 69.4, 66.0, 51.1, 47.0, 28.1, 27.8, 19.8, 1.3; *m*/*z* (EI) 335 (16, M^+), 318 (68), 244 (62), 91 (100), 75 (24), 73 (31), 71 (41%). HRMS (EI): M^+, found 335.1918. $C_{18}H_{29}NO_3Si$ requires 335.1917. Data for **18c**: R_f (20% EtOAc/hexanes) 0.37; $[\alpha]_D^{20}$ +4.2 (*c* 0.6, $CHCl_3$); ν_{max} (film) 2924, 1463, 1248, 842 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 353 K) 7.42–7.25 (5H, m, Ar–H), 4.59 (1H, d, *J* 12.1, OCH_aH_bPh), 4.49 (1H, d, *J* 12.1, OCH_aH_bPh), 3.87–3.80 (1H, m, H-4), 3.61 (1H, br s, H-3a), 2.91–2.74 (2H, m, H-7), 2.34 (1H, t, *J* 12.1, CH_aH_b-3), 1.97 (1H, dd, *J* 5.4, 12.1, CH_aH_b-3), 1.75–1.64 (2H, m, CH_aH_b-5, CH_aH_b-6), 1.37 (3H, s, C2-CH_3), 1.34–1.32 (1H, m, CH_aH_b-5), 1.31–1.27 (1H, m, CH_aH_b-6), 0.12 (9H, s, Me_3-Si); δ_C (75 MHz; DMSO-d_6, 353 K) 138.3, 127.6, 127.0, 126.7, 103.5, 73.8, 69.7, 62.8, 51.3, 41.1, 28.7, 24.6, 19.5, 1.1; *m*/*z* (EI) 335 (13, M^+), 319 (18), 318 (61), 244 (55), 172 (21), 91 (100), 75 (38), 73 (32), 71 (46%). HRMS (EI): M^+, found 335.1916. $C_{18}H_{29}NO_3Si$ requires 335.1917.

4.3.4. (2S,3aR,4S)-2-Ethoxycarbonyl-4-(benzyloxy)-hexahydro-isoxazolo[2,3-a]pyridine (**16d**), (2R,3aR,4S)-2-ethoxycarbonyl-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**17d**) and (2S,3aS,4S)-2-ethoxycarbonyl-4-(benzyloxy)-hexahydro-isoxazolo[2,3-a]pyridine (**18d**)

Following the general procedure, a solution of ethyl acrylate **15d** (2.59 mL, 24.4 mmol) in CH_2Cl_2 (2 mL) was added to a solution of nitrone **7** (0.500 g, 2.44 mmol) in CH_2Cl_2 (11 mL) and the mixture stirred at room temperature for 3 h. Purification of the residue by flash column chromatography eluting with EtOAc/hexanes (gradient 5% to 15%) gave the *title compounds* **16d** (0.059 g, 8%), **17d** (0.41 g, 55%) and **18d** (0.18 g, 24%) as yellow oils. Data for **16d**: R_f (50% EtOAc/hexane) 0.54; $[\alpha]_D^{20}$ +99.0 (*c* 1.04, $CHCl_3$); ν_{max} (film) 2935, 2862, 1753, 1729, 1454, 1200, 1175, 1075 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.38–7.24 (5H, m, Ar–H), 4.61 (1H, d, *J* 12.1, OCH_aH_bPh), 4.51 (1H, d, *J* 12.1, OCH_aH_bPh), 4.45 (1H, dd, *J* 8.9, 6.6, H-2), 4.15 (2H, qd, *J* 7.1, 1.6, $CO_2CH_2CH_3$), 3.43 (1H, ddd, *J* 9.6, 8.2, 4.3, H-4), 3.23 (1H, dt, *J* 10.0, 3.9, CH_aH_b-7), 2.69 (1H, ddd, *J* 11.8, 8.9, 6.0, CH_aH_b-3), 2.58–2.47 (2H, m, CH_aH_b-7, H-3a), 2.23 (1H, ddd, *J*=11.8, 9.0, 6.6, CH_aH_b-3), 2.10–1.99 (1H, m, CH_aH_b-5), 1.82–1.70 (1H, m, CH_aH_b-6), 1.64–1.47 (1H, m, CH_aH_b-6), 1.32–1.20 (1H, m, CH_aH_b-5), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (75 MHz; DMSO-d_6, 373 K) 170.8, 138.2, 127.3, 126.6, 126.5, 76.5, 73.0, 69.5, 67.9, 59.5, 51.9, 35.9, 28.0, 20.1, 13.1; *m*/*z* (EI) 305 (11, M^+), 126 (9), 91 (100), 71 (62), 65 (10), 43 (15%). HRMS (EI): M^+, found 305.1632. $C_{17}H_{23}NO_4$ requires 305.1627. Data for **17d**: R_f (50% EtOAc/hexane) 0.46; $[\alpha]_D^{20}$ +48.9 (*c* 0.95, $CHCl_3$); ν_{max} (film) 2938, 2860, 1748, 1733, 1454, 1194, 1091, 1074 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.38–7.24 (5H, m, Ar–H), 4.61 (1H, d, *J* 12.0, OCH_aH_bPh), 4.52 (1H, d, *J* 12.0, OCH_aH_bPh), 4.48 (1H, dd, *J* 8.7, 5.2, H-2), 4.16 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.46 (1H, ddd, *J* 9.1, 7.8, 4.2, H-4), 3.21–3.12 (1H, m, CH_aH_b-7), 2.71–2.60 (2H, m, CH_aH_b-7, H-3a), 2.47–2.36 (2H, m, H-3), 2.02 (1H, dq, *J* 12.8, 4.2, CH_aH_b-5), 1.80–1.68 (1H, m, CH_aH_b-6), 1.65–1.48 (1H, m, CH_aH_b-6), 1.38–1.27 (1H, m, CH_aH_b-5), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (75 MHz; DMSO-d_6, 373 K) 170.1, 138.2, 127.3, 126.6, 126.5, 76.0, 72.9, 69.5, 66.2, 59.7, 51.2, 35.8, 27.4, 19.8, 13.1; *m*/*z* (EI) 305 (6, M^+), 232 (8), 126 (13), 91 (100), 71 (57), 65 (11), 43 (12%). HRMS (EI): M^+, found 305.1616. $C_{17}H_{23}NO_4$ requires 305.1627. Data for **18d**: R_f (50% EtOAc/hexane) 0.34; $[\alpha]_D^{20}$ −4.6 (*c* 1.20, $CHCl_3$); ν_{max} (film) 2928, 2856, 1734, 1454, 1193, 1094 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.38–7.24 (5H, m, Ar–H), 4.65 (1H, *J* 10.1, 3.7, H-2), 4.60 (1H, d, *J* 12.1, OCH_aH_bPh), 4.52 (1H, d, *J* 12.1, OCH_aH_bPh), 4.16 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.94–3.86 (1H, m, H-4), 3.40 (1H, br s, H-3a), 2.87–2.74 (2H, m, H-7), 2.60 (1H, ddd, *J* 12.5, 10.8, 10.1, CH_aH_b-3), 2.18 (1H, ddd, *J* 12.5, 6.8, 3.7, CH_aH_b-3), 1.80–1.63 (2H, m, CH_aH_b-5, CH_aH_b-6), 1.63–1.48 (1H, m, CH_aH_b-5), 1.48–1.34 (1H, m, CH_aH_b-6), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (75 MHz; DMSO-d_6, 373 K) 170.2, 138.2, 127.3, 126.6, 126.5, 73.6 (2C), 69.8, 63.4, 59.7, 49.9, 31.2, 24.1, 19.3, 13.1; *m*/*z* (EI) 305 (5, M^+), 232 (6) 126 (14), 91 (100), 71 (57), 65 (10), 43 (16%). HRMS (EI): M^+, found 305.1630. $C_{17}H_{23}NO_4$ requires 305.1627.

4.3.5. (2S,3aR,4S)-2-Hydroxymethyl-4-(benzyloxy)-hexahydro-isoxazolo[2,3-a]pyridine (**16e**), (2R,3aR,4S)-2-hydroxy-methyl-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**17e**) and (2S,3aS,4S)-2-hydroxymethyl-4-(benzyloxy)-hexahydro-isoxazolo[2,3-a]pyridine (**18e**)

Following the general procedure, a solution of allyl alcohol **15e** (1.39 g, 24.0 mmol) in toluene (5 mL) was added to a solution of nitrone **7** (0.33 g, 1.6 mmol) in toluene (5 mL) and the mixture stirred under reflux for 24 h. Purification of the residue by flash column chromatography eluting with methanol/Et_2O (99:1) gave the *title compounds* **16e** (0.030 g, 7%), **17e** (0.17 g, 40%) and **18e**

(0.041 g, 10%) as yellow oils. Data for **16e**: R_f (5% MeOH/Et_2O) 0.53; $[\alpha]_D^{20}$ +126.2 (*c* 0.57, $CHCl_3$); ν_{max} (film) 3381, 2932, 2860, 1454, 1354, 1253, 1089, 1012, 736, 697 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.38–7.22 (5H, m, OCH_2Ar), 4.60 (1H, d, *J* 12.1, OCH_aH_bPh), 4.52 (1H, d, *J* 12.1, OCH_aH_bPh), 4.07 (1H, br s, O*H*), 4.06–3.95 (1H, m, H-2), 3.54–3.44 (1H, m, CH_aH_bOH), 3.42–3.32 (2H, m, CH_aH_bOH, H-4), 3.24–3.16 (1H, m, CH_aH_b-7), 2.48–2.37 (3H, m, CH_aH_b-3, C-3a, CH_aH_b-7), 2.11–2.01 (1H, m, CH_aH_b-5), 1.86–1.67 (2H, m, CH_aH_b-3, CH_aH_b-6), 1.64–1.46 (1H, m, CH_aH_b-6), 1.22 (1H, tdd, *J* 12.6, 10.1, 4.8, CH_aH_b-5); δ_C (75 MHz; DMSO-d_6, 373 K) 138.4, 127.3, 126.6, 126.4, 77.1, 76.4, 69.5, 68.5, 63.7, 52.0, 35.1, 28.6, 20.4; *m*/*z* (EI) 263 (12, M^+), 232 (3), 172 (22), 126 (7), 116 (12), 91 (100), 84 (24), 71 (99), 66 (27), 43 (27), 41 (18%). HRMS (EI): M^+, found 263.1515. $C_{15}H_{21}NO_3$ requires 263.1521. Data for **17e**: R_f (5% MeOH/Et_2O) 0.47; $[\alpha]_D^{20}$ +35.6 (*c* 0.92, $CHCl_3$); ν_{max} (film) 3381, 2936, 2861, 1454, 1354, 1090, 1072, 736, 697 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.36–7.24 (5H, m, Ar–H), 4.60 (1H, d, *J* 12.0, OCH_aH_bPh), 4.52 (1H, d, *J* 12.0, OCH_aH_bPh), 4.04 (1H, dq, *J* 7.8, 5.3 H-2), 3.49–3.37 (3H, m, CH_2OH, H-4), 3.16–3.07 (1H, m, CH_aH_b-7), 2.59–2.47 (2H, m, H-3a, CH_aH_b-7), 2.13–2.06 (2H, m, H-3), 2.00 (1H, dq, *J* 12.9, 4.3, CH_aH_b-5), 1.80–1.68 (1H, m, CH_aH_b-6), 1.62–1.46 (1H, m, CH_aH_b-6), 1.28 (1H, dddd, *J* 12.9, 11.4, 9.1, 4.5, CH_aH_b-5); δ_C (75 MHz; DMSO-d_6, 373 K) 138.4, 127.3, 126.6, 126.4, 76.6, 75.9, 69.5, 67.3, 62.7, 51.4, 34.2, 27.7, 20.1; *m*/*z* (EI) 263 (14, M^+), 232 (4), 172 (24), 126 (8), 116 (19), 91 (99), 71 (100), 65 (13), 43 (24%). HRMS (EI): M^+, found 263.1527. $C_{15}H_{21}NO_3$ requires 263.1521. Data for **18e**: R_f (5% MeOH/Et_2O) 0.41; $[\alpha]_D^{20}$ −1.4 (*c* 2.9, $CHCl_3$); ν_{max} (film) 3380, 2951, 2868, 1453, 1359, 1247, 1089, 1028, 735, 697 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.38–7.23 (5H, m, Ar–H), 4.59 (1H, d, *J* 12.0, OCH_aH_bPh), 4.52 (1H, d, *J* 12.0, OCH_aH_bPh), 4.30–4.19 (1H, m, H-2), 4.13 (1H, br s, O*H*), 3.90–3.80 (1H, m, H-4), 3.46–3.39 (2H, m, CH_2OH), 3.30 (1H, br s, H-3a), 2.80–2.68 (2H, m, H-7), 2.32 (1H, ddd, *J* 12.1, 10.9, 9.4, CH_aH_b-3), 1.87 (1H, ddd, *J* 12.1, 7.2, 3.9, CH_aH_b-3), 1.77–1.61 (2H, m, CH_aH_b-5, CH_aH_b-6), 1.60–1.47 (1H, m, CH_aH_b-5), 1.45–1.28 (1H, m, CH_aH_b-6); δ_C (75 MHz; DMSO-d_6, 373 K) 138.3, 127.3, 126.6, 126.4, 76.1, 73.8, 69.6, 63.8, 62.7, 49.7, 29.0, 24.2, 19.5; *m*/*z* (EI) 263 (14, M^+), 232 (4), 172 (22), 126 (8), 91 (99), 84 (10), 71 (100), 65 (13), 43 (25), 41 (15%). HRMS (EI): M^+, found 263.1512. $C_{15}H_{21}NO_3$ requires 263.1521.

*4.3.6. Synthesis of (2R,3aR,4S)-2-[2′-(tert-butyldimethylsilyloxy)-ethyl]-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**17f**) and (2S,3aS,4S)-2-[2′-(tert-butyldimethylsilyloxy)ethyl]-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (**18f**)*

Following the general procedure, a solution of alkene **15f** in toluene (2 mL) was added to a solution of nitrone **7** (0.12 g, 0.58 mmol) in toluene (2 mL) and the mixture stirred at 80 °C for 12 h. Purification of the residue by flash column chromatography eluting with hexanes/EtOAc (9.5:1.5) gave the *title compounds* **17f** (0.12 g, 52%) and **18f** (0.045 g, 20%) as yellow oils. Data for **17f**: R_f (50% EtOAc/hexane) 0.63; $[\alpha]_D^{20}$ +56.4 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3422, 2949, 2856, 1471, 1255, 1098 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 373 K) 7.38–7.25 (5H, m, Ar–H), 4.59 (1H, d, *J* 12.0, OCH_aH_bPh), 4.49 (1H, d, *J* 12.0, OCH_aH_bPh), 4.15–4.02 (1H, m, H-2), 3.67 (2H, td, *J* 6.4, 1.2, H-2′), 3.40 (1H, ddd, *J* 9.0, 8.2, 4.2, H-4), 3.16–3.06 (1H, m, CH_aH_b-7), 2.57–2.38 (2H, m, H-3a, CH_aH_b-7), 2.16 (1H, ddd, *J* 9.0, 9.0, 11.8, CH_aH_b-3), 2.07–1.95 (2H, m, CH_aH_b-3, CH_aH_b-5), 1.81–1.60 (3H, m, CH_aH_b-6, H-1′), 1.60–1.43 (1H, m, CH_aH_b-6), 1.35–1.16 (1H, m, CH_aH_b-5), 0.89 (9H, s, ^{t}Bu), 0.05 (6H, s, $OSiMe_2$); δ_C (75 MHz; DMSO-d_6, 353 K) 138.4, 127.4, 126.8, 126.6, 76.7, 72.3, 69.5, 67.9, 59.2, 51.7, 37.6, 37.5, 28.0, 25.2, 20.3, 17.2, −6.0; *m*/*z* (EI) 391 (7, M^+), 300 (14), 142 (14), 131 (10), 101 (21), 97 (16), 91 (100), 75 (15), 71 (41), 65 (8), 57 (18), 41 (15%). HRMS (EI): M^+, found 391.2537. $C_{22}H_{37}NO_3Si$ requires 391.2543. Data for **18f**: R_f (50% EtOAc/hexane) 0.54; $[\alpha]_D^{20}$ −20.9 (*c* 0.9, $CHCl_3$); ν_{max} (film) 3434, 2953, 2856, 1471, 1255, 1097 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 368 K) 7.38–7.23 (5H, m, Ar–H), 4.58 (1H, d, *J* 12.1, OCH_aH_bPh), 4.51 (1H, d, *J* 12.1, OCH_aH_bPh), 4.36–4.24 (1H, m, H-2), 3.90–3.81 (1H, m, H-4), 3.67 (2H, td, *J* 6.5, 1.1, H-2′), 3.25 (1H, br s, H-3a), 2.83–2.72 (1H, m, CH_aH_b-7), 2.72–2.61 (1H, m, CH_aH_b-7), 2.39 (1H, ddd, *J* 9.2, 10.9, 12.0, CH_aH_b-3), 1.80–1.45 (6H, m, CH_aH_b-3, 5-H, CH_aH_b-6, H-1′), 1.45–1.31 (1H, m, CH_aH_b-6), 0.90 (9H, s, ^{t}Bu), 0.05 (6H, s, $OSiMe_2$); δ_C (75 MHz; DMSO-d_6, 368 K) 138.3, 127.3, 126.6, 126.5, 73.7, 72.3, 69.7, 63.9, 59.2, 49.7, 37.7, 32.1, 25.1, 24.4, 19.6, 17.1, −6.1; *m*/*z* (EI) 391 (25, M^+), 300 (27), 142 (10), 131 (21), 101 (21), 96 (12), 91 (100), 71 (55), 59 (10), 43 (12%). HRMS (EI): M^+, found 391.2543. $C_{22}H_{37}NO_3Si$ requires 391.2543.

4.4. General procedure for the reduction of cycloadducts

Procedure A. A solution of cycloadduct in glacial acetic acid was added to a suspension of copper(II) acetate (0.07 equiv) and zinc powder (5.6 equiv) in glacial acetic acid and one drop of water at room temperature. The reaction mixture was then stirred under reflux for 1 h, cooled to room temperature and the pH adjusted to 9 by careful addition of 6 M $NaOH_{(aq)}$. The mixture was then extracted with chloroform and the organic extract washed with brine, dried over $MgSO_4$ then concentrated under reduced pressure and purified by column chromatography.

Procedure B. Indium powder (10 mol %) and zinc powder (2.0 equiv) were added to a solution of cycloadduct in EtOH/saturated $NH_4Cl_{(aq)}$ (2:1) at room temperature. The reaction was then stirred under reflux for 12 h, cooled to room temperature and concentrated under reduced pressure. Saturated $NaCO_{3(aq)}$ (5 mL) and EtOAc (15 mL) were added and the layers separated. The aqueous layer was further extracted with EtOAc (2×15 mL) and the combined organic extracts dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by column chromatography eluting with CH_2Cl_2/MeOH (49:1).

*4.4.1. 2(R)-1-[(2′R,3′S)-3′-(Benzyloxy)piperidin-2′-yl]-2-hydroxy-2-phenylethanol (**20a**)*

Following the general procedure A, a solution of cycloadduct **17a** (0.04 g, 0.13 mmol) in glacial acetic acid (0.2 mL) was added to a suspension of copper(II) acetate (0.0016 g, 0.009 mmol) and zinc powder (0.048 g, 0.73 mmol) in glacial acetic acid (0.12 mL). Purification by flash chromatography eluting with CH_2Cl_2/MeOH (9:1) gave the *title compound* as a yellow solid (0.031 g, 77%). Mp 73–76 °C; R_f (5% MeOH/CH_2Cl_2) 0.11; $[\alpha]_D^{20}$ +44.4 (*c* 0.31, $CHCl_3$); ν_{max} (solid) 3322, 2942, 1454 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.36–7.21 (10H, m, Ar–H), 5.00 (1H, dd, *J* 3.2, 8.1, H-2), 4.64 (1H, d, *J* 11.6, OCH_aH_bPh), 4.45 (1H, d, *J* 11.6, OCH_aH_bPh), 3.74 (2H, br s, N*H*, O*H*), 3.32 (1H, ddd, *J* 4.0, 9.4, 9.1, H-3′), 3.00–2.97 (1H, m, CH_aH_b-6′), 2.85–2.81 (1H, m, CH_aH_b-2′), 2.53 (1H, ddd, *J* 2.9, 11.8, 12.1, CH_aH_b-6′), 2.26–2.22 (1H, m, CH_aH_b-4′), 2.09 (1H, ddd, *J* 3.4, 6.9, 14.6, CH_aH_b-1), 1.92 (1H, ddd, *J* 2.7, 8.2, 14.6, CH_aH_b-1), 1.78–1.73 (1H, m, CH_aH_b-5′), 1.53–1.42 (1H, m, CH_aH_b-5′), 1.38–1.29 (1H, m, CH_aH_b-4′); δ_C (75 MHz; $CDCl_3$) 145.1, 138.4, 128.4, 128.2, 127.7, 127.6, 126.8, 125.6, 77.1, 71.9, 70.3, 58.5, 45.3, 39.6, 29.3, 24.8; *m*/*z* (EI) 311 (2, M^+), 220 (29), 205 (10), 202 (6), 190 (6), 114 (100), 107 (23), 98 (29), 96 (21), 91 (52), 79 (21), 77 (12), 71 (48%). HRMS (EI): M^+, found 311.1884. $C_{20}H_{25}NO_2$ requires 311.1885.

*4.4.2. 1-[(2′R,3′S)-3′-(Benzyloxy)piperidin-2-yl]propan-2-one (**20c**)*

Following the general procedure A, a solution of cycloadduct **17c** (0.058 g, 0.17 mmol) in glacial acetic acid (0.25 mL) was added to a suspension of copper(II) acetate (0.0022 g, 0.012 mmol) and zinc powder (0.064 g, 0.98 mmol) in glacial acetic acid (0.16 mL). Purification by flash chromatography eluting with CH_2Cl_2/MeOH (19:1) as eluent gave the *title compound* as a yellow oil (0.029 g, 68%). R_f (5% MeOH/CH_2Cl_2) 0.23; $[\alpha]_D^{20}$ +93.0 (*c* 0.2, $CHCl_3$); ν_{max} (film) 2933, 1709, 1455, 1098 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.37–7.28 (5H, m, Ar–H), 4.63 (1H, d, *J* 11.6, OCH_aH_bPh), 4.39 (1H, d, *J* 11.6, OCH_aH_bPh),

3.12–3.03 (2H, m, C*H*$_a$,H$_b$-1, C*H*-3′), 2.96–2.86 (2H, m, H-2′, C*H*$_a$,H$_b$-6′), 2.61 (1H, td, *J* 11.9, 2.7, CH$_a$*H*$_b$-6′), 2.51 (1H, br s, N*H*), 2.39 (1H, dd, *J* 8.9, 17.4, CH$_a$*H*$_b$-1), 2.30–2.22 (1H, td, *J* 11.9, 2.7, C*H*$_a$,H$_b$-4′), 2.11 (3H, s, H-3), 1.79–1.71 (1H, m, C*H*$_a$H$_b$-5′), 1.55–1.40 (1H, m, CH$_a$*H*$_b$-5′), 1.37–1.24 (1H, m, CH$_a$*H*$_b$-4′); δ_C (75 MHz; $CDCl_3$) 208.9, 138.5, 128.4, 127.8, 127.6, 78.3, 70.5, 57.6, 46.4, 45.9, 30.4, 30.0, 25.1; *m*/*z* (CI, NH_3) 248 (56, MH^+), 190 (30), 159 (15), 156 (99), 141 (22), 139 (27), 114 (23), 98 (41), 96 (36), 91 (100), 77 (12), 71 (49%). HRMS (CI, NH_3): MH^+, found 248.1650. $C_{15}H_{22}NO_2$ requires 248.1651.

*4.4.3. (2R)-3-[(2′R,3′S)-3-(Benzyloxy)piperidin-2′-yl]propane-1,2-diol (**20e**)*

Following the general procedure B, reaction of cycloadduct **17e** (0.096 g, 0.37 mmol) with indium powder (0.004 g, 0.036 mmol) and zinc powder (0.048 g, 0.73 mmol) in EtOH/saturated $NH_4Cl_{(aq)}$ (2:1) (2 mL) gave the *title compound* as a yellow oil (0.043 g, 45%). R_f (10% MeOH/CH_2Cl_2) 0.03; $[\alpha]_D^{20}$ +50.9 (*c* 0.79, $CHCl_3$); ν_{max} (film) 3292, 2930, 2858, 1453, 1354, 1090, 1071, 1026, 736, 697 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.37–7.24 (5H, m, Ar–H), 4.63 (1H, d, *J* 11.5, OC*H*$_a$,H$_b$Ph), 4.61 (3H, br s, 2×O*H*, N*H*), 4.44 (1H, d, *J* 11.5, OCH$_a$,*H*$_b$Ph), 3.98–3.86 (1H, m, H-2), 3.55 (1H, dd, *J* 11.3, 3.9, C*H*$_a$,H$_b$-1), 3.47 (1H, dd, *J* 11.3, 6.1, CH$_a$,*H*$_b$-1), 3.40–3.30 (1H, m, H-3′), 3.15–3.04 (1H, m, C*H*$_a$,H$_b$-6′), 2.97 (1H, td, *J* 8.0, 2.7, H-2′), 2.62 (1H, td, *J* 12.2, 2.9, CH$_a$,*H*$_b$-6′), 2.30–2.20 (1H, m, C*H*$_a$,H$_b$-4′), 1.98–1.88 (1H, m, C*H*$_a$,H$_b$-3), 1.83–1.72 (2H, m, C*H*$_a$,H$_b$-5′, CH$_a$,*H*$_b$-3), 1.68–1.52 (1H, m, CH$_a$,*H*$_b$-5′), 1.43–1.29 (1H, m, CH$_a$,*H*$_b$-4′); δ_C (100 MHz; $CDCl_3$) 138.0, 128.4, 127.7 (2C), 76.7, 70.6, 69.1, 66.5, 58.2, 44.9, 33.7, 28.9, 23.3; *m*/*z* (CI, NH_3) 266 (6, MH^+), 248 (11), 174 (22), 159 (8), 156 (98), 141 (39), 139 (14), 135 (10), 126 (12), 120 (26), 105 (42), 96 (20), 91 (100), 86 (20), 75 (64%). HRMS (CI, NH_3): MH^+, found 266.1761. $C_{15}H_{24}NO_3$ requires 266.1756.

*4.4.4. (3R)-4-[(2′R,3′S)-3′-(Benzyloxy)piperidin-2′-yl]-1-(tert-butyldimethylsilyloxy)butan-3-ol (**20f**)*

Following the general procedure B, reaction of **17f** (0.060 g, 0.15 mmol) with indium powder (0.002 g, 0.015 mmol) and zinc powder (0.02 g, 0.31 mmol) in saturated $NH_4Cl_{(aq)}$ (0.9 mL) gave *the title compound* as a colourless oil (0.032 g, 53%). R_f (5% MeOH/CH_2Cl_2) 0.11; $[\alpha]_D^{20}$ −29.2 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3293, 2928, 2855, 1455, 1252, 1090, 833 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.38–7.23 (5H, m, Ar–H), 4.64 (1H, d, *J* 11.7, OC*H*$_a$,H$_b$Ph), 4.44 (1H, d, *J* 11.7, OCH$_a$,*H*$_b$Ph), 4.08–3.97 (1H, m, H-3), 3.85–3.68 (4H, br m, N*H*, O*H*, H-1), 3.32–3.22 (1H, m, H-3′), 3.06–2.95 (1H, m, C*H*$_a$,H$_b$-6′), 2.89 (1H, ddd, *J* 8.9, 6.1, 4.1, H-2′), 2.57 (1H, td, *J* 11.7, 2.7, CH$_a$,*H*$_b$-6′), 2.31–2.20 (1H, m, C*H*$_a$,H$_b$-4′), 1.85–1.68 (4H, m, C*H*$_a$,H$_b$-5′, H-4, C*H*$_a$,H$_b$-2), 1.68–1.55 (1H, m, CH$_a$,*H*$_b$-2), 1.55–1.42 (1H, m, CH$_a$,*H*$_b$-5′), 1.42–1.28 (1H, m, CH$_a$,*H*$_b$-4′), 0.90 (9H, s, ^{t}Bu), 0.06 (6H, s, $OSiMe_2$); δ_C (75 MHz; $CDCl_3$) 138.5, 128.3, 127.7, 127.6, 77.3, 70.5, 67.6, 61.3, 58.7, 45.4, 39.9, 37.8, 29.5, 25.9, 24.6, 18.2, −5.4; *m*/*z* (EI) 393 (0.6, M^+), 336 (29), 302 (33), 287 (14), 284 (41), 228 (28), 189 (16), 131 (24), 114 (30), 101 (15), 91 (100), 89 (38), 75 (37), 73 (44), 56 (12), 43 (18%). HRMS (EI): M^+, found 393.2696. $C_{22}H_{39}NO_3Si$ requires 393.2699.

4.5. 2-[(2′*R*,3′*S*)-1′-Benzyl-3′-(benzyloxy)piperidin-2′-yl]-ethan-1-ol (21)

Benzyl bromide (0.13 mL, 1.10 mmol) was added dropwise to a stirred solution of cycloadduct **17b** (0.29 g, 1.05 mmol) in CH_2Cl_2 (12 mL) at room temperature. The reaction was then stirred overnight and concentrated under reduced pressure to give a yellow oil. The residue was diluted with THF (15 mL) and $LiAlH_4$ (0.060 g, 1.58 mmol) was added portionwise. The mixture was then stirred under reflux for 3 h, cooled to 0 °C and diluted with EtOAc (15 mL). A saturated solution of Rochelle's salt (5 mL) was added and the mixture stirred for 30 min., filtered through Celite® and extracted with ethyl acetate (4×50 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (1:49) to give the *title compound* as a yellow oil (0.20 g, 59% over two steps). R_f (5% MeOH/CH_2Cl_2) 0.23; $[\alpha]_D^{20}$ +4.0 (*c* 0.80, $CHCl_3$); ν_{max} (film) 3402, 2936, 2861, 1452, 1070, 732 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.39–7.20 (10H, m, Ar–H), 4.63 (1H, d, *J* 11.7, OC*H*$_a$,H$_b$Ph), 4.48 (1H, d, *J* 11.7, OCH$_a$,*H*$_b$Ph), 4.27 (1H, d, *J* 13.0, NC*H*$_a$,H$_b$Ph), 3.87–3.70 (2H, m, H-1), 3.67 (1H, d, *J* 13.0, NCH$_a$,*H*$_b$Ph), 3.44 (1H, ddd, *J* 6.6, 5.3, 3.5, H-3′), 3.00–2.92 (1H, m, C*H*$_a$,H$_b$-6′), 2.92–2.84 (1H, m, H-2′), 2.31 (1H, ddd, *J* 13.1, 7.1, 3.2, CH$_a$,*H*$_b$-6′), 2.19–2.05 (1H, m, C*H*$_a$,H$_b$-2), 2.05–1.93 (1H, m, C*H*$_a$,H$_b$-4′), 1.93–1.81 (1H, m, C*H*$_a$,H$_b$-5′), 1.77–1.59 (2H, m, CH$_a$,*H*$_b$-4′, CH$_a$,*H*$_b$-2), 1.38–1.24 (1H, m, CH$_a$,*H*$_b$-5′); δ_C (75 MHz; $CDCl_3$) 138.7, 138.6, 129.2, 128.4, 128.3, 127.6, 127.5, 127.1, 76.3, 70.6, 63.6, 62.3, 58.4, 47.9, 29.0, 27.0, 17.9; *m*/*z* (EI) 325 (0.3, M^+), 280 (5), 234 (12), 91 (100), 65 (14), 41 (4%). HRMS (EI): M^+, found 325.2048. $C_{21}H_{27}NO_2$ requires 325.2042.

4.6. 2-[(2′*R*,3′*S*)-3′-(Benzyloxy)piperidin-2′-yl]-ethan-1-ol (22)

Palladium on carbon (4.5 mg) was added portionwise to a solution of *N*-benzylpiperidine (0.045 g, 0.14 mmol) **21** in MeOH (4.5 mL) and the mixture stirred under hydrogen for 6 h then filtered through Celite®. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (9:1) to give the title compound as a white solid (0.03 g, 100%). White solid, mp 68–70.8 °C; R_f (5% MeOH/CH_2Cl_2) 0.03; $[\alpha]_D^{20}$ +62.5 (*c* 0.56, $CHCl_3$); ν_{max} (solid) 3301, 3136, 2946, 2919, 2857, 2836, 1454, 1093, 1054 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.38–7.23 (5H, m, Ar–H), 4.64 (1H, d, *J* 11.5, OC*H*$_a$,H$_b$Ph), 4.43 (1H, d, *J* 11.5, OCH$_a$,*H*$_b$Ph), 3.83–3.76 (2H, m, H-1), 3.08 (1H, ddd, *J* 9.4, 8.7, 4.1, H-3′), 3.02 (1H, br s, O*H*), 2.99–2.89 (1H, m, C*H*$_a$,H$_b$-6′), 2.75 (1H, td, *J* 8.7, 2.8 H-2′), 2.59–2.48 (1H, m, CH$_a$,*H*$_b$-6′), 2.27–2.18 (1H, m, C*H*$_a$,H$_b$-4′), 2.05–1.94 (1H, m, C*H*$_a$,H$_b$-2), 1.83–1.70 (1H, m, C*H*$_a$,H$_b$-5′), 1.66–1.52 (1H, m, CH$_a$,*H*$_b$-2), 1.45–1.35 (2H, m, CH$_a$,*H*$_b$-4′, CH$_a$,*H*$_b$-5′), δ_C (75 MHz; $CDCl_3$) 138.4, 128.3, 127.7, 127.6, 78.2, 70.4, 62.7, 62.1, 45.1, 33.1, 29.3, 25.7; *m*/*z* (FAB$^+$, *m*-nitrobenzylalcohol) 236 (5, MH^+), 154 (100), 136 (70), 124 (10), 120 (10), 107 (22), 89 (20%). HRMS (FAB$^+$, *m*-nitrobenzylalcohol): MH^+, found 236.1652. $C_{14}H_{22}NO_2$ requires 236.1651.

4.7. (2*R*,8*S*,8a*R*)-Hydroxy-,8-benzyloxyoctahydro-3-indolizidinone (23)

Following the general reduction procedure A, a solution of cycloadduct **17d** (0.050 g, 0.16 mmol) in glacial acetic acid (0.25 mL) was added to a suspension of copper(II) acetate (0.002 g, 0.011 mmol) and zinc powder (0.059 g, 0.92 mmol) in glacial acetic acid (0.25 mL). Purification by flash chromatography eluting with MeOH/CH_2Cl_2 (19:1) gave the *title compound* as a yellow oil (0.040 g, 94%). R_f (5% MeOH/CH_2Cl_2) 0.20; $[\alpha]_D^{20}$ +172.3 (*c* 0.67, $CHCl_3$); ν_{max} (film) 3292, 2989, 2962, 2925, 2866, 1688, 1485, 1435, 1288, 1267, 1097, 734 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.39–7.25 (5H, m, Ar–H), 4.67 (1H, d, *J* 11.7, OC*H*$_a$,H$_b$Ph), 4.58 (1H, br s, O*H*), 4.50 (1H, d, *J* 11.7, OCH$_a$,*H*$_b$Ph), 4.34 (1H, t, *J* 8.6, H-2), 4.08–3.98 (1H, m, C*H*$_a$,H$_b$-5), 3.26–3.16 (1H, m, H-8a), 3.11 (1H, ddd, *J* 3.9, 9.2, 10.2, H-8), 2.79 (1H, ddd, *J* 13.1, 8.6, 6.4, C*H*$_a$,H$_b$-1), 2.64–2.50 (1H, m, CH$_a$,*H*$_b$-5), 2.33–2.22 (1H, m, C*H*$_a$,H$_b$-7), 1.87–1.75 (1H, m, C*H*$_a$,H$_b$-6), 1.68 (1H, ddd, *J* 13.1, 8.6, 7.4, CH$_a$,*H*$_b$-1), 1.52–1.23 (2H, m, CH$_a$,*H*$_b$-6, CH$_a$,*H*$_b$-7); δ_C (75 MHz; $CDCl_3$) 173.9, 137.9, 128.4, 127.8, 127.7, 80.6, 71.0, 69.5, 57.6, 39.4, 33.4, 29.4, 22.6; *m*/*z* (EI) 261 (5, M^+), 170 (94), 155 (71), 153 (6), 142 (33), 124 (13), 98 (31), 91 (100), 71 (71), 65 (16), 56 (6), 43 (27), 41 (17%). HRMS (EI): M^+, found 261.1362. $C_{15}H_{19}NO_3$ requires 261.1365.

4.8. (2*R*,8*S*,9*R*)-2-Hydroxy-8-benzyloxyindolizidine (24)

$BH_3 \cdot SMe_2$ (1.9 mL, 1 M) was added dropwise to a stirred solution of lactam **23** (0.065 g, 0.25 mmol) in THF (4 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 10 min, then at room temperature for 30 min and finally at 66 °C for 4 h. The mixture was then cooled to room temperature and H_2O (5 mL) added dropwise. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Palladium on carbon (7.5 mg) was added portionwise to a solution of the residue (0.054 g, 0.22 mmol) in MeOH (3 mL) and the mixture stirred at room temperature for 5 h then filtered over Celite®. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography eluting with CH_2Cl_2/MeOH (19:1) to give the *title compound* (0.055 g, 89%) as a yellow oil. R_f (5% MeOH/CH_2Cl_2) 0.16; $[\alpha]_D^{20}$ +67.3 (*c* 0.69, $CHCl_3$); ν_{max} (film) 3337, 2936, 1454, 1113 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.38–7.23 (5H, m, Ar–H), 4.64 (1H, d, *J* 11.7, OC*H*$_a$H$_b$Ph), 4.52 (1H, d, *J* 11.7, OCH$_a$,*H*$_b$Ph), 4.34–4.26 (1H, m, H-2), 3.49 (1H, ddd, *J* 4.3, 9.2, 10.5, H-8), 3.16–3.05 (2H, m, C*H*$_a$H$_b$-3, C*H*$_a$H$_b$-5), 2.75–2.63 (1H, m, C*H*$_a$H$_b$-1), 2.45 (1H, dd, *J* 10.6, 5.9, CH$_a$,*H*$_b$-3), 2.29–2.18 (1H, m, C*H*$_a$H$_b$-7), 2.11–1.99 (2H, m, H-9, CH$_a$,*H*$_b$-5), 1.83–1.73 (2H, m, H-6), 1.73–1.61 (1H, m, CH$_a$,*H*$_b$-1), 1.31–1.14 (1H, m, CH$_a$,*H*$_b$-7); δ_C (75 MHz; $CDCl_3$) 138.4, 128.3, 127.6 (2C), 80.0, 71.1, 68.8, 68.4, 63.7, 51.3, 40.2, 30.0, 23.3; *m*/*z* (CI, NH_3) 248 (40, MH^+), 156 (100), 141 (39), 120 (19), 91 (32), 86 (20), 77 (12), 71 (47%). HRMS (CI, NH_3): MH^+, found 248.1655. $C_{15}H_{22}NO_2$ requires 248.1651.

4.9. Synthesis of (+)-febrifugine (1)

*4.9.1. Synthesis of (2R,3aR,4S)-4-(benzyloxy)-2-[(4″-oxo-4H-quinazolin-3″-yl)methyl]hexahydroisoxazolo[2,3-a]pyridine (**28**) and (2S,3aS,4S)-4-(benzyloxy)-2-[(4″-oxo-4H-quinazolin-3″-yl)methyl]hexahydroisoxazolo[2,3-a]pyridine (**29**)*

Allyl quinazolinone **26** (0.34 g, 1.84 mmol) was added to a stirred solution of nitrone **7** (0.38 g, 1.85 mmol) in toluene (45 mL) at room temperature. The reaction mixture was stirred under reflux for 24 h then cooled to room temperature and filtered through Celite©. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography eluting with Et_2O/MeOH (49:1) to give the *title compounds* **28** (0.35 g, 48%) and **29** (0.13 g, 18%) as colourless oils. Data for **28**: R_f (2% MeOH/Et_2O) 0.56; $[\alpha]_D^{20}$ −41.4 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3062, 2944, 1674, 1564, 1473, 1097 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 363 K) 8.22 (1H, s, H-2″), 8.19 (1H, dd, *J* 8.1, 1.4, H-5″), 7.81 (1H, ddd, *J* 8.5, 7.1, 1.1, H-7″), 7.67 (1H, d, *J* 7.7, H-8″), 7.54 (1H, ddd, *J* 8.1, 7.1, 1.1, H-6″), 7.36–7.22 (5H, m, Ar–H), 4.57 (1H, d, *J* 12.0, OC*H*$_a$H$_b$Ph), 4.48 (1H, d, *J* 12.0, OCH$_a$,*H*$_b$Ph), 4.43–4.35 (1H, m, H-2), 4.22 (1H, dd, *J* 13.9, 4.0, C*H*$_a$H$_b$-1′), 4.05 (1H, dd, *J* 13.9, 7.5, CH$_a$,*H*$_b$-1′), 3.46–3.37 (1H, m, H-4), 3.16–3.09 (1H, m, C*H*$_a$H$_b$-7), 2.66–2.58 (2H, m, H-3a, CH$_a$,*H*$_b$-7), 2.31–2.24 (1H, m, C*H*$_a$H$_b$-3), 2.22–2.12 (1H, m, CH$_a$,*H*$_b$-3), 2.00 (1H, dq, *J* 12.7, 4.2, C*H*$_a$H$_b$-5), 1.74–1.64 (1H, m, C*H*$_a$H$_b$-6), 1.60–1.45 (1H, m, CH$_a$,*H*$_b$-6), 1.32–1.20 (1H, m, CH$_a$,*H*$_b$-5); δ_C (75 MHz; DMSO-d_6, 363 K) 159.8, 147.5, 147.4, 138.3, 133.5, 127.4, 126.8, 126.6, 126.5, 126.2, 125.5, 121.0, 76.0, 72.5, 69.5, 66.3, 51.1, 48.4, 38.6, 27.5, 19.8; *m*/*z* (EI) 391 (18, M^+), 300, (7), 283 (15), 232 (17), 154 (18), 147, (12), 130 (12), 96 (15), 91 (100), 71 (37%). HRMS (EI): M^+, found 391.1893. $C_{23}H_{25}N_3O_3$ requires 391.1896. Data for **29**: R_f (2% MeOH/Et_2O) 0.37; $[\alpha]_D^{20}$ +9.2 (*c* 0.36, $CHCl_3$); ν_{max} (film) 3031, 2949, 1673, 1566, 1475, 1092 cm^{-1}; δ_H (300 MHz; DMSO-d_6, 363 K) 8.24 (1H, s, H-2″), 8.19 (1H, dd, *J* 8.2, 1.5, H-5″), 7.81 (1H, ddd, *J* 8.4, 7.1, 1.6, H-7″), 7.68 (1H, d, *J* 7.7, H-8″), 7.53 (1H, ddd, *J* 8.2, 7.4, 1.2, H-6″), 7.35–7.23 (5H, m, Ar–H), 4.64–4.58 (1H, m, H-2), 4.51 (1H, d, *J* 12.0, OC*H*$_a$H$_b$Ph), 4.45 (1H, d, *J* 12.0, OCH$_a$,*H*$_b$Ph), 4.22 (1H, dd, *J* 13.9, 4.1, C*H*$_a$H$_b$-1′), 4.10 (1H, dd, *J* 13.9, 6.8, CH$_a$,*H*$_b$-1′), 3.84–3.78 (1H, m, H-4), 3.30 (1H, br s, H-3a), 2.73 (2H, br s, H-7), 2.51–2.40 (1H, m, C*H*$_a$H$_b$-3), 1.93 (1H, ddd, *J* 12.6, 7.0, 3.7, CH$_a$,*H*$_b$-3), 1.74–1.63 (2H, m, C*H*$_a$H$_b$-5, C*H*$_a$H$_b$-6), 1.56–1.45 (1H, m, CH$_a$,*H*$_b$-5), 1.38–1.27 (1H, m, CH$_a$,*H*$_b$-6), δ_C (75 MHz; DMSO-d_6, 363 K) 159.9, 147.5, 147.4, 138.2, 133.5, 127.5, 126.7, 126.6, 126.5, 126.2, 125.5, 121.0, 73.5, 73.0, 69.6, 63.6, 49.8, 48.4, 29.9, 24.1, 19.4; *m*/*z* (EI) 391 (21, M^+), 300 (6), 283 (10), 232 (14), 154 (18), 147 (12), 130 (11), 96 (19), 91 (100), 71 (38%). HRMS (EI): M^+, found 391.1898. $C_{23}H_{25}N_3O_3$ requires 391.1896.

*4.9.2. (2R,2′R,3S)-3-Benzyloxy-2-[(2′R)-2′-hydroxy-3′-(4″-oxo-4H-quinazolin-3″-yl)propyl]piperidine (**30**)*

Zinc powder (0.27 g, 4.13 mmol) was added to a stirred solution of isoxazolidine **28** (0.15 g, 0.38 mmol) in 50% aqueous acetic acid (2.5 mL) at room temperature. The mixture was heated under reflux for 5 h then cooled to room temperature and 5 M $KOH_{(aq)}$ (3 mL) added dropwise. The mixture was extracted with $CHCl_3$ (3×10 mL) and the combined organic extracts dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (9:1) to give the *title compound* (0.08 g, 53%) as a yellow oil. R_f (2% MeOH/CH_2Cl_2) 0.52; $[\alpha]_D^{20}$ −8.11 (*c* 0.85, $CHCl_3$); ν_{max} (film) 3345, 2927, 1672, 1564, 1474, 1105 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.28 (1H, dd, *J* 8.2, 0.9, H-5″), 8.15 (1H, s, H-2″), 7.76–7.67 (2H, m, H-8″, H-7″), 7.46 (1H, ddd, *J* 8.2, 6.6, 1.8, H-6″), 7.35–7.23 (5H, m, Ar–H), 4.64 (1H, d, *J* 11.4, OC*H*$_a$H$_b$Ph), 4.45 (1H, d, *J* 11.4, OCH$_a$,*H*$_b$Ph), 4.25–4.19 (2H, m, H-2′, C*H*$_a$H$_b$-3′), 3.78 (1H, dd, *J* 14.1, 8.3, CH$_a$,*H*$_b$-3′), 3.32 (1H, ddd, *J* 9.6, 9.5, 4.1, H-3), 3.05–2.95 (2H, m, H-2, C*H*$_a$H$_b$-6), 2.56 (1H, ddd, *J* 11.9, 11.8, 2.7, CH$_a$,*H*$_b$-6), 2.30–2.24 (1H, m, C*H*$_a$H$_b$-4), 2.02 (1H, ddd, *J* 14.6, 6.5, 2.8, C*H*$_a$H$_b$-1′), 1.80–1.72 (2H, m, CH$_a$,*H*$_b$-1′, C*H*$_a$H$_b$-5), 1.59–1.44 (1H, m, CH$_a$,*H*$_b$-5), 1.41–1.33 (1H, m, CH$_a$,*H*$_b$-4); δ_C (75 MHz; $CDCl_3$) 161.4, 148.2, 147.8, 137.9, 134.1, 128.5, 128.0, 127.8, 127.4, 126.9, 126.6, 122.0, 76.2, 70.6, 67.1, 58.6, 52.0, 45.1, 34.5, 29.1, 23.8; *m*/*z* (CI, NH_3) 394 (9, MH^+), 378 (14), 270 (37), 232 (24), 203 (28), 190 (29), 147 (100), 124 (34), 105 (19), 91 (18%). HRMS (CI, NH_3): MH^+, found 394.2134. $C_{23}H_{28}N_3O_3$ requires 394.2131.

*4.9.3. (2R,3S)-N-(tert-Butoxycarbonyl)-3-(benzyloxy)-2-[(2′S)-2′-hydroxy-3′-(4″-oxo-4H-quinazolin-3″-yl)propyl]piperidine (**31**)*

Et_3N (0.11 mL, 0.79 mmol) and di-*tert*-butyl dicarbonate (0.10 g, 0.46 mmol) were added to a stirred solution of piperidine **30** (0.12 g, 0.30 mmol) in CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred for 20 h at room temperature then concentrated under reduced pressure. Purification of the residue by flash chromatography eluting with hexanes/EtOAc (1:4) gave the *title compound* (0.12 g, 80%) as a colourless oil. R_f (80% EtOAc/hexane) 0.42; $[\alpha]_D^{20}$ −72.3 (*c* 1.04, EtOH); ν_{max} (film) 3383, 3053, 2983, 1675 cm^{-1}; δ_H (300 MHz; benzene-d_6) 8.51–8.49 (1H, m, H-5″), 8.16 (1H, s, H-2″), 7.78–7.26 (1H, m, H-8″), 7.24–7.22 (2H, m, Ar–H), 7.21–7.20 (1H, m, H-7″), 7.13–7.04 (3H, m, Ar–H), 7.03–6.99 (1H, m, H-6″), 4.81–4.78 (1H, m, H-2), 4.34 (1H, d, *J* 12.0, OC*H*$_a$H$_b$Ph), 4.14 (1H, d, *J* 12.0, OCH$_a$,*H*$_b$Ph), 4.05–4.02 (1H, m, C*H*$_a$H$_b$-3′), 3.85–3.83 (2H, m, H-2′, C*H*$_a$H$_b$-6), 3.37 (1H, dd, *J* 13.5, 7.4, CH$_a$,*H*$_b$-3′), 2.98 (1H, br s, H-3), 2.41–2.34 (1H, m, CH$_a$,*H*$_b$-6), 1.89–1.77 (1H, m, C*H*$_a$H$_b$-5), 1.61 (1H, td, *J* 13.6, 2.2, C*H*$_a$H$_b$-1′), 1.53–1.49 (1H, m, C*H*$_a$H$_b$-4), 1.22 (9H, s, ^{t}*Bu*O), 1.12–1.04 (1H, m, CH$_a$,*H*$_b$-4), 1.00–0.93 (1H, m, CH$_a$,*H*$_b$-1′), 0.91–0.89 (1H, m, CH$_a$,*H*$_b$-5); δ_C (75 MHz; $CDCl_3$) 161.4, 157.2, 148.2, 147.9, 138.4, 134.2, 128.3, 127.6 (2C), 127.4, 126.9, 126.6, 121.9, 80.7, 74.5, 70.0, 65.7, 51.2, 49.1, 39.3, 33.7, 28.3, 24.6, 19.4; *m*/*z* (EI) 493 (1, M^+), 392 (20), 285 (29), 266 (32), 234 (13), 160 (12), 147 (19), 120 (40), 91 (100), 77 (10), 71 (15%). HRMS (EI): M^+, found 493.2578. $C_{28}H_{35}N_3O_5$ requires 493.2577.

*4.9.4. (2R,3S)-N-(tert-Butoxycarbonyl)-3-(benzyloxy)-2-[2′-oxo-3′-(4″-oxo-4H-quinazolin-3″-yl)propyl]piperidine (**32**)*

Dess–Martin periodinane (0.66 g, 1.56 mmol) was added to a stirred solution of alcohol **31** (0.31 g, 0.63 mmol) and pyridine (0.51 mL) in CH_2Cl_2 (11 mL) at room temperature. The reaction

mixture was stirred at room temperature for 2 h, diluted with Et_2O (11 mL) and saturated solutions of $NaS_2O_{3(aq)}$ (4 mL) and $NaHCO_{3(aq)}$ (8 mL) were added. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:4) to give the *title compound* (0.31 g, 99%) as a colourless oil. R_f (80% EtOAc/hexane) 0.31; $[\alpha]_D^{20}$ −42.3 (*c* 0.9, $CHCl_3$); ν_{max} (film) 2932, 1733, 1679, 1613, 1475 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.28–8.26 (1H, m, H-5″), 7.94 (1H, s, H-2″), 7.79–7.73 (2H, m, H-7″, H-8″), 7.51 (1H, ddd, *J* 8.2, 6.2, 2.1, H-6″), 7.36–7.25 (5H, m, Ar–H), 5.00–4.95 (3H, m, H-2, H-3′), 4.68 (1H, d, *J* 11.9, OC*H*$_a$,H$_b$Ph), 4.53 (1H, d, *J* 11.9, OCH$_a$,*H*$_b$Ph), 3.98 (1H, br s, C*H*$_a$,H$_b$-6), 3.49 (1H, br s, H-3), 2.93–2.82 (2H, m, C*H*$_a$,H$_b$-1′, CH$_a$,*H*$_b$-6), 2.72 (1H, dd, *J* 14.3, 5.8, CH$_a$,*H*$_b$-1′), 1.97–1.87 (2H, m, C*H*$_a$,H$_b$-4, C*H*$_a$,H$_b$-5), 1.69–1.60 (1H, m, CH$_a$,*H*$_b$-4), 1.45 (9H, s, ^tBuO), 1.41–1.40 (1H, m, CH$_a$,*H*$_b$-5); δ_C (100 MHz; $CDCl_3$) 200.0, 160.9, 155.7, 148.3, 146.5, 138.3, 134.4, 128.3, 127.6 (2C), 127.5, 127.2, 126.7, 121.8, 80.2, 73.9, 70.3, 53.8, 50.0, 40.9, 39.2, 28.4, 24.4, 19.4; *m*/*z* (EI) 491 (1, M^+) 390 (13), 283, (21), 202 (27), 187 (23), 160 (52), 137 (15), 130 (20), 98 (14), 91 (100), 77 (11), 71 (14%). HRMS (EI): M^+, found 491.2420. $C_{28}H_{33}N_3O_5$ requires 491.2420.

4.9.5. (2R,3S)-3-Hydroxy-2-[2′-oxo-3′-(4″-oxo-4H-quinazolin-3″-yl)propyl]piperidine ((+)-febrifugine) (**1**)

A solution of *N*-, *O*-protected febrifugine **32** (0.28 g, 0.57 mmol) in 6 M $HCl_{(aq)}$ (35 mL) was stirred under reflux for 40 min. The mixture was cooled to room temperature and basified to pH 9 by careful addition of saturated $K_2CO_{3(aq)}$. The reaction mixture was extracted with $CHCl_3$ (3×20 mL) and the combined organic layers dried over anhydrous K_2CO_3, concentrated under reduced pressure and purified by reverse phase (C_{18}) flash chromatography eluting with H_2O/CH_3CN (10:1) to give the *title compound* (0.12 g, 67%) as a white solid. Recrystallisation of this material using EtOAc gave colourless crystals. Mp 139–141 °C; R_f (20% MeOH/$CHCl_3$) 0.31; $[\alpha]_D^{20}$ +26.4 (*c* 0.1, EtOH); ν_{max} (solid) 3285, 3149, 2930, 2854, 1723, 1673, 1611, 1473 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.20 (1H, dd, *J* 8.2, 1.1, H-5″), 7.90 (1H, s, H-2″), 7.78 (1H, ddd, *J* 8.4, 7.0, 1.5, H-7″), 7.73 (1H, dd, *J* 8.4, 1.3, H-8″), 7.51 (1H, ddd, *J* 8.2, 6.7, 1.7, H-6″), 4.89 (1H, d, *J* 17.4, C*H*$_a$,H$_b$-3′), 4.82 (1H, d, *J* 17.4, CH$_a$,*H*$_b$-3′), 3.28 (1H, ddd, *J* 10.4, 9.1, 4.4, H-3), 3.11 (1H, dd, *J* 15.9, 4.7, C*H*$_a$,H$_b$-1′), 3.00–2.93 (1H, m, C*H*$_a$,H$_b$-6), 2.87 (1H, ddd, *J* 8.9, 7.4, 4.7, H-2), 2.63 (1H, dd, *J* 15.9, 7.4, CH$_a$,*H*$_b$-1′), 2.58 (1H, td, *J* 12.1, 2.9, CH$_a$,*H*$_b$-6), 2.12–2.05 (1H, m, C*H*$_a$,H$_b$-4), 1.75–1.71 (1H, m, C*H*$_a$,H$_b$-5), 1.57–1.48 (1H, m, CH$_a$,*H*$_b$-5), 1.37–1.31 (1H, m, CH$_a$,*H*$_b$-4); δ_C (75 MHz; $CDCl_3$) 202.6, 161.0, 148.2, 146.4, 134.5, 127.6, 127.4, 126.8, 121.9, 72.3, 60.2, 54.8, 46.0, 44.1, 34.5, 25.6. HRMS (FAB^+): MH^+, found 302.1510. $C_{16}H_{20}N_3O_3$ requires 302.1505.

Acknowledgements

We thank The University of Auckland Staff Research Committee and Doctoral Scholarship Scheme for funding of this work.

References and notes

1. (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69* 1837; (b) Koepfli, J. A.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1949**, *69*, 1048–1054; (c) Kopefli, J. B.; Brockman, J. A., Jr.; Moffat, J. *J. Am. Chem. Soc.* **1950**, *72* 3323.
2. Desideri, N.; Galli, A.; Sestili, J.; Stein, M. L. *Arch. Pharm.* **1992**, *35*, 490–501.
3. Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Gouratel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425–441.
4. (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055–2056; (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *29*, 29–32; (c) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579–8629.
5. For recent approaches to synthetic building blocks of this type see: (a) Jourdant, J.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7033–7036; (b) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193–3195; (c) Iradier, F.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2001**, *2*, 2957–2960; (d) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823; (e) Fronicola, R. S.; Subbaraj, K.; Montogomery, J. *Org. Lett.* **2002**, *4*, 615–617; (f) Monterde, M. I.; Brieva, R.; Gotor, V. *Tetrahedron: Asymmetry* **2001**, *12*, 525–528; (g) Enders, D.; Nolte, B.; Runsink, J. *Tetrahedron: Asymmetry* **2002**, *13*, 587–593; (h) Huang, P.-Q.; Liu, L.-X.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927–1929; (i) Katoh, M.; Matsune, R.; Nagase, H.; Honda, T. *Tetrahedron Lett.* **2004**, *45*, 6221–6223; (j) Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199–8205; (k) Bodas, M.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 8461–8463; (l) Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767–4773; (m) Lemire, A.; Grenon, M.; Pourashraf, M.; Charrette, A. B. *Org. Lett.* **2004**, *6*, 3517–3520; (n) Liang, N.; Datta, A. *J. Org. Chem.* **2005**, *70*, 10182–10185; (o) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747–2750; (p) Liu, L.-X.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2006**, *17*, 3265–3272; (q) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289–7293; (r) Feng, C.-G.; Chen, J.; Ye, J.-L.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *Tetrahedron* **2006**, *62*, 7459–7465.
6. For reviews see: (a) Merino, P. *Sci. Synth.* **2004**, *27*, 511–580; (b) Koumbis, A. E.; Gallos, J. E. *Curr. Org. Chem.* **2003**, *7*, 585–628; (c) Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695–713; (d) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759–774; (e) De March, P.; Figueredo, M.; Font, J. *Heterocycles* **1999**, *50*, 1213–1226; (f) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905–917; (g) Tsay, S.-C.; Patel, H. V.; Hwu, J. R. *Synlett* **1998**, 939–949; (h) Fredrickson, M. *Tetrahedron* **1997**, *53*, 403–425; (i) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–127; (j) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403.
7. (a) Pulz, R.; Cicchi, S.; Brandi, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153–1156; (b) Cardona, F.; Goti, A.; Brandi, A. *Org. Lett.* **2003**, *5*, 1475–1478; (c) Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. *Tetrahedron* **2003**, *59*, 5231–5240; (d) Pisaneschi, F.; Della Monica, C.; Cordero, F. M.; Brandi, A. *Tetrahedron Lett.* **2002**, *43*, 5711–5714; (e) Cordero, F. M.; Pisaneschi, F.; Gensini, M.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2002**, 1941–1951; (f) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633–3645; (g) Zorn, C.; Anichini, B.; Goti, B.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A.; Citti, L. *J. Org. Chem.* **1999**, *64*, 7846–7855; (h) Goti, A.; Cacciarini, M.; Cardona, F.; Brandi, A. *Tetrahedron Lett.* **1999**, *40*, 2853–2856; (i) Cardona, F.; Valenza, S.; Picasso, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1998**, *63*, 7311–7318; (j) Murahashi, S.-I.; Ohtake, H.; Imada, Y. *Tetrahedron Lett.* **1998**, *39*, 2765–2766; (k) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748.
8. (a) Herczegh, P.; Kovacs, I.; Szilagyi, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron* **1993**, *34*, 1211–1214; (b) Van den Broek, L. A. G. M. *Tetrahedron* **1996**, *52*, 4467–4487; (c) Peer, A.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1044–1065; (d) Berge, J. M.; Copley, R. C. B.; Eggleston, D. S.; Hamprecht, D. W.; Jarvest, R. L.; Mensah, L. M.; O'Hanlon, P. J.; Pope, A. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1811–1814; (e) Duff, F. J.; Vivien, V.; Wightman, R. H. *Chem. Commun.* **2000**, 2127–2128; (f) Brandi, A.; Cicchi, S.; Paschetta, V.; Pardo, D. G.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357–9359; (g) Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002**, 1344–1346.
9. Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953–955.
10. Ashoorzadeh, A.; Caprio, V. *Synlett* **2005**, 346–348.
11. Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417–420.
12. Masaguer, C. F.; Bleriot, Y.; Charlwood, J.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron* **1997**, *53*, 15147–15156.
13. Gmiener, P.; Dagmar, J. *J. Org. Chem.* **1995**, *60*, 3910–3915.
14. For recent examples see: (a) AliSk, A. *Tetrahedron Lett.* **1993**, *34*, 5325–5326; (b) Macours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415–1428; (c) Cordero, F. M.; Machetti, F.; De Sarlo, F.; Brandi, A. *Gazz. Chim. Ital.* **1997**, *127*, 25–29; (d) Tian, L.; Xu, G.-Y.; Ye, Y.; Liu, L.-Y. *Synlett* **2003**, 1329–1334.
15. Cicchi, S.; Maradi, M.; Goti, A.; Brandi. *Tetrahedron Lett.* **2001**, *42*, 6503–6505.
16. Ali, Sk. A.; Wazeer, I. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 597–605.
17. Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119–3125.
18. Camiletti, C.; Dhavale, D. D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3157–3165.
19. Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773–1776.
20. Na, H. S.; Yu, J.; Shin, J. J.; Yoo, K. H.; Kim, D. J.; Park, S. W. *Heterocycles* **1998**, *48*, 2365–2378.
21. (a) Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Thou, T. C. *Science* **1946**, *103*, 59; (b) Hewitt, R. I.; Wallace, W. S.; Gill, E. R.; Williams, J. H. *Am. J. Trop. Med. Hyg.* **1952**, *1*, 768–772.
22. Murata, K.; Takano, F.; Fushiya, S.; Oshima, Y. *Biochem. Pharmacol.* **1999**, *58*, 1593–1601.
23. (a) For other syntheses of febrifugine see: Baker, B. R.; Schaub, R. E.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 132–140; (b) Baker, B. R.; Schaub, R. E.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 153–177; (c) Baker, B. R.; McEvoy, F. J.; Schaub, R. E.; Joseph, J. P.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 178–183; (d) Baker, B. R.; McEvoy, F. J. *J. Org. Chem.* **1955**, *20*, 118–135; (e) Baker, B. R.; McEvoy, F. J. *J. Org. Chem.* **1955**, *20*, 136–142; (f) Hill, R. K.; Edwards, A. G. *Chem. Ind. (London)* **1962**, 858; (g) Barringer, D. F., Jr.; Beakelhammer, G. B.; Wayne, R. S. *J. Org. Chem.* **1973**, *38*, 1937–1940; (h) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3225–3258; (i) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814–1818; (j) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, S. *J. Org. Chem.* **1999**, *64*, 6833–6841; (k) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. *Chem. Commun.* **2000**, 1643–1644; (l) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989–990; (m) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Kim, H.-S.; Wataya, Y.; Harayama, T. *Tetrahedron* **2001**, *57*, 1213–1218; (n) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayshi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510–12517; (o) Takeuchi, Y.; Harayama, T. *Trends Heterocycl. Chem.* **2001**, *7*, 65–74; (p) Takeuchi, Y.; Oshige, M.; Azuma, K.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **2005**, *53*, 868–869; (q) Katoh, M.; Matsune, R.; Honda, T. *Heterocycles* **2006**, *67*, 189–204.
24. Ranganathan, D.; Rathi, R.; Kesavan, K.; Pal Singh, W. *Tetrahedron* **1986**, *42*, 4873–4878.