PERKIN 1

Asymmetric synthesis of (+)-loline, a pyrrolizidine alkaloid from rye grass and tall fescue

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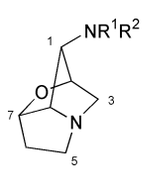
(+)-Loline (**1**) was synthesized *via* a pathway that employed intramolecular [4 + 2] cycloaddition of an acylnitrosodiene, **25** or **26**, as a key step. The acylnitrosodienes, which were used *in situ*, were obtained by oxidation of the corresponding hydroxamic acids, **17** and **24**, and these were prepared from either glucose *via* aldehyde **9** or more directly from (*S*)-malic acid (**18**). The *endo* dihydrooxazines **27** and **29**, obtained in a mixture with their *exo* stereoisomer, were transformed by reductive N–O bond cleavage and reannulation into pyrrolizines **34** and **35**. The latter was subjected to Sharpless aminohydroxylation in the presence of $(DHQD)_2PHAL$ to give **50** along with its regioisomer **51**. *N*-Methylation of tosyl amide **50**, followed by mesylation of alcohol **52** and reduction of the γ-lactam **53** with borane, afforded pyrrolizidine **54**. Cleavage of the *p*-methoxybenzyl ether and subsequent thermal treatment of **55** resulted in intramolecular etherification to yield *N*-tosylloline (**57**). Final reductive cleavage of the *N*-tosyl residue produced (+)-loline, characterized as its dihydrochloride.

Introduction

The rye grass *Lolium cuneatum* and the tall fescue *Festuca arundinacea* are important pasture grasses in the United States that provide feedstock for grazing cattle in regions where drought or poor drainage is commonplace.[1] The alkaloidal content of these grasses was first investigated after cattle grazing on *F. arundinacea* were found to develop a lameness known as "fescue foot".[2] Subsequent reports of abdominal fat necrosis[3] and increased respiration[4] in cattle feeding on this grass added impetus to investigations directed towards identification of the causative agent(s) of these symptoms.[5] This led to the isolation of seven closely related alkaloids, of which (+)-loline (**1**) is the principal member and all of which have been chemically interrelated.[6] Other members of the *Lolium* family include norloline (**2**) and the *N*-acyl derivatives **3** and **4**. Most recently, **1** was discovered in the roots of the tropical liana *Argyreia mollis*.[7]

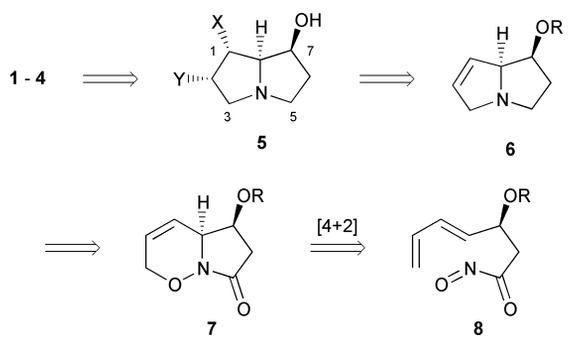


(+)-loline (**1**) R^1 = Me, R^2 = H
norloline (**2**) R^1 = H, R^2 = H
N-formylloline (**3**) R^1 = Me, R^2 = CHO
N-acetylloline (**4**) R^1 = Me, R^2 = Ac

The isolation of **1** from *L. cuneatum* was complicated initially by misassignment of its structure.[6a,b] This was later corrected by X-ray crystallographic analysis of loline dihydrochloride,[8] which proved that the parent alkaloid contains a pyrrolizidine nucleus possessing a unique ether linkage bridging C2 and C7. Numerous synthetic approaches to loline failed to reach the target[8c,d,9] until a successful route to (±)-**1** was reported in 1986 by Tufariello *et al.*[10]

Although fescue toxicity in cattle does not appear to be directly associated with the alkaloidal content of *F. arundinacea*,[11] sustained interest in the pharmacology of loline and its congeners[12] has revealed new biological properties of this family. For example, acylated derivatives of **1** are now known to be toxic to larvae of the horn fly *Haematobia irritans*, an important ectoparasite of cattle.[13] The convergence of chemical and biological incentives, particularly the absence of an asymmetric synthesis of **1**, led us to devise a route to (+)-loline which could be generalized in principle to all members of that alkaloid family.[14]

The strategy envisioned for assembling the 2-oxa-6-azatricyclo[4.2.1.$0^{3,7}$]nonane core of **1** is outlined in Scheme 1 and



Scheme 1

postulates formation of the internal ether linkage at a late stage from a hydroxylated pyrrolizidine **5**. A critical feature of this plan is the placement of appropriate substituents, denoted as X and Y, on the *exo* face of the pyrrolizidine nucleus at C1 and C2. The dehydropyrrolizidine **6** therefore became a focal intermediate in our plan, and a route to this substance was projected employing chemistry along lines developed by Keck and Kibayashi in their studies of the synthesis of indolizidine,[15] and pyrrolizidine[16] alkaloids. The key step in this sequence is an intramolecular hetero-Diels–Alder cycloaddition of an acylnitrosodiene **8**, in which the center bearing the oxygen substituent controls the stereochemical outcome of the reaction that leads to dihydrooxazine **7**. The latter can be converted to a pyrrolizidine through a reannulation sequence involving reductive scission of the N–O bond.

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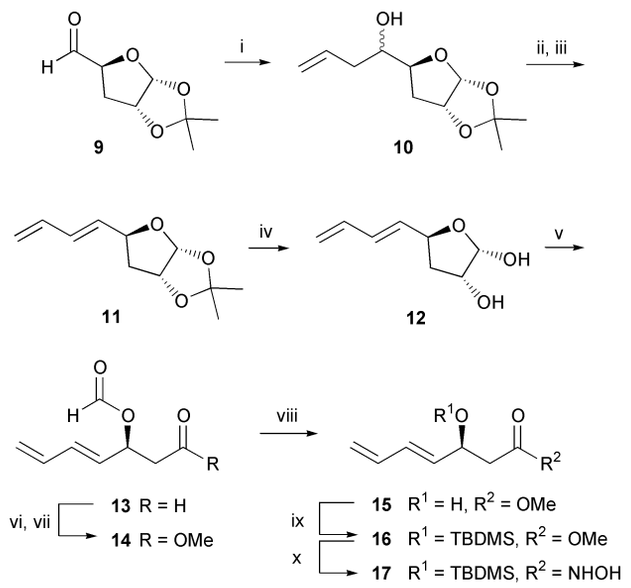
Results and discussion

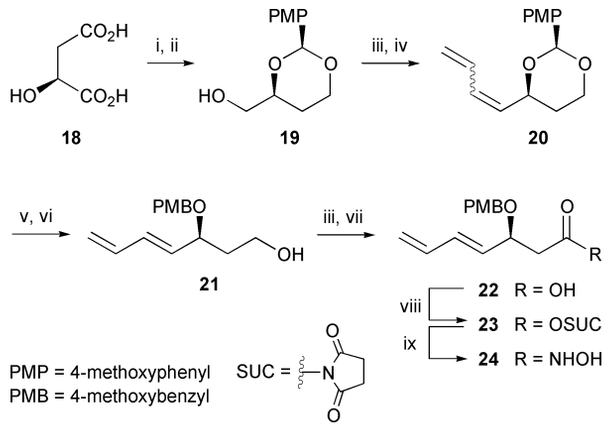
Our initial approach to the acylnitrosodiene **8** commenced from the known aldehyde **9**,[17] available in three steps from glucose bisacetonide (Scheme 2). Addition of allylmagnesium chloride



Scheme 2 *Reagents and conditions*: (i), allylmagnesium chloride, THF, 0 °C, 80%; (ii), MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii), DBU, toluene, 90 °C, 64% (2 steps); (iv), TFA–H_2O–THF (1 : 1 : 5), reflux, 89%; (v), $NaIO_4$, Et_2O, pH 7 buffer; (vi), $NaClO_2$, NaH_2PO_4·H_2O, 2-methylbut-2-ene, *t*-BuOH–H_2O; (vii), CH_2N_2, Et_2O; (viii), K_2CO_3, MeOH, 87% (4 steps); (ix), TBDMSCl, imidazole, DMF, 97%; (x), $HONH_2$·HCl, KOH, MeOH, 91%.

to **9** gave alcohol **10** as a mixture of stereoisomers, which, after mesylation and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), afforded conjugated diene **11**. Hydrolysis of **11** under acid catalysis yielded diol **12**, and subsequent oxidative cleavage with sodium periodate gave the formate aldehyde **13**. Oxidation of this aldehyde to a carboxylic acid,[18] followed by treatment with diazomethane, produced the methyl ester **14**. The formate of ester **14** was cleaved selectively employing basic methanolysis to furnish hydroxy ester **15**, which was protected as its *tert*-butyldimethylsilyl ether **16** before exposure to hydroxylamine hydrochloride in basic methanol. The resultant hydroxamic acid **17** was obtained in 35% overall yield for the ten steps from **9**.

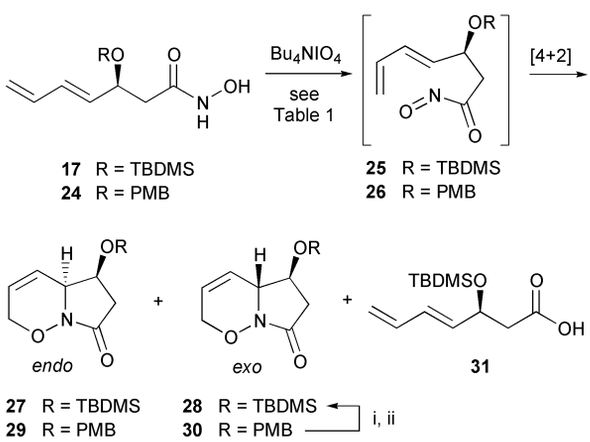
Although the synthesis of **17** from glucose bisacetonide was relatively efficient, a more direct route to this hydroxamic acid which incorporated the single stereogenic center without erasing three additional configurations would obviously possess greater economy. It was also felt that a protecting group different from the *tert*-butyldimethylsilyl ether of **17** should be examined as a controlling element in the intramolecular cycloaddition of **8**. To this end, a modified version of a route developed by Kibayashi[19] was employed in which (*S*)-(−)-malic acid (**18**) was reduced with borane,[20] and the resultant triol was converted to its *p*-methoxyphenyl acetal **19** as a single diastereomer (Scheme 3). The unstable aldehyde obtained by Swern oxidation of **19** was subjected to a Wittig reaction with allylidenetriphenylphosphorane to yield diene **20** as a 3 : 7 mixture of *E* and *Z* isomers, respectively. The diene mixture was reduced with excess diisobutylaluminium hydride, after which isomerization of the mixture with catalytic iodine under irradiation with a medium pressure mercury lamp produced the diene **21** with an *E* : *Z* ratio that was now ≥95 : 5. Oxidation of this primary alcohol, first to an aldehyde and then to carboxylic acid **22** using buffered sodium chlorite,[18] was followed by treatment with *N*-trifluoroacetoxysuccinimide[21] to give *O*-succinimidyl ester **23**. Displacement with hydroxylamine then



Scheme 3 *Reagents and conditions*: (i), BH_3·SMe_2, $B(OMe)_3$, THF, 0 °C to rt; (ii), $PMPCH(OMe)_2$, PPTS, CH_2Cl_2, reflux, 64% (2 steps); (iii), $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, then Et_3N, −60 °C to rt; (iv), allyltriphenylphosphonium bromide, BuLi, THF, −30 °C to rt, 40% (2 steps); (v), DIBAL-H, CH_2Cl_2, 0 °C to rt; (vi), I_2, *hν*, C_6H_6, rt, 63% (2 steps); (vii), $NaClO_2$, NaH_2PO_4·H_2O, 2-methylbut-2-ene, *t*-BuOH–H_2O, 0 °C to rt; (viii), CF_3CO_2SUC, Py, THF, rt; (ix), $HONH_2$·HCl, Et_3N, CH_2Cl_2, 0 °C, 75% (4 steps).

gave the protected hydroxamic acid **24**. The overall yield for the ten steps from **18** to **24** was only 19%, but this route was more amenable to the preparation of **24** on multi-gram scale than that shown in Scheme 2.

Oxidation of hydroxamic acids **17** and **24** was carried out with tetra-*n*-butylammonium periodate under a variety of conditions (Scheme 4 and Table 1). The resultant acylnitrosodienes



Scheme 4 *Reagents and conditions*: (i), DDQ, CH_2Cl_2–H_2O (20 : 1), rt, 100%; (ii), TBSOTf, collidine, CH_2Cl_2, 0 °C, 70%.

25 and **26** in each case underwent spontaneous intramolecular cycloaddition to give stereoisomeric bicyclic dihydrooxazines **27**–**30**, accompanied by variable quantities of carboxylic acids **22** and **31**. It was found that in benzene or toluene as the solvent, **17** gave predominantly the *endo* isomer **27**, with the yield increasing but selectivity decreasing as the temperature of the reaction was raised from −20 to 80 °C (entries 1–4). In chlorocarbon solvents (dichloromethane and chloroform), the yield of dihydrooxazines improved but the selectivity for **27** diminished to near zero (entries 5–7). Although the pairs of stereoisomeric dihydrooxazines were readily separable by chromatography, structural assignment to *endo* (**27** and **29**) and *exo* (**28** and **30**) isomers was difficult to make on the basis of NMR experiments alone. Fortunately, **28** proved to be crystalline and its structure was conclusively established by an X-ray crystallographic analysis (Fig. 1). A simple two step sequence converted **30** into **28** and thus provided indirect confirmation of structure for dihydrooxazines **29** and **30**. Oxidation of hydroxamic acid **24** with tetra-*n*-butylammonium periodate in chloroform (entry 8) gave a result very similar to that noted

Table 1 Oxidation of hydroxamic acids to acylnitrosodienes and *in situ* [4 + 2] cycloaddition

Entry	Hydroxamic acid	Oxidant	Solvent	Temp./°C)	Yield[a] (%)	Product (ratio)[b]
1	**17**	Bu_4NIO_4	PhMe	−20	49	**27** : **28** (70 : 30)
2	**17**	Bu_4NIO_4	C_6H_6	0	60	**27** : **28** (71 : 29)
3	**17**	Bu_4NIO_4	C_6H_6	22	64	**27** : **28** (70 : 30)
4	**17**	Bu_4NIO_4	C_6H_6	80	80	**27** : **28** (60 : 40)
5	**17**	Bu_4NIO_4	CH_2Cl_2	−78	86	**27** : **28** (50 : 50)
6	**17**	Bu_4NIO_4	CH_2Cl_2	0	73	**27** : **28** (45 : 55)
7	**17**	Bu_4NIO_4	$CHCl_3$	22	91	**27** : **28** (55 : 45)
8	**24**	Bu_4NIO_4	$CHCl_3$	22	87	**29** : **30** (57 : 44)
9	**17**	$NaIO_4$	THF–H_2O (1 : 1)	0	97	**27** : **28** (27 : 73)

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.

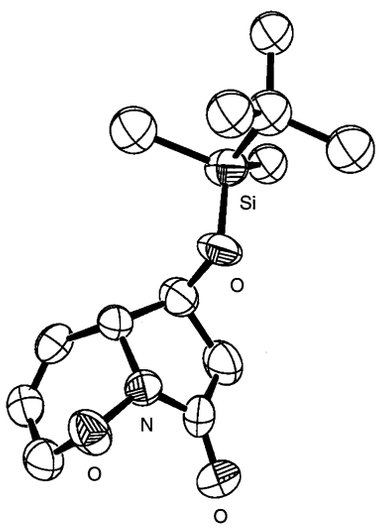
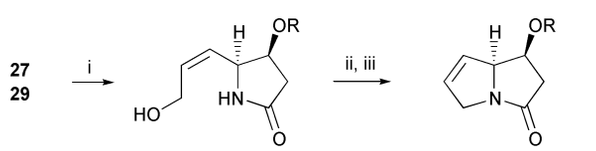


Fig. 1 ORTEP representation of one of the two chemically identical molecules in the asymmetric unit of **28**.

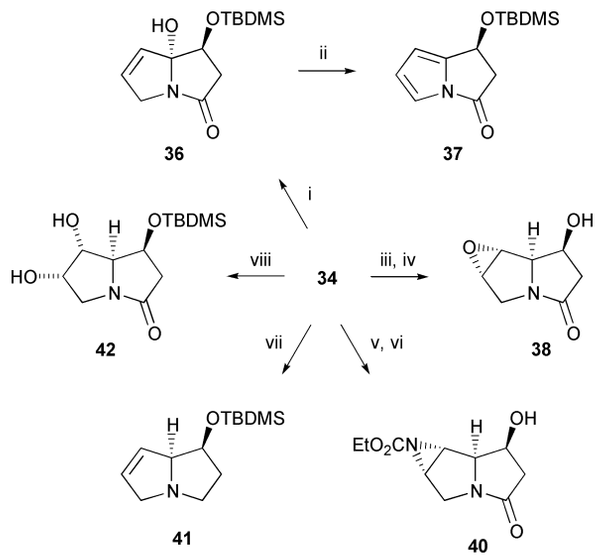
for **17** under the same conditions (entry 7). However, when **17** was oxidized with sodium periodate in an aqueous THF medium, selectivity was reversed in favor of the *exo* cycloadduct **28** (entry 9). The effect of water on the stereoselectivity of a closely related cycloaddition has also been noted by Kibayashi and co-workers[19] but is without a satisfactory explanation at this time.

The *endo* dihydrooxazines **27** and **29** were each reduced with 6% sodium amalgam to give the lactam alcohols **32** and **33**, respectively, resulting from N–O bond cleavage (Scheme 5).



Scheme 5 *Reagents and conditions*: (i), 6% Na(Hg), Na_2HPO_4, EtOH, 0 °C; (ii), MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii), LDA, THF, −78 to 0 °C.

Each of these allylic alcohols was converted to the corresponding mesylate and then treated with lithium diisopropylamide. The intermediate metallated lactams immediately cyclized to the corresponding dehydropyrrolizidinones **34** and **35**, in which a double bond is conveniently placed for the further elaboration needed to transform this template into the tricyclic nucleus of loline. Exploratory experiments along these lines were carried out with **34**, which was oxidized with dimethyldioxirane in the expectation that an epoxide of *exo* configuration would be formed (Scheme 6). Surprisingly, the sole product was alcohol **36**, the result of angular hydroxylation rather than epoxidation. Abstraction of an allylic hydrogen by dimethyldioxirane in



Scheme 6 *Reagents and conditions*: (i), dimethyldioxirane, acetone, 0 °C, pH 11 work-up, 92%; (ii), AcOH, CH_2Cl_2, 100%; (iii), MCPBA, 2,6-di-*tert*-butyl-4-methylphenol (BHT), Na_2CO_3, $(CH_2Cl)_2$, reflux, 50%; (iv), TBAF, THF, 97%; (v), $EtO_2CNHONs$ (**39**; Ns = *p*-nitrobenzenesulfonyl), CaO, CH_2Cl_2, rt; (vi), TBAF, THF, 22% (2 steps); (vii), LAH, THF, rt, 34%; (viii), OsO_4, NMO, acetone–H_2O (5 : 1), 89%.

preference to epoxidation, although unusual, is precedented.[22] Exposure of **36** to acetic acid led in quantitative yield to pyrrole **37**. In contrast to its reaction with dimethyldioxirane, **34** gave exclusively the desired epoxide when treated with buffered *m*-chloroperbenzoic acid, although in only modest yield. Subsequent cleavage of the silyl ether of this oxirane afforded alcohol **38**, but all attempts to effect opening of the epoxide by intramolecular attack across the *endo* face of the pyrrolizidine with the hydroxy function at C7 were unsuccessful.

An alternative and more direct entry to the loline skeleton from **34** would be *via* aziridination of the double bond, and to this end **34** was reacted with an excess of the *p*-nitrobenzenesulfonate of *N*-hydroxyurethane (**39**) in the presence of calcium oxide.[23] The nitrene generated by this means underwent *in situ* addition to **34** and yielded an aziridine in which the alcohol was immediately deprotected to give **40**. Again, the *endo* alcohol **40** failed to participate in intramolecular opening of the aziridine. The negative outcome with both **38** and **40** led to speculation that the lactam carbonyl was inhibiting transannular attack by the C7 hydroxy function at the three-membered ring, and a conformational analysis of these structures clearly showed that the flattened γ-lactam ring prevented close approach of the two reacting sites. Conversely, removal of the lactam carbonyl would permit the pyrrolizidine to adopt a "puckered" conformation[24] which should bring the hydroxy group and three-membered ring into sufficient proximity for transannular displacement to occur. With the intent of testing this hypothesis, **34** was reduced with lithium aluminium hydride

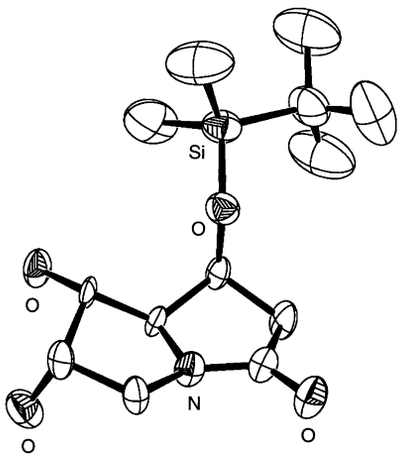
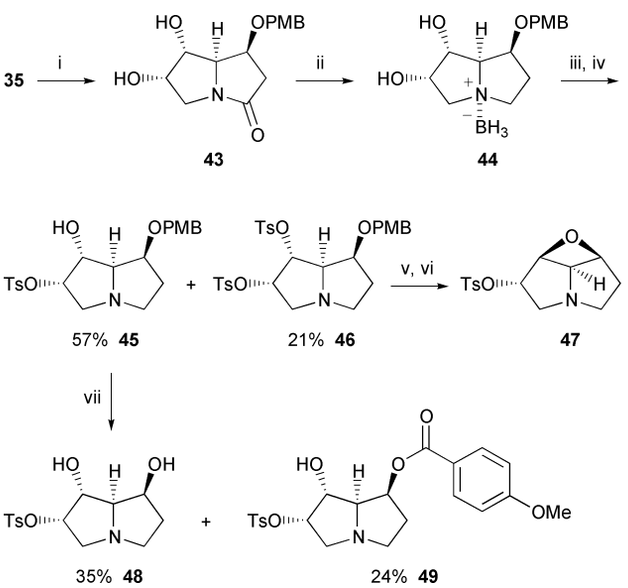


Fig. 2 ORTEP representation of one of the two chemically identical molecules in the asymmetric unit of **42**.

to **41**. Unfortunately, this pyrrolizidine was now more susceptible to oxidation at the basic nitrogen atom and, not surprisingly, efforts to secure a derivative of **41** in which the double bond was functionalized by oxidative means were completely unsuccessful. This result indicated that the pyrrolizidinone double bond must be modified prior to reduction of the lactam carbonyl, and a promising development in this direction was realized with osmylation of **34**. The crystalline *exo* diol **42** was obtained in high yield, and its configuration was confirmed by X-ray crystallographic analysis (Fig. 2).

For a variety of reasons, including the greater ease of scale-up, it proved to be more practical to move forward from the *p*-methoxybenzyl ether **35** than the corresponding silyl ether **34**. The osmylation of **35** afforded diol **43** which underwent quantitative reduction of the lactam carbonyl with excess borane (Scheme 7). The product isolated from this reduction was the



Scheme 7 *Reagents and conditions*: (i), OsO_4, NMO, acetone–H_2O (5 : 1), 65%; (ii), BH_3·SMe_2, THF, rt, 100%; (iii), TsCl, Et_3N, CH_2Cl_2, rt; (iv), $Pd(OH)_2$/C, MeOH, rt; (v), DDQ, CH_2Cl_2–H_2O (20 : 1), rt, 80%; (vi), K_2CO_3, MeOH–H_2O (5 : 1), reflux, 76%; (vii), CAN, MeCN–H_2O (5 : 1), rt.

stable, crystalline pyrrolizidine–borane **44** whose crystal structure is shown in Fig. 3. Protection of the basic pyrrolizidine nitrogen in this way permitted tosylation of the diol without complication, but a mixture of mono- and bis-tosylates **45** and **46** resulted from this reaction. After removal of the borane by methanolysis in the presence of Pearlman's catalyst, the mono- and bis-tosylates were readily separated by chrom-

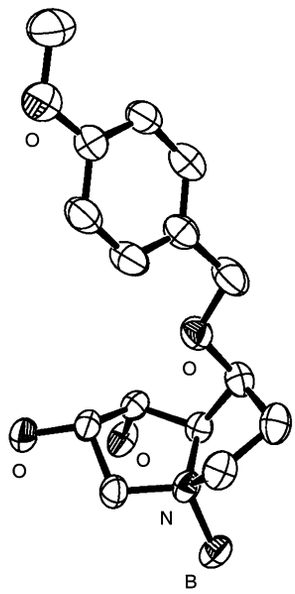
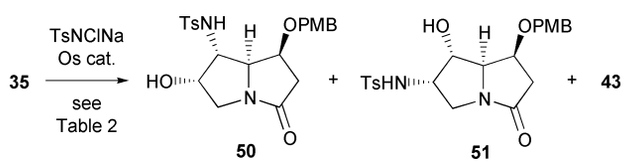


Fig. 3 ORTEP representation of **44**.

atography. Cleavage of the *p*-methoxybenzyl ether from **46** occurred cleanly with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), but when the resulting alcohol was exposed to potassium carbonate in refluxing aqueous methanol, we were surprised to find that the sole product was the oxetane **47**, resulting from displacement of the proximal tosylate rather than the expected tricyclic skeleton characteristic of **1**. The structure of **47** was evident from the unusually high chemical shift of H7 (5.05 pm) and the absence of coupling between H1 and H2 ($J_{1,2} = 0$ Hz). In contrast to **46**, debenzylation of **45** was more problematic, DDQ being ineffective while ceric ammonium nitrate (CAN) gave a mixture of diol **48** and the *p*-methoxybenzoate **49**. Neither of these substances was useful as platforms from which to launch the final moves towards loline.

It was recognized at this point that the difficulties attending cyclization of tosylate **46** could probably be circumvented if aminohydroxylation rather than dihydroxylation of **35** was used to functionalize the double bond (see Scheme 8 and Table



Scheme 8

2). Osmylation of **35** in the presence of excess chloramine-T under the original catalytic conditions reported by Sharpless[25] yielded principally the diol **43** together with small amounts of the masked amino alcohols **50** and **51** (entry 1). More recent results from Sharpless,[26] and others,[27] have demonstrated the profound influence of added biscinchona alkaloid ligands on the facial selectivity and regioselectivity of osmium catalyzed olefin aminohydroxylation. Furthermore, solvent systems incorporating water, which encourage high catalyst turn-over rates, can be utilized in the presence of these ligands without their usual promotion of an intrusive dihydroxylation pathway.[26] Cognizant of these results, aminohydroxylation of **35** was attempted in the presence of hydroquinidine phthalazine-1,4-diyl diether [$(DHQD)_2PHAL$] in an acetonitrile–water mixture (entry 2). To our surprise, an even greater proportion of diol **43** was produced and only traces of the desired hydroxysulfonamides could be found. Fortunately, the yield of aminohydroxylation products **50** and **51** was considerably improved

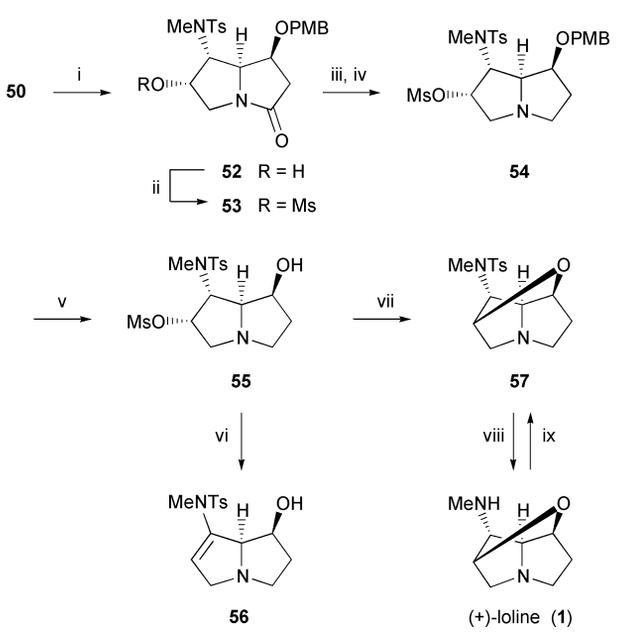
Table 2 Aminohydroxylation of dehydropyrrolizidinone **35**[a]

Entry	Os cat. (mol %)	Additive (mol%)	Solvent	Temp./°C	Time/h	Yield[b] (%) **50** + **51**	Yield[b] (%) **43**	Ratio[c] **50** : **51**
1	OsO_4 (5)	None	*t*-BuOH	60	43	18	29	85 : 15
2	$K_2OsO_2(OH)_4$ (8)	$(DHQD)_2PHAL$[d] (8)	MeCN–H_2O (1 : 1)	22	3	<5	73	—
3	$K_2OsO_2(OH)_4$ (4)	$(DHQD)_2PHAL$[d] (8)	*t*-BuOH–H_2O (1 : 1)	22	24	47	48	80 : 20
4	$K_2OsO_2(OH)_4$ (1 × 3)	$(DHQD)_2PHAL$[d] (25)	*t*-BuOH–H_2O (1 : 1)	22	72	52	21	75 : 25
5	$K_2OsO_2(OH)_4$ (4)	$(DHQ)_2PHAL$[e] (8)	*t*-BuOH–H_2O (1 : 1)	22	24	38	39	65 : 35

[a] Chloramine-T dihydrate (2–3 equiv.) added to each reaction. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] $(DHQD)_2PHAL$ = hydroquinidine phthalazine-1,4-diyl diether. [e] $(DHQ)_2PHAL$ = hydroquinine phthalazine-1,4-diyl diether.

if the reaction was run in a *tert*-butyl alcohol–water mixture (entry 3), and optimization studies revealed that maintaining a high ligand to Os(VIII) ratio further suppressed diol formation. Slow addition of the potassium osmate pre-catalyst gave an acceptable yield of **50** and **51** with a 3 : 1 regioselectivity in favor of **50** (entry 4). The use of hydroquinine phthalazine-1,4-diyl diether [$(DHQ)_2PHAL$] as additive resulted in a lower proportion of aminohydroxylation products, although the predominant regioisomer was again **50** (entry 5).

Incorporation of the secondary amino function of **50** as its sulfonamide during the aminohydroxylation of **35** provided a convenient opportunity to introduce the *N*-methyl substituent characteristic of loline. This was accomplished by treatment of the potassium salt of the tosyl amide **50** with methyl iodide,[28] after which the hydroxy group of **52** was converted to its mesylate in quantitative yield (Scheme 9). Reduction of



Scheme 9 *Reagents and conditions*: (i), MeI, *t*-BuOK, *t*-BuOH, 50 °C, 76%; (ii), MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; (iii), $BH_3{\cdot}SMe_2$, THF, rt; (iv), $Pd(OH)_2/C$, MeOH, rt, 73% (2 steps); (v), DDQ, CH_2Cl_2–H_2O (20 : 1), rt, 70%; (vi), KHMDS, THF, 0 °C, 70%; (vii), *o*-$Cl_2C_6H_4$, 180 °C, 75%; (viii), sodium naphthalenide, DME, −60 °C, 48%; (ix), TsCl, DMAP, Et_3N, $CHCl_3$, rt, 77%.

γ-lactam **53** again proceeded smoothly with borane–dimethyl sulfide to give the pyrrolizidine–borane complex, from which **54** was liberated with methanol in the presence of Pearlman's catalyst. Removal of the *p*-methoxybenzyl ether from **54** with DDQ furnished the crystalline alcohol **55**, our intended substrate for the intramolecular etherification that would yield the loline framework. An X-ray crystallographic structure determination of **55** (Fig. 4) confirmed that the C7 hydroxy group of **55** is indeed in sufficient proximity to C2 to effect displacement and consequent cyclization. Initial attempts to

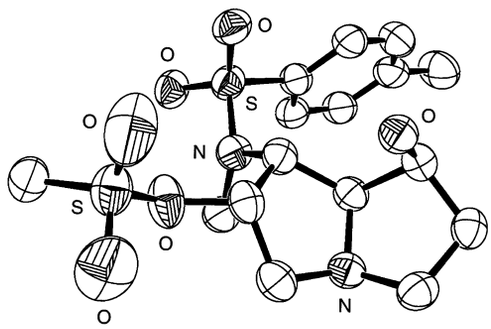


Fig. 4 ORTEP representation of **55**.

effect this final ring closure were unpromising, however. Bases such as potassium hexamethyldisilazane, which presumably generate an alkoxide from **55**, gave exclusively the product **56** from 1,2-elimination. Evidently, the hydrogen at C1 is abstracted in preference to displacement at C2 under these conditions. The problem was conveniently circumvented by subjecting **55** to a purely thermal cyclization, and in *o*-dichlorobenzene at 180 °C. Compound **55** underwent clean cyclization to *N*-tosylloline (**57**). Removal of the tosyl group by reductive cleavage with sodium naphthalenide afforded (+)-loline (**1**), isolated as its dihydrochloride salt. The ^{1}H and ^{13}C NMR spectra of synthetic material were in good agreement with those reported for natural loline (Tables 3 and 4).[29] Additional confirmation of the identity of our synthesized material was made by converting a sample of the natural alkaloid to its *N*-tosyl derivative **57**, at which point the complete identity of the synthetic and naturally prepared materials was unambiguous. *N*-Tosylloline (**57**), derived in 21 steps from (−)-malic acid (**18**), exhibited $[\alpha]_D^{22}$ +40.9 (*c* 0.11, $CHCl_3$) while that obtained from natural (+)-loline had $[\alpha]_D^{22}$ +38.0 (*c* 0.10, $CHCl_3$).

Experimental

All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of Ar. DME, THF and Et_2O were freshly distilled from sodium–benzophenone ketyl prior to use. DMSO was distilled from CaH_2 at 15 mmHg. CH_2Cl_2 was freshly distilled from CaH_2. Anhydrous ethanol was obtained by distillation from its magnesium alkoxide and stored under Ar over activated 4 Å molecular sieves. Preparative chromatographic separations were performed on EM Science silica gel 60 (35–75 μm), and reactions were followed by TLC analysis using EM Science silica plates with fluorescent indicator (254 nm) and were visualized with UV, phosphomolybdic acid or potassium permanganate. All commercially available reagents were purchased from Aldrich and were typically used as supplied.

Melting points were recorded using open capillary tubes on a Büchi melting point apparatus and are uncorrected. Specific optical rotations were measured at ambient temperature (23 °C) from $CHCl_3$ solutions on a Perkin-Elmer 243 polarimeter using a 1 mL cell with 1 dm path length. Infra-red spectra were

Table 3 ^{1}H NMR data for natural and synthetic loline dihydrochloride

	Natural (+)-loline dihydrochloride[ab]			Synthetic (+)-loline dihydrochloride[a]		
Position	δ (ppm)	Multiplicity	J/Hz	δ (ppm)	Multiplicity	J/Hz
H1	4.23	dd	<2, 1.9	4.23	br d	2.3
H2	4.79	dd	<2, 1.0	4.77–4.80	m	—
$H3_A$	4.15	dd	13.9, 1.0	4.12	dd	13.9, 1.3
$H3_B$	3.55	d	13.9	3.57	d	13.9, 1.3
$H5_A$	3.73	ddd	12.8, 8.2, 7.7	3.70	ddd	12.8, 9.5, 7.8
$H5_B$	3.73	ddd	12.8, 9.6, 5.0	3.75	ddd	12.8, 8.8, 5.5
$H6_A$	2.28	dddd	14.6, 8.2, 5.0, 4.8	2.38	dddd	15.4, 9.5, 5.5, 4.6
$H6_B$	2.37	ddd	14.6, 9.6, 7.7	2.27	ddd	15.4, 8.8, 7.8
H7	4.72	dd	4.8, 2.2	Not observed[c]	—	—
H8	4.79	dd	2.2, 1.9	4.77–4.80	m	—
NH	4.76	br m	—	Obscured[c]	—	—
NMe	2.79	s	—	2.79	s	—

[a] Recorded in D_2O at 300 MHz. [b] Data taken from ref. 29. [c] Obscured by HOD.

Table 4 Comparison of ^{13}C NMR data for natural and synthetic loline dihydrochloride

	δ (ppm)		
Position	Natural[ab]	Synthetic[a]	$\Delta\delta$
C1	65.9	66.0	−0.1
C2	73.9	74.0	−0.1
C3	64.2	64.2	0.0
C5	58.1	58.2	−0.1
C6	31.6	31.6	0.0
C7	83.2	83.4	−0.2
C8	72.2	72.2	0.0
NMe	36.5	36.4	+0.1

[a] Recorded in D_2O at 75 MHz. [b] Data taken from ref. 29.

recorded on a Nicolet 5DXB spectrometer using a thin film supported between NaCl plates or KBr discs. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified either on a Bruker AC300 or AM400 spectrometer. Spectra were obtained from $CDCl_3$ solutions in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform (δ_H = 7.25 ppm, or δ_C = 77.0 ppm). Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in Hz. Low (MS) and high (HRMS) resolution mass spectra were determined using a Kratos MS50 spectrometer. Ion mass/charge (m/z) ratios are reported as values in atomic mass units.

X-Ray crystallographic structure determinations† were conducted on a Siemens P4 instrument controlled by the program XSCANS V2.20,[30] and equipped with a sealed tube Cu anode, a graphite monochromator, and a modified Siemens LT2 low temperature device. After verifying the quality of the crystal by means of a rotational photograph, the crystal was oriented using a set of reflections found by an automated search routine. This cell was then transformed to its highest symmetry setting, refined using high-angle reflections, and ambiguous symmetry elements checked by means of axial photographs and/or automated methods. Data were collected based on the assumed crystal system, including at least all the unique data for the particular Laue class, and their Bijvoet pairs. Data were automatically corrected for Lorentz and polarization effects by the diffractometer control program. Unless otherwise indicated, correction for effects of absorption anisotropy was carried out based on semi-empirical methods (psi-scans)[31] as programmed in XEMP V4.3.[32]

† CCDC reference numbers 163574–163577. See http://www.rsc.org/suppdata/p1/b1/b103936a/ for crystallographic files in .cif or other electronic format.

The structures were solved using direct methods as programmed in SHELXS-97,[33] and any remaining atoms were subsequently found by difference Fourier map techniques using the program SHELXL-97.[33] Unless otherwise stated, hydrogen atoms were included in geometrically idealized positions, and refined as riding groups with an isotropic displacement parameter equal to 1.5 (methyl group) or 1.2 (all other types) times the U_{eq} of the atom to which it is attached. Where appropriate, an absolute structure parameter (Flack X parameter)[34] was refined in order to confirm or determine the absolute configuration of the structure under study.

1-[(3a*R*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]but-3-en-1-ol (10)

A solution of **9**[17] (37 mg, 0.21 mmol) in THF (10 mL) was stirred over 4 Å molecular sieves for 30 min and then added dropwise to allylmagnesium chloride (0.16 mL, 2.0 M in THF, 0.32 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and sat. aq. NH_4Cl (15 mL) and Et_2O (15 mL) were added. The phases were separated and the aqueous phase extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with 33–50% EtOAc in hexanes) to yield **10** (36 mg, 0.17 mmol, 80%) as a 1 : 1 mixture of diastereoisomers: IR (neat) 3478, 2984, 2936, 1374, 1216, 1163, 1054, 1020, 918, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 6H), 1.51 (s, 6H), 1.74–2.01 (m, 4H), 2.20 (t, J = 7 Hz, 2H), 2.31 (t, J = 7 Hz, 2H), 2.47 (br s, 2H), 3.53–3.60 (m, 1H), 3.95 (br s, 1H), 4.15–4.22 (m, 2H), 4.75 (br s, 2H), 5.10–5.16 (m, 4H), 5.79–5.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.2, 26.7, 26.8, 31.7, 34.8, 37.4, 38.6, 69.8, 72.0, 80.4, 80.5, 80.6, 80.7, 105.2, 105.4, 111.2, 111.4, 117.7, 117.8, 134.1, 134.3; MS (EI) m/z 215 $(M + H)^+$, 199, 173, 157, 143, 139, 115; HRMS (EI) m/z 199.0969 $(M - CH_3)^+$ (calcd for $C_{10}H_{15}O_4$: 199.1029).

(3a*R*,6a*R*)-5-(Buta-1,3-dienyl)-2,2-dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxolane (11)

To a solution of **10** (867 mg, 4.05 mmol) and triethylamine (819 mg, 8.10 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise methanesulfonyl chloride (557 mg, 4.86 mmol). The solution was allowed to warm to rt and stirred for 2 h. Sat. aq. NH_4Cl (15 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude mesylate was dissolved in toluene (50 mL) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.08 g, 20.3 mmol) at 100 °C for 9 h. The mixture was allowed to cool to rt, and sat.

aq. NH_4Cl (25 mL), H_2O (5 mL) and Et_2O (25 mL) were added. The layers were separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 10–15% EtOAc in hexane) to yield crude **11** (~1 g) as a 15 : 1 mixture of *E* and *Z* isomers, respectively. The mixture was dissolved in MeOH (6 mL), H_2O (30 mL) was added slowly, and the product was allowed to crystallize at 5 °C. The resulting fine yellow plates were collected by filtration and dried to afford **11** (508 mg, 2.59 mmol, 64% for two steps) with $E : Z = 40 : 1$ (determined by ^{1}H NMR analysis): $[\alpha]_D^{23}$ −34.3 (*c* 1.23, CH_2Cl_2); IR (neat) 2987, 2976, 2961, 2931, 2882, 1371, 1256, 1157, 1081, 1048, 1013, 966, 928, 912, 858, 845 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.51 (s, 3H), 1.60 (ddd, J = 13, 11, 5 Hz, 1H), 2.15 (dd, J = 13, 4 Hz, 1H), 4.66 (ddd, J = 11, 7, 4 Hz, 1H), 4.72 (t, J = 4 Hz, 1H), 5.09 (dm, J = 10 Hz, 1H), 5.21 (dm, J = 15 Hz, 1H), 5.65 (ddm, J = 15, 7 Hz, 1H), 5.82 (d, J = 4 Hz, 1H), 6.24–6.38 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.6, 39.6, 77.9, 80.5, 105.3, 111.0, 118.3, 131.3, 133.2, 136.1; MS (EI) *m*/*z* 196 M$^+$, 181, 138, 121; HRMS (EI) *m*/*z* 196.1099 (calcd for $C_{11}H_{16}O_3$: 196.1099).

(*E*,3*R*,5*S*)-5-(Buta-1,3-dien-1-yl)-2,3-dihydroxyoxolane (12)

A solution of **11** (1.15 g, 5.88 mmol) in TFA–THF–H_2O (5 : 1 : 1, 40 mL) was stirred at 60 °C for 5 h. The mixture was allowed to cool and sat. aq. $NaHCO_3$ added until pH 7 was reached (*ca*. 40 mL). EtOAc (30 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc (5 × 40 mL), and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 50–66% EtOAc in hexanes) to yield **12** (820 mg, 5.25 mmol, 89%) as a variable mixture of anomers: IR (neat) 3348, 2940, 1610, 1417, 1358, 1009, 961, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8–2.2 (m, 4H), 3.0–3.6 (m, 4H), 4.2–4.35 (m, 2H), 4.7–4.85 (m, 2H), 5.05–5.45 (m, 6H), 5.55–5.8 (m, 2H), 6.15–6.4 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.1, 39.0, 71.5, 76.9, 80.0, 96.9, 102.6, 118.2, 132.2, 132.6, 133.1, 134.7, 135.9; MS (CI) *m*/*z* 156 M$^+$, 139, 138, 110; HRMS (CI) *m*/*z* 156.0786 (calcd for $C_8H_{12}O_3$: 156.0786).

Methyl (*E*,3*S*)-3-hydroxyhepta-4,6-dienoate (15)

To a stirred suspension of **12** (820 mg, 5.25 mmol) and sodium periodate (1.46 g, 6.83 mmol) in ether (80 mL) at rt was added dropwise a pH 7 aqueous phosphate buffer solution (1.5 mL). After stirring for 3 h, Et_2O (100 mL) was added and the mixture was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude aldehyde **13** was dissolved in *t*-BuOH (100 mL) and 2-methylbutene (25 mL), and the solution was cooled to 0 °C and treated with a solution of $NaClO_2$ (4.37 g, 48.3 mmol) and $NaH_2PO_4{\cdot}H_2O$ (5.07 g, 36.8 mmol) in H_2O (50 mL). The resulting mixture was stirred for 1 h while warming to ambient temperature and H_2O (150 mL) was added. The aqueous phase was separated, acidified to pH 3 with 10% aq. HCl, and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield crude carboxylic acid **31**. The acid was immediately dissolved in Et_2O (40 mL) and diazomethane (*ca*. 22 mL, 0.25 M in Et_2O, 5.5 mmol) was added until a light yellow colour persisted. The solution was stirred at rt overnight and concentrated *in vacuo* to give 950 mg of crude methyl ester **14**. The ester was dissolved in MeOH (50 mL), K_2CO_3 (100 mg, 0.72 mmol) and H_2O (10 drops) were added, and the resulting mixture was stirred at rt for 1 h. Solid NH_4Cl was added (100 mg) and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 15–25% EtOAc in hexanes) to give **15** (717 mg, 4.59 mmol, 87% for four steps) as a colourless oil: $[\alpha]_D^{23}$ +5.7 (*c* 2.11, CH_2Cl_2); IR (neat) 3448, 2953, 1732, 1438, 1276, 1176, 1100, 1006, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50–2.64 (m, 2H), 3.00 (br s, OH), 3.70 (s, 3H), 4.58 (q, J = 6 Hz, 1H), 5.11 (dm, J = 10 Hz, 1H), 5.22 (dm, J = 16 Hz, 1H), 5.70 (ddm, J = 15, 6 Hz, 1H), 6.25–6.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.1, 51.8, 68.3, 118.2, 131.5, 133.8, 136.0, 172.5; MS (CI) *m*/*z* 156 M$^+$, 139, 124; HRMS (CI) *m*/*z* 156.0786 (calcd for $C_8H_{12}O_3$: 156.0786).

Methyl (*E*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]hepta-4,6-dienoate (16)

To a stirred solution of **15** (561 mg, 3.59 mmol) and imidazole (416 mg, 6.1 mmol) in DMF (20 mL) at rt was added *tert*-butyldimethylsilyl chloride (676 mg, 4.49 mmol). After stirring of the solution for 24 h, H_2O (50 mL) and Et_2O (150 mL) were added and the phases separated. The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The slightly volatile residue was purified by column chromatography (eluting with 25% Et_2O in pentane) to yield **16** (942 mg, 3.48 mmol, 97%) as a colourless oil: $[\alpha]_D^{23}$ −2.2 (*c* 2.77, CH_2Cl_2); IR (neat) 2954, 2857, 1742, 1437, 1361, 1256, 1107, 1004, 836, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 2.43 (dd, J = 15, 5 Hz, 1H), 2.54 (dd, J = 15, 8 Hz, 1H), 3.65 (s, 3H), 4.62 (q, J = 6 Hz, 1H), 5.08 (dm, J = 10 Hz, 1H), 5.19 (dm, J = 15 Hz, 1H), 5.67 (dd, J = 15, 7 Hz, 1H), 6.18 (dd, J = 15, 10 Hz, 1H), 6.29 (dt, J = 16, 10 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.4, 18.0, 25.7 (3C), 43.6, 51.5, 70.1, 117.6, 130.7, 135.5, 136.2, 171.4; MS (CI) *m*/*z* 271 (M + H)$^+$, 255, 213, 197, 139; HRMS (CI) *m*/*z* 271.1730 (calcd for $C_{14}H_{27}SiO_3$: 271.1729).

(*E*,3*S*)-*N*-Hydroxy-3-[(*tert*-butyldimethylsilyl)oxy]hepta-4,6-dienamide (17)

To a solution of hydroxylamine hydrochloride (1.21 g, 17.4 mmol) in MeOH (10 mL) at rt was added a solution of potassium hydroxide in MeOH (16 mL, 1.8 M, 29 mmol). After stirring the mixture for 30 min, the precipitated potassium chloride was allowed to settle and the supernatant liquor added to the neat ester **16** (942 mg, 3.48 mmol) during 3 h (10 mL was added during the first 10 min). The solution was stirred at 35 °C for a further 5 h, H_2O (60 mL) was added, and the mixture was acidified to pH 3 with 10% aq. HCl. The solution was extracted with Et_2O (6 × 90 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 50% EtOAc in hexanes) to give **17** (860 mg, 3.17 mmol, 91%) as a colourless oil: $[\alpha]_D^{23}$ −2.3 (*c* 0.87, CH_2Cl_2); IR (neat) 3211, 3086, 3040, 3002, 2955, 2928, 2885, 2856, 1650, 1606, 1471, 1463, 1389, 1361, 1255, 1109, 1074, 1004, 950, 904, 837, 778; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 2.34 (dd, J = 15, 7 Hz, 1H), 2.45 (dd, J = 14, 4 Hz, 1H), 4.55 (q, J = 6 Hz, 1H), 5.10 (dm, J = 10 Hz, 1H), 5.20 (dm, J = 16 Hz, 1H), 5.64 (dd, J = 15, 7 Hz, 1H), 6.18 (dd, J = 15, 10 Hz, 1H), 6.28 (dt, J = 16, 10 Hz, 1H), 8.0–9.5 (br s, NHOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.5, 18.1, 25.8 (3C), 42.2, 69.8, 118.2, 131.4, 134.2, 135.9, 168.7; MS (CI) *m*/*z* 272 (M + H)$^+$, 271 M$^+$, 270, 256, 245, 214, 199, 140; HRMS (CI) *m*/*z* 272.1681 (calcd for $C_{13}H_{26}NO_3Si$: 272.1682).

[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]methanol (19)

A stirred biphasic mixture of (*S*)-butane-1,2,4-triol[20] (2.80 g, 26.4 mmol) and anhydrous CH_2Cl_2 (80 mL) at rt under Ar, was treated with 4-methoxybenzaldehyde dimethyl acetal (4.70 mL, ρ = 1.07, 5.03 g, 27.6 mmol). After addition of PPTS (330 mg, 1.31 mmol), the mixture was heated at reflux for 20 h. The resulting homogeneous solution was allowed to cool and was concentrated *in vacuo*, and the crude residue was purified by column chromatography (eluting with 50% EtOAc in hexanes) to afford **19** (3.81 g, 17.0 mmol, 64%) as a colourless oil: $[\alpha]_D^{23}$

+9.9 (*c* 0.96, $CHCl_3$); IR (neat) 3500, 2835, 1613, 1587, 1514, 1507, 1392, 1302, 1242, 1171, 1028, 827, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (dm, J = 13 Hz, 1H), 1.85 (qd, J = 13, 5 Hz, 1H), 2.51 (t, J = 6 Hz, 1H), 3.60 (t, J = 5 Hz, 2H), 3.78 (s, 3H), 3.86–3.97 (m, 2H), 4.25 (dd, J = 12, 5 Hz, 1H), 5.46 (s, 1H), 6.88 (d, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 55.2, 65.5, 66.4, 77.4, 101.0, 113.5 (2C), 127.3 (2C), 130.8, 159.9; MS (FAB) *m*/*z* 225 $(M + H)^+$, 223, 193, 137; HRMS (FAB) *m*/*z* 225.1128 (calcd for $C_{12}H_{17}O_4$: 225.1127).

(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxane-4-carbaldehyde

To a stirred solution of oxalyl chloride (3.84 mL, 5.61 g, 44.1 mmol) in anhydrous CH_2Cl_2 (60 mL) at −60 °C under Ar was added dropwise a solution of dimethyl sulfoxide (5.46 mL, 6.01 g, 77.0 mmol) in anhydrous CH_2Cl_2 (50 mL) during 20 min. After stirring the mixture for an additional 25 min a solution of **19** (6.15 g, 27.4 mmol) in anhydrous CH_2Cl_2 (40 mL) was added during 20 min. The resulting cloudy mixture was stirred for a further 20 min, treated with triethylamine (26.8 mL, ρ = 0.726, 19.5 g, 193 mmol), and was allowed to warm to rt during 1 h. The reaction mixture was quenched with H_2O (100 mL), and the layers were vigorously shaken and then separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were washed successively with H_2O (50 mL) and brine (20 mL), and dried (Na_2SO_4). The extract was concentrated *in vacuo* (CARE! stench), and the crude residue was purified by column chromatography (eluting with 50–80% EtOAc in hexanes) to yield a mixture of the aldehyde and inseparable oligomers (5.42 g) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$, selected for free aldehyde) δ 1.79 (dm, J = 13 Hz, 1H), 1.97 (qd, J = 13, 5 Hz, 1H), 3.82 (s, 3H), 4.01 (td, J = 12, 3 Hz, 1H), 4.30–4.40 (m, 2H), 5.57 (s, 1H), 6.92 (d, J = 9 Hz, 2H), 7.46 (d, J = 9 Hz, 2H), 9.73 (s, 1H).

(2*S*,4*S*)-4-(Buta-1,3-dienyl)-2-(4-methoxyphenyl)-1,3-dioxane (20)

A stirred suspension of allyltriphenylphosphonium bromide (14.0 g, 36.6 mmol) in anhydrous THF (250 mL) at −30 °C under Ar was treated dropwise with *n*-butyllithium (21.6 mL, 1.47 M in hexanes, 31.8 mmol) and the resulting orange solution was stirred for 40 min. A solution of the aldehyde and its oligomers obtained (5.42 g) in anhydrous THF (20 mL) was added dropwise, causing a lightening in colour to yellow and the formation of a precipitate. The mixture was allowed to warm to rt over 2 h and quenched by the addition of H_2O (50 mL). After dilution with Et_2O (200 mL), the layers were shaken vigorously and separated. The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 20% Et_2O in hexanes) to yield **20** (2.68 g, 10.9 mmol, 40% from **19**, colourless oil) as an inseparable mixture of isomers (E : Z = 3 : 7 by ^1H NMR): IR (neat) 2955, 2834, 1724, 1613, 1588, 1515, 1462, 1392, 1370, 1301, 1241, 1212, 1170, 1116, 1066, 911, 880, 828, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, E–Z mixture) δ 1.47–1.61 (m, $1H_{E+Z}$), 1.85–2.04 (m, $1H_{E+Z}$), 3.78 (s, $3H_Z$), 3.79 (s, $3H_E$), 3.92–4.10 (m, $1H_{E+Z}$), 4.26 (dd, J = 12, 5 Hz, $1H_{E+Z}$), 4.40 (ddd, J = 11, 5, 2 Hz, $1H_E$), 4.81 (ddd, J = 11, 9, 2 Hz, $1H_Z$), 5.07–5.32 (m, $2H_{E+Z}$), 5.49–5.57 (m, $2H_Z$ + $1H_E$), 5.78 (dd, J = 15, 6 Hz, $1H_E$), 6.09 (t, J = 11 Hz, $1H_Z$), 6.22–6.40 (m, $2H_E$), 6.68 (dt, J = 17, 11 Hz, $1H_Z$), 6.88 (d, J = 7 Hz, $2H_{E+Z}$), 7.42 (d, J = 7 Hz, $2H_Z$), 7.43 (d, J = 5 Hz, $2H_E$); ^{13}C NMR (75 MHz, $CDCl_3$, E–Z mixture) δ 31.1_E, 31.2_Z, 55.0_{E+Z}, 66.5_{E+Z}, 73.6_Z, 76.7_E, 100.8_{E+Z}, 113.3_{E+Z} (2C), 117.7_E, 119.3_Z, 127.2_{E+Z} (2C), 130.5_Z, 130.8_Z, 131.0_E, 131.0_E, 131.1_Z, 131.6_Z, 132.9_E, 136.2_E, 159.7_{E+Z}; MS (CI) *m*/*z* 246 M^+, 221, 200, 173, 137, 121, 109, 93; HRMS (CI) *m*/*z* 246.1256 (calcd for $C_{15}H_{18}O_3$: 246.1256).

(*E*,*S*)-3-(4-Methoxybenzyloxy)hepta-4,6-dien-1-ol (21)

To a stirred solution of **20** (319 mg, 1.30 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under Ar was added dropwise a solution of diisobutylaluminium hydride (12.7 mL, 0.51 M in CH_2Cl_2, 6.5 mmol). The cooling bath was removed and the clear mixture allowed to stir at rt for 1.5 h. The reaction was quenched with H_2O (1 mL, CARE!) and stirred vigorously for 10 min. After dilution of the mixture with CH_2Cl_2 (50 mL), solid Na_2SO_4 (20 g) was added and the resulting suspension stirred vigorously for 10 min. Solids were removed by filtration through a Celite pad and the residue was washed thoroughly with CH_2Cl_2 (4 × 50 mL). The combined filtrate and washings were concentrated *in vacuo* to yield 319 mg of crude dienol isomers. The mixture of isomers (E : Z = 3 : 7) was dissolved in PhH (30 mL) and the solution was treated with iodine (4 mg, 16 μmol, *ca*. 1 mol%). After transfer to a photolysis apparatus (quartz window) and a 10 min sparge with Ar, the solution was irradiated with a medium-pressure Hanovia Hg discharge lamp (120 V, 450 W) for 1 h. The solution was diluted with EtOAc (20 mL), and the combined organic solutions were washed successively with 10% w/v aq. $Na_2S_2O_3$ (20 mL) and brine (10 mL), and dried (Na_2SO_4). The organic solution was concentrated *in vacuo*, and the residue was purified by column chromatography (eluting with 40% EtOAc in hexanes) to yield **21** (204 mg, 0.82 mmol, 63%) as a clear oil (E : Z > 95 : 5 by ^1H NMR analysis): $[\alpha]_D^{23}$ −60.3 (*c* 1.10, $CHCl_3$); IR (neat) 2829, 1609, 1584, 1507, 1462, 1300, 1240, 1171, 1030, 954, 906, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70–1.94 (m, 2H), 2.49 (br s, 1H), 3.65–3.80 (m, 2H), 3.80 (s, 3H), 4.05 (td, J = 8, 5 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 4.55 (d, J = 11 Hz, 1H), 5.15 (dd, J = 10, 1 Hz, 1H), 5.25 (dd, J = 16, 1 Hz, 1H), 5.65 (dd, J = 15, 8 Hz, 1H), 6.23 (dd, J = 15, 11 Hz, 1H), 6.38 (dt, J = 17, 10 Hz, 1H), 6.88 (d, J = 9 Hz, 2H), 7.24 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 55.2, 60.6, 69.9, 78.6, 113.8 (2C), 118.0, 129.4 (2C), 130.2, 133.3, 133.6, 136.1, 159.2; MS (CI) *m*/*z* 248 (M^+), 137, 121, 109; HRMS (CI) *m*/*z* 248.1409 (calcd for $C_{15}H_{20}O_3$: 248.1412).

(*E*,3*S*)-*N*-Hydroxy-3-(4-methoxybenzyloxy)hepta-4,6-dienamide (24)

A stirred solution of oxalyl chloride (1.0 mL, 1.46 g, 11.5 mmol) in anhydrous CH_2Cl_2 (20 mL) at −60 °C under Ar was treated dropwise by cannula with a cold solution of anhydrous dimethyl sulfoxide (1.45 mL, 1.60 g, 20.5 mmol) in anhydrous CH_2Cl_2 (20 mL) over 10 min. After an additional 20 min, a solution of **21** (1.82 g, 7.33 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise during 5 min. The resulting cloudy mixture was stirred for 25 min and treated with triethylamine (7.1 mL, 5.15 g, 51.0 mmol). The mixture was allowed to warm to rt during 1.5 h, H_2O (30 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed successively with H_2O (20 mL) and brine (20 mL), and dried (Na_2SO_4). The extract was oncentrated *in vacuo* to yield 2.44 g of crude (*E*,*S*)-3-(4-methoxybenzyloxy)hepta-4,6-dienal. This material was immediately dissolved in a mixture of *t*-BuOH (150 mL) and 2-methylbut-2-ene (36 mL), and the resulting solution was cooled to 0 °C with stirring. A solution of $NaClO_2$ (3.30 g, 36.7 mmol) and $NaH_2PO_4 \cdot H_2O$ (5.0 g, 36.2 mmol) in H_2O (75 mL) was added, the cooling bath was removed, and the biphasic mixture was stirred vigorously for 40 min. H_2O (100 mL) and CH_2Cl_2 (100 mL) were added and the pH of the aqueous layer was adjusted to 3 by careful addition of 1 M HCl. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford 2.67 g of crude **22**. Without further purification, **22** was dissolved in anhydrous THF (50 mL), the solution was placed under an

atmosphere of Ar, and pyridine (1.20 mL, 1.17 g, 14.9 mmol) was added. The resulting solution was treated with *N*-(trifluoroacetyloxy)succinimide (2.32 g, 11.0 mmol), and the mixture was stirred for 20 h at rt The mixture was diluted with EtOAc (100 mL) and washed successively with 0.2 M HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (20 mL), and dried (Na_2SO_4). The solution was concentrated *in vacuo* to yield 3.13 g of **23**. In a separate flask, a stirred suspension of $HONH_2{\cdot}HCl$ (2.54 g, 36.5 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under Ar, was treated dropwise with a solution of Et_3N (10.2 mL, 7.41 g, 73.3 mmol) in anhydrous CH_2Cl_2 (20 mL) during 15 min. The resulting suspension was stirred for 20 min and treated dropwise with a solution of the previously prepared succinimidyl ester **23** (3.13 g) in anhydrous CH_2Cl_2 (20 mL) during 10 min. The mixture was allowed to warm to rt and stirred for a further 3 h, after which EtOAc (100 mL) was added and the solution shaken with sat. aq. NH_4Cl (75 mL). The layers were separated and the aqueous phase extracted EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 5% MeOH in CH_2Cl_2) to yield pure **24** (1.51 g, 5.44 mmol, 75%) as a pale golden oil: $[\alpha]_D^{23}$ −30.2 (*c* 0.97, $CHCl_3$); IR (neat) 3200, 2900, 1651, 1614, 1514, 1463, 1302, 1249, 1175, 1071, 1034, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28–2.43 (m, 2H), 3.78 (s, 3H), 4.19 (q, J = 7 Hz, 1H), 4.27 (d, J = 11 Hz, 1H), 4.48 (d, J = 11 Hz, 1H), 5.16 (d, J = 10 Hz, 1H), 5.26 (d, J = 16 Hz, 1H), 5.56 (dd, J = 14, 7 Hz, 1H), 6.23 (dd, J = 14, 10 Hz, 1H), 6.33 (dt, J = 16, 10 Hz, 1H), 6.86 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.8, 55.2, 70.4, 75.6, 113.9 (2C), 118.8, 129.5, 129.5 (2C), 131.6, 134.2, 135.7, 159.3, 168.7; MS (FAB) *m*/*z* 278 (M + H)$^+$, 121; HRMS (FAB) *m*/*z* 278.1391 (calcd for $C_{15}H_{20}O_4N$: 278.1392).

Oxidation of hydroxamic acids 17 and 24 to acylnitrosodienes 25 and 26 and their *in situ* cycloaddition (Table 1)

A solution of the hydroxamic acid (**17** or **24**, 5 mmol) in the specified solvent (40 mL) was added dropwise during 30 min to a stirred solution of the periodate oxidant (10 mmol) in the same solvent (60 mL) at the indicated temperature. After stirring for an additional 2 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (40 mL). The biphasic mixture was stirred vigorously for 45 min at rt and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed successively with H_2O (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 60–75% EtOAc). In each case the less polar *endo* isomer (**27** or **29**) was eluted before the corresponding *exo* isomer (**28** or **30**).

(4a*S*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2,4a,5,6-tetrahydro-7*H*-pyrrolo[1,2-*b*]oxazin-7-one (27). Mp 69–71 °C; $[\alpha]_D^{23}$ +93.9 (*c* 1.99, Et_2O); IR ($CDCl_3$) 2955, 2929, 2899, 2858, 1712, 1471, 1463, 1387, 1258, 1129, 1101, 1062, 839; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 3H), 0.79 (s, 3H), 0.87 (s, 9H), 2.26 (dd, J = 17, 4 Hz, 1H), 2.65 (dd, J = 17, 7 Hz, 1H), 4.23–4.30 (m, 1H), 4.37–4.40 (m, 1H), 4.47–4.53 (m, 1H), 4.72–4.79 (m, 1H), 5.88–5.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.8, 18.0, 25.6, 38.6, 58.2, 64.8, 68.6, 122.7, 125.6, 168.2; MS (CI) *m*/*z* 270 (M + H)$^+$, 254, 212, 170, 101, 75; HRMS (CI) *m*/*z* 270.1523 (calcd for $C_{13}H_{24}NO_3Si$: 270.1526).

(4a*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2,4a,5,6-tetrahydro-7*H*-pyrrolo[1,2-*b*]oxazin-7-one (28). Mp 110–111 °C; $[\alpha]_D^{23}$ −91.0 (*c* 2.90, $CHCl_3$); IR (neat) 2950, 2927, 2856, 1719, 1470, 1462, 1445, 1371, 1359, 1350, 1283, 1259, 1214, 1090, 1049, 1004, 977, 922, 899, 837, 780; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 2.43 (dd, J = 17, 6 Hz, 1H), 2.64 (dd, J = 17, 8 Hz, 1H), 4.04–4.14 (m, 2H), 4.29 (td, J = 16, 3 Hz, 1H), 4.66 (dd, J = 16, 2 Hz, 1H), 5.88–5.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.7, 17.9, 25.6, 39.1, 61.4, 69.0, 124.1, 125.3, 166.5; MS (CI) *m*/*z* 270 (M + H)$^+$, 254, 212, 170, 123, 109, 101, 97, 71, 69; HRMS (CI) *m*/*z* 270.1522 (calcd for $C_{13}H_{24}NO_3Si$: 270.1526).

$C_{13}H_{23}NO_3Si$, M = 269.41, monoclinic, space group $P2_1$, a = 13.645(2), b = 6.180(1) c = 18.791(3) Å, β = 94.73(1)°, V = 1579.2(4) Å^3, T = 290 K, Z = 4, μ(Cu-Kα) = 1.327 mm^{-1}, colorless block, crystal dimensions 0.20 × 0.20 × 0.20 mm. The crystal was oriented from a total of 63 reflections with 5.23 < θ < 23.34°. A total of 3443 data were measured (2.4 < θ < 57.1°), with 2862 independent reflections (merging R_{int} = 0.039). Full matrix least squares based on F^2 yielded the residuals of $R1$ = 0.068, $wR2$ = 0.188, for 328 refined parameters and 7 restraints (floating origin restraint, and distance restraints to aid in the modeling of the disordered TBDMS groups).

The TBDMS groups of both independent molecules found in the asymmetric unit were found to be disordered over two positions, and careful examination of the difference Fourier maps revealed the positions of all the atoms. Two models were considered in the final refinement of the structure: one where the TBDMS group atoms were kept with isotropic displacement parameters (a), and one with fully anisotropic ones (b). Though model (b) yielded slightly lower residuals than (a), it also added several new refined variables. Thus, in order to maintain a favorable data-to-parameter ratio, model (a) was selected as the end point in this refinement. For this refinement, the final value of the absolute structure parameter was −0.01(10) confirming the fact that the depicted model accurately represents the enantiomer of the molecule under study.

(4a*S*,5*S*)-5-(4-Methoxybenzyloxy)-2,4a,5,6-tetrahydro-7*H*-pyrrolo[1,2-*b*]oxazin-7-one (29). Mp 80–90 °C (Et_2O); $[\alpha]_D^{23}$ +86.0 (*c* 0.71, $CHCl_3$); IR (neat) 2898, 2834, 1721, 1610, 1513, 1462, 1354, 1247, 1173, 1090, 1031, 983, 823, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (dd, J = 17, 5 Hz, 1H), 2.63 (dd, J = 17, 7 Hz, 1H), 3.81 (s, 3H), 4.20–4.30 (m, 2H), 4.45 (d, J = 12 Hz, 1H), 4.46–4.55 (m, 1H), 4.54 (d, J = 12 Hz, 1H), 4.80 (dm, J = 17 Hz, 1H), 5.95–6.05 (m, 2H), 6.89 (d, J = 9 Hz, 2H), 7.25 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.1, 55.2, 56.8, 68.3, 69.8, 71.3, 113.9 (2C), 122.4, 125.7, 129.0, 129.3 (2C), 159.4, 168.4; MS (CI) *m*/*z* 276 (M + H)$^+$, 121; HRMS (CI) *m*/*z* 276.1239 (calcd for $C_{15}H_{18}NO_4$: 276.1236).

(4a*R*,5*S*)-5-(4-Methoxybenzyloxy)-2,4a,5,6-tetrahydro-7*H*-pyrrolo[1,2-*b*]oxazin-7-one (30). Oil; $[\alpha]_D^{23}$ −75.5 (*c* 2.45, $CHCl_3$); IR (neat) 2905, 1731, 1614, 1514, 1455, 1359, 1247, 1174, 1030, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (dd, J = 17, 5 Hz, 1H), 2.66 (dd, J = 17, 8 Hz, 1H), 3.81 (s, 3H), 3.90 (ddd, J = 8, 6, 4 Hz, 1H), 4.21–4.35 (m, 2H), 4.48 (d, J = 11 Hz, 1H), 4.53 (d, J = 11 Hz, 1H), 4.68 (dd, J = 15, 3 Hz, 1H), 5.87–5.93 (m, 2H), 6.90 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 55.2, 59.0, 68.6, 71.2, 73.9, 113.9 (2C), 124.4, 125.3, 128.9, 129.3 (2C), 159.5, 167.0; MS (CI) *m*/*z* 276 (M + H)$^+$, 121; HRMS (CI) *m*/*z* 276.1238 (calcd for $C_{15}H_{18}NO_4$: 276.1236).

(*Z*,4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-(3-hydroxyprop-enyl)pyrrolidin-2-one (32)

The oxazine **27** (195 mg, 0.72 mmol) was reduced to **32** (185 mg, 0.68 mmol, 94%) by the protocol below for the conversion of **29** to **33**. Compound **32**: colourless solid; mp 97–98 °C; $[\alpha]_D^{23}$ +18.8 (*c* 0.66, CH_2Cl_2); IR (neat) 3417, 3221, 2926, 1650, 1362, 1256, 1098, 1038, 949, 840, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 2.29 (dd, J = 17, 4 Hz, 1H), 2.56 (dd, J = 17, 6 Hz, 1H), 4.14 (dd, J = 13, 5 Hz, 1H), 4.29 (dd, J = 13, 7 Hz, 1H), 4.46 (td, J = 6, 3 Hz, 1H), 4.53 (dd,

J = 9, 5 Hz), 5.67 (ddt, J = 11, 9, 1 Hz, 1H), 5.87 (ddd, J = 11, 7, 5 Hz, 1H), 6.49 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.9, 18.0, 25.6 (3C), 41.0, 56.1, 58.0, 70.1, 127.2, 133.1, 176.5; MS (CI) *m/z* 272 $(M + H)^+$, 254, 214, 198, 122; HRMS (CI) *m/z* 272.1679 (calcd for $C_{13}H_{26}NO_3Si$: 272.1682).

(*Z*,4*S*,5*S*)-5-(3-Hydroxypropenyl)-4-(4-methoxybenzyloxy)-pyrrolidin-2-one (33)

A stirred suspension of **29** (548 mg, 1.99 mmol) and Na_2HPO_4 (3.40 g, 23.9 mmol) in anhydrous EtOH (40 mL) at 0 °C under Ar was treated with 3 equal portions of 6 wt% Na(Hg) (total of 7.60 g, 19.8 mmol e^-) at 2 hourly intervals. After an additional 14 h at 0 °C, the reaction was quenched with sat. aq. NH_4Cl (20 mL) and the mixture was stirred vigorously for 20 min. The mixture was diluted with H_2O (20 mL) and EtOAc (20 mL) and filtered to remove residual Hg. The collected solids were washed successively with H_2O (10 mL) and EtOAc (3 × 10 mL), and the two layers of the filtrate and combined washings were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield pure **33** (504 mg, 1.82 mmol, 91%) as a colorless solid: mp 112–114 °C (EtOAc); $[\alpha]_D^{23}$ +26.8 (*c* 0.91, $CHCl_3$); IR (KBr) 3253, 1676, 1611, 1510, 1443, 1351, 1304, 1244, 1063, 1033, 1002, 816 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (dd, J = 17, 5 Hz, 1H), 2.53 (dd, J = 17, 7 Hz, 1H), 3.10 (br s, 1H), 3.79 (s, 3H), 4.08 (dd, J = 13, 5 Hz, 1H), 4.19–4.30 (m, 2H), 4.39 (d, J = 11 Hz, 1H), 4.44 (d, J = 11 Hz, 1H), 4.66 (dd, J = 9, 6 Hz, 1H), 5.77 (t, J = 10 Hz, 1H), 5.91 (dt, J = 10, 7 Hz, 1H), 6.87 (d, J = 8 Hz, 2H), 7.09 (br s, 1H), 7.22 (d, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.1, 54.6, 55.2, 58.1, 71.3, 75.1, 113.9 (2C), 127.2, 129.3 (2C), 129.3, 133.2, 159.4, 175.8; MS (FAB) *m/z* 278 $(M + H)^+$, 121; HRMS (FAB) *m/z* 278.1397 (calcd for $C_{15}H_{20}NO_4$: 278.1392).

(1*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1,2,5,7a-tetrahydro-3*H*-pyrrolizin-3-one (34)

The hydroxylactam **32** (104 mg, 0.39 mmol) was transformed to **34** (57.4 mg, 0.23 mmol, 58%) by the protocol below for the conversion of **33** to **35**. The product was purified by column chromatography (eluting with 35% EtOAc in hexanes) to give **34** as a colourless oil: $[\alpha]_D^{23}$ −71.3 (*c* 1.37, CH_2Cl_2); IR (neat) 2926, 2854, 1704, 1471, 1378, 1254, 1085, 942, 837, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.79 (s, 9H), 2.17 (d, J = 16 Hz, 1H), 2.81 (dd, J = 16, 4 Hz, 1H), 3.64 (dm, J = 15 Hz, 1H), 4.33 (ddt, J = 15, 4, 2 Hz, 1H), 4.52 (t, J = 4 Hz, 1H), 4.62–4.65 (m, 1H), 5.67 (dq, J = 6, 2 Hz, 1H), 5.85 (dd, J = 6, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.7, 18.0, 25.5 (3C), 44.8, 50.0, 71.2, 74.1, 126.2, 128.6, 176.5; MS (CI) *m/z* 254 $(M + H)^+$, 238, 196; HRMS (CI) *m/z* 254.1577 (calcd for $C_{13}H_{24}NO_2Si$: 254.1576).

(1*S*,7a*S*)-1-(4-Methoxybenzyloxy)-1,2,5,7a-tetrahydro-3*H*-pyrrolizin-3-one (35)

A stirred solution of **33** (400 mg, 1.44 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C under Ar was treated with Et_3N (0.40 mL, 290 mg, 2.87 mmol) followed by methanesulfonyl chloride (0.17 mL, 252 mg, 2.20 mmol). After stirring for 30 min, the mixture was allowed to warm to rt and stirred for a further 20 min. Sat. aq. NH_4Cl (20 mL) was added and the mixture was stirred vigorously for 5 min. H_2O (10 mL) was added, and the layers were shaken and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield 553 mg of the crude mesylate. This material was immediately dissolved in anhydrous THF (10 mL) and the solution was added dropwise to a stirred solution of freshly prepared lithium diisopropylamide (2.0 mmol) in anhydrous THF (30 mL) at −78 °C under Ar. After stirring at −78 °C for 1.5 h, the mixture was allowed to warm to rt, stirred for a further 30 min, and quenched with aq. NH_4Cl (20 mL). The mixture was diluted with H_2O (10 mL) and EtOAc (15 mL), the layers were shaken, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 5% MeOH in CH_2Cl_2) to yield **35** (326 mg, 1.26 mmol, 88%) as a colourless oil which slowly crystallised upon standing: mp 55–56 °C; $[\alpha]_D^{23}$ −72.0 (*c* 0.50, $CHCl_3$); IR (neat) 2920, 1693, 1612, 1513, 1463, 1392, 1352, 1301, 1246, 1172, 1076, 1031, 939, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (d, J = 17 Hz, 1H), 2.79 (dd, J = 17, 5 Hz, 1H), 3.70 (dm, J = 15 Hz, 1H), 3.79 (s, 3H), 4.29 (t, J = 4 Hz, 1H), 4.37 (d, J = 12 Hz, 1H), 4.43 (ddd, J = 14, 4, 2 Hz, 1H), 4.50 (d, J = 12 Hz, 1H), 4.73–4.80 (m, 1H), 5.86–5.91 (m, 1H), 5.92–5.98 (m, 1H), 6.87 (d, J = 9 Hz, 2H), 7.20 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.8, 49.6, 55.2, 70.3, 72.8, 76.4, 113.7 (2C), 126.0, 129.0 (2C), 129.2, 129.6, 159.2, 175.9; MS (CI) *m/z* 260 $(M + H)^+$, 138, 121; HRMS (CI) *m/z* 260.1283 (calcd for $C_{15}H_{18}NO_3$: 260.1287).

(1*S*,7a*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-7a-hydroxy-1,2,5,7a-tetrahydro-3*H*-pyrrolizin-3-one (36)

A solution of dimethyldioxirane in acetone (1.8 mL, *ca.* 45 μmol) was added to **34** (7.6 mg, 30 μmol) at 0 °C. After stirring of the solution for 2 h, a solution of KOH (1.0 mL, 0.05 M in EtOH) was added, the mixture was filtered through silica gel, and the collected solids were washed with EtOAc–Et_3N (10 : 1). The filtrate and combined washings were concentrated *in vacuo* and the residue was purified by column chromatography [eluting with hexanes–EtOAc–Et_3N (10 : 20 : 1)] to yield **36** (7.4 mg, 28 μmol, 92%) as a colourless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.83 (s, 9H), 2.18 (d, J = 16 Hz, 1H), 3.19 (dd, J = 16, 4 Hz, 1H), 3.83 (br d, J = 16 Hz, 1H), 4.24 (dt, J = 16, 1 Hz, 1H), 4.41 (d, J = 4 Hz, 1H), 5.40 (br OH), 5.86 (dt, J = 6, 2 Hz, 1H), 6.06 (br d, J = 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.7, 18.0, 25.6 (3C), 43.2, 48.5, 75.2, 105.2, 129.3, 130.6, 177.3; MS (CI) *m/z* 270 $(M + H)^+$, 252 $(M - OH)^+$, 194, 152; HRMS (CI) *m/z* 270.1527 (calcd for $C_{13}H_{24}NO_3Si$: 270.1526).

(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1,2-dihydro-3*H*-pyrrolizin-3-one (37)

A solution of acetic acid (2 mL, 50% v/v in CH_2Cl_2) was added to **36** (1.0 mg, 3.7 μmol). After stirring at rt for 10 min, the solution was concentrated *in vacuo* to yield pure **37** (0.9 mg, 3.7 μmol, 100%) as a colourless oil: $[\alpha]_D^{23}$ −24.7 (*c* 1.79, CH_2Cl_2); IR (neat) 2953, 2927, 2856, 1763, 1463, 1393, 1294, 1274, 1086, 936, 837, 779 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 2.88 (dd, J = 18, 3 Hz, 1H), 3.34 (dd, J = 18, 7 Hz, 1H), 5.28 (ddd, J = 7, 3, 1 Hz, 1H), 6.13 (dd, J = 2, 1 Hz, 1H), 6.46 (t, J = 3 Hz, 1H), 7.02 (dd, J = 3, 1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.6, 18.1, 25.7 (3C), 46.2, 62.9, 106.2, 111.5, 119.1, 142.0, 169.5; MS (CI) *m/z* 252 $(M + H)^+$, 194, 152, 120; HRMS (CI) *m/z* 252.1420 (calcd for $C_{13}H_{22}NO_2Si$: 252.1420).

(1*R*,2*R*,4*S*,9*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-3-oxa-6-azatricyclo[4.3.0.0^{2,4}]nonan-7-one

A stirred suspension of **34** (14.0 mg, 55 μmol) and sodium carbonate (11.7 mg, 0.11 mmol) in 1,2-dichloroethane (3 mL) was treated with 2,6-di-*tert*-butyl-4-methylphenol (BHT, 0.6 mg) followed by anhydrous 3-chloroperbenzoic acid (43 mg, 0.25 mmol). The stirred mixture was heated at reflux for 3 h, additional portions of sodium carbonate and 3-chloroperoxy-

benzoic acid (as before) were added, and heating was continued for a further 2 h. The mixture was allowed to cool, diluted with CH_2Cl_2 (10 mL), and shaken with 5% w/v aq. NaOH (5 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed successively with 5% w/v aq. NaOH (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 50–60% EtOAc in hexanes) to yield the title compound (7.5 mg, 28 μmol, 50%) as a colourless oil: $[\alpha]_D^{23}$ −2.1 (*c* 1.67, CH_2Cl_2); IR (neat) 2926, 2854, 1705, 1357, 1255, 1169, 1081, 944, 836, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 2.18 (d, *J* = 16 Hz, 1H), 2.77 (dd, *J* = 16, 4 Hz, 1H), 3.28 (d, *J* = 13 Hz, 1H), 3.78 (d, *J* = 3 Hz, 1H), 3.83 (dd, *J* = 13, 2 Hz, 1H), 3.89 (t, *J* = 3 Hz, 1H), 4.05 (d, *J* = 4 Hz, 1H), 4.58 (t, *J* = 4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.5, 17.9, 25.6 (3C), 44.3, 46.5, 58.2, 59.6, 68.6, 70.0, 176.5; MS (CI) *m*/*z* 270 $(M + H)^+$, 254, 212, 196; HRMS (CI) *m*/*z* 270.1523 (calcd for $C_{13}H_{24}NO_3Si$: 270.1526).

(1*R*,2*R*,4*S*,9*S*)-9-Hydroxy-3-oxa-6-azatricyclo[4.3.0.0^{2,4}]nonan-7-one (38)

To a stirred solution of (1*R*,2*R*,4*S*,9*S*)-9-[(*tert*-butyldimethylsilyl)oxy]-3-oxa-6-azatricyclo[4.3.0.0^{2,4}]nonan-7-one prepared above (2.5 mg, 9.3 μmol) in THF (1 mL) at 0 °C was added a solution of tetra-*n*-butylammonium fluoride (TBAF, 10 μL, 10 μmol, 1.0M in THF). After stirring at 0 °C for 1 h, the mixture was filtered through a pad of silica gel and the collected solids were washed with MeOH–$CHCl_3$ (1 : 9, 30 mL). The filtrate and combined washings were concentrated *in vacuo* to give pure **38** (1.4 mg, 9.0 μmol, 97%) as a colourless oil which crystallized upon standing: ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (d, *J* = 17 Hz, 1H), 2.89 (dd, *J* = 17, 4 Hz, 1H), 3.28 (d, *J* = 13 Hz, 1H), 3.87 (dd, *J* = 13, 2 Hz, 1H), 3.92–3.96 (m, 2H), 4.07 (d, *J* = 4 Hz, 1H), 4.66 (t, *J* = 4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 44.6, 46.3, 57.7, 59.9, 68.1, 69.3, 176; MS (CI) *m*/*z* 156 $(M + H)^+$, 155, 154, 140, 138, 126; HRMS (CI) *m*/*z* 156.0659 (calcd for $C_7H_{10}NO_3$: 156.0661).

Ethyl [(1*R*,2*R*,4*S*,9*S*)-9-hydroxy-7-oxo-3,6-diazatricyclo-[4.3.0.0^{2,4}]nonan-3-yl]formate (40)

To a solution of **34** (27.6 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added *O*-ethyl *N*-(4-nitrophenyl)sulfonyloxycarbamate[23a] (**39**, 95 mg, 0.33 mmol) followed by calcium oxide (18 mg, 0.33 mmol). The mixture was stirred for 8 h at rt and then a further quantity of **39** (95 mg, 0.33 mmol) and calcium oxide (18 mg, 0.33 mmol) were added. After stirring for an additional 20 h, the mixture was filtered through a Celite pad and the collected solids were washed with CH_2Cl_2. The filtrate and combined washings were concentrated *in vacuo* and the residue was purified by column chromatography (eluting with 66% EtOAc in hexanes) to yield 12.7 mg of the desired aziridine contaminated by some diethyl azodicarboxylate. The crude aziridine was immediately dissolved in THF (1 mL), and the solution was cooled to 0 °C and treated with tetra-*n*-butylammonium fluoride (36 μL, 1.0 M in THF, 36 μmol). After stirring for 2 h, silica gel was added to the mixture which was concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 10% MeOH in $CHCl_3$) to give **40** (5.5 mg, 25 μmol, 22% for two steps) as a colourless oil: $[\alpha]_D^{23}$ +31.5 (*c* 0.27, CH_2Cl_2); IR (neat) 3329, 2982, 1694, 1462, 1373, 1252, 1182, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7 Hz, 3H), 2.28 (d, *J* = 17 Hz, 1H), 2.88 (dd, *J* = 17, 4 Hz), 3.26 (d, *J* = 13 Hz, 1H), 3.52 (t, *J* = 5 Hz, 1H), 3.59 (d, *J* = 5 Hz, 1H), 3.90 (dd, *J* = 13, 4 Hz, 1H), 4.08 (d, *J* = 4 Hz, 1H), 4.19 (q, *J* = 7 Hz, 2H), 4.64 (t, *J* = 4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 42.9, 44.5, 45.7, 45.8, 63.0, 68.2, 69.1, 161.5, 175.5; MS (CI) *m*/*z* 227 $(M + H)^+$, 197, 154, 138; HRMS (CI) *m*/*z* 227.1028 (calcd for $C_{10}H_{15}N_2O_4$: 227.1032).

(1*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (41)

A solution of **34** (5.6 mg, 22 μmol) in THF (2 mL) at rt was treated with lithium aluminium hydride (7 mg, 0.18 mmol) and stirred for 4 h, after which $Na_2SO_4 \cdot 10H_2O$ (250 mg) was added and the mixture was stirred for a further 15 min. The resulting suspension was filtered through a Celite pad and the collected solids were washed with MeOH–$CHCl_3$ (1 : 9, 20 mL). The filtrate and combined washings were concentrated *in vacuo* and the residue was purified by column chromatography (eluting with 10% MeOH in $CHCl_3$) to yield **41** (1.8 mg, 7.5 μmol, 34%) as a colourless oil: IR (neat) 2950, 2925, 2852, 1461, 1256, 1176, 1125, 1062, 931, 840, 783; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.95–2.09 (m, 1H), 2.27 (tdd, *J* = 12, 7, 3 Hz, 1H), 3.06 (td, *J* = 11, 6 Hz, 1H), 3.55–3.69 (m, 1H), 3.95–4.03 (m, 1H), 4.45–4.55 (m, 2H), 4.95–5.02 (m, 1H), 5.65–5.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.8, 17.9, 25.6 (3C), 29.8, 36.1, 60.5, 62.8, 70.7, 124.7, 125.0; MS (CI) *m*/*z* 240 $(M + H)^+$, 238, 224, 182; HRMS (CI) *m*/*z* 240.1777 (calcd for $C_{13}H_{26}NOSi$: 240.1784).

(1*R*,2*S*,7S,7a*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1,2-dihydroxyhexahydro-1*H*-pyrrolizin-5-one (42)

The olefin **34** (6.5 mg, 26 μmol) was oxidized to **42** (6.6 mg, 23 μmol, 89%) by the same protocol used below for the conversion of **35** to **43**. The crystalline diol **42** exhibited the following spectral characteristics: ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 2.25 (d, *J* = 17 Hz, 1H), 2.83 (dd, *J* = 17, 5 Hz, 1H), 3.11 (dd, *J* = 13, 6 Hz, 1H), 3.88 (dd, *J* = 13, 5 Hz, 1H), 3.98 (t, *J* = 6 Hz, 1H), 4.27–4.35 (m, 2H), 4.57 (t, *J* = 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.7, 18.1, 25.7 (3C), 44.6, 48.0, 68.0, 69.7, 70.1, 73.0, 174.0.

$C_{13}H_{25}NO_4Si$, *M* = 287.43, monoclinic, space group *C*2, *a* = 14.546(1), *b* = 6.262(1), *c* = 35.155(3) Å, β = 98.72(1)°, *V* = 3165.2(6) Å^3, *T* = 290 K, *Z* = 8, μ(Cu-Kα) = 1.401 mm^{-1}, colorless block, crystal dimensions 0.20 × 0.20 × 0.20 mm. The crystal was oriented from a total of 92 reflections with 5.09 < θ < 24.73°. A total of 3443 data were measured (5.1 < θ < 67.6°), with 3006 independent reflections (merging R_{int} = 0.046). Full matrix least squares based on F^2 yielded the residuals of *R*1 = 0.0510, *wR*2 = 0.1329, for 346 refined parameters and one restraint (floating origin restraint). The absolute structure coefficient refined to a value of 0.00(4) indicating the model presented corresponds to the correct enantiomer of the compound examined.

(1*R*,2*S*,7S,7a*S*)-1,2-Dihydroxy-7-(4-methoxybenzyloxy)hexahydro-1*H*-pyrrolizin-5-one (43)

A stirred solution of **35** (100 mg, 386 μmol) in acetone (5 mL) at rt was treated with a solution of *N*-methylmorpholine *N*-oxide (137 mg, 1.17 mmol) in H_2O (1 mL) followed by 4 wt% aq. osmium tetraoxide (0.24 mL, 250 mg, 39 μmol). After stirring for 30 h, sat. aq. $Na_2S_2O_3$ (5 mL) was added to the mixture which was vigorously stirred for a further 10 min. The mixture was diluted with H_2O (10 mL) and CH_2Cl_2 (15 mL), and the layers were shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 7% MeOH in CH_2Cl_2) to give **43** (74 mg, 252 μmol, 65%) as a colourless oil: $[\alpha]_D^{23}$ +15.4 (*c* 2.35, $CHCl_3$); IR (neat) 1653, 1512, 1440, 1301, 1246, 1173, 1073, 1030, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 (d, *J* = 17 Hz, 1H), 2.76 (dd, *J* = 17, 5 Hz, 1H), 3.12 (d, *J* = 13 Hz, 1H), 3.22 (br s, 1H), 3.42 (br s, 1H), 3.77 (d, *J* = 5 Hz, 1H), 3.80 (s, 3H), 4.04 (dd, *J* = 6, 6 Hz, 1H), 4.25–4.36 (m, 3H), 4.43 (d, *J* = 11 Hz, 1H), 4.52 (d, *J* = 11 Hz, 1H), 6.87 (d, *J* = 9 Hz, 2H), 7.23 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.3, 48.2,

55.2, 68.9, 69.2, 71.0, 72.8, 73.1, 113.8 (2C), 129.2 (2C), 129.4, 159.3, 173.8; MS (FAB) *m/z* 294 $(M + H)^+$, 148, 121; HRMS (FAB) *m/z* 294.1346 (calcd for $C_{15}H_{20}NO_5$: 294.1342).

(1*R*,2*S*,7S,7a*S*)-1,2-Dihydroxy-7-(4-methoxybenzyloxy)hexahydro-1*H*-pyrrolizine–borane (44)

A stirred solution of **43** (74 mg, 252 μmol) in anhydrous THF (25 mL) at rt under Ar was treated dropwise with borane–dimethyl sulfide complex (0.75 mL, 600 mg, 7.89 mmol). The resulting mixture was stirred for 4 h and MeOH (10 mL) was added. After a further 30 min the solvent was removed *in vacuo*, and the residue was re-dissolved in MeOH (5 mL). The solution was again concentrated *in vacuo* to yield pure **44** (74 mg, 252 μmol, 100%) as a colourless crystalline solid: mp 117–119 °C ($CHCl_3$); $[\alpha]_D^{23}$ +35.8 (*c* 1.20, $CHCl_3$); IR (KBr) 3460, 2928, 1611, 1513, 1459, 1343, 1303, 1252, 1220, 1158, 1104, 1081, 1034, 955, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (ddt, $J = 13$, 6, 3 Hz, 1H), 2.20 (dddd, $J = 13$, 11, 7, 4 Hz, 1H), 2.87 (br s, 1H), 2.98 (td, $J = 11$, 6 Hz, 1H), 3.08 (br s, 1H), 3.20 (dd, $J = 12$, 6 Hz, 1H), 3.31 (ddd, $J = 10$, 7, 3 Hz, 1H), 3.39 (dd, $J = 12$, 7 Hz, 1H), 3.75 (dd, $J = 6$, 2 Hz, 1H), 3.81 (s, 3H), 4.20–4.25 (m, 1H), 4.32–4.40 (m, 2H), 4.40 (d, $J = 11$ Hz, 1H), 4.51 (d, $J = 11$ Hz, 1H), 6.89 (d, $J = 8$ Hz, 2H), 7.22 (d, $J = 8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 55.3, 62.7, 66.6, 71.3, 71.7, 72.2, 77.6, 82.0, 113.9 (2C), 129.3 (2C), 129.3, 159.4; MS (FAB) *m/z* 292 $(M - H)^+$, 280, 162, 148, 121; HRMS (FAB) *m/z* 280.1552 (calcd for $C_{15}H_{22}NO_4$: 280.1549).

$C_{15}H_{24}NO_4B$, $M = 293.16$, orthorhombic, space group $P2_12_12_1$, $a = 8.480(1)$, $b = 9.322(2)$, $c = 20.143(3)$ Å, $V = 1592.3(5)$ Å^3, $T = 290$ K, $Z = 4$, μ(Cu-Kα) = 0.702 mm^{-1}, colorless block, crystal dimensions 0.40 × 0.40 × 0.10 mm. The crystal was oriented from a total of 65 reflections with $7.25 < \theta < 26.48°$. A total of 3209 data were measured ($4.4 < \theta < 67.8°$), with 2654 independent reflections (merging $R_{int} = 0.069$). Full matrix least squares based on F^2 yielded the residuals of $R1 = 0.0447$, $wR2 = 0.0955$, for 214 refined parameters. The absolute structure coefficient refined to a value of 0.1(3) indicating the model presented corresponds to the correct enantiomer of the compound examined.

Tosylation of 44

A solution of **44** (18 mg, 61.4 μmol) and Et_3N (43 μL, 31 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at rt under Ar was treated with toluene-4-sulfonyl chloride (23 mg, 0.12 mmol) and stirred for 44 h. The mixture was diluted with additional CH_2Cl_2 (5 mL) and shaken with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$–H_2O (1 : 1, 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue (31 mg) was dissolved in MeOH (5 mL), treated with Pearlman's catalyst (40 mg, 20 wt% Pd, 50% wetted), and stirred for 30 h. After filtration through a Celite pad, the filtrate was concentrated *in vacuo* and the residue purified by column chromatography (eluting with 3–10% MeOH in CH_2Cl_2) to yield, in order of elution, the ditosylate **46** (7.5 mg, 12.8 μmol, 21%) and monotosylate **45** (15.3 mg, 35.3 μmol, 57%), both as colourless oils.

(1*R*,2*S*,7*S*,7a*S*)-1-Hydroxy-7-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]oxy}hexahydro-1*H*-pyrrolizine (45). $[\alpha]_D^{23}$ +6.2 (*c* 0.33, $CHCl_3$); IR (neat) 2931, 1513, 1359, 1247, 1175, 1034, 815, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72–1.85 (m, 1H), 2.05 (dd, $J = 13$, 6 Hz, 1H), 2.10–2.25 (m, OH), 2.43 (s, 3H), 2.50 (ddd, $J = 12$, 9, 6 Hz, 1H), 2.73 (dd, $J = 12$, 5 Hz), 3.09 (t, $J = 8$ Hz, 1H), 3.17 (dd, $J = 12$, 6 Hz, 1H), 3.50 (t, $J = 4$ Hz, 1H), 3.82 (s, 3H), 4.00 (t, $J = 4$ Hz, 1H), 4.37 (d, $J = 11$ Hz, 1H), 4.43 (t, $J = 4$ Hz, 1H), 4.50 (d, $J = 11$ Hz, 1H), 4.95 (q, $J = 5$ Hz, 1H), 6.90 (d, $J = 9$ Hz, 2H), 7.22 (d, $J = 9$ Hz, 2H), 7.28 (d, $J = 10$ Hz, 2H), 7.76 (d, $J = 10$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 32.3, 53.0, 55.3, 55.9, 70.2, 70.7, 73.1, 77.0, 82.1, 113.9 (2C), 127.9 (2C), 129.0 (2C), 129.9 (2C), 130.2, 133.3, 145.0, 159.2; MS (FAB) *m/z* 434 $(M + H)^+$, 280, 149, 121; HRMS (FAB) *m/z* 434.1634 (calcd for $C_{22}H_{28}NO_6S$: 434.1637).

(1*R*,2*S*,7*S*,7a*R*)-1,2-Bis{[(4-methylphenyl)sulfonyl]oxy}-7-[(4-methoxybenzyl)oxy]hexahydro-1*H*-pyrrolizine (46). $[\alpha]_D^{23}$ +13.2 (*c* 0.37, $CHCl_3$); IR (neat) 2919, 1513, 1365, 1176, 1033, 813, 670, 554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (tdd, $J = 13$, 7, 3 Hz, 1H), 2.06 (dd, $J = 13$, 5 Hz, 1H), 2.42 (s, 6H), 2.42–2.50 (m, 1H), 2.71 (dd, $J = 12$, 5 Hz, 1H), 3.09 (t, $J = 8$ Hz, 1H), 3.17 (dd, $J = 12$, 6 Hz, 1H), 3.66 (t, $J = 4$ Hz, 1H), 3.84 (s, 3H), 3.89 (t, $J = 4$ Hz, 1H), 4.26 (d, $J = 11$ Hz, 1H), 4.45 (d, $J = 11$ Hz, 1H), 4.89 (q, $J = 5$ Hz, 1H), 5.04 (dd, $J = 5$, 4 Hz, 1H), 6.90 (d, $J = 9$ Hz, 2H), 7.17 (d, $J = 9$ Hz, 2H), 7.24 (d, $J = 8$ Hz, 2H), 7.25 (d, $J = 8$ Hz, 2H), 7.68 (d, $J = 8$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7 (2C), 32.2, 52.9, 55.3, 55.9, 70.5, 71.3, 76.8, 77.2, 78.4, 113.9 (2C), 128.0 (4C), 129.0 (2C), 129.7 (4C), 130.1, 133.3, 144.8, 159.3; MS (FAB) *m/z* 588 $(M + H)^+$, 434, 121; HRMS (FAB) *m/z* 588.1715 (calcd for $C_{29}H_{34}NO_8S_2$: 588.1726).

(1*R*,2*S*,7*S*,7a*R*)-1,2-Bis{[(4-methylphenyl)sulfonyl]oxy}-7-hydroxyhexahydro-1*H*-pyrrolizine

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2.3 mg, 10.1 μmol) in CH_2Cl_2 (0.5 mL) was added to **46** (3.0 mg, 5.1 μmol) and the mixture was stirred for 3.5 h at rt. At this time, H_2O (25 μL) was added and stirring was continued for 1.5 h. Solid Na_2SO_4 (1 g) was added, and the mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 5% MeOH in CH_2Cl_2) to yield the title compound (1.9 mg, 4.1 μmol, 80%) as a colourless oil: $[\alpha]_D^{23}$ +7.1 (*c* 0.09, $CHCl_3$); IR (neat) 2921, 1364, 1190, 1175, 1031, 813, 554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91–2.10 (m, 2H), 2.45 (s, 3H), 2.47 (s, 3H), 2.58 (ddd, $J = 11$, 9, 7 Hz, 1H), 2.73 (dd, $J = 12$, 4 Hz, 1H), 3.11 (t, $J = 8$ Hz, 1H), 3.25 (dd, $J = 12$, 3 Hz, 1H), 3.73 (dd, $J = 5$, 5 Hz, 1H), 4.27 (t, $J = 4$ Hz, 1H), 4.97–5.05 (m, 2H), 7.31 (d, $J = 9$ Hz, 2H), 7.34 (d, $J = 9$ Hz, 2H), 7.74 (d, $J = 8$ Hz, 2H), 7.77 (d, $J = 8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7 (2C), 37.2, 52.6, 56.6, 69.3, 70.9, 75.6, 81.0, 128.0 (2C), 129.8, 129.9, 132.9, 133.5, 144.9, 145.3; MS (FAB) *m/z* 468 $(M + H)^+$, 314; HRMS (FAB) *m/z* 468.1156 (calcd for $C_{21}H_{26}NO_7S_2$: 468.1151).

[(3*S*,4*S*,6*S*,9*R*)-5-Oxa-1-azatricyclo[4.2.1.0^{4,9}]nonan-3-yl] 4-methylbenzenesulfonate (47)

A solution of the alcohol prepared above (2.3 mg, 4.9 μmol) in MeOH–H_2O (5 : 1, 1.2 mL) was treated with K_2CO_3 (2.7 mg, 20 μmol) and the mixture was stirred at a gentle reflux for 5 h. The mixture was allowed to cool and was concentrated *in vacuo*. The residue was taken up into CH_2Cl_2 (5 mL) and H_2O (5 mL), and the layers were shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude oil was purified by column chromatography (eluting with 5% MeOH in CH_2Cl_2) to furnish **47** (1.1 mg, 3.7 μmol, 76%) as a colourless oil: IR (neat) 2915, 1366, 1176, 973, 834, 554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, loline numbering is used for assignment) δ 1.84 (dtd, $J = 15$, 8, 4 Hz, 1H, $H6_A$), 2.00 (ddd, $J = 15$, 7, 5 Hz, 1H, $H6_B$), 2.46 (s, 3H, Ts), 2.95 (dt, $J = 11$, 7 Hz, 1H, $H5_A$), 3.10 (dd, $J = 13$, 5 Hz, 1H, $H3_A$), 3.24 (ddd, $J = 11$, 8, 4 Hz, 1H, $H5_B$), 3.45 (dd, $J = 13$, 6 Hz, 1H, $H3_B$), 4.18 (t, $J = 3$ Hz, 1H, H8), 4.84 (d, $J = 3$ Hz, 1H, H1), 4.92 (t, $J = 5$ Hz, 1H, H2), 5.05 (t, $J = 4$ Hz, 1H, H7), 7.36 (d, $J = 8$ Hz, 2H, Ts), 7.79 (d, $J = 8$ Hz, 2H, Ts); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 33.8, 55.1, 60.7, 68.6, 83.5, 83.9, 84.4, 127.9 (2C), 130.0 (2C), 133.2, 145.1; MS (FAB) *m/z* 296 $(M + H)^+$, 142; HRMS (FAB) *m/z* 296.0961 (calcd for $C_{14}H_{18}NO_4S$: 296.0957).

Deprotection of 45

A solution of **45** (4.0 mg, 9.2 μmol) in MeCN–H_2O (5 : 1, 1.2 mL) at rt was treated with ceric ammonium nitrate (CAN, 30 mg, 55 μmol) and the mixture was stirred for 21 h. A further quantity of CAN (10 mg, 18 μmol) was added and stirring was continued for 2 h. The mixture was diluted with CH_2Cl_2 (10 mL) and shaken with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 5–15% MeOH in CH_2Cl_2) to afford, in order of elution, **49** (1.0 mg, 2.2 μmol, 24%) followed by **48** (1.0 mg, 3.2 μmol, 35%), both as colourless oils.

(1*R*,2*S*,7*S*,7a*R*)-1,7-Dihydroxy-2-{[(4-methylphenyl)sulfonyl]-oxy}hexahydro-1*H*-pyrrolizine (48). $[a]_D^{23}$ +5.9 (*c* 0.09, $CHCl_3$); IR (neat) 2914, 1352, 1174, 1018, 910, 814, 670, 554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85–1.92 (m, 1H), 1.98 (ddd, *J* = 12, 8, 4 Hz, 1H), 2.46 (s, 3H), 2.60 (ddd, *J* = 11, 9, 6 Hz, 1H), 2.78 (dd, *J* = 12, 5 Hz, 1H), 3.13 (tm, *J* = 7 Hz, 1H), 3.21 (dd, *J* = 12, 5 Hz, 1H), 3.47 (t, *J* = 5 Hz, 1H), 4.37 (td, *J* = 4, 1 Hz, 1H), 4.44 (t, *J* = 6 Hz, 1H), 5.05 (q, *J* = 5 Hz, 1H), 7.36 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 36.9, 52.8, 56.2, 70.0, 73.6, 82.7, 128.0 (2C), 130.0 (2C), 133.3, 145.2; MS (FAB) *m*/*z* 314 $(M + H)^+$, 154, 136; HRMS (FAB) *m*/*z* 314.1058 (calcd for $C_{14}H_{20}NO_5S$: 314.1062).

(1*R*,2*S*,7*S*,7a*S*)-1-Hydroxy-7-[(4-methoxybenzoyl)oxy]-2-{[(4-methylphenyl)sulfonyl]oxy}hexahydro-1*H*-pyrrolizine (49). IR (neat) 2911, 2845, 1714, 1604, 1360, 1256, 1174, 1097, 1022, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12–2.18 (m, 2H), 2.44 (s, 3H), 2.63 (q, *J* = 9 Hz, 1H), 2.87 (dd, *J* = 12, 5 Hz, 1H), 3.20–3.27 (m, 1H), 3.30 (dd, *J* = 12, 5 Hz, 1H), 3.73 (t, *J* = 5 Hz, 1H), 3.89 (s, 3H), 4.24 (t, *J* = 4 Hz, 1H), 5.12 (q, *J* = 5 Hz, 1H), 5.48 (dt, *J* = 5, 3 Hz, 1H), 6.96 (d, *J* = 7 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H), 7.97 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, quaternary carbons not observed) δ 21.7, 34.3, 53.1, 55.5, 55.7, 70.5, 72.2, 73.7, 81.8, 113.9 (2C), 127.9 (2C), 129.9 (2C), 131.7 (2C); MS (FAB) *m*/*z* 448 $(M + H)^+$, 294, 135; HRMS (FAB) *m*/*z* 448.1489 (calcd for $C_{22}H_{26}NO_7S$: 448.1430).

Aminohydroxylation of 35 (Table 2, entry 4)

A stirred solution of **35** (39.1 mg, 151 μmol) and $(DHQD)_2$-PHAL (29 mg, 38 μmol, 25 mol%) in *t*-BuOH–H_2O (1 : 1, 3.5 mL) at rt was treated with chloramine-T dihydrate (99 mg, 376 μmol, 2.5 eq.). Potassium osmate was added in three equal portions of 0.6 mg (1.6 μmol, 1 mol%) at 24 h intervals and after addition of the final portion, the mixture was stirred for a further 24 h. Sat. aq. $NaHSO_3$ (5 mL) was added and the mixture was stirred vigorously for 15 min. The mixture was diluted with H_2O (5 mL) and CH_2Cl_2 (10 mL), and the resultant layers were shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the extract was washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 5–10% MeOH in CH_2Cl_2) to afford, in order of elution, a mixture of sulfonamides **50** and **51** (35.2 mg, 79 μmol, 52%, colourless oil) followed by **43** (9.5 mg, 32 μmol, 21%, colourless oil). ^1H NMR analysis of the mixture of sulfonamides indicated a ratio **50** : **51** = 75 : 25. The isomers could be separated by careful column chromatography (eluting with 5% MeOH in CH_2Cl_2) with **51** eluting first.

***N*-[(1*R*,2*S*,7*S*,7a*S*)-2-Hydroxy-7-(4-methoxybenzyloxy)-5-oxohexahydro-1*H*-pyrrolizin-1-yl]-4-methylbenzenesulfonamide (50).** $[a]_D^{23}$ −15.4 (*c* 0.07, $CHCl_3$); IR (neat) 1667, 1513, 1435, 1328, 1246, 1157, 1091, 815, 678, 565 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.46 (d, *J* = 17 Hz, 1H), 2.72 (dd, *J* = 17, 5 Hz, 1H), 3.10 (d, *J* = 13 Hz, 1H), 3.75 (dd, *J* = 13, 6 Hz, 1H), 3.80–3.84 (m, 1H), 3.83 (s, 3H), 4.07 (dd, *J* = 8, 5 Hz, 1H), 2.10 (t, *J* = 5 Hz, 1H), 4.22–4.27 (m, 1H), 4.31 (d, *J* = 11 Hz, 1H), 4.39 (d, *J* = 11 Hz, 1H), 5.23 (br d, *J* = 7 Hz, NH), 6.89 (d, *J* = 9 Hz, 2H), 7.20 (d, *J* = 9 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 40.6, 49.3, 53.3, 55.3, 67.7, 70.9, 72.0, 72.8, 113.9 (2C), 127.2 (2C), 129.3, 129.5 (2C), 129.9 (2C), 136.4, 144.0, 159.4, 173.4; MS (FAB) *m*/*z* 469 $(M + Na)^+$, 447 $(M + H)^+$, 121; HRMS (FAB) *m*/*z* 447.1591 (calcd for $C_{22}H_{27}N_2O_6S$: 447.1590).

***N*-[(1*R*,2*S*,7*S*,7a*S*)-1-Hydroxy-7-(4-methoxybenzyloxy)-5-oxohexahydro-1*H*-pyrrolizin-2-yl]-4-methylbenzenesulfonamide (51).** $[a]_D^{23}$ −16.6 (*c* 1.16, $CHCl_3$); IR (neat) 2917, 1670, 1336, 1246, 1160, 1091, 1031, 815, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.45 (d, *J* = 17 Hz, 1H), 2.63 (dd, *J* = 17, 5 Hz, 1H), 2.80 (dd, *J* = 12, 9 Hz, 1H), 3.52–3.58 (m, 1H), 3.82–3.86 (m, 1H), 3.83 (s, 3H), 3.94 (dd, *J* = 5, 3 Hz, 1H), 4.26 (t, *J* = 5 Hz, 1H), 4.27 (d, *J* = 11 Hz, 1H), 4.40 (dd, *J* = 6, 3 Hz, 1H), 4.49 (d, *J* = 11 Hz, 1H), 4.98–5.03 (m, NH), 6.91 (d, *J* = 7 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.66 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 39.4, 45.4, 55.3, 56.0, 69.1, 70.4, 71.4, 74.3, 113.9 (2C), 127.1 (2C), 129.2 (2C), 129.3, 129.9 (2C), 136.5, 143.9, 159.4, 175.0; MS (FAB) *m*/*z* 447 $(M + H)^+$, 121; HRMS (FAB) *m*/*z* 447.1593 (calcd for $C_{22}H_{27}N_2O_6S$: 447.1590).

***N*-[(1*R*,2*S*,7*S*,7a*S*)-2-Hydroxy-7-(4-methoxybenzyloxy)-5-oxohexahydro-1*H*-pyrrolizin-1-yl]-4,*N*-dimethylbenzenesulfonamide (52)**

A solution of **50** (62 mg, 139 μmol) in *t*-BuOH (4 mL) at rt was treated with potassium *tert*-butoxide (20 mg, 180 μmol), and the mixture was stirred for 15 min. Methyl iodide (0.17 mL, 388 mg, 2.73 mmol) was added and the solution was heated at 50 °C. After 16 h the solution was allowed to cool, and H_2O (10 mL) and CH_2Cl_2 (15 mL) were added. The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 5% MeOH in CH_2Cl_2) to yield **52** (48.5 mg, 105 μmol, 76%) as a clear oil: $[a]_D^{23}$ +49.0 (*c* 0.55, $CHCl_3$); IR (neat) 3373, 2929, 1687, 1514, 1335, 1249, 1155, 1088, 1032, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.48 (d, *J* = 17 Hz, 1H), 2.64 (dd, *J* = 17, 5 Hz, 1H), 2.76–2.79 (m, 1H), 2.89 (s, 3H), 3.12 (dd, *J* = 13, 3 Hz, 1H), 3.82 (s, 3H), 3.85 (dd, *J* = 13, 6 Hz, 1H), 3.94 (t, *J* = 5 Hz, 1H), 4.09 (dd, *J* = 8, 5 Hz, 1H), 4.10 (d, *J* = 11 Hz, 1H), 4.21 (dd, *J* = 8, 5 Hz, 1H), 4.30 (d, *J* = 12 Hz, 1H), 4.60–4.66 (m, 1H), 6.84 (d, *J* = 9 Hz, 2H), 6.99 (d, *J* = 9 Hz, 2H), 7.25 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 34.2, 39.8, 48.2, 55.3, 58.2, 65.0, 69.9, 72.8, 73.7, 113.9 (2C), 127.6 (2C), 128.7, 129.5 (2C), 129.8 (2C), 134.4, 144.0, 159.5, 172.7; MS (FAB) *m*/*z* 461 $(M + H)^+$, 121; HRMS (FAB) 461.1740 (calcd for $C_{23}H_{29}N_2O_6S$: 461.1746).

{(1*R*,2*S*,7*S*,7a*S*)-7-(4-Methoxybenzyloxy)-1-[methyl(4-tolylsulfonyl)amino]-5-oxohexahydro-1*H*-pyrrolizin-2-yl} methanesulfonate (53)

To a stirred solution of **52** (48.5 mg, 105 μmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under Ar, was added Et_3N (50 μL, 36 mg, 359 μmol) followed by methanesulfonyl chloride (16 μL, 24 mg, 207 μmol) using dropwise addition. After stirring for 15 min, the mixture was shaken with sat. aq. $NaHCO_3$ (5 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated

in vacuo to yield pure **53** (56 mg, 104 μmol, 99%) as a colourless solid: mp 187–190 °C (decomp.); $[\alpha]_D^{23}$ +66.1 (*c* 0.70, $CHCl_3$); IR (KBr) 2928, 1696, 1517, 1350, 1247, 1166, 1071, 981, 907, 679, 548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.46 (d, *J* = 17 Hz, 1H), 2.61 (dd, *J* = 17, 5 Hz, 1H), 2.88 (s, 3H), 3.14 (s, 3H), 3.44 (dd, *J* = 14, 2 Hz, 1H), 3.81 (s, 3H), 3.94 (t, *J* = 5 Hz, 1H), 4.04 (dd, *J* = 14, 6 Hz, 1H), 4.09 (d, *J* = 12 Hz, 1H), 4.22 (dd, *J* = 9, 5 Hz, 1H), 4.24 (d, *J* = 12 Hz, 1H), 4.56 (dd, *J* = 9, 6 Hz, 1H), 5.35 (td, *J* = 5, 3 Hz, 1H), 6.83 (d, *J* = 9 Hz, 2H), 6.93 (d, *J* = 9 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H), 7.68 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 33.0, 38.4, 39.4, 47.9, 55.3, 56.2, 64.1, 69.7, 71.3, 83.0, 114.0 (2C), 127.5 (2C), 128.3, 129.5 (2C), 129.8 (2C), 135.5, 144.0, 159.6, 172.7; MS (FAB) *m*/*z* 534 $(M + H)^+$, 185, 121; HRMS (FAB) *m*/*z* 539.1517 (calcd for $C_{24}H_{31}N_2O_8S_2$: 539.1522).

{(1*R*,2*S*,7*S*,7a*S*)-7-(4-Methoxybenzyloxy)-1-[methyl(4-tolylsulfonyl)amino]hexahydro-1*H*-pyrrolizin-2-yl} methanesulfonate (54)

A stirred solution of **53** (21.2 mg, 39.4 μmol) in anhydrous THF (10 mL) at rt under Ar, was treated with a large excess of borane–dimethyl sulfide complex (0.12 mL, 10 M neat, 1.2 mmol, 30 eq.). The solution was stirred for 5 h, MeOH (5 mL) was added, and the solution was concentrated *in vacuo*. The residual oil was redissolved in MeOH (5 mL), and palladium hydroxide on carbon (25 mg, 20 wt% Pd content) was added. After stirring at rt for 14 h, the suspension was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residual oil was purified by column chromatography (eluting with 2.5 to 5% MeOH in CH_2Cl_2) to give **54** (15.0 mg, 28.6 μmol, 73%) as a clear oil: $[\alpha]_D^{23}$ +73.3 (*c* 0.51, $CHCl_3$); IR (neat) 2933, 1705, 1610, 1519, 1334, 1248, 1177, 1029, 920, 810, 663, 549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (dddd, *J* = 14, 11, 8, 4 Hz, 1H), 2.10 (ddm, *J* = 14, 6 Hz, 1H), 2.39 (s, 3H), 2.57 (ddd, *J* = 11, 10, 6 Hz, 1H), 2.91 (dd, *J* = 12, 5 Hz, 1H), 2.92 (s, 3H), 3.08 (s, 3H), 3.09–3.15 (m, 1H), 3.31 (dd, *J* = 12, 4 Hz, 1H), 3.32 (t, *J* = 5 Hz, 1H), 3.55 (t, *J* = 4 Hz, 1H), 3.82 (s, 3H), 4.22 (d, *J* = 12 Hz, 1H), 4.49 (d, *J* = 12 Hz, 1H), 4.90 (t, *J* = 6 Hz, 1H), 5.23 (td, *J* = 6, 4 Hz, 1H), 6.93 (d, *J* = 9 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 9 Hz, 2H), 7.57 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 31.9, 32.2, 38.4, 52.7, 55.3, 55.8, 59.7, 68.2, 70.1, 83.4, 114.0 (2C), 127.2 (2C), 129.0 (2C), 129.6 (2C), 129.9, 136.1, 143.4, 159.3; MS (FAB) *m*/*z* 525 $(M + H)^+$, 121; HRMS (FAB) *m*/*z* 525.1722 (calcd for $C_{24}H_{33}N_2O_7S_2$: 525.1729).

{(1*R*,2*S*,7*S*,7a*S*)-7-Hydroxy-1-[methyl(4-tolylsulfonyl)amino]-hexahydro-1*H*-pyrrolizin-2-yl} methanesulfonate (55)

A stirred biphasic solution of **54** (10.2 mg, 19.4 μmol) in CH_2Cl_2–H_2O (20 : 1, 2.1 mL) at rt was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 9 mg, 40 μmol). After stirring of the mixture for 22 h, TLC analysis indicated that the reaction was only *ca*. 40% complete. Additional quantities of DDQ (9 mg) and H_2O (0.1 mL) were added at this time, and a further quantity of DDQ (5 mg) was added after a further 26 h. After an additional 16 h, TLC analysis indicated complete consumption of **54**. The mixture was partitioned between sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL), and the layers shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed successively with half-saturated aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluting with 10% MeOH in CH_2Cl_2) to afford **55** (5.5 mg, 13.6 μmol, 70%) as a colourless crystalline solid: mp 175 °C (decomp.) (CH_2Cl_2); $[\alpha]_D^{23}$ +45.8 (*c* 0.28, $CHCl_3$); IR (neat) 3415, 2956, 1333, 1254, 1170, 1092, 1041, 948, 823, 790, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98–2.10 (m, 2H), 2.44 (s, 3H), 2.65 (ddd, *J* = 12, 9, 6 Hz, 1H), 2.84 (dd, *J* = 12, 4 Hz, 1H), 3.03 (s, 3H), 3.05 (s, 3H), 3.14 (tm, *J* = 9 Hz, 1H), 3.34 (dd, *J* = 12, 2 Hz, 1H), 3.60 (dd, *J* = 8, 4 Hz, 1H), 3.99–4.03 (m, 1H), 4.64 (dd, *J* = 8, 5 Hz, 1H), 5.15 (dd, *J* = 5, 2 Hz, 1H), 7.33 (d, *J* = 8 Hz, 2H), 7.76 (d, *J* = 8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 32.1, 37.3, 38.6, 52.5, 55.4, 59.6, 67.7, 69.7, 85.3, 127.3 (2C), 129.8 (2C), 136.0, 143.9; MS (FAB) *m*/*z* 405 $(M + H)^+$; HRMS (FAB) *m*/*z* 405.1158 (calcd for $C_{16}H_{25}N_2O_6S_2$: 405.1154).

$C_{16}H_{24}N_2O_6S_2$, *M* = 404.49, tetragonal, space group $P4_1$, *a* = 9.649(1), *c* = 20.808(3) Å, *V* = 1937.3(3) $Å^3$, *T* = 290 K, *Z* = 4, μ(Cu-Kα) = 2.801 mm^{-1}, colorless block, crystal dimensions 0.40 × 0.10 × 0.10 mm. The crystal was oriented from a total of 40 reflections with 12.12 < θ < 36.35°. A total of 4372 data were measured (5.6 < θ < 67.6°), with 1912 independent reflections (merging R_{int} = 0.108). Full matrix least squares based on F^2 yielded the residuals of $R1$ = 0.0665, $wR2$ = 0.180, for 236 refined parameters and one restraint (floating origin). The absolute structure coefficient refined to a value of −0.04(3) indicating the model presented corresponds to the correct enantiomer of the compound examined.

(7*S*)-7-Hydroxy-1-{methyl[(4-methylphenyl)sulfonyl]amino}-5,6,7,7a-tetrahydro-3*H*-pyrrolizine (56)

A stirred solution of **55** (1.6 mg, 4.0 μmol) in anhydrous THF (0.5 mL) at 0 °C under Ar, was treated with potassium hexamethyldisilazane (0.14 mL, 0.056 M in THF–toluene, 8 μmol). After 20 min, the reaction was quenched by the addition of H_2O (5 mL) and the mixture was diluted with CH_2Cl_2 (5 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield **56** (~0.9 mg, 2.8 μmol, 70%) as a colourless oil: IR (neat) 2917, 1345, 1159, 1095, 809, 687, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95–2.02 (m, 2H), 2.43 (s, 3H), 2.76 (ddd, *J* = 11, 9, 7 Hz, 1H), 3.02 (s, 3H), 3.24 (ddd, *J* = 9, 6, 3 Hz, 1H), 3.35 (ddd, *J* = 15, 5, 2 Hz, 1H), 3.83 (dt, *J* = 15, 2 Hz, 1H), 4.55–4.61 (m, 2H), 5.08 (q, *J* = 2 Hz, 1H), 7.32 (d, *J* = 8 Hz, 2H), 7.66 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 35.2, 37.6, 54.7, 60.9, 71.8, 116.4, 127.2, 127.6 (2C), 129.8 (2C), 137.7, 144.2; MS (FAB) *m*/*z* 309 $(M + H)^+$, 185, 93; HRMS (FAB) *m*/*z* 309.1276 (calcd for $C_{15}H_{21}N_2O_3S$: 309.1273).

N-Tosylloline (57)

A. From 55. A stirred solution of **55** (4.1 mg, 10.1 μmol) in 1,2-dichlorobenzene (1 mL) under Ar was heated at a gentle reflux for 22 h. The resulting black mixture was allowed to cool to rt and partitioned between CH_2Cl_2 (5 mL) and 10% w/v aq. NaOH (5 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 10% MeOH in CH_2Cl_2) to yield **57** (2.3 mg, 7.5 μmol, 74%) as a clear oil: $[\alpha]_D^{23}$ +40.9 (*c* 0.11, $CHCl_3$); IR (neat) 2921, 1458, 1368, 1168, 1096, 1023, 957, 812, 661, 546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (dddd, *J* = 14, 9, 4, 4 Hz, 1H), 2.06 (ddd, *J* = 14, 9, 7 Hz), 2.44 (s, 3H), 2.46 (dm, *J* ≈ 10 Hz, 1H), 2.90 (s, 3H), 2.94 (ddd, *J* = 13, 9, 7 Hz, 1H), 3.10 (ddd, *J* = 12, 8, 3 Hz, 1H), 3.12 (t, *J* = 2 Hz, 1H), 3.29–3.31 (m, 1H), 3.71 (dd, *J* = 11, 1 Hz, 1H), 4.32 (dd, *J* = 5, 2 Hz, 1H), 4.59 (dm, *J* = 2 Hz, 1H), 7.36 (d, *J* = 8Hz, 2H), 7.71 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 33.5, 35.6, 54.9, 61.5, 65.6, 69.9, 76.4, 81.0, 128.0 (2C), 129.8 (2C), 132.4, 143.9; MS (FAB) *m*/*z* 309 $(M + H)^+$; HRMS (FAB) *m*/*z* 309.1267 (calcd for $C_{15}H_{21}N_2O_3S$: 309.1273).

B. From loline (1). A stirred solution of loline dihydrochloride (1.9 mg, 8.4 μmol) in $CHCl_3$ (1 mL) was treated with Et_3N (6 μL, 4.4 mg, 44 μmol) followed by toluene-4-sulfonyl

chloride (3.2 mg, 17 μmol). After stirring of the solution for 1 d, additional quantities of Et_3N (10 μL, 73 μmol) and toluene-4-sulfonyl chloride (6 mg, 31 μmol) were added together with 4-(dimethylamino)pyridine (DMAP, 1 mg, 8 μmol). After stirring for a further 1 d, the mixture was diluted with CH_2Cl_2 (5 mL) and shaken with 10% w/v aq. NaOH (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 10% MeOH in CH_2Cl_2) to yield *N*-tosylloline (**57**, 2.0 mg, 6.5 μmol, 77%) as a colourless oil: $[a]_D^{23}$ +38.0 (*c* 0.10, $CHCl_3$). Spectral properties (^{1}H NMR, ^{13}C NMR and IR) were identical to those obtained for **57** prepared from **55**.

Loline dihydrochloride

A solution of **57** (4.5 mg, 15 μmol) in anhydrous DME (1 mL) at −60 °C under Ar was treated dropwise with a freshly prepared solution of sodium naphthalenide (0.7 mL, *ca*. 0.25 M in DME) until a green colour persisted. After 20 min, the reaction was quenched with 1.5 M aq. HCl (2 mL) and was allowed to warm to rt. The mixture was diluted with H_2O (3 mL) and washed with Et_2O (4 × 3 mL). The aqueous phase was made basic (pH 12) with 10% w/v aq. NaOH and extracted with $CHCl_3$ (6 × 4 mL). The resulting solution of **1** in $CHCl_3$ was dried (Na_2SO_4), treated with methanolic HCl (3 mL, half-saturated), and concentrated *in vacuo* to yield loline dihydrochloride (1.6 mg, 48%) as a colourless oil. Spectral data are given in Tables 3 and 4.

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