# Intramolecular Cycloaddition/Rearrangement of Alkylidenecyclopropane Nitrones from Palladium(0)-Catalyzed Alkylation of Amino Acid Derivatives

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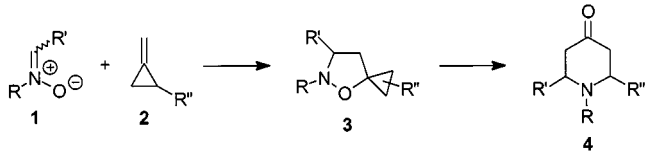
*Dedicated to Prof. Armin de Meijere on the occasion of his 60th birthday*

**Keywords:** Alkylidenecyclopropanes / Palladium / Intramolecular 1,3-dipolar cycloaddition / Thermal rearrangement / Pyrrolo[3,4-*b*]pyridine

Several alkylidenecyclopropanes have been synthesized in high yields and optical purity by palladium(0)-catalyzed substitution of 1-tosyloxy-1-vinyl cyclopropane using *N*-tosylamino esters or glycolic ester as nucleophiles. The new alkylidenecyclopropanes were transformed to the corresponding nitrones without loss of optical purity, except in the case of the phenylglycine derivative. The alkylidenecyclopropane nitrones underwent smooth in situ intramolecular cycloaddition with a stereoselectivity that was moderate with most substituted substrates, but complete with phenylglycine and proline derivatives. The spirocyclopropane isoxazolidines were transformed by selective thermal rearrangements in octahydro-2*H*-pyrrolo[3,4-*b*]pyridin-7-ones and octahydrofuro[3,4-*b*]pyridin-7-one, uncommon ring systems resembling biologically active natural and nonnatural products. An example of the extension of the process to an alkylidenecyclopropane nitrile oxide is also reported.

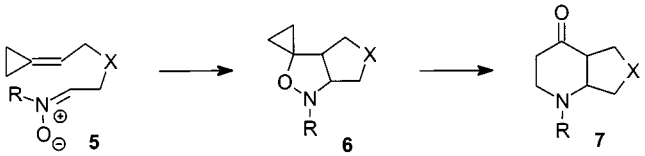
## Introduction

The impetus to organic synthesis is supplied by the challenge to discover new selective methods able to match the structural complexity that nature introduces in natural products. The result of the challenge is the growing interest in chemoselectivity, regioselectivity, and stereoselectivity, and more recently in "atom economy"[1] and environmentally friendly synthesis. Brandi and co-workers have developed a method[2] for the synthesis of tetrahydropyridones by a thermal rearrangement of 5-spirocyclopropane isoxazolidines, in turn obtained by 1,3-dipolar cycloaddition of nitrones **1** to methylenecyclopropanes **2**, inspired by these concepts (Scheme 1).



Scheme 1. Intermolecular cycloaddition/rearrangement process

The method, indeed, has been successfully applied to the synthesis of natural products with high chemo-, regio- and stereoselectivity.[3] It also fulfills the requirements of "atom economy" as only thermal induction is necessary without any added catalyst for the process to take place, and it often occurs in a multistep cascade manner. The performance of the process is best in its intramolecular version,[4] which leads to the formation of ring-fused tetrahydropyridones, because it profits from all the positive characteristic features whilst minimizing or eliminating the negative ones (Scheme 2).



Scheme 2. Intramolecular cycloaddition/rearrangement process

The possibility of synthesizing alkylidenecyclopropane nitrones **5** that undergo intramolecular cycloaddition, with the correct regioselectivity for the rearrangement, is a great opportunity for the extension of the application of this method to organic synthesis. Alkylidenecyclopropanes form a peculiar class of strained olefinic compounds, with remarkable synthetic potential;[5][6] they undergo ring opening with palladium dichloride to produce π-allyl palladium complexes,[7] carbopalladation with vinyl- and arylhalides in the presence of $Pd^0$,[8] regioselective $Pd^0$-catalyzed [3 + 2] cycloaddition with olefinic and acetylenic substrates,[5][9] and Pauson−Khand cyclization with dicobalt hexacarbonyl complexes of acetylene.[10][11] Most of these reactions have been reported to occur both inter- and intramolecularly. Moreover, alkylidenecyclopropanes constitute the most

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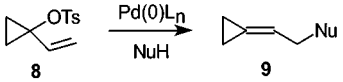
suitable precursors for cyclobutanone synthesis.[12] As for many cyclopropane derivatives, they are also endowed with specific bioactivities.[13] Optically active alkylidenecyclopropanes have recently been prepared by the regio- and stereoselective $Pd^0$-catalyzed reduction of asymmetric 1-(1-alkenyl)cyclopropyl esters by sodium formate.[14]

Among the syntheses of alkylidenecyclopropanes, recently extensively reviewed,[15] the synthesis developed by Salaün, de Meijere and co-workers, which consists of a $Pd^0$-catalyzed nucleophilic substitution of 1-tosyloxy-1-vinylcyclopropane **8**,[16] (readily available from vinylation and tosylation[17] of cyclopropanone hemiacetal)[18] is by far the best, because it complies with all the requirements of chemo-, regio- and stereoselectivity previously mentioned (Scheme 3).



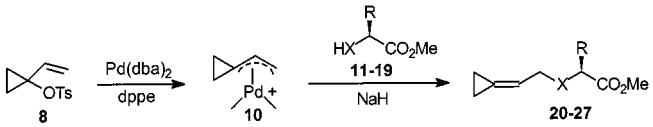

Scheme 3. Palladium(0)-catalyzed alkylation of 1-tosyloxy-1-vinylcyclopropane

In this paper we report the successful combination of the described methods for the synthesis of new optically pure octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-4-ones,[19] one hexahydro-6*H*-pyrrolo[3,4-*b*]pyridin-4-one, and of an octahydrofuro[3,4-*b*]pyridin-4-one.

## Results and Discussion

### Synthesis of Alkylidenecyclopropanes

Despite the large amount of literature regarding palladium(0)-catalyzed nucleophilic substitution of allyl acetates or analogues,[20] the use of amines as nucleophiles has been only of comparatively limited interest.[16,21,22] In particular, use of amino acids as nucleophiles has not so far been reported.[23][24] We now report the results of the reactions of the eight α-amino esters **11**−**18** and of the methyl glycolate **19** with 1-tosyloxy-1-vinylcyclopropane **8** (Scheme 4, Table 1). *N*-Tosyl protected amino esters were used instead of unprotected ones to avoid double alkylation of the nitrogen[16] and to provide a protected nitrogen for further steps of the synthesis (Table 1, entries *a*, *c*−*g*). The *N*-Boc protected glycine ester **12** failed to give the expected alkylidenecyclopropane (entry *b*). $Pd(dba)_2$ and dppe were found to be the best source of generating $Pd^0$ complexes in situ. The reaction gave in all cases excellent yields of the alkylidene compounds **20**−**27** at room temperature. Methyl glycolate **19** gave **27** with a yield similar to all the other amino esters (entry *i*). Although NaH (1 equiv. relative to amino esters) was used to deprotonate *N*-tosyl nitrogen, *C*-alkylation was never observed and all the products were obtained with ee >98% as confirmed by $^1$H-NMR analysis with a shift reagent, $Eu(hfc)_3$. An excess of NaH did provoke racemization. The regioselectivity of the substitution was complete, as the primary position of the allyl system was always attacked. It is worth noting that if this position is favoured by steric hindrance, attack at this position produces a strained alkylidenecyclopropane, whereas attack on the tertiary carbon would reduce the final strain of the system. This regioselectivity has already been observed for other nucleophiles, and must be related to the role of the cyclopropane ring, as the analogous 1,1-dimethylallyl acetate gives allylation with much lower selectivity.[16] Furthermore, the latter is much less reactive.




Scheme 4. Palladium(0)-catalyzed 1,1-dimethyleneallylation of α-amino- and α-hydroxy esters

To explain such different behaviour and justify the experimental data we might suppose a different structure for the π-1,1-dimethyleneallyl palladium complex **10** and the corresponding π-1,1-dimethylallyl palladium complex. Computer calculations were performed for both the π-allyl palladium complexes **28** and **29** having two molecules of $PH_3$ as ligands (Figure 1) using the semiempirical method PM3(tm);[25a] the results were refined using ab initio calculations with a 3-21G(*) basis.[25b] The study suggests that in **28** palladium is closer to the cyclopropyl carbon C-1 than to the other allylic terminus C-2′ (2.14 Å and 2.29 Å, respectively), while in **29** the trend is reversed with the metal being closer to the primary carbon C-3 than to the tertiary carbon C-1 (2.20 Å and 2.31 Å, respectively). Lacking any relevant electronic effect, these data provide evidence for the higher accessibility of the primary carbon in complex **10** and explain both the higher reactivity and regioselectivity

Table 1. Syntheses of the alkylidenecyclopropanes **20**−**27** through palladium(0)-catalyzed nucleophilic substitution of **8**[a]

| Entry | R | X | Nucleophile | mol-% $Pd(dba)_2$[b] | Reaction Time | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| *a* | H | NTs | **11** | 6 | 11h | **20** | 81 |
| *b* | H | NBoc | **12** | 5 | 17d | | − |
| *c* | Me | NTs | **13** | 6 | 11h | **21** | 95 |
| *d* | *i*Pr | NTs | **14** | 5 | 12h | **22** | 82 |
| *e* | Ph | NTs | **15** | 5 | 13h | **23** | 85 |
| *f* | $PhCH_2$ | NTs | **16** | 6 | 11h | **24** | 77 |
| *g* | 3-Indolyl-$CH_2$ | NTs | **17** | 5 | 11d | **25** | 92 |
| *h* | $CH_2CH_2CH_2N$ | | **18** | 5 | 11d | **26** | 80 |
| *i* | H | O | **19** | 6 | 12h | **27** | 82 |

[a] All reactions were performed in THF at room temp. − [b] dppe was employed in 1.2:1 molecular ratio with $Pd(dba)_2$, in all cases.

of the complex **10** towards nucleophilic attack. This study confirms previous calculations carried out on the corresponding 1,1-dimethylene- and 1,1-dimethylallyl cations.[16]

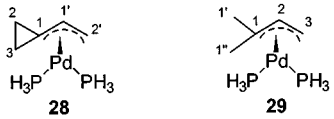
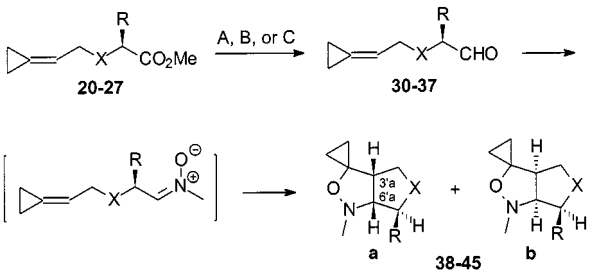



Figure 1. Model 1,1-dimethylene and 1,1-dimethylallyl palladium complexes

## Cycloadditions and Thermal Rearrangements

The introduction of the nitrone moiety in the alkylidenecypropanes, necessary to perform the intramolecular 1,3-dipolar cycloaddition (Scheme 2), required conversion of the ester group into aldehyde with retention of the stereochemistry at the α carbon atom. Several direct and indirect methods were used to convert the esters **20−27** into the corresponding aldehydes **30−37** (Scheme 5), but none proved to be of general application. The unbranched esters **20** and **27** and the phenyl derivative **23** were reduced to **30**, **33**, and **37**, respectively, by DIBALH (Diisobutylaluminum hydride) in high yields (Table 2, entries *a*, *d*, *h*), but the other esters afforded only mixtures of different products. The reductions of the ester to alcohol followed by a Swern oxidation[26a] gave the best results with **21**, **22**, **24**, and **26** (entries *b*, *c*, *e*, *g*), while the tryptophan derivative **35** was




Scheme 5. Methods: A) DIBAH (0.9 equiv.), entries *a*, *h*; 2 equiv., entry *d*), $CH_2Cl_2$, −78°C; B) *i*. DIBAH (excess), $CH_2Cl_2$, −78°C then room temp., *ii* $(COCl)_2$, DMSO, *i*$Pr_2NEt$ or $Et_3N$, $CH_2Cl_2$, −78°C then room temp.; C) *i*. LiOH, MeOH/$H_2O$ 3:1, room temp., *ii*. MeNHOMe · HCl, pyridine, DCC, $CH_2Cl_2$, room temp., *iii*. $LiAlH_4$, $Et_2O$, room temp.

obtained through Castro′s method (entry *f*).[26b] The use of the most suitable procedure allowed each aldehyde to be obtained in a very fair yield and purity. All the aldehydes **30−37** were characterized by spectroscopic means and used in the next step without further purification in order to avoid any likely decomposition or racemization.

The cyclopropylidene aldehydes **30−37** reacted at room temperature with *N*-methylhydroxylamine to give the corresponding *N*-methylnitrones which spontaneously evolved to the tricyclic isoxazolidines **38−45**, respectively, in the reaction conditions (Scheme 5). The strain introduced by the cyclopropylidene ring increases the cycloaddition rate dramatically.[27] As expected, only "fused" cycloadducts were obtained as the strain caused by the chain joining the two reactive sites, prevents the formation of regioisomeric "bridged" adducts.[27][19]

The coupling constants between the two bridgehead hydrogens in **38−45** ($J_{H3'a\text{-}H6'a}$ = 6.6−8.8 Hz) show that all the adducts are *cis*-fused; furthermore, the formation of *trans*-fused analogues would be disfavoured by a greater ring-fusion strain.

The tricyclic isoxazolidines **38** and **45** were obtained from the unbranched alkylidenecyclopropanes **30** and **37** in 71% and 90% yield, respectively (Table 2, entries *a*, *h*). All the other substituted substrates **31−36** afforded two diastereoisomeric products, **39−44a** and **b** in similar ratios with the exception of the phenylglycine and proline derivatives **33** and **36**, which afforded **41a** and **44a** (entries *d* and *g*, Table 2), isolated as a single diastereoisomer. The isoxazolidine **41a**, however, showed no optical rotation suggesting that the aldehyde or the corresponding nitrone racemized during the reaction. The lower stability of phenyl intermediates could also account for the lower yield observed. All the other adducts could be easily separated by flash chromatography on silica gel in their two diastereoisomers and were obtained enantiomerically pure, as proved by $^1$H-NMR analysis in the presence of a chiral shift reagent, in good yields.

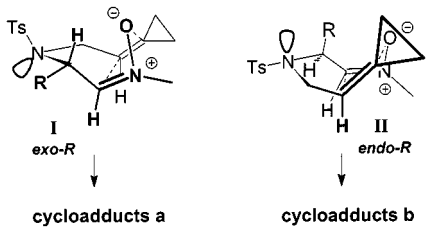
The stereochemical assignment to isomers **a** and **b** has been made on the basis of the values of the vicinal coupling constants between $H^{6'a}$ and $H^{6'}$ protons. All the cycloadducts of type **a** are characterized by a vicinal coupling constant in accord with a *trans* relationship, smaller ($J_{trans}$ =

Table 2. Conversion of the esters **20−27** into the corresponding aldehydes **30−37** and syntheses of the spirocyclopropaneisoxazolidines **38−45** through intramolecular 1,3-dipolar cycloaddition

| Entry | R | X | Ester | Method | Aldehyde | Yield (%) | Adducts | **a/b** | Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|---|
| *a* | H | NTs | **20** | A | **30** | 98 | **38**[a] | – | 71[d] |
| *b* | Me | NTs | **21** | B | **31** | 98 | **39**[a] | 45:55 | 81 |
| *c* | *i*Pr | NTs | **22** | B | **32** | 98 | **40**[b] | 39:61 | 62 |
| *d* | Ph | NTs | **23** | A | **33** | 81 | **41**[b] | > 99:1 | 46[d] |
| *e* | $PhCH_2$ | NTs | **24** | B | **34** | 95 | **42**[a] | 38:62 | 74 |
| *f* | 3-Indolyl-$CH_2$ | NTs | **25** | C | **35** | 78 | **43**[b] | 61:39 | 63 |
| *g* | $CH_2CH_2CH_2N$ | | **26** | B | **36** | 89 | **44**[b] | > 99:1 | 95 |
| *h* | H | O | **27** | A | **37** | > 98 | **45**[b] | – | 90[d] |

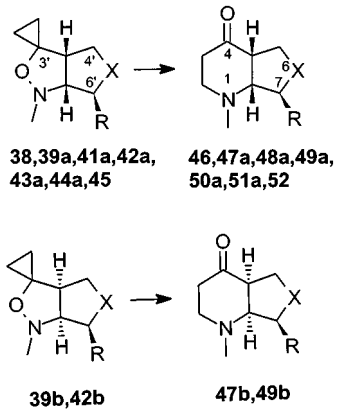
[a] Reaction performed in $H_2O$ with excess *N*-methylhydroxylamine hydrochloride and pyridine at room temp. – [b] Same as [a] with $NEt_3$ or *i*$Pr_2EtN$ in $CCl_4$ or $CH_2Cl_2$. – [c] Yields of isolated compounds. – [d] Racemic.

2.7−5.2 Hz) than those observed for diastereoisomers **b** ($J_{cis}$ = 6.2−8.6 Hz), suggesting that the R substituents occupy the convex face of the molecule in compounds **a**. These data contrast somewhat with the values of coupling constants found by Aurich in analogous cycloadducts.[27] The discrepancy must be ascribed to a different conformation in compounds **a** and **b** caused by the spirocyclopropane ring and by the *N*-tosyl substituent which causes the flattening of the nitrogen. Since the nitrone moiety should react in these conditions in its most stable (*Z*)-configuration,[28] compounds **a** and **b** should derive from the *exo*-R (**I**) and *endo*-R (**II**)[29] transition states, respectively (Scheme 6).




Scheme 6. Transition states for intramolecular cycloadditions

The methyl group is too small to induce diastereoselectivity in the formation of cycloadducts **39a** and **39b** (d.e. = 10%), whereas bulkier substituents such as isopropyl and benzyl appeared to favour the formation of **40b** and **42b** derived from the *endo*-R (**II**) transition state, and unexpectedly to the same extent (d.e. = 22 and 24%, respectively). On the other hand, the phenyl and proline groups provided diastereoselectively pure cycloadducts **41a** and **44a** (d.e. = >99%) arising from the *exo*-R (**I**) transition state. It is noteworthy that nitrones prepared from the corresponding *N*-allyl amino acids, and thus with no cyclopropane ring strain, have recently been reported to provide diastereomerically pure (1*R*,5*R*,8*S*)-3-oxa-2,7-diazabicyclo[3.3.0]octanes, therefore also exclusively derived from an *exo*-R transition state.[27] Calculation of transition-state energies by simple molecular mechanic calculation (MAD),[30] demonstrates that the *exo*-R (**I**) and *endo*-R (**II**) transition states are only slightly different in energy when R = Me ($\Delta E$ = 1.5 kcal/mol) justifying this lack of diastereoselection, but markedly better when R = Ph ($\Delta E$ = 4.4 kcal/mol). A possible added stabilization by π-stacking effects between the planar *N*-tosyl group and the equatorial phenyl in cycloadduct **41a**, relative to **41b** (axial phenyl group) could be also taken into account to interpret this total diastereoselectivity. For the proline derivative, the strain introduced by the fused ring clearly favoured the *exo*-R (**I**) transition state ($\Delta E$ = 10 kcal/mol) and entailed the exclusive formation of the cycloadduct **44a**.



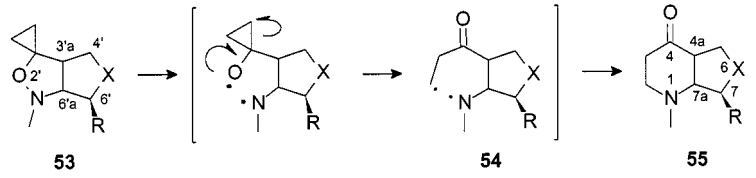

Scheme 7. Thermal rearrangements

The separated diastereomeric cycloadducts of Table 3 were subjected to heating in xylenes at temperatures ranging from 126 to 140°C for the required time (Scheme 7, Table 3) and underwent ring expansion with formation of the pyrrolo[3,4-*b*]pyridin-4-ones **46−50**, the furano analogue **52** and the pyrido[2,3-*a*]pyrrolizine **51a**, in satisfactory yields and as a single product. The thermal rearrangements proceeded through a homolysis of the weak N−O bond in **53**, followed by opening of the cyclopropane ring and intramolecular radical coupling between the nitrogen and the terminal carbon atoms of **54** (Scheme 8). The process turned out to be completely chemo- and regioselective as only bicyclic products **55** were recovered; the formation of open isomers, which could originate by concomitant 1,5-H shift,[2] was not observed. The ring fusion must induce the fast cyclization of the diradical **54** by reducing the rotational equilibria of the two chains.

Table 3. Thermal rearrangement of the spirocyclopropaneisoxazolidines **38−45**

| Entry | R | X | Isoxazolidine | Time[a] | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| *a* | H | NTs | (±)-**38** | 6 h | (±)-**46** | 49 |
| *b* | Me | NTs | (−)-**39a** | 6 h | (−)-**47a** | 64 |
| *c* | Me | NTs | (−)-**39b** | 6 h | (+)-**47b** | 43 |
| *d* | Ph | NTs | (±)-**41a** | 42 h | (±)-**48a** | 53 |
| *e* | $PhCH_2$ | NTs | (−)-**42a** | 6 h | (+)-**49a** | 44 |
| *f* | $PhCH_2$ | NTs | (−)-**42b** | 6 h | (−)-**49b** | 43 |
| *g* | 3-Indolyl-$CH_2$[c] | NTs | (+)-**43a** | 33 h | (+)-**50a** | 41 |
| *i* | $CH_2CH_2CH_2N$ | | (−)-**44a** | 5 h | (−)-**51a** | 70 |
| *j* | H | O | (±)-**45** | 36 h | (±)-**52** | 73 |

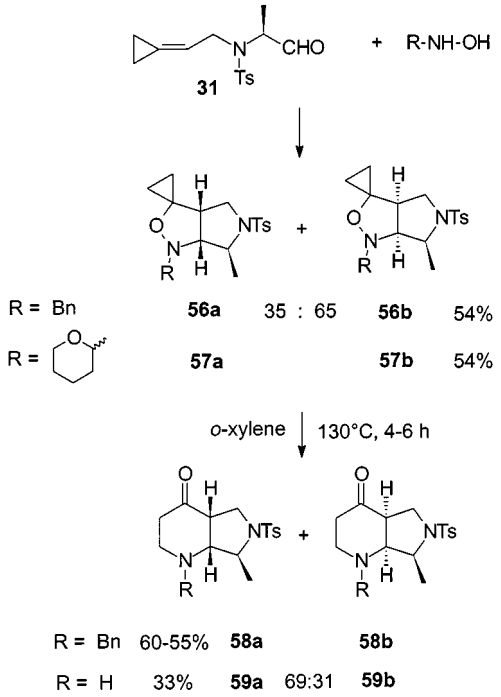
[a] Reaction was performed in refluxing xylenes (136−140°C) (entries *a*, *b*, *c*, *e*, *f*), or in *o*-xylene at 130°C (entries *d*, *g*, and *j*) or at 126°C (entry *i*) − [b] Yields refer to isolated compounds. − [c] Isomer **43b** decomposed in the reaction conditions.




Scheme 8. Mechanism of the rearrangement

The stereochemistry at the stereogenic centers 3′a, 6′, and 6′a in the tricyclic isoxazolidines was retained at the corresponding positions 4a, 7, and 7a in the bicyclic pyridones as none of these atoms were involved in the rearrangement process (Scheme 8). The fusion in the final products was confirmed by the observation in the $^1$H NMR spectrum, when possible, of a pattern of coupling constant between $H^{4a}$ and $H^{7a}$ ($J_{cis}$ = 4.7−7.4 Hz), consistent with a *cis* relationship in a six-membered ring.

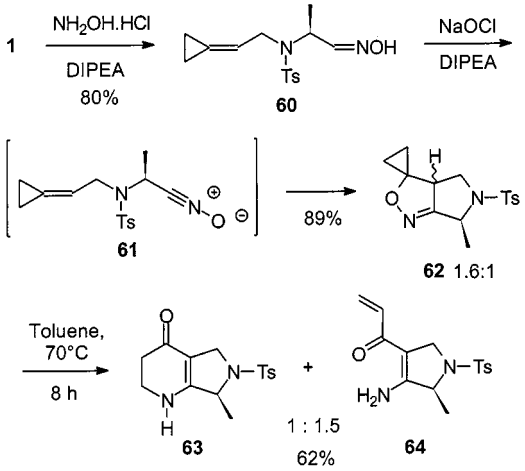
Interest in the application of the 6*H*-pyrrolo or furano[3,4-*b*]pyridine ring system of **46−52** for the synthesis of bioactive compounds,[19][31] stimulated the study of possible modifications of their structures to allow more efficient employment in the synthesis. The *N*-methyl protection in **46−52** is not the most appropriate for further elaboration of the structures. Other protecting groups that could be removed in different reaction conditions were then studied. *N*-Benzyl-substituted isoxazolidines **56a/56b** (35:65 ratio, 54% yield) were isolated by analogous from aldehyde **31** using *N*-benzylhydroxylamine to generate the nitrone (Scheme 9).




Scheme 9. Cycloaddition/rearrangement with *N*-benzyl and *N*-tetrahydropyranyl nitrones

The thermal rearrangement led to the pyrrolo[3,4-*b*]pyridones **58a** and **58b** in a yield of 55−60% similar to that of *N*-methyl derivatives. This result is somewhat unexpected as *N*-benzylisoxazolidines were previously[32] found to be unstable in the thermal rearrangement conditions, probably because of the formation of an unstable *N*-benzyl diradical intermediate. The good yield obtained in this case might be ascribed to the fast ring closure of the diradical intermediate favoured by the fusion with the second ring. Another approach consists of the protection of the nitrogen as hemiaminal, ready to be cleaved under acidic conditions. This has been done by reacting the aldehyde **31** with the oxime of 5-hydroxypentanaldehyde, which is in equilibrium in solution with 2-hydroxylaminotetrahydropyran (Scheme 9). The resulting nitrone, without isolation, afforded a complex mixture of diastereomeric isoxazolidines **57a**, **b** in 54% yield. Thermal rearrangement afforded the unprotected pyrrolo[3,4-*b*]pyridones **59a**, **b** in poor yield (33%, 69:31 ratio), as the protecting group was lost during purification by silica gel chromatography.

Another possibility offered by the methodology, is the extension of the process to cyclopropylidene nitrile oxides, by simply replacing substituted hydroxylamines with the parent one. Treatment of the aldehyde **31** with $NH_2OH \cdot HCl$ and diisopropylethylamine (DIPEA) afforded the oxime **60** which, upon oxidation with NaOCl and DIPEA, gave the nitrile oxide **61** immediately undergoing cycloaddition to a 1.6:1 mixture of diastereomeric isoxazolines **62** in 89% yield from the oxime (Scheme 10). The thermal rearrangement occurred readily in toluene to give a mixture of the hexahydropyrrolo[3,4-*b*]pyridone **63** and its open-chain isomer **64** in 1:1.5 ratio and 62% com-




Scheme 10. Cycloaddition/rearrangement of an alkylidenecyclopropane nitrile oxide

bined yield. The pyrroline **64** was most likely derived from a preferred 1,5-H shift of the diradical intermediate.

## Conclusion

The combination of a new synthesis of optically pure alkylidenecyclopropanes by palladium(0)-catalyzed substitution of 1-tosyloxy-1-vinylcyclopropane with *N*-tosyl amino esters, and thermal rearrangement of spirocyclopropane isoxazolidines derived from those alkylidenecyclopropanes, has produced a new convenient synthesis of octahydro-6*H*-pyrrolo[3,4-*b*]pyridine-4-ones. This ring system has, until now, only been of limited interest in the literature, although very recently an interesting biological activity has been observed as a substance P antagonist[19] or as part of potent DNA gyrase inhibitors.[31]

Moreover, the same partially dehydrogenated ring system is present in the B and C rings of camptothecin (**65**),[33] the potent antitumor agent mappicine (**66**),[34] the related natural potent antiviral agent pumiloside (**67**),[35] and non-natural products (Figure 2). The reported synthesis provides straightforward access to the pyrrolo[3,4-*b*]pyridine ring system and is sufficiently general to allow the incorporation of different substituents and functionalization on the ring. For example, the introduction of an A ring on the route to camptothecin analogues can be easily achieved, as already shown,[2b] using alkylidenenorcarane starting materials. Studies along these lines are currently under investigation in our laboratories.

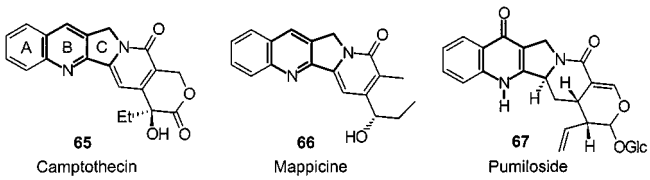



Figure 2. Camptothecin and related alkaloids

## Experimental Section

**General Remarks:** All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately dried before use. − $R_f$ values refer to TLC on 0.25 mm silica gel plates (Merck $F_{254}$) obtained using the same eluent as in the column chromatographies, except where indicated. − Melting points were determined on a RCH Kofler or on a Mettler FP-5 apparatus. − Polarimetric measurements were performed on a JASCO DIP-370 or on a Perkin−Elmer 241 polarimeter. − NMR spectra were recorded on Varian Gemini ($^1$H 200 MHz), Bruker AC200 ($^1$H 200 MHz), Bruker AM250 ($^1$H 250 MHz), VXR 300 ($^1$H 300 MHz) and Bruker DRX-500 ($^1$H 500 MHz), with $CDCl_3$ as solvent, except where indicated; the NMR data are reported in δ (ppm) from TMS. − IR spectra were recorded in $CDCl_3$ solution on a Perkin−Elmer 881 or on a Perkin−Elmer 682 spectrophotometer. − Mass spectra were recorded on a QMD 1000 Carlo Erba, Hewlett−Packard 5792A or Nermag R-10 coupled with a OKI DP 125 gas chromatographer. Relative percentages are shown in brackets. Accurate mass spectra were recorded on a MAT 95S. − Elemental analyses were performed with a Perkin−Elmer 240 C analyzer or by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette (France).

**Starting Material:** 1-Tosyloxy-1-vinylcyclopropane (**8**) was prepared according to a published procedure.[16,17,18]

**General Procedure for the Palladium(0)-Catalysed Nucleophilic Substitution of the 1-Tosyloxy-1-vinylcyclopropane (8):** A mixture of $Pd(dba)_2$ (5−6 mol-%) and dppe (6.0−7.2 mol-%) was degassed under vacuum for 1 h. Then, under argon, was added a 0.05−1.4 M solution of 1-tosyloxy-1-vinylcyclopropane **8** (1.87−14.3 mol) in THF. After 10 min the mixture, which had turned green, was added to a solution of the sodium methyl amino esters (or sodium methyl glycolate) [prepared in a separated flask from the methyl amino esters **11** and **13**−**18** (or methyl glycolate **19**) (1.0−2.0 equiv., 0.06−1.2 M in THF) which were added slowly to pentane-washed sodium hydride (1.0−2.4 equiv.)]. After the mixture had been stirred 1 h to 1d at room temp., evaporation of the solvent and flash chromatography on silica gel of the residue gave the alkylidenecyclopropanes **20**−**27** in 77−95% yields.

**Methyl *N*-(2-Cyclopropylideneethyl)-*N*-tosylglycinate (20):** Yellow oil, 81% yield (eluent pentane/diethyl ether, 3:1, $R_f$ = 0.12). − $^1$H NMR (200 MHz): δ = 7.75 (d, *J* = 8.5 Hz, 2 H, Ts), 7.31 (d, *J* = 8.5 Hz, 2 H, Ts), 5.64 (m, 1 H, $CH_2CH$), 4.03 (d, *J* = 6.6 Hz, 2 H, $CHCH_2$), 4.00 (s, 2 H, $NCH_2$), 3.63 (s, 3 H, $CO_2CH_3$), 2.44 (s, 3 H, $C_6H_4CH_3$), 1.18−1.05 (m, 2 H, $CH_2$ cyclopropyl), 1.05−0.90 (m, 2 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 169.5 (s), 143.4 (s), 137.0 (s), 129.5 (d, 2 C), 128.8 (s), 127.4 (d, 2 C), 112.0 (d), 52.0 (q), 49.3 (t), 47.0 (t), 21.5 (q), 2.6 (t), 1.6 (t). − IR: $\tilde{\nu}$ = 3000 $cm^{-1}$, 2930, 1749, 1708, 1340, 1150. − MS (EI): *m*/*z* = 309 (0.1) [$M^+$], 155 (48), 154 (69), 94 (80), 91 (100), 65 (32). − $C_{15}H_{19}NO_4S$ (309.4): calcd. C 58.23, H 6.19, N 4.53; found C 58.50, H 6.32, N 4.46.

**Methyl *N*-(2-Cyclopropylideneethyl)-*N*-tosyl-L-alaninate (21):** Yellow oil, 95% yield (eluent pentane/diethyl ether, 3:1, $R_f$ = 0.18); $[\alpha]_D^{20}$ = −23.8 (*c* = 1.18, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.72 (d, *J* = 8.4 Hz, 2 H, Ts), 7.28 (d, *J* = 8.4 Hz, 2 H, Ts), 5.75 (m, 1 H, $CH_2CH$), 4.69 (q, *J* = 7.2, 1 H, NC*H*), 3.99 (d, *J* = 6.9 Hz, 2 H, $NCH_2$), 3.55 (s, 3 H, $CO_2CH_3$), 2.42 (s, 3 H, $C_6H_4CH_3$), 1.37 (d, *J* = 7.2 Hz, 3 H, $CHCH_3$), 1.03 (br s, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 172.0 (s), 143.2 (s), 137.5 (s), 129.4 (d, 2 C), 127.3 (d, 2 C), 127.2 (s), 114.6 (d), 54.5 (q), 52.0 (d), 46.6 (t), 21.5 (q), 15.9 (q), 2.3 (t), 1.7 (t). − IR: $\tilde{\nu}$ = 2910 $cm^{-1}$, 2850, 1736, 1340, 1150. − MS (EI): *m*/*z* = 323 (0.4) [$M^+$], 264 (13), 168 (45), 155 (50), 108 (82), 91 (100), 80 (16), 65 (40). − $C_{16}H_{21}NO_4S$ (323.4): calcd. C 59.42, H 6.54, N 4.33; found C 59.70, H 6.58, N 4.31.

**Methyl *N*-(2-Cyclopropylideneethyl)-*N*-tosyl-L-valinate (22):** White solid, 82% yield (eluent petroleum ether/diethyl ether, 3:1); m.p. 52−54°C; $[\alpha]_D^{20}$ = −95.7 (*c* = 1.15, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.70 (d, *J* = 8.4 Hz, 2 H, Ts), 7.26 (d, *J* = 8.4 Hz, 2 H, Ts), 5.78 (m, 1 H, $CH_2CH$), 4.19 (dd, *J* = 15.6, 7.6 Hz, 1 H, NC*H*H), 4.16 (d, *J* = 10.6 Hz, 1 H, NC*H*), 3.98 (ddm, *J* = 15.6, 5.7 Hz, 1 H, NC*H*H), 3.43 (s, 3 H, $CO_2CH_3$), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.12 (m, 1 H, $CH_3CH$), 1.04 (br s, 4 H, cyclopropyl), 1.00 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$), 0.92 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$). − $^{13}$C NMR (63 MHz): δ = 170.9 (s), 143.0 (s), 137.1 (s), 129.0 (d, 2 C), 127.3 (d, 2 C), 125.2 (s), 114.8 (d), 65.1 (d), 51.1 (q), 46.1 (t), 28.0 (d), 21.3 (q), 19.3 (q, 2 C), 2.2 (t), 1.5 (t). − IR: $\tilde{\nu}$ = 3080 $cm^{-1}$, 3040, 2980, 1745, 1340, 1150. − MS (EI): *m*/*z* = 351 (0.9) [$M^+$], 292 (19), 196 (100), 155 (31), 136 (29), 91 (83), 80 (19), 65 (40). − $C_{18}H_{25}NO_4S$ (351.5): calcd. C 61.51, H 7.17, N 3.99; found C 61.29, H 7.06, N 3.92.

**Methyl *N*-(2-Cyclopropylideneethyl)-*N*-tosyl-L-phenylglycinate (23):** White solid, 85% yield (eluent petroleum ether/diethyl ether, 2:1, $R_f$ = 0.35); m.p. 85−86°C; $[\alpha]_D^{20}$ = −3.7 (*c* = 0.94, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.73 (d, *J* = 8.4 Hz, 2 H, Ts), 7.32−7.19 (m, 7 H, Ts and Ph), 5.84 (s, 1 H, PhC*H*), 5.39 (m, 1 H, $CH_2CH$), 4.02 (m, 2 H, $NCH_2$), 3.63 (s, 3 H, $CO_2CH_3$), 2.45 (s, 3 H, $C_6H_4CH_3$), 0.91−0,74 (m, 3 H, $CH_2CH$H cyclopropyl), 0.64−0.59 (m, 1 H, $CH_2CH$H cyclopropyl). − $^{13}$C NMR (75 MHz): δ = 170.5 (s), 143.3 (s), 137.3 (s), 134.0 (s), 129.4 (d, 2 C), 129.0 (d, 2 C), 128.6 (d, 2 C), 128.6 (d), 127.4 (d, 2 C), 124.7 (s), 115.0 (d), 62.7 (d), 52.0 (q), 47.3 (t), 21.5 (q), 2.1 (t), 1.4 (t). − IR: $\tilde{\nu}$ = 3060 $cm^{-1}$, 3040, 2990, 2960, 1750, 1625, 1600, 1340, 1160. − MS (EI): *m*/*z* = 385 (0.5) [$M^+$], 230 (19), 170 (18), 155 (13), 91 (100), 80 (17), 77 (17), 65 (17). − $C_{21}H_{23}NO_4S$ (385.5): calcd. C 65.43, H 6.01, N 3.63; found C 65.20, H 6.10, N 3.30.

**Methyl *N*-(2-Cyclopropylideneethyl)-*N*-tosyl-L-phenylalaninate (24):** White solid, 77% yield (eluent pentane/diethyl ether, 3:1, $R_f$ = 0.27); m.p. 72−74°C; $[\alpha]_D^{20}$ = −38.5 (*c* = 1.12, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.50 (d, *J* = 8.1 Hz, 2 H, Ts), 7.33−7.16 (m, 7 H, Ts and Ph), 5.68 (m, 1 H, $NCH_2CH$), 4.87 (t, *J* = 7.7 Hz, 1 H, NC*H*), 4.00 (d, *J* = 6.6 Hz, 2 H, $NCH_2$), 3.52 (s, 3 H, $CO_2CH_3$), 3.32 (dd, *J* = 14.1, 7.3 Hz, 1 H, PhC*H*H), 2.95 (dd, *J* = 14.1, 7.9 Hz, 1 H, PhC*H*H), 2.39 (s, 3 H, $C_6H_4CH_3$), 1.06 (br s, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 171.1 (s), 143.1 (s), 137.4 (s), 137.1 (s), 129.2 (d, 4 C), 128.5 (d, 2 C), 127.5 (d, 2 C), 126.7 (d), 126.5 (s), 114.3 (d), 60.4 (d), 51.9 (q), 46.9 (t), 36.2 (t), 21.5 (q), 2.4 (t), 1.8 (t). − IR: $\tilde{\nu}$ = 3080 $cm^{-1}$, 3040, 2960, 1736, 1340, 1150. − MS (EI): *m*/*z* = 399 (0.2) [$M^+$], 308 (10), 248 (57), 184 (13), 155 (36), 91 (100), 65 (34). − $C_{22}H_{25}NO_4S$ (399.5): calcd. C 66.14, H 6.31, N 3.51; found C 66.50, H 6.41, N 3.47.

**Methyl *N*-(2-Cyclopropylideneethyl)-*N*-tosyl-L-tryptophanate (25):** White solid, 92% yield (eluent diethyl ether/petroleum ether, 3:2, $R_f$ = 0.26); m.p. 96−97°C; $[\alpha]_D^{20}$ = −16.1 (*c* = 0.92, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 8.02 (br s, 1 H, N*H*), 7.59 (d, *J* = 7.7 Hz, 2 H, Ts), 7.56 (d, *J* = 7.3 Hz, 1 H, indolyl), 7.36 (d, *J* = 7.7 Hz, 1 H, indolyl), 7.24−7.09 (m, 5 H, Ts and indolyl), 5.70 (m, 1 H, $NCH_2CH$), 4.92 (t, *J* = 7.6 Hz, 1 H, NC*H*$CH_2$), 4.07 (br d, *J* = 7.0 Hz, 2 H, $NCH_2$), 3.50 (s, 3 H, $CO_2CH_3$), 3.47 (dd, *J* = 14.9, 7.2 Hz, 1 H, NCHC*H*H), 3.16 (dd, *J* = 14.9, 7.9 Hz, 1 H, NCHC*H*H), 2.39 (s, 3 H, $C_6H_4CH_3$), 1.00 (br s, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 170.6 (s), 142.2 (s), 136.5 (s), 135.2 (s), 128.3 (d, 2 C), 126.5 (d, 2 C), 126.2 (s), 125.4 (s), 122.4 (d), 121.0 (d), 118.5 (d), 117.4 (d), 113.7 (d), 110.4 (d), 109.7 (s), 58.5 (d), 51.0 (q), 46.1 (t), 25.4 (t), 20.6 (q), 1.5 (t), 0.9 (t). − IR: $\tilde{\nu}$ = 3480 $cm^{-1}$, 3410, 3060, 3020, 2950, 1740, 1600, 1340, 1160. − MS (EI): *m*/*z* = 438 (12) [$M^+$], 283 (38), 155 (23), 154 (44), 131 (77), 130 (100), 91 (89), 77 (39), 65 (33). − $C_{24}H_{26}N_2O_4S$ (438.5): calcd. C 65.73, H 5.98, N 6.39; found C 65.97, H 6.16, N 5.89.

**Methyl *N*-(2-Cyclopropylideneethyl)-L-prolinate (26):** Yellow oil, 80% yield (eluent petroleum ether/diethyl ether, 2:1, $R_f$ = 0.13); $[\alpha]_D^{20}$ = −109.8 (*c* = 1.22, $CHCl_3$). − $^1$H NMR (500 MHz): δ = 5.89 (tp, *J* = 7.0, 2.0 Hz, 1 H, $NCH_2CH$), 3.69 (s, 3 H, $CO_2CH_3$), 3.37 (dd, *J* = 12.7, 7.0 Hz, 1 H, NC*H*HCH), 3.30 (dd, *J* = 12.7, 6.8 Hz, 1 H, NC*H*HCH), 3.18−3.14 (m, 1 H, NC*H*$HCH_2$), 3.13 (dd, *J* = 9.1, 6.5 Hz, 1 H, NC*H*), 2.40 (q, *J* = 8.5 Hz, 1 H, NC*H*$HCH_2$), 2.12 (m, 1 H, NCHC*H*H), 1.92 (m, 2 H, $NCH_2CH_2$), 1.79 (m, 1 H, NCHC*H*H), 1.09−0.99 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 174.8 (s), 125.7 (s), 114.6 (d), 65.3 (d), 55.8 (t), 53.6 (t), 51.7 (q), 29.5 (t), 23.0 (t), 2.3 (t), 1.6 (t). − IR: $\tilde{\nu}$ = 3059−2813 $cm^{-1}$, 1754, 1437, 1281, 1196. − MS (EI): *m*/*z* = 195 (2) [$M^+$], 136 (87), 86 (64), 84 (100). − $C_{11}H_{17}NO_2$ (195.3): calcd. C 67.66, H 8.78; found C 68.03, H 8.89.

**Methyl *O*-(2-Cyclopropylideneethyl)glycolate (27):** Colourless oil, 82% yield (eluent petroleum ether/diethyl ether, 4:1, $R_f$ = 0.29). − $^1$H NMR (250 MHz): δ = 5.95 (m, 1 H, C*H*), 4.23 (d, *J* = 6.8 Hz, 2 H, $CHCH_2$), 4.09 (s, 2 H, $CH_2CO_2CH_3$), 3.77 (s, 3 H, $CO_2CH_3$), 1.12 (br s, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 170.7 (s), 128.2 (s), 113.5 (d), 71.1 (t), 66.6 (t) 51.6 (q), 2.2 (t), 1.5 (t). − IR: $\tilde{\nu}$ = 2950 $cm^{-1}$, 1755, 1285, 1215, 1130. − MS (EI): *m*/*z* = 156 (0.4) [$M^+$], 99 (27), 98 (27), 83 (100), 74 (29), 73 (14), 67 (83), 66(25), 65 (37), 59 (17), 58 (34), 57 (32), 55 (22); HRMS: found 156.0794, $C_8H_{12}O_3$ requires 156.0786.

**General Procedure for the Direct Reduction of the Esters to Aldehydes:** To a 0.4 M $CH_2Cl_2$ solution of the methyl esters **20**, **23**, or **27** (0.78−1.36 mmol) at −78°C was added dropwise, within one hour, a 1 M solution of DIBALH in hexane (0.9−2.0 equiv.). The mixture was stirred at − 78°C 1−2 h, then hydrolysed in turn by methanol and by saturated sodium and potassium tartrate solution in water. The aqueous phase was extracted four times by twice its volume of $CH_2Cl_2$. The combined organic extracts were dried with anhydrous $Na_2SO_4$; evaporation of the solvent gave the aldehydes **30**, **33**, or **37** sufficiently pure, which were used in the next step without further purification.

***N*-(2-Cyclopropylideneethyl)-*N*-tosylaminoethanal (30):** Yellow oil, 98% yield; $R_f$ = 0.36 (eluent pentane/diethyl ether, 4:1). − $^1$H NMR (200 MHz): δ = 9.55 (t, *J* = 1.4 Hz, 1 H, C*H*O), 7.71 (d, *J* = 8.4 Hz, 2 H, Ts), 7.34 (d, *J* = 8.4 Hz, 2 H, Ts), 5.69 (m, 1 H, CC*H*$CH_2$), 3.91 (d, *J* = 7.6 Hz, 2 H, $CCHCH_2$), 3.69 (d, *J* = 1.4 Hz, 2 H, $CH_2CHO$), 2.45 (s, 3 H, $C_6H_4CH_3$), 1.10−0.90 (m, 4 H, $CH_2$ cyclopropyl).

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]-2-phenylethanal (33):** Yellow oil, 81% yield (the reaction gave the aldehyde **33** with the corresponding phenylglycinol in 83:17 ratio); $R_f$ = 0.57 (eluent pentane/diethyl ether, 1:1). − $^1$H NMR (200 MHz): δ = 9.80 (d, *J* = 1.1 Hz, 1 H, C*H*O), 7.70 (d, *J* = 8.1 Hz, 2 H, Ts), 7.36−7.18 (m, 7 H, Ts and Ph), 5.44 (m, 1 H, $CH_2CH$), 5.30 (d, *J* = 1.1 Hz, 1 H, PhC*H*), 3.92 (d, *J* = 6.9 Hz, 2 H, $NCH_2$), 2.44 (s, 3 H, $C_6H_4CH_3$), 0.94−0.62 (m, 4 H, $CH_2$ cyclopropyl).

***O*-(2-Cyclopropylideneethyl)glycolaldehyde (37):** Colourless oil, >98% yield; $R_f$ = 0.26 (eluent $CH_2Cl_2$). − $^1$H NMR (250 MHz): δ = 9.75 (s, 1 H, C*H*O), 5.96 (m, 1 H, CC*H*$CH_2$), 4.24 (d, *J* = 6.7 Hz, 2 H, $CCHCH_2$), 3.50 (s, 2 H, $CH_2CHO$), 1.11 (br s, 4 H, $CH_2$ cyclopropyl).

**General Procedure for the Reduction of Esters to Alcohols and Oxidation to Aldehydes under Swern Conditions:**[26a] To a 0.3 M $CH_2Cl_2$ solution of the methyl esters **21**, **22**, **24**, or **26** (0.73−5.12 mmol) at −78°C was added dropwise, within one hour, a 0.5 M solution of DIBALH in hexane (2.5−3.0 equiv.). The mixture was stirred for 3 h, allowed to reach room temp. and hydrolysed in turn by methanol and by saturated sodium and potassium tartrate solution in water. The aqueous phase was extracted three times by twice its volume of $CH_2Cl_2$ and the combined organic extracts dried with anhydrous $Na_2SO_4$. Evaporation of the solvent gave the alcohols, which were purified by chromatography on silica gel and used for the next step.

DMSO (2.5 equiv.) was added to a 0.15 M solution of oxalyl chloride (1.1 equiv.) in $CH_2Cl_2$ at −78°C followed by dropwise addition of a 0.14 M solution of the alcohols (0.34−1.60 mmol) in $CH_2Cl_2$. After stirring at −78°C for 15 min, the mixture was added of $i$Pr$_2$EtN (5 equiv.), allowed to reach room temp., and poured into an equal volume of water. The aqueous phase was extracted twice by an equal volume of $CH_2Cl_2$. The collected organic phases were dried with anhydrous $Na_2SO_4$ and concentrated to give the alde-

hydes **31**, **32**, **34**, or **36** sufficiently pure, which were used in the next step without further purification.

**Conversion of 21 to Aldehyde 31**

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]propanol:** Colourless oil, 94% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.36); $[\alpha]_D^{20}$ = 70.6 (*c* = 1.07, $CHCl_3$). − $^1$H NMR (250 MHz): δ = 7.73 (d, *J* = 8.5 Hz, 2 H, Ts), 7.30 (d, *J* = 8.5 Hz, 2 H, Ts), 5.87 (m, 1 H, $NCH_2CH$), 4.16−3.95 (m, 2 H, NC*H* and NC*H*H), 3.84 (dd, 1 H, *J* = 15.8, 8.1 Hz, NC*H*H), 3.55 (dd, 1 H, *J* = 11.6, 8.5 Hz, C*H*HOH), 3.45 (dd, 1 H, *J* = 11.6, 5.3 Hz, C*H*HOH), 2.43 (s, 3 H, $C_6H_4CH_3$), 1.78 (br s, 1 H, O*H*), 1.08 (br s, 4 H, $CH_2$ cyclopropyl), 0.95 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$). − $^{13}$C NMR (63 MHz): δ = 143.1 (s), 137.7 (s), 129.5 (d, 2 C), 126.9 (d, 2 C), 125.6 (s), 115.4 (d), 64.4 (t), 55.2 (d), 44.7 (t), 21.3 (q), 14.3 (q), 2.3 (t), 1.6 (t). − IR: ṽ = 3700 cm$^{-1}$, 3660−3500, 3020−2860, 1720, 1600. − MS (EI): *m*/*z* = 264 (38) [$M^+$ − $CH_2OH$], 155 (17), 108 (55), 91 (100); MS (CI with $NH_3$): *m*/*z* = 296 (100) [$MH^+$]. − $C_{15}H_{21}NO_3S$ (295.4): calcd. C 60.99, H 7.17, N 4.74; found C 60.74, H 6.81, N 4.78.

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]propanal (31):** Yellow oil, 98% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.78). − $^1$H NMR (200 MHz): δ = 9.58 (s, 1 H, C*H*O), 7.74 (d, *J* = 8.0 Hz, 2 H, Ts), 7.33 (d, *J* = 8.0 Hz, 2 H, Ts), 5.73 (m, 1 H, $CH_2CH$), 4.34 (q, *J* = 7.0, 1 H, NC*H*), 4.23 (dd, *J* = 14.4, 5.4 Hz, 1 H, NC*H*H), 3.68 (dd, *J* = 14.4, 8.8, 1 H, NC*H*H), 2.45 (s, 3 H, $C_6H_4CH_3$), 1.10 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$), 1.10−0.95 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 199.8 (d), 143.6 (s), 137.1 (s), 129.8 (d, 2 C), 129.6 (s), 126.9 (d, 2 C), 112.8 (d), 60.7 (d), 46.2 (t), 21.4 (q), 10.8 (q), 2.4 (t), 1.9 (t). − IR: ṽ = 3000−2780 cm$^{-1}$, 1730, 1600. − MS (EI): *m*/*z* = 264 (50) [$M^+$ − CHO], 155 (14), 108 (47), 91 (100), 67 (49); MS (CI with $NH_3$): *m*/*z* = 311 (68) [$MNH_4^+$], 294 (56) [$MH^+$].

**Conversion of 22 to Aldehyde 32**

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]-3-methylbutanol:** Colourless oil, 93% yield (eluent $CH_2Cl_2$/$CH_3OH$, 70:1, $R_f$ = 0.18). − $^1$H NMR (200 MHz): δ = 7.74 (d, *J* = 8.3 Hz, 2 H, Ts), 7.28 (d, *J* = 8.3 Hz, 2 H, Ts), 5.86 (m, 1 H, $NCH_2CH$), 4.10 (ddm, *J* = 15.9, 6.0 Hz, 1 H, NC*H*H), 3.86 (br dd, *J* = 15.9, 7.3 Hz, 1 H, NC*H*H), 3.79−3.67 (m, 1 H, NC*H*), 3.63−3.48 (m, 2 H, $CH_2OH$), 2.42 (s, 3 H, $C_6H_4CH_3$), 1.89 (br s, 1 H, O*H*), 1.77 (m, 1 H, $CH_3CH$), 1.06 (br s, 4 H, $CH_2$ cyclopropyl), 0.91 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.71 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$). − $^{13}$C NMR (50 MHz): δ = 143.0 (s), 138.2 (s), 129.3 (d, 2 C), 127.3 (d, 2 C), 125.7 (s), 115.2 (d), 66.2 (d), 61.9 (t), 45.4 (t), 27.8 (d), 21.3 (q), 20.5 (q), 20.0 (q), 2.3 (t), 1.6 (t). − IR: ṽ = 3700−3400 cm$^{-1}$, 3060, 2968, 1598, 1329, 1148. − MS (EI): *m*/*z* = 292 (70) [$M^+$ − $CH_2OH$], 184 (33), 155 (93), 136 (62), 94 (54), 91 (100), 67 (97), 65 (61); HRMS: found 323.1555, $C_{17}H_{25}NO_3S$ requires 323.1555.

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]-3-methylbutanal (32):** Pale yellow oil, 98% yield (eluent $CH_2Cl_2$/$CH_3OH$, 70:1, $R_f$ = 0.19). − $^1$H NMR (200 MHz): δ = 9.43 (s, 1 H, C*H*O), 7.68 (d, *J* = 8.4 Hz, 2 H, Ts), 7.25 (d, *J* = 8.4 Hz, 2 H, Ts), 5.67 (m, 1 H, $CH_2CH$), 4.02 (dd, *J* = 15.7, 6.4 Hz, 1 H, NC*H*H), 3.89 (d, *J* = 10.2 Hz, 1 H, NC*H*), 3.77 (dd, *J* = 15.7, 7.7 Hz, 1 H, NC*H*H), 2.37 (s, 3 H, $C_6H_4CH_3$), 2.10 (m, 1 H, $CH_3CH$), 1.11 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.97 (m, 4 H, $CH_2$ cyclopropyl), 0.78 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$). − $^{13}$C NMR (50 MHz): δ = 198.5 (d), 143.4 (s), 137.7 (s), 129.5 (d, 2 C), 128.0 (s), 127.1 (d, 2 C), 113.7 (d), 70.8 (d), 47.0 (t), 26.1 (d), 21.3 (q), 20.0 (q), 19.6 (q), 2.3 (t), 1.6 (t).

**Conversion of 24 to Aldehyde 34**

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]-3-phenylpropanol:** Colourless oil, 95% yield (eluent diethyl ether/pentane, 4:1, $R_f$ = 0.52); $[\alpha]_D^{20}$ = −40.0 (*c* = 1.18, $CH_2Cl_2$). − $^1$H NMR (200 MHz): δ = 7.62 (d, *J* = 8.0 Hz, 2 H, Ts), 7.30−7.10 (m, 5 H, Ts and Ph), 7.04−7.00 (m, 2 H, Ph), 5.90 (m, 1 H, $CCHCH_2$), 4.20−3.90 (m, 3 H, $NCH_2$ and NC*H*), 3.70−3.50 (m, 2 H, $CH_2OH$), 2.69 (m, 2 H, $PhCH_2$), 2.41 (s, 3 H, $C_6H_4CH_3$), 1.91 (dd, *J* = 7.2, 5.4 Hz, 1 H, O*H*), 1.12 (br s, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.2 (s), 137.7 (s, 2 C), 129.6 (d, 2 C), 128.9 (d, 2 C), 128.5 (d, 2 C), 127.2 (d), 126.5 (d, 2 C), 126.2 (s), 115.4 (d), 62.5 (t), 61.7 (d), 45.8 (t), 36.2 (t), 21.5 (q), 2.5 (t), 1.9 (t). − IR: ṽ = 3680 cm$^{-1}$, 3640−3440, 3100−2800, 1600. − MS (EI): *m*/*z* = 340 (8) [$M^+$ − $CH_2OH$], 155 (15), 91 (100); MS (CI with $NH_3$): *m*/*z* = 389 (32) [$MNH_4^+$], 372 (48) [$MH^+$]. − $C_{21}H_{25}NO_3S$ (371.5): calcd. C 67.90, H 6.78, N 3.77; found C 67.80, H 6.55, N 3.74.

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]-3-phenylpropanal (34):** Yellow oil, 95% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.63). − $^1$H NMR (200 MHz): δ = 9.65 (s, 1 H, C*H*O), 7.45 (d, *J* = 8.0 Hz, 2 H, Ts), 7.22−7.14 (m, 5 H, Ts and Ph), 7.07−7.02 (m, 2 H, Ph), 5.76 (m, 1 H, $CCHCH_2$), 4.53 (dd, *J* = 8.8, 5.5 Hz, 1 H, NC*H*), 4.03 (dd, *J* = 15.2, 5.8 Hz, 1 H, NC*H*H), 3.85 (dd, *J* = 15.2, 8.4 Hz, 1 H, NC*H*H), 3.35 (dd, *J* = 14.6, 5.5 Hz, 1 H, PhC*H*H), 2.68 (dd, *J* = 14.6, 8.8 Hz, 1 H, PhC*H*H), 2.40 (s, 3 H, $C_6H_4CH_3$), 1.10−0.95 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 199.2 (d), 143.4 (s), 137.3 (s, 2 C), 129.6 (d, 2 C), 129.0 (d, 2 C), 128.6 (d, 2 C), 127.2 (d), 126.6 (d, 2 C), 115.4 (s), 113.2 (d), 67.0 (d), 47.0 (t), 32.4 (t), 21.5 (q), 2.6 (t), 2.0 (t). − IR: ṽ = 3100−2780 cm$^{-1}$, 1730, 1600. − MS (EI): *m*/*z* = 340 (25) [$M^+$ − CHO], 91 (100), 67 (26); MS (CI with $NH_3$): *m*/*z* = 387 (100) [$MNH_4^+$], 370 (58) [$MH^+$].

**Conversion of 26 to Aldehyde 36**

***N*-(2-Cyclopropylideneethyl)-L-prolinol:** Yellow oil, 85% yield (eluent $CH_2Cl_2$/$CH_3OH$ + 1% $NH_4OH$, 5:1, $R_f$ = 0.27); $[\alpha]_D^{20}$ = −48.8 (*c* = 1.34, $CH_3OH$). − $^1$H NMR (200 MHz): δ = 5.87 (ddp, *J* = 7.3, 5.7, 1.8 Hz, 1 H, CC*H*), 3.64 (dd, *J* = 10.6, 3.7 Hz, 1 H, C*H*HOH), 3.48 (ddp, *J* = 12.8, 5.7, 1.5 Hz, 1 H, NC*H*HCH), 3.40 (dd, *J* = 10.6, 2.7 Hz, 1 H, C*H*HOH), 3.17−3.02 (m, 2 H, NC*H*HCH and $NCHHCH_2$), 2.78 (br s, 1 H, O*H*), 2.72−2.58 (m, 1 H, NC*H*), 2.35 (q, *J* = 8.6 Hz, 1 H, $NCHHCH_2$), 2.00−1.61 (m, 4 H, $NCH_2CH_2$ and $NCHCH_2CH_2$), 1.12−0.98 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 128.2 (s), 114.8 (d), 63.9 (d), 62.3 (t), 55.2 (t), 54.0 (t), 27.4 (t), 22.9 (t), 2.0 (t), 1.4 (t). − IR: ṽ = 3672 cm$^{-1}$, 3621, 3600−3200, 3057, 2963, 1602, 1406. − MS (EI): *m*/*z* = 167 (1) [$M^+$], 136 (100), 134 (24), 117 (17), 114 (23), 96 (19), 86 (37), 84 (69), 70 (68), 67 (58), 65 (24), 55 (19). − $C_{10}H_{17}NO$ (167.3): calcd. C 71.81, H 10.25, N 8.37; found C 72.15, H 10.11, N 8.69.

**(2*S*)-1-[*N*-(2-Cyclopropylideneethyl)]-2-formylpyrroline (36):** Yellow oil, 89% yield. − $^1$H NMR (200 MHz): δ = 9.40 (s, *J* = 4.0 Hz, 1 H, C*H*O), 5.85 (ddp, *J* = 8.0, 6.2, 1.8 Hz, 1 H, $CCHCH_2$), 3.37 (ddp, *J* = 12.5, 6.6, 1.4 Hz, 1 H, NC*H*HCH), 3.21 (dd, *J* = 12.5, 8.0 Hz, 1 H, NC*H*HCH), 3.20−3.10 (m, 1 H, $NCHHCH_2$), 2.88−2.78 (m, 1 H, NC*H*), 2.47−2.34 (m, 1 H, $NCHHCH_2$), 2.00−1.77 (m, 4 H, $CHCH_2CH_2$), 1.12−0.88 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 203.0 (d), 127.0 (s), 114.5 (d), 71.6 (d), 56.3 (t), 54.4 (t), 26.4 (t), 23.6 (t), 2.3 (t), 1.8 (t).

**Conversion of 25 to Aldehyde 35 by Castro's Methodology:**[26b] To a solution of the ester **25** (1.34 g, 3.09 mmol) in 75 mL of methanol and 25 mL of water at 0°C was added LiOH (0.11 g, 4.64 mmol,

1.5 equiv.). The mixture was stirred at room temperature overnight, then the solvent was concentrated to a small volume and a 10% HCl aqueous solution was added until pH = 1. The aqueous phase was extracted by ethyl acetate (4 × 30 mL), the combined organic extracts washed by saturated NaCl solution (30 mL), dried with anhydrous $Na_2SO_4$, and evaporated to give *N*-(2-cyclopropylideneethyl)-*N*-tosyl-L-tryptophane (1.29 g, 3.03 mmol, 98%): colourless oil, $R_f$ = 0.30 (diethyl ether/petroleum ether + 1% $HCO_2H$, 2:1). − $^1$H NMR (200 MHz): δ = 9.56 (br s, 1 H, O*H*), 8.26 (br s, 1 H, N*H*), 7.55 (d, *J* = 8.0 Hz, 2 H, Ts), 7.47 (d, *J* = 7.3 Hz, 1 H, indolyl), 7.33 (d, *J* = 8.1 Hz, 1 H, indolyl), 7.22−7.03 (m, 3 H, indolyl), 7.11 (d, *J* = 8.0 Hz, 2 H, Ts), 5.73 (m, 1 H, CC*H*$CH_2$), 4.88 (dd, *J* = 8.2, 6.6 Hz, 1 H, NC*H*$CH_2$), 4.22−3.87 (m, 2 H, NC$H_2$), 3.51 (dd, *J* = 14.9, 6.6 Hz, 1 H, NCHC*H*H), 3.19 (dd, *J* = 14.9, 8.2 Hz, 1 H, NCHC*H*H), 2.35 (s, 3 H, $C_6H_4CH_3$), 0.98 (br s, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (75 MHz): δ = 176.0 (s), 143.3 (s), 136.9 (s), 136.1 (s), 129.2 (d, 2 C), 127.3 (d, 2 C), 126.9 (s, 2 C), 123.4 (d), 121.9 (d), 119.4 (d), 118.1 (d), 114.2 (d), 111.3 (d), 110.3 (s), 59.4 (d), 47.2 (t), 25.9 (t), 21.4 (q), 2.4 (t), 1.7 (t). − IR: $\tilde{\nu}$ = 3482 cm$^{-1}$, 3415, 3300−2500, 1713, 1598, 1417, 1333, 1148. − MS (EI): *m*/*z* = 424 (21) [$M^+$], 131 (100), 91 (17). − $C_{23}H_{24}N_2O_4S$ (424.5): calcd. C 65.08, H 5.70, N 6.60; found C 64.54, H 5.96, N 5.79.

To a solution of *N*-(2-cyclopropylideneethyl)-*N*-tosyl-L-tryptophane (0.62 g, 1.46 mmol) in 35 mL of $CH_2Cl_2$ were added, in sequence, *O*,*N*-dimethylhydroxylamine hydrochloride (0.35 g, 3.63 mmol, 2.5 equiv.), pyridine (350 µL, 4.33 mmol, 3 equiv.), and DCC (0.79 g, 3.63 mmol, 2.5 equiv.). After 2.5 d the reaction mixture was washed by saturated NaCl solution (6 mL), the organic solution dried with anhydrous $Na_2SO_4$ and the solvent evaporated. Chromatography on silica gel (eluent petroleum ether/diethyl ether, 1:3, $R_f$ = 0.25) of the residue gave *N*-(2-cyclopropylideneethyl)-*N*-tosyl-L-tryptophane *N*-methoxy-*N*-methylamide (0.55 g, 1.18 mmol, 81%) as a colourless oil: $^1$H NMR (200 MHz): δ = 8.02 (br s, 1 H), 7.66 (d, *J* = 8.0 Hz, 2 H, Ts), 7.62 (m, 1 H, indolyl), 7.34 (d, *J* = 7.7 Hz, 1 H, indolyl), 7.22−7.06 (m, 5 H, Ts and indolyl), 5.77 (m, 1 H, CC*H*$CH_2$), 5.47 (br m, 1 H, NC*H*$CH_2$), 4.46 (dd, *J* = 16.6, 7.2 Hz, 1 H, NC*H*H), 4.23 (dd, *J* = 16.6, 6.1 Hz, 1 H, NC*H*H), 3.44−3.34 (m, 1 H, NCHC*H*H), 3.34 (s, 3 H, O$CH_3$), 3.03 (dd, *J* = 14.2, 5.8 Hz, 1 H, NCHC*H*H), 2.97 (s, 3 H, N$CH_3$), 2.39 (s, 3 H, $C_6H_4CH_3$), 1.10−0.86 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 171.1 (s), 142.9 (s), 137.5 (s), 136.1 (s), 129.2 (d, 2 C), 127.2 (d, 2 C), 124.6 (s, 2 C), 123.3 (d), 121.7 (d), 119.2 (d), 118.3 (d), 115.9 (d), 111.2 (d), 110.4 (s), 61.1 (q), 54.7 (d), 46.2 (t), 31.8 (q), 26.6 (t), 21.3 (q), 2.2 (t), 1.8 (t). − IR: $\tilde{\nu}$ = 3481 cm$^{-1}$, 3409, 3062, 2937, 1652, 1598, 1441, 1332, 1148. − MS (EI): *m*/*z* = 130 (100), 91 (50). − HRMS: found 467.1864, $C_{25}H_{29}N_3O_4S$ requires 467.1879.

Lithium aluminum hydride (58.4 mg, 1.54 mmol, 5 equiv.) was added to a stirred solution of *N*-(2-cyclopropylideneethyl)-*N*-tosyl-L-tryptophane *N*-methoxy-*N*-methylamide (0.55 g, 1.18 mmol) in 60 mL of diethyl ether at 0°C. After stirring for 1.5 h at room temp. wet $Na_2SO_4$ was added, and then the suspension was dried with anhydrous $Na_2SO_4$. Removal of the solvent gave the aldehyde **35** (0.47 g, 1.16 mmol, 98%), a yellow oil, which was used in the next step without further purification.

**(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]-3-(indol-3-yl)-1-propanal (35):** $R_f$ = 0.65 (diethyl ether/petroleum ether, 3:1). − $^1$H NMR (200 MHz): δ = 9.69 (s, 1 H, C*H*O), 7.96 (br s, 1 H, N*H*), 7.50 (d, *J* = 8.4 Hz, 2 H, Ts), 7.40 (d, *J* = 7.9 Hz, 1 H, indolyl), 7.33 (d, *J* = 7.7 Hz, 1 H, indolyl), 7.20 (dd, *J* = 7.9, 7.1 Hz, 1 H, indolyl), 7.11 (d, *J* = 8.4 Hz, 2 H, Ts), 7.11−7.06 (m, 1 H, indolyl), 6.88 (d, *J* = 2.4 Hz, 1 H, indolyl), 5.75 (m, 1 H, CC*H*$CH_2$), 4.59 (dd, *J* = 8.5, 6.0 Hz, 1 H, NC*H*$CH_2$), 4.05 (br dd, *J* = 15.0, 6.3 Hz, 1 H, NC*H*H), 3.94 (dd, *J* = 15.0, 8.5 Hz, 1 H, NC*H*H), 3.50 (dd, *J* = 15.2, 6.0 Hz, 1 H, NCHC*H*H), 2.97 (dd, *J* = 15.2, 8.5 Hz, 1 H, NCHC*H*H), 2.38 (s, 3 H, $C_6H_4CH_3$), 1.10−0.97 (m, 2 H, $CH_2$ cyclopropyl), 0.97−0.82 (m, 2 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 199.7 (d), 143.1 (s), 136.9 (s), 136.0 (s), 129.2 (d, 2 C), 129.0 (s), 126.6 (d, 2 C), 126.5 (s), 123.1 (d), 121.6 (d), 119.0 (d), 117.7 (d), 113.3 (d), 111.2 (d), 110.0 (s), 65.3 (d), 46.9 (t), 24.7 (t), 21.1 (q), 2.2 (t), 1.6 (t).

**General Procedure for Nitrone Formation − Intramolecular Cycloaddition of Aldehydes 30−35 and 37**

**Method A:** To a 0.07 M solution of the aldehydes **30**, **31**, or **34** (1.3 mmol) in water were added 1.2 equiv. of *N*-methylhydroxylamine hydrochloride and 1.4 equiv. of pyridine. The mixture was stirred overnight at room temp., the solvent was removed and the crude mixture was separated by chromatography on silica gel to give the expected isoxazolidines **38**, **39**, or **42**.

**Method B:** To a 0.02 M solution of the aldehydes **32**, **33**, **35**, or **37** (0.22−2.35 mmol) in $CCl_4$ cooled to 0°C were added 3 equiv. of *N*-methylhydroxylamine hydrochloride and 3 equiv. of triethylamine (or *i*$Pr_2$EtN). The mixture was stirred overnight at room temp. and the salts were eliminated by filtration over Celite. The solvent was removed and the crude mixture was separated by chromatography on silica gel to give the expected isoxazolidines **40**, **41**, **43**, or **45**.

**(3′a*R**,6′a*R**)-1′-Methyl-5′-tosylspiro[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (38):** White solid, 71% yield (method A, eluent diethyl ether, $R_f$ = 0.27); m.p. 130°C. − $^1$H NMR (200 MHz): δ = 7.68 (d, *J* = 8.2 Hz, 2 H, Ts), 7.32 (d, *J* = 8.2 Hz, 2 H, Ts), 3.81 (br q, *J* = 7.6 Hz, 1 H, NC*H*), 3.61 [br dd, *J* = 9.5, 8.0 Hz, 1 H, N($CH_3$)CHC*H*H], 3.45 [dd, *J* = 9.5, 7.5 Hz, 1 H, N($CH_3$)CHC*H*H], 3.06 (dt, *J* = 5.8, 7.6 Hz, 1 H, CC*H*$CH_2$), 2.97−2.89 (m, 2 H, CCHC$H_2$), 2.73 (s, 3 H, NC$H_3$), 2.45 (s, 3 H, $C_6H_4CH_3$), 1.10−0.95 (m, 1 H, C*H*H cyclopropyl), 0.95−0.70 (m, 2 H, $CH_2$ cyclopropyl), 0.70−0.50 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.9 (s), 132.0 (s), 129.7 (d, 2 C), 128.0 (d, 2 C), 73.1 (d), 65.3 (s), 52.9 (t), 51.6 (t), 50.1 (d), 45.4 (q), 21.5 (q), 14.4 (t), 3.7 (t). − IR: $\tilde{\nu}$ = 3000−2840 cm$^{-1}$, 1590. − MS (EI): *m*/*z* = 155 (7), 153 (67), 124 (61), 112 (100), 91 (32), 42 (38). − MS (CI with $NH_3$): *m*/*z* = 309 (100) [$MH^+$]. − $C_{15}H_{20}N_2O_3S$ (308.4): calcd. C 58.42, H 6.54, N 9.08; found C 58.76, H 6.67, N 8.97.

**(3′a*R*,6′*S*,6′a*R*)-1′,6′-Dimethyl-5′-tosylspiro[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (39a):** Colourless oil, 36% yield (method A, eluent pentane/diethyl ether, 1:4, $R_f$ = 0.18); $[\alpha]_D^{20}$ = −136.2 (*c* = 0.81, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.70 (d, *J* = 8.0 Hz, 2 H, Ts), 7.30 (d, *J* = 8.0 Hz, 2 H, Ts), 3.80−3.60 (m, 1 H, CC*H*$CH_2$), 3.35 [dd, *J* = 7.0, 5.4 Hz, 1 H, N($CH_3$)C*H*], 3.20 (p, *J* = 6.0 Hz, 1 H, $CH_3CH$), 3.10−2.95 (m, 2 H, NC$H_2$), 2.70 (s, 3 H, NC$H_3$), 2.40 (s, 3 H, $C_6H_4CH_3$), 1.47 (d, *J* = 6.2 Hz, 3 H, CHC$H_3$), 1.00−0.85 (m, 1 H, C*H*H cyclopropyl), 0.80−0.50 (m, 2 H, $CH_2$ cyclopropyl), 0.50−0.35 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.6 (s), 133.2 (s), 129.5 (d, 2 C), 127.8 (d, 2 C), 81.7 (d), 65.5 (s), 60.9 (d), 52.4 (t), 47.7 (d), 45.5 (q), 21.5 (q), 20.2 (q), 14.5 (t), 3.7 (t). − IR: $\tilde{\nu}$ = 3080−2850 cm$^{-1}$, 1600. − MS (EI): *m*/*z* = 124 (28), 112 (31), 56 (100), 42 (38); MS (CI with $NH_3$): *m*/*z* = 323 (100) [$MH^+$]; HRMS: found 322.13559, $C_{16}H_{22}N_2O_3S$ requires 322.13510.

**(3′a*S*,6′*S*,6′a*S*)-1′,6′-Dimethyl-5′-tosylspiro[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (39b):** White solid, 45% yield (method A, eluent pentane/diethyl ether, 1:4, $R_f$ = 0.29); m.p.

137°C; $[\alpha]_D^{20}$ = −110.6 (*c* = 1.04, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.72 (d, *J* = 8.2 Hz, 2 H, Ts), 7.35 (d, *J* = 8.2 Hz, 2 H, Ts), 3.67 (m, 1 H, $CH_3CH$), 3.54 (t, *J* = 7.6 Hz, 1 H, $CH_3NCH$), 3.43−3.30 (m, 2 H, $NCH_2$), 2.87 (dt, *J* = 6.1, 7.6 Hz, 1 H, $CH_2CH$), 2.73 (s, 3 H, $NCH_3$), 2.44 (s, 3 H, $C_6H_4CH_3$), 1.35 (d, *J* = 6.0 Hz, 3 H, $CHCH_3$), 1.05−0.90 (m, 2 H, $CH_2$ cyclopropyl), 0.80−0.60 (m, 2 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.5 (s), 134.5 (s), 129.6 (d, 2 C), 127.5 (d, 2 C), 76.0 (d), 65.3 (s), 58.5 (d), 50.6 (t), 49.2 (d), 46.3 (q), 21.5 (q), 15.4 (q), 14.8 (t), 3.1 (t). − IR: $\tilde{\nu}$ = 3080−2850 $cm^{-1}$, 1600. − MS (EI): *m*/*z* = 167 (16), 124 (27), 112 (32), 56 (100); MS (CI with $NH_3$): *m*/*z* = 323 (100) [$MH^+$]; HRMS: found 322.13456, $C_{16}H_{22}N_2O_3S$ requires 322.13510.

**(3′a*R*,6′*S*,6′a*R*)-6′-Isopropyl-1′-methyl-5′-tosylspiro-[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (40a):** Pale yellow oil, 24% yield (method B, eluent $CH_2Cl_2/CH_3OH$ + 1% $NH_4OH$, 200:1, $R_f$ = 0.16); $[\alpha]_D^{21}$ = −66.9 (*c* = 0.70, $CHCl_3$). − $^1$H NMR (500 MHz): δ = 7.75 (d, *J* = 8.1 Hz, 2 H, Ts), 7.29 (d, *J* = 8.1 Hz, 2 H, Ts), 3.57 [dd, *J* = 5.8, 2.7, 1 H, N(Ts)C*H*], 3.56 (dd, *J* = 10.8, 7.9, 1 H, CHC*H*H), 3.47 [dd, *J* = 7.4, 2.7 Hz, 1 H, N($CH_3$)C*H*], 3.35 (dd, *J* = 10.8, 5.0 Hz, 1 H, CHC*H*H), 2.92 (dt, *J* = 5.0, 7.5 Hz, 1 H, CC*H*$CH_2$), 2.61 (s, 3 H, $NCH_3$), 2.45−2.41 [m, 1 H, C*H*($CH_3$)$_2$], 2.41 (s, 3 H, $C_6H_4CH_3$), 0.98 (d, *J* = 7.1 Hz, 3 H, $CHCH_3$), 0.95 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 0.87−0.82 (m, 1 H, C*H*H cyclopropyl), 0.64−0.59 (m, 1 H, C*H*H cyclopropyl), 0.45−0.40 (m, 1 H, C*H*H cyclopropyl), 0.36−0.31 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.2 (s), 135.0 (s), 129.4 (d, 2 C), 127.9 (d, 2 C), 75.2 (d), 70.6 (d), 65.6 (s), 52.5 (t), 49.9 (d), 44.5 (q), 31.4 (d), 21.5 (q), 19.2 (q), 16.2 (q), 13.7 (t), 5.2 (t). − IR: $\tilde{\nu}$ = 3035 $cm^{-1}$, 2965, 1598, 1335, 1152. − MS (EI): *m*/*z* = 350 (3) [$M^+$], 307 (35), 251 (17), 195 (35), 155 (93), 112 (29), 95 (40), 91 (100), 90 (28), 84 (99), 83 (36), 70 (33), 68 (67), 65 (20), 55 (65). − $C_{18}H_{26}N_2O_3S$ (350.5): calcd.. C 61.69, H 7.48, N 7.99; found C 61.66, H 7.61, N 7.66.

**(3′a*S*,6′*S*,6′a*S*)-6′-Isopropyl-1′-methyl-5′-tosylspiro-[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (40b):** White solid, 38% yield (method B, eluent $CH_2Cl_2/CH_3OH$ + 1% $NH_4OH$, 200:1, $R_f$ = 0.41); m.p. 123−124°C; $[\alpha]_D^{21}$ = 104.5 (*c* = 0.31, $CHCl_3$). − $^1$H NMR (500 MHz): δ = 7.72 (d, *J* = 8.2 Hz, 2 H, Ts), 7.31 (d, *J* = 8.2 Hz, 2 H, Ts), 3.76 [t, *J* = 8.4 Hz, 1 H, N(Ts)C*H*], 3.73 (dd, *J* = 13.2, 8.7 Hz, 1 H, CHC*H*H), 3.58 [t, *J* = 8.7 Hz, 1 H, N($CH_3$)C*H*], 3.13 (dd, *J* = 13.2, 9.6 Hz, 1 H, CHC*H*H), 2.71 (s, 3 H, $NCH_3$), 2.52 (q, *J* = 9.0 Hz, 1 H, CC*H*$CH_2$), 2.44 (s, 3 H, $C_6H_4CH_3$), 2.15 [m, 1 H, C*H*($CH_3$)$_2$], 1.07 (d, *J* = 6.4 Hz, 3 H, $CHCH_3$), 0.99 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 0.90−0.80 (m, 2 H, $CH_2$ cyclopropyl), 0.67−0.62 (m, 1 H, C*H*H cyclopropyl), 0.55−0.51 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.6 (s), 136.6 (s), 129.8 (d, 2 C), 127.4 (d, 2 C), 76.2 (d), 68.1 (d), 64.1 (s), 52.6 (d), 50.2 (t), 46.7 (q), 27.9 (d), 22.0 (q), 21.5 (q), 19.4 (q), 14.5 (t), 1.3 (t). − IR: $\tilde{\nu}$ = 3067 $cm^{-1}$, 2962, 1598, 1339, 1152. − MS (EI): *m*/*z* = 350 (2) [$M^+$], 307 (18), 195 (88), 155 (67), 112 (24), 95 (30), 91 (95), 90 (22), 84 (100), 83 (37), 82 (21), 72 (24), 70 (28), 68 (81), 67 (31), 65 (22), 55 (74). − $C_{18}H_{26}N_2O_3S$ (350.5): calcd. C 61.69, H 7.48, N 7.99; found C 61.95, H 7.64, N 8.02.

**(3′a*R**,6′*S**,6′a*R**)-1′-Methyl-6′-phenyl-5′-tosylspiro-[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (41a):** Waxy white solid, 46% yield (method B, eluent petroleum ether/diethyl ether, 1:1, $R_f$ = 0.17). − $^1$H NMR (200 MHz): δ = 7.60 (d, *J* = 8.0 Hz, 2 H, Ts), 7.35−7.23 (m, 7 H, Ts and Ph), 4.47 (d, *J* = 4.4, 1 H, PhC*H*), 3.87 (dd, *J* = 10.4, 8.0 Hz, 1 H, CHC*H*H), 3.67 [dd, *J* = 7.3, 4.4 Hz, 1 H, N($CH_3$)C*H*], 3.44 (dd, *J* = 10.4, 5.4 Hz, 1 H, CHC*H*H), 3.13 (dt, *J* = 5.4, 7.9 Hz, 1 H, CC*H*$CH_2$), 2.65 (s, 3 H, $NCH_3$), 2.41 (s, 3 H, $C_6H_4CH_3$), 0.98−0.82 (m, 1 H, C*H*H cyclopropyl), 0.76−0.42 (m, 3 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.4 (s), 140.8 (s), 134.1 (s), 129.3 (d, 2 C), 128.5 (d, 2 C), 127.9 (d, 2 C), 127.6 (d), 126.7 (d, 2 C), 83.8 (d), 69.2 (d), 65.6 (s), 52.6 (t), 48.7 (d), 45.4 (q), 21.4 (q), 14.3 (t), 4.1 (t). − IR: $\tilde{\nu}$ = 3068 $cm^{-1}$, 3033, 2974, 1599, 1346, 1158. − MS (EI): *m*/*z* = 229 (77) [$M^+$ − Ts], 155 (14), 118 (97), 106 (21), 105 (17), 91 (100), 89 (18), 77 (30), 69 (15), 68 (91), 65 (55), 58 (17), 57 (24), 55 (48). − $C_{21}H_{24}N_2O_3S$ (384.5): calcd. C 65.60, H 6.29, N 7.29; found C 65.28, H 6.47, N 7.00.

**(3′a*R*,6′*S*,6′a*R*)-6′-Benzyl-1′-methyl-5′-tosylspiro[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (42a):** Yellow oil, 28% yield (method A, eluent pentane/diethyl ether, 1:4, $R_f$ = 0.45); $[\alpha]_D^{20}$ = −28.3 (*c* = 1.02, $CHCl_3$). − $^1$H NMR (250 MHz): δ = 7.80 (d, *J* = 8.2 Hz, 2 H, Ts), 7.40−7.15 (m, 7 H, Ts and Ph), 3.87 [dt, *J* = 9.0, 3.3 Hz, 1 H, N(Ts)C*H*], 3.46 (dd, *J* = 10.4, 7.8 Hz, 1 H, NC*H*H), 3.48−3.40 [m, 1 H, N($CH_3$)C*H*], 3.35 (dd, *J* = 13.7, 3.7 Hz, 1 H, PhC*H*H), 3.24 (dd, *J* = 10.4, 5.5 Hz, 1 H, NC*H*H), 2.99 (dd, *J* = 13.7, 9.0 Hz, 1 H, PhC*H*H), 2.77 (dt, *J* = 5.5, 7.5 Hz, 1 H, CC*H*$CH_2$), 2.44 (s, 3 H, $C_6H_4CH_3$), 2.29 (s, 3 H, $NCH_3$), 0.90−0.70 (m, 1 H, C*H*H cyclopropyl), 0.65−0.40 (m, 2 H, $CH_2$ cyclopropyl), 0.40−0.25 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (63 MHz): δ = 143.3 (s), 137.0 (s), 134.6 (s), 129.7 (d, 2 C), 129.4 (d, 2 C), 128.4 (d, 2 C), 127.6 (d, 2 C), 126.5 (d), 77.9 (d), 66.1 (s), 65.2 (d), 51.8 (t), 49.0 (d), 44.3 (q), 40.4 (t), 21.4 (q) 13.2 (t), 5.0 (t). − IR: $\tilde{\nu}$ = 3100−2820 $cm^{-1}$, 1600. − MS (EI): *m*/*z* = 243 (41), 132 (100), 124 (53), 112 (50), 91 (57); MS (CI with $NH_3$): *m*/*z* = 399 (48) [$MH^+$]; HRMS: found 398.16676, $C_{22}H_{26}N_2O_3S$ requires 398.16640.

**(3′a*S*,6′*S*,6′a*S*)-6′-Benzyl-1′-methyl-5′-tosylspiro[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (42b):** White solid, 46% yield (method A, eluent pentane/diethyl ether, 1:4, $R_f$ = 0.52); m.p. 144°C; $[\alpha]_D^{20}$ = −93.8 (*c* = 1.01, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.58 (d, *J* = 8.0 Hz, 2 H, Ts), 7.40−7.20 (m, 7 H, Ts and Ph), 3.97 [q, *J* = 5.9 Hz, 1 H, N(Ts)C*H*], 3.70 [t, *J* = 6.4 Hz, 1 H, N($CH_3$)C*H*], 3.57 (dd, *J* = 9.5, 6.7 Hz, 1 H, NC*H*H), 3.44 (dd, *J* = 9.5, 5.2 Hz, 1 H, NC*H*H), 3.25 (dd, *J* = 11.2, 6.1 Hz, 1 H, PhC*H*H), 3.08 (dd, *J* = 11.2, 6.0 Hz, 1 H, PhC*H*H), 2.89 (dt, *J* = 5.2, 6.7 Hz, 1 H, CC*H*$CH_2$), 2.71 (s, 3 H, $NCH_3$), 2.48 (s, 3 H, $C_6H_4CH_3$), 1.03 (br s, 2 H, $CH_2$ cyclopropyl), 0.76 (m, 2 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (63 MHz): δ = 143.5 (s), 139.1 (s), 134.4 (s), 129.4 (d, 4 C), 127.9 (d, 2 C), 127.5 (d, 2 C), 125.8 (d), 75.2 (d), 65.4 (s), 64.6 (d), 50.9 (t), 50.0 (d), 46.1 (q), 34.9 (t), 21.4 (q) 15.3 (t), 2.0 (t). − IR: $\tilde{\nu}$ = 3140−2800 $cm^{-1}$, 1600. − MS (EI): *m*/*z* = 307 (38), 243 (76), 132 (100), 124 (91), 112 (81), 105 (71); MS (CI with $NH_3$): *m*/*z* = 399 (100) [$MH^+$]; HRMS: found 398.16670, $C_{22}H_{26}N_2O_3S$ requires 398.16640.

**(3′a*R*,6′*S*,6′a*R*)-6′-(3-Indolylmethyl)-1′-methyl-5′-tosylspiro-[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (43a):** White solid, 38% yield (method B, eluent petroleum ether/ethyl acetate, 4:3, $R_f$ = 0.26); m.p. 74−76°C; $[\alpha]_D^{20}$ = 9.1 (*c* = 0.41, $CHCl_3$). − $^1$H NMR (500 MHz): δ = 8.28 (br s, 1 H, N*H*), 7.82 (d, *J* = 8.2 Hz, 2 H, Ts), 7.72 (d, *J* = 7.5 Hz, 1 H, indolyl), 7.37 (d, *J* = 7.5 Hz, 1 H, indolyl), 7.31 (d, *J* = 8.2 Hz, 2 H, Ts), 7.22−7.14 (m, 3 H, indolyl), 3.93 [dt, *J* = 8.5, 3.0 Hz, 1 H, N(Ts)C*H*], 3.55−3.50 [m, 1 H, N($CH_3$)C*H*], 3.51 (dd, *J* = 10.7, 8.0 Hz, 1 H, NC*H*H), 3.43 (dd, *J* = 15.0, 3.0 Hz, 1 H, NCHC*H*H), 3.26 (dd, *J* = 10.7, 5.2 Hz, 1 H, NC*H*H), 3.22 (dd, *J* = 15.0, 8.5 Hz, 1 H, NCHC*H*H), 2.76 (dt, *J* = 5.2, 7.5 Hz, 1 H, CC*H*$CH_2$), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.33 (s, 3 H, $NCH_3$), 0.79 (m, 1 H, C*H*H cyclopropyl), 0.53 (m, 1 H, C*H*H cyclopropyl), 0.45 (m, 1 H, C*H*H

cyclopropyl), 0.32 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 143.4 (s), 136.0 (s), 134.6 (s), 129.5 (d, 2 C), 128.0 (s), 127.8 (d, 2 C), 123.6 (d), 121.9 (d), 119.6 (d), 118.6 (d), 111.2 (d), 110.8 (s), 78.6 (d), 68.3 (d), 65.4 (s), 52.1 (t), 48.8 (d), 44.6 (q), 29.6 (t), 21.5 (q) 13.7 (t), 4.9 (t). − IR: ṽ = 3481 cm$^{-1}$, 3411, 3063, 2975, 1599, 1336, 1154. − MS (EI): *m*/*z* = 437 (1) [$M^+$], 307 (22), 282 (24), 171 (20), 151 (22), 130 (100), 124 (20), 112 (38), 91 (40); HRMS: found 437.1775, $C_{24}H_{27}N_3O_3S$ requires 437.1773. − $C_{24}H_{27}N_3O_3S$ (437.6): calcd. C 65.88, H 6.22, N 9.60; found C 65.35, H 6.62, N 9.26.

**(3′a*S*,6′*S*,6′a*S*)-6′-(3-Indolylmethyl)-1′-methyl-5′-tosylspiro-[cyclopropane-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (43b):** White solid, 25% yield (method B, eluent petroleum ether/ethyl acetate, 4:3, $R_f$ = 0.37). **43b** is unstable and could not be fully characterised. m.p. 177−178 °C. − $^1$H NMR (500 MHz): δ = 7.91 (br s, 1 H, N*H*), 7.66 (d, *J* = 7.9 Hz, 1 H, indolyl), 7.60 (d, *J* = 8.2 Hz, 2 H, Ts), 7.33 (d, *J* = 8.0 Hz, 1 H, indolyl), 7.17 (d, *J* = 8.2 Hz, 2 H, Ts), 7.19−7.07 (m, 3 H, indolyl), 4.09 [q, *J* = 7.3 Hz, 1 H, N(Ts)C*H*], 3.66 [t, *J* = 7.8 Hz, 1 H, N(CH$_3$)C*H*], 3.64 (dd, *J* = 11.8, 8.2 Hz, 1 H, NC*H*H), 3.52 (dd, *J* = 11.8, 6.8 Hz, 1 H, NC*H*H), 3.40 (dd, *J* = 14.4, 8.5 Hz, 1 H, NCHC*H*H), 3.24 (dd, *J* = 14.4, 6.0 Hz, 1 H, NCHC*H*H), 2.85 (q, *J* = 7.8, 1 H, CC*H*CH$_2$), 2.66 (s, 3 H, NC*H*$_3$), 2.38 (s, 3 H, C$_6$H$_4$C*H*$_3$), 0.98 (br s, 2 H, C*H*$_2$ cyclopropyl), 0.77−0.66 (m, 2 H, C*H*$_2$ cyclopropyl). − IR: ṽ = 3483 cm$^{-1}$, 2929, 1598, 1345, 1153. − MS (EI): *m*/*z* = 437 (0.5) [$M^+$], 130 (100), 91 (52), 65 (17); HRMS: found 437.1769, $C_{24}H_{27}N_3O_3S$ requires 437.1773. − $C_{24}H_{27}N_3O_3S$ (437.6): calcd. C 65.88, H 6.22, N 9.60; found C 65.00, H 6.81, N 8.80.

**(3′a*S**,6′a*R**)-1′-Methylspiro[cyclopropane-1,3′-tetrahydro-4*H*,6*H*-furo[3,4-*c*]isoxazole] (45):** Colourless oil, 90% yield (method B, eluent CH$_2$Cl$_2$/CH$_3$OH + 1% NH$_4$OH, 20:1, $R_f$ = 0.26). − $^1$H NMR (500 MHz): δ = 3.90 (br m, 1 H, NC*H*), 3.85−3.79 (m, 4 H, C*H*$_2$OC*H*$_2$), 3.06 (dt, *J* = 4.6, 7.0 Hz, 1 H, CC*H*), 2.80 (s, 3 H, NC*H*$_3$), 1.05−1.01 (m, 1 H, C*H*H cyclopropyl), 0.99−0.95 (m, 1 H, C*H*H cyclopropyl), 0.78−0.74 (m, 1 H, C*H*H cyclopropyl), 0.72−0.67 (m, 1 H, C*H*H cyclopropyl). − $^{13}$C NMR (63 MHz): δ = 75.0 (d), 73.2 (t), 72.2 (t), 65.6 (s), 51.5 (d), 45.8 (q), 14.2 (t), 3.8 (t). − IR: ṽ = 2980 cm$^{-1}$, 2870, 1070. − MS (EI): *m*/*z* = 155 (12) [$M^+$], 96 (20), 70 (57), 69 (23), 68 (35), 55 (19), 42 (100), 41 (21); HRMS: found 155.0952, $C_8H_{13}NO_2$ requires 155.0946.

**Nitrone Formation−Intramolecular Cycloaddition of Aldehyde 36:** To a CH$_2$Cl$_2$ solution (160 mL) of the aldehyde **36** (235.0 mg, 1.42 mmol) at 0 °C were added *N*-methylhydroxylamine hydrochloride (348.0 mg, 4.17 mmol, 3 equiv.) and *i*Pr$_2$EtN (720 µL, 4.17 mmol, 2 equiv.). After stirring for one night at room temp., the solvent was removed and the crude mixture separated by chromatography on silica gel (eluent CH$_2$Cl$_2$/CH$_3$OH + 1% NH$_4$OH, 5:1). The product was then dissolved in *i*Pr$_2$EtN (20 mL), treated with K$_2$CO$_3$ for one night, filtered, and evaporated to give the expected isoxazolidine **44a** (264.0 mg, 1.36 mmol, 95%).

**(3′a*R*,8′a*S*,8′b*R*)-1′-methylspiro[cyclopropane-1,3′-octahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine] (44a):** Pale yellow oil (eluent CH$_2$Cl$_2$/CH$_3$OH + 1% NH$_4$OH, 5:1, $R_f$ = 0.11); $[\alpha]_D^{20}$ = −152.6 (*c* = 0.54, CH$_3$OH). − $^1$H NMR (500 MHz): δ = 3.49 (dt, *J* = 7.3, 5.2 Hz, 1 H, NC*H*CH$_2$), 3.46−3.41 [m, 1 H, N(CH$_3$)C*H*], 3.14 (dt, *J* = 4.3, 7.3 Hz, 1 H, CC*H*), 3.06 (dd, *J* = 11.0, 4.3 Hz, 1 H, CHC*H*HN), 3.01 (ddd, *J* = 10.7, 7.9, 4.9 Hz, 1 H, NC*H*HCH$_2$), 2.86 (dd, *J* = 11.0, 7.4 Hz, 1 H, CHC*H*HN), 2.80 (s, 3 H, NC*H*$_3$), 2.56 (dt, *J* = 10.7, 7.3 Hz, 1 H, NC*H*HCH$_2$), 2.13−2.05 (m, 1 H, NCHC*H*H), 1.95−1.86 (m, 1 H, NCH$_2$C*H*H), 1.83−1.73 (m, 1 H, NCH$_2$C*H*H), 1.65−1.56 (m, 1 H, NCHC*H*H), 1.04−0.96 (m, 2 H, C*H*$_2$ cyclopropyl), 0.74−0.64 (m, 2 H, C*H*$_2$ cyclopropyl). − $^1$H NMR (500 MHz, C$_6$D$_6$): δ = 3.60 (dt, *J* = 7.3, 4.9 Hz, 1 H, NC*H*CH$_2$), 3.09−3.03 [m, 1 H, N(CH$_3$)C*H*], 3.01 (dd, *J* = 11.0, 4.9 Hz, 1 H, CHC*H*HN), 2.88 (ddd, *J* = 10.1, 7.9, 4.9 Hz, 1 H, NC*H*HCH$_2$), 2.64 (dt, *J* = 7.9, 4.9 Hz, 1 H, CC*H*), 2.61 (s, 3 H, NC*H*$_3$), 2.58 (dd, *J* = 11.0, 7.3 Hz, 1 H, CHC*H*HN), 2.27 (dt, *J* = 10.1, 7.9 Hz, 1 H, NC*H*HCH$_2$), 1.92−1.82 (m, 1 H, NCHC*H*H), 1.63−1.54 (m, 2 H, NCH$_2$C*H*$_2$), 1.40−1.32 (m, 1 H, NCHC*H*H), 0.96−0.84 (m, 2 H, C*H*$_2$ cyclopropyl), 0.46−0.36 (m, 2 H, C*H*$_2$ cyclopropyl). − $^{13}$C NMR (50 MHz): δ = 80.6 (d), 71.2 (d), 65.9 (s), 57.0 (t), 53.4 (t), 50.9 (d), 45.8 (q), 29.6 (t), 24.4 (t), 14.7 (t), 3.8 (t). − IR: ṽ = 3085 cm$^{-1}$, 2963, 1452, 1091. − MS (EI): *m*/*z* = 194 (0.5) [$M^+$], 138 (14), 135 (14), 121 (10), 110 (13), 109 (12), 106 (23), 93 (61), 84 (53), 79 (74), 66 (100). − $C_{11}H_{18}N_2O$ (194.3): calcd. C 68.01, H 9.34, N 14.42; found C 68.24, H 9.38, N 14.65.

**General Procedure for Thermal Rearrangement of Adducts 38, 39a, 39b, 41a, 42a, 42b, 43a, 44a, and 45:** A solution in xylenes of the adducts (50−80 mL, 0.31−0.70 mmol) was heated at reflux for 6 h (or in *o*-xylene at 126 °C for 5 h, or at 130 °C for 33.5−42 h). After cooling to room temp., the solvent was removed and the crude mixture was separated by chromatography on silica gel to give the diazaheterocycles **46**, **47a**, **47b**, **48a**, **49a**, **49b**, **50a**, **51a**, and **52**.

**(4a*R**,7a*R**)-1-Methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]-pyridine (46):** Brown oil, 49% yield (eluent ethyl acetate/CH$_3$OH, 9:1, $R_f$ = 0.43). − $^1$H NMR (200 MHz): δ = 7.69 (d, *J* = 8.1 Hz, 2 H, Ts), 7.32 (d, *J* = 8.1 Hz, 2 H, Ts), 3.60−3.35 (m, 4 H, C*H*$_2$NC*H*$_2$), 2.95−2.60 [m, 5 H, COC*H*, NC*H*, COC*H*$_2$ and N(CH$_3$)C*H*H], 2.55−2.40 [m, 1 H, N(CH$_3$)C*H*H], 2.45 (s, 3 H, C$_6$H$_4$C*H*$_3$), 2.30 (s, 3 H, NC*H*$_3$). − $^{13}$C NMR (50 MHz): δ = 206.6 (s), 143.8 (s), 132.5 (s), 129.7 (d, 2 C), 127.7 (d, 2 C), 65.4 (d), 51.6 (t), 50.3 (t), 49.4 (d), 46.8 (t), 43.5 (q), 39.1 (t), 21.5 (q). − IR: ṽ = 3020−2740 cm$^{-1}$, 1720, 1595. − MS (EI): *m*/*z* = 155 (38), 124 (42), 112 (74), 42 (100); MS (CI with NH$_3$): *m*/*z* = 309 (100) [$MH^+$]; HRMS: found 308.1197, $C_{15}H_{20}N_2O_3S$ requires 308.1195.

**(4a*R*,7*S*,7a*R*)-1,7-Dimethyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo-[3,4-*b*]pyridine (47a):** Yellow oil, 64% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.09); $[\alpha]_D^{20}$ = −58.1 (*c* = 1.57, CHCl$_3$). − $^1$H NMR (250 MHz): δ = 7.75 (d, *J* = 8.1 Hz, 2 H, Ts), 7.30 (d, *J* = 8.1 Hz, 2 H, Ts), 3.82 (dq, *J* = 1.5, 6.7 Hz, 1 H, CH$_3$C*H*), 3.53 (d, *J* = 9.3 Hz, 2 H), 2.98 (ddt, *J* = 6.0, 0.9, 8.7 Hz, 1 H), 2.78 (ddd, *J* = 10.8, 5.8, 2.4 Hz, 1 H, COC*H*H), 2.52 [dd, *J* = 5.3, 1.6 Hz, 1 H, N(CH$_3$)C*H*], 2.43 (s, 3 H, C$_6$H$_4$C*H*$_3$), 2.47−2.19 (m, 3 H), 2.11 (s, 3 H, NC*H*$_3$), 1.29 (d, *J* = 6.7 Hz, 3 H, CHC*H*$_3$). − $^{13}$C NMR (63 MHz): δ = 206.5 (s), 143.4 (s), 134.6 (s), 129.3 (d, 2 C), 127.6 (d, 2 C), 73.9 (d), 66.7 (d), 59.4 (d), 53.8 (t), 49.4 (t), 49.0 (q), 42.7 (q), 38.2 (t), 21.5 (q). − IR: ṽ = 3120−2700 cm$^{-1}$, 1720, 1600. − MS (EI): *m*/*z* = 167 (17), 124 (27), 112 (29), 57 (100); MS (CI with NH$_3$): *m*/*z* = 323 (100) [$MH^+$]. − $C_{16}H_{22}N_2O_3S$ (322.4): calcd. C 59.60, H 6.88, N 8.69; found C 59.52, H 6.83, N 8.08.

**(4a*S*,7*S*,7a*S*)-1,7-Dimethyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo-[3,4-*b*]pyridine (47b):** Yellow oil, 43% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.23); $[\alpha]_D^{20}$ = 31.6 (*c* = 1.32, CHCl$_3$). − $^1$H NMR (250 MHz): δ = 7.72 (d, *J* = 7.9 Hz, 2 H, Ts), 7.30 (d, *J* = 7.9 Hz, 2 H, Ts), 4.12 (p, *J* = 6.6, 1 H, CH$_3$C*H*), 3.87 (dd, *J* = 11.5, 4.4 Hz, 1 H, CHC*H*H), 3.60−3.50 (m, 1 H, CHC*H*H), 3.05−2.85 [m, 3 H, COC*H*, COC*H*H and N(CH$_3$)C*H*], 2.78 (ddd, *J* = 12.2, 7.3, 1.5 Hz, 1 H, COC*H*H), 2.57 [ddd, *J* = 17.9, 10.6, 7.3 Hz, 1 H, N(CH$_3$)C*H*H], 2.43 (s, 3 H, C$_6$H$_4$C*H*$_3$), 2.35 [ddd, *J* = 17.9, 4.7, 1.5 Hz, 1 H, N(CH$_3$)C*H*H], 2.27 (m, 3 H, NC*H*$_3$), 0.79 (d, *J* = 6.7 Hz, 3 H, CHC*H*$_3$). − $^{13}$C NMR (63 MHz): δ = 208.4 (s), 143.4 (s), 136.7 (s), 129.7 (d, 2 C), 127.1 (d, 2 C), 68.1 (d), 57.8 (d), 50.9 (t), 47.4 (d), 44.2 (q), 39.8 (t), 29.7 (t), 21.5 (q), 14.2 (q). − IR: ṽ = 3120−2700 cm$^{-1}$, 1720, 1600. − MS (EI): *m*/*z* = 167 (27), 124 (44),

112 (47), 56 (100); MS (CI with $NH_3$): *m*/*z* = 323 (100) [$MH^+$]; HRMS: found 322.1361, $C_{16}H_{22}N_2O_3S$ requires 322.1351.

**(4a*R**,7*S**,7a*R**)-1-Methyl-4-oxo-7-phenyl-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridine (48a):** White solid, 53% yield (eluent petroleum ether/ethyl acetate, 4:3, $R_f$ = 0.23); m.p. 146−148°C. − $^1$H NMR (500 MHz): δ = 7.69 (d, *J* = 8.3 Hz, 2 H, Ts), 7.33−7.24 (m, 7 H, Ts and Ph), 4.97 (s, 1 H, PhC*H*), 3.81 (t, *J* = 9.7 Hz, 1 H, CHC*H*H), 3.75 (t, *J* = 8.9 Hz, 1 H, CHC*H*H), 2.95 (dt, *J* = 4.7, 8.9 Hz, 1 H, COC*H*), 2.90 (ddd, *J* = 11.7, 5.8, 3.5 Hz, 1 H, COC*H*H), 2.84 [d, *J* = 4.7 Hz, 1 H, N(CH$_3$)C*H*], 2.58 [ddd, *J* = 15.3, 11.5, 5.8 Hz, 1 H, N(CH$_3$)C*H*H], 2.44 (s, 3 H, $C_6H_4CH_3$), 2.42 (dt, *J* = 2.8, 11.6 Hz, 1 H, COC*H*H), 2.27 (s, 3 H, NC$H_3$), 2.23 [br m, 1 H, N(CH$_3$)C*H*H]. − $^{13}$C NMR (50 MHz): δ = 206.2 (s), 143.5 (s), 140.1 (s), 135.0 (s), 129.3 (d, 2 C), 128.5 (d. 2 C), 127.7 (d, 2 C), 127.5 (d), 126.3 (d, 2 C), 76.0 (d), 66.6 (d), 53.7 (t), 49.3 (t), 49.0 (d), 43.0 (q), 38.2 (t), 21.5 (q). − IR: ṽ = 3090 cm$^{-1}$, 3068, 3033, 2964, 2800, 1717, 1599, 1346, 1157. − MS (EI): *m*/*z* = 229 (80) [$M^+$ − Ts], 124 (71), 119 (21), 118 (100), 91 (95), 65 (15). − $C_{21}H_{24}N_2O_3S$ (384.5): calcd. C 65.60, H 6.29, N 7.29; found C 65.66, H 6.20, N 7.19.

**(4a*R*,7*S*,7a*R*)-7-Benzyl-1-methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridine (49a):** Yellow oil, 44% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.32); $[\alpha]_D^{20}$ = 29.2 (*c* = 1.44, $CHCl_3$). − $^1$H NMR (250 MHz): δ = 7.79 (d, *J* = 8.2 Hz, 2 H, Ts), 7.50−7.20 (m, 7 H, Ts and Ph), 4.00 [dd, *J* = 10.0, 3.3 Hz, 1 H, N(Ts)C*H*], 3.60−3.35 (m, 2 H), 3.20 (dd, *J* = 13.5, 3.4 Hz, 1 H, PhC*H*H), 2.85−2.62 (m, 3 H), 2.55 [d, *J* = 5.0 Hz, 1 H, N(CH$_3$)C*H*], 2.43 (s, 3 H, $C_6H_4CH_3$), 2.50−2.35 (m, 1 H), 2.25−2.05 (m, 2 H), 1.67 (s, 3 H, NC$H_3$). − $^{13}$C NMR (63 MHz): δ = 206.6 (s), 143.5 (s), 137.4 (s), 134.2 (s), 129.4 (d, 2 C), 129.3 (d, 2 C), 128.5 (d, 2 C), 127.7 (d, 2 C), 126.7 (d), 70.2 (d), 65.6 (d), 54.1 (t), 49.7 (d), 49.6 (q), 42.1 (t), 41.4 (t), 38.2 (t), 21.5 (q). − IR: ṽ = 3120−2640 cm$^{-1}$, 1710, 1595. − (EI): *m*/*z* = 243 (41), 132 (100), 124 (52), 112 (43), 91 (73); MS (CI with $NH_3$): *m*/*z* = 399 (36) [$MH^+$]; HRMS: found 398.1662, $C_{22}H_{26}N_2O_3S$ requires 398.1664.

**(4a*S*,7*S*,7a*S*)-7-Benzyl-1-methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridine (49b):** White solid, 43% yield (eluent pentane/diethyl ether, 1:4, $R_f$ = 0.30); m.p. 176°C; $[\alpha]_D^{20}$ = −8.7 (*c* = 0.97, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.40−7.03 (m, 9 H, Ts and Ph), 4.41 (p, *J* = 5.2 Hz, 1 H), 3.90−3.60 (m, 2 H), 3.25−3.10 (m, 1 H), 3.09−2.93 (m, 3 H), 2.92−2.80 (m, 2 H), 2.76 (d, *J* = 4.4 Hz, 1 H), 2.70−2.50 (m, 1 H), 2.36 (s, 3 H, $C_6H_4CH_3$), 2.28 (s, 3 H, NC$H_3$), 2.13 (dd, *J* = 14.3, 10.3 Hz, 1 H). − $^{13}$C NMR (50 MHz): δ = 209.0 (s), 143.1 (s), 138.5 (s), 136.4 (s), 129.4 (d, 4 C), 128.1 (d, 2 C), 127.2 (d, 2 C), 126.0 (d), 68.9 (d), 63.4 (d), 51.1 (t), 47.5 (d), 44.5 (q), 42.9 (t), 39.8 (t), 34.4 (t), 21.4 (q). − IR: ṽ = 3120−2660 cm$^{-1}$, 1720, 1600. − MS (EI): *m*/*z* = 243 (34), 132 (100), 124 (43), 112 (29); MS (CI with $NH_3$): *m*/*z* = 399 (61) [$MH^+$]; HRMS: found 398.1665, $C_{22}H_{26}N_2O_3S$ requires 398.1664.

**(4a*R*,7*S*,7a*R*)-7-(3-Indolylmethyl)-1-methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*] pyridine (50a):** White solid, 41% yield (eluent petroleum ether/ethyl acetate, 4:5, $R_f$ = 0.29); m.p. 208−210°C; $[\alpha]_D^{20}$ = 59.1 (*c* = 1.04, $CHCl_3$). − $^1$H NMR (500 MHz): δ = 8.20 (br s, 1 H, N*H*), 7.85 (d, *J* = 7.2 Hz, 1 H, indolyl), 7.83 (d, *J* = 8.3 Hz, 2 H, Ts), 7.37 (d, *J* = 7.2 Hz, 1 H, indolyl), 7.32 (d, *J* = 8.3 Hz, 2 H, Ts), 7.28−7.19 (m, 2 H, indolyl), 7.06 (d, *J* = 2.2 Hz, 1 H, indolyl), 4.14 [dd, *J* = 10.5, 3.3 Hz, 1 H, N(Ts)C*H*], 3.58 [t, *J* = 8.9 Hz, 1 H, N(Ts)C*H*H], 3.48 [t, *J* = 8.8 Hz, 1 H, N(Ts)C*H*H], 3.37 (dd, *J* = 14.5, 3.3 Hz, 1 H, NCHC*H*H), 2.87 (dd, *J* = 14.5, 10.6 Hz, 1 H, NCHC*H*H), 2.93−2.81 (m, 1 H, COC*H*), 2.67 (ddd, *J* = 12.2, 6.1, 3.0 Hz, 1 H, COC*H*H), 2.64 [d, *J* = 5.5 Hz, 1 H, N(CH$_3$)C*H*], 2.43 (s, 3 H, $C_6H_4CH_3$), 2.43−2.33 (m, 1 H), 2.22−2.05 [m, 2 H, N(CH$_3$)C*H*H], 1.60 (s, 3 H, NC$H_3$). − $^{13}$C NMR (50 MHz): δ = 207.0 (s), 143.5 (s), 136.2 (s), 134.4 (s), 129.4 (d, 2 C), 127.9 (d, 2 C), 127.8 (s), 122.8 (d), 122.2 (d), 119.8 (d), 119.0 (d), 111.8 (s), 111.2 (d), 70.9 (d), 64.6 (d), 54.1 (t), 49.8 (t), 49.6 (d), 42.2 (q), 38.2 (t), 31.2 (t), 21.5 (q). − IR: ṽ = 3482 cm$^{-1}$, 3064, 2958, 2803, 1713, 1598, 1339, 1157. − MS (EI): *m*/*z* = 437 (0.8) [$M^+$], 283 (32), 171 (18), 151 (29), 143 (17), 130 (100), 124 (20), 112 (27), 91 (23). − $C_{24}H_{27}N_3O_3S$ (437.6): calcd. C 65.88, H 6.22, N 9.60; found C 65.15, H 6.30, N 10.00.

**(4a*R*,9a*S*,9b*R*)-1-Methyl-4-oxodecahydro-5*H*-pyrido[2,3-*a*]-pyrrolizine (51a):** Yellow oil, 70% yield (eluent $CH_2Cl_2$/$CH_3OH$ + 1% $NH_4OH$, 5:1, $R_f$ = 0.07); $[\alpha]_D^{20}$ = −63.4 (*c* = 0.62, $CHCl_3$). − $^1$H NMR (500 MHz): δ = 3.52 (dt, *J* = 3.7, 7.3 Hz, 1 H, NC*H*CH$_2$), 3.43 (dd, *J* = 10.1, 7.0 Hz, 1 H, NC*H*HCH), 3.06 (ddd, *J* = 9.5, 6.7, 3.7 Hz, 1 H, NC*H*HCH$_2$CH$_2$), 3.03−2.98 (m, 1 H), 2.90−2.80 (m, 2 H), 2.71 [dd, *J* = 6.7, 3.7 Hz, 1 H, N(CH$_3$)C*H*], 2.64−2.57 (m, 2 H), 2.49 (dt, *J* = 6.1, 9.5 Hz, 1H1 H, NC*H*HCH$_2$CH$_2$), 2.43−2.38 (m, 1 H), 2.38 (s, 3 H, NC$H_3$), 2.10−2.03 (m, 1 H, NCHC*H*H), 1.85−1.72 (m, 2 H, NCH$_2$C$H_2$ CH$_2$), 1.52−1.43 (m, 1 H, NCHC*H*H); $^1$H NMR (500 MHz, $C_6D_6$): δ = 3.52 (dd, *J* = 11.0, 7.9 Hz, 1 H, NC*H*HCH), 3.39 (dt, *J* = 3.7, 7.3 Hz, 1 H, NC*H*CH$_2$), 2.89 (ddd, *J* = 9.7, 6.3, 3.0 Hz, 1 H, NC*H*HCH$_2$CH$_2$), 2.64 (dd, *J* = 11.0, 6.7 Hz, 1 H, NC*H*HCH), 2.55 (ddd, *J* = 7.9, 7.0, 6.7 Hz, 1 H, COC*H*), 2.49−2.43 (m, 1 H, COC*H*H), 2.36−2.29 (m, 1 H), 2.18 [dd, *J* = 7.0, 3.7 Hz, 1 H, N(CH$_3$)C*H*], 2.14 (dt, *J* = 6.1, 9.2 Hz, 1 H, NC*H*HCH$_2$CH$_2$), 2.10−2.01 [m, 2 H, N(CH$_3$)C*H*H], 1.96 (s, 3 H, NC$H_3$), 1.70−1.62 (m, 1 H, NCHC*H*H), 1.54−1.40 (m, 2 H, NCH$_2$C$H_2$ CH$_2$), 1.08−0.99 (m, 1 H, NCHC*H*H). − $^{13}$C NMR (50 MHz): δ = 209.2 (s), 74.1 (d), 67.9 (d), 54.9 (t), 54.8 (t), 52.8 (t), 50.7 (d), 43.4 (q), 39.4 (t), 31.8 (t), 26.0 (t). − IR: ṽ = 2966 cm$^{-1}$, 1710, 1453, 1287, 1126. − MS (EI): *m*/*z* = 194 (1) [*M*], 83 (100), 55 (57). − $C_{11}H_{18}N_2O$ (194.3): calcd. C 68.01, H 9.34, N 14.42; found C 67.69, H 9.21, N 14.26.

**(4a*S**,7a*R**)-1-Methyl-4-oxooctahydrofuro[3,4-*b*]pyridine (52):** Colourless oil, 73% yield (eluent $CH_2Cl_2$/$CH_3OH$ + 1% $NH_4OH$, 20:1, $R_f$ = 0.21). − $^1$H NMR (500 MHz): δ = 4.07 (t, *J* = 8.5 Hz, 1 H, NCHC*H*H), 3.97 (t, *J* = 8.7 Hz, 1 H, NCHC*H*H), 3.88 (dd, *J* = 9.5, 5.5 Hz, 1 H, COCHC*H*H), 3.82 (dd, *J* = 9.5, 4.0 Hz, 1 H, COCHC*H*H), 3.09 (dt, *J* = 7.4, 4.5 Hz, 1 H, COC*H*), 3.03−2.96 (m, 1 H, COC*H*H), 2.90 (q, *J* = 8.0 Hz, 1 H, NC*H*), 2.72−2.65 (m, 2 H, COC*H*H and NC*H*H), 2.46−2.38 (m, 1 H, NC*H*H), 2.34 (s, 3 H, NC$H_3$). − $^{13}$C NMR (75 MHz): δ = 208.0 (s), 72.7 (t), 68.6 (t), 67.2 (d), 53.0 (t), 51.3 (d), 43.8 (q), 39.1 (t). − IR: ṽ = 2958 cm$^{-1}$, 2859, 2802, 1710, 1070. − MS (EI): *m*/*z* = 155 (14) [$M^+$], 140 (63), 125 (23), 124 (23), 97 (24), 96 (100), 82 (90), 69 (31), 68 (64), 55 (29); HRMS: found 155.0939, $C_8H_{13}NO_2$ requires 155.0946.

**Nitrone Formation − Intramolecular Cycloaddition of Aldehyde 31 with *N*-Benzylhydroxylamine:** To a $CCl_4$ solution (25 mL) of the aldehyde **31** (161.6 mg, 0.55 mmol) at 0°C were added *N*-benzylhydroxylamine hydrochloride (175.9 mg, 1.10 mmol, 2 equiv.) and *i*Pr$_2$EtN (190 µL, 1.11 mmol, 2 equiv.). After stirring for 2 d at room temp., the reaction mixture was filtered over Celite, the solvent removed and the crude mixture separated by chromatography on silica gel (eluent diethyl ether/petroleum ether, 1:1 + 0.06% $NEt_3$) to give a mixture of the expected isoxazolidines **56a** and **56b** (118.4 mg, 0.29 mmol, 54%), in a 35:65 ratio. Compounds **56a** and **56b** were obtained in enriched form after fractional crystallisation from diethyl ether and petroleum ether.

**(3a*R*,6*S*,6a*R*)-1-Benzyl-6-methyl-5-tosylspiro[cyclopropanehexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (56a):** Colourless oil,

$R_f$ = 0.32 (diethyl ether/petroleum ether, 1:1 + 0.06% $NEt_3$). − $^1H$ NMR (200 MHz): δ = 7.70 (d, *J* = 8.5 Hz, 2 H, Ts), 7.34−7.27 (m, 7 H, Ts and Ph), 4.17 (d, *J* = 12.9 Hz, 1 H, PhC*H*H), 3.89 (d, *J* = 12.9 Hz, 1 H, PhC*H*H), 3.75 (dd, *J* = 12.2, 10.8 Hz, 1 H, CHC*H*H), 3.50 (dd, *J* = 7.4, 5.5 Hz, 1 H, C*H*NO), 3.15−2.96 (m, 3 H, CHC*H*H, $CH_3CH$ and $CH_2CH$), 2.44 (s, 3 H, $C_6H_4CH_3$), 1.26 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.00−0.42 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}C$ NMR (50 MHz): δ = 143.6 (s), 136.5 (s), 133.0 (s), 129.6 (d, 2 C), 129.0 (d, 2 C), 128.4 (d, 2 C), 127.9 (d, 2 C), 127.6 (d), 78.8 (d), 66.0 (s), 61.7 (t), 61.1 (d), 52.7 (t), 47.6 (d), 21.5 (q), 19.6 (q), 14.5 (t), 3.7 (t). − IR: $\tilde{\nu}$ = 3033 $cm^{-1}$, 2969, 2931, 1599, 1342, 1159. − MS (EI): *m*/*z* = 398 (2) [$M^+$], 243 (32), 188 (35), 155 (20), 91 (100), 65 (17), 56 (81). − $C_{22}H_{26}N_2O_3S$ (mixture of **56a** and **56b**) (398.5): calcd. C 66.31, H 6.58, N 7.03; found C 66.14, H 6.51, N 6.94.

**(3a*S*,6*S*,6a*S*)-1-Benzyl-6-methyl-5-tosylspiro[cyclopropanehexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (56b):** White solid; $R_f$ = 0.32 (diethyl ether/petroleum ether, 1:1 + 0.06% $NEt_3$). − $^1H$ NMR (200 MHz): δ = 7.68 (d, *J* = 8.1 Hz, 2 H, Ts), 7.31−7.27 (m, 7 H, Ts and Ph), 4.24 (d, *J* = 12.8 Hz, 1 H, PhC*H*H), 3.91 (d, *J* = 12.8 Hz, 1 H, PhC*H*H), 3.74 (t, *J* = 8.1 Hz, 1 H, C*H*NO), 3.57−3.43 (m, 2 H, CHC*H*H, $CH_3CH$), 3.34 (dd, *J* = 11.0, 7.7 Hz, 1 H, CHC*H*H), 2.87 (dt, *J* = 5.3, 8.0 Hz, 1 H, $CH_2CH$), 2.43 (s, 3 H, $C_6H_4CH_3$), 1.33 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.99 (br s, 2 H, $CH_2$ cyclopropyl), 0.81−0.63 (m, 2 H, $CH_2$ cyclopropyl). − $^{13}C$ NMR (50 MHz): δ = 143.5 (s), 137.0 (s), 134.6 (s), 129.6 (d, 2 C), 128.9 (d, 2 C), 128.4 (d, 2 C), 127.6 (d, 2 C), 127.5 (d), 73.0 (d), 66.2 (s), 62.0 (t), 58.7 (d), 50.9 (t), 49.2 (d), 21.5 (q), 15.7 (q), 15.1 (t), 3.3 (t). − IR: $\tilde{\nu}$ = 2989 $cm^{-1}$, 1599, 1344, 1155. − MS (EI): *m*/*z* = 398 (0.1) [$M^+$], 243 (26), 200 (22), 188 (28), 144 (37), 91 (100), 56 (80). − $C_{22}H_{26}N_2O_3S$ (mixture of **56a** and **56b**) (398.5): calcd. C 66.31, H 6.58, N 7.03; found C 66.41, H 6.53, N 6.94.

**General Procedure for Thermal Rearrangement of Adducts 56a and 56b:** A solution of the adducts in *o*-xylene (8 mL, 51−60 μmol) was heated at 130°C for 4 h. After cooling to room temp., the solvent was removed and the crude mixture was separated by chromatography on silica gel to give the diazaheterocycles **58a** and **58b**.

**(4a*R*,7*S*,7a*R*)-1-Benzyl-7-methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridine (58a):** Yellow oil, 60% yield (eluent diethyl ether/petroleum ether, 1:1, $R_f$ = 0.14). − $^1H$ NMR (500 MHz): δ = 7.78 (d, *J* = 8.2 Hz, 2 H, Ts), 7.34 (d, *J* = 8.2 Hz, 2 H, Ts), 7.28−7.26 (m, 3 H, Ph), 7.02−7.00 (m, 2 H, Ph), 3.90 (d, *J* = 13.6 Hz, 1 H, PhC*H*H), 3.81 (dq, *J* = 2.9, 6.5 Hz, 1 H, $CH_3CH$), 3.76 (t, *J* = 9.0 Hz, 1 H, CHC*H*H), 3.60 (dd, *J* = 9.3, 7.5 Hz, 1 H, CHC*H*H), 3.21 (d, *J* = 13.6 Hz, 1 H, PhC*H*H), 3.01 (br q, *J* = 7.3 Hz, 1 H, COC*H*), 2.95 [dd, *J* = 5.9, 2.9 Hz, 1 H, N($CH_2$Ph)C*H*], 2.86−2.82 (m, 1 H, COC*H*H), 2.47 (s, 3 H, $C_6H_4CH_3$), 2.39−2.29 (m, 2 H, $CH_2CH$HN and COC*H*H), 2.27−2.21 (m, 1 H, $CH_2CH$HN), 1.40 (d, *J* = 6.5 Hz, 3 H, $CHCH_3$). − $^{13}C$ NMR (75 MHz): δ = 206.2 (s), 143.4 (s), 137.6 (s), 134.6 (s), 129.7 (d, 2 C), 128.4 (d, 2 C), 128.4 (d, 2 C), 127.8 (d, 2 C), 127.4 (d), 72.8 (d), 58.7 (d), 58.4 (t), 49.5 (t), 49.2 (d), 48.8 (t), 38.1 (t), 21.7 (q, 2 C). − IR: $\tilde{\nu}$ = 3034 $cm^{-1}$, 2978, 1713, 1598, 1344, 1160. − MS (EI): *m*/*z* = 243 (14) [$M^+$ − Ts], 200 (18), 188 (21), 91 (49), 56 (100); HRMS: found 398.1672, $C_{22}H_{26}N_2O_3S$ requires 398.1664.

**(4a*S*,7*S*,7a*S*)-1-Benzyl-7-methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridine (58b):** Yellow oil, 55% yield (eluent diethyl ether/petroleum ether, 3:2, $R_f$ = 0.22). − $^1H$ NMR (500 MHz): δ = 7.73 (d, *J* = 8.1 Hz, 2 H), 7.33−7.25 (m, 7 H), 4.15 (p, *J* = 6.6 Hz, 1 H, $CH_3CH$), 3.96 (dd, *J* = 11.5, 4.5 Hz, 1 H, CHC*H*H), 3.79 (d, *J* = 13.8 Hz, 1 H, PhC*H*H), 3.55 (dd, *J* = 11.5, 9.5 Hz, 1 H, CHC*H*H), 3.37 (d, *J* = 13.8 Hz, 1 H, PhC*H*H), 3.29 [dd, *J* = 10.7, 6.4 Hz, 1 H, N($CH_2$Ph)C*H*], 3.00 (ddd, *J* = 10.7, 9.5, 4.5 Hz, 1 H, COC*H*), 2.89 (ddd, *J* = 12.4, 7.1, 1.7 Hz, 1 H, COC*H*H), 2.79 (dt, *J* = 4.6, 11.5 Hz, 1 H, COC*H*H), 2.48 (ddd, *J* = 18.2, 10.8, 7.1 Hz, 1 H, $CH_2CH$HN), 2.45 (s, 3 H, $C_6H_4CH_3$), 2.35 (ddd, *J* = 18.2, 4.6, 1.7 Hz, 1 H, $CH_2CH$HN), 0.95 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$). − $^{13}C$ NMR (75 MHz): δ = 208.4 (s), 143.4 (s), 137.3 (s), 136.7 (s), 129.7 (d, 2 C), 128.6 (d, 2 C), 128.5 (d, 2 C), 127.6 (d), 127.2 (d, 2 C), 66.0 (d), 60.0 (t), 57.7 (d), 47.6 (d), 46.7 (t), 42.6 (t), 40.0 (t), 21.5 (q), 15.1 (q). − IR: $\tilde{\nu}$ = 3031 $cm^{-1}$, 2815, 1720, 1598, 1344, 1157. − MS (EI): *m*/*z* = 155 (33), 91 (100), 65 (28), 56 (22); HRMS: found 398.1671, $C_{22}H_{26}N_2O_3S$ requires 398.1664.

**Nitrone Formation − Intramolecular Cycloaddition of Aldehyde 31 with *N*-Tetrahydropyranylhydroxylamine:** A chloroform solution (30 mL) of the aldehyde **31** (173.4 mg, 0.59 mmol) and of 5-hydroxypentanal oxime (199.0 mg, 1.70 mmol, 3 equiv.) was refluxed in presence of 4-Å molecular sieves in pellets for 1 d. After concentration, the residue was filtered through a short pad of silica gel (eluent diethyl ether/petroleum ether, 1:1 + 0.2% $NEt_3$) to give a complex mixture of the four isomers **57a**, **a′** and **57b**, **b′** (125.2 mg, 0.32 mmol, 54%), a colourless oil, in a 3.6:2.7:1.8:1 ratio, which was used in the next step without further purification.

**(6*S*)-1-(Tetrahydro-2*H*-pyran-2-yl)-6-methyl-5-tosylspiro-[cyclopropane-1′,3-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (57a, a′ and 57b, b′):** $R_f$ = 0.39. − IR (mixture of four isomers): $\tilde{\nu}$ = 2948 $cm^{-1}$, 1598, 1341, 1157. − MS (EI, four isomers mixture): *m*/*z* = 392 (0.4) [$M^+$], 237 (19), 155 (32), 91 (100), 85 (68), 65 (30), 56 (77); HRMS (mixture of four isomers): found 392.1771, $C_{20}H_{28}N_2O_4S$ requires 392.1770.

**Thermal Rearrangement of Adducts 57a, a′ and 57b, b′:** An *o*-xylene solution (1.3 mL) of the four isomers **57a**, **a′** and **57b**, **b′** (40.0 mg, 100 μmol) was heated at 130°C for 6 h. After cooling to room temp., the solvent was removed and the crude mixture was separated by chromatography on silica gel (eluent ethyl acetate + 0.2% $NEt_3$) to give a mixture of **59a** and **59b** (10.0 mg, 33 μmol, 33%), a colourless oil, in a 69:31 ratio.

**(4a*R*,7*S*,7a*R*)-7-Methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]-pyridine (59a):** $R_f$ = 0.30. − $^1H$ NMR (500 MHz): δ = 7.76 (d, *J* = 8.2 Hz, 2 H, Ts), 7.34 (d, *J* = 8.2 Hz, 2 H, Ts), 3.61−3.53 (m, 3 H, $CH_3CH$ and $CHCH_2$), 3.26 (dd, *J* = 4.9, 1.9 Hz, 1 H, NHC*H*), 3.04 (ddd, *J* = 12.8, 6.2, 3.5 Hz, 1 H, COC*H*H), 2.97 (dt, *J* = 4.9, 8.9 Hz, 1 H, COC*H*), 2.82 (ddd, *J* = 12.8, 10.7, 3.6 Hz, 1 H, COC*H*H), 2.45 (s, 3 H, $C_6H_4CH_3$), 2.34 (ddd, *J* = 15.2, 10.6, 6.2 Hz, 1 H, NHC*H*H), 2.23 (dt, *J* = 15.2, 3.2 Hz, 1 H, NHC*H*H), 1.30 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$). − $^{13}C$ NMR (75 MHz): δ = 206.7 (s), 143.6 (s), 134.6 (s), 129.6 (d, 2 C), 127.6 (d, 2 C), 66.6 (d), 61.9 (d), 50.9 (d), 48.2 (t), 44.1 (t), 39.8 (t), 21.5 (q), 20.8 (q). − IR (mixture of two isomers): $\tilde{\nu}$ = 3450−3300 $cm^{-1}$, 2931, 1710, 1599, 1343, 1159. − MS (EI, mixture of two isomers): *m*/*z* = 308 (0.1) [$M^+$], 153 (54), 110 (58), 98 (39), 91 (43), 65 (18), 56 (100); HRMS (mixture of two isomers): found 308.1201, $C_{15}H_{20}N_2O_3S$ requires 308.1195.

**(4a*S*,7*S*,7a*S*)-7-Methyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridine (59b):** $R_f$ = 0.30. − $^1H$ NMR (500 MHz, selection of signals): δ = 7.72 (d, *J* = 8.1 Hz, 2 H, Ts), 7.34 (d, *J* = 8.1 Hz, 2 H, Ts), 3.74 (t, *J* = 11.0, 1 H, CHC*H*H), 3.63 (dd, *J* = 11.3, 8.9 Hz, 1 H, CHC*H*H), 3.40 (t, *J* = 4.8 Hz, 1 H, NHC*H*), 2.86 (dt, *J* = 3.3, 12.2 Hz, 1 H, COC*H*H), 2.53 (ddd, *J* = 16.0, 12.2, 7.6 Hz, 1 H, NHC*H*H), 2.45 (s, 3 H, $C_6H_4CH_3$), 2.35−2.26 (m, 2 H, COC*H*H and NHC*H*H), 1.44 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$). − $^{13}C$ NMR (75 MHz, selection of signals): δ = 208.0 (s), 129.9 (d, 2 C), 127.5 (d, 2 C), 63.5 (d), 60.3 (d), 52.2 (d), 49.4 (t), 44.6 (t), 21.5 (q).

**Conversion of 31 in the Corresponding (*Z*)- and (*E*)-Oximes 60:** To a chloroform solution (25 mL) of **31** (398.5 mg, 1.36 mmol) at 0°C were added hydroxylamine hydrochloride (142.6 mg, 2.05 mmol, 1.5 equiv.) and *i*$Pr_2$EtN (340 μL, 1.99 mmol, 1.45 equiv.). The mixture was stirred overnight at room temp., the solvent was removed and the residue was dissolved in 40 mL of $CH_2Cl_2$. The organic phase was extracted by 15 mL of water, the aqueous phase was extracted by 2 × 30 mL of $CH_2Cl_2$ and the collected organic phases were washed by 15 mL of saturated NaCl solution and then dried with anhydrous $Na_2SO_4$. The solvent was removed to give the crude oximes **60** (335.4 mg, 1.09 mmol, 80% in a (*E*/*Z*) ratio of 3:1) that were used in the next step without further purification.

**(*E*) and (*Z*)-(2*S*)-2-[*N*-(2-Cyclopropylideneethyl)-*N*-tosylamino]propanal Oximes (60):** Pale yellow oil, $R_f$ = 0.41 and 0.28 (petroleum ether/diethyl ether, 1:1). − $^1$H NMR (200 MHz, *E* and *Z* mixture): δ = 8.20 (br s, 1 H, O*H Z*), 7.82 (br s, 1 H, O*H E*), 7.68 (d, *J* = 8.4 Hz, 2 H, Ts), 7.35−7.18 (m, 2 H, Ts + 1 H, C*H*NOH *E*), 6.72 (d, *J* = 5.5 Hz, 1H C*H*NOH *Z*), 5.82 (m, 1 H, $CH_2$C*H Z*), 5.74 (m, 1 H, $CH_2$C*H E*), 5.15 (p, *J* = 5.5 Hz, $CH_3$C*H Z*), 4.69 (dq, *J* = 4.1, 6.9 Hz, $CH_3$C*H E*), 4.11−3.95 (m, 1 H, NC*H*H *E* + 2 H, $NCH_{2\ Z}$), 3.86 (br dd, *J* = 15.5, 7.5 Hz, NC*H*H *E*), 2.39 (s, 3 H, $C_6H_4CH_{3\ E}$), 2.39 (s, 3 H, $C_6H_4CH_{3\ Z}$), 1.29 (d, *J* = 7.0 Hz, 3 H, $CH_3$C*H Z*), 1.21 (d, *J* = 6.9 Hz, 3 H, $CH_3$C*H E*), 1.04 (br s, 4 H, $CH_2$ cyclopropyl *Z*), 1.01 (br s, 4 H, $CH_2$ cyclopropyl *E*). − $^{13}$C NMR (50 MHz, *E* isomer): δ = 150.8 (d), 143.3 (s), 137.7 (s), 129.6 (d, 2 C), 126.9 (d, 2 C), 126.5 (s), 114.6 (d), 52.3 (d), 45.5 (t), 21.3 (q), 15.5 (q), 2.2 (t), 1.6 (t); $^{13}$C NMR (50 MHz, *Z* isomer): δ = 151.8 (d), 143.2 (s), 137.6 (s), 129.4 (d, 2 C), 126.9 (d, 2 C), 126.4 (s), 114.7 (d), 48.6 (d), 46.8 (t), 21.3 (q), 16.6 (q), 2.2 (t), 1.6 (t).

**Nitrile Oxide Formation−Intramolecular Cycloaddition of the Oximes 60:** To a $CH_2Cl_2$ solution (9 mL) of **60** (73 mg, 0.24 mmol) and *i*$Pr_2$EtN (7 μL, 43 μmol, 0.18 equiv.) at 0°C was added dropwise a 6.5% aqueous solution of sodium hypochlorite (0.7 mL, 3 equiv.). The mixture was stirred for 5 h and the aqueous phase was extracted by 2 × 2 mL of $CH_2Cl_2$, the collected organic phases were washed by 2 mL of saturated NaCl solution and than dried with anhydrous $Na_2SO_4$. The solvent was removed to give the crude isoxazolines **62** (65 mg, 89% in a diastereoisomeric ratio of 61:39) that were used in the next step without further purification. The isoxazolines **62** are unstable as even at room temp. they slowly yield the thermal rearrangement products **63** and **64**.

**(6*S*)-6-Methyl-5-tosylspiro[cyclopropane-1,3′-3,3a,5,6-tetrahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] (62):** Colourless oil, $R_f$ = 0.28 (petroleum ether/diethyl ether, 1:1). − $^1$H NMR (200 MHz, two diastereoisomers mixture): δ = 7.80−7.64 (m, 2 H, Ts), 7.34 (d, *J* = 8.4 Hz, 2 H, Ts), 4.45 (q, *J* = 6.4 Hz, 1 H, $CH_3$C*H* major diast.), 4.24 (q, *J* = 6.8 Hz, 1 H, $CH_3$C*H* minor diast.), 4.14 (t, *J* = 9.0 Hz, 1 H, minor diast.), 3.75 (dd, *J* = 10.6, 8.6 Hz, 1 H, major diast.), 3.75−3.64 (hidden signal, 1 H, minor diast.), 3.54 (dd, *J* = 9.9, 8.6 Hz, 1 H, major diast.), 3.26 (t, *J* = 10.6 Hz, 1 H, major diast.), 2.79 (dd, *J* = 9.9, 8.8 Hz, 1 H, minor diast.), 2.44 (s, 3 H, $C_6H_4CH_3$), 1.61 (d, *J* = 6.8 Hz, 3 H, CHC$H_3$ minor diast.), 1.60 (d, *J* = 6.4 Hz, 3 H, CHC$H_3$ major diast.), 1.35−0.48 (m, 4 H, $CH_2$ cyclopropyl). − $^{13}$C NMR (50 MHz, two diastereoisomers mixture, selection of signals): δ = 60.6 (d), 52.2 (d), 52.1 (d), 50.5 (t), 48.2 (t), 21.5 (q), 19.3 (q), 10.9 (t), 7.7 (t).

**Thermal Rearrangement of Adducts 62:** A toluene solution (3 mL) of the isoxazolines **62** (65 mg, 0.2 mmol) was heated at 70°C for 8 h. After cooling to room temp., the solvent was removed and the crude mixture was separated by chromatography on silica gel (eluent with increasing polarity from ethyl acetate/petroleum ether, 1:1 + 0.6% $NEt_3$, to ethyl acetate + 0.6% $NEt_3$) to give **63** (16 mg, 25%) and **64** (24 mg, 37%).

**(7*S*)-7-Methyl-4-oxo-6-tosylhexahydro-1*H*-pyrrolo[3,4-*b*]pyridine (63):** $R_f$ = 0.16 (ethyl acetate + 0.6% $NEt_3$); $[\alpha]_D^{20}$ = −2.9 (*c* = 0.14, $CHCl_3$). − $^1$H NMR (200 MHz): δ = 7.71 (d, *J* = 8.2 Hz, 2 H, Ts), 7.32 (d, *J* = 8.2 Hz, 2 H, Ts), 4.95 (br s, 1 H, N*H*), 4.51 (dq, *J* = 2.6, 6.6 Hz, 1 H, $CH_3$C*H*), 4.25 (dd, *J* = 11.6, 2.2 Hz, 1 H, CC*H*H), 4.14 (d, *J* = 11.6 Hz, 1 H, CC*H*H), 3.61−3.50 (m, 2 H), 2.43 (s, 3 H, $C_6H_4CH_3$), 2.43−2.28 (m, 2 H), 1.29 (d, *J* = 6.6 Hz, 3 H, CHC$H_3$). − $^{13}$C NMR (75 MHz): δ = 187.5 (s), 162.4 (s), 143.8 (s), 134.2 (s), 129.9 (d, 2 C), 127.5 (d, 2 C), 103.2 (s), 60.7 (d), 50.6 (t), 43.0 (t), 35.4 (t), 21.5 (q), 21.1 (q). − IR: $\tilde{\nu}$ = 3439 $cm^{-1}$, 2977, 2923, 1606, 1345, 1159, 1090. − MS (EI): *m*/*z* = 306 (5) [$M^+$], 305 (8), 151 (37), 150 (100), 109 (26), 91 (54), 65 (18). − $C_{15}H_{18}N_2O_3S$ (306.4): calcd. C 58.80, H 5.92, N 9.14; found C 58.46, H 6.10, N 8.75.

**1-[(5*S*)-4-Amino-5-methyl-1-tosyl-2,5-dihydro-1*H*-pyrrol-3-yl]-propenone (64):** $R_f$ = 0.32 (ethyl acetate/petroleum ether, 1:1 + 0.6% $NEt_3$). − $^1$H NMR (200 MHz): δ = 7.72 (d, *J* = 8.4 Hz, 2 H, Ts), 7.32 (d, *J* = 8.4 Hz, 2 H, Ts), 6.28 (d, *J* = 8.4 Hz, 1 H, CHC*H*H), 6.26 (d, *J* = 3.7 Hz, 1 H, CHC*H*H), 5.62 (dd, *J* = 8.5, 4.1 Hz, 1 H, $CH_2$C*H*), 4.47 (d, *J* = 9.4 Hz, 1 H, CC*H*H), 4.30 (d, *J* = 9.4 Hz, 1 H, CC*H*H), 4.12 (q, *J* = 7.3 Hz, 1 H, NC*H*), 2.43 (s, 3 H, $C_6H_4CH_3$) 1.58 (d, *J* = 7.3 Hz, 3 H, CHC$H_3$). − $^{13}$C NMR (50 MHz): δ = 184.5 (s), 160.9 (s), 143.8 (s), 134.1 (s), 133.7 (d), 129.8 (d, 2 C), 127.3 (d, 2 C), 127.1 (t), 99.4 (s), 60.8 (d), 51.5 (t), 21.4 (q), 21.1 (q). − IR: $\tilde{\nu}$ = 3632 $cm^{-1}$, 3492, 2982, 2932, 1729, 1651, 1617, 1510, 1344, 1158. − MS (EI): *m*/*z* = 306 (7) [$M^+$], 305 (12), 155 (16), 151 (38), 149 (100), 91 (46), 65 (15); HRMS: found 306.1039, $C_{15}H_{18}N_2O_3S$ requires 306.1038.

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