A concise approach to the core structures of pinnaic acid and halichlorine†

Sung-Hyun Yang, G. R. Clark and Vittorio Caprio*

Received 25th February 2009, Accepted 15th May 2009
First published as an Advance Article on the web 15th June 2009
DOI: 10.1039/b903904j

An efficient and flexible synthetic approach to the core structures of pinnaic acid and halichlorine is described using spirocyclic nitrone **4** as a key intermediate. 1,3-Dipolar cycloaddition of **4** with dipolarophile **8** provides access to the azaspirocyclic core of pinnaic acid **5** while the spiroquinolizidine core of halichlorine **6** has been synthesised *via* cycloaddition of **4** with dipolarophile **29**. Nitrone **4** is accessed by oxidative ring opening of isoxazolidine **9**. The utility of this synthetic strategy in the synthesis of C5 substituted analogues of pinnaic acid is also demonstrated.

Introduction

The 6-azaspiro[4.5]decane alkaloid pinnaic acid **1**, isolated along with tauropinnaic acid **2** (Fig. 1), from the marine bivalve *Pinna muricata* is a potent inhibitor of cytosolic phospholipase A_2 ($cPLA_2$).[1] This enzyme cleaves arachidonic acid from phospholipids in the cell membrane for conversion into prostaglandins and thus, pinnaic acid displays anti-inflammatory properties. The 6-azaspiro[4.5]decane system is also embedded within the spiroquinolizidine core structure of halichlorine, isolated from the black marine sponge *Halichondria okadai*.[2] Halichlorine **3** inhibits the expression of vascular cellular adhesion molecule-1 (VCAM-1), a peptide involved in the recruitment and trafficking of leukocytes to sites of tissue trauma. Inhibitors of VCAM-1 have been postulated as treatments for a wide variety of diseases believed to arise from extreme inflammatory and autoimmune responses such as atherosclerosis,[3] rheumatoid arthritis,[4] organ transplant rejection and a wide number of autoimmune conditions.[5]

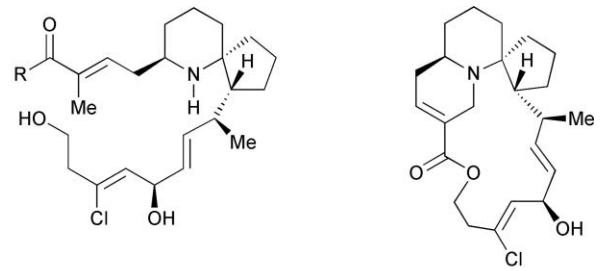
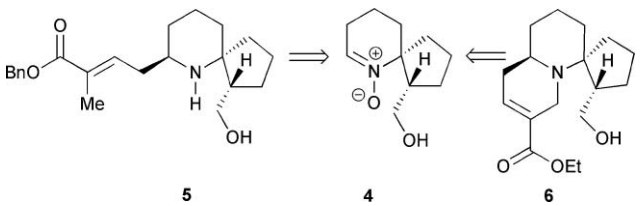


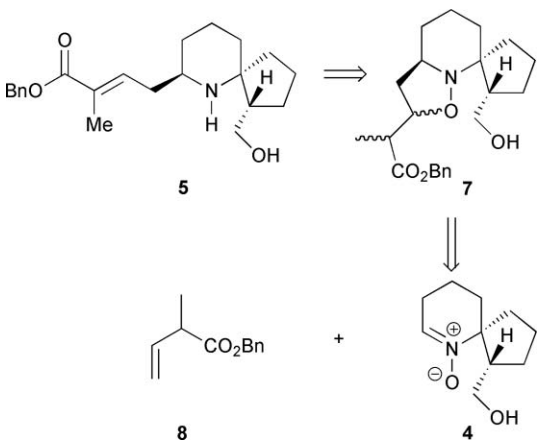
Fig. 1 Structures of pinnaic acid **1**, tauropinnaic acid **2** and halichlorine **3**.

The unique structures and interesting bioactivity of pinnaic acid and halichlorine have inspired the development of a number of total and partial syntheses.[6,7] We have devised an approach using spirocyclic nitrone **4** as a key intermediate (Scheme 1). Nitrones are known to exhibit a diverse reactivity profile, undergoing 1,3-dipolar cycloaddition with an array of electron deficient and electron rich alkenes[8] and also nucleophilic addition with organometallic species.[9] Thus, we envisioned that **4** would provide ready access to both core structures **5** and **6** and also a wide range of analogues. We have recently applied this strategy to the core structure of pinnaic acid **5** and analogues[7d] and we now report this work in full along with the synthesis of the spiroquinolizidine **6**.



Scheme 1

It was planned to access the core structure of pinnaic acid **5** by synthetic manipulation of the isoxazolidine **7** arising from 1,3-dipolar cycloaddition of nitrone **4** with 2-methylbutenoate **8** as shown in Scheme 2.



Scheme 2

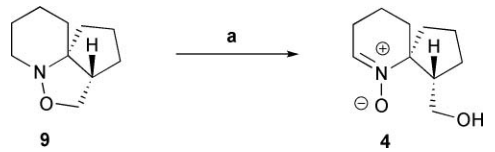
Department of Chemistry, The University of Auckland, 23 Symonds Street, Auckland, New Zealand. E-mail: v.caprio@auckland.ac.nz; Fax: +(64)(9)3737422; Tel: +(64)(9)3737599

† Electronic supplementary information (ESI) available: Additional experimental procedures for the preparation of compounds **12a–d**, **13a–d**, **14**, **17–19**, **20–24** and **32**, copies of all ^1H and ^{13}C NMR spectra. CCDC reference numbers 725418–725421 (**10**, **12a**, **18** and **43**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b903904j

Results and discussion

Nitrone **4** was accessed by oxidation of isoxazolidine **9** which was synthesised in four steps from 1,5-dibromopentane, according to the method of Gossinger *et al.*[10]

Oxidative cleavage of **9** was effected by slow addition of a solution of mCPBA in dichloromethane to give **4** in multi-gram quantities (Scheme 3).[11]



Scheme 3 Synthesis of nitrone **4**. *Reagents and conditions:* (a) mCPBA, CH_2Cl_2, 0 °C → rt, 89%.

Nitrone **4** is isolated as an orange solid after purification. Recrystallisation of this compound from diethyl ether and hexane yielded crystals of suitable quality for X-ray analysis (Fig. 2).† This revealed that nitrone **4** is present in the solid state as the oxazine tautomer **10** (Scheme 4). Dissolution of the oxazine **10** in $CDCl_3$ and immediate recording of a ^{1}H NMR spectrum indicated rapid, and quantitative conversion back to the nitrone in solution, as evidenced by the relative integral of the C7 proton signal at δ 7.34. This tautomerism has been observed previously during studies of acyclic nitrones.[11,12]

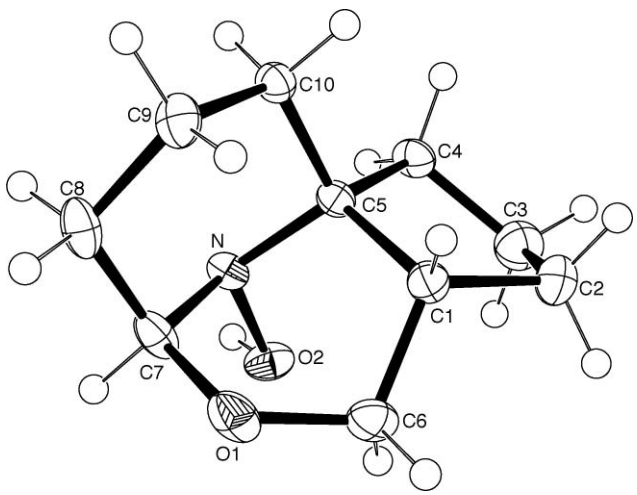
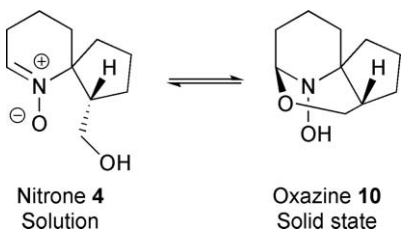


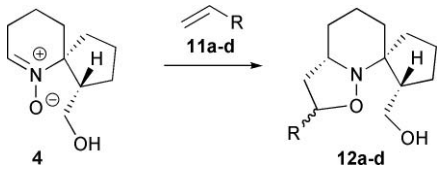
Fig. 2 X-Ray crystal structure of oxazine **10** (displacement ellipsoid plots drawn at 50% probability level).



Scheme 4 Tautomerism of nitrone **4**.

With quantities of nitrone **4** in hand we next embarked on a model study aimed at probing the reactivity and utility of this intermediate. Thus, the 1,3-dipolar cycloaddition of **4** with a number of dipolarophiles was examined along with conditions required for reductive ring opening of the resulting cycloadducts. The results of this study are summarised in Table 1. A variety of reaction conditions were screened and those specified result in optimum yields of the product. Nitrone **4** undergoes cycloaddition with a range of alkenes, including both electron poor (entry 2) and electron rich (entry 3) substrates, in good yield to give isoxazolidines **12a–d** as single stereoisomers.

Table 1 1,3-Dipolar cycloaddition of nitrone **4** with dipolarophiles **11a–d**



Entry	Alkene **11**[a]	R	Solvent	Temp/°C	Time/h	**12**[c]	Yield[d] (%)
1	**11a**	Ph	PhMe	110	13	**12a**	64
2	**11b**[b]	CO_2Et	CH_2Cl_2	25	48	**12b**	94
3	**11c**[b]	OEt	EtOH	40	55	**12c**	80
4	**11d**	CH_2CH_2OBz	PhMe	110	8	**12d**	70

[a] Unless otherwise stated, cycloadditions were carried out using 3 equiv. of dipolarophile. [b] Cycloaddition carried out using 17 equiv. of dipolarophile. [c] Relative stereochemistry determined by 2D-NOESY studies performed on azaspirodecanes **13a**, **b**, **d** and **14** (Table 2). [d] Isolated, chromatographically pure products.

An X-ray structure of the crystalline styrene-derived cycloadduct **12a**, obtained as the single product from the cycloaddition of **4** with styrene **11a** (Fig. 3), reveals that cycloaddition occurred, with *exo*-selectivity, from the undesired α-face of nitrone **4**.

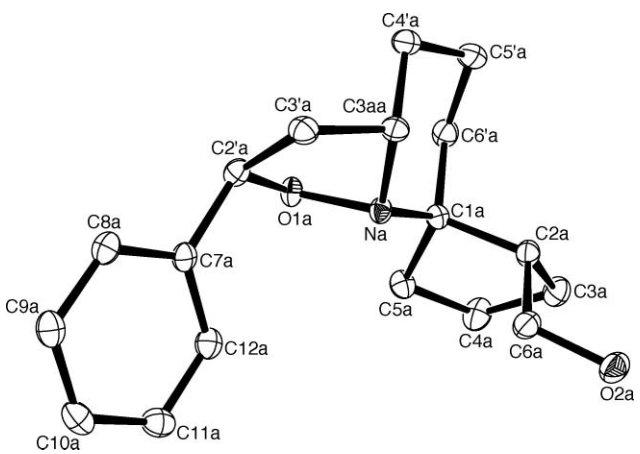
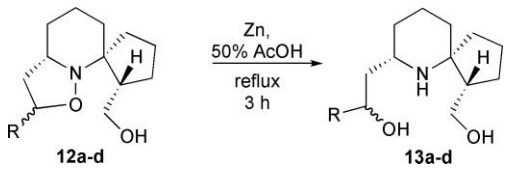


Fig. 3 X-Ray crystal structure of cycloadduct **12a** (displacement ellipsoid plots drawn at 50% probability level). There are two independent enantiomeric crystal structures of **12a** and only one is shown here.

As crucial signals overlapped in the ^{1}H NMR spectra of isoxazolidines **12** the stereochemistry of the other cycloadducts was most conveniently determined by 2D-NOESY studies performed on the reduced products **13**. Unfortunately this did not allow an assignation of *exo*/*endo* stereochemistry. Reductive ring opening of the cycloadducts proceeded smoothly, in high yield under

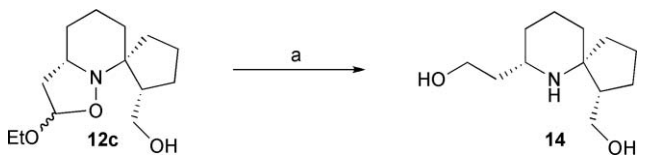
Table 2 Reductive cleavage of cycloadducts **12**



Entry	Cycloadduct	R	13[a]	Yield (%)[b]
1	**12a**	Ph	**13a**	76
2	**12b**	CO_2Et	**13b**	70
3	**12d**	CH_2CH_2OBz	**13d**	81

[a] Relative stereochemistry determined by 2D-NOESY studies. [b] Isolated, chromatographically pure product.

standard conditions, using zinc in acetic acid under reflux to give 6-azaspiro[4.5]decanes **13a**, **b** and **13d** (Table 2). Cycloadduct **12c** decomposed under a variety of reduction conditions and reductive cleavage of this compound could only be effected by hydrogenation in the presence of $Pd(OH)_2$ to give diol **14** in modest yield (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) H_2, 20 mol% $Pd(OH)_2$, MeOH, rt, 48 h, 44%.

The stereochemistry of the cycloaddition was readily determined by analysis of the 2D-NOESY spectra obtained for compounds **13** (Fig. 4). Strong correlations were observed between the axial proton at C7 and the protons of the hydroxymethyl group and those at C1. In addition, there was complete absence of any NOE between C7 and the protons at C4, confirming that cycloaddition occurred from the undesired α-face resulting in azaspiro[4.5]decanes with unnatural stereochemistry at C7. Nevertheless, this short model study reveals that a range of C7-modified analogues of pinnaic acid and halichlorine are readily available from nitrone **4**.

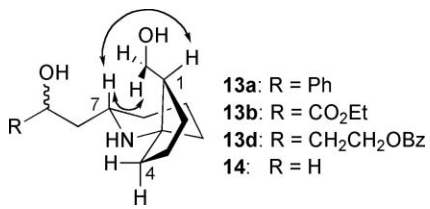


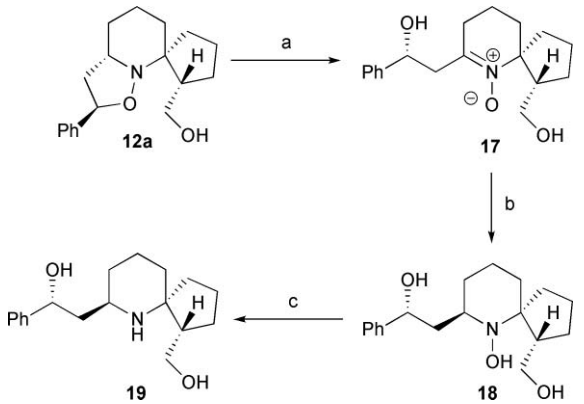
Fig. 4 Selected NOE observed in azaspirodecanes **13** and **14**.

The reduction of imines/iminium ions[13] and nitrones structurally related to **4** is also observed to occur from the α-face.[14] For instance, Zhang *et al.* obtained *N*-hydroxyazaspiro[4.5]decane **15** as the sole diastereomer on reduction of nitrone **16** with sodium borohydride (Scheme 6).[14]

These results indicate that azaspirodecanes with the desired relative stereochemistry could be accessed by oxidative cleavage of isoxazolidines **12** followed by reduction of the resulting nitrone.

Scheme 6 *Reagents and conditions:* (a) $NaBH_4$, MeOH, 0 °C to rt, 96%.

Indeed, oxidation of cycloadduct **12a** to nitrone **17** followed by reduction using sodium borohydride[14,15] then N–O bond cleavage with aqueous titanium trichloride in MeOH[16] gave the C5-epimer **19** (Scheme 7).



Scheme 7 *Reagents and conditions:* (a) mCPBA, CH_2Cl_2, 0 °C, 1 h, 85%, (b) $NaBH_4$, MeOH, 0 °C, 20 min, 90%, (c) 20% $TiCl_{3(aq)}$, H_2O, MeOH, rt, 3 h, 92%.

The stereochemistry was readily deduced by 2D-NOESY analysis of *N*-hydroxyazaspiro[4.5]decane **18** (Fig. 5). Strong NOE cross-peaks were observed between the C7 proton and protons at C4 and also those at C9 while NOE's between this proton and those at C1 were absent (Fig. 4). Compound **18** was obtained as a crystalline solid and an X-ray crystal structure further confirmed the relative stereochemistry (Fig. 6).

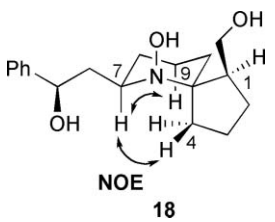


Fig. 5 Selected NOE observed in azaspirodecane **18**.

We then applied this general strategy to the synthesis of the pinnaic acid core structure **5**. Dipolarophile **8** was accessed by esterification of 2-methylbut-3-enoic acid. The acid was conveniently obtained by quenching of the Grignard reagent formed from crotyl chloride with carbon dioxide.[17] Cycloaddition of **8** with nitrone **4** occurred in moderate yield under conventional thermal conditions (37%, toluene, reflux) to give *exo*-isoxazolidine **20** as a separable 1 : 1 mixture of diastereomers. Much better yields of cycloadduct were obtained using toluene as solvent under microwave irradiation. Compound **20** was then elaborated to the pinnaic acid core structure (Scheme 8). The desired relative stereochemistry was installed by oxidative ring opening of

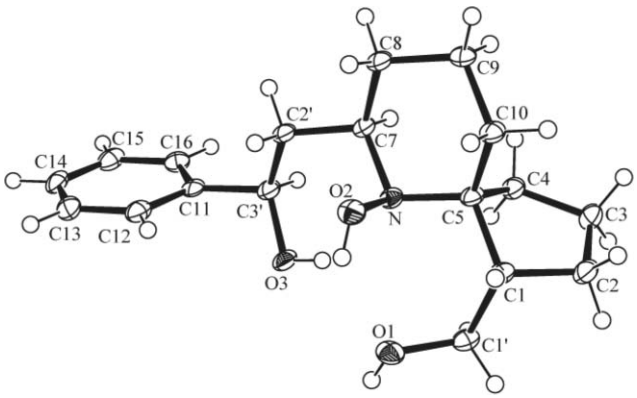
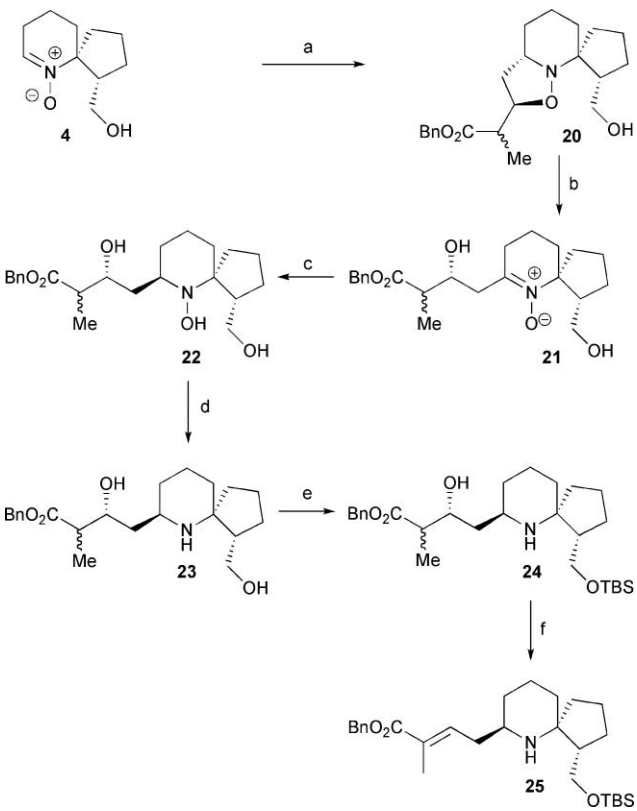


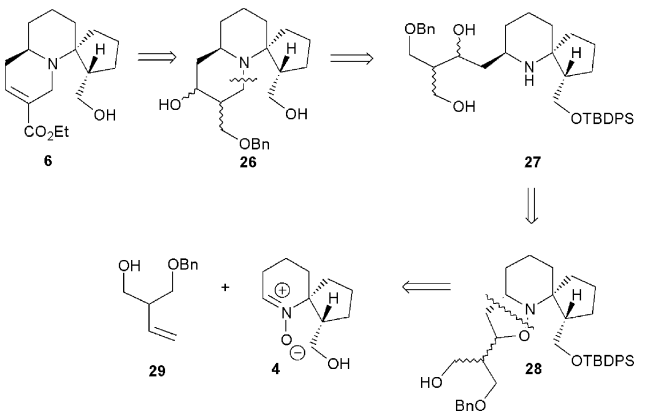
Fig. 6 X-Ray crystal structure of azaspirodecane **18** (displacement ellipsoid plots drawn at 50% probability level).



Scheme 8 *Reagents and conditions:* (a) 2 equiv. **8**, PhMe, 165 °C, 50 min, MW, 85%, (b) mCPBA, CH_2Cl_2, 0 °C to rt, 91%, (c) $NaBH_4$, MeOH, 0 °C, 30 min, 68%, (d) cat. In, 2 equiv. Zn, EtOH–$NH_4Cl_{(aq)}$ (2 : 1), reflux, rt, 4 h, 100%, (e) TBSCl, DMAP, Et_3N, 0 °C to rt, 89%, (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 24 h; (ii) NaH, THF, rt, 85% over 2 steps.

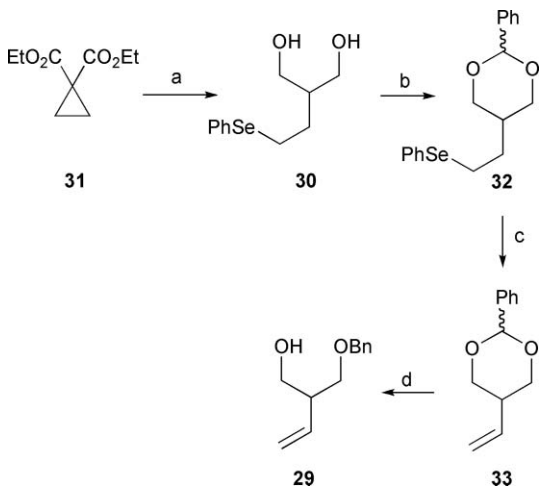
isoxazolidine **20** followed by reduction using sodium borohydride. While N–O bond cleavage was achieved in good yield using aqueous titanium trichloride, *N*-hydroxyazaspiro[4.5]decane **22** was reduced to amine **23** quantitatively using catalytic indium in the presence of two equivalents of zinc.[18] The primary alcohol was then protected as the *tert*-butylsilyl ether. Elimination of the secondary alcohol was achieved by conversion to a 1 : 1 mixture of mesylates followed by treatment of the crude product with sodium hydride. As (*E*)-alkene **25** is obtained as the sole product, this elimination is independent of the stereochemistry of the mesylate and thus likely proceeds *via* an $E_{1c}B$-type mechanism.

The next phase of investigation centred on application of nitrone **4** to the synthesis of the core structure of halichlorine **6**. Our retrosynthesis of **6** is shown in Scheme 9. Functional group interconversion (FGI) leads to mono-protected triol **26**. It was planned to construct the quinolizidine core of **26** by cyclisation of azaspiro[4.5]decane **27**, accessed by synthetic manipulation of isoxazolidine **28**. It was envisioned that **28** could be accessed by 1,3-dipolar cycloaddition of nitrone **4** with alkene **29**.



Scheme 9

The synthetic route to dipolarophile **29** centred on the synthesis of dihydroxyselenide **30**. This compound was accessed by reaction of cyclopropane **31** with *in situ* generated sodium phenylselenolate, followed by the reduction of the resulting malonate, according to the procedure developed by Kocienski and Yates (Scheme 10).[19] Conversion of **30** to the benzylidene acetal **32** followed by oxidative elimination to the known olefin **33** and reduction of the acetal moiety yielded alkene **29**.[20]



Scheme 10 *Reagents and conditions:* (a) (i) Ph_2Se_2, $NaBH_4$, EtOH, rt, 24 h, 77%, (ii) $LiAlH_4$, Et_2O, 0 °C, 24 h, 92%, (b) $Ph(OMe)_2$, pTSA, PhMe, reflux, 6 h, 100%, (c) 30% $H_2O_{2(aq)}$, py, CH_2Cl_2, 0 °C, reflux, 3 h, 95%, (d) DIBAL-H, PhMe–CH_2Cl_2, −78 °C to rt, 3.5 h, 100%.

Cycloaddition of nitrone **4** with dipolarophile **29** occurred in high yield and stereoselectivity, under microwave irradiation, to give isoxazolidine **34** as a 1 : 1 mixture of inseparable diastereomers. Both diastereomers were then converted to the core structure of halichlorine **6** (Scheme 11). Selective mono-protection of diol **34** was effected using TBDPSCl. The resulting silyl ether **28** was subjected to the oxidation–reduction conditions developed previously to give 6-azaspiro[4,5]decane **27**. Cyclisation was achieved on treatment of **27** with two equivalents of mesyl chloride in the presence of triethylamine to give mesyloxyspiroquinolizidine **37a/b** as a separable mixture of *trans*/*cis* diastereomers. After some experimentation it was discovered that debenzylation of **37a/b** was best achieved using lithium di-*tert*-butylbiphenylide (LiDBB). Oxidation of the resulting diastereomeric mixture of alcohols **38** was effected, with concomitant elimination, using Dess–Martin periodinane, to give α,β-unsaturated aldehyde **39**. Further oxidation to the carboxylic acid under Pinnick conditions followed by esterification and deprotection of the silyl ether gave core structure target **6**. The structure of **6** was further confirmed by X-ray crystal analysis of the hydrochloride salt **43** (Fig. 7).

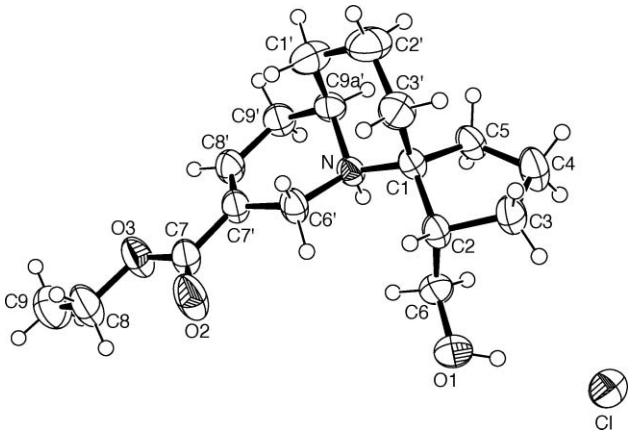


Fig. 7 X-Ray crystal structure of hydrochloride **43** (displacement ellipsoid plots drawn at 50% probability level).

Conclusions

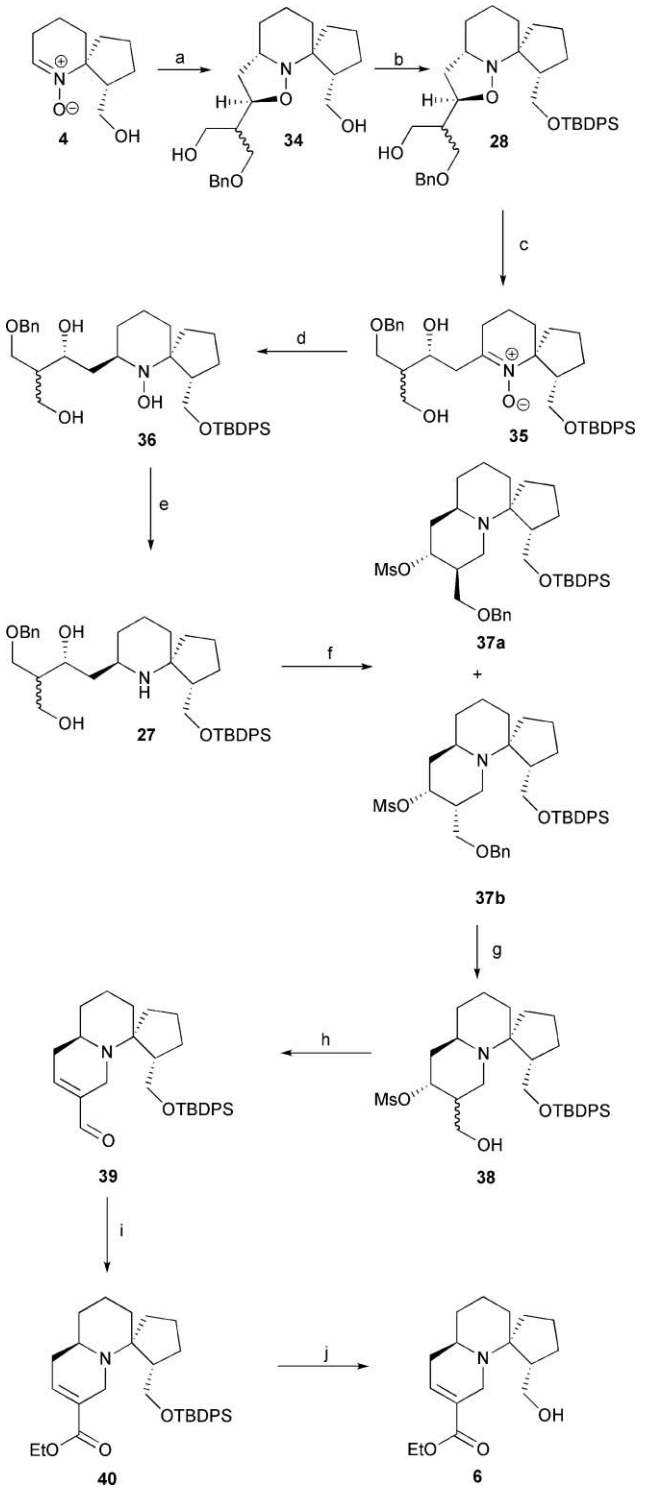
In conclusion, a flexible and concise synthetic strategy towards the azaspirocyclic core structures of pinnaic acid and halichlorine, utilising spironitrone **4** as a key intermediate, has been developed. This synthetic strategy centres on the 1,3-dipolar cycloaddition of **4** with the requisite alkene followed by synthetic manipulation of the resulting cycloadducts.

Nitrone **4** can be accessed in multi-gram quantities by oxidative cleavage of spirocyclic isoxazolidine **9** and thus, our approach is highly amenable to scale-up. Moreover, as **4** has been shown to undergo cycloaddition with a range of alkenes this strategy can be readily adapted to the synthesis of a wide range of analogues of both targets.

Experimental

General

All reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried by distillation



Scheme 11 *Reagents and Conditions*: (a) **29**, PhMe, 210 °C, MW, 2 h, 78%, (b) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 93%, (c) mCPBA, CH_2Cl_2, 0 °C to rt, 1 h, 93%, (d) $NaBH_4$, MeOH, 0 °C to rt, 30 min, 89%, (e) cat. In, Zn, EtOH–$NH_4Cl_{(aq)}$, (2 : 1), reflux, 4 h, 100%, (f) 2 equiv. MsCl, Et_3N, CH_2Cl_2, 0 °C to reflux, 6 h, 99%, (g) LiDBB, THF, 0 °C to rt, 89%, (h) Dess–Martin periodinane, 0 °C to rt, 1 h, 80%, (i) (1) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, 0 °C, 24 h, 74%, (2) DCC, EtOH, DMAP, CH_2Cl_2, 0 °C to rt, 24 h, 65%. (j) TREAT·HF, NEt_3, MeCN, reflux, 4 h, 94%.

from calcium hydride (CH_2Cl_2, DMF, toluene) or sodium benzophenone (THF and diethyl ether). Flash chromatography was performed using Scharlau 60 (230–400 mesh ASTM) silica gel. 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. 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 shifts δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; 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. The ^{1}H and ^{13}C NMR spectra of compounds **32** and **34** are complicated by the presence of a mixture of diastereoisomers. Resonances for individual diastereomers are denoted by asterisks. 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%).

(1*S,5*S**)-1-Hydroxymethyl-6-azaspiro[4.5]dec-6-ene-6-oxide 4.** A solution of *meta*-chloroperoxybenzoic acid (70%, 5.7 g, 33.0 mmol) in dichloromethane (70 mL) was added, dropwise, over 7 h to a stirred solution of isoxazolidine **9** (3.80 g, 22.7 mmol) in dichloromethane (120 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 20 h then a mixture of saturated aqueous sodium bicarbonate–saturated aqueous sodium thiosulfate (1 : 1, 60 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and the combined organic phases dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 95% dichloromethane–methanol as eluent to afford nitrone **4** (3.71 g, 89%) as an orange solid. Recrystallisation of the nitrone **4** from diethyl ether and hexane yielded crystals suitable for X-ray crystallography. Mp 69.5–73.2 °C, ν_{max} (film)/cm^{-1} 3410, 2961, 1642, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.30–2.10 (10H, m, 1-H, H-2, H-3, H-4, H-10$_a$, H-9), 2.45–2.52 (2H, m, 8-H), 2.70–2.85 (1H, m, 10$_b$-H), 3.65–3.80 (2H, m, CH_2OH), 7.34 (1H, t, J = 4.0 Hz, 7-H), δ_c (75 MHz, $CDCl_3$, Me_4Si) 15.4 (CH_2), 24.0 (CH_2), 26.3 (CH_2), 28.3 (CH_2), 37.0 (CH_2), 38.5 (CH_2), 52.7 (CH), 61.1 (CH_2), 76.5 (C), 142.0 (CH), m/z (EI) 183.1259 (M^+ $C_{10}H_{17}NO_2$ requires 183.1253), 183 (M^+, 70%), 166 (70), 124 (100), 111 (47), 95 (56), 81 (83), 79 (56), 67 (69), 55 (42), 41 (77), 39 (39).

Crystal structure determination of oxazine 10.

Crystal data. $C_{10}H_{27}NO_2$, M = 183.25, monoclinic, a = 8.5510(2), b = 10.7255(2), c = 10.3379(2) Å, β = 96.350(2)°, U = 942.35(3), T = 84 K, space group $P2_1/n$, Z = 4, 5788 reflections measured, 2069 unique (R_{int} = 0.024) which were used in all calculations. The final R was 0.063 (all data).

General procedure for cycloaddition of alkenes 11 with nitrone 4. A solution of alkene **11** and nitrone **4** was reacted using the solvents, reagent ratios and conditions specified in Table 1. After the time specified in Table 1 the reaction mixture was concentrated and the crude residue purified by column chromatography to give the cycloadducts **12**.

General procedure for reduction of cycloadducts 12. Zinc dust (9–11 equiv.) was added to a stirred solution of isoxazolidine **12** in 50% aqueous acetic acid at room temperature. The reaction mixture was stirred under reflux for 3 h then a saturated aqueous solution of sodium bicarbonate added. The aqueous phase was extracted with dichloromethane and the combined organic phases dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 90% dichloromethane–methanol as eluent to afford the reduction product **13**.

(1*S,2*S**,2′*S**,3*a*′*S**)-2′-(1″-(Benzyloxy)-3″-hydroxypropan-2″-yl)-2-(hydroxymethyl)hexahydrospiro[cyclopentane-1,7′-isoxazolo[2,3-*a*]pyridine] 34.** A 10 mL microwave reaction vial was charged with nitrone **4** (0.23 g, 1.22 mmol) and dipolarophile **29** (0.35 g, 1.84 mmol) in toluene (5 mL). The vial was sealed with a cap containing a silicon septum, loaded into the cavity of a focussed microwave reactor (Discover® CEM, 300 W) and heated for 2 h at 210 °C. (The following microwave conditions were used. Power: 250 KW, ramp time: 5 min 30 s, hold time: 120 min.) The reaction mixture was cooled to room temperature and concentrated. The crude residue was purified by column chromatography with 50% ethyl acetate–hexanes as eluent to afford isoxazolidine **34** (0.36 g, 78%) as a yellow oil and as a diastereomeric mixture. υ_{max} (film)/cm^{-1}: 3412, 2937, 2876, 1645, 1454, 1071, 1027, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.30–1.45 (3H, m, H-4′, H-6′$_a$), 1.45–1.60 (5H, m, H-3$_a$, H-4$_a$, H-5′, H-6′$_b$), 1.60–1.73 (2H, m, H-4$_b$, H-5$_a$), 1.73–1.82 (1H, m, H-3$_b$), 1.88–2.01 (1.5H, m, H-2″, H-3′$_a$, H-5$_b$), 2.01–2.08 (0.5H, m, H-2″*), 2.08–2.20 (1H, m, H-2), 2.20–2.28 (1H, m, H-3′$_b$), 3.38–3.48 (1H, m, H-3*a*′), 3.48–3.63 (3H, m, CH_2OH, H-1″$_a$), 3.63–3.69 (1H, m, H-1″$_b$), 3.69–3.82 (2H, m, H-3″), 4.19–4.30 (1H, m, H-2′), 4.47 (2H, d, J = 5.3, CH_2Ph), 7.24–7.35 (5H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.1 (CH_2), 20.6 (CH_2), 20.8 (CH_2*), 25.9 (CH_2), 26.1 (CH_2*), 27.1 (CH_2), 27.3 (CH_2*), 28.9 (CH_2), 29.5 (CH_2*), 37.7 (CH_2), 37.9 (CH_2*), 38.3 (CH_2), 39.7 (CH_2*), 45.3 (CH), 45.4 (CH*), 45.5 (CH), 45.9 (CH*), 57.3 (CH), 57.6 (CH*), 62.1 (CH_2), 62.2 (CH_2*), 64.3 (CH_2), 64.6 (CH_2*), 68.5 (C), 68.7 (C*), 69.8 (CH_2), 70.0 (CH_2*), 73.1 (CH_2), 73.2 (CH_2*), 73.4 (CH), 74.6 (CH*), 127.4 (CH) 2C, 128.2 (CH), 137.9 (C), 138.0 (C*), m/z (EI) 375.2416 (M^+ $C_{22}H_{32}NO_4$ requires 375.2409), 375 (M^+, 44%), 358 (29), 316 (69), 284 (13), 210 (15), 138 (37), 109 (27), 91 (100), 55 (26), 41 (32).

(1*S,2*S**,2′*S**,3*a*′*S**)-2′-(1″-(Benzyloxy)-3″-hydroxypropan-2″-yl)-2-(*tert*-butyldiphenylsilyloxymethyl)hexahydrospiro[cyclopentane-1,7′-isoxazolo[2,3-*a*]pyridine] 28.** A solution of *tert*-butyldiphenylsilyl chloride (1.26 g, 4.62 mmol) was added dropwise to a stirred solution of diol **34** (1.57 g, 4.20 mmol), triethylamine (3.49 mL, 25.2 mmol) and DMAP (0.05 g, 0.42 mmol) in dichloromethane (160 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h then diluted with water (100 mL). The aqueous phase was extracted with dichloromethane (3 × 75 mL) and the combined organic phases

dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 15% ethyl acetate–hexane as eluent to afford silyl ether **28** (2.40 g, 93%) as a yellow oil and as a separable diastereomeric mixture. Data for less polar diastereomer: υ_{max} (film)/cm^{-1}: 3434 (br), 2933, 2857, 1647, 1454, 1427, 1262, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.06 (9H, s, C(CH_3)$_3$), 1.08–1.40 (4H, m, H-4′, H-5′$_a$, H-6′$_a$), 1.40–1.68 (4H, m, H-4$_a$, H-5$_a$, H-5′$_b$, H-6′$_b$), 1.68–1.95 (5H, m, H-3$_a$, H-3′$_a$, H-2″, H-4$_b$, H-5$_b$), 1.95–2.11 (3H, m, H-2, H-3$_b$, H-3′$_b$), 2.41–2.59 (1H, br s, H-3$_a$′), 3.39–3.58 (3H, m, CH_aH$_b$OTBDPS, CH_2OBn,), 3.58–3.95 (3H, m, CH$_a$$H_b$OTBDPS, C$H_2$OH), 4.14–4.20 (1H, m, H-2′), 4.44 (2H, s, CH_2Ph) 7.24–7.39 (11H, m, H-Ar), 7.65–7.69 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.2 (C), 19.5 (CH_2), 20.0 (CH_2), 25.8 (CH_2), 26.5 (CH_2), 26.9 (CH_3), 28.1 (CH_2), 37.6 (CH_2), 39.4 (CH_2), 45.7 (CH), 46.6 (CH), 56.5 (CH), 61.2 (CH_2), 63.3 (CH_2), 67.2 (C), 70.4 (CH_2), 73.1 (CH_2), 74.3 (CH), 127.4 (CH), 127.5 (CH), 128.2 (CH), 129.4 (CH), 134.0 (C), 134.3 (C), 135.5 (CH), 135.7 (CH), 138.3 (C), *m/z* (EI) 613.3587 ($C_{38}H_{51}NO_4Si$ requires M$^+$ 613.3587), 613 (62%), 448 (20), 316 (32), 199 (34), 135 (26), 91 (100). Data for more polar diastereomer: υ_{max} (film)/cm^{-1}: 3430, 3069, 2932, 2857, 1588, 1472, 1427, 1263, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.05 (9H, s, C(CH_3)$_3$), 1.15–1.42 (6H, m, H-4′, H-5′, H-6′), 1.42–1.59 (2H, m, H-4$_a$, H-5$_a$), 1.59–1.81 (3H, m, H-3$_a$, H-4$_b$, H-5$_b$), 1.81–1.98 (3H, m, H-3′, H-2″), 1.98–2.14 (2H, H-2, H-3$_b$), 2.42 (1H, br s, H-3*a*′), 3.37–3.46 (3H, m, CH_aH$_b$OTBDPS, CH_2OBn), 3.46–3.75 (3H, m, CH$_a$$H_b$OTBDPS, H-3″), 4.11 (1H, br s, H-2′), 4.35 (2H, s, CH_2Ph), 7.26–7.39 (11H, m, H-Ar), 7.65–7.69 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.2 (C), 19.7 (CH_2) (2C), 25.6 (CH_2), 26.3 (CH_2), 26.9 (CH_3), 28.5 (CH_2), 37.3 (CH_2) 2C, 45.0 (CH), 46.2 (CH), 56.7 (CH), 61.9 (CH_2), 63.2 (CH_2), 67.3 (C), 70.0 (CH_2), 73.1 (CH_2), 73.8 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 129.4 (CH), 134.0 (C), 134.2 (C), 135.5 (CH), 135.7 (CH), 138.1 (C), *m/z* (EI) 613.3583 ($C_{38}H_{51}NO_4Si$ requires M$^+$ 613.3587), 613 (M$^+$, 81%), 448 (28), 316 (39), 199 (38), 135 (31), 91 (100).

(1*S,5*S**)-7-((2′*R**)-3′-(Benzyloxymethyl)-2′,4′-dihydroxybutyl)-1-(*tert*-butyldiphenylsilyloxymethyl)-6-azaspiro[4.5]dec-6-ene 6-oxide 35.** A solution of mCPBA (1.50 g, 8.71 mmol) in dichloromethane (130 mL) was added dropwise, over 1 h, to a stirred solution of isoxazolidine **28** (2.67 g, 4.35 mmol) in dichloromethane (80 mL) at 0 °C and the reaction mixture stirred for a further 10 min at this temperature. A mixture of saturated aqueous sodium thiosulfate–sodium hydrogen carbonate (1 : 1, 200 mL) was added and the aqueous phase extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 5% methanol–dichloromethane to afford nitrone **35** (2.54 g, 93%) as a yellow oil and as a separable diastereomeric mixture: data for less polar diastereomer: υ_{max} (film)/cm^{-1}: 3429, 2954, 2858, 1655, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.03 (9H, s, C(CH_3)$_3$), 1.45–1.64 (2H, m, H-3$_a$, H-9$_a$), 1.64–1.94 (7H, m, H-3$_b$, H-4$_a$, H-3′, H-8, H-9$_b$, H-10$_a$), 1.94–2.13 (2H, m, H-1, H-1′$_a$), 2.13–2.48 (3H, m, H-2, H-10$_b$), 2.56–2.68 (1H, m, H-4$_b$), 3.26 (1H, d, J = 10.5 Hz, H-1′$_b$), 3.58 (2H, d, J = 5.9 Hz, CH_2OBn), 3.73–3.96 (3H, m, CH_aH$_b$OTBDPS, H-4′), 4.06 (1H, dd, J = 10.3, 7.8 Hz, CH$_a$$H_b$OTBDPS), 4.14 (1H, ddd, J = 10.5, 5.7, 1.9 Hz, H-2′), 4.48 (2H, d, J = 4.1 Hz, CH_2Ph), 7.17–7.49 (11H, m, H-Ar), 7.59–7.78 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 16.7 (CH_2), 18.9 (C), 24.4 (CH_2), 26.7 (CH_3), 30.9 (CH_2), 31.4 (CH_2), 37.5 (CH_2), 38.8 (CH_2), 39.9 (CH_2), 47.0 (CH), 54.4 (CH), 62.7 (CH_2), 64.9 (CH_2), 69.9 (CH_2), 73.2 (CH_2), 73.7 (CH), 76.4 (C), 127.4 (CH), 127.5 (CH), 128.1 (CH), 129.4 (CH), 133.4 (C), 133.5 (C), 135.3 (CH) (2C), 138.0 (C), 150.9 (C), *m/z* 629.3527 ($C_{38}H_{51}NO_5Si$ requires M$^+$ 629.3536), (EI) 629 (M$^+$, 0.3%), 435 (19), 418 (53), 378 (32), 199 (58), 179 (59), 162 (38), 135 (71), 107 (64), 91 (100), 79 (34), 41 (24). Data for more polar diastereomer: υ_{max} (film)/cm^{-1}: 3413, 2932, 2858, 1654, 1472, 1427, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.02 (9H, s, C(CH_3)$_3$), 1.42–1.53 (1H, m, H-3$_a$), 1.53–1.86 (6H, m, H-4$_a$, H-8, H-9, H-10$_a$), 1.86–1.96 (2H, m, H-3$_b$, H-3′), 1.96–2.19 (1H, m, H-1), 2.19–2.22 (2H, m, H-1′$_a$, H-10$_b$), 2.22–2.39 (1H, m, H-2$_a$), 2.39–2.54 (1H, m, H-2$_b$), 2.54–2.67 (1H, m, H-4$_b$), 3.26 (1H, d, J = 11.2 Hz, H-1′$_b$), 3.68–3.91 (5H, m, H-4′, CH_aH$_b$OTBDPS, CH_2OBn), 4.01–4.12 (1H, m, CH$_a$$H_b$OTBDPS), 4.20 (1H, ddd J = 11.2, 4.9, 1.4 Hz, H-2′), 4.49 (2H, d, J = 1.8 Hz, CH_2Ph), 7.17–7.44 (11H, m, H-Ar), 7.59–7.72 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 16.7 (CH_2), 18.9 (C), 24.3 (CH_2), 26.7 (CH_3), 30.8 (CH_2), 31.3 (CH_2), 37.5 (CH_2), 37.8 (CH_2), 39.9 (CH_2), 46.7 (CH), 54.3 (CH), 63.1 (CH_2), 64.6 (CH_2), 69.2 (CH_2), 72.5 (CH), 73.1 (CH_2), 76.3 (C), 127.3 (CH), 127.4 (CH), 128.1 (CH), 129.4 (CH), 135.3 (CH) (2C), 135.4 (C), 135.5 (C), 138.0 (C), 151.0 (C), *m/z* (FAB) 630.3614 ($C_{38}H_{52}NO_5Si$ requires MH 630.3614), 630 (MH$^+$, 20%), 460 (2), 391 (5), 307 (22), 289 (11), 219 (4), 154 (100), 136 (68), 107 (23), 91 (27), 77 (19).

(1*S,5*S**,7*R**)-7-((2′*R**)-3′-(Benzyloxymethyl)-2′,4′-dihydroxybutyl)-1-(*tert*-butyldiphenylsilyloxymethyl)-6-azaspiro[4.5]decan-6-ol 36.** Sodium borohydride (0.73 g, 19.2 mmol) was added to a stirred solution of nitrone **35** (2.42 g, 3.85 mmol) in methanol (180 mL) at 0 °C. The mixture was allowed warm to room temperature and stirred for 30 min then concentrated. The crude residue was diluted with ethyl acetate (80 cm^3) and saturated brine (120 mL) and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated and the crude residue purified by column chromatography with 30% ethyl acetate–hexane as eluent to afford *N*-hydroxyazaspiro[4.5]decane **36** (2.16 g, 89%) as a yellow oil and as a separable diastereomeric mixture. Data for less polar diastereomer: υ_{max} (film)/cm^{-1}: 3391, 2955, 2858, 1655, 1428, 1112, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.04 (9H, s, C(CH_3)$_3$), 1.07–1.16 (1H, m, H-8$_a$), 1.16–1.33 (2H, m, H-1′$_a$, H-10$_a$), 1.45–1.60 (3H, m, H-3, H-4$_a$), 1.60–1.73 (2H, m, H-9), 1.73–1.87 (3H, m, H-2, H-3'), 1.84–1.96 (2H, m, H-4$_b$, H-8$_b$), 2.00–2.16 (2H, m, H-1, H-10$_b$), 2.18–2.29 (1H, m, H-1′b), 3.02 (1H, d, J = 11.5 Hz, H-7), 3.30 (1H, dd, J = 10.8, 1.8 Hz, CH_aH$_b$OTBDPS), 3.65 (2H, d, J = 6.1 Hz, H-4′), 3.81–3.95 (2H, m, CH_aH$_b$OBn, CH$_a$$H_b$OTBDPS), 3.98 (1H, dd, J = 11.0, 3.3 Hz, CH$_a$$H_b$OBn), 4.15 (1H, ddd, J = 10.6, 5.2, 1.2 Hz, H-2′), 4.53 (2H, d, J = 3.8 Hz, CH_2Ph), 7.25–7.44 (11H, m, H-Ar), 7.65–7.73 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 18.8 (C), 20.5 (CH_2), 20.9 (CH_2), 24.0 (CH_2), 26.5 (CH_2), 26.6 (CH_3), 27.0 (CH_2), 29.8 (CH_2), 35.5 (CH_2), 46.5 (CH), 51.6 (CH), 62.1 (CH), 63.6 (CH_2), 67.2 (CH_2), 70.3 (CH_2), 71.5 (C), 73.3 (CH_2), 75.6 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 132.1 (CH), 132.2 (C), 132.5 (CH), 132.6 (C), 135.5 (CH), 135.6 (CH), 138.4 (C), *m/z* (FAB) 632.3785 ($C_{38}H_{54}NO_5Si$ requires MH 632.3771), 632 (MH$^+$, 32%), 197 (18), 166 (23), 135 (47), 91 (100), 179 (59), 73 (23). Data for more polar diastereomer: υ_{max} (film)/cm^{-1}: 3395, 2931, 2858, 1644, 1427, 1112,

δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.05 (9H, s, C(CH_3)$_3$), 1.08–1.23 (2H, m, H-1′$_a$, H-8$_a$), 1.23–1.32 (1H, m, H-10$_a$), 1.44–1.59 (2H, m, H-3$_a$, H-4$_a$), 1.59–1.74 (2H, m, H-9), 1.74–1.83 (2H, m, H-2), 1.85–1.96 (3H, m, H-4$_b$, H-3′, H-8$_b$), 2.00–2.15 (3H, m, H-1, H-3$_b$, H-10$_b$), 2.18–2.27 (1H, m, H-1′$_b$), 3.01 (1H, d, J = 11.0 Hz, H-7), 3.30 (1H, dd, J = 10.5, 1.7 Hz, CH_aH$_b$OTBDPS), 3.74 (2H, d, J = 6.1 Hz, H-4′), 3.80–3.95 (3H, m, CH$_a$$H_b$OTBDPS, C$H_2$OBn), 4.21 (1H, ddd, 10.3, 5.5, 1.3 Hz, H-2′), 4.51 (2H, s, CH_2Ph), 7.25–7.43 (11H, m, H-Ar), 7.65–7.80 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 18.8 (C), 20.4 (CH_2), 20.9 (CH_2), 24.0 (CH_2), 26.5 (CH_2), 26.7 (CH_3), 27.0 (CH_2), 29.8 (CH_2), 34.3 (CH_2), 45.8 (CH), 51.6 (CH), 62.1 (CH), 64.7 (CH_2), 67.1 (CH_2), 68.9 (CH_2), 71.5 (C), 73.3 (CH_2), 75.5 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 129.8 (CH), 129.9 (CH), 132.0 (C), 132.4 (C), 135.5 (CH), 135.7 (CH), 138.4 (C), m/z (FAB) 632.3779 ($C_{38}H_{54}NO_5Si$ requires MH 632.3771), 632 (MH^+, 59%), 614 (12), 307 (20), 154 (100), 136 (79), 91 (73), 77 (26).

(1*S,5*S**,7*R**)-7-((2′*R**)-3′-(Benzyloxymethyl)-2′,4′-hydroxybutyl)-1-(*tert*-butyldiphenylsilyloxymethyl)-6-azaspiro[4.5]decane 27.** A solution of hydroxylamine **36** (1.67 g, 2.65 mmol) in ethanol (85 mL) was transferred *via* cannula to a flask containing indium powder (0.015 g, 0.13 mmol) and zinc powder (0.43 g, 6.64 mmol). A solution of saturated aqueous ammonium chloride (4.42 mL) was added and the reaction mixture stirred under reflux for 4 h. The reaction mixture was cooled to room temperature, filtered though a pad of Celite® and concentrated. The residue was diluted with ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate (50 mL) and the layers separated. The aqueous phase was further extracted with ethyl acetate (3 × 30 mL) and the combined organic phases dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 5% methanol–dichloromethane as eluent to afford azaspiro[4.5]decane **27** (1.57 g, 96%) as a yellow oil and as a separable diastereomeric mixture: Data for less polar diastereomer: υ_{max} (film)/cm^{-1}: 3436, 2929, 2858, 1655, 1427, 1111, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.07 (9H, s, C(CH_3)$_3$), 0.99–1.13 (1H, m, H-8$_a$), 1.13–1.27 (1H, m, H-2$_a$), 1.38–1.62 (5H, m, H-2$_b$, H-1′, H-3$_a$, H-10$_a$), 1.62–1.83 (8H, m, H-3$_b$, H-4, H-3′, H-8$_b$, H-9, H-10$_b$), 1.83–1.95 (1H, m, H-1), 2.88 (1H, d, J = 10.8 Hz, H-7), 3.63 (2H, d, J = 6.1 Hz, CH_2OBn), 3.73 (2H, dd, J = 18.9, 9.8 Hz, CH_2OTBDPS), 3.84 (1H, dd, J = 11.1, 5.1 Hz H-4′$_a$), 3.96 (1H, dd, J = 11.1, 3.5 Hz, H-4′$_b$), 4.13 (1H, ddd, J = 10.5, 4.9,1.9, H-2′), 4.50 (2H, d, J = 3.2 Hz, CH_2Ph), 7.21–7.47 (11H, m, H-Ar), 7.64–7.72 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.0 (C), 22.4 (CH_2), 23.6 (CH_2), 26.8 (CH_3), 27.8 (CH_2), 33.8 (CH_2), 36.3 (CH_2), 37.6 (CH_2), 40.5 (CH_2), 46.3 (CH), 51.7 (CH), 53.5 (CH), 62.5 (C), 63.1 (CH_2), 64.4 (CH_2), 70.2 (CH_2), 73.2 (CH_2), 74.8 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 129.6 (CH), 129.8 (CH), 132.8 (C), 133.1 (C), 135.4 (CH), 138.2 (C), m/z (EI) 615.3751 ($C_{38}H_{53}NO_4Si$ requires M$^+$ 615.3743), 615 (M^+, 51%), 572 (18), 558 (30), 450 (24), 407 (28), 318 (27), 199 (39), 135 (24), 135 (24), 110 (28), 91 (100), 77 (11), 55 (12), 41 (13). Data for more polar diastereomer: υ_{max} (film)/cm^{-1}: 3422, 2928, 2857, 1648, 1427, 1111, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.07 (9H, s, C(CH_3)$_3$), 1.10–1.25 (2H, m, H-2$_a$, H-8$_a$), 1.37–1.54 (3H, m, H-1′$_a$, H-3$_a$, H-10$_a$), 1.54–1.64 (2H, m, H-1′$_b$, H-2$_b$), 1.64–1.86 (7H, m, H-3$_b$, H-4, H-8$_b$, H-9, H-10$_b$), 1.86–2.00 (2H, m, H-1, H-3′), 2.87 (1H, d, J = 10.8 Hz, H-7), 3.59–3.90 (6H, m, CH_2OTBDPS, H-4′, CH_2OBn), 4.16 (1H, ddd, J = 10.5, 4.5, 2.5 Hz, H-2′), 4.49 (2H, d, J = 3.8 Hz, CH_2Ph), 7.25–7.41 (11H, m, H-Ar), 7.66–7.71 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.0 (C), 22.3 (CH_2), 23.5 (CH_2), 26.7 (CH_3), 27.7 (CH_2), 33.9 (CH_2), 36.3 (CH_2), 37.6 (CH_2), 39.1 (CH_2), 45.9 (CH), 51.7 (CH), 53.6 (CH), 62.5 (C), 63.9 (CH_2), 64.4 (CH_2), 69.2 (CH_2), 73.2 (CH_2), 74.1 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 129.6 (CH), 129.7 (CH), 132.9 (C), 133.1 (C), 135.3 (CH), 135.4 (CH), 138.2 (C), m/z (FAB) 616.3827 ($C_{38}H_{54}NO_4Si$ requires MH 616.3822), 616 (MH^+, 100%), 197 (7), 135(17), 91 (39).

(1*S,2*S**,7′*R**,8′*S**,9*a*′*R**)-2-((*tert*-Butyldiphenylsilyloxy)-methyl)-7′-(benzyloxymethyl)-8′-(methansulfonyloxy)octahydrospiro[cyclopentane-1,4′-quinolizine] 37a and (1*S**,2*S**,7′*S**,8′*S**,9*a*′*R**)-2-((*tert*-butyldiphenylsilyloxy)methyl)-7′-(benzyloxymethyl)-8′-(methansulfonyloxy)octahydrospiro[cyclopentane-1,4′-quinolizine] 37b.** Mesyl chloride (0.64 g, 5.61 mmol) was added dropwise to a stirred solution of aminoalcohol **27** (1.57 g, 2.55 mmol) and triethylamine (1.55 g, 15.3 mmol) in dichloromethane (79 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred at this temperature for 3 h and then under reflux for 4 h. Water (30 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 90% ethyl acetate–hexane as eluent to afford the product (1.51 g, 88%) as a yellow oil and as a separable 1 : 1 mixture of *trans* **37a** and *cis* **37b** isomers.

Data for **37a**: υ_{max} (film)/cm^{-1}: 2931, 2858, 1458, 1359, 1175, 1111, 903, δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.82–0.93 (1H, m, H-3′$_a$), 0.97 (9H, s, C(CH_3)$_3$), 1.24–1.64 (9H, m, H-1′, H-2′, H-3$_a$, H-3′$_b$, H-4$_a$, H-5$_a$, H-9′$_a$), 1.64–1.78 (1H, m, H-4$_b$), 1.78–2.01 (6H, m, H-2, H-3$_b$, H-5$_b$, H-6′$_a$, H-7′, H-9$_b$′), 2.23–2.46 (2H, m, H-6′$_b$, H-9*a*′), 3.08 (3H, s, SO_2CH_3), 3.15 (1H, dd, J = 9.2, 7.5 Hz, CH_aH$_b$OBn), 3.37 (1H, dd, J = 9.2, 7.0 Hz, CH$_a$$H_b$OBn), 3.67 (1H, dd, J = 10.1, 8.1 Hz, CH_aH$_b$OTBDPS), 3.94 (1H, dd, J = 10.1, 4.4 Hz, CH$_a$$H_b$OTBDPS), 4.37 (2H, d, J = 6.3 Hz, CH_2Ph), 4.97 (1H, br s, H-8′), 7.15–7.33 (5H, m, H-Ar), 7.33–7.52 (6H, m, H-Ar), 7.58–7.74 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 18.6 (C), 21.3 (CH_2), 23.5 (CH_2), 26.5 (CH_3), 27.5 (CH_2), 31.6 (CH_2), 32.7 (CH_2), 37.5 (CH_3), 39.3 (CH_2), 39.7 (CH), 40.3 (CH_2), 45.9 (CH_2), 51.1 (CH), 55.2 (CH), 63.8 (CH_2), 66.5 (C), 68.4 (CH_2), 71.7 (CH_2), 77.1 (CH), 127.0 (CH), 127.2 (CH), 127.6 (CH), 128.0 (CH), 129.5 (CH), 133.1 (C), 133.3 (C), 134.9 (CH), 138.2 (C), m/z (FAB) 676.3497 ($C_{39}H_{54}NO_5SSi$ requires MH 676.3492), 676 (MH^+, 38%), 307 (24), 154 (100), 136 (65), 107 (19), 89 (20), 77 (19).

Data for **37b**: υ_{max} (film)/cm^{-1}: 2931, 2858, 1455, 1358, 1176, 1111, 915, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.03 (9H, s, C(CH_3)$_3$), 1.21–1.28 (2H, m, H-1′), 1.43–1.64 (7H, m, H-2′, H-3$_a$, H-3′$_a$, H-4$_a$, H-5$_a$, H-9′$_a$), 1.64–1.82 (4H, m, H-3′$_b$, H-4$_b$, H-5$_b$, H-9′$_b$), 1.82–2.01 (3H, m, H-2, H-3$_b$, H-7′), 2.41–2.57 (3H, m, H-6′, H-9*a*′), 3.06 (3H, s, SO_2CH_3), 3.32–3.46 (2H, m, CH_2OBn), 3.68 (1H, dd, J = 10.5, 8.5 Hz, CH_aH$_b$OTBDPS), 3.97 (1H, dd, J = 10.5, 3.6, CH$_a$$H_b$OTBDPS), 4.22 (1H, d, J = 12.1 Hz, CH_aH$_b$Ph), 4.33 (1H, d, J = 12.1 Hz, CH$_a$$H_b$Ph), 4.67–4.76 (1H, m, H-8′), 7.18–7.34 (5H, m, H-Ar), 7.34–7.49 (6H, m, H-Ar), 7.60–7.72 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 18.1 (C), 20.5 (CH_2), 21.7 (CH_2), 26.2 (CH_3), 28.0 (CH_2), 29.1 (CH_2) (2C), 35.4 (CH_2)

(2C), 37.6 (CH_3), 40.0 (CH), 43.8 (CH_2), 51.0 (CH), 53.4 (CH), 63.1 (CH_2), 66.5 (C), 68.4 (CH_2), 71.5 (CH_2), 76.7 (CH), 126.6 (CH), 127.0 (CH), 127.4 (CH), 128.9 (CH), 133.2 (C) (2C), 134.5 (CH), 137.7 (C), *m/z* (EI) 675.3412 ($C_{39}H_{53}NO_5SSi$ requires M^+ 675.3413), 675 (M^+, 22%), 579 (60), 473 (25), 259 (41), 163 (97), 135 (38), 91 (100).

(1*S, 2*S**, 7′*R**, 8′*S**, 9*a*′*R**)-2-((*tert*-butyldiphenylsilyloxy)-methyl)-7′-(hydroxymethyl)-8′-(methansulfonyloxy)octahydrospiro[cyclopentane-1,4′-quinolizine] 38a and (1*S**,2*S**,7′*S**,8′*S**, 9*a*′*R**)-2-((*tert*-butyldiphenylsilyloxy)methyl)-7′-(hydroxymethyl)-8′-methansulfonyloxyoctahydrospiro[cyclopentane-1,4′-quinolizine] 38b.** A freshly prepared solution of lithium di-*tert*-butylbiphenylide in tetrahydrofuran (0.24 M, 99 mL, 23.7 mmol) was added dropwise to a stirred solution of benzyl ether **37a/b** (1.69 g, 2.50 mmol) in tetrahydrofuran (126 mL) at −78 °C. The reaction mixture was stirred for a further 30 min and saturated aqueous ammonium chloride (80 mL) was added. The mixture was then allowed warm to room temperature and the aqueous phase extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography with 30% ethyl acetate–hexane as eluent to afford alcohol **38** (1.25 g, 86%) as a yellow oil and as a separable 1 : 1 mixture of *trans* **38a** and *cis* **38b** isomers.

Data for **38a**: υ_{max} (film)/cm^{-1}: 3434, 2932, 2858, 1348, 1172, 1111, 904, δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.76–0.94 (1H, m, H-3′$_a$), 1.05 (9H, s, C(CH_3)$_3$), 1.29–1.52 (6H, m, H-1′$_a$, H-2′$_a$, H-3$_a$, H-3′$_b$, H-5$_a$, H-9′$_a$), 1.52–1.59 (2H, m, H-2′$_b$, H-4$_a$), 1.59–1.77 (3H, m, H-1′$_b$, H-2, H-4$_b$), 1.83–2.00 (4H, m, H-3$_b$, H-6′$_a$, H-7′, H-9′$_b$), 2.00–2.13 (2H, m, H-5$_b$, H-6′$_b$), 2.24–2.38 (1H, br s, H-9*a*′), 3.00 (3H, s, SO_2CH_3), 3.17 (1H, dd, *J* = 10.5, 4.8 Hz, CH_aH$_b$OTBDPS), 3.34 (1H, d, *J* = 10.5 Hz, CH$_a$$H_b$OTBDPS), 3.57 (1H, d, *J* = 10.2 Hz, CH_aCH$_b$OH), 3.97 (1H, dd, *J* = 10.2, 4.5 Hz, CH$_a$CH_bOH), 4.93 (1H, br s, H-8′), 7.36–7.44 (6H, m, H-Ar), 7.60–7.82 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.1 (C), 21.7 (CH_2), 24.0 (CH_2), 26.8 (CH_3), 28.0 (CH_2), 32.1 (CH_2), 33.2 (CH_2), 37.9 (CH_3), 39.8 (CH_2), 40.8 (CH_2), 42.4 (CH), 45.6 (CH_2), 51.6 (CH), 55.6 (CH), 60.6 (CH_2), 64.2 (CH_2), 67.0 (C), 77.1 (CH), 127.5 (CH), 129.4 (CH), 134.0 (C), 134.1 (C), 135.6 (CH), *m/z* (FAB) 586.3027 ($C_{32}H_{48}NO_5SSi$ requires MH^+ 586.3022), 586 (MH^+, 100%), 154 (58), 136 (47), 107 (13), 89 (13), 77 (14). Data for **38b**: υ_{max} (film)/cm^{-1}: 3428, 2957, 2857, 1350, 1174, 1111, 909, δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.93–1.15 (1H, m, H-3′$_a$), 1.06 (9H, s, C(CH_3)$_3$), 1.15–1.38 (2H, m, H-1′$_a$, H-3′$_b$), 1.38–1.66 (6H, m, H-1′$_b$, H-2′, H-3$_a$, H-4$_a$, H-5$_a$), 1.66–1.91 (4H, m, H-2, H-4$_b$, H-9′), 1.91–2.15 (3H, m, H-3$_b$, H-5$_b$, H-7′), 2.27–2.72 (3H, m, H-6′, H-9*a*′), 2.95 (3H, s, SO_2CH_3), 3.24–4.06 (4H, m, CH_2OTBDPS, CH_2OH), 4.76–4.87 (1H, br s, H-8′), 7.28–7.49 (6H, m, H-Ar), 7.58–7.75 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.0 (C), 21.4 (CH_2), 23.8 (CH_2), 26.8 (CH_3), 27.4 (CH_2), 32.0 (CH_2), 33.1 (CH_2), 37.1 (CH_2), 38.2 (CH_3), 40.7 (CH_2), 40.7 (CH), 47.1 (CH_2), 51.8 (CH), 55.8 (CH), 63.9 (CH_2) (2C), 67.7 (C), 79.6 (CH), 127.4 (CH), 129.4 (CH), 133.9 (C) (2C), 135.5 (CH), *m/z* (EI) 585.2944 ($C_{32}H_{47}NO_5SSi$ requires M^+ 585.2944.585) 585 (M^+, 15%), 489 (86), 459 (39), 432 (31), 199 (55), 192 (52), 179 (100), 149 (39), 135 (37), 41 (38).

(1*S, 2*S**, 9*a*′*R**)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-7′-formyl-1′, 2′, 3′, 6′, 9′, 9*a*′-hexahydrospiro[cyclopentane-1, 4′-quinolizine] 39.** Dess–Martin periodinane (0.67 g, 1.57 mmol) was added to a stirred solution of alcohol **38a/b** (0.46 g, 0.78 mmol) and pyridine (0.38 mL, 4.71 mmol) in dichloromethane (31 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. A mixture of saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (30 mL) was added and the aqueous phase extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), concentrated and the crude residue purified by column chromatography with 15% ethyl acetate–hexane as eluent to afford aldehyde **39** (0.31 g, 80%) as a yellow oil. υ_{max} (film)/cm^{-1}: 2930, 2856, 1684, 1472, 1110, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.02 (9H, s, C(CH_3)$_3$), 1.19–1.38 (3H, m, H-1′$_a$, H-3′), 1.44–1.98 (9H, m, H-1′$_b$, H-2′, H-3, H-4, H-5), 2.00–2.13 (2H, m, H-2, H-9′$_a$), 2.47 (1H, d, *J* = 19.5 Hz, H-9′$_b$), 2.71 (1H, br s, H-9*a*′), 3.09 (1H, d, *J* = 16.9 Hz, H-6′$_a$), 3.38 (1H, d, *J* = 16.9 Hz, H-6′$_b$), 3.53 (1H, d, *J* = 10.3 Hz, CH_aH$_b$OTBDPS), 3.88 (1H, dd, *J* = 10.3, 4.4 Hz, CH$_a$$H_b$OTBDPS), 6.67 (1H, br s, H-8′), 7.24–7.48 (6H, m, H-Ar), 7.58–7.79 (4H, m, H-Ar), 9.33 (1H, s, C*H*O), δ_C (75 MHz, $CDCl_3$, Me_4Si) 19.1 (C), 21.1 (CH_2), 21.7 (CH_2) (2C), 26.7 (CH_3), 27.8 (CH_2) (2C), 30.4 (CH_2), 34.6 (CH_2), 41.4 (CH_2), 51.5 (CH), 52.8 (CH), 63.2 (CH_2), 67.5 (C), 127.5 (CH), 129.3 (CH), 133.9 (C), 135.5 (CH), 139.4 (C), 147.0 (CH), 192.1 (CH), *m/z* (EI) 487.2910 ($C_{31}H_{41}NO_2Si$ requires M^+ 487.2906), 487 (M^+, 79%), 430 (20), 348 (30), 190 (41), 177 (100), 135 (23), 108 (19), 41 (20).

(1*S, 2*S**, 9*a*′*R**)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-7′-ethyloxycarbonyl-1′, 2′, 3′, 6′, 9′, 9*a*′-hexahydrospiro[cyclopentane-1,4′-quinolizine] 40.** A solution of sodium chlorite (0.18 g, 1.95 mmol) and sodium dihydrogen phosphate (0.62 g, 4.50 mmol) in water (5.2 mL) was added dropwise to a stirred solution of aldehyde **39** (0.32 g, 0.65 mmol) and 2-methyl-2-butene (11.5 mL) in *tert*-butanol (20 mL) at 0 °C and the reaction mixture stirred for 24 h. Saturated aqueous ammonium chloride (100 mL) was added and the aqueous phase extracted with ethyl acetate (3 × 150 mL). The combined organic phases were washed with saturated brine (200 mL), dried ($MgSO_4$) and concentrated. The crude residue was diluted with dichloromethane (20 mL) and ethanol (3 mL), then a catalytic quantity of DMAP and a solution of DCC (0.44 g, 2.11 mmol) in dichloromethane (5.0 mL) were added at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then warmed to room temperature and stirred for a further 24 h. The reaction mixture was then filtered through a pad of Celite® and the filtrate diluted by addition of saturated aqueous citric acid (10 mL) and saturated aqueous sodium bicarbonate (25 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), concentrated and the crude residue purified by column chromatography using 10% ethyl acetate–hexanes as eluent to afford ester **40** (0.23 g, 65% over the two steps) as a yellow oil. υ_{max} (film)/cm^{-1}: 2931, 2857, 1711, 1670, 1253, 1112, 1079, δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.95 (9H, s, C(CH_3)$_3$), 1.18 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.18–1.26 (4H, m, H-1′, H-3′), 1.41–1.54 (3H, m, H-2′, H-4$_a$), 1.62–1.70 (3H, m, H-4$_b$, H-5), 1.70–1.79 (2H, m, H-3), 1.79–1.87 (1H, m, H-9′a), 1.87–1.96 (1H, m, H-2), 2.18–2.33 (1H, H-9′$_b$), 2.44–2.62 (1H, br s, H-9*a*′), 3.03 (1H, br d, *J* = 17.0 Hz, H-6′$_a$), 3.34 (1H, dd *J* = 17.0, 1.7 Hz, 6″$_b$-H), 3.49 (1H, dd, *J* = 10.2, 8.6 Hz, CH_aH$_b$OTBDPS), 3.87 (1H, dd, *J* = 10.2, 4.6 Hz, CH$_a$$H_b$OTBDPS), 4.09 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 6.74–6.79

(1H, m, H-8′), 7.23–7.31 (6H, m, H-Ar), 7.58–7.67 (4H, m, H-Ar), δ_C (75 MHz, $CDCl_3$, Me_4Si) 14.2 (CH_3), 19.1 (C), 21.3 (CH_2), 21.9 (CH_2) (2C), 26.8 (CH_3), 28.7 (CH_2) (2C), 30.2 (CH_2), 34.0 (CH_2), 43.9 (CH_2), 50.9 (CH), 53.1 (CH), 60.1 (CH_2), 63.5 (CH_2), 67.5 (C), 127.4 (CH), 128.4 (C), 129.3 (CH), 134.1 (C), 135.6 (CH), 135.9 (CH), 165.9 (C), *m*/*z* (EI) 531.3167 ($C_{33}H_{45}NO_3Si$ requires M^+ 531.3168), 531 (M^+, 61%), 474 (12), 348 (10), 234 (30), 221 (100), 152 (20).

(1*S,2*S**,9*a*′*R**)-2-(Hydroxymethyl)-7′-(ethoxycarbonyl)-1′,2′,3′,6′,9′,9*a*′-hexahydrospiro[cyclopentane-1,4′-quinolizine] 6.** A mixture of silyl ether **40** (0.64 g, 1.19 mmol), triethylamine trihydrofluoride (1.95 mL, 11.9 mmol) and triethylamine (1.99 mL, 14.3 mmol) in acetonitrile (120 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and then quenched by addition of saturated aqueous sodium bicarbonate (70 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography using 5% methanol–dichloromethane as eluent to afford alcohol **6** (0.33 g, 94%) as a yellow oil. υ_{max} (film)/cm^{-1}: 3428, 2931, 2857, 1643, 1258, 1079, δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.29 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 1.29–1.91 (11H, m, H-1′, H-2′, H-3, H-3′, H-4, H-5_a), 2.03–2.24 (3H, m, H-2, H-5_b, H-$9'_a$), 2.42–2.59 (1H, m, H-$9'_b$), 2.59–2.78 (1H, br s, H-9*a*′), 3.63–3.77 (2H, m, H-6′), 3.77–3.91 (2H, m, CH_2OH), 4.20 (2H, q, $J =$ 7.1, CH_2CH_3), 6.89 (1H, br s, H-8′), δ_C (75 MHz, $CDCl_3$, Me_4Si) 14.1 (CH_3), 20.6 (CH_2), 23.1 (CH_2) (2C), 29.1 (CH_2) (3C), 34.5 (CH_2), 46.4 (CH_2), 51.2 (CH), 53.1 (CH), 60.4 (CH_2), 65.0 (CH_2), 69.9 (C), 127.8 (C), 136.1 (CH), 165.3 (C), *m*/*z* (EI) 293.1987 ($C_{17}H_{27}NO_3$ requires M^+ 293.1990). 293 (M^+, 26%), 276 (14), 234 (44), 221 (100), 149 (25), 55 (27), 41 (34).

Hydrochloride salt **43**, obtained by dissolution of **6** in chloroform and concentration of the solvent under reduced pressure, was recrystallised from diethyl ether and hexane to give crystals suitable for X-ray crystallography.

Crystal structure determination of hydrochloride 43

Crystal data. $C_{17}H_{28}ClNO_3$, $M = 329.85$, triclinic, $a = 8.3424(1)$, $b = 9.2501(2)$, $c = 11.6434(2)$ Å, $\alpha = 98.854(1)°$, $\beta = 97.190(1)°$, $\gamma = 94.937(1)°$, $U = 875.71(2)$, $T = 285$ K, space group *P*-1, $Z = 2$, 20 945 reflections measured, 4189 unique ($R_{int} = 0.037$) which were used in all calculations. The final *R* was 0.070 (all data).

Acknowledgements

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

Notes and references

1 T. Chou, Y. Otani, M. Shikano, K. Ozawa and D. Uemura, *Tetrahedron Lett.*, 1996, **37**, 3871.
2 M. Kuramoto, C. Tong, K. Yamada, T. Chiba, Y. Hayashi and D. Uemura, *Tetrahedron Lett.*, 1996, **37**, 3867.
3 M. A. Cascieri, *Nat. Rev. Drug Discovery*, 2002, 122.
4 R. A. Carter and I. P. Wicks, *Arthritis Rheum.*, 2001, **44**, 985.
5 H. Yusuf-Makagiansar, M. E. Anderson, T. V. Yakovleva, J. S. Murray and T. Siahaan, *Med. Res. Rev.*, 2002, **22**, 146.
6 For a review covering synthetic work up to 2005 see: D. L. J. Clive, M. Yu, J. Wang, V. S. C. Yeh and S. Kang, *Chem. Rev.*, 2005, **105**, 4483.
7 For synthetic approaches not covered in ref. 6 see: (*a*) G. E. Keck and S. A. Heumann, *Org. Lett.*, 2008, **10**, 4783; (*b*) P. B. Hurley and G. R. Dake, *J. Org. Chem.*, 2008, **73**, 4131; (*c*) S. Xu, H. Arimoto and D. Uemura, *Angew. Chem., Int. Ed.*, 2007, **46**, 5746; (*d*) S. H. Yang and V. Caprio, *Synlett*, 2007, 1219; (*e*) H. Wu, H. Zhang and G. Zhao, *Tetrahedron*, 2007, **63**, 6454; (*f*) R. B. Andrade and S. F. Martin, *Org. Lett.*, 2005, **7**, 5733.
8 For reviews covering the cycloadditions of nitrones see: (*a*) J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396; (*b*) P. N. Confalone and E. M. Huie, *Org. React.*, 1988, **36**, 1; (*c*) M. Fredrickson, *Tetrahedron*, 1997, **53**, 403; (*d*) P. De March, M. Figueredo and J. Font, *Heterocycles*, 1999, **50**, 1213; (*e*) A. E. Koumbis and J. E. Gallos, *Curr. Org. Chem.*, 2003, **7**, 585.
9 For reviews covering nucleophilic additions to nitrones see: (*a*) M. Lombardo and C. Trombini, *Synthesis*, 2000, 759; (*b*) P. Merino, S. Franco, F. L. Merchan and C. Trombini, *Curr. Org. Chem.*, 2002, **2**, 695.
10 E. Gössinger, R. Imhof and H. Wehrli, *Helv. Chim. Acta*, 1975, **58**, 96.
11 N. A. LeBel, M. E. Post and D. Hwang, *J. Org. Chem.*, 1979, **44**, 1819.
12 S. M. A. Hashmi, S. A. Ali and M. Wazeer, *Tetrahedron*, 1998, **54**, 12959.
13 (*a*) H. Arimoto, S. Asano and D. Uemura, *Tetrahedron Lett.*, 1999, **40**, 3583; (*b*) Y. Matsumura, S. Aoyagi and C. Kibayashi, *Org. Lett.*, 2003, **5**, 3429; (*c*) I. Hayakawa, H. Arimoto and D. Uemura, *Heterocycles*, 2003, **59**, 441; (*d*) I. Hayakawa, H. Arimoto and D. Uemura, *Chem. Commun.*, 2004, 1222; (*e*) Y. Matsumara, S. Aoyagi and C. Kibayahi, *Org. Lett.*, 2004, **6**, 965.
14 H.-L. Zhang, G. Zhao and Y. Ding, *J. Org. Chem.*, 2005, **70**, 4954.
15 S. A. Ali, *Tetrahedron*, 1993, **34**, 5325.
16 K. Yamada, K. Kishikawa and M. Yamamoto, *J. Org. Chem.*, 1987, **52**, 2327.
17 P. R. Andreana, P. S. McLellan, Y. Chen and R. G. Wang, *Org. Lett.*, 2002, **4**, 3875.
18 S. Cicchi, M. Bonanni, F. Cardona and J. Revuelta, *Org. Lett.*, 2003, **5**, 1773.
19 P. Kocienski and C. Yates, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1879.
20 J. N. Zonjee, H. L. Koning and W. N. Speckamp, *Tetrahedron*, 1989, **45**, 7553.

