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ASYMMETRY

Diastereoselective cycloaddition of alkylidenecyclopropane nitrones from palladium(0)-catalyzed nucleophilic substitution of asymmetric 1-alkenylcyclopropyl esters by amino acids

Federica Pisaneschi,[a,b] Franca M. Cordero,[a] Andrea Goti,[a] Renée Paugam,[b] Jean Ollivier,[b] Alberto Brandi [a,*] and Jacques Salaün [b,*]

[a]*Dipartimento di Chimica Organica 'Ugo Schiff', Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e Ioro Applicazioni, CNR, Università degli Studi di Firenze, via G. Capponi 9, I-50121 Firenze, Italy*

[b]*Laboratoire des Carbocycles (Associé au CNRS), Institut de Chimie Moléculaire d'Orsay Bât. 420, Université de Paris-Sud, 91405 Orsay, France*

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Abstract

The asymmetric construction of perhydropyrrolo[3,4-*b*]pyridine derivatives was performed by chemo- and regioselective formation of enantiopure alkylidenecyclopropane nitrones, followed by diastereoselective intramolecular 1,3-dipolar cycloaddition. The resulting spirocyclopropane isoxazolidines then underwent thermally induced regioselective ring expansion into optically active diazaheterocycles.

1. Introduction

In spite of their inherent ring strain (40.9 kcal mol^{-1}) alkylidenecyclopropanes are now readily available[1] and form a class of olefinic compounds which offer a huge potential in organic synthesis.[2,3] For instance, we have recently reported that the nitrones (*S*)-**2**, derived from the alkylidenecyclopropane esters (*S*)-**1**, prepared from the palladium(0)-catalyzed alkylation of either *N*-tosyl α-amino acid esters (X=NTs) or glycolic esters (X=O), spontaneously underwent regioselective intramolecular 1,3-dipolar cycloaddition[4] to provide the *cis*-fused tricyclic isoxazolidines **3** (Scheme 1).[5] The diastereoselectivity of the reaction appeared dependent on the steric effect of the substituents R of the α-amino acids; it was complete only for phenylglycine and proline derivatives. The diastereomeric cycloadducts *exo*- or *endo*-**3**, which were readily separated by chromatography, then underwent regio- and diastereoselective thermally induced ring expansion into the octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-4-ones or furano analogue **4**.[5]

* Corresponding authors. E-mail: jasalaun@icmo.u-psud.fr

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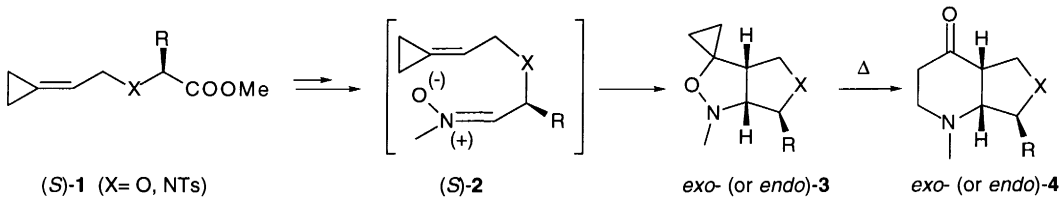
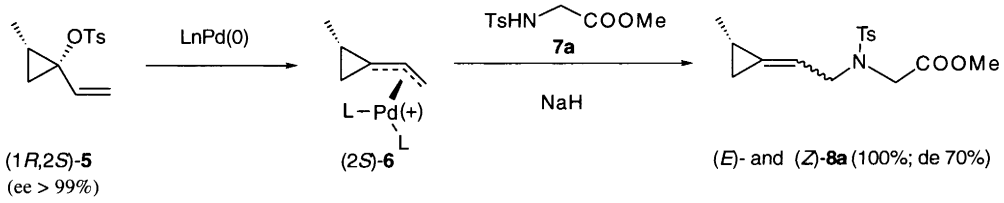


Scheme 1.

We report now that simple asymmetric substitution on the three-membered ring of the alkylidene cyclopropane nitrones can improve the diastereoselectivity of the cycloaddition and offer straightforward access to optically active diazaheterocycles of biological importance.[6–8]

2. Simple asymmetric induction

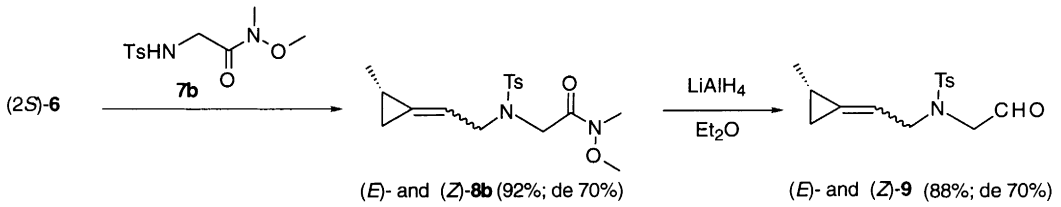
The (1*R*,2*S*)-2-methyl-1-tosyloxy-1-vinylcyclopropane **5** (Scheme 2), obtained in a diastereomerically pure form from commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (>99% ee)[9] or alternatively from dimethyl (2*S*)-2-methylsuccinate (enzymatic resolution)[10] (de >92%) underwent regioselective palladium(0)-catalyzed [$Pd(dba)_2$, 2 PPh_3] amination[11] by methyl *N*-tosylglycinate **7a** in the presence of 1 equivalent of NaH in THF at room temperature to provide, through the π-1,1-dimethyleneallyl palladium complex (2*S*)-**6**,[12] an 85:15 diastereomeric mixture of (*E*)- and (*Z*)-methyl *N*-[2-(2-methyl cyclopropylidene)ethyl]-*N*-tosylglycinates **8a**, quantitatively.



Scheme 2.

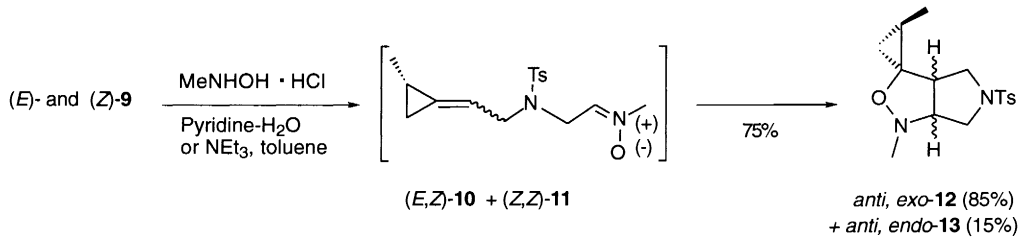
While substitutions of the palladium complex (2*S*)-**6** and derivatives at the cyclopropane terminus by *hard* nucleophiles, i.e., azide[9] and hydride (arising from *n*-butylzinc chloride or from sodium formate),[10,13] were highly diastereoselective (de: 92–100%), substitutions by *soft* nucleophiles, i.e., dialkyl sodiomalonates[14] and α-amino acid derivatives, which occurred on the primary allylic end of (2*S*)-**6** exclusively,[12] unfortunately produced a mixture of (*E*)- and (*Z*)-alkylidene(2-methylcyclopropanes) (de: 64–70%). Attempts to increase the diastereoselectivity of the formation of (*E*)-**8a**, based on the steric effect of the trivalent phosphorus ligands which are well known to dominate the chemical behaviour of transition metal complexes,[15] and which were highly effective in monitoring the regioselectivity of the palladium(0)-catalyzed allyl esters reduction,[13] failed; thus, for instance, dppe, tri(*o*-tolyl)- and tri(*o*-anisyl)phosphines, and tri(2,6-dimethoxyphenyl)phosphine, induced lower diastereoselectivities (de: 40–58%) than triphenylphosphine (de: 70%).

Contrary to our previous report concerning the partial reduction of (*S*)-**1**,[5] reduction of the esters (*E*)- and (*Z*)-**8a** by 0.9 equivalent of DIBAH gave a mixture of the expected aldehydes, besides the corresponding alcohols arising from overreduction, and unreacted **8a**. To overcome this problem, the *N*′-methyl-*N*′-methoxy-*N*-tosylglycinamide **7b** (Scheme 3)[16] was used instead of the methyl glycinate **7a** as the nucleophile to produce in 95% yield again as an 85:15 mixture of (*E*)- and (*Z*)-alkylidenecyclopropanes **8b**, which after reduction by $LiAlH_4$ in diethyl ether led to the expected aldehydes **9**, in 88% yield.



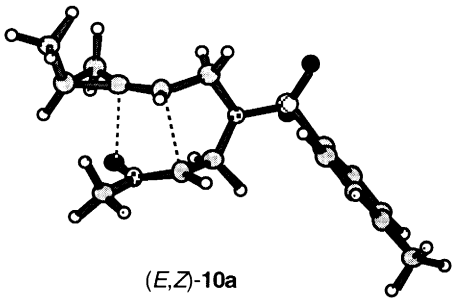
Scheme 3.

This 85:15 diastereomeric mixture of (*E*)- and (*Z*)-aldehydes **9** was then allowed to react with MeNHOH·HCl either in a solution of 1.4 equivalents of pyridine in water or in a solution of triethylamine in toluene to provide in 47 and 75% yields, respectively, an 85:15 diastereomeric mixture of the isoxazolidines *anti*, *exo*-**12** and *anti*, *endo*-**13** (Scheme 4).[17] First of all, it was noteworthy that 61:39 and 87:13 diastereomeric mixtures of (*E*)- and (*Z*)-aldehydes **9** led to the same 61:39 and 82:18 diastereomeric mixtures of fused cycloadducts **12** and **13**. Thus the nitrone (*E*,*Z*)-**10**[18] produced the *anti*, *exo* (2*S*,3′*S*,3′a*R*,6′a*R*)-spiro[(2-methylcyclopropane)-1,3′-hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazole] **12**, while the nitrone (*Z*,*Z*)-**11** led to the *anti*, *endo* (2*S*,3′*S*,3′a*S*,6′a*S*)-2-methylpyrroloisoxazole **13**, exclusively. Therefore the cycloaddition can be regarded as totally regio- and diastereoselective.

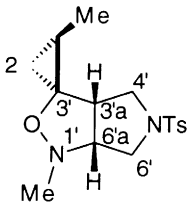


Scheme 4.

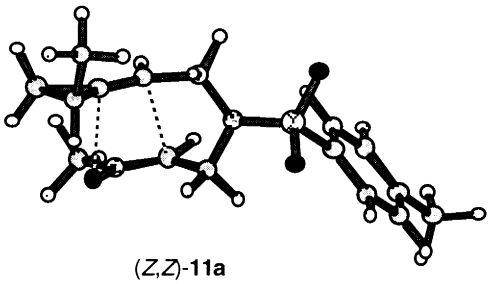
Effectively, *fused cycloadducts* were only obtained because the strain experienced by the chain joining the two reactive sites (i.e., the nitrone and the alkylidenecyclopropanes moieties) prevented the formation of regioisomeric *bridged cycloadducts*.[4] Thus, the coupling constant between the two bridgehead atoms in *anti*, *exo*-**12** ($J_{H3'aH6'a}$=7.8 Hz) proved that this cycloadduct was really *cis*-fused.[5] The formation of the cycloadduct *anti*, *exo*-**12**, observed from the nitrone (*E*,*Z*)-**10a**, probably resulted from the single possible (or most favourable due to the cyclopropanemethyl congestion) approach of the dipolarophile by the (*Z*)-nitrone moiety, from the less hindered side of the alkylidenecyclopropane plane entailing an *anti* relationship between the (2*S*)-methyl group and the new carbon–oxygen bond, while the formation of the *anti*, *endo*-**13** would result similarly from the nitrone (*Z*,*Z*)-**11a** involving the same *anti* relationship.



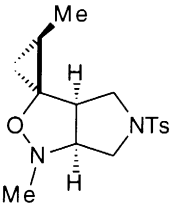
(*E*,*Z*)-**10a**



anti, exo-**12**

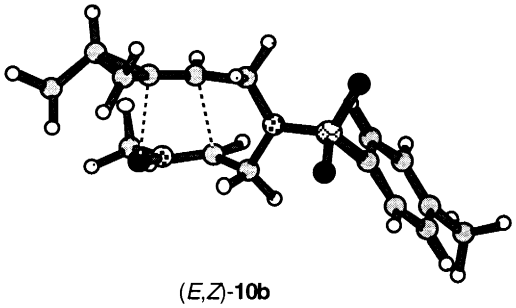


(*Z*,*Z*)-**11a**

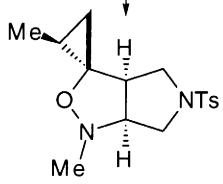


anti, endo-**13**

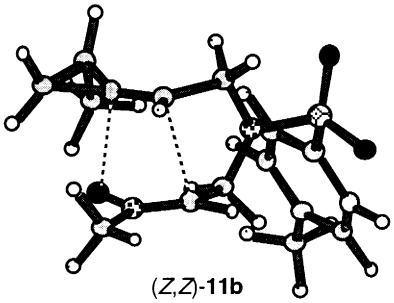
Simple molecular mechanics calculations (Hyperchem)[19] have supported these results;[5] thus the differences of energies between the conformations of the transition states (*E*,*Z*)-**10a** and (*E*,*Z*)-**10b** (ΔE=4.8 kcal mol^{-1}) leading from the same nitrone (*E*,*Z*)-**10** to either the *anti*, *exo*-**12** or to the *syn*, *exo*-**14**, respectively, and between the conformations of the transition states (*Z*,*Z*)-**11a** and (*Z*,*Z*)-**11b** (ΔE=1.7 kcal mol^{-1}) leading from the nitrone (*Z*,*Z*)-**11** to either the *anti*, *endo*-**13** or to the *syn*, *endo*-**15**, respectively, have confirmed the observed diastereoselectivity induced by the presence of the (2*S*)-methyl group.



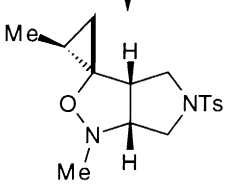
(*E*,*Z*)-**10b**



syn, exo-**14**



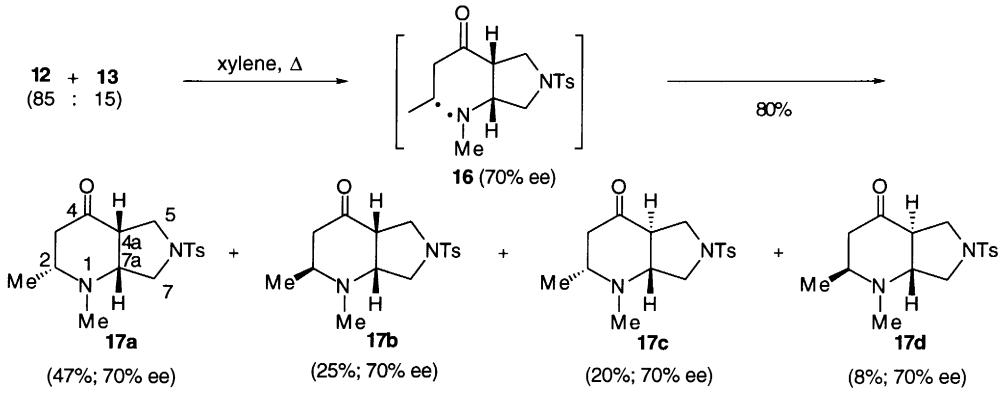
(*Z*,*Z*)-**11b**



syn, endo-**15**

The 85:15 mixture of isoxazolidines **12** and **13**, which were also inseparable by silica gel chromatography, then underwent thermal rearrangement on heating in xylene at reflux for 5 h to provide, in 80% yield, a 47:25:20:8 diastereo- and enantiomeric mixture of pyrrolo[3,4-*b*]pyridin-4-ones **18a**–**d**.

First of all, the cyclopropane ring opening subsequent to the N–O isoxazolidine bond homolysis, followed by intramolecular diradical coupling to provide bicyclic diazaheterocycles,[5] appeared totally regioselective. In fact only 2-methyl derivatives **17a**–**d**, resulting from the cleavage of the more substituted cyclopropane bond of the isoxazolidines *anti*, *exo*-**12** and *anti*, *endo*-**13** into the diradical intermediate **16**, were formed as proved by ^{13}C NMR data (i.e., tertiary carbons in α of a nitrogen at δ 66.2, 53.9, 64.3 and 46.1 ppm, respectively) (Scheme 5). The pyridones **17a** and **17c** were readily isolated and purified by simple flash chromatography; the pyridone **17b** was obtained in a mixture with **17a**, and the minor product **17d** was not isolated. NOESY experiments disclosed a *cis* relationship for the H_2 and H_{7a} protons of the major adduct **17a**. However, this ring closure was not totally diastereoselective as a 67:33 mixture of **17a**,**c** (with a (2*R*)-methyl) and **17b**,**d** (with a (2*S*)-methyl) was obtained from the 85:15 mixture of isoxazolidines *anti*, *exo*-**12** and *anti*, *endo*-**13**. The pyridones **17c** and **17d** were derived from epimerization of the carbon **4a**, due to the easy enolization of the carbonyl group at C_4. Effectively, a mixture of **17a**,**b**, obtained by flash chromatography, underwent epimerization into **17c**,**d** upon treatment with NaH in THF at room temperature overnight.



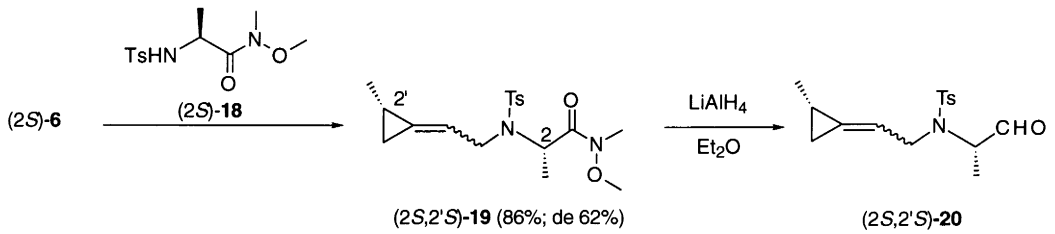
Scheme 5.

The diradical intermediate **16**, resulting from the ring opening of the diastereomeric cyclopropyloxy radicals arising from the 85:15 mixture of the isoxazolidines **12** and **13**, respectively, was obtained as an 85:15 enantiomeric mixture. Thus all the products **17a**–**d** were generated in 70% enantiomeric excesses, proved unambiguously by ^1H NMR spectra recorded in the presence of the shift reagent $Eu(hfc)_3$, which disclosed the shift of the *N*-methyl singlets.

3. Double asymmetric induction

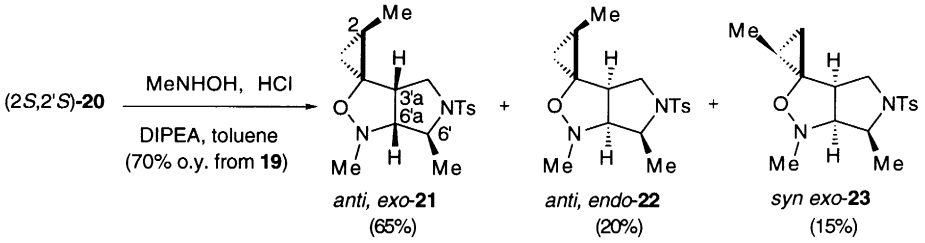
In the same way, nucleophilic substitution of the palladium complex (2*S*)-**6**,[9] by the *N*′-methyl *N*′-methoxy-*N*-tosyl-L-alaninamide (2*S*)-**18**,[16] in the presence of NaH in THF produced in 86% yield an 81:19 diastereomeric mixture of (*E*)- and (*Z*)-alkylidene(2-methylcyclopropane) (2*S*,2′*S*)-**19**, which upon reduction by $LiAlH_4$ in diethyl ether gave the crude aldehydes (2*S*,2′*S*)-**20** (Scheme 6).

Reaction of this crude diastereomeric aldehyde mixture (2*S*,2′*S*)-**20** (de: 62%) with MeNHOH, HCl in toluene containing 1 equivalent of diisopropylethylamine (DIPEA) produced in 70% overall yield from (2*S*,2′*S*)-**19** a 65:20:15 diastereomeric mixture of tricycloadducts **21**–**23** (Scheme 7). The *anti*, *exo* stereochemistry of the major isoxazolidine (2*S*,3′a*R*,6′*S*,6′a*R*)-**21**, isolated by simple chromatography, has been established from its ^1H NMR coupling data; thus, after irradiation of the methyl on carbon $C_{6'}$, the measured coupling value of $J_{H6'H6'a}$=4.9 Hz proved the *trans* relationship of these two vicinal pyrrol-



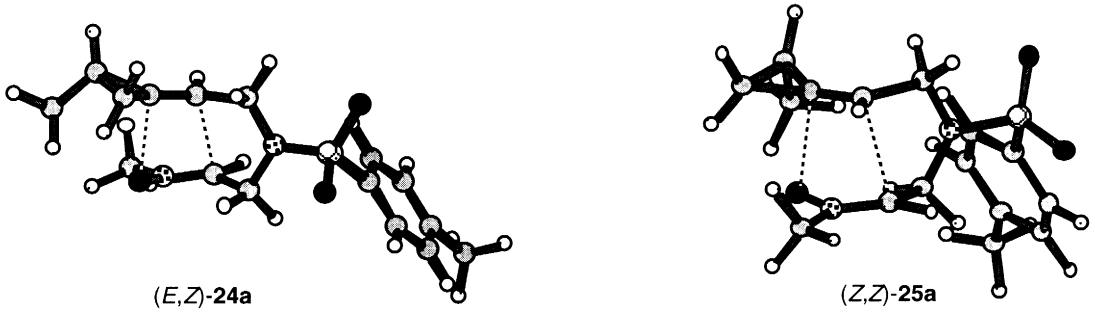
Scheme 6.

idine protons. Moreover, NOESY effects were observed between the methyl group on the cyclopropane carbon (2*S*) and the proton on carbon $C_{3'a}$, as well as between the methyl on carbon $C_{6'}$ and the proton on carbon $C_{6'a}$. The minor cycloadduct **22** was isolated by recrystallization and **23** was obtained as a mixture with **22**; the *cis* relationship between the protons on carbons $C_{6'}$ and $C_{6'a}$ of **22** and **23** was also deduced from their ^{1}H NMR coupling constant values ($J_{H6'H6'a}$=7.9 Hz).



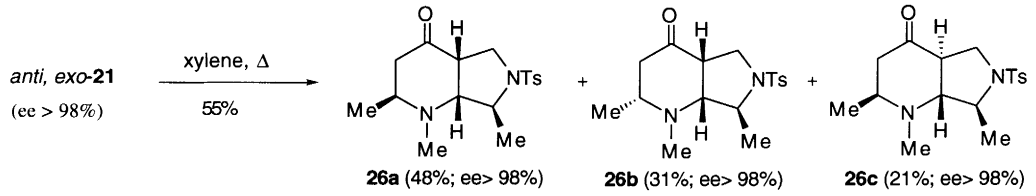
Scheme 7.

It is likely that the major adduct *anti*, *exo*-**21** (65%) arose from the 1,3-dipolar cycloaddition of the (*E*,*Z*)-nitrone **24a**,[18] resulting from the most favoured *anti* approach of the dipolarophile by the nitrone moiety entailing the formation of an *exo*-methyl on carbon (2*S*), while the *anti*, *endo*-**22** (20%) arose from the nitrone (*Z*,*Z*)-**25a**. However, as shown from molecular mechanics calculation[20] the weaker difference of energies between the conformation of the corresponding transition states (ΔE=0.7 kcal mol^{-1}, vide supra) allowed, from the (*E*,*Z*)-nitrone **24a**, also the *syn* approach of the dipolarophile and the formation of *syn*, *exo*-**23** (15%).



The cycloaddition of (*S*)-**2**, prepared from methyl alaninate (R=Me, X=NTs), has been reported to provide a 45:55 diastereomeric mixture of *exo*- and *endo*-isoxazolidines **3** (R=Me, X=NTs) (de: 10%). Therefore the diastereoselectivity was slightly increased by the simple introduction of a methyl substituent on the cyclopropane ring, since a 65:35 diastereomeric mixture of *exo*-**21** and *endo*-**22**+**23**[21] (de: 30%) was obtained, most likely due to the matched interaction between the two stereocentres. Higher diastereoselectivity can therefore be expected from bulkier groups, both on the alkylidenecyclopropane moiety and nitrone moieties.

Finally, thermally induced ring expansion (xylenes, 115°C) of the pure *anti*, *exo*-**21** provided, in 55% isolated yield, a 48:31:21 diastereomeric mixture of enantiomerically pure 1,2,7-trimethylpyrrolo[3,4-*b*]pyridin-4-ones **26a**–**c** (Scheme 8); all were separated by flash chromatography and their structures determined from NOESY effects observed between the methyl on carbon C_7 and the protons on carbons C_{4a} and C_{7a} on the diazaheterocycles **26a** and **26b**, and between the protons on the carbons C_2 and C_{7a} on **26b**.



Scheme 8.

In conclusion, while the inseparable diastereomeric isoxazolidines **12** and **13** provided with 70% enantiomeric excesses the bicyclic diazaheterocycles **17a**–**d**, because the thermal N–O bond cleavage entailed the formation of the diradical intermediate **16** (70% ee), on the other hand the thermal ring expansion of the isolated pure isoxazolidine **21**, likely involving an enantiomerically pure radical intermediate, led to the pyrrolo[3,4-*b*]pyridin-4-ones **26a**–**c**, with>98% enantiomeric excesses. The partial epimerization on carbon C_{4a} which provided **17c**,**d** and **26c** was likely the result of the increased strain in the *cis*-fused bicyclic heterocycles induced by the methyl substituent; this fact was not observed in the previous examples when this substituent was absent.[5]

4. Experimental

4.1. General

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 an RCH Kofler or on a Mettler FP-5 apparatus. Polarimetric measures 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 an OKI DP 125 gas chromatograph. Relative percentages are shown in brackets. Accurate mass spectra were recorded on an MAT 95S. Elemental analyses were performed with a Perkin–Elmer 2400 C analyser or by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette.

Starting material, (1*R*,2*S*) 2-Methyl-1-tosyloxy-1-vinylcyclopropane **5**, was prepared according to published procedures.[9,10]

4.2. General procedure for the synthesis of N′-methyl, N′-methoxyamide of N-tosylamino acids

To a 0.04 M solution of methyl *N*-tosyl aminocarboxylate (1 equiv.) in dichloromethane MeNHOMe·HCl (1.5 equiv.), pyridine (2 equiv.) and DCC (1.5 equiv.) were added. The mixture was stirred overnight, then the organic phase was washed with a saturated solution of NaCl and dried over Na_2SO_4. After filtration and evaporation at reduced pressure, diethyl ether was added and salts were removed by filtration. After purification on silica gel, the desired products were obtained.

4.2.1. N′-Methyl-N′-methoxy-N-tosylglycinamide **7b**

White solid, 85% yield (eluent petroleum ether:diethyl ether 1:5, R_f=0.15); ^{1}H NMR (200 MHz) δ 7.69 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 5.20 (bs, 1H), 3.83 (s, 2H), 3.58 (s, 3H), 3.05 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (50.3 MHz) δ 168.1 (s), 143.4 (s), 135.9 (s), 129.5 (d), 127.0 (d), 61.3 (q), 42.9 (t), 32.1 (q), 21.2 (q); IR 3674, 2940, 1705, 1665, 1362, 1220, 1157 cm^{-1}; MS *m*/*z* (EI) 273 (59), 225 (10), 212 (15), 184 (98), 155 (100), 91 (91).

4.2.2. N′-Methyl-N′-methoxy-N-tosylalaninamide **18**

Yellow oil, 74% yield (eluent diethyl ether, R_f=0.41); ^{1}H NMR (200 MHz) δ 7.69 (d, J=8.4 Hz, 2H), 7.25 (d, J=8.1 Hz, 2H), 5.71 (bd, J=9.2 Hz, 1H), 4.29 (m, 1H), 3.52 (s, 3H), 2.96 (s, 3H), 2.37 (s, 3H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz) δ 172.2 (s), 143.3 (s), 137.0 (s), 129.4 (d), 127.2 (d), 61.3 (q), 48.7 (q), 32.0 (d), 21.3 (q), 19.8 (q); IR 3322, 2978, 2937, 1660, 1380, 1336, 1145, 1079 cm^{-1}; MS *m*/*z* 287 (MH^+, 2), 199 (10), 198 (91), 155 (93), 91 (100).

4.3. General procedure for the palladium(0)-catalyzed nucleophilic substitution of (1R,2S) 2-methyl-1-tosyloxy-1-vinylcyclopropane **5**

A solution of $Pd(dba)_2$ (5 mol%) and PPh_3 (12 mol.%) was degassed under vacuum for 1 h and put under argon or nitrogen atmosphere. Then a 0.05 M solution of (1*R*,2*S*)-**5**[16] (from 0.20 to 0.79 mmol) in THF was added. After 10 min the mixture, which had turned green, was added to a solution of sodium salt of the nucleophile prepared in a separate flask from the amino acid derivatives **7a**,**b** and **18** (1.1 equiv.), 0.06 M in THF, which was added slowly to pentane (or petroleum ether) washed sodium hydride (1.5 equiv.). After the mixture was stirred from 1 h to 1 day at room temperature, evaporation of the solvent and flash chromatography on silica gel of the residue gave the alkylidenecyclopropanes **8a**,**b** and **19** as a mixture of two inseparable diasteroisomers.

4.3.1. Methyl N-[2-(2-methylcyclopropylidene)ethyl]-N-tosylglycinate **8a**

Yellow oil, 100% yield (eluent petrol ether:diethyl ether 9:1, R_f=0.18); ^{1}H NMR (200 MHz, *major diastereoisomer*) δ 7.75 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 5.6 (tq, J=7.0, 1.9 Hz, 1H), 4.0 (dd, J=7.7, 4.1 Hz, 2H), 4.0 (s, 3H), 3.62 (s, 2H), 2.43 (s, 3H), 1.06 (d, J=6.0 Hz, 3H), 1.60–0.50 (m, 3H); ^{13}C NMR (50.3 MHz, *major diastereoisomer*) δ 169.5 (s), 143.3 (s), 137.0 (s), 135.8 (s), 128.6 (d), 127.3 (d), 111.1 (d), 52.0 (q), 49.3 (t), 46.9 (t), 21.5 (q), 17.7 (t), 10.0 (d), 9.1 (t); IR (*mixture of diastereoisomers*) 2960, 1760, 1440, 1350, 1220, 1160 cm^{-1}; MS (*mixture of diastereoisomers*) *m*/*z* (EI) 341 (MNH_4^+, 40), 324 ($MH^{+\cdot}$, 23), 323 ($M^{+\cdot}$, 11), 261 (23), 170 (81), 168 (100), 155 (5), 108 (37); HRMS found: 323.1196; required for $C_{16}H_{21}NO_4S$: 323.1191.

4.3.2. N′-*Methyl*-N′-*methoxy*-N-*[2-(2-methyl)-cyclopropylidene)ethyl]*-N-*tosylglycinamide* ***8b***

Yellow oil, 95% yield (eluent petrol ether:diethyl ether 1:1, R_f=0.14); ^{1}H NMR (200 MHz, *major diastereoisomer*) δ 7.80 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H), 5.71 (tq, J=6.6 Hz, 2.19 Hz, 1H), 4.24 (s, 2H), 4.01 (d, J=6.6 Hz, 2H), 3.67 (s, 3H), 3.12 (s, 3H), 2.42 (s, 3H), 1.07 (d, J=5.8 Hz, 3H), 1.60–0.45 (m, 3H); ^{13}C NMR (50.3 MHz, *major diastereoisomer*) δ 169.2 (s),142.9 (s), 137.3 (s), 135.0 (s), 129.2 (d), 127.3 (d), 111.5 (d), 61.1 (q), 48.9 (t), 45.7 (t), 32.2 (q), 21.3 (q), 17.5 (q), 9.7 (d), 9.0 (t); IR (*mixture of diastereoisomers*) 3049, 2959, 1679, 1598, 1443, 1335, 1151, 1088 cm^{-1}; MS (*mixture of diastereoisomers*) *m/z* (EI) 264 (1), 197 (43), 155 (29), 109 (24), 108 (100), 91 (79). HRMS (M+Na) found: 375.13553; required for $C_{17}H_{24}N_2O_4SNa$: 375.13540.

4.3.3. N′-*Methyl*-N′-*methoxy*-N-*[2-(2-methylcyclopropylidene)ethyl]*-N-*tosyl*-L-*alaninamide* ***19***

Yellow oil, 86% yield (eluent petroleum ether:diethyl ether 1:1, R_f=0.21); ^{1}H NMR (200 MHz) (*major diastereoisomer*) δ 7.69 (d, J=8.4 Hz, 2H), 7.25 (d, J=8.4 Hz, 2H), 5.83 (m, 1H), 5.10 (q, J=7.0 Hz, 1H), 4.26–4.01 (m, 2H), 3.76 (s, 3H), 3.08 (s, 3H), 2.40 (s, 3H), 1.25 (d, J=7.3 Hz, 3H), 1.07 (d, J=5.9 Hz, 3H), 1.49–0.62 (m, 3H) and (*minor diastereoisomer*) 5.73 (m, 1H).^{13}C NMR (50.3 MHz) (*major diastereoisomer*) δ 172.2 (s), 143.1 (s), 137.5 (s), 131.6 (s), 129.3 (d), 127.3 (d), 115.2 (d), 61.5 (q), 51.1 (q), 46.1 (t), 32.0 (d), 21.3 (q), 17.5 (q), 15.7 (q), 9.5 (d), 9.3 (t); (*minor diastereoisomer*: distinguishable signals) 45.8 (t), 17.4 (q), 15.2 (q), 10.0 (d); IR (*mixture of diastereoisomers*) 2976, 1660, 1445, 1335, 1151 cm^{-1}; MS *m/z* (EI) (*mixture of diastereoisomers*) 278 (5), 211 (18), 155 (26), 123 (10), 91 (71), 84 (100).

4.4. N-*[2-(2-Methylcyclopropylidene)ethyl]*-N-*tosylaminoethanal (*E*)- and (Z)-****9***

4.4.1. From direct reduction of ***8a***

To a solution of 320 mg (0.99 mmol) of **8a** in 20 ml of CH_2Cl_2 at −78°C 1.19ml (0.9 equiv., 0.89 mmol) of 1 M solution of DIBALH in hexane was added dropwise. The mixture was stirred for 20 min at −78°C and then hydrolyzed by methanol and by a saturated sodium and potassium tartrate solution in water. The aqueous phase was extracted four times with CH_2Cl_2. The combined organic extracts were dried on anhydrous Na_2SO_4; evaporation of the solvent gave the crude aldehydes **9** purified by flash chromatography, besides unreacted **8a** and the corresponding alcohol.

4.4.2. From reduction of ***8b***

To a solution of 166.8 mg of **8b** (0.47 mmol) in 25 ml of diethyl ether were added 28.4 mg of $LiAlH_4$ (0.71 mmol) and the mixture was stirred for 2 h. Then wet Na_2SO_4 was added, salts were filtered through a short pad of Celite and dried on Na_2SO_4. After purification on silica gel, 120.6 mg of desired aldehyde **9** were obtained, as a mixture of two inseparable diastereoisomers.

(*E*)- and (*Z*)-(**9**): Yellow oil, 99% yield (eluent petroleum ether:diethyl ether 1:1, R_f=0.30); ^{1}H NMR (200 MHz) (*major* (*E*)-*diastereoisomer*) δ 9.56 (t, J=1.5 Hz, 1H), 7.71 (d, J=8.3 Hz, 2H), 7.51 (d, J=8.3, 2H), 5.70 (tq, J=7.32, 1.59 Hz, 1H), 3.89 (d, J=7.32 Hz, 2H), 3.69 (d, J=1.5 Hz, 2H), 2.45 (s, 3H), 1.06 (d, J=6.5 Hz, 1H), 0.5–1.5 (m, 3H); ^{13}C NMR (50 MHz) (*major diastereoisomer*) 199.3 (d), 144.3 (s), 137.7 (s), 135.9 (s), 130.3(d), 127.7 (d), 111.2 (d), 56.7 (t), 51.5 (t), 21.9 (q), 17.7 (q), 10.7 (d), 9.7 (t); IR (*mixture of diastereoisomers*) 2980, 1740, 1350, 1260, 1170 cm^{-1}; MS *m/z* (CI, NH_3) (*mixture of diastereoisomers*) 264 (15),155 (45), 138 (33), 91 (84), 81 (100).

4.5. 2-{N-[2-(2-Methylcyclopropylidene)ethyl]-N-tosylamino}propanal **20**

To a solution of 237.1 mg of **19** (0.65 mmol) in 18 ml of diethyl ether was added, at 0°C, 0.97 ml of a 1 M solution of $LiAlH_4$ (0.97 mmol) in THF and the mixture was stirred for 40 min. Then wet Na_2SO_4 was added and the salts were removed by filtration through a short pad of Celite and dried on Na_2SO_4. After evaporation under reduced pressure, 218.4 mg of expected aldehyde **20** were obtained, as a mixture of inseparable diastereoisomers, which were used in the next step without further purification.

4.6. General procedure for the nitrone formation and intramolecular cycloaddition

To 0.02 M solutions of the aldehydes **9** and **20** in toluene, cooled to 0°C, were added 1.5 equiv. of *N*-methylhydroxylamine hydrochloride and 1.5 equiv. of triethylamine (or *i*-Pr_2EtN). The mixture was stirred overnight at room temperature and the salts were eliminated by filtration over Celite, the solvent was removed under reduced pressure and the crude mixture was separated by chromatography on silica gel to give the expected isoxazolidines. From glycine derivatives, two inseparable isoxazolidines **12** and **13** were obtained; from L-alanine ones, three isoxazolidines **21**–**23** were obtained: two of them were isolated and the third one was obtained as a mixture with the second one.

4.7. 1′,2-Dimethyl-5′-tosylspiro[cyclopropane-1,3′-hexahydro-4H-pyrrolo[3,4-c]isoxazoles] (2S,3′S,3′aR,6′aR)-**12** and (2S,3′S,3′aS,6′aS)-**13**

White solid, 75% yield (eluent petroleum ether: diethyl ether 1:9, R_f=0.31); ^{1}H NMR (200 MHz) (*mixture of diastereomers*) δ 7.70 (d, J=6.6 Hz, 2H), 7.34 (d, J=6.6 Hz, 2H), 3.90–3.60 (m, 2H), 3.55–3.44 (m, 1H), 3.12–3.00 (m, 1H), 2.96–2.84 (m, 2H), 2.63 (s, 3H), 2.45 (s, 3H), 1.42–0.69 (m, 2H), 0.99 (d, J=6.0 Hz, 3H), 0.35 (t, 1H, *minor diastereomer*), 0.10 (t, 1H, *major diastereomer*); ^{13}C NMR (50.3 MHz) (*major diastereomer*) δ 144.2 (s), 132.5 (s), 130.2 (d), 128.4 (d), 73.5 (d), 69.9 (s), 52.5 (t), 52.2 (t), 50.9 (d), 44.7 (q), 21.9 (q), 19.0 (q), 14.6 (d), 11.6 (t); MS *m/z* (EI) 155 (7), 153 (67), 124 (61), 112 (100), 91 (32), 42 (38); IR (*mixture of diastereomers*) 3002, 2960, 2930, 2880, 1350, 1185 cm^{-1}; MS *m/z* (CI with NH_3) (*mixture of diastereomers*) 323 (MH^+, 12), 322 (M^+, 8), 309 (26), 292 (49), 136 (100). Anal. calcd for $C_{16}H_{22}N_2O_3S$: C, 59.60; H, 6.88; N, 8.69. Found: C, 59.44; H, 6.94; N, 8.61.

4.8. (5′-Tosyl-1′,2,6′-trimethylspiro[cyclopropane-1,3′-hexahydro-4H-pyrrolo[3,4-c]isoxazole] (2S,3′S,3′aR,6′S,6′aS)-**21**

White solid, 46% yield (eluent petroleum ether: diethyl ether 1:1, R_f=0.06); Mp=102–104°C; $[\alpha]_D^{24}$=−156 ($CHCl_3$, c=0.415 g cm^{-3}); ^{1}H NMR (500 MHz) δ 7.71 (d, J=8.2 Hz, 2H), 7.32 (d, J=7.7 Hz, 2H), 3.69 (dd, J=9.5, 7.5 Hz, 1H), 3.30 (dd, J=6.8, 5.6 Hz, 1H), 3.22 (dq, J=6.7, 5.7 Hz, 1H), 3.03–2.96 (m, 2H), 2.59 (s, 3H), 2.43 (s, 3H), 1.51 (d, J=6.7 Hz, 3H), 1.07–1.01 (m, 1H), 0.95 (d, J=6.1 Hz, 3H), 0.69 (dd, J=9.8, 6.7 Hz, 1H), −0.04 (t, J=6.3 Hz, 1H); ^{13}C NMR (50 MHz) δ 143.6 (s), 133.3 (s), 129.6 (d), 127.9 (d), 81.9 (d), 69.4 (s), 60.8 (d), 52.9 (t), 45.3 (d), 41.8 (q), 21.5 (q), 20.3 (q), 18.5 (q), 14.2 (d), 11.2 (t); IR ($CDCl_3$) 2961, 2928, 1341, 1157 cm^{-1}; MS *m/z* (EI) 336 (M^+, 0.24), 222 (27), 181 (27), 155 (5), 91 (63), 56 (100). Anal. calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 60.66; H, 7.26; N, 8.16.

*4.8.1. (2*S,*3′*S,*3′a*S,*6′*S,*6′a*R*)*-**22***

White solid, 14% yield (eluent: petroleum ether: diethyl ether 1:1, R_f=0.15); $[\alpha]_D^{24}$=+93.6 ($CHCl_3$, c=0.415 g cm^{-3}); ^{1}H NMR (500 MHz) δ 7.72 (d, J=7.9 Hz, 2H), 7.31 (d, J=7.9 Hz, 2H), 3.70 (dq, J=7.3, 6.7 Hz, 1H), 3.51 (t, J=7.9 Hz, 1H), 3.41 (dd, J=10.9, 5.5 Hz, 1H), 2.85 (dt, J=7.9, 5.5 Hz, 1H), 2.63 (s, 3H), 2.43 (s, 3H), 1.35 (d, J=6.7 Hz, 3H), 1.07 (d, J=6.1 Hz, 3H), 0.90–0.82 (m, 2H), 0.47 (t, J=6.1 Hz, 1H); ^{13}C NMR (50 MHz) δ 143.5 (s), 135.1 (s), 129.7 (d), 127.7 (d), 75.2 (d), 69.6 (s), 58.4 (d), 50.4 (t), 50.3 (d), 45.9 (q), 21.5 (q), 19.9 (q), 15.2 (q), 13.9 (d), 11.0 (t); IR 2994, 2966, 2935, 1339, 1155, 1085 cm^{-1}; MS *m/z* (EI) 336 (0.19), 222 (19), 181 (20), 155 (14), 91 (41), 56 (100).

*4.8.2. (2*S,*3′*R,*3′a*S,*6′*S,*6′a*R*)*-**23***

White solid, 10.5% yield (eluent: petroleum ether: diethyl ether 1:1, R_f=0.15); ^{1}H NMR (500 MHz) δ 7.73 (d, J=8.5 Hz, 2H), 7.32 (d, J=7.9 Hz, 2H), 4.00 (dp, J=7.3, 6.7 Hz, 1H), 3.78 (dd, J=11.6, 8.5 Hz, 1H), 3.59 (t, J=7.9 Hz, 1H), 3.32 (dd, J=11.6, 8.5 Hz, 1H), 2.81 (bq, J=8.5 Hz, 1H), 2.73 (s, 3H), 2.63 (s, 3H), 1.29 (d, J=6.71 Hz, 3H), 1.25–1.19 (m, 1H), 1.07 (d, J=6.7 Hz, 3H), 1.02 (dd, J=10.4, 5.5 Hz, 1H), 0.38 (t, 1H).

4.9. General procedure for the thermal rearrangement of adducts anti, exo-***12*** *and* anti, endo-***13***, *or* anti, exo-***21***

A solution of 0.40 mmol of the mixture of adducts in 5 ml of xylenes was heated at reflux for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure and the crude mixture was purified by chromatography on silica gel to give the diazaheterocycles **17a**–**d** and **26a**–**c** in 80 and 57% yields, respectively.

*4.10. 1,2-Dimethyl-4-oxo-6-tosyloctahydro-1*H*-pyrrolo[3,4-*b*]pyridines **17a**,**c***

*4.10.1. (2*R,*4a*R,*7a*R*)*-**17a***

Colourless oil (eluent ethyl acetate, R_f=0.23); $[\alpha]_D^{24}$=+24.6 ($CHCl_3$, c=0.72 g cm^{-3}); ^{1}H NMR (200 MHz) δ 7.71 (d, J=8.3 Hz, 2H), 7.33 (d, J=7.8 Hz, 2H), 3.80 (dd, J=10.0, 3.9 Hz, 1H), 3.71 (bq, J=7.6 Hz, 1H), 3.43 (dd, J=9.4, 7.4 Hz, 1H), 3.31 (dd, J=10.1, 7.5 Hz, 1H), 2.96–2.89 (m, 3H), 2.44 (s, 3H), 2.38 (s, 4H), 2.25 (dd, J=8.4, 4.7 Hz, 1H), 1.09 (d, J=6.3 Hz, 3H); ^{13}C NMR (50.3 MHz) δ 206.5 (s), 144.1 (s), 135.7 (s), 130.1 (d), 128.1 (d), 64.3 (d), 53.8 (d), 49.9 (q), 47.5 (t), 46.4 (t), 46.1 (t), 39.9 (d), 22.0 (q), 18.3 (q); IR 2940, 1730, 1680, 1605, 1460, 1350, 1170 cm^{-1}; MS *m/z* (CI, NH_3) 323 (MH^+, 100), 322 (M^+, 19), 167 (6).

*4.10.2. (2*R,*4a*S*R,*7a*R*)*-**17c***

Colourless oil (eluent petroleum ether: ethyl acetate 1:1, R_f=0.23); $[\alpha]_D^{24}$=−12.5 ($CHCl_3$, c=0.36 g cm^{-3}); ^{1}H NMR (200 MHz) δ 7.71 (d, J=8.2 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 3.68 (dd, J=9.8, 6.3 Hz, 1H), 3.59 (dd, J=10.7, 8.8 Hz, 1H), 3.37 (dd, J=10.7, 7.8 Hz, 1H), 3.19 (dt, J=8.7, 6.8 Hz, 1H), 2.99 (bq, J=8.3 Hz, 1H), 2.76 (dd, J=9.3, 6.8 Hz, 1H), 2.84–2.70 (m, 1H), 2.46 (dd, J=17.1, 4.4 Hz, 1H), 2,44 (s, 3H), 2.19 (s, 3H), 2.14 (dd, J=17.1, 10.3 Hz, 1H), 1.07 (d, J=6.3 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 206.9 (s), 129.9 (s), 129.7 (d), 127.9 (d), 127.3 (s), 66.2 (d), 55.9 (d), 53.9 (d), 49.5 (q), 47.5 (t), 47.2 (t), 39.5 (t), 21.5 (q), 20.3 (q); IR 3000, 1740, 1610, 1350, 1170 cm^{-1}; MS *m/z* (CI, NH_3) 323 (MH^+,100), 322 (M^+, 5), 167 (5). Anal. calcd for $C_{16}H_{22}N_2O_3S$: C, 59.60; H, 6.88; N, 8.69. Found: C, 59.64; H, 6.99; N, 9.06.

4.11. 4-Oxo-6-tosyl-1,2,7-trimethyloctahydro-1H-pyrrolo[3,4-b]pyridines **26a–c**

4.11.1. (2S,4aR,7S,7aR)-**26a**

Colourless oil (eluent petroleum ether: ethyl ether 1:3, R_f=0.16); $[\alpha]_D^{24}$=−33.4 ($CHCl_3$, c=0.16 g cm^{-3}); ^{1}H NMR (500 MHz) δ 7.74 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 3.72 (dd, J=10.0, 7.7 Hz, 2H), 3.72–3.69 (m, 1H), 3.50 (dd, J=9.7, 8.0 Hz, 1H) 3.04–2.98 (m, 2H). 2.89 (q, J=7.2 Hz, 1H), 2.44 (s, 3H), 2.44 (dd, J=14.2, 4.5 Hz, 1H), 2.24 (s, 3H), 2.10 (dd, J=14.2, 5.7 Hz, 1H), 1.32 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR (50.3 MHz) δ 206.7 (s), 143.3 (s), 135.2 (s), 129.3 (d), 127.7 (d), 70.5 (d), 57.7 (d), 55.4 (d), 48.6 (d), 48.2 (t), 44.8 (t), 38.8 (q), 21.5 (q), 21.4 (q), 13.6 (q); IR 2960, 2927, 2857, 1711, 1450, 1342, 1159 cm^{-1}; MS *m/z* (EI) 181 (28), 155 (2), 149 (8), 138 (34), 126 (26), 91 (26), 56 (100). Anal. calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 60.51; H, 6.89; N, 8.45.

4.11.2. (2R,4aR,7S,7aR)-**26b**

Colourless oil (eluent petroleum ether: ethyl acetate 1:1, R_f=0.12); $[\alpha]_D^{21}$=+17.9 ($CHCl_3$, c=0.24 g cm^{-3}); ^{1}H NMR (500 MHz) δ 7.76 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 4.00 (q, J=6.8 Hz, 1H), 3.61 (t, J=9.1 Hz, 1H), 3.44 (t, J=10.2 Hz, 1H), 3.06–2.97 (m, 1H), 2.44 (s, 3H), 2.32–2.28 (m, 1H), 2.16–2.13 (m, 2H), 2.00 (s, 3H), 1.29 (d, J=6.8 Hz, 3H), 0.94 (d, J=5.7 Hz, 3H); ^{13}C NMR (50.3 MHz) δ 206.4 (s), 143.2 (s), 129.5 (s), 129.2 (d), 127.8 (d), 74.2 (d), 61.8 (d), 58.2 (d), 50.3 (d), 49.6 (t), 45.9 (t), 39.2 (q), 21.7 (q), 21.5 (q), 21.3 (q); IR 3050–2803, 1715, 1658, 1598, 1343, 1161, 1091 cm^{-1}; MS *m/z* (EI) 336 (M^+,4), 293 (6), 251 (3), 222 (3), 191 (28), 155 (6), 138 (42), 126 (43), 56 (100). Anal. calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 60.90; H, 7.26; N, 8.73.

4.11.3. (2S,4aS,7S,7aR)-**26c**

Colourless oil (eluent petroleum ether: ethyl acetate 2:3, R_f=0.30); $[\alpha]_D^{24}$=+39.0 ($CHCl_3$, c=0.27 g cm^{-3}); ^{1}H NMR (500 MHz) δ 7.72 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 4.09 (dd. J=11.4, 3.4 Hz, 1H), 3.37 (dd, J=10.8, 6.8 Hz, 1H), 3.30 (p, J=6.3 Hz, 1H), 3.18 (t, J=7.0 Hz, 1H), 2.81 (td, J=6.8, 3.4 Hz, 1H), 2.75 (ddd J=12.5, 5.7, 1.1 HZ, 1H), 2.55–2.48 (m, 1H), 2.50 (s, 3H), 2.43 (s, 3H), 2.42 (dd, J=12.5, 9.1 Hz, 1H), 1.42 (d. J=6.3 Hz, 1H), 0.79 (d, J=6.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 207.0 (s), 143.2 (s), 134.9 (s), 129.3 (6), 127.8 (d), 74.4 (d), 57.5 (d), 55.3 (d), 47.1 (d), 46.3 (t), 43.8 (d), 40.6 (q), 21.6 (q), 21.5 (q), 12.5 (q); IR 3400–2800, 1710, 1598, 1448, 1341, 1263, 1160, 1083 cm^{-1}; MS *m/z* (EI) 181 (24), 138 (25), 126 (18), 91 (24), 56 (100); MS *m/z* (CI, NH_3) 337 (MH^+, 100), 336 (M^+, 47); HRMS (M+Na) found: 359.14140; required for $C_{17}H_{24}N_2O_3SNa$: 359.14053.

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21. *exo* and *endo* concern here the configurations of the methyl on the carbon $C_{6'}$, relative to the convex face of the isoxazolidines.