NEW ACYLNITROSO COMPOUNDS FOR THE ASYMMETRIC OXYAMINATION OF DIENES

V. Gouverneur, S. J. McCarthy, C. Mineur, D. Belotti, G. Dive† and L. Ghosez*

*Laboratoire de Chimie organique de Synthèse, Université catholique de Louvain, place Louis Pasteur, 1, B -1348 Louvain-la-Neuve, Belgium
†Université de Liège, Centre d'Ingénierie des Protéines, Bâtiment B.6, B - 4000 Sart Tilman/Lièges, Belgium

Received 17 March 1998; revised 7 April 1998; accepted 17 April 1998

**Abstract**: a series of new enantiomerically pure acylnitroso compounds have been prepared and tested as dienophiles for the asymmetric oxyamination of dienes. Very high selectivities were obtained with acylnitroso compounds derived from diphenylmethoxymethyl pyrrolidine 2c, the C2-symmetric pyrrolidines 2d-e and camphorsultam 2f. © 1998 Elsevier Science Ltd. All rights reserved.

**Key words**: asymmetric amination, Diels-Alder reaction, acylnitroso compounds.

INTRODUCTION AND PRELIMINARY RESULTS

The asymmetric addition of dienes to nitroso compounds is a useful route towards enantiomerically pure amino alcohols and amino acids. Excellent results have been obtained with α-chloronitroso compounds derived from epiandrosterone and D-mannose.1 However, α-chloronitroso compounds cannot be added to highly nucleophilic dienes which decompose under the reaction conditions.2 This has been ascribed to the intermediate formation of an iminium adduct which reacts with the nucleophilic diene (Scheme 1).

![Scheme 1](image)

In a preliminary attempt to overcome this problem, we had selected nitroso compound 1 as a potential oxyamination reagent of these sensitive dienes (Scheme 2). It was readily prepared by nitrosation of the commercial Oppolzer's sultam. Surprisingly, it was totally inert towards a wide variety of reactive dienes even in the presence of a Lewis acid catalyst. This probably results from the fact that the SO2 group does not suppress electron donation from the nitrogen atom to the highly electrophilic nitroso group.

**Footnotes**: *Fax : + 32-10-47.41.68; E-mail : ghosez@chor.ucl.ac.be

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**PII**: S0040-4020(98)00504-3
In contrast, acylnitroso compounds have been shown to be excellent dienophiles. However, only moderate facial selectivities were obtained by using enantiomerically pure acylnitroso compounds derived from mandelic acid or proline.\textsuperscript{3,4} In two preliminary communications, we reported the efficiency of acylnitroso compounds 5d and 5f for the asymmetric amination of dienes.\textsuperscript{5,6} The full details and extensions of these studies are presented here.

**RESULTS**

1. **Synthesis of enantiomerically pure hydroxamic acids**

Acylnitroso compounds are usually unstable and must be generated *in situ* by oxidation of the corresponding hydroxamic acids. A series of hydroxamic acids derived from enantiomerically pure compounds 2a-f were prepared by the routes described in Scheme 3 and Table 1.

Compounds 2a, b, d, e and f were first transformed into their corresponding carbamoyl chlorides 3. The chlorocarboxylation of 2f required the deprotonation of the sultam nitrogen prior to acylation with triphosgene. With 2b, d and e, conversion to the carbamoyl chlorides proceeded cleanly and without rearrangement.\textsuperscript{7} The crude carbamoyl chlorides were converted into their corresponding hydroxamic acids using either hydroxylamine hydrochloride in the presence of sodium hydroxide or N,O-bis(trimethylsilyl)hydroxylamine. The acid sensitive pyrrolidine 2c was directly converted into 4c by transacylation with p-nitrophenoxhydroxamic acid. This transacylation could not be applied to D-bornane-2,10-sultame 2f for the preparation of compound 4f (3 % yield) because of the weaker nucleophilicity of the nitrogen atom of the sultam function. For compound 4f, we also developed a one-pot procedure using diisopropylethylamine and triphosgene in ether, then hydroxylamine hydrochloride and K$_2$CO$_3$ in water. This one-pot procedure gave a much better yield (85 %) than the two step sequence described above (41 % overall yield).
Reagents: (a) : COCl₂, toluene or ether, -30 °C; (b) : NaH, toluene then triphosgene; (c) : NH₂OH.HCl, NaOH, MeOH/H₂O; (d) : Me₃SiNHOSiMe₃ then MeOH; (e) : NaHMDS, THF, p-O₂N-C₆H₄-O-CO-NHOH, -78 °C to rt; (f) : triphosgene, NEt(iPr)₂ then NH₂OH.HCl, K₂CO₃, H₂O/ether.

Scheme 3

Table 1: Synthesis of Enantiomerically Pure Hydroxamic Acids

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions</th>
<th>Yield 3 (%)</th>
<th>Yield 4 (%)</th>
<th>Global yield 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>a then c</td>
<td>82</td>
<td>76</td>
<td>62</td>
</tr>
<tr>
<td>2b</td>
<td>a then d</td>
<td>91</td>
<td>71</td>
<td>64</td>
</tr>
<tr>
<td>2c</td>
<td>e</td>
<td>--</td>
<td>--</td>
<td>40</td>
</tr>
<tr>
<td>2d</td>
<td>a then d</td>
<td>95a</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>2e</td>
<td>a then d</td>
<td>95a</td>
<td>82</td>
<td>78</td>
</tr>
<tr>
<td>2f</td>
<td>b then d</td>
<td>51</td>
<td>80</td>
<td>41</td>
</tr>
<tr>
<td>2f</td>
<td>f</td>
<td>--</td>
<td>--</td>
<td>85</td>
</tr>
</tbody>
</table>

a: yields of crude compounds
2. Asymmetric cycloadditions

Acylnitroso compounds 5a-f were generated in the presence of excess diene by oxidation of hydroxamic acids 4a-f with tetraethylammonium periodate. These very reactive dienophiles gave good yields of cycloadducts under these very mild conditions (Scheme 4, Table 2).

\[ \text{Scheme 4} \]
Acylnitroso compound 5a derived from menthol gave very low diastereomeric excesses (Table 2, entries 1 and 2), a result which can be explained by several reactive conformations. For similar reasons, poor diastereoselectivities were obtained with acylnitroso 5b derived from proline (Table 2, entries 3 and 4). This had been previously observed by Streith et al.\textsuperscript{4}

Several possibilities were considered in order to improve the diastereoselectivities. We have selected a pyrrolidine derivative bearing a bulkier group α to the nitrogen. Dienophile 5c derived from α,α-diphenylmethoxymethylpyrrolidine reacted at 0°C with cyclohexadiene to give adduct 7c as a single diastereomer (d.e. > 98 %; Table 2, entry 5). Complete control of the diastereoselectivity was also observed with functionalised dienes (Table 2, entries 6, 7 and 8). For those reactions involving non symmetrical dienes, only one regioiseromer was detected by \textsuperscript{1}H NMR analysis of the crude mixtures. The primary adduct from the reaction of 1-methoxycyclohexadiene with 5e was not isolated but directly hydrolysed to yield 9c. These results showed that the presence of a large substituent on the pyrrolidine ring significantly enhanced the diastereomeric excess of the cycloaddition.

### Table 2: Cycloadditions of Acylnitroso Compounds with Dienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acylnitroso 5</th>
<th>Diene</th>
<th>t (° C)</th>
<th>Adduct</th>
<th>Yield (%)\textsuperscript{a}</th>
<th>d.e. (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>cyclopentadiene</td>
<td>0</td>
<td>6a</td>
<td>65</td>
<td>12\textsuperscript{c}</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>cyclohexadiene</td>
<td>0</td>
<td>7a</td>
<td>74</td>
<td>20\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td>cyclopentadiene</td>
<td>0</td>
<td>6b</td>
<td>71</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>5b</td>
<td>cyclohexadiene</td>
<td>0</td>
<td>7b</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>5c</td>
<td>cyclohexadiene</td>
<td>0</td>
<td>7c</td>
<td>75</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>6</td>
<td>5c</td>
<td>1-carboxymethylcyclohexadiene</td>
<td>0</td>
<td>8c</td>
<td>40</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>7</td>
<td>5c</td>
<td>1-methoxycyclohexadiene</td>
<td>0</td>
<td>9c</td>
<td>68</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>8</td>
<td>5c</td>
<td>1-methoxybutadiene</td>
<td>0</td>
<td>10c</td>
<td>51</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>9</td>
<td>5d</td>
<td>cyclopentadiene</td>
<td>-25</td>
<td>6d</td>
<td>83</td>
<td>87 (98\textsuperscript{d})</td>
</tr>
<tr>
<td>10</td>
<td>5d</td>
<td>cyclohexadiene</td>
<td>20</td>
<td>7d</td>
<td>88</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>11</td>
<td>5d</td>
<td>cycloheptadiene</td>
<td>20</td>
<td>11d</td>
<td>70</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>12</td>
<td>5e</td>
<td>cyclohexadiene</td>
<td>20</td>
<td>6e</td>
<td>82</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>13</td>
<td>5f</td>
<td>cyclopentadiene</td>
<td>0</td>
<td>6f</td>
<td>91</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>14</td>
<td>5f</td>
<td>cyclohexadiene</td>
<td>0</td>
<td>7f</td>
<td>94</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>15</td>
<td>5f</td>
<td>1-carboxymethylcyclohexadiene</td>
<td>-20</td>
<td>8f</td>
<td>75</td>
<td>&gt; 98</td>
</tr>
</tbody>
</table>

\textsuperscript{a} : yields of purified compounds; \textsuperscript{b} : determined by \textsuperscript{1}H NMR on the crude compounds; \textsuperscript{c} : approximated by quantitative \textsuperscript{13}C NMR; \textsuperscript{d} : after purification.
Excellent levels of asymmetric induction were also observed with acylnitroso compounds 5d and 5e derived from C₂-symmetric pyrrolidines (Table 2, entries 9-12).  

Finally, nitroso compound 5f derived from camphor sultam also proved to be an efficient stereodirecting chiral heterodienophile. It reacted with cyclohexadiene, cyclopentadiene and 1-carboxymethylcyclohexadiene to give the expected adducts with more than 98% d.e. (Table 2, entries 13, 14 and 15). The reaction with 1-carboxymethylcyclohexadiene was also totally regiospecific (Table 2, entry 15).

The determination of the diastereomeric excesses rested upon the ¹H NMR analysis of the crude mixtures. For the bicyclic adducts, the d.e. were deduced from the examination of the signals of the bridgehead protons. A control experiment was performed on an equimolecular mixture of diastereomers prepared independently following Scheme 5. This authentic mixture showed well separated ¹H NMR signals for the bridgehead protons (Scheme 5).

The hydrolysed product 9c showed only one signal at 58.9 ppm for the newly created asymmetric carbon atom. Similarly product 10 showed only one signal at 100.1 ppm for the new asymmetric carbon atom.

The structure and absolute configurations of adducts 7c, 9c were assigned by X-ray diffraction analysis by reference to the known absolute configuration of the asymmetric carbon atoms of the pyrrolidine ring. We also obtained an X-ray diffraction analysis on compound 12 resulting from the reduction of 7d (Scheme 6).
The absolute configuration of adduct 7f was established by an independent synthesis from the known enantiomerically pure (1R,4S)-oxazine10 (Scheme 7).

3. Cleavage of the chiral auxiliaries

We have previously described that the hydrolytic cleavage of the chiral auxiliary from adducts prepared by cycloaddition of acyl nitroso compound 5d and 2-azadienes was possible by refluxing the adduct in 6M HCl. Under those conditions, concomitant demethylation of the methoxymethyl groups of the pyrrolidine ring was observed.10

In a preliminary study, we have found that similar strong acidic conditions only gave a poor yield in the case of 7c. This is probably due to the instability of the bicyclic oxazine under these conditions.
On the other hand, the cleavage of the imide bond of 7f could be effected with H$_2$O$_2$ - LiOH as shown earlier. Here again we observed some decomposition of the oxazine. Further studies are in progress to optimise these steps.

![Chemical structure](image)

(a) HCl/MeOH then CH$_3$COCl, Et$_3$N, 28 %; (b) H$_2$O$_2$, LiOH then CH$_3$COCl, Et$_3$N, 35 %

**Scheme 8**

4. Transition state models

The excellent diastereoselectivities observed for the reactions of acylnitroso 5c, 5d and 5f with cyclohexadiene, cyclopentadiene or functionalised dienes could be rationalised in the following manner.

For acylnitroso compound 5d, one could consider the two *endo* transition states A and B.

In contrast with other acylnitroso compounds, the carbamoyl nitroso prefers a *syn* conformation. *Ab initio* calculations using the basis sets MINI-1$^{12,13}$ and 6-31G$^*$ predict this *syn* conformation to be 7.039 and 6.911 Kcal (AG) more stable than the corresponding *anti* conformation. The *anti* conformation corresponds to an energy maximum in both basis sets. This results from repulsive interactions between the oxygen atom of the N=O group and the bulky substituent on the pyrrolidine ring atom. In transition state A, the diene approaches in an *endo* fashion from the less hindered side of the dienophile. Transition state A is clearly lower in energy than transition state B and leads to the experimentally observed adduct.
The facial diastereoselectivity observed for the cycloaddition of dienophile 5f with cyclohexadiene is consistent with transition state models C or D.

Transition state C results from an *endo* approach of the dienophile from the less hindered side of the dienophile in a *syn-syn* conformation around the SO$_2$N-CO and CO-NO bond. Transition state D results from an *exo* approach of the diene from the less hindered face of the dienophile in an *anti-syn* conformation. The four conformers resulting from the rotation around the SO$_2$N-CO and CO-NO bonds have been fully optimised by *ab initio* calculations using minimal MINI-1$^{12-13}$, double 6-31G$^{14}$ and 6-31G* basis sets$^{15}$ (Table 3). Except for the *syn-anti* conformer which corresponds to an energy maximum following the reaction coordinate, all three other conformers are true minima.

Table 3: Conformational Energy Differences (kcal) for Dienophile 5f

<table>
<thead>
<tr>
<th></th>
<th>Syn-Syn</th>
<th>Anti-Syn</th>
<th>Syn-Anti</th>
<th>Anti-Anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINI-1'</td>
<td>ΔE</td>
<td>1.458</td>
<td>0.000</td>
<td>8.363</td>
</tr>
<tr>
<td></td>
<td>ΔG</td>
<td>1.433</td>
<td>0.000</td>
<td>9.044</td>
</tr>
<tr>
<td>6-31G</td>
<td>ΔE</td>
<td>3.989</td>
<td>0.000</td>
<td>9.954</td>
</tr>
<tr>
<td></td>
<td>ΔG</td>
<td>3.900</td>
<td>0.000</td>
<td>10.487</td>
</tr>
<tr>
<td>6.31G*</td>
<td>ΔE</td>
<td>3.167</td>
<td>0.000</td>
<td>8.514</td>
</tr>
<tr>
<td></td>
<td>ΔG</td>
<td>3.001</td>
<td>0.000</td>
<td>9.326</td>
</tr>
</tbody>
</table>

Inspection of molecular models suggests that in transition state D the large SO$_2$ group could interact with the approaching diene. This should not be the case in transition state C which should therefore be preferred. Furthermore, an *endo* approach of diene and nitroso dienophile would be in agreement with what was previously observed for other chiral acylnitroso compounds.
For acylnitroso compound 5d, \textit{ab initio} calculations using the basis sets MINI-1 and 6-31G predicted the \textit{anti-syn} conformation as the most stable one (Table 4).

<table>
<thead>
<tr>
<th></th>
<th>Syn-Syn</th>
<th>Anti-Syn</th>
<th>Syn-Anti</th>
<th>Anti-Anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINI-1</td>
<td>ΔE</td>
<td>1.164</td>
<td>0.000</td>
<td>5.874</td>
</tr>
<tr>
<td></td>
<td>ΔG</td>
<td>0.682</td>
<td>0.000</td>
<td>6.042</td>
</tr>
<tr>
<td>6-31G</td>
<td>ΔE</td>
<td>6.075</td>
<td>0.000</td>
<td>10.289</td>
</tr>
<tr>
<td></td>
<td>ΔG</td>
<td>4.814</td>
<td>0.000</td>
<td>10.113</td>
</tr>
</tbody>
</table>

Both transition states E and F resulting from an \textit{endo} approach of the dienophile in an \textit{anti-syn} conformation have been considered. Transition state E resulting from the approach from the less hindered face of the pyrrolidine ring should be favoured. It leads to the experimentally observed adducts.

CONCLUSION

Among the various acylnitroso compounds we have prepared, 5c, 5d and 5f yielded cycloadducts with high facial selectivity. Transition state models have been proposed which allow prediction of the absolute configuration of an adduct starting from a given chiral auxiliary. The acylnitroso compound derived from the commercial Oppolzer's sultam presently appears to be the best choice: it gives high yields of cycloadducts with excellent diastereomeric excesses. However a proper evaluation of the new chiral nitroso compounds with respect to those described earlier\textsuperscript{16,17,18} also rests upon a study of the cleavage and recovery of the chiral auxiliary.
EXPERIMENTAL SECTION

IR spectra were recorded on Perkin-Elmer 297 or 681 spectrophotometers. \(^1\)H NMR spectra were obtained if not specified otherwise on Varian XL-200 or VXR-200 spectrometers (\(\delta=0\)(TMS), CDCl\(_3\), J in Hertz). \(^13\)C-NMR spectra were recorded at 20MHz on Varian CFT-20 and at 50MHz on Varian XL-200 or VXR-200 (\(\delta\) in ppm relative to internal TMS, J in Hertz). Mass spectra were measured on Varian MAT-44 or Finnigan MAT-TSQ70 spectrometers (electronic impact 70eV or chemical ionisation 100V with 200\(\mu\)Bar isobutane as ionising gas). Optical rotations were measured on polarimeter Perkin-Elmer 241 MC. Column chromatographies were performed on Merck 60 silicagel (70-230 Mesh) and flash-chromatography on Merck 60 silicagel (230-400 Mesh). Chromatographic solvents were distilled before use. TLC were performed on Merck 60 F\(_{254}\) plastic or glass plates. All dry solvents were distilled under argon or \textit{in vacuo}. Benzene, toluene, tetrahydrofurane (THF) and ether (Et\(_2\)O) were distilled from benzophenone ketyl. Dichloromethane, chloroform and acetonitrile were distilled from P\(_2\)O\(_5\). Cyclohexane was dried by azeotropic distillation. Ethyl acetate was refluxed on solid K\(_2\)CO\(_3\) and distilled. Methanol and ethanol were distilled from their respective magmasial alkoxydes.

(2S)-Methoxymethylpyrrolidine \(^{19}\), (2S)-methoxydiphenylmethylpyrrolidine \(^{20}\), (2R,5R)-methoxymethylpyrrolidine \(^{21}\), (7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,0\,3,7]-decane-5,5-dioxide \(^{22}\), carboxyethylcyclohexadiene \(^{23}\) have been prepared following the procedures described in the literature.

For the theoretical calculations, all the geometric degrees of freedom have been fully optimised at \textit{ab in iti o} level using the minimal basis set MINI-1 \(^{12,13}\) and the double zeta basis sets 6-31G \(^{14}\) and 6-31G* \(^{15}\). The nature of the critical point was determined by analytical frequency calculation available in Gaussian 94 \(^{24}\). The free energy calculations were performed at 298.15K and 1 atm.

4-(\(\text{N-Nitroso})\)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,0\,3,7]-decane-5,5-dioxide 1

To a solution of 0.33g (1.52mmol, leq.) of sultam 2f in 2ml THF was added dropwise a solution of 0.3ml (2.28mmol, 1.5eq.) of t-butylnitrite in 2rot THF. The mixture immediately turned yellow. After 30 min, all starting material had disappeared (TLC). After evaporation, the yellow solid was washed with pentane, filtered and dried \textit{in vacuo}. It was used without further purification. Yield: 0.37g (99 %); Rf: 0.92 (ethylacetate); IR (film, cm\(^{-1}\)): 1460, 1360; m/z(E.I.) 244(M); \(^1\)H NMR (200MHz, CDCl\(_3\)): 3.60 and 3.47 (2H, AB, J=13.9), 2.1 (2H, m), 1.9 (3H, m), 1.4 (2H, m), 1.08 (3H, s), 0.99 (3H, s); \([\alpha]_D^{20} +116^\circ (c=0.48, \text{CH}_3\text{OH}).

4) \textit{SYNTHESIS OF OPTICALLY PURE HYDROXAMIC ACIDS}

\textit{Synthesis of (l)-menthoxycarboxylic acid 4a}

To a solution of 3.2ml (0.045mol, 3eq) of phosgene and 20ml of toluene at -20\(^\circ\) C, was added dropwise 2.3g (0.015mole, 1eq.) of l(·)-menthol dissolved in 10ml of toluene. After the addition, the mixture was stirred for 5 hours at -10\(^\circ\) C and then at room temperature for one hour. After evaporation of the solvent and the excess of phosgene, the residual oil was purified by column chromatography to give 2.7g of (l)-menthoxycarboxylic acid 3a (82 %); Rf: 0.84 (ethylacetate/cyclohexane:2/8); IR (film, cm\(^{-1}\)): 1775, 1470, 1370; To a suspension of 4.24g (0.0611mole, 5eq) of hydroxylamine hydrochloride in a mixture 1/1 methanol/water (30ml) was added at once 3.42g (7eq.) of NaOH dissolved in 20ml of a 1/1 mixture of methanol/water. After addition of 2.7g (0.0122mole, 1eq) of (l)-menthol chlorocarbamate 3a, the reaction mixture was stirred overnight. The solvents were evaporated and the residue was treated with 1N HCl until acidic pH. After three extractions with dichloromethane, the organic phase was dried over MgSO\(_4\) and evaporated under reduced pressure to give a residual solid which was purified by column chromatography and recrystallised in a mixture of ethylacetate/cyclohexane; yield: 1.99g (76 %); Rf:0.55 (ethylacetate/cyclohexane: 1/1); IR(film, cm\(^{-1}\)) 3430, 1725; \(^1\)H NMR (200MHz, CDCl\(_3\)): 7.26(1H, br s), 6.89 (1H, br s), 4.65 (1H, dxt, J=4.5, J=10.9), 2.08 to 0.76 (9H, m), 0.91 (3H, d, J= 6.4), 0.88 (3H, d, J=7.1), 0.76 ( 3H, d, J=6.9);
(2S)-(methoxymethyl)pyrrolidinocarbohydroxamic acid 4b
Same procedure as for 3a with 3g (0.026mmol) of (2S)-methoxymethylpyrrolidine, 5.5ml (0.078mol) of phosgene; yield: 2.1g (91 %) of crude N-(carbamoyl)-(2S)-(methoxymethyl)pyrrolidine 3b; IR (film, cm⁻¹) 1740; A mixture of 2.1g (0.012mol) of carbamoyl chloride 3b, 4.6g (5.6ml, 0.026mol, 2.2eq.) of N,O-bis(trimethylsilyl)hydroxylamine and 4eq. of methanol was heated for 2 hours at 60 °C; After addition of 1ml of methanol, the mixture was stirred for another 15 minutes then evaporated under vacuo; the residue was purified by column chromatography; yield: 2.1g (91 %) of crude N-(carbamoyl)-(2S)-(methoxymethyl)pyrrolidine 3b as a white solid; recrystallised in cyclohexane; m.p. 90.8 °C; IR(film, cm⁻¹) 1740; 1H NMR (200MHz, CDCl₃): 0.83 (1H, m), 1.35 (1H, m), 1.67 - 2.20 (3H, m), 2.92 (3H, s), 3.63 (1H, m), 4.98 (1H, dxd, J=2.9, J=9.2), 6.93 (1H, br s), 7.4 (2H, m, Ar) and 9.04 (1H, br s, OH); 13C NMR (50MHz, CDCl₃) 162.7, 137.0, 135.7, 129.9, 128.2, 84.9, 64.2, 51.7, 47.4, 28.8, 22.0; LRMS (FAB) 327 (M+1); [α]D₂⁰ = -126.4 ° (c=0.97, CH3OH).

Diphenylmethoxymethylpyrrolidinocarbohydroxamic acid 4c
NaHMDS 1.0M in THF (0.67ml, 0.67mmol) was added dropwise to a suspension of 2-diphenylmethoxymethylpyrrolidine hydrochloride (100mg, 0.33mmol) in 10ml THF at -78 °C under an Argon atmosphere. The mixture was stirred for 30 minutes in which time the solid went into solution. A solution of p-nitrophenyl-N-hydroxycarbamate (72rag, 0.36mmol) in THF was added dropwise, this was accompanied by the solution turning yellow in colour due to the liberation of p-nitrophenol. The reaction was allowed to warm to room temperature over several hours, and the reaction was quenched with 10ml saturated NH₄Cl solution. The organic phase was extracted with Et₂O (25ml) and was washed with water (2x10ml) and brine (10ml). The organic phase was dried (MgSO₄) and the solvent removed in vacuo to afford a yellow solid. The crude product was purified by flash column chromatography using ethylacetate/cyclohexane(2/1) as eluant; yield: 40 % yield (43rag, 0.13mmol), m.p. 72-74 °C; IR(film, cm⁻¹) 3291, 1656; 1H (200MHz, CDCl₃) 4.09 (2H, m), 3.50 (4H, m), 3.37 (3H, s), 3.34 (3H, s), 2.19 - 1.92 (4H, m); 13C NMR (50MHz, CDCl₃) 146.5, 73.2, 71.2, 60.4, 61.3, 60.4, 61.3, 59.4, 28.9, 26.7; then same procedure as for 4b with 1.46g (0.007mol, 1eq.) of carbamoyl chloride 3d, 2.58g (0.015mol, 2.2eq) of N,O-bis(trimethylsilyl)hydroxylamine; yield: 1.81g (82 %); colourless solid; m.p. 125.5 °C; Rf=0.5(ethylacetate/cyclohexane, 1/2); IR(film, cm⁻¹) 3260, 1650; 1H NMR (500MHz, CDCl₃) 8.65 (1H, br s), 6.32 (1H, br s), 4.01 (2H, m), 3.44 (4H, m), 3.33 (6H, s), 2.05 to 1.15 (4H, m); 13C NMR (500MHz, CDCl₃) 161.5, 154.1, 153.7, 132.1, 128.2, 128.2, 63.8 (1H, s), 4.01 (2H, m), 3.44 (4H, m), 3.33 (6H, s), 2.05 to 1.15 (4H, m); 13C NMR (500MHz, CDCl₃) 161.5, 154.1, 153.7, 132.1, 128.2, 128.2, 63.8 (1H, s), 4.01 (2H, m), 3.44 (4H, m), 3.33 (6H, s), 2.05 to 1.15 (4H, m); m/z (EI) 418; [α]D₂⁰ = +111.6 ° (c=0.62, CH3OH).
The two steps procedure: 1st step: 0.105g (0.002mol) of Nai 60 %; 2ml toluene; 0.5g (0.0023mol) of sultam 2f; 0.23g (0.77mmol; 0.3eq.) of triphosgene; yield: 0.288g (51%) of crude carbamoyl chloride 3f.

2nd step: 0.225ml (0.93mmol, 2eq.) of \( \text{N,O-bis(trimethylsilyl)hydroxylamine} \); 0.12g of carbamoyl chloride 3f, cat DMAP; yield: 1.81g (82 %);

The one-pot procedure: To a solution of 1g (4.64mmol, leq.) of sultam 2f, 2.43 ml (13.9 mmol, 3eq.) and iPr2EtN in 35ml dry ether at 0 ° C was added in once 1.38g (4.64mmol) of triphosgene. After 15 minutes at 0 ° C, the reaction mixture was stirred at rt for 18 hours. 1.61g (23.2mol, 5eq.) of hydroxylamine hydrochloride was then added all at once as well as a solution of K2CO3 (1.92g, 13.93mmol in 5ml H2O). After 5 hours at rt, the organic phase was washed with water, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography; yield: 1.08g (85 %); white solid; m p 250 ° C(dec); Rf=0.25 (ethylacetate/cyclohexane: 1/1); IR (film, cm\(^{-1}\)) 3260, 1660, 1360; IH NMR (500MHz, CDCI3) 8.30(br s, 1H), 6.80(br s, IH), 3.87(1H, dxd, J=7.7, J=5.1), 3.39(2H,s), 2.1-1.8 and 1.5-1.2 (7H,m), 1.1 (3H,s), 0.95 (3H,s); t3C NMR (50MHz, CDCI3): 152.9, 64.2, 51.7, 49.5, 47.9, 44.3, 37.3, 32.1, 26.6, 20.3, 19.8; m/z(E.I.) 274 M+; \([\alpha]_{D}^{25} = -69 ° \) (c=1.05, CHC13).

2) ASYMMETRIC CYCLOADDITIONS

General procedure: A solution of tetraethylammonium periodate in CH2C12 was added over a 15 min period to a stirred solution of hydroxamic acid and of the diene at the given temperature. After completion of the reaction (disappearance of the hydroxamic acid according to TLC), the reaction mixture was diluted with CH2C12, washed with 10 % aqueous NaHSO3, saturated NaHCO3 and brine. The organic phase was dried over MgSO+ and the solvent removed under reduced pressure. The residue was purified by column chromatography.

3-(menthyloxycarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,1]-hept-2-ene 6a
0.2g(0.93mmol, leq.) of 4a, 0.35g(1.2mmol, 1.2 eq.) of Et4N+IO4-, 1ml of cyclopentadiene; 0 ° C; d.e.=12 % estimated by quantitative \(^1^C\) NMR; yield: 65 %; IR=0.49 (AcOEt/cyclohexane:3/7); IR(film, cm\(^{-1}\)) 1725; \(^1^H\) NMR (500MHz, CDC13) : 6.43-6.37(2H, m), 5.24(1H,m), 5.04(1H,m), 4.61(4.49*)(1H, txd, J=10.9, J=4.4), 2.00-0.75(9H, m), 0.9(0.93*) (3H, d, J=7.4 (J=6.4*)), 0.87(0.89*)(3H, d, J=6.9 (J=6.3*)), 0.76(0.78*) (3H, d, J=7.0 (J=7.0*)); \(^1^3^C\) NMR (125MHz, CDC13): 159.4(159.2*), 134.3(134.1*), 132.9(132.8*), 83.5(83.47*), 76.4(76.6*), 65.0(64.8*), 53.0(53.1*), 51.9(52.1*), 45.9, 39.1(39.2*), 36.3(36.33*), 31.2(31.1*), 28.5(20.2*), 26.9(27.0*), 25.6(25.8*), 21.3(20.9*) m/z(E.I.) : 280(M+1)

3-(menthyloxycarbonyl)-2-oxa-3-aza-3-bicyclo[2,2,2]-oct-2-ene 7a
0.32g(1.5mmol, leq) of 4a, 0.56g(1.8mmol, 1.2eq.) of EhN+IO4-, 0.36g(4.5mmol, 3eq) of cyclohexadiene; rt; d.e.=20 % estimated by quantitative \(^1^C\) NMR; yield: 0.33g(74 %); IR=0.6(AcOEt/cyclohexane:3/7); IR(film, cm\(^{-1}\)) 1725; \(^1^H\) NMR (500MHz, CDC13) : 6.01(2H,m), 4.26(1H, m), 4.21(1H,m), 4.09(1H,t,x,d,J=10.9, J=4.4), 2.00-0.75(13H, m), 0.90 (3H,d, J=6.5), 0.88(3H, d, J=7.0), 0.75 (3H, d, J=6.9); \(^1^3^C\) NMR (125MHz, CDC13): 158.4(158.2*), 131.7(131.4*), 131.3(131.2*), 75.9, 70.4, 50.0, 46.8, 40.7(40.69*), 33.9, 31.1, 26.0(25.9*), 23.4, 23.0(23.3*), 21.7, 20.3(20.5*), 20.1(20.2*), 16.2(15.0*); m/z(E.I.): 280(M+1)

3-(2'S-methxymethy)pyrridincarbny)-2-xa-3-aza-3-bicyc[2,2,2]hept-5-ene 6b
0.085g(0.49mmol, leq.) of 4b, 0.154g(0.49mmol, 1.2 eq.) of Et4N+IO4-, 0.12ml (0.15mmol, 3eq.) of cyclopentadiene; -25 ° C; d.e.=34 %; yield: 0.083g(71 %); 2 diastereomers not separated by column chromatography major diastereomer: IR=0.46 (AcOEt); IR(film, cm\(^{-1}\)) 1680, 1640; \(^1^H\) NMR (500MHz, CDC13) 6.58(1H, m), 6.31(1H,m), 5.05(1H,br s), 4.15(1H,m), 3.58(1H, m), 3.50(1H, dxd, J=9.5, J=3.6), 3.35(1H, m), 3.31(3H, s), 3.26(1H, dxd, J=9.5, J=7.1), 2.1-1.6(6H, m); minor diastereomer:
Rf = 0.57 (AcOEt); \[ \text{H NMR (500MHz, CDCl}_3\text{)} 6.47(1H, m), 6.41(1H,m), 5.12(1H,br s), 5.10(1H, br s), 4.05(1H, m), 3.66(1H, m), 3.52(1H, dxd, J=9.4, J=3.4), 3.33(3H, s), 3.24(1H, dxd, J=9.5, J=7.1), 2.1-1.6(6H, m).

3-(2'S-methoxymethylpyrrolidinocarbonyl)-2-oxa-3-aza-3-bicycle[2,2,2]-oct-5-ene 7b
0.12g (0.7mmol, leq.) of 4b, 0.22g (0.7mmol, 1.2 eq.) of Et₄N÷IO₄, 0.17g (0.2mmol, 3 eq.) of cyclopentadiene; 0 ° C; d.e. = 72 %; recrystallisation in CH₂Cl₂/ether; yield (2 diastereomers): 0.14g (80 %); 2 diastereomers separated by column chromatography (105mg major; 17mg minor)

major diastereomer:
Rf = 0.52 (AcOEt); IR (film, cm⁻¹) 1680, 1640; \[ \text{H NMR (500MHz, CDCl}_3\text{)} 6.60(1H, dxd, J=8.3, J=5.8, J=1.7), 6.53(1H, dxd, J=8.3, J=5.7, J=1.8), 4.64(1H, m), 4.45(1H, m), 3.36(1H, m), 3.34(3H, s), 3.30(1H, dxd, J=9.3, J=7.7), 2.14(2H, m), 1.86(3H, m), 1.7(1H, m), 1.64(1H, m), 1.35(1H, m); \]

13C NMR (125MHz, CDCl₃): 161.9, 133.3, 131.3, 73.3, 70.2, 58.9, 57.8, 50.2, 48.4, 27.6, 24.1, 23.5, 20.1; m/z (EI): 252 (M⁺).  

3-(2-(N,N-Diphenylmethoxymethylpyrrolidinocarbonyl)-2-oxa-3-aza-bicyclo[2,2,2]oct-5-ene 7c
0.05g (0.153mol, leq.) of 4c; 0.049 (0.153mol, leq.) of Et₄N÷IO₄; 21.9p.l (0.23mmol) of 1,3-cyclohexadiene; 2ml dry CH₂Cl₂; -70 ° C then 0 ° C; white solid; yield: 46mg (75 %) recrystallised in ethylacetate/cyclohexane (2/1); yield: 44mg (75 %); d.e. > 98 %; m.p. 140 ° C; IR (KBr, cm⁻¹) 2938, 1641, 1396; \[ \text{H NMR (500MHz, CDCl}_3\text{)} 0.84(1H,m), 1.41(2H,m), 1.45(2H,m), 2.11(1H,m), 2.17(2H,m), 2.25(1H,m), 2.31(1H,m), 2.97(3H,s), 3.31(1H,m), 4.45(1H, dxd, J=1.5, J=5.8), 4.74(1H, dxd, J=1.3, J=5.8), 5.59(1H, dxd, J=3.1, J=9.0), 6.5(1H,dxd, J=1.5, J=5.8, J=8.2), 6.63(1H,dxd, J=1.5, J=5.8, J=8.2), 7.2-7.5(10H, m); \]

13C NMR (125MHz, CHCl₃) 20.5, 23.5, 24.1, 26.2, 50.4, 51.5, 51.9, 59.2, 70.1, 85.8, 126.9, 127.1, 127.4, 127.6, 129.4, 129.8, 130.0, 131.2, 140.9, 142.4, 163.7; LRMS (FAB) 405 (M⁺I)+; C₂₅H₂₈N₂O₃: calculated: C, 74.25; H, 6.93; N, 6.93; Found: C, 74.54; H, 6.75; N, 6.95; Absolute Configuration by X-Ray: IR, 4S, 2'S; \[ [\alpha]_D^{20} = -139.4° (c=1.25, CHCl₃). \]

1-methoxycarbamate-3-(2-(N,N-Diphenylmethoxymethylpyrrolidinocarbonyl)-2-oxa-3-aza-bicyclo[2,2,2]oct-5-ene 8c
0.05g (0.153mol, leq.) of 4c; 0.049 (0.153mol, leq.) of Et₄N÷IO₄; 28mg (0.18mmol) of ethyl cyclohexa-l,3-diene carboxylate; 1ml dry CH₂Cl₂; -70 ° C then 0 ° C; d.e. > 98 %; colourless oil; purification by column chromatography (AcOEt/dichloromethane: 20/80); yield: 29.1mg (40 %); IR (KBr, cm⁻¹) 2940, 1758, 1695, 1645, 1447; \[ \text{H NMR (500MHz, CDCl}_3\text{)} 0.84(1H,m), 1.41(2H,m), 1.45(2H,m), 2.11(1H,m), 2.17(2H,m), 2.25(1H,m), 2.31(1H,m), 2.97(3H,s), 3.31(1H,m), 4.45(1H, dxd, J=1.5, J=5.8), 4.74(1H, dxd, J=1.3, J=5.8), 5.59(1H, dxd, J=3.1, J=8.9), 6.60(1H, dxd, J=6.3, J=8.2), 6.75(1H, dxd, J=1.4, J=8.2), 7.2-7.5(10H, m); \]

13C NMR (125MHz, CHCl₃) 14.1, 20.6, 22.3, 23.8, 26.2, 27.6, 50.4, 51.3, 52.2, 59.9, 61.7, 68.2, 85.7, 127.0, 127.3, 127.4, 127.6, 129.3, 129.5, 129.8, 129.9, 131.0, 132.2, 140.4, 141.9, 163.0, 169.7; \[ [\alpha]_D^{20} = -74.3° (c=0.6, CHCl₃). \]

N,N,N-(hydroxy-4'-cyclohexenonyl-(cc,~)-diphenyimethoxymethylpyrrolidino-carbonyl)amine 9c
0.05g (0.153mol, leq.) of 4c; 0.049 (0.153mol, leq.) of Et₄N÷IO₄; 54.4µl (0.18mmol) of 1-methoxycyclohexa-1,3-diene carboxylate; 1ml dry CH₂Cl₂; -70 ° C then 0 ° C; d.e. > 98 %; colourless oil; purification by column chromatography (AcOEt/dichloromethane: 2/1); yield: 47mg (68 %); recrystallisation in CH₂Cl₂/EtOAc/cyclohexane; white solid; 42mg (65 %); m.p. 197 ° C; IR (KBr, cm⁻¹): 3333, 2932, 1695, 1445; \[ \text{H NMR (500MHz, CDCl}_3\text{)} 1.15(1H,m), 1.56(1H,m), 1.96(2H,m), 2.46(2H,m), 2.69(1H,m), 2.97(3H,s), 3.35(1H,m), 4.42(1H, dxd, J=2.2, J=2.5), 5.6(1H, dxd, J=3.1, J=9.0), 6.2(1H, dxdxd, J=1.6, J=2.2, J=10.5), 6.89(1H, dxd, J=0.8, J=2.5, J=10.5), 7.02(1H, s, OH), 7.24-7.4(10H,m); \]

13C NMR (125MHz, CDCl₃): 23.8, 26.7, 27.0, 36.6, 49.8, 51.9, 58.9, 61.1, 86.4, 127.2, 127.7, 127.9,
N-((a,a)-diphenylmethoxymethylpyrrolidino-carbonyl)-1-oxa-2-aza-6-methoxy-cyclohex-4-ene 10c

0.05g (0.15mol, leq.) of 4c; 0.05g (0.15mol, leq.) of Et₄N+IO₄; 38.8 l~l (0.18mmol) of 1-methoxycyclohexa-1,3-diene; 2ml dry CH₂Cl₂; -30 °C then 0 °C; d.e. >98 %; purification by column chromatography (AcOEt/cyclohexane: 1/2); white foam; yield: 32rag (51%); IR(KBr, cm⁻¹) 2975, 1654; IH NMR(500MHz, CHCI₃): 1.07(IH,m), 1.49(IH,m), 1.89(IH,m), 2.14(1H,m), 2.34(1H,m), 2.97(3H,s), 3.45(3H,s), 3.58(IH,m), 3.83(IH, dxdxd, J=1.5, J=4.9, J=17.1), 7.2-7.5(IOH, m); C NMR(125MHz, CDCI₃): 24.3, 26.4, 45.8, 49.9, 51.9, 57.7, 59.7, 86.1, 100.1, 123.4, 126.8, 126.9, 127.4, 127.5, 127.6, 129.9, - 140.5, 141.5, 162.0; [α]D° = -2.27 o (c=0.75, CHCI₃).

3-((2'R,5'R)-bis(methoxymethyl)pyrrolidinocarbonyl-2-oxa-3-aza-3-bicyclo-[2,2,1] hept-5-ene 6d

0.15g (0.70mmol, 1.1 eq.) of 4d, 0.27g (0.77mmol, 1. leq.) of Et₄N+IO₄ , 0.18ml of cyclopentadiene; -25 ° C; d.e. crude mixture 87 % ; >98 % after purification by column chromatography; yield: 0.164g (83 %); recrystallisation in pentane afforded 10ling (51%) of the major diastereomer as a white solid and 52mg of a mixture of both diastereomers as an oil; major diastereomer Rf:0.58 (ethylacetate); IR(film, cm⁻¹) 1680, 1640; IH NMR (500MHz, CDC1₃) 6.40(1H, dxdxd, J=5.7, J=3.7, J=1.9), 6.35(1H, dxdxd, J=5.6, J=4.4, J=2.0), 5.12(2H,m), 4.23(2H,m), 3.43(2H, dxd, J=9.4, J=3.2), 3.3(6H,s), 3.22(2H, dxd, J=9.4, J=3.4), 1.98(2H,m), 1.86(2H,m), 1.80(1H,m), 1.70(1H,m); C NMR (125MHz, CDC1₃): 161.3, 134.9, 134.6, 83.2, 72.5, 64.5, 58.9, 57.7, 48.1, 25.8; Absolute configuration: 1S, 4R, 2'R, 5'R; [α]D° = +149.5 ° (c=0.19, CH₃OH); minor diastereomer (colourless oil): Rf:0.54(ethylacetate); IR(film, cm⁻¹) 1680, 1640; H NMR (500MHz, CDC1₃) 6.45(1H, dxdxd, J=5.45, J=2.16, J=1.00), 6.39(1H, dxdxd, J=5.7, J=4.4, J=1.0), 5.08(1H,m), 5.03(1H,m) 4.04(2H m), 3.49(2H, dxd, J=9.4, J=3.2), 3.35(6H,s), 3.20(2H, dxd, J=9.4, J=8.4), 2.10-1.70(6H,m); Absolute configuration: IR, 4S, 2'R, 5'R; m/z(E.I.): 282(M ).

3.((2'R,5'R)-bis(methoxymethyl)pyrrolidinocarbonyl)-2-oxa-3-aza-3-bicyclo [3,2,2] non-5-ene 11d

0.12g (0.55mmol, leq.) of 4d, 0.2g (0.63mmol, 1.1 eq.) of Et₄N+IO₄ -, 0.16ml (.189mmol, 3eq.) iof cycloheptadiene; rt; d.e. >98 %; yield: 0.143g (88 %); Rf:0.48 (ethylacetate); IR(film, cm⁻¹) 1680, 1640; H NMR (500MHz, CDC1₃) 6.58(1H, dxdxd, J=8.2, J=5.7, J=1.7), 6.52(1H, dxdxd, J=8.2, J=6.1, J=1.6); 4.7(2H,m), 4.23(2H,m), 3.41(2H, dxd, J=9.3, J=3.2), 3.33(6H,s), 3.21(2H, dxd, J=9.3, J=5.4), 2.15(2H,m), 1.98(2H,m), 1.86(2H,m), 1.45(2H,m); C NMR (125MHz, CDC1₃): 161.3, 134.9, 127.8, 130.7, 72.2, 70.3, 58.8, 57.8, 50.7, 25.6, 23.4, 20.4; Absolute configuration: 1S, 4R, 2'R, 5'R; Cl₆H₂₄N₂O₄: Calculated: C, 61.79; H, 8.16; N, 4.95. Found: C, 60.81; H, 8.20; N, 4.94; [α]D° = +106.8° (c=1.24, CH₃OH); m/z(E.I.): 296(M+).

Diastereomer (1R, 4S, 2'R, 5'R) prepared by independent synthesis IR(film, cm⁻¹) 1680, 1640; Rf: 0.65(ethylacetate); H NMR (500MHz, CDC1₃) 6.68(1H, dxdxd, J=8.3, J=5.7, J=1.6), 6.47(1H, dxdxd, J=8.3, J=5.8, J=1.8); 4.77 (1H,m), 4.57 (1H,m); 4.36(2H,m), 3.47(2H, dxd, J=9.3, J=3.3), 3.33(6H, s), 3.19(2H, dxd, J=0.3, J=8.4), 2.13(1H,m), 2.03(1H,m), 1.95(2H,m), 1.84(2H,m), 1.51(1H,m), 1.35(1H,m); C NMR (125MHz, CDC1₃): 159.9, 131.7, 131.3, 72.9, 70.3, 58.8, 57.8, 50.7, 25.6, 23.4, 20.4; Absolute configuration: 1S, 4R, 2'R, 5'R: C₁₁H₂₄N₂O₄: Calculated: C, 67.36; H, 9.69; N, 6.06. Found: C, 67.43; H, 9.68; N, 6.11; [α]D° = +106.8° (c=1.24, CH₃OH); m/z(E.I.): 296(M⁺).

3.((2'R,5'R)-bis(methoxymethyl)pyrrolidinocarbonyl)-2-oxa-3-aza-3-bicyclo [3,2,2] oct-5-ene 7d

0.12g (0.55mmol, leq.) of 4d, 0.2g (0.63mmol, 1.1 eq.) of Et₄N+IO₄ , 0.16ml (.189mmol, 3eq.) of cyclohexadiene; rt; d.e. >98 %; yield: 0.143g (88 %); Rf:0.48(ethylacetate); IR(film, cm⁻¹) 1680, 1640; H NMR (500MHz, CDC1₃) 6.58(1H, dxdxd, J=8.2, J=5.7, J=1.7), 6.52(1H, dxdxd, J=8.2, J=6.1, J=1.6); 4.7(2H,m), 4.23(2H,m), 3.41(2H, dxd, J=9.3, J=3.2), 3.33(6H,s), 3.21(2H, dxd, J=9.3, J=5.4), 2.15(2H,m), 1.98(2H,m), 1.86(2H,m), 1.45(2H,m); C NMR (125MHz, CDC1₃): 161.6, 134.9, 130.7, 72.2, 70.4, 58.9, 57.8, 49.3, 25.6, 24.5, 20.2; Absolute configuration: IR, 4S, 2'R, 5'R; m/z(E.I.): 282(M⁺).
8.47; N, 9.07; $[\alpha]_D^{20} = +94.9^\circ$ (c=0.69, CH$_3$OH); Absolute configuration: 1'S, 4'R, 2'R, 5'R; m/z(E.I.): 310(M$^+$).

N-(1'S,4'R-hydroxycyclohex-2'-en)-2,5-bis(methoxymethyl)pyrrolidino-carboxamide 12

To a solution of 0.115g (0.39mmol) of 7d in 3 ml of dry methanol was added portionwise 1.2g of 5 % Na/Hg; After 25 minutes, the reaction mixture was filtered on celite; After evaporation under reduced pressure, the solid residue was crystallised in EtOAc; yield:0.094g (81%); white solid; m.p. 104.2 °C; R$_f$:0.34 (ethylacetate); IR(film, cm$^{-1}$) 3350, 1640; H NMR (500MHz, CDC$_3$) 6.68(1H, dxdxd, J=7.5), 5.78(2H,m), 4.28(1H,m), 4.18(1H,m), 3.95(2H,m), 3.55(2H,m), 3.34(2H,m), 3.3(6H,s), 2.25(1H, br s), 2.05-1.50(8H,m); Absolute configuration: 1'S, 4'R, 2'R, 5'R; C$_{12}$H$_{26}$N$_2$O$_4$: Calculated: C, 60.38; H, 8.78; N, 9.39; Found: C, 60.41; H, 8.82; N, 9.45; $[\alpha]_D$ = +151.73° (c=0.66, CH$_3$OH); m/z(E.I.) 298(M$^+$).

3-(25-bis(t-butyldimethysilyloxy)pyrridincarbnyl)-2-xa-3-aza-3-bicyc[2.2.1]oct-5-ene 7e

0.1g (0.24mmol, leq.) of 4e, 0.12g (0.72mmol, 1.5eq.) of Et$_4$N+IO$_4$ -, 0.07g (0.72mmol, 3eq.) of cyclohexadiene; rt; d.e. >98 %; yield: 0.097g (82 %); R$_f$:0.47(ethylacetate:cyclohexane/3:7); IR(film, cm$^{-1}$) 1660; H NMR (500MHz, CDC$_3$) 6.54(1H, dxdxd, J=8.2, J=5.8, J=1.7), 6.47(1H, dxdxd, J=8.2, J=6.2, J=1.6), 4.63(1H,m), 4.88(2H,m), 3.61(2H, dxd, J=9.71, J=3.29), 3.38(2H, did, J=9.7, J=7.4), 2.15(2H,m), 1.94-1.84(4H,m), 1.37(2H,m), 0.86(18H,s), 0.018(6H,s), 0.071(6H,s); $^{13}$C NMR (125MHz, CDC$_3$): 160.1, 131.9, 131.3, 70.3, 63.4, 60.2, 50.8, 25.9, 25.3, 23.6, 20.6, 18.3, -5.34; Absolute configuration: 1'S, 4'R, 2'R, 5'R; m/z(E.I.): 496(M$^+$).

4-(2'-oxa-3'-aza-bicyclo[2,2,1]hept-5'-ene-3'-carbonyl)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,0$_3$,7]decane-5,5-dioxide 6f

0.1g (0.36mmol, leq.) of 4f, 0.176g (0.54mmol, 1.5eq.) of Et$_4$N+IO$_4$ -, 0.3ml (3.6mmol, 10eq.) of cyclopentadiene; 0 °C during 10min; d.e. >98 %; recristallisation in CH$_2$Cl$_2$/ether; yield: 0.1 lg(91%); m.p. 160 °C (dec); R$_f$=0.33 (AcOEt/cyclohexane 1/1); IR(film, cm$^{-1}$) 1720, 1340; H NMR(500MHz, CDC$_3$) 6.47(1H, dxdxd, J=5.5, J=4.0, J=1.6), 6.23(1H, dxdxd, J=5.5, J=3.9, J=2.1), 5.55(1H,m), 5.35(1H,m), 3.99(1H, dxd, J=7.7, J=4.3), 3.44(2H,s), 2.13(1H,m), 1.9(3H,m), 1.8-1.7(2H,m), 1.46(1H,m), 1.35(2H,m), 1.25(3H,s), 0.99(3H,s); $^{13}$C NMR (125MHz, CDC$_3$): 156.1, 133.5, 131.3, 84.6, 69.0, 64.9, 52.7, 48.5, 48.3, 47.9, 44.7, 37.2, 32.4, 26.7, 20.5, 19.9; Absolute configuration: 7S, 1'R, 4'S; $[\alpha]_D$ = -89.4° (c=0.06, CH$_3$OH); m/z(FAB): 677(2M$^+$+1).

4-(2'-oxa-3'-aza-bicyclo[2,2,2]oct-5'-ene-3'-carbonyl)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,0$_3$,7]decane-5,5-dioxide 7f

0.1g (0.36mmol, leq.) of 4f, 0.176g (0.54mmol, 1.5eq.) of Et$_4$N+IO$_4$ -, 0.3ml (3.6mmol, 10eq.) of cyclohexadiene; 0 °C; d.e. >98 %; recristallisation in AcOEt; mp 195-200 °C(dec); R$_f$:0.42(AcOEt/cyclohexane:l/1); IR(film, cm$^{-1}$) 1710, 1345; diastereomer 7S, 1'R, 4'S: H NMR(500MHz, CDC$_3$) 6.69(IH, dxdxd, J=8.3, J=5.7, J=1.6); 5.03(1H,m), 4.83(1H,m), 4.10(1H, dxd, J=7.5, J=6.0, J=1.6), 6.54(1H, dxdxd, J=8.3, J=5.7, J=1.6), 4.83(1H,m), 4.10(1H, dxd, J=7.5, J=4.8), 3.36 and 3.34(2H, AB, J=13.5), 2.40-2.20(2H,m), 2.09(1H,m), 1.96-1.80(4H,m), 1.47(2H,m), 1.26(2H,m), 1.20(3H,s), 0.97(3H,s); $^{13}$C NMR (125MHz, CDC$_3$): 154.3, 133.3, 131.9, 71.5, 66.7, 53.3, 51.1, 48.3, 47.6, 45.4, 38.2, 33.3, 26.4, 23.6, 21.5, 20.8, 19.9.
4-((1'-methoxycarbonyl-2'-oxa-3'-aza-bicyclo[2,2,2]oct-5'-ene-3'-carbonyl)-(7S)-10,10-dimethyl-5-thia-4-aza-tricyclo[5,2,1,03,7]decane-5,5-dioxide 8f
0.24 g (1.5 mmol, 1.5 eq) of methyl cyclohexa-1,3-dienecarboxylate, 0.3 g (1 eq) of 4f, 1 eq. of E4N+IO4-;
yield: 75 %; -20 ° C; d.e. > 98 %; m.p.: 155.5 ° C (dec); IR (film, cm⁻¹) 1740, 1720, 1340; mH NMR (500MHz,
CDC13) 6.79 (1H, dxd, J=8.3, J=1.7), 6.45 (1H, dxd, J=8.3, J=5.9); 5.04 (1H, m), 4.32 (2H, m), 3.98 (2H,
dxd, J=7.6, J=6.4), 3.4 (2H, s), 2.50 - 2.30 (2H, m), 2.00 - 1.40 (9H, m), 1.35 (3H, t, J=7.13), 1.19 (3H, s),
0.97 (3H, s); ¹³C NMR (125MHz, CDC13): 168.8, 154.9, 131.9, 129.4, 78.0, 64.8, 61.9, 54.4, 52.5, 48.3,
47.7, 44.4, 37.2, 32.2, 27.7, 26.5, 20.4, 20.3, 19.7, 13.9; C20H25N2O6SI: Calculated: C, 56.58; H, 6.65;
N, 6.60; Found: C, 56.46; H, 6.61; N, 6.55; [α]D²⁰ = -83.1 ° (c=1.00, CHCl₃); m/z (E.I.) 425(M, 100 %).

(1R, 4S)-N-acetyl-3-aza-2-oxabicyclo[2,2,2]oct-5-ene 13
From adduct 7f: To a solution of 7f (100 mg) in THF was added H₂O₂ (30 % solution in water) and then a
solution of LiOH in H₂O. After stirring at r.t. for 24h, Na₂S₂O₄ was added and the mixture was extracted
twice with ethylacetate. After evaporation, the residue was treated with CH₂COC₁ and Et₃N; yield: 15mg
(35 %); From adduct 7c: Adduct 7c (100mg) was dissolved in a solution of HCl 5M in MeOH; the solution
was refluxed in a sealed vial; After 10h, the mixture was evaporated and the residue treated with CH₂COC₁
and Et₃N; yield: 9mg (28 %); ¹H NMR(200MHz): 6.69 - 6.40 (m, 2H), 1.98 (s, 3H), 1.67 - 1.39 (m, 2H).

Acknowledgements
This work was generously supported by the Ministère de l'Education et de la Recherche Scientifique de la
Communauté française de Belgique (Action Concertée 86/91-84), by the "Fonds pour la formation à la
Recherche dans L'industrie et dans l'Agriculture" (fellowship to C.M.) and by the University of Louvain
(assistantship to V.G., fellowships to D.B. and S.McC). This text also presents research results of the
Belgian programme on Interuniversity Poles of Attraction initiated by the Belgian State, Prime Minister's

REFERENCES
53, 13769.
Chim. Acta 1992, 75, 109; (d) Miller, A.; Mc Paterson, T.C.; Procter, G. Synlett 1989, 32; (e)
8. (a) Gouverneur, V.; Ghosez, L. Tetrahedron Lett. 1991, 39, 5349; (b) see also : Defoin, A.;
2, 1209.
9. We thank Prof. Declercq, J.P. and Dr. Tinant, B. for the crystallographic studies.