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Asymmetric nitrone–vinyl sulfoxide cycloadditions

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Abstract: The cycloaddition of (Z) and (E)-vinyl sulfoxides with cyclic nitrones **1** and **2** is reported. Best diastereoselection is achieved with (Z)-vinyl sulfoxides ***7a–d*** as dipolarophiles. This methodology allows the highly stereoselective synthesis of (+)-sedridine ***9a***, (−)-hygroline **10** and (−)-(2S)-N-carbomethoxypelletierine ***11a***. © 1997, Elsevier Science Ltd. All rights reserved.

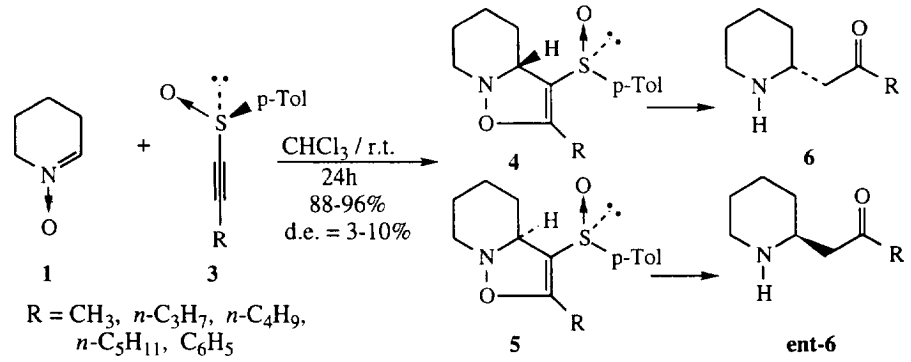
Introduction

The sulfoxide group has emerged as an efficient chiral auxiliary in numerous asymmetric syntheses[1]. In particular, α,β-unsaturated sulfoxides have been used successfully to control the stereochemistry in Diels–Alder reactions[2], Michael additions[3] and, to a lesser extent, 1,3-dipolar cycloadditions[4].

Research in our laboratory has focused on the stereoselective synthesis of piperidine alkaloids. In this context, we recently developed a simple two-step pathway to enantiomerically pure β-amino ketones[5]. The key step of the sequence, outlined in Scheme 1, is an asymmetric 1,3-dipolar cycloaddition between the cyclic nitrone **1** and an enantiomerically pure acetylenic sulfoxide **3**.

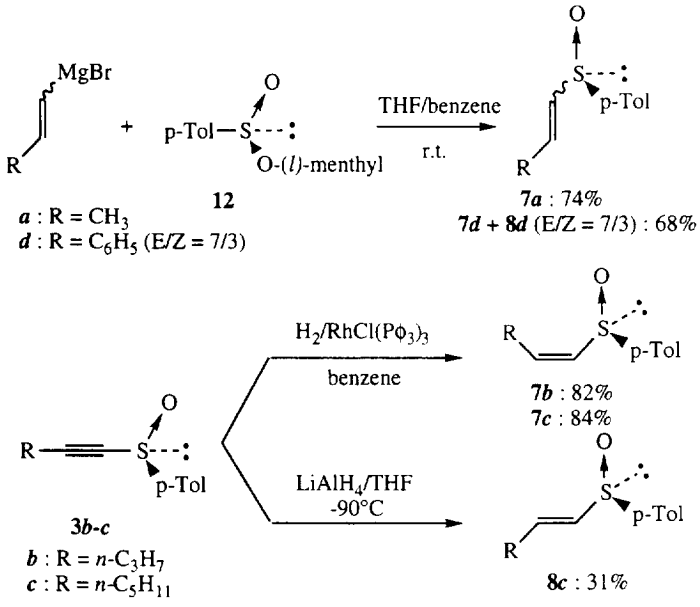
The cycloadditions proceed with high yields but with very low stereoselectivities. After ready chromatographic separation, the diastereomeric isoxazolines **4** and **5** are converted by catalytic hydrogenolysis into the enantiomeric ketones **6** and **ent-6**, respectively. This approach constitutes an interesting alternative to the resolution of a β-amino ketone.

In contrast with their acetylenic counterparts[6], vinyl sulfoxides are known to react with high levels of stereodifferentiation in Diels–Alder reactions[2b]. Moreover, excellent stereochemical control has already been reported in some vinyl sulfoxide 1,3-dipolar cycloadditions[4]. In the light of these results, we decided to study the cycloaddition of cyclic nitrones **1** and **2** with (Z) and (E)-vinyl sulfoxides **7** and **8**. In this paper, we report the high diastereoselectivity observed in these reactions involving (Z)-



Scheme 1.

* Corresponding author.



Scheme 2.

vinyl sulfoxides **7**. Based on this process, a highly enantioselective synthesis of the piperidine alkaloid (+)-sedridine **9a** (Scheme 8) has been achieved. The same methodology allows the preparation of the pyrrolidine alkaloid (−)-hygroline **10** (Scheme 9) and the piperidine amino ketone (−)-(2S)-N-carbomethoxypelletierine **11*a*** (Scheme 12).

Preparation of chiral vinyl sulfoxides 7 and 8

(Z)-(R)$_S$-Propenyl p-tolyl sulfoxide **7*a*** was obtained in 74% yield by the Andersen method through the action of (Z)-propenylmagnesium bromide on (−)-menthyl (S)$_S$-p-toluenesulfinate **12**[7]. The same procedure was applied to the synthesis of sulfoxide **7*d*** (Scheme 2).

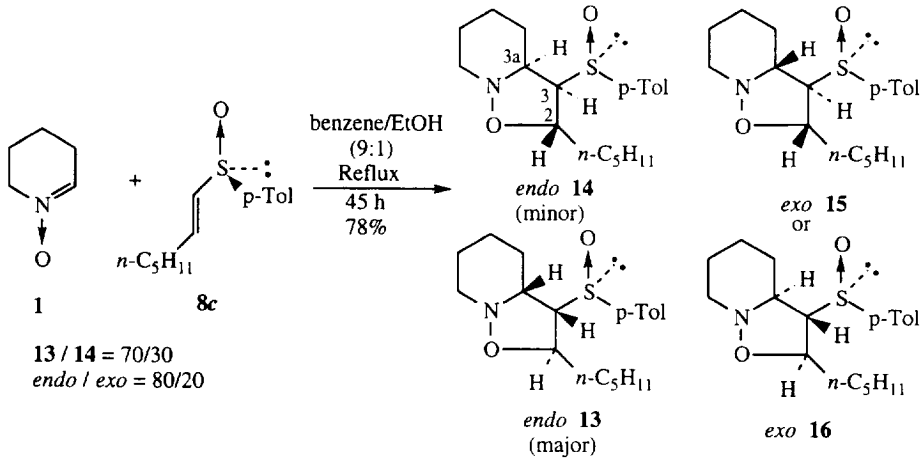
Dipolarophiles **7*b***, **7*c*** and **8*c*** were synthesized by stereoselective reduction of acetylenic sulfoxides **3*b*** and **3*c*** (Scheme 2)[8]. The latter compounds were prepared according to literature procedures[8]. Catalytic hydrogenation of **3*b*** and **3*c*** using Wilkinson's catalyst afforded (Z)-sulfoxides **7*b*** and **7*c*** in 82% and 84% yield, respectively. On the other hand, treatment of **3*c*** with $LiAlH_4$ gave (E)-derivative **8*c***.

Nitrone–vinyl sulfoxide cycloadditions

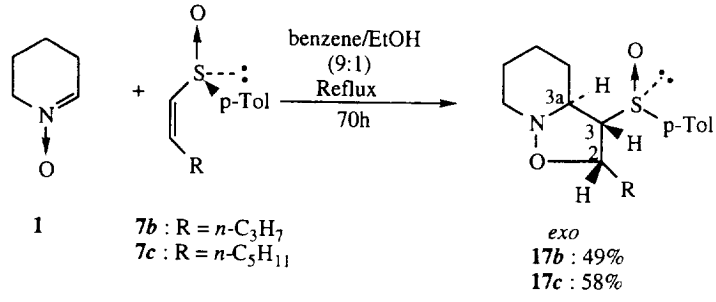
Initially, we chose to investigate the addition of nitrone **1** onto (E)-vinyl sulfoxide **8*c***. The reaction was carried out in the mixed solvent benzene/ethanol (9:1)[9], at reflux temperature; a threefold molar excess of dipole **1** was used. As expected, the reaction turned out to be very regioselective[10] and gave only 3-sulfinylisoxazolidines **13**, **14** and **15** (or **16**) in 78% isolated yield (Scheme 3). The stereochemical outcome of the reaction was however disappointing: the *endo*/*exo* selectivity (80/20) and the facial diastereoselectivity (% d.e. *endo*=40% by ^{1}H NMR) were quite low.

Structural and stereochemical assignments for isoxazolidines **13** and **14** follow from their conversion into known optically active compounds (*vide infra*). The same method was used to establish the *exo* configuration of the minor cycloadduct; however we were unable to further discriminate between structures **15** and **16**.

As opposed to its stereoisomer, (Z)-vinyl sulfoxide **7*c*** underwent highly diastereoselective addition



Scheme 3.



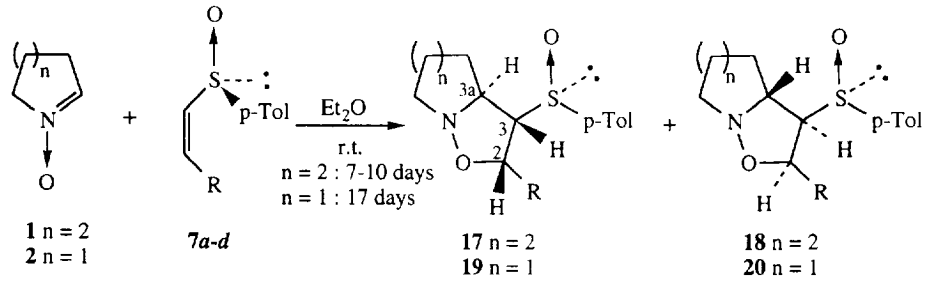
Scheme 4.

to **1** to yield a single adduct **17*c***, which arose from an *exo* transition state (Scheme 4). A similar result was obtained using **7*b*** as a dipolarophile.

Since (Z)-vinyl sulfoxides **7** seemed very promising for asymmetric synthesis, we undertook a study of the cycloaddition of dipole **1** onto **7*b*** under several different conditions. Replacement of the mixed solvent benzene/ethanol (9:1) by methylene chloride, 1,2-dichloroethane or 1,4-dioxane did not improve the yield of the addition. On the other hand, conducting the reaction in water[11] or in a 5 M ethereal $LiClO_4$ solution[12] at room temperature led to a decrease of the facial selectivity (**17/18**=90:10 and 88:12, respectively). Eventually, ether proved to be a suitable solvent to perform the cycloaddition. Hence, cycloaddition of 2,3,4,5-tetrahydropyridine-1-oxide **1** (3–5 equiv) to (Z)-(R)$_S$-vinyl sulfoxides **7*a–d*** (1 equiv) in ether proceeded at room temperature for 7–10 days to give a mixture of isoxazolidines **17*a–d*** and **18*a–d*** (Scheme 5). As can be seen from the results summarized in Table 1, yields and diastereomeric ratios are high.

With regard to the regio- and stereochemistry, the cyclic nitrones **1** and **2** behaved similarly towards addition onto (Z)-vinyl sulfoxide **7*a***. Yet, a slight drop in both the yield and the degree of facial selectivity was observed on going from 2,3,4,5-tetrahydropyridine-1-oxide **1** to Δ^1-pyrroline-1-oxide **2** (Table 1, entries 1 and 5).

Relative and absolute configurations of isoxazolidines **17*a–d***, **18*a–d***, **19** and **20** were unambiguously assigned by chemical correlations with either known natural compounds or cycloadducts of established



1 n = 2
2 n = 1

7*a-d*

17 n = 2
19 n = 1

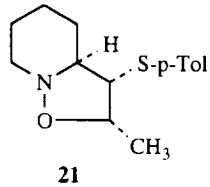
18 n = 2
20 n = 1

Scheme 5.

Table 1. Nitrone cycloaddition to (Z)-(R)-vinyl sulfoxides in ether

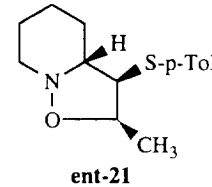
Entry	Sulfoxide	Nitrone	R	Yield[a](%)	**17 / 18**	
1	**7*a***	**1**	CH_3	95	94 : 6[b]	(91 : 9)[c]
2	**7*b***	**1**	*n*-C_3H_7	90	95 : 5[b]	(93 : 7)[c]
3	**7*c***	**1**	*n*-C_5H_{11}	85	95 : 5[b]	(93 : 7)[c]
4	**7*d***	**1**	C_6H_5	97	99 : 1[b]	(> 98 : 2)[c]
Entry	Sulfoxide	Nitrone	R	Yield[a](%)	**19 / 20**	
5	**7*a***	**2**	CH_3	72	87 : 13[b]	(82 : 18)[c]

[a]Isolated yields; [b]Isolated ratios; [c]Determined by ^1H NMR on the crude reaction product



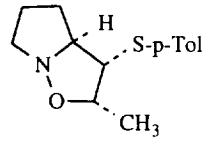
21

$[\alpha]_D^{22}$ − 58 ($CHCl_3$; c 0.4)



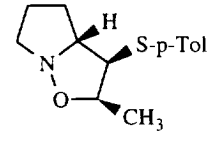
ent-21

$[\alpha]_D^{22}$ + 56 ($CHCl_3$; c 0.8)



22

$[\alpha]_D^{22}$ − 47 (CH_2Cl_2; c 0.8)

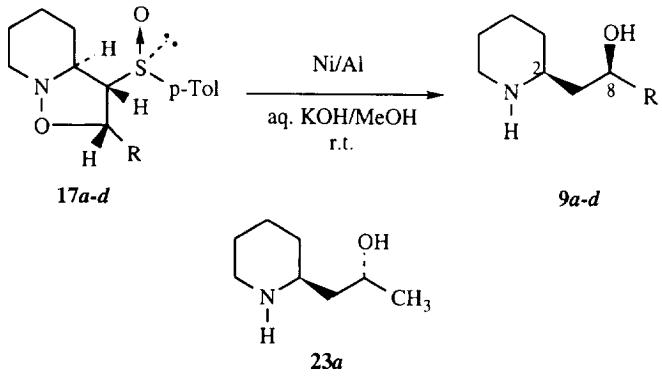


ent-22

$[\alpha]_D^{22}$ + 47 (CH_2Cl_2; c 0.6)

Figure 1.

stereochemistry. Thus, isoxazolidines **17*a*** and **18*a*** afforded enantiomeric sulfides **21** and **ent-21** after TMSI/NaI reduction[13] (Figure 1), indicating that both cycloadducts possess the same relative configuration at C3a, C3 and C2. Hence they are diastereomeric due to the sulfoxide chirality and the **17*a–d*/18*a–d*** ratios presented in Table 1 reflect the degree of asymmetric induction during the cycloaddition process. A similar stereochemical relationship exists between adducts **19** and **20**, as indicated by their conversion into enantiomeric **22** and **ent-22** respectively.



17*a-d* **9*a-d*** **23*a***

Scheme 6.

Table 2. Reductive cleavage of isoxazolidines **3** using Ni/Al alloy

Entry	Isoxazolidine	Amino alcohol	Yield (%)	$[\alpha]_D^{22}$ [b] **9**	c	$[\alpha]_D^{22}$ [b] **9** lit.	c	Ref
1	**17*a***	**9*a*** [a]	37	+23	1.1	+28.5	2.32	27
2	**17*b***	**9*b***	60	+17	0.4	+19.6	0.6	21
3	**17*c***	**9*c***	43	+9	0.7			
4	**17*d***	**9*d***	0					

[a]Isolated as a 95 : 5 mixture of **9*a*** /**23*a***; [b]Measured for solutions in EtOH

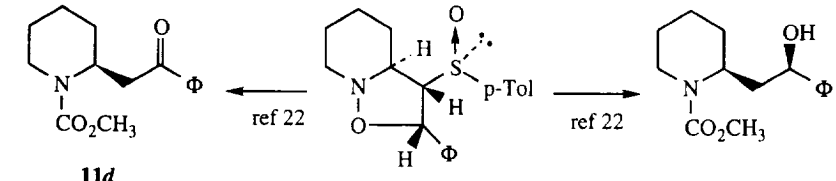
Synthesis of 1,3-amino alcohols ***9***

Isoxazolidines are versatile synthons and can be converted into a variety of compounds with complete control of stereochemistry[14]. The low dissociation energy of their N–O bond has driven the hydrogenolytic, homolytic and heterolytic ring-openings reported so far. Reductive cleavage of the N–O bond of the isoxazolidine nucleus unmasks the 1,3-amino alcohol moiety. Thus, isoxazolidines **17** can be viewed as direct precursors of γ-amino alcohols **9** (Scheme 6). Reductive cleavage of cycloadduct **17*a*** proved difficult. W2 Raney nickel[15] and nickel boride[16] were both ineffective: in each case, the desired γ-amino alcohol **9*a*** was recovered in low yield along with side-products arising from either oxidation to the ketone (Ni_2B) or epimerization of the alcohol (W2 Raney Ni/H_2 at r.t.) or opening of the piperidine ring (W2 Raney Ni in refluxing ethanol). We were able to achieve the one-step transformation of isoxazolidines **17** into amino alcohols **9** using nickel–aluminium alloy in alkaline medium[17] (Scheme 6). The results are summarized in Table 2 and deserve some comments.

(1) Compounds **9*a–c*** were obtained in quite modest yields.

(2) Specific rotations collected in Table 2 are somewhat lower than the reported values. Treatment of cycloadduct **17*a*** with Ni/Al afforded (+)-sedridine **9*a*** accompanied by 5–10% allosedridine **23*a***. The presence of the latter compound indicates that some epimerization occurred during the reductive desulfurization process. Raney nickel-promoted epimerization of alcohols has already been reported[18] and is generally assumed to proceed *via* oxidation to the corresponding ketone and subsequent non stereoselective reduction. The intermediate β-amino ketone **ent-6** (Scheme 1) is prone to racemization[19], especially in a polar solvent like methanol. Because of these epimerization/racemization problems, the reduction described in Scheme 6 is not a useful synthetic process.

(3) (+)-Sedridine[20] **9*a*** and (−)-halosaline[21] **ent-9*b*** are piperidine alkaloids isolated from *Sedum acre* and *Haloxylon salicornicum* respectively. Relative and absolute configurations of the



11*d*
$[\alpha]_D^{22}$ +18 ($CHCl_3$; c 0.4)

17*d*

26*d*

Scheme 7.

dextrorotatory bases were unambiguously determined as (2S,8S). Therefore we assign the homologous dextrorotatory amino alcohol **9*c*** the same (2S,8S) configuration from the sign of optical rotation and from the similar chromatographic behaviour of the diastereomeric isoxazolidines throughout the series. The described transformation allows us to ascribe the (R_S,2S,3S,3aS) configuration to the major cycloadducts **17*a–c***. We used a similar reduction (W2 Raney nickel/H_2) to determine the configuration of cycloadducts **13, 14** and **15** (or **16**).

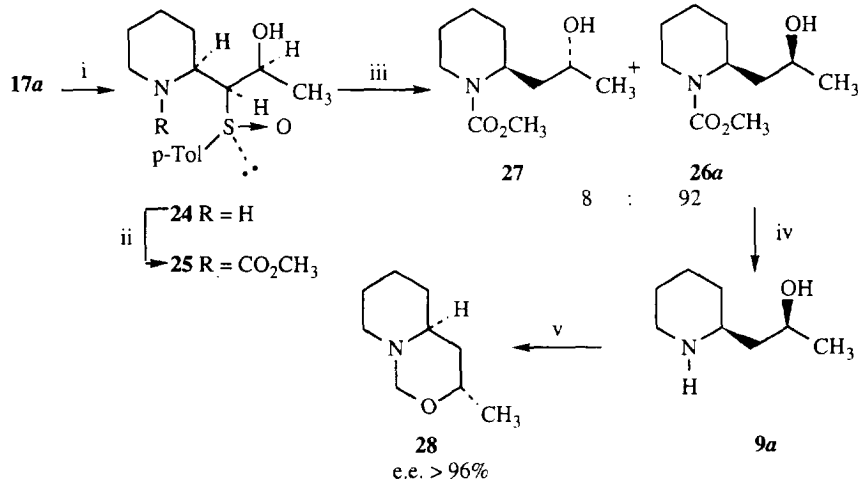
(4) Attempted reduction/desulfurization of isoxazolidine **17*d*** under the same conditions gave a complex mixture, the alkaloid (+)-norallosedamine **9*d*** being undetected. This observation was not surprising as benzylic alcohols have already been reported to undergo several reactions (oxidation, deoxygenation, ...) in the presence of Ni/Al alloy[17]. Stereochemical assignment for **17*d*** follows unambiguously from its conversion into N-carbomethoxynorallosedamine **26*d*** and (+)-N-carbomethoxynorsedaminone **11*d***[22] (Scheme 7).

To overcome the epimerization/racemization problems, we first reduced compound **17*a*** with a slight excess of Ni/Al alloy. Under these conditions, the isoxazolidine nucleus was selectively opened without any concomitant desulfurization (Scheme 8). When treated with an excess of W6 Raney nickel[23] in methanol at room temperature, N-protected amino alcohol **25** afforded a mixture of N-carbomethoxysedridine **26*a*** (38%), N-carbomethoxypelletierine **11*a*** (Scheme 12, 9%) and unreacted starting material **25** (21%). Here again, incomplete desulfurization was accompanied by partial oxidation to the ketone **11*a***. However, the protection of the amine functionality prevents any racemization from taking place at this stage. We were fortunate to see that almost complete desulfurization of compound **25** was achieved when performing the same reaction under a hydrogen atmosphere (Scheme 8). Under these conditions, the ketone **11*a*** was completely reduced and N-acylsedridine **26*a*** and its epimer **27** were produced in a 84% yield and in a 92:8 isolated ratio. These diastereomers were readily separated by column chromatography on alumina. The deprotection procedure developed by Jung[24] was used to convert **26*a*** into (+)-sedridine **9*a*** {$[\alpha]_D^{22}$+26 (EtOH; c 1.3); $[\alpha]_D^{22}$ lit.[27]+28.5 (EtOH; c 2.32)} in 97% yield. In order to determine its e.e., **9*a*** was converted into the tetrahydrooxazine **28** by treatment with formaldehyde in methanol. The e.e. of compound **28** was shown to be more than 96% by 250 MHz ^{1}H NMR spectroscopy with the chiral NMR shift reagent Eu(hfc)$_3$. The synthetic pathway outlined here represents an effective approach to the asymmetric synthesis of the piperidine alkaloid (+)-sedridine **9*a*** (62% overall yield from **7*a***).

*Synthesis of (−)-hygroline **10***

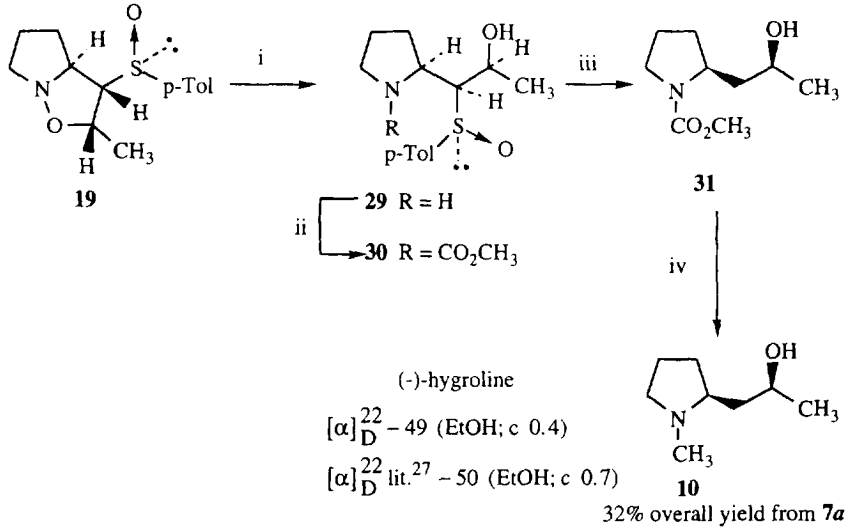
(−)-Hygroline **10** is a pyrrolidine alkaloid isolated from *Erythoxylum coca*.[25] We achieved its diastereo- and enantioselective synthesis by an analogous sequence (Scheme 9).

Thus, the major cycloadduct **19** was treated with Ni/Al alloy to give the amino alcohol **29** in 85% yield. Protection of compound **29** was followed by W6 Raney nickel reduction. Especially noteworthy is the absence of any epimerization of alcohol **31** during the desulfurization process. Lithium aluminium hydride reduction of carbamate **31** produced (−)-hygroline **10** in 83% yield. The synthetic sample is



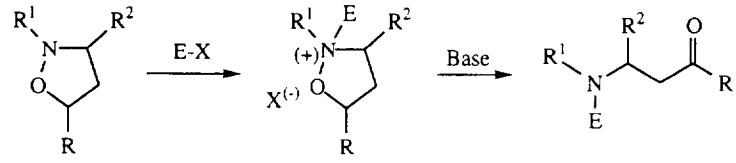
Reagents and conditions : i : Ni/Al (3x weight), aq. KOH 1M/MeOH, r.t., 2h. (93%); ii: $ClCO_2CH_3$ (10 equiv), aq. K_2CO_3, r.t., overnight (98%); iii: W6 Raney Nickel/H_2, MeOH, overnight (84%); iv: (a) TMSI, CH_2Cl_2, reflux, 1h. (b) MeOH, r.t., 10 min (97%); v: CH_2O, MeOH, r.t., 15 min (83%).

Scheme 8.

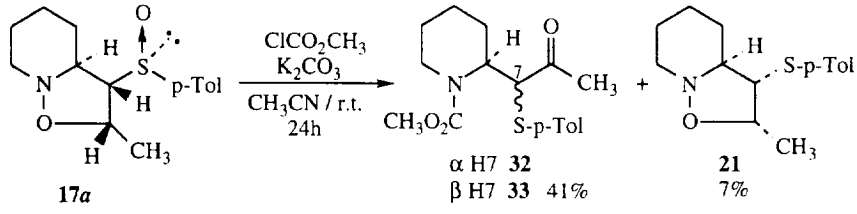


Reagents and conditions : i : Ni/Al (3x weight), aq. KOH 1M/MeOH, r.t., 2h. (85%); ii: $ClCO_2CH_3$ (10 equiv), aq. K_2CO_3, r.t., overnight (95%); iii: W6 Raney Nickel/H_2, MeOH, 6h. (75%); iv: $LiAlH_4$, THF, reflux, 40 min. (83%).

Scheme 9.



Scheme 10.



Scheme 11.

spectroscopically identical with the natural compound[26] and its optical rotation is in agreement with the literature value {$[\alpha]_D^{22}$ −49 (EtOH; c 0.4); $[\alpha]_D^{22}$ lit.[27] −50 (EtOH; c 0.7)}.

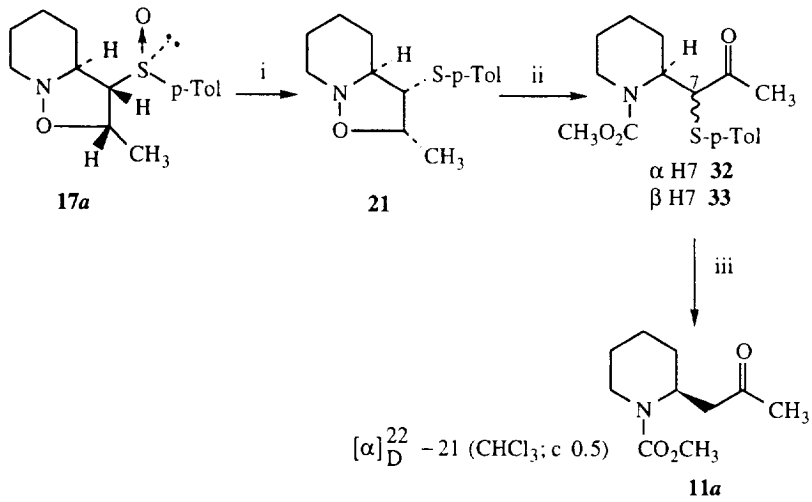
Synthesis of N-protected amino ketone ***11a***

As already pointed out, isoxazolidines are valuable intermediates in the formation of numerous open chain derivatives. In addition to the hydrogenolytic cleavage of their N–O bond exploited so far, these heterocycles can be submitted to heterolytic ring-opening reactions. In particular, activation of the nucleus through quaternization of the nitrogen atom, followed by a Hofmann-like elimination process, leads to an N-substituted β-amino ketone[14] (Scheme 10).

Since N-alkyl β-amino ketones are known to racemize rapidly in basic medium[19], we envisaged the synthesis of carbamate **11*a***. To this end, bicyclic isoxazolidine **17*a*** was simultaneously treated with methyl chloroformate and a non nucleophilic base (K_2CO_3) (Scheme 11). The reaction was conducted at room temperature in acetonitrile for 24 h and afforded a mixture of sulfide **21** (7%), C7-epimeric ketones **32** and **33** (41% yield) along with unreacted starting material. Apparently, adduct **17*a*** underwent first reduction to the sulfide **21**, the latter producing subsequently ketone **32** through the N-acylation/elimination sequence outlined above. Purification by column chromatography on alumina then resulted in C7-epimerization of ketone **32**.

Even if acylating agents have been reported to reduce sulfoxides[28], the chemoselective O-acylation of the sulfinyl group of **17*a*** was surprising. This chemoselectivity problem might account partially for the low yield of the N-acyl amino ketones **32+33**. To circumvent this difficulty, we performed the same reaction on the sulfide **21** derived from **17*a*** (Scheme 12). Under these conditions, the ketones **32+33** were obtained in a satisfactory 64% yield and the starting sulfide was partially recovered (5%). Prior reduction to the sulfide **21** appears to be necessary in order to effect the base-promoted ring-opening of the isoxazolidine nucleus.

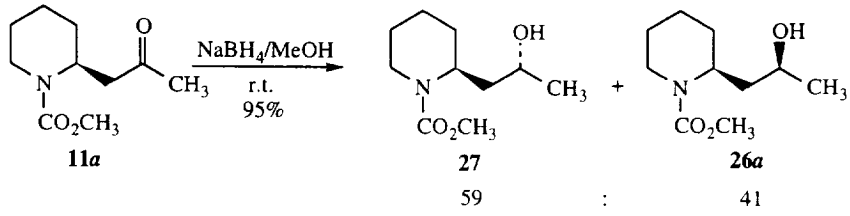
Heating a mixture of epimeric ketones **32** and **33** (**32/33**=2:1) in ethanol in the presence of zinc dust and acetic acid gave (−)-(2S)-N-carbomethoxypelletierine **11*a*** in 89% yield. The e.e. of **11*a*** was assayed *via* the amino alcohol **26*a*** as already described above (Scheme 13). The derived tetrahydrooxazine **28** was found to be of high enantiomeric purity (e.e. >96%) by 250 MHz ^{1}H NMR spectroscopy with the chiral shift reagent Eu(hfc)$_3$.



17*a* 21 11*a*

Reagents and conditions : i : TMSI/NaI, CH_3CN, r.t., 2h. (90%); ii: $ClCO_2CH_3$ (25 equiv), K_2CO_3 (21 equiv), r.t., 48h. (64%); iii: Zn/AcOH, EtOH, reflux, 2h30 (89%).

Scheme 12.



11*a* 27 26*a*

59 : 41

Scheme 13.

Discussion

The cycloadditions of nitrones **1** and **2** onto (Z)-vinyl sulfoxides ***7a–d*** exhibit a high degree of both regio- and stereoselectivity. All reactions were performed under conditions which would reflect kinetic rather than thermodynamic factors. This was confirmed in a control experiment: pure isoxazolidines **17*a***, **18*a***, **19** and **20** when subjected to cycloaddition conditions (ether at r.t. for 1–2 weeks) remained unchanged indicating that no cycloreversion took place.

The regiochemistry[30] and the *exo* vs *endo* stereoselectivity[31] of similar kinetically controlled cycloadditions have been successfully explained in terms of molecular orbitals interaction and steric hindrance in the transition state. Thus, the observed regioselectivity is in agreement with Houk's perturbation treatment of 1,3-dipolar cycloadditions and adducts **17**, **18**, **19** and **20** all arise from a sterically favoured *exo* transition state (Figure 2). Similar factors would account for the selective formation of isoxazolidines **13** and **14** from (E)-vinyl sulfoxide **8*c***. In this case, the *endo* transition state depicted in Figure 2, would allow secondary orbital interaction between the nitrogen atom of the nitrone and the sulfinyl group; in the same time steric repulsion between the dipole and the dipolarophile alkyl group would be minimized.

The stereochemical course of 1,3-dipolar cycloadditions of chiral sulfinylethenes has been discussed by Koizumi[4b]. Facial selectivity has been believed to originate from the preferred dipole approach

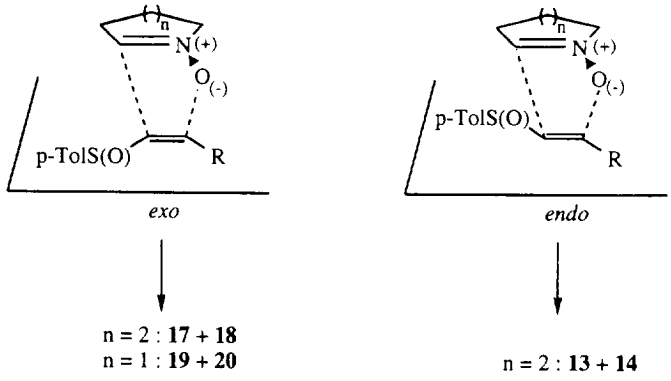


Figure 2.

Figure 3.

from the less hindered face of the vinyl sulfoxide; the latter has been assumed to react *via* its most stable conformation. However, in view of recently published results[32], the ground state conformations proposed by Koizumi for vinyl sulfoxides are to be questioned. Indeed, according to *ab initio* calculations (6-31G*), the most stable conformers of vinyl sulfoxides are those depicted in Figure 3. While (E)-isomers predominantly adopt the conformation **A**, structure **B** appears to be energetically favoured for the (Z)-sulfinylethenes. The latter rotamer was found to predominate in the solid state for compound ***7d***[33].

Hence, a speculative but reasonable interpretation of the high facial stereoselectivity observed in the cycloadditions with (Z)-vinyl sulfoxides **7**, is that the dipole adds to the most stable conformation **7-B** from the less crowded face (Figure 4). According to the Curtin–Hammett principle, conformer **7-A** cannot be disregarded. Nevertheless, since major cycloadducts **17** and **19** would arise from the nitrone approach to **7-A** from the most sterically hindered side, we assume that conformation **7-A** doesn't dictate the cycloaddition facial diastereoselectivity.

Conclusion

In conclusion, the reaction of dipoles **1** and **2** with (Z)-vinyl sulfoxides **7** represents the first highly selective 1,3-dipolar cycloaddition between an α,β-unsaturated sulfoxide and a cyclic nitrone. Based on this very diastereoselective process, we developed an efficient asymmetric synthesis of the piperidine alkaloid (+)-sedridine **9a** and the pyrrolidine natural compound (−)-hygroline **10**. Using a heterolytic ring-opening of the major cycloadduct ***17a***, we achieved an enantioselective synthesis of the N-protected amino ketone ***11a***. Starting from commercially available (+)-menthyl (R)S-p-toluenesulfinate **ent-12**, the same sequences would lead to **ent-*9a***, **ent-10** and **ent-*11a***.

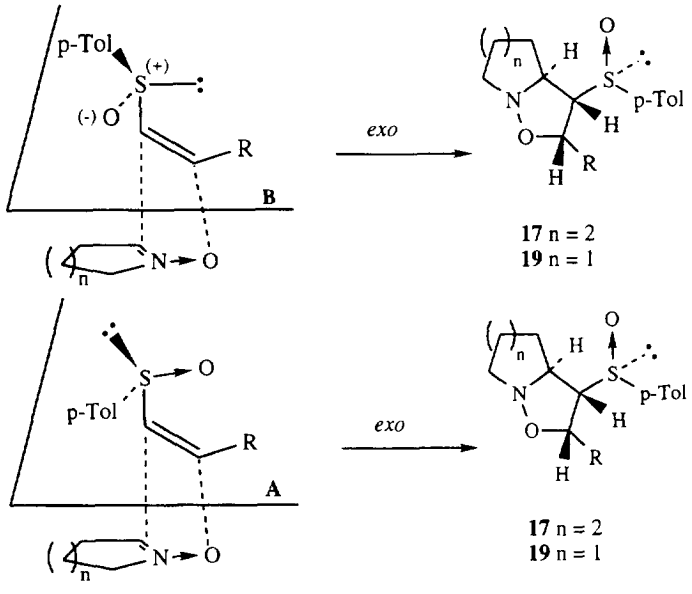


Figure 4.

Experimental

General details

Mass spectral data were obtained on a Micromass 7070 spectrometer or a Fison Autospec spectrometer (high resolution measurements). ^{1}H and ^{13}C NMR spectra were recorded either on a Bruker WM 250 (^{1}H: 250 MHz; ^{13}C: 62.8 MHz) or an AMX 400 (^{1}H: 360 MHz; ^{13}C: 90.6 MHz) apparatus in $CDCl_3$ with TMS as internal standard unless otherwise stated; chemical shifts (δ) are reported in ppm and J values in Hz follow the multiplicities. IR spectral data were recorded on a Bruker IFS 25 spectrometer in CCl_4 solution, ν values are given in cm^{-1}. Optical rotations were obtained on a Perkin–Elmer 141 polarimeter. Melting points are uncorrected and were obtained on a Kofler microscope. Analytical thin-layer chromatography was performed on Polygram Sil G/UV254 plates and on Merck aluminium sheets (aluminium oxide 60 F 254 neutral, type E). Components were visualized either by ethanolic phosphomolybdic acid solution followed by heating (silica gel) or by iodine followed by Dragendorff's reagent (alumina). Column chromatography was performed with silica gel (Merck MN Kieselgel 60) or basic alumina (ICN).

Synthesis of (Z)-(R)$_S$-propenyl p-tolyl sulfoxide ***7a***

Compound ***7a*** was prepared in 74% yield from (−)-menthyl (S)$_S$-p-toluenesulfinate[34] and (Z)-1-bromopropene as described[7]. White solid recrystallized from petroleum ether (30–45), m.p. 53°C (lit.[7a] m.p. 54–55°C), $[\alpha]_D^{22}$ −322 (acetone; c 1.3) ($[\alpha]_D^{22}$ lit.[2a] −289 (acetone; c 1.045)), ^{1}H NMR: 7.50 (2H, d, 8, Ar H), 7.30 (2H, d, 8, Ar H), 6.32–6.18 (2H, m, H1, H2), 2.40 (3H, s, ArCH_3), 2.13 (3H, d, 5.5, H3), ^{13}C NMR: 142.0, 141.5, 138.5, 136.9 (C1, C2), 130.3, 124.4, 21.7 (ArCH_3), 15.5 (C3), MS, *m/z*: 180 ($M^{+\cdot}$, 28%), 163 ($M^{+\cdot}$–HO$^{\cdot}$, 30), 139 (16), 132 (75), 123 (45), 117 (43), 101 (25), 92 (48), 91 (47), 79 (14), 77 (16), 65 (28), 59 (69), 45 (21), 43 (100), 41 (25), 39 (40), IR: 2949, 2923, 2854, 1625 (ν C=C), 1493, 1439, 1380, 1086, 1046 (ν S–O).

*Synthesis of (Z)-(R)$_S$-β-styryl p-tolyl sulfoxide **7d** and (E)-(R)$_S$-β-styryl p-tolyl sulfoxide **8d***

Compounds **7d** and **8d** were prepared in 22% and 46% yield from (−)-menthyl (S)$_S$-p-toluenesulfinate[34] and a (Z/E: 3/7) mixture of β-bromostyrenes as described[7]. They were separated by flash chromatography (hexane/acetone: 7/3).

*(Z)-derivative **7d***

White solid recrystallized from pentane, m.p. 57–58°C (lit.[7b] m.p. 51–52°C), $[\alpha]_D^{22}$ −738 ($CHCl_3$; c 1.0) ($[\alpha]_D^{22}$ lit.[7b] −735 ($CHCl_3$; c 1.0)), ^{1}H NMR: 7.56–7.53 (4H, m), 7.44–7.26 (5H, m), 7.06 (1H, d, 11, H2), 6.42 (1H, d, 11, H1), 2.37 (3H, s, ArCH_3), ^{13}C NMR: 141.7, 141.6, 138.6, 137.3 (C1, C2), 134.1, 130.3, 130.0, 129.7, 128.8, 124.6, 21.6 (ArCH_3), MS, *m/z*: 242 ($M^{+\cdot}$, 1%), 226 (6), 213 (69), 194 ($M^{+\cdot}$–SO, 100), 179 (76), 165 (7), 139 (p-TolSO$^+$, 7), 134 (10), 123 (p-TolS$^+$, 11), 103 (20), 91 (75).

*(E)-derivative **8d***

White solid recrystallized from hexane, m.p. 75°C (lit.[7b] m.p. 81–82°C), $[\alpha]_D^{22}$+159 ($CHCl_3$; c 1.0) ($[\alpha]_D^{22}$ lit.[7b]+165 ($CHCl_3$; c 1.0)), ^{1}H NMR: 7.55 (2H, d, 8, Ar H), 7.40–7.24 (8H, m), 6.81 (1H, d, 15.5), 2.33 (3H, s, ArCH_3), ^{13}C NMR: 141.7, 140.9, 135.8 (C2), 133.9, 133.4 (C1), 130.2, 129.7, 128.9, 127.8, 124.9, 21.4 (ArCH_3), MS, *m/z*: 242 ($M^{+\cdot}$, 1%), 226 (2), 213 (15), 194 ($M^{+\cdot}$–SO, 100), 179 (36).

*Synthesis of (Z)-(R)$_S$-pent-1-enyl p-tolyl sulfoxide **7b***

Compound **7b** was prepared in 83% yield by catalytic hydrogenation (Wilkinson's catalyst: 12% wt) of acetylenic sulfoxide **3b** as described[8]. Colourless oil, $[\alpha]_D^{22}$−298 (acetone; c 1.1) ($[\alpha]_D^{22}$ lit.[8] −322 (acetone; c 0.5)), ^{1}H NMR: 7.50 (2H, d, 8, Ar H), 7.30 (2H, d, 8, Ar H), 6.24–6.12 (2H, m, H1, H2), 2.63–2.42 (2H, m, H3), 2.40 (3H, s, ArCH_3), 1.54 (2H, sext, 7, H4), 1.00 (3H, t, 7, H5), ^{13}C NMR: 142.0 (C2 or C1), 142.0, 141.4, 137.7 (C1 or C2), 130.3, 124.5, 31.6, 22.7, 21.7, 14.0, MS, *m/z*: 208 ($M^{+\cdot}$, 19%), 191 ($M^{+\cdot}$–HO$^\cdot$, 100), 163 (19), 149 (35), 140 (24), 139 (p-TolSO$^+$, 16), 131 (51), 123 (49), 99 (28), 92 (64), 91 (66).

*Synthesis of (Z)-(R)$_S$-hept-1-enyl p-tolyl sulfoxide **7c***

Compound **7c** was prepared in 86% yield by catalytic hydrogenation (Wilkinson's catalyst: 12% wt) of acetylenic sulfoxide **3c** as described[8]. Colourless oil, $[\alpha]_D^{22}$−291 (acetone; c 0.8) ($[\alpha]_D^{22}$ lit.[8] −305 (acetone; c 0.6)), ^{1}H NMR: 7.50 (2H, d, 8, Ar H), 7.30 (2H, d, 8, Ar H), 6.23–6.12 (2H, m, H1, H2), 2.67–2.43 (2H, m, H3), 2.40 (3H, s, ArCH_3), 1.56–1.32 (6H, m), 0.91 (3H, t, 7, H7), ^{13}C NMR: 141.9 (C2 or C1), 141.7, 141.1, 137.1 (C1 or C2), 130.0, 124.1, 31.3 (C3), 29.3, 28.7, 22.4, 21.3 (ArCH_3), 13.9 (C7), MS, *m/z*: 236 ($M^{+\cdot}$, 14%), 219 ($M^{+\cdot}$–HO$^\cdot$, 100), 193 (4), 188 (3), 163 (48), 140 (p-TolSOH$^{+\cdot}$, 21), 137 (17), 131 (24), 124 (p-TolSH$^{+\cdot}$, 22), 123 (p-TolS$^+$, 20), 95 (19), 91 (29), IR: 2960, 2930, 2874, 2860, 1620 (ν C=C), 1494, 1468, 1458, 1084, 1048 (ν S–O), 1016.

*Synthesis of (E)-(R)$_S$-hept-1-enyl p-tolyl sulfoxide **8c***

Compound **8c** was prepared in 31% yield by $LiAlH_4$ reduction of acetylenic sulfoxide **3c** as described[8]. Colourless oil, $[\alpha]_D^{22}$+147 (acetone; c 1.5) ($[\alpha]_D^{22}$ lit.[8]+148 (acetone; c 0.5)), ^{1}H NMR: 7.50 (2H, d, 8, Ar H), 7.30 (2H, d, 8, Ar H), 6.60 (1H, dt, 15 and 7, H2), 6.21 (1H, dt, 15 and 1.5, H1), 2.41 (3H, s, ArCH_3), 2.21 (2H, qd, 7 and 1.5, H3), 1.46 (2H, quint, 7, H4), 1.31–1.25(4H, m, H5, H6), 0.88 (3H, t, 7, H7), MS, *m/z*: 236 ($M^{+\cdot}$, 10%), 220 (2), 219 ($M^{+\cdot}$–HO$^\cdot$, 2), 207 (4), 188 (65), 140 (8), 139 (p-TolSO$^+$, 7), 137 (12), 131 (100), 123 (p-TolS$^+$, 36), 118 (43), 108 (11), 105 (15), 92 (23), 91 (26), 65 (13), 55 (21), 41 (25).

*Synthesis of 2,3,4,5-tetrahydropyridine-1-oxide **1***

Yellow mercuric oxide (2 equiv) was added slowly to a stirred solution of N-hydroxypiperidine (1 equiv) in CH_2Cl_2 (2 mL/mmol N-hydroxypiperidine) at 0°C. The reaction mixture was then allowed

to warm up to r.t.. The reaction was complete in 10 min (TLC, alumina, AcOEt) and the slurry was filtered through celite with CH_2Cl_2. After evaporation of the solvent under reduced pressure, the crude nitrone (100% yield) was immediately mixed with the dipolarophile in the cycloaddition solvent.

Synthesis of Δ^1-pyrroline-1-oxide 2

Nitrone **2** was prepared in 15% yield by oxidation of pyrrolidine according to Murahashi's procedure[35]. Yellow oil, ^{1}H NMR: 6.92–6.89 (1H, m, H2), 4.02–3.93 (2H, m, H5), 2.80–2.71 (2H, m, H3), 2.33–2.21 (2H, m, H4), ^{13}C NMR: 135.6 (C2), 62.4 (C5), 29.0, 19.4, MS, *m/z*: 85 ($M^{+\cdot}$, 100%), 57 (38), 55 (59), 53 (30), 51 (11), 41 (28), 39 (43).

Cycloaddition of nitrone 1 with (E)-derivative 8c

A solution of nitrone **1** (5.64 10^{-4} mol; 3.6 equiv) and (E)-(R)$_S$-hept-1-enyl p-tolyl sulfoxide **8c** (1.56 10^{-4} mol; 1 equiv) in benzene/EtOH (9/1, 5 mL) was heated at reflux for 2 days. After removal of the solvent under reduced pressure, the cycloadducts were purified by 3 successive chromatographies (alumina, hexane/AcOEt 7/1 then alumina, hexane/AcOEt 3/1 then alumina, CH_2Cl_2).

Isoxazolidine 15 or 16

15% yield, ^{1}H NMR: 7.58 (2H, d, 8, Ar H), 7.33 (2H, d, 8, Ar H), 3.75–3.73 (1H, m), 3.40 (1H, m), 3.05–2.86 (1H, m), 2.66 (1H, m), 2.51 (1H, m), 2.42 (3H, s, ArCH_3), 1.94–1.06 (13H, m), 0.88–0.68 (4H, m), MS, *m/z*: 336 (0.1%) (Calculated for $C_{19}H_{30}NO_2S$, $M^{+\cdot}$+H$^{\cdot}$, 336.1997, found 336.1984), 195 ($M^{+\cdot}$–p-TolSOH, 11), 124 (100), IR: 2956, 2934, 2860, 1463, 1086, 1054 (ν S–O), 1018.

Isoxazolidine 13

43% yield, ^{1}H NMR: 7.64 (2H, d, 8, Ar H), 7.33 (2H, d, 8, Ar H), 3.50 (1H, m, eq H7), 3.41 (1H, dt, 8 and 6, H2), 3.08 (1H, t, 6, H3), 2.60 (1H, ddd, 12, 6 and 2, H3a), 2.52–2.33 (5H, m), 2.03 (1H, td, 12 and 4, ax H7), 1.93–1.68 (3H, m), 1.29–0.82 (9H, m), 0.76 (3H, t, 7, CH_3), 0.58 (1H, m), ^{13}C NMR: 142.9, 139.2, 130.1, 126.4, 76.6, 75.4 (C2, C3a), 69.8 (C3), 55.6 (C7), 32.7, 31.2, 27.1, 24.8, 24.5, 24.1, 22.1, 21.5 (ArCH_3), 13.8 (CH_3), MS, *m/z*: 336 (8%), 335 (33) (Calculated for $C_{19}H_{29}NO_2S$, $M^{+\cdot}$, 335.1919, found 335.1928), 318 ($M^{+\cdot}$–OH$^{\cdot}$, 9), 237 (38), 220 (6), 196 ($M^{+\cdot}$–p-TolSO$^{\cdot}$, 100), 195 (7), 194 (11), 152 (7), 140 (5), 139 (p-TolSO$^+$, 23), 124 (54), IR: 2956, 2934, 2860, 2826, 1494, 1468, 1454, 1442, 1322, 1120, 1084, 1054 (ν S–O), 1018.

Isoxazolidine 14

20% yield, ^{1}H NMR: 7.48 (2H, d, 8, Ar H), 7.31 (2H, d, 8, Ar H), 4.41 (1H, m, H2), 3.51 (1H, m, eq H7), 2.86 (1H, dd, 7 and 5.5, H3), 2.52 (1H, q, 7), 2.41–2.32 (4H, m), 2.09–2.01 (2H, m), 1.88–1.70 (4H, m), 1.25–1.07 (7H, m), 0.86–0.77 (4H, m), MS, *m/z*: 336 (7%), 335 (27) (Calculated for $C_{19}H_{29}NO_2S$, $M^{+\cdot}$, 335.1919, found 335.1924), 318 ($M^{+\cdot}$–OH$^{\cdot}$, 8), 237 (25), 220 (7), 196 ($M^{+\cdot}$–p-TolSO$^{\cdot}$, 79), 195 ($M^{+\cdot}$–p-TolSOH, 32), 194 (43), 152 (22), 140 (p-TolSOH$^{+\cdot}$, 14), 139 (58), 124 (100), 123 (p-TolS$^+$, 6), 100 (23), 97 (20), 91 (20), 84 (19), IR: 2954, 2934, 2860, 1120, 1090, 1058 (ν S–O), 1018.

General procedure for the cycloaddition of cyclic nitrones with (Z)-derivatives 7a–d

A solution of nitrone (3–5 equiv) and dipolarophile **7a–d** (1 equiv) in ether (5 mL/mmol **7a–d**) was left at room temperature for 7–10 days (nitrone **1**) or 17 days (nitrone **2**). After removal of the solvent under reduced pressure, the cycloadducts were purified by chromatography as described below.

Isoxazolidine 17a

89% yield, white solid purified by flash chromatography on silica gel (AcOEt) followed by chromatography on alumina (hexane/AcOEt 1/2), $[\alpha]_D^{22}$+219 ($CHCl_3$, c 1.3), ^{1}H NMR: 7.49 (2H, d, 8, Ar H), 7.32 (2H, d, 8, Ar H), 4.38 (1H, m, H2), 3.42 (1H, m, eq H7), 3.06 (1H, bt, 8, H3), 2.87 (1H, m, H3a), 2.63 (1H, m, ax H7), 2.42 (3H, s, ArCH_3), 1.68–1.48 (6H, m), 1.23–1.11 (2H, m),

0.93 (1H, m), ^{13}C NMR: 141.7, 139.5, 130.3, 124.7, 74.7 (C2), 71.5 (C3a), 64.0 (C3), 55.4 (C7), 30.2 (C4), 24.9, 24.0, 21.8 (Ar*C*H$_3$), 15.8 (*C*H$_3$), MS, *m/z*: 280 (0.1%) (Calculated for $C_{15}H_{22}NO_2S$, $M^{+\cdot}$+H$^{\cdot}$, 280.1371, found 280.1363), 164 (6), 140 (13), 139 (60), 124 (100), IR: 2941, 2879, 2860, 2833, 1125, 1112, 1096, 1085, 1058 (ν S–O).

Isoxazolidine ***18a***

6% yield, white solid purified by flash chromatography on silica gel (AcOEt) followed by chromatography on alumina (hexane/AcOEt 1/2), $[\alpha]_D^{22}$+90 ($CHCl_3$, c 0.9), ^{1}H NMR: 7.62 (2H, d, 8, Ar H), 7.34 (2H, d, 8, Ar H), 4.44 (1H, m, H2), 3.41 (1H, m, eq H7), 3.23 (1H, bt, 8, H3a), 2.43 (4H, m), 1.81–1.15 (7H, m), 1.00–0.85 (2H, m), 0.10 (1H, m), ^{13}C NMR: 143.3, 139.5, 130.5, 126.3, 75.6 (C2), 75.6 (C3a), 68.1 (C3), 55.5 (C7), 28.5 (C4), 24.7, 24.1, 21.9 (Ar*C*H$_3$), 15.1 (*C*H$_3$), MS, *m/z*: 279 (0.2%) (Calculated for $C_{15}H_{21}NO_2S$, $M^{+\cdot}$, 279.1293, found 279.1291), 164 (4), 139 (87), 125 (6), 124 (100), IR: 2943, 2930, 1124, 1114, 1084, 1049 (ν S–O).

Isoxazolidine ***17b***

85% yield, white solid purified by flash chromatography on silica gel (hexane/AcOEt 3/1) followed by chromatography on alumina (hexane/AcOEt 3/1), $[\alpha]_D^{22}$+190 ($CHCl_3$; c 1.2), ^{1}H NMR: 7.46 (2H, d, 8, Ar H), 7.31 (2H, d, 8, Ar H), 4.24 (1H, m, H2), 3.43 (1H, m, eq H7), 3.03 (1H, bt, 8, H3), 2.85 (1H, m, H3a), 2.61 (1H, m, ax H7), 2.41 (3H, s, ArC*H*$_3$), 2.15–1.98 (2H, m), 1.73–1.46 (5H, m), 1.16–1.08 (2H, m), 1.01 (3H, t, 7, C*H*$_3$), 0.79 (1H, m), ^{13}C NMR: 141.6, 139.7, 130.3, 124.6, 78.9 (C2), 71.7 (C3a), 63.3 (C3), 55.4 (C7), 32.7, 30.3, 25.0, 24.0, 21.8 (Ar*C*H$_3$), 20.9, 14.4 (*C*H$_3$), MS, *m/z*: 307 (0.1%) (Calculated for $C_{17}H_{25}NO_2S$, $M^{+\cdot}$, 307.1606, found 307.1620), 167 ($M^{+\cdot}$–p-TolSOH, 13), 139 (3), 124 (100).

Isoxazolidine ***18b***

5% yield, purified by flash chromatography on silica gel (hexane/AcOEt 3/1) followed by chromatography on alumina (hexane/AcOEt 3/1), ^{1}H NMR: 7.62 (2H, d, 8, Ar H), 7.33 (2H, d, 8, Ar H), 4.31 (1H, m, H2), 3.42 (1H, m, eq H7), 3.23 (1H, bt, 8, H3a), 2.43 (3H, s, ArC*H*$_3$), 2.40–2.27 (2H, m), 2.04 (1H, m), 1.78–1.26 (7H, m), 1.01 (3H, t, 7, C*H*$_3$), 0.90–0.81 (1H, m), 0.07 (1H, m), MS, *m/z*: 307 (0.2%) (Calculated for $C_{17}H_{25}NO_2S$, $M^{+\cdot}$, 307.1606, found 307.1607), 168 ($M^{+\cdot}$–p-TolSO$^{\cdot}$, 7), 167 ($M^{+\cdot}$–p-TolSOH, 15), 140 (p-TolSOH$^{+\cdot}$, 2), 139 (p-TolSO$^+$, 4), 124 (100).

Isoxazolidine ***17c***

80% yield, white solid purified by flash chromatography on silica gel (hexane/AcOEt 4/1) followed by chromatography on alumina (hexane/AcOEt 4/1), $[\alpha]_D^{22}$+175 ($CHCl_3$; c 1.1), ^{1}H NMR: 7.46 (2H, d, 8, Ar H), 7.31 (2H, d, 8, Ar H), 4.23 (1H, m, H2), 3.43 (1H, m, eq H7), 3.04 (1H, bt, 8, H3), 2.85 (1H, m, H3a), 2.61 (1H, m, ax H7), 2.41 (3H, s, ArC*H*$_3$), 2.21–2.05 (2H, m), 1.69–1.34 (9H, m), 1.16–1.08 (2H, m), 0.90 (3H, t, 7, C*H*$_3$), 0.79 (1H, m), ^{13}C NMR: 141.5, 139.5, 130.2, 124.5, 79.1 (C2), 71.5 (C3a), 63.2 (C3), 55.3 (C7), 32.0, 30.4, 30.2, 27.2, 24.9, 24.0, 22.9, 21.7 (Ar*C*H$_3$), 14.3 (*C*H$_3$), MS, *m/z*: 318 (0.1%) (Calculated for $C_{19}H_{28}NOS$, $M^{+\cdot}$–HO$^{\cdot}$, 318.1892, found 318.1908), 139 (p-TolSO$^+$, 28), 124 (100), 91 (16), IR: 2956, 2934, 1468, 1456, 1442, 1126, 1112, 1088, 1058 (ν S–O), 1018.

Isoxazolidine ***18c***

5% yield, purified by flash chromatography on silica gel (hexane/AcOEt 4/1) followed by chromatography on alumina (hexane/AcOEt 4/1), ^{1}H NMR: 7.61 (2H, d, 8, Ar H), 7.33 (2H, d, 8, Ar H), 4.28 (1H, m, H2), 3.42 (1H, m, eq H7), 3.23 (1H, bt, 8, H3a), 2.43 (3H, s, ArC*H*$_3$), 2.38–2.29 (2H, m), 2.04 (1H, m), 1.75–1.25 (10H, m), 0.90–0.83 (5H; m), 0.07 (1H, m), MS, *m/z*: 335 (0.1%)

(Calculated for $C_{19}H_{29}NO_2S$, $M^{+\cdot}$, 335.1919, found 335.1922), 195 ($M^{+\cdot}$–p-TolSOH, 11), 124 (100), IR: 2956, 2932, 1494, 1466, 1456, 1442, 1114, 1084, 1050 (ν S–O), 1018.

*Isoxazolidine **17d***

95% yield, white solid purified by flash chromatography on silica gel (hexane/AcOEt 3/1) followed by chromatography on alumina (hexane/AcOEt 1/1), $[\alpha]_D^{22}$+50 ($CHCl_3$; c 1.1), ^{1}H NMR: 7.36–7.28 (5H, m), 7.12 (2H, d, 8, H p-Tol), 7.03 (2H, d, 8, H p-Tol), 5.04 (1H, bd, 8.5, H2), 3.55 (2H, m), 3.10 (1H, bt, 9), 2.78 (1H, bt, 9, ax H7), 2.34 (3H, s, ArCH_3), 1.86–1.65 (4H, m), 1.50–1.30 (2H, m), ^{13}C NMR: 141.3, 140.0, 135.0, 129.5, 129.0, 128.7, 128.0, 125.0, 80.3 (C2), 73.3 (C3a), 67.6 (C3), 55.2 (C7), 30.2 (C4), 24.4, 23.5, 21.2 (ArCH_3), MS, *m/z*: 242 (12%) (Calculated for $C_{15}H_{14}OS$, ϕ-C=C–S(O)–p-Tol, 242.0765, found 242.0781), 226 (ϕ-C=C–S–p-Tol, 52), 201 (100) (Calculated for $C_{13}H_{15}NO$, $M^{+\cdot}$–p-TolSOH, 201.1154, found 201.1146), 200 (61), 194 (35), 139 (p-TolSO^+, 35), 124 (95), 105 (60), 91 (74), 77 (66), IR: 2943, 2861, 2829, 1455, 1085, 1047 (ν S–O).

*Isoxazolidine **18d***

1% yield, purified by flash chromatography on silica gel (hexane/AcOEt 3/1) followed by chromatography on alumina (hexane/AcOEt 1/1), ^{1}H NMR: 7.58–7.26 (9H, m), 5.38 (1H, m, H2), 3.49 (3H, m), 2.61 (1H, m), 2.40 (3H, s, ArCH_3), 2.07 (1H, m), 1.69–0.85 (4H, m), 0.23–0.19 (1H, m), MS, *m/z*: 325 (3%) (Calculated for $C_{20}H_{23}NOS$, $M^{+\cdot}$–O, 325.1499, found 325.151), 226 (ϕ-C=C–S–p-Tol, 84), 202 (26), 201 ($M^{+\cdot}$–p-TolSOH, 50), 194 (31), 139 (p-TolSO^+, 27), 124 (78), 105 (82), 91 (100), IR: 2944, 2934, 1110, 1084, 1054 (ν S–O), 1016.

*Isoxazolidine **19***

63% yield, white solid purified by chromatography on alumina (hexane/AcOEt 1/2), $[\alpha]_D^{22}$+134 ($CHCl_3$; c 0.9), ^{1}H NMR: 7.52 (2H, d, 8, Ar H), 7.33 (2H, d, 8, Ar H), 4.50 (1H, quint, 6.5, H2), 4.23 (1H, m, H3a), 3.06 (3H, t, 6.5, H3, 2H6), 2.42 (3H, s, ArCH_3), 1.79–1.61 (3H, m), 1.58 (3H, d, 6.5, CH_3), 1.15 (1H, m), ^{13}C NMR: 142.0, 140.2, 130.5, 124.7, 77.0 (C2), 74.6 (C3a), 62.1 (C3), 56.2 (C6), 31.8 (C4), 24.0 (C5), 21.8 (ArCH_3), 16.6 (CH_3), MS, *m/z*: 265 (0.3%) (Calculated for $C_{14}H_{19}NO_2S$, $M^{+\cdot}$, 265.1136, found 265.1133), 125 ($M^{+\cdot}$–p-TolSOH, 76), 110 (100), IR: 2973, 2944, 2873, 1494, 1455, 1442, 1379, 1116, 1088, 1061 (ν S–O).

*Isoxazolidine **20***

9% yield, white solid purified by chromatography on alumina (hexane/AcOEt 1/2), $[\alpha]_D^{22}$+195 ($CHCl_3$; c 1.2), ^{1}H NMR: 7.64 (2H, d, 8, Ar H), 7.35 (2H, d, 8, Ar H), 4.65 (1H, quint, 6, H2), 3.28–3.23 (2H, m, H3, H3a), 3.10 (1H, dt, 12 and 6, H6), 2.94 (1H, dt, 12 and 6, H6), 2.43 (3H, s, ArCH_3), 1.79–1.65 (4H, m), 1.53 (1H, m), 1.33 (1H, m), 0.88 (1H, m), ^{1}H NMR (C_6D_6): 7.43 (2H, d, 8, Ar H), 6.83 (2H, d, 8, Ar H), 4.50 (1H, quint, 6, H2), 3.13 (1H, m), 3.06 (1H, t, 6), 2.91 (1H, m, H6), 2.68 (1H, m, H6), 1.95 (3H, s, ArCH_3), 1.86 (3H, d, 6, CH_3), 1.43–1.25 (1H, m), 1.11–0.81 (2H, m), 0.48 (1H, m), ^{13}C NMR: 143.2, 139.9, 130.6, 126.1, 80.0 (C2), 75.4 (C3a), 65.4 (C3), 56.5 (C6), 31.2 (C4), 23.9 (C5), 21.9 (ArCH_3), 16.2 (CH_3), MS, *m/z*: 265 (0.4%) (Calculated for $C_{14}H_{19}NO_2S$, $M^{+\cdot}$, 265.1136, found 265.1134), 164 (5), 140 (6), 139 (p-TolSO^+, 23), 126 ($M^{+\cdot}$–p-Tol$SO^{\cdot}$, 75), 125 ($M^{+\cdot}$–p-TolSOH, 100), 110 (74), 91 (18), IR: 2976, 2947, 2872, 1494, 1455, 1446, 1375, 1116, 1084, 1056 (ν S–O).

General procedure for the TMSI/NaI reduction of cycloadducts

Trimethylsilyl iodide (10 equiv) was added to a stirred solution of sodium iodide (4 equiv) and the cycloadduct (1 equiv) in dry acetonitrile (5 mL/mmol isoxazolidine) at room temperature. After 1.5–2 h, the mixture was taken up in ether (75 mL/mmol isoxazolidine) and washed with aqueous sodium thiosulfate and ammonia. The aqueous solution was then extracted with CH_2Cl_2 (3×150 mL/mmol

isoxazolidine), the combined organic layers were dried ($MgSO_4$) and, after removal of the solvent under reduced pressure, the crude mixture was purified by chromatography on silica gel.

*Isoxazolidine **21***

90% yield from **17*a***, colourless oil purified by chromatography on silica gel (hexane/AcOEt 3/1), $[\alpha]_D^{22}$ −58.5 ($CHCl_3$; c 0.4), ^{1}H NMR: 7.22 (2H, d, 8, Ar H), 7.09 (2H, d, 8, Ar H), 4.40 (1H, bquint, 6.5, H2), 3.66 (1H, bt, 9, H3a), 3.43 (1H, bd, 9, eq H7), 2.46 (1H, bt, 9, ax H7), 2.31 (3H, s, ArCH_3), 2.13–1.98 (2H, m), 1.82–1.58 (3H, m), 1.42–1.21 (5H, m), ^{13}C NMR: 136.4, 132.8, 130.0, 130.0, 75.0 (C2), 72.6 (C3a), 57.4 (C3), 55.4 (C7), 28.9 (C4), 24.9, 23.9, 21.1 (ArCH_3), 16.7 (CH_3), MS, *m/z*: 263 (10%) (Calculated for $C_{15}H_{21}NOS$, $M^{+\cdot}$, 263.1344, found 263.1350), 164 (Me–C=C–S–p-Tol, 100), 149 (12), 124 (5), 123 (p-TolS^+, 4), 100 (39), 91 (6), IR: 2979, 2944, 2862, 2829, 1494, 1442, 1379, 1124, 1112, 1092.

*Isoxazolidine ent-**21***

55% yield from **18*a***, colourless oil purified by chromatography on silica gel (hexane/AcOEt 3/1), $[\alpha]_D^{22}$ +56 ($CHCl_3$; c 0.8), ^{1}H NMR: 7.22 (2H, d, 8, Ar H), 7.09 (2H, d, 8, Ar H), 4.40 (1H, bquint, 6.5, H2), 3.67 (1H, bt, 9, H3a), 3.43 (1H, bd, 9, eq H7), 2.46 (1H, m, ax H7), 2.31 (3H, s, ArCH_3), 2.13–1.98 (2H, m), 1.91–1.63 (3H, m), 1.58–1.21 (5H, m), ^{13}C NMR: 136.9, 133.2, 130.5, 130.4, 75.3 (C2), 73.0 (C3a), 57.8 (C3), 55.8 (C7), 29.2 (C4), 25.2, 24.2, 21.4 (ArCH_3), 17.0 (CH_3), MS, *m/z*: 263 (9%) (Calculated for $C_{15}H_{21}NOS$, $M^{+\cdot}$, 263.1344, found 263.1350), 164 (Me–C=C–S–p-Tol, 100), 149 (13), 123 (p-TolS^+, 6), 100 (35), 91 (8), IR: 2944, 2862, 2828, 1494, 1124, 1112, 1092.

*Isoxazolidine **22***

91% yield from **19**, colourless oil purified by chromatography on silica gel (AcOEt), $[\alpha]_D^{22}$ −47 (CH_2Cl_2; c 0.8), ^{1}H NMR: 7.31 (2H, d, 8, Ar H), 7.11 (2H, d, 8, Ar H), 4.41 (1H, quint, 6, H2), 3.69 (1H, m, H3a), 3.58 (1H, t, 5.5), 3.20–3.01 (2H, m), 2.33 (3H, s, ArCH_3), 2.07–1.56 (4H, m), 1.35 (3H, d, 6, CH_3), ^{13}C NMR: 137.6, 132.0, 132.0, 130.5, 75.9 (C2), 71.9 (C3a), 61.2 (C3), 57.3 (C6), 31.6 (C4), 24.1 (C5), 21.4 (ArCH_3), 16.2 (CH_3), MS, *m/z*: 249 (5%) (Calculated for $C_{14}H_{19}NOS$, $M^{+\cdot}$, 249.1187, found 249.1191), 164 (Me–C=C–S–p-Tol, 100), 149 (12), 123 (4), 91 (6), IR: 2970, 2946, 2936, 2872, 1494, 1444, 1376, 1120, 1094, 1080.

*Isoxazolidine ent-**22***

92% yield from **20**, colourless oil purified by chromatography on silica gel (AcOEt), $[\alpha]_D^{22}$ +47 (CH_2Cl_2; c 0.6), ^{1}H NMR: 7.30 (2H, d, 8, Ar H), 7.11 (2H, d, 8, Ar H), 4.41 (1H, quint, 6, H2), 3.69 (1H, m, H3a), 3.57 (1H, t, 5.5), 3.17–3.03 (2H, m), 2.32 (3H, s, ArCH_3), 1.99–1.59 (4H, m), 1.35 (3H, d, 6, CH_3), ^{13}C NMR: 137.5, 132.2, 131.9, 130.3, 75.8 (C2), 71.9 (C3a), 61.2 (C3), 57.3 (C6), 31.6 (C4), 24.1 (C5), 21.5 (ArCH_3), 16.2 (CH_3), MS, *m/z*: 249 (4%) (Calculated for $C_{14}H_{19}NOS$, $M^{+\cdot}$, 249.1187, found 249.1189), 164 (Me–C=C–S–p-Tol, 100), 149 (17), 123 (6), 91 (8), IR: 2970, 2946, 2936, 2872, 1494, 1444, 1376, 1094, 1080.

*General procedure for the W2 Raney nickel hydrogenolysis of cycloadducts **13** and **14***

The cycloadduct was dissolved in methanol (35 mL/mmol isoxazolidine) and hydrogenated over a large excess of W2 Raney nickel (purchased from Aldrich) at room temperature and atmospheric pressure. After completion of the reaction (30 min), the solution was filtered through celite and nickel was washed with hot methanol (caution: Raney nickel is pyrophoric). After removal of the solvent under reduced pressure, the residue was dissolved in $CHCl_3$ (35 mL/mmol isoxazolidine) and the solution was extracted with 0.6 M aqueous HCl (3×35 mL/mmol isoxazolidine). The aqueous solution was then basified with NaOH and extracted with chloroform (3×110 mL/mmol isoxazolidine). Removal of the solvent under reduced pressure yielded a mixture of amino alcohol **9*c*** along with its C8-epimer **23*c***.

Amino alcohol ent-9c

From **13** 60% yield of a mixture of **ent-9c** together with 20–25% of epimeric **ent-23c**, $[\alpha]_D^{22}-7$ (EtOH; c 1.7)[36], ^{1}H NMR: 3.87 (1H **ent-9c**, tt, 7 and 3.5, H8 **ent-9c**), 3.81–3.78 (1H **ent-23c**, m, H8 **ent-23c**), 3.07–2.84 (4H **ent-9c**+3H **ent-23c**, m, N*H*, O*H*, eq H6 **ent-9c+ent-23c**, H2 **ent-9c**), 2.70 (1H **ent-23c**, tt, 11 and 2.5, H2 **ent-23c**), 2.56 (1H **ent-9c+ent-23c**, td, 12 and 3, ax H6 **ent-9c+ent-23c**), 1.83–1.80 (1H **ent-9c+ent-23c**, m, eq H7 **ent-9c+ent-23c**), 1.63–1.28 (15H **ent-9c+ent-23c**, m), 0.89 (3H **ent-9c+ent-23c**, t, 7, C*H*$_3$ **ent-9c+ent-23c**). Other spectral properties of **9c** are described below.

Amino alcohol 9c

From **14** 65% yield of a mixture of **9c** together with 5–10% of epimeric **23c**, $[\alpha]_D^{22}+9$ (EtOH; c 0.3)[36].

General procedure for the Ni/Al hydrogenolysis of cycloadducts 17a–c

A 1 M aqueous KOH solution (25 mL/mmol isoxazolidine) was added to a stirred solution of **17a–c** in methanol (25 mL/mmol isoxazolidine). Ni/Al alloy (10× weight of **17a–c**) was then added slowly. The reaction mixture was stirred at room temperature overnight and another portion of Ni/Al was then added (5× weight of **17a–c**) along with methanol (12.5 mL/mmol isoxazolidine) and 1 M aqueous KOH (12.5 mL/mmol isoxazolidine). 4 or 5 h after the second addition, nickel was removed by filtration through a pad of celite and washed with hot methanol (100–200 mL/mmol isoxazolidine, caution: Raney nickel is pyrophoric). After evaporation of the methanol under reduced pressure, aqueous NaOH (50 mL/mmol isoxazolidine) was added to the residue and the aqueous solution was extracted with CH_2Cl_2 (4×50 mL/mmol isoxazolidine). Removal of the solvent under reduced pressure gave the amino alcohol **9a–c** without any further purification, unless otherwise stated.

Amino alcohol 9a

Purification by sublimation (0.01 Torr, 30°C), from **17a** 37% yield of a mixture of **9a** together with 5–10% of epimeric **23a**, $[\alpha]_D^{22}+23$ (EtOH; c 1.1) ($[\alpha]_D^{22}$ lit.[27] +28.5 (EtOH; c 2.32)), ^{1}H NMR: 4.10 (1H **9a**, qt, 6 and 3.5, H8 **9a**), 3.08–3.02 (3H **9a+23a**, m, N*H*, O*H*, eq H6 **9a+23a**), 2.87 (1H **9a**, m, $W_{1/2}$=19, H2 **9a**), 2.56 (1H **9a+23a**, td, 12 and 3, ax H6 **9a+23a**), 1.81 (1H **9a+23a**, m, eq H7 **9a+23a**), 1.62–1.28 (7H **9a+23a**, m), 1.17 (3H **9a**, d, 6, H9 **9a**), 1.13 (3H **23a**, d, 6, H9 **23a**). Other spectral properties of **9a** are described below.

Amino alcohol 9b

From **17b** 60% yield of **9b** ((+)-halosaline), white solid, $[\alpha]_D^{22}+17$ (EtOH; c 0.45) ($[\alpha]_D^{22}$ lit.[21] +19.5 (EtOH; c 0.6)), ^{1}H NMR: 3.89 (1H, tt, 8 and 4, H8), 3.07–2.84 (4H, m, N*H*, O*H*, eq H6, H2), 2.56 (1H, td, 12 and 3, ax H6), 1.81 (1H, m, eq H7), 1.62–1.26 (11H, m), 0.92 (3H, t, 7, C*H*$_3$), ^{13}C NMR: 69.1 (C8), 55.1 (C2), 47.2 (C6), 42.3 (C7), 40.4, 31.8 (C3), 26.4, 25.0, 19.3, 14.5 (*C*H$_3$), MS, *m/z*: 171 (2%) (Calculated for $C_{10}H_{21}NO$, $M^{+\cdot}$, 171.1623, found 171.1655), 128 (10), 110 (9), 98 (7), 84 (100).

Amino alcohol 9c

Purified by chromatography on alumina ($CHCl_3$ then $CHCl_3$/MeOH 95/5), 43% yield from **17c**, $[\alpha]_D^{22}+9$ (EtOH; c 0.7), ^{1}H NMR: 3.87 (1H, tt, 7 and 3.5, H8), 3.07–2.84 (4H, m, N*H*, O*H*, eq H6, H2), 2.56 (1H, td, 12 and 3, ax H6), 1.81 (1H, m, eq H7), 1.63–1.28 (15H, m), 0.89 (3H, t, 7, C*H*$_3$), ^{13}C NMR: 69.1 (C8), 54.8 (C2), 46.9 (C6), 42.1 (C7), 37.9, 32.0, 31.5, 26.1, 25.6, 24.8, 22.7, 14.0 (*C*H$_3$), MS, *m/z*: 199 (1%) (Calculated for $C_{12}H_{25}NO$, $M^{+\cdot}$, 199.1936, found 199.1960), 128 (3), 124 (4), 112 (9), 110 (8), 84 (100).

Reductive opening of the isoxazolidine nucleus of 17a

A 1 M aqueous KOH solution (3.5 mL) was added to a well-stirred solution of cycloadduct **17a** (79.6 mg, 2.85 10^{-4} mol) in methanol (3.5 mL) at room temperature. Ni/Al alloy (244 mg, 3× weight

17*a*) was added slowly. The reaction was checked by TLC (alumina, AcOEt) and after 1.75 h the reaction mixture was filtered through a pad of celite with ethanol (50 mL, Caution: Raney nickel is pyrophoric) and the solvent was removed under reduced pressure. Nickel was dissolved with 6 M aqueous HCl (100 mL) and the aqueous solution was basified with NaOH. The residue from the evaporation of ethanol was added to the aqueous solution which was then extracted with CH_2Cl_2 (4×100 mL). Removal of the solvent under reduced pressure yielded pure amino alcohol **24** (74.0 mg, 92%). $[\alpha]_D^{22}$+291 ($CHCl_3$; c 0.8), ^{1}H NMR: 7.46 (2H, d, 8, Ar H), 7.34 (2H, d, 8, Ar H), 4.71 (1H, qd, 6.5 and 2, H8), 4.10 (2H, bs, N*H*, O*H*), 3.33 (1H, dt, 11 and 2, H2), 2.99 (1H, dt, 12 and 4, eq H6), 2.52 (1H, td, 12 and 3, ax H6), 2.43 (3H, s, ArCH_3), 2.11 (1H, t, 2, H7), 1.75–1.08 (9H, m), ^{13}C NMR: 141.1, 141.0, 130.2, 124.3, 73.7 (C8), 66.1 (C2), 55.1 (C7), 46.4 (C6), 30.6 (C3), 25.5, 24.8, 21.8 (*C*H_3), 21.5 (*C*H_3), MS, *m/z*: 282 (0.3%) (Calculated for $C_{15}H_{24}NO_2S$, $M^{+\cdot}$+$H^{\cdot}$, 282.1528, found 282.1526), 141 ($M^{+\cdot}$–p-TolSOH, 60), 140 (p-TolSOH$^{+\cdot}$, 37), 139 (p-TolSO$^+$, 42), 126 ($M^{+\cdot}$–p-TolSOH–$CH_3^{\cdot}$, 100), 124 (68), 123 (57), IR: 3480 (ν O–H), 3283, 2977, 2936, 2859, 1470, 1440, 1151, 1110, 1085, 1041 (ν S–O), 1017.

*N-acylation of **24***

Potassium carbonate (401.8 mg, 2.91 10^{-3} mol, 11 equiv) and methyl chloroformate (0.21 mL, 2.7 10^{-3} mol, 10 equiv) were added to a well-stirred suspension of amino alcohol **24** (74.0 mg, 2.63 10^{-4} mol) in water (6 mL) at room temperature. More K_2CO_3 was added so as to keep pH >7 and the reaction mixture was left at r.t. overnight. Water (4 mL) was added to the suspension and the mixture was extracted with CH_2Cl_2 (4×10 mL). Evaporation of the solvent under reduced pressure yielded the pure carbamate **25** (87.8 mg, 98%). $[\alpha]_D^{22}$+105 ($CHCl_3$; c 0.8), ^{1}H NMR: 7.42 (2H, d, 8, Ar H), 7.30 (2H, d, 8, Ar H), 4.88 (1H, m, H2), 4.28 (1H, bs, O*H*), 3.98 (1H, m, H8), 3.74 (3H, s, NC(O)OCH_3), 2.96 (1H, bd, 11, eq H6), 2.47 (1H, bt, 11, ax H6), 2.41 (3H, s, ArCH_3), 1.77–1.15 (8H, m), 0.67 (1H, m), ^{13}C NMR: 157.6 (N*C*(O)OCH$_3$), 143.0, 140.3, 130.1, 123.7, 68.4 (C8), 64.7 (C7), 53.5 (NC(O)O*C*H$_3$), 47.7 (C2), 40.9 (C6), 27.3, 25.0, 21.8 (*C*H_3), 21.5 (*C*H_3), 18.4 (C4), MS, *m/z*: 340 (0.1%) (Calculated for $C_{17}H_{26}NO_4S$, $M^{+\cdot}$+$H^{\cdot}$, 340.1582, found 340.1582), 200 ($M^{+\cdot}$–p-TolSO$^{\cdot}$, 44), 182 ($M^{+\cdot}$–H_2O–p-TolSO$^{\cdot}$, 13), 156 (12), 143 (8), 142 (100), 140 (p-TolSOH$^{+\cdot}$, 10), 139 (p-TolSO$^+$, 8), IR: 3452 (ν O–H), 2941, 2932, 2866, 1682 (ν C=O), 1471, 1448, 1408, 1314, 1181, 1172, 1091, 1056 (ν S–O), 1043 (ν S–O).

*W6 Raney nickel desulfurization of **25***

Caution: W6 Raney nickel shouldn't be exposed to high temperature[23]. Carbamate **25** (73.2 mg, 2.16 10^{-4} mol) was dissolved in methanol (7 mL) and hydrogenated over a large excess of W6 Raney nickel[23] at room temperature and atmospheric pressure. The reaction was checked by TLC (alumina, hexane/AcOEt 1/1) and portions of nickel were added after 5 h, 24 h and 30 h. After completion (35 h), the mixture was filtered through celite and nickel was washed with methanol (400 mL, caution: Raney nickel is pyrophoric). After removal of the solvent under reduced pressure, aqueous diluted ammonia (5 mL) was added to the residue and the aqueous solution was extracted with CH_2Cl_2 (4×10 mL). Evaporation of the solvent under reduced pressure was followed by chromatography on alumina (hexane/AcOEt 1/1) which yielded pure compounds **26*a*** (33.7 mg, 77%) and **27** (2.8 mg, 6%).

*Carbamate **26a***

Colourless oil, ^{1}H NMR: 4.51–4.46 (1H, m, H2), 4.01–3.96 (2H, m, eq H6, O*H*), 3.72 (3H, s, NC(O)OCH_3), 3.57 (1H, m, H8), 2.74 (1H, td, 14 and 2, ax H6), 2.00 (1H, ddd, 14, 12 and 2, 1H7), 1.78–1.23 (7H, m), 1.19 (3H, d, 6, CH_3), ^{13}C NMR: 157.9 (N*C*(O)OCH$_3$), 63.9 (C8), 53.2 (NC(O)O*C*H$_3$), 47.9 (C2), 39.9, 39.7 (C6, C7), 29.9, 25.9, 23.0 (*C*H$_3$), 19.6 (C4), MS, *m/z*: 201 (6%) (Calculated for $C_{10}H_{19}NO_3$, $M^{+\cdot}$, 201.1365, found 201.1359), 143 (9), 142 (100), IR: 3480 (ν O–H), 2969, 2941, 2866, 1679 (ν C=O), 1472, 1451, 1411, 1372, 1261, 1178 (ν C–O).

Carbamate 27

Colourless oil, ^{1}H NMR: 4.39 (1H, m, H2), 3.98 (1H, m, eq H6), 3.88–3.75 (1H, m, H8), 3.69 (3H, s, NC(O)OC*H*$_3$), 2.89 (1H, td, 13 and 2.5, ax H6), 2.8–1.9 (1H, bs, O*H*), 1.84 (1H, dt, 14 and 8, 1H7), 1.67–1.26 (7H, m), 1.22 (3H, d, 6, C*H*$_3$), ^{13}C NMR: 156.7 (N*C*(O)OCH$_3$), 66.5 (C8), 52.8 (NC(O)O*C*H$_3$), 49.2 (C2), 40.2, 39.7 (C6, C7), 29.6, 25.7, 23.9 (*C*H$_3$), 19.3 (C4), MS, *m/z*: 201 (2%) (Calculated for $C_{10}H_{19}NO_3$, $M^{+\cdot}$, 201.1365, found 201.1361), 142 (100), IR: 3450 (ν O–H), 2940, 2865, 1698 (ν C=O), 1450, 1411, 1370, 1264, 1177 (ν C–O).

TMSI/MeOH deprotection of ***26a***

Trimethylsilyl iodide (0.24 mL, 1.7 mmol, 10 equiv) was added to a solution of **26*a*** (32.9 mg, 1.63 10^{-4} mol) in dry CH_2Cl_2 (4 mL). The reaction mixture was heated at reflux for 1 h and, after cooling, a few drops of methanol were added. After 10 min at room temperature, the volatile components were removed under reduced pressure and the residue was taken up in aqueous NaOH solution (5 mL). The solution was extracted with CH_2Cl_2 (4×10 mL) and evaporation of the solvent under reduced pressure yielded pure (+)-sedridine **9*a*** (22.7 mg, 97%). $[\alpha]_D^{22}$+26 (EtOH; c 1.3) ($[\alpha]_D^{22}$ lit[27]+28.5 (EtOH; c 2.32)), ^{1}H NMR: 4.10 (1H, qt, 6 and 3.5, H8), 3.21 (2H, bs, N*H*, O*H*), 3.05 (1H, m, eq H6), 2.87 (1H, m, $W_{1/2}$=19, H2), 2.56 (1H, td, 12 and 3, ax H6), 1.81 (1H, m, eq H7), 1.62–1.20 (7H, m), 1.17 (3H, d, 6, H9), ^{13}C NMR: 65.4 (C8), 55.1 (C2), 47.3, 44.2 (C6, C7), 31.8 (C3), 26.4, 25.1 (C5, C4), 23.9 (*C*H$_3$), MS, *m/z*: 143 (3%) (Calculated for $C_8H_{17}NO$, $M^{+\cdot}$, 143.1310, found 143.1317), 84 (100), IR: 3343 (br, ν N–H et ν O–H), 2967, 2934, 2858, 2819, 1451, 1147, 1116.

Synthesis of tetrahydrooxazine ***28***

A 0.37% aqueous solution of formaldehyde (1.20 mL, 1.48 10^{-4} mol, 1 equiv) was added to a solution of (+)-sedridine **9*a*** (21.2 mg, 1.48 10^{-4} mol) in methanol (1 mL) at room temperature. After 25 min the solvent was removed under reduced pressure. The residue was taken up in aqueous diluted ammonia (5 mL) and the solution was extracted with CH_2Cl_2 (3×10 mL). Evaporation of the solvent under reduced pressure yielded pure tetrahydrooxazine **28** (19.0 mg, 83%). ^{1}H NMR: 4.21 (1H, quint d, 7 and 1, H8), 4.08 (1H, d, 8, 1H10), 3.98 (1H, d, 8, 1H10), 2.74 (1H, dtd, 11, 4 and 1, eq H6), 2.36 (1H, m, H2 or ax H6), 2.09–1.83 (2H, m), 1.77–1.45 (4H, m), 1.41–1.24 (6H, m), ^{13}C NMR: 79.0 (C10), 68.4 (C8), 54.7 (C2), 49.1 (C6), 35.8 (C7), 31.9, 25.0, 24.0, 16.9 (*C*H$_3$), MS, *m/z*: 155 (22%) (Calculated for $C_9H_{17}NO$, $M^{+\cdot}$, 155.1310, found 155.1305), 154 ($M^{+\cdot}$–H$^{\cdot}$, 33), 138 ($M^{+\cdot}$–HO$^{\cdot}$, 21), 112 (56), 98 (37), 84 (100), 83 (73), IR: 2938, 2812 (Bohlmann), 2778 (Bohlmann), 2756 (Bohlmann), 1256, 1126. Racemic **28** in the presence of Eu(hfc)$_3$, ^{1}H NMR: 5.65 (1H (**2R,8R**), bd, 7, 1H10 (**2R,8R**)), 5.31 (1H (**2S,8S**), d, 8, 1H10 (**2S,8S**)), 4.94–4.90 (1H+1H (**2R,8R**), m, H8+1H10 (**2R,8R**)), 4.75 (1H (**2S,8S**), d, 8, 1H10 (**2S,8S**)), 3.17 (1H, m, eq H6), 3.00–2.82 (1H, m, H2 or ax H6), 2.74–2.33 (2H, m), 1.95–1.45 (10H, m).

Reductive opening of the isoxazolidine nucleus of ***19***

A 1 M aqueous KOH solution (3.2 mL) was added to a well-stirred solution of cycloadduct **19** (74.7 mg, 2.81 10^{-4} mol) in methanol (3.2 mL) at room temperature. Ni/Al alloy (230 mg, 3× weight **19**) was added slowly. The reaction was checked by TLC (alumina, AcOEt) and after 2.25 h the reaction mixture was filtered through a pad of celite with ethanol (50 mL, caution: Raney nickel is pyrophoric) and the solvent was removed under reduced pressure. Nickel was dissolved with 6 M aqueous HCl (100 mL) and the aqueous solution was basified with NaOH. The residue from the evaporation of ethanol was added to the aqueous solution which was then extracted with CH_2Cl_2 (4×125 mL). Removal of the solvent under reduced pressure yielded pure amino alcohol **29** (64.2 mg, 85%). White solid, $[\alpha]_D^{22}$+265 ($CHCl_3$; c 0.8), ^{1}H NMR: 7.44 (2H, d, 8, Ar H), 7.31 (2H, d, 8, Ar H), 4.49 (1H, q, 6.5, H7), 4.5–3.0 (2H, bs, N*H*, O*H*), 3.83 (1H, m, H2), 3.00–2.86 (2H, m, H5), 2.51 (1H, s, H6), 2.41 (3H, s, ArC*H*$_3$), 1.80–1.48 (7H, m), ^{13}C NMR: 142.0, 140.8, 130.1, 124.2, 74.7 (C7), 65.5 (C2), 54.4 (C6), 46.7 (C5), 30.3, 25.0, 21.8 (C*H*$_3$), 21.5 (C*H*$_3$), MS, *m/z*: 267 (0.1%) (Calculated for $C_{14}H_{21}NO_2S$,

$M^{+\cdot}$, 267.1293, found 267.1298), 139 (8), 128 (12), 127 ($M^{+\cdot}$–p-TolSOH, 61), 112 (100), IR: 3425 (br, ν O–H), 3324 (ν N–H), 2958, 2934, 1178, 1138, 1108, 1048 (ν S–O).

N-acylation of ***29***

Potassium carbonate (336.0 mg, 2.43 10^{-3} mol, 10 equiv) and methyl chloroformate (0.19 mL, 2.4 10^{-3} mol, 10 equiv) were added to a well-stirred suspension of amino alcohol **29** (63.7 mg, 2.38 10^{-4} mol) in water (4.5 mL) at room temperature. More K_2CO_3 was added so as to keep pH >7 and the reaction mixture was left at r.t. overnight. Water (5 mL) was added to the suspension and the mixture was extracted with CH_2Cl_2 (4×15 mL). Evaporation of the solvent under reduced pressure yielded the crude carbamate **30** which was purified by chromatography on silica gel (AcOEt) (73.6 mg, 95%). White solid, $[\alpha]_D^{22}$+83 ($CHCl_3$; c 0.7), ^{1}H NMR: 7.44 (2H, d, 8, Ar H), 7.30 (2H, d, 8, Ar H), 4.92 (1H, bs, O*H*), 4.68 (1H, bt, 8, H2), 4.17 (1H, m, H7), 3.71 (3H, s, NC(O)OCH_3), 3.39–3.33 (1H, m, H5), 3.17 (1H, ddd, 11.5, 8 and 3.5, H5), 2.56 (1H, bd, 9, H6), 2.41 (3H, s, ArCH_3), 1.91–1.47 (7H, m), ^{13}C NMR: 157.9 (N*C*(O)OCH$_3$), 143.1, 140.7, 130.3, 124.2, 73.6 (C7), 65.5 (C6), 54.9, 53.4 (C2, NC(O)O*C*H$_3$), 46.8 (C5), 30.4, 23.6, 22.1 (CH_3), 21.7 (CH_3), MS, *m/z*: 325 (0.4%) (Calculated for $C_{16}H_{23}NO_4S$, $M^{+\cdot}$, 325.1348, found 325.1347), 186 ($M^{+\cdot}$–p-TolSO$^{\cdot}$, 31), 168 (11), 154 (6), 142 (44), 139 (p-TolSO$^+$, 8), 128 (100).

W6 Raney nickel desulfurization of ***30***

Carbamate **30** (73.6 mg, 2.26 10^{-4} mol) was dissolved in methanol (8 mL) and hydrogenated over a large excess of W6 Raney nickel[23] at room temperature and atmospheric pressure. The reaction was checked by TLC (alumina, hexane/AcOEt 1/1). After completion (6 h), the mixture was filtered through celite and nickel was washed with methanol (400 mL, caution: Raney nickel is pyrophoric). After removal of the solvent under reduced pressure, aqueous diluted ammonia (5 mL) was added to the residue and the aqueous solution was extracted with CH_2Cl_2 (4×10 mL). Evaporation of the solvent under reduced pressure was followed by chromatography on alumina (hexane/AcOEt 1/1) which yielded pure compound **31** (31.9 mg, 75%). Colourless oil, $[\alpha]_D^{22}$–2 (CH_2Cl_2; c 0.7), ^{1}H NMR: 4.69 (1H, bs, O*H*), 4.22 (1H, m), 3.71 (4H, m), 3.42–3.34 (2H, m), 2.04–1.85 (3H, m), 1.71–1.26 (3H, m), 1.17 (3H, d, 6.5, CH_3), ^{13}C NMR: 157.8 (N*C*(O)OCH$_3$), 63.9 (C7), 54.9, 52.8 (C2, NC(O)O*C*H$_3$), 46.5, 45.7 (C6, C5), 31.4, 23.8, 22.8 (*C*H$_3$), MS, *m/z*:: 187 (3%) (Calculated for $C_9H_{17}NO_3$, $M^{+\cdot}$, 187.1208, found 187.1212), 169 ($M^{+\cdot}$–H_2O, 4), 154 (5), 149 (5), 142 (14), 128 (100), 114 (6), IR: 3466 (ν O–H), 2970, 2960, 2932, 1688 (ν C=O), 1454, 1386, 1196, 1132, 1114.

Synthesis of (−)-hygroline ***10***

$LiAlH_4$ (64.1 mg, 1.69 mmol, 10 equiv) was added to a solution of carbamate **31** (30.5 mg, 1.63 10^{-4} mol) in dry THF (9 mL) and the reaction mixture was heated at reflux temperature for 40 min. After cooling, excess hydride was decomposed by addition of a few drops of water and the mixture was filtered through celite with THF (50 mL). After removal of the solvent under reduced pressure, the residue was taken up in aqueous NaOH (5 mL) and the solution was extracted with CH_2Cl_2 (4×10 mL). Evaporation of the solvent under reduced pressure (caution: (−)-hygroline is a rather volatile compound) yielded pure (−)-hygroline **10** (19.4 mg, 83%). Yellow oil which crystallized on storage (−20°C), $[\alpha]_D^{22}$–49 (EtOH; c 0.4) ($[\alpha]_D^{22}$ lit.[27] –50 (EtOH; c 0.77)), ^{1}H NMR (CCl_4+capillary $CD_3C(O)CD_3$): 5 (1H, bs, O*H*), 3.99 (1H, m, H7), 3.11–3.05 (1H, m), 2.48 (1H, m), 2.33 (3H, s, NCH_3), 2.11 (1H, m), 1.88–1.59 (5H, m), 1.32 (1H, m), 1.02 (3H, d, 6, CH_3), ^{1}H NMR: 6–5 (1H, bs, O*H*), 4.16 (1H, m, H7), 3.06 (1H, m), 2.58 (1H, m), 2.34 (3H, s, NCH_3), 2.15 (1H, m), 1.98–1.67 (5H, m), 1.43 (1H, dt, 15 and 2), 1.14 (3H, d, 6, CH_3), ^{13}C NMR: 65.6, 65.3 (C7, C2), 57.8 (C5), 41.2 (N*C*H$_3$), 37.8 (C6), 29.0, 24.4 (*C*H$_3$), 24.0, MS, *m/z*: 143 (2%) (Calculated for $C_8H_{17}NO$, $M^{+\cdot}$, 143.1310, found 143.1301), 84 (100), IR: 3322 (ν O–H), 2970, 2928, 2878, 2846, 2794, 1458, 1442, 1266 (ν C–N).

Heterolytic ring-opening of ***21***

Freshly distilled methyl chloroformate (0.47 mL, 6.0 mmol, 14 equiv) and dry potassium carbonate (827.4 mg, 5.99 mmol, 14 equiv) were added to a well-stirred solution of sulfide **21** (112.1 mg, 4.26 10^{-4} mol) in dry acetonitrile (11 mL). The reaction mixture was left at room temperature for 24 h and more K_2CO_3 (453.0 mg, 3.28 mmol, 7.7 equiv) and methyl chloroformate (0.37 mL, 4.7 mmol, 11 equiv) were added to the suspension. 24 h after the second addition, aqueous diluted ammonia (55 mL) was added and the mixture was extracted with CH_2Cl_2 (4×60 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Chromatography on silica gel (hexane/AcOEt 3/1) followed by chromatography on alumina (hexane/AcOEt 7/1) yielded epimeric ketones **32**, **33**, and unreacted sulfide **21** (5.8 mg, 5%).

β-Amino ketone ***32***

62.6 mg, 46%, white solid isolated after chromatography on silica gel. $[\alpha]_D^{22}-86$ ($CHCl_3$; c 1.1), ^{1}H NMR: 7.27 (2H, d, 8, Ar H), 7.10 (2H, d, 8, Ar H), 4.66 (1H, m, H2), 4.01 (1H, d, 12, H7), 3.86 (1H, m, eq H6), 3.67 (3H, s, NC(O)OCH_3), 2.84 (1H, m, ax H6), 2.31 (3H, s, ArCH_3), 2.25 (3H, s, CH_3–C(O)), 1.68–1.31 (6H, m), ^{13}C NMR: 204.6 (C8), 156.0 (N*C*(O)OCH$_3$), 138.2, 132.2, 130.1, 129.7, 58.9 (C7), 52.8, 51.6 (C2, NC(O)O*C*H$_3$), 40.0, 25.5, 25.0, 24.8, 21.1 (C9, Ar*C*H$_3$), 19.0 (C4), MS, *m/z*: 321 (0.5%) (Calculated for $C_{17}H_{23}NO_3S$, $M^{+\cdot}$, 321.1399, found 321.1396), 180 (p-TolS–C=C(OH)Me$^{+\cdot}$, 12), 142 (100), 123 (p-TolS$^+$, 4), 91 (3), IR: 2952, 2867, 1705 (ν C=O), 1445, 1407, 1262, 1172 (ν C–O).

β-Amino ketones ***32+33*** *(2/1)*

25.0 mg, 18%, colourless oil isolated after chromatography on alumina. ^{1}H NMR: 7.28 (2H **33**, d, 8, Ar H **33**), 7.27 (2H **32**, d, 8, Ar H **32**), 7.10 (2H **32+33**, d, 8, Ar H **32+33**), 4.66 (1H **32+33**, m, H2 **32+33**), 4.11–3.86 (2H **32+33**, m, H7, eq H6 **32+33**), 3.76 (3H **33**, s, NC(O)OCH_3 **33**), 3.67 (3H **32**, s, NC(O)OCH_3 **32**), 2.86 (1H **32+33**, m, ax H6 **32+33**), 2.31 (3H **32+33**, s, ArCH_3 **32+33**), 2.28 (3H **33**, s, CH_3–C(O) **33**), 2.25 (3H **32**, s, CH_3–C(O) **32**), 1.75–1.42 (6H **32+33**, m), MS, *m/z*: 321 (0.5%), (Calculated for $C_{17}H_{23}NO_3S$, $M^{+\cdot}$, 321.1399, found 321.1409), 180 (p-TolS–C=C(OH)Me$^{+\cdot}$, 14), 156 (5), 142 (100), IR: 2951, 2867, 1703 (ν C=O), 1446, 1407, 1262, 1172 (ν C–O).

Desulfurization of ***32+33***

Powdered Zn (81.0 mg, 1.24 mmol, 12 equiv) was added to a solution of β-amino ketones **32** and **33** (**32/33** 2/1, 33.1 mg, 1.03 10^{-4} mol) in ethanol (1 mL) and acetic acid (0.32 mL). The mixture was heated at reflux for 2 h. More Zn (21.9 mg, 3.35 10^{-4} mol, 3 equiv) and AcOH (0.08 mL) were added to the suspension and the mixture was heated at reflux for another 30 min. After cooling, water (8 mL) was added to the suspension. After basification with NaOH, the aqueous solution was extracted with CH_2Cl_2 (4×10 mL). After removal of the solvent under reduced pressure the compound was purified by chromatography on silica gel (hexane/AcOEt 1/1). Starting material (1.2 mg, 4%) was partially recovered and pure (−)-(2S)-N-carbomethoxypelletierine ***11a*** (18.3 mg) was isolated in 89% yield. $[\alpha]_D^{22}-21$ ($CHCl_3$; c 0.5) ([α]$_D^{22}$ **ent-11*a***^{29}+16 ($CHCl_3$; c 1.5)), ^{1}H NMR: 4.75 (1H, m, H2), 4.00 (1H, m, eq H6), 3.68 (3H, s, NC(O)OCH_3), 2.83 (1H, m, ax H6), 2.74–2.66 (2H, m, H7), 2.18 (3H, s, H9), 1.77–1.26 (6H, m), ^{13}C NMR: 207.4 (C8), 156.6 (N*C*(O)OCH$_3$), 53.0 (NC(O)O*C*H$_3$), 48.0 (C2), 44.9 (C7), 40.3 (C6), 30.5 (C9), 28.8, 25.7, 19.3 (C4), MS, *m/z*: 199 (6%) (Calculated for $C_{10}H_{17}NO_3$, $M^{+\cdot}$, 199.1208, found 199.1205), 142 (100), 140 ($M^{+\cdot}$–$CH_3O^{\cdot}$–CO, 43), IR: 2943, 1700 (ν C=O), 1447, 1409, 1369, 1262.

NaBH$_4$/MeOH reduction of (−)-N-carbomethoxypelletierine ***11a***

$NaBH_4$ (16.2 mg, 4.3 10^{-4} mol, 5.4 equiv) was added to a solution of ketone **11*a*** (15.8 mg, 7.9 10^{-5} mol) in methanol (1.5 mL) and the reaction mixture was left at room temperature for 45 min. Methanol was removed under reduced pressure and the residue was taken up in water (4 mL). The

aqueous solution was extracted with CH_2Cl_2 (4×10 mL). After removal of the solvent under reduced pressure, chromatography on alumina (hexane/AcOEt 1/=1) yielded pure amino alcohols **26*a*** (6.2 mg, 39%) and **27** (8.9 mg, 56%). The enantiomeric purity of **26*a*** was assayed *via* the tetrahydrooxazine **28** obtained in two steps as described above.

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