Studies towards Syntheses of Enantiopure 1-Azaadamantane-2-carboxylic Acid Derivatives.

Verhaar, M.T.

Citation for published version (APA):
CHAPTER 4

SYNTHESIS OF A 1-AZAADAMANTANE-2-CARBOXYLIC ESTER
VIA A CYCLIC N-ACYLIMINIUM ION

4.1 Introduction

In the previous chapter glycine-derived radicals were employed for the formation of 3-azabicyclononane-2-carboxylic acid methyl esters. The early transition state of the free radical cyclisation together with the relatively long lifetime of the captodative radical allowed C-C bond formation between the double bond of the cyclohex-3-ene moiety and the glycine radical equivalent. In contrast, the corresponding glycine cation equivalent does not cyclise, due to steric interactions which preclude the approach of the bulky π-nucleophile to the cationic centre in its favoured (E)-iminium geometry. Previous studies from our research group, however, have shown that cyclic N-acyliminium ions, which are forced in a (Z)-geometry, thus lacking this steric problem, do permit the nucleophilic attack of the cyclohex-3-ene double bond to form bicyclo[3.3.1] nonanes in excellent yields.

\[
\begin{align*}
1 & \quad \text{CO}_2\text{Me} \quad \xrightarrow{\text{Z}} \quad \mathcal{Z} \quad 2 \quad \text{X} \\
& \quad \text{cyclic } N\text{-acyliminium ion}
\end{align*}
\]

We assumed that with a suitable and readily available cyclic N-acyliminium ion precursor for 3 we would have a practical starting point (eq 4.1) for a regiocontrolled enantioselective synthesis of bicyclic α-amino acid derivatives from 2 and hence access to enantiopure 1-azaadamantane-2-carboxylic esters 1.

4.1.1 Cyclisations of cyclic N-acyliminium ions

A number of cyclic N-acyliminium ions have been reported to react intramolecularly with a cyclohex-3-enylmethyl group to form tricyclic systems. Table 4.1 shows that cyclic N-acyliminium ions with a certain structural variety such as those derived from alkoxy lactams (\(4a^{1a}, 5a^{1a}, 6a^{1b}\)), alkoxy thiazolidinones (\(7a, 8a\)) and an alkoxy morpholinone (\(9a^{1b}\)) all give similar results. Apart from one exception (entry 8), all N-acyliminium ion cyclisations gave
rise to approximately 1:1 mixtures of formate regioisomers along with variable amounts of alkenes when carried out at rt. The 1,2-hydride migration (see also section 2.1.2) causing the formate mixtures is most striking in the cyclisation of morpholinone 9a which resulted in the sole formation of the formate 9c. Interestingly, when the cyclisation reactions of dimethyl-substituted pyrrolidinone 6a and thiazolidinone 8a were performed in refluxing HCOOH (entries 4 and 7) the corresponding alkenes products (d) were isolated as single products.

**Table 4.1**

<table>
<thead>
<tr>
<th>entry</th>
<th>alkoxy lactam</th>
<th>X</th>
<th>n</th>
<th>R1</th>
<th>Product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>CH₂</td>
<td>1</td>
<td>H</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>CH₂</td>
<td>2</td>
<td>H</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>6a</td>
<td>CH₂</td>
<td>1</td>
<td>CH₃</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>6a</td>
<td>CH₂</td>
<td>1</td>
<td>CH₃</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>7a</td>
<td>S</td>
<td>1</td>
<td>H</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>8a</td>
<td>S</td>
<td>1</td>
<td>CH₃</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>8a</td>
<td>S</td>
<td>1</td>
<td>CH₃</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>9a</td>
<td>OCH₂</td>
<td>1</td>
<td>H</td>
<td>100 (71%)</td>
</tr>
</tbody>
</table>

*reflux (100 °C). *Isolated yield

The hydride shift forms a severe drawback for our intended sequence. However, we may be able to overcome this problem using the tools presented in Chapter 2, by: (i) raising the reaction temperature, (ii) using a more highly substituted alkene leading to a more stable bicyclic cation, (iii) using the iodide participation presented by Overman et al., or (iv) using an allylsilane as nucleophile.
4.1.2 Suitable cyclic N-acyliminium ion precursors

The literature was examined in search for suitable cyclic N-acyliminium ion precursors. A suitable cyclic building block should meet the following requirements: it should be (i) readily available, (ii) easy to couple to a cyclohexenylmethyl group, (iii) stable towards acidic cyclisation conditions and (iv) cleavable under mild conditions.

The first candidate that drew our attention was the 3-methoxy-2,5-morpholinedione system\textsuperscript{3a} 10 which was studied by Steckhan \textit{et al.}\textsuperscript{3} This system together with its nitrogen analog, the methoxy-diketopiperazine\textsuperscript{3b} 11 were studied as enantiopure electrophilic glycine-derived building blocks in nucleophilic addition reactions and showed good to excellent diastereoselectivity. After acidic hydrolysis (aqueous 6 N HCl, reflux 6–10 h) of 12 the amino acid products were obtained in good yields, while the chiral auxiliary could be recovered. However, due to the multistep preparation and the anticipated difficulty of attaching the amide nitrogen to a cyclohexenylmethyl group, this route was not pursued.

![Chemical structure](image)

The second alternative was the iminium ion precursor 15 (eq 4.3) which should be readily accessible from oxazolidine-2,4-dione\textsuperscript{4,5} via a Mitsunobu coupling\textsuperscript{4b} with an appropriate alcohol and NaBH\textsubscript{4} reduction. Moreover, facile hydrolysis (NaOH, EtOH)\textsuperscript{7} of the ring after the N-acyliminium ion reaction should give rise to the corresponding β-amino alcohol 13, which in turn can be transformed into the desired amino acid.

![Chemical structure](image)

This chapter will deal with the chemistry of the oxazolidone-derived N-acyliminium ion 14 leading to tricyclic systems \textit{en route} to bi- and tricyclic α-amino esters.
4.2 Synthesis of 4-ethoxy and 4-acetoxy-oxazolidine-2-ones

The synthesis of the cyclisation precursors requires oxazolidine-2,4-dione, which is readily synthesised using various methods. In our hands, the compound was obtained in satisfactory yields of 50–60% by refluxing glycolamide with 1.2 equiv of diethyl carbonate in dry methanol in the presence of 1 equiv of potassium tert-butoxide.

The synthesis of three cyclisation precursors is shown in eq 4.4. The Mitsunobu coupling of the alcohols 16–18 with oxazolidine-2,4-dione using diethyl azodicarboxylate and triphenylphosphine proceeded smoothly. Alcohols 17 and 18 were used in both racemic and enantiopure form, whereas alcohol 16 was used only in racemic form. Where available, only the experiments with enantiopure material are described.

Reagents and conditions: (a) oxazolidine-2,4-dione, diethyl azodicarboxylate, PPh₃, THF, 0 °C. (b) NaBH₄, EtOH, cat. H₂SO₄, 0 °C; then H₂SO₄ (pH–2). (c) NaBH₄, MeOH, rt. (d) Ac₂O, cat. DMAP, pyridine, CH₂Cl₂, rt.

Reduction of the imides 19 and 20 with NaBH₄ in ethanol, in the presence of a small amount of acid, resulted in the corresponding hydroxy-oxazolidinones. After TLC indicated complete consumption of the starting material the reaction mixture was acidified to pH = 2 with 2 N H₂SO₄ in ethanol, resulting in the formation of ethoxylactams 22 and 23. Due to the acid sensitivity of the allylsilane 21, the NaBH₄ reduction of this compound was performed in methanol, followed by acylation of the hydroxy-oxazolidinone with Ac₂O to give 24 in excellent yield.
4.3 Cyclisation reactions

The N-acyliminium ion precursor 22 was dissolved in HCOOH and stirred for 18 h. After evaporating the solvent $^1$H NMR showed a mixture of products. The uncyclised oxazolone 29 was formed in 24% and a small amount (5%) of alkene 27 was detected as well. The major part of the product consisted of the two formates 25 and 26 in a 1:2 ratio in favour of the 1,2-H migration product.

Upon performing the reaction in refluxing HCOOH, (100 °C) $^1$H NMR showed only signals of the tricyclic components. The mixture of products clearly indicated the occurrence of a 1,2-H migration. The sequence of steps is explained in Scheme 4.1. After cyclisation of the N-acyliminium ion the bicyclic cation 30 rearranges partially to cation 31. Subsequent nucleophilic attack of formic acid or proton loss leads to the complex product mixture.
To prevent the 1,2-hydride migration the conditions described by Overman et al.\textsuperscript{2a} were applied (Bu\textsubscript{4}NI, TfOH, CHCl\textsubscript{3}, rt) to the oxazolone 29, but no cyclisation was observed. A modification\textsuperscript{8} of this procedure, \textit{i.e.} stirring of the starting material 22 in a saturated solution of NaI in HCOOH (1 g/mL) at rt did afford only cyclised products according to the \textsuperscript{1}H NMR spectrum of the reaction mixture.

\[
\begin{array}{ccc}
\text{product ratio} & 34 & 37 & 27 & 28 & 25 & 29 \\
32 & 33 & 8 & 2 & 7 & 12
\end{array}
\]

Clearly, the rate of nucleophilic attack by iodide is superior to that of formic acid, because the product consisted of the iodides 32 and 33 in 71\%, compared to 7\% of formate 25. In contrast to the cyclisation reported by Overman (see also section 2.1.2) in which kinetic participation of iodide resulted in exclusive formation of the desired product, the iodides were formed in a 1:1 ratio. In view of the rather difficult purification of the cyclisation products further synthetic elaboration of this unsubstituted cyclohexene system to \(\alpha\)-amino acids was not pursued.

On the other hand, when \(N\)-acyliminium ion precursor 23 was dissolved in HCOOH and stirred overnight, alkene 34 was obtained as a single crystalline product (eq 4.7). The stereochemistry was confirmed after elucidation of the X-ray crystal structure (Figure 4.1).

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{EtO} & \quad \text{HCOOH} \\
\text{N} & \quad \text{rt, 18 h} \\
\text{O} & \quad \text{Me} \\
23 & \quad 34 (72\%) \\
\text{(mp 126-128 °C, [\(\alpha\)]D -84.9)}
\end{align*}
\]

According to our expectations, the BF\textsubscript{3}\textcdot OEt\textsubscript{2} mediated \(N\)-acyliminium ion cyclisation of allylsilane 24 resulted in the formation of the tricyclic systems 35 and 36 with an exocyclic double bond (eq 4.8). The major product 35 (72\%) bears the oxazolidone ring in a equatorial orientation, which was confirmed by the X-ray crystal structure (Figure 4.2). The minor product 36 containing the axial oxazolidone ring was formed in 10\% yield.
The formation of product 36 is probably the result of the more nucleophilic character of the allylsilane compared to that of a double bond, allowing the axial approach of the iminium ion towards the nucleophile (see also Section 5.4.2). An experiment at −78 °C showed that the ratio is rather independent of the reaction temperature, whereas cyclisation at room temperature resulted in much lower yield. Further synthetic elaboration of the two products 35 and 36 will be detailed in Chapter 5.

![Figure 4.1: Chem 3D™ representation of the crystal structure of 34.](image)

![Figure 4.2: Chem 3D™ representation of the crystal structure of 35.](image)

### 4.4 Opening of the oxazolidone ring to aminoalcohols

β-Amino alcohols have been frequently used as intermediates in amino acid synthesis. Very recently β-amino alcohols were employed as chiral ligands in asymmetric transfer hydrogenation of ketones.

\[
\text{[RuCl}_2\text{(HMB)}_2 \text{(0.25 mol%)}, \text{Ligand (2 mol%)}, \text{i-PrOK (2.5 mol%)}, \text{i-PrOH, rt)} \rightarrow \text{[O]} \rightarrow \text{OH}
\]

(HMB = hexamethylbenzene)

37a: R = H, conv. 92%, ee 95%, 5 h
37b: R = Me, conv. 85%, ee 0%, 16 h (run at 83 °C)
The asymmetric ruthenium-catalysed hydrogenation of aromatic ketones was described by Andersson et al.\textsuperscript{9a} The β-amino alcohol 37a, with its bicyclic azanorbornyl backbone, gave an excellent result (92% conversion after 5 h, ee 95%) when used as ligand. With the sterically more hindered ligand 37b, no reaction was observed at rt, while complete loss of enantioselectivity occurred at higher temperatures. Because the origin of the induction is not yet identified, we decided to investigate our system in a similar hydrogenation experiment.

\[
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (91\%)
\end{array}
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (91\%)
\end{array}
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (4.10)
\end{array}
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (83\%)
\end{array}
\]

Reagents and conditions: (a) H\textsubscript{2}, cat. Pd/C, EtOH, rt. (b) NaOH, EtOH, H\textsubscript{2}O, reflux.

In order to arrive at a suitable amino alcohol, compound 34 was hydrogenated to give 39 to eliminate the possibility of complexation of ruthenium to the double bond. Next, the amino alcohols 38 and 40 were obtained after hydrolysis\textsuperscript{7} with ethanolic NaOH of 34 and 39, respectively. These amino alcohols were tested for their catalytic properties under the aforementioned conditions. Unfortunately, both amino alcohols proved to be very poor ligands (conversion and ee <5%), probably due to steric hindrance.

### 4.5 Synthesis of enantiopure bi- and tricyclic α-amino esters

Prior to oxidation of the amino alcohol 38 to the amino acid, the nitrogen atom was protected as the tert-butyl carbamate with Boc\textsubscript{2}O to give 41. This protective group was especially chosen for its acid lability. Thus a separate deprotection step before the final Mannich reaction with formaldehyde would not be necessary, since this reaction is conducted in formic acid.

\[
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{OH} (87\%)
\end{array}
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (90\%)
\end{array}
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (4.11)
\end{array}
\begin{array}{c}
\text{Me} \quad \text{N} \quad \text{OH} \\
\text{Me} \quad \text{N} \quad \text{O} \\
\text{Me} \quad \text{N} \quad \text{OH} (85\%)
\end{array}
\]

Reagents and conditions: (a) Boc\textsubscript{2}O, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, rt. (b) Swern oxidation: (COCl)\textsubscript{2}, DMSO, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, −78 °C. (c) NaClO\textsubscript{2}, aqueous 1 M NaH\textsubscript{2}PO\textsubscript{4} buffer, tert-BuOH, 2-methyl-2-butene, 0 °C. (d) CH\textsubscript{3}N\textsubscript{2}, Et\textsubscript{2}O, rt.
The Boc-protected amino-alcohol 41 was oxidised in an efficient two step procedure. First a Swern oxidation\textsuperscript{11} gave the aldehyde 42, which was directly further oxidised using NaClO\textsubscript{2}\textsuperscript{12} in a buffered mixture of H\textsubscript{2}O and tert-BuOH. To avoid reaction of the double bond with the \textit{in situ} formed chlorine dioxide and chlorine\textsuperscript{12} a large excess of 2-methyl-2-butene was added. After extracting the N-Boc protected amino acid from the reaction mixture it was treated with diazomethane to afford the methyl ester 43 in good yield.

\[
\begin{align*}
\text{Boc} & \quad \text{HCl MeOH} \\
& \quad \text{HCOOH} \quad \text{43} \\
& \quad \text{44 (quant.)}
\end{align*}
\]

The nitrogen was easily deprotected with either HCl/methanol or HCOOH to give the corresponding HCl or HCOOH salt of the amine 44. Being assured that the \textit{tert}-butyl carbamate is readily hydrolysed in formic acid, carbamate 43 was dissolved in a solution of paraformaldehyde in HCOOH. After stirring for several hours, the solution was evaporated. According to \textsuperscript{1}H and \textsuperscript{13}C NMR, supported by COSY, HETCOR and NOE experiments, the residue consisted of 1-azaadamantane-2-carboxylic acid derivative 45\textit{a} together with some minor impurities. However, purification by aqueous basic work up and/or flash chromatography (silica or alumina) led to complete loss of material. Apparently, the 1-azaadamantane with the free amine readily decomposes, in contrast to the adamantanes described in Chapters 2 and 3. Purification of the adamantane, however, was successful when kept in the protonated stage. By applying a methanolic solution of the HCOOH salt on a strongly acidic DOWEX ion exchange column the formic acid is replaced by the immobilised sulfonic acid group. After washing the column with methanol, the product was collected as its pure HCl salt 45\textit{b} (see Figure 4.3) by eluting the column with dry methanolic HCl.

\[
\begin{align*}
\text{rt, quant.} & \quad \text{H}_{2}\text{CO, HCOOH} \\
& \quad \text{DOWEX; then HCl MeOH} \\
& \quad \text{43} \\
& \quad \text{45a (B=HCO}_2\text{)} \\
& \quad \text{45b (B=Cl)}
\end{align*}
\]

A viable explanation for the formation of the axial hydroxy-group is shown in Scheme 4.2. After reaction of the double bond with the iminium ion in 46 the carbocation 47 is formed. The methyl substituent stabilises this cation but at the same time hinders the attack of formic acid. Stabilisation by the proximate ester group could lead to the more stable dioxy carbeneion 48. Hydrolysis of 48 at the dioxy carbeneion results in the product 45.
Possibly, the fast decomposition of 45 under neutral or slightly basic conditions occurs via a reverse pathway. The formation of intermediate 47 from 45 might explain facile fragmentation reactions, while this pathway is prevented due to the protonated state of the nitrogen atom in product 45.

Figure 4.3 shows the $^1$H NMR spectrum of the purified adamantane 45b. Characteristic for the 1-azaadamantane are the rather broad signals. The $^{13}$C NMR is shown in Figure 4.4.

**Figure 4.3** $^1$H NMR (400 MHz, CD$_3$OD) spectrum of 45b
4.6 Structural proof

Identification of the products was mainly based on $^1$H NMR and $^{13}$C NMR especially in the bi- and tricyclic systems supported by 2D NMR techniques such as COSY, HETCOR, and NOE experiments. The 3-azatricycles 25, 26, 32 and 33 showed characteristic signals for H–10 and H–11. Proton H–10 of compounds 26 and 33 shows a nice symmetrical finesplitting, which clearly indicates the axial orientation. Proton H–11 is observed as a broad singlet. Although the stereochemistry of H–11 of compounds 25 and 32 is not proven, the equatorial orientation seems most logical, which would be the result of an expected attack of the nucleophile from the least hindered side in the cyclisation process.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Proton</th>
<th>ppm (mult.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 ($R^1 = \text{OCHO}, R^2 = \text{H}$)</td>
<td>H–11</td>
<td>5.30 (s)</td>
</tr>
<tr>
<td>32 ($R^1 = \text{I}, R^2 = \text{H}$)</td>
<td>H–11</td>
<td>5.04 (s)</td>
</tr>
<tr>
<td>26 ($R^1 = \text{H}, R^2 = \text{OCHO}$)</td>
<td>H–10</td>
<td>5.23 (sept, $J = 6.0$ Hz)</td>
</tr>
<tr>
<td>33 ($R^1 = \text{H}, R^2 = \text{I}$)</td>
<td>H–10</td>
<td>4.58 (sept, $J = 5.5$ Hz)</td>
</tr>
</tbody>
</table>

The formic acid salt of 1-azaadamantane-2-carboxylic acid 45 was characterised with $^1$H NMR and $^{13}$C NMR, using COSY and HETCOR experiments. The stereochemistry was confirmed by a NOE experiment (Figure 4.5), while the mass spectrum (FAB) showed a strong [M+H]$^+$ at $m/z$ 226 (rel. int. = 100%) confirming the molecular formula of $C_{12}H_{19}NO_3$. 

Figure 4.5 

![Figure 4.5](image-url) +1.5% NOE
4.7 Concluding remarks

In this chapter, a stereoselective synthesis of an enantiopure 1-azaadamantane-2-carboxylic acid derivative has been described. After a sequence of 9 steps from an enantiopure alcohol the adamantane was obtained as its HCl-salt. The key step was the stereoselective intramolecular cyclisation of the N-acyliminium ion derived from oxazolidinone to the 4-methyl-cyclohex-3-enylmethyl group.

4.8 Acknowledgements

T. Rob is kindly acknowledged for his contribution to this chapter. D. G. I. Petra is acknowledged for performing the ruthenium catalysed hydrogen transfer experiments with compounds 38 and 40. K. Goubitz and J. Fraanje of the Department of Crystallography are acknowledged for the X-ray structure determination of 34. H. Kooijman of the Department of Crystal and Structural Chemistry of the Bijvoet Center for Biomolecular Research, Utrecht University is acknowledged for the X-ray structure determination of 35.

4.9 Experimental section

General Information. For general information, see Section 2.9. Oxazolidine-2,4-dione was prepared according to a literature procedure.

General procedures

A: Procedure for the synthesis of oxazolidine-2,4-diones. To a cooled (0 °C) solution of the alcohol, oxazolidine-2,4-dione (1.05 equiv) and PPh₃ (1.05 equiv) in THF (0.5 M) was added diethyl azodicarboxylate (1.05 equiv). The mixture was stirred overnight at rt. After evaporation of the solvent in vacuo, the product was isolated from the residue by flash chromatography.

B: Preparation of ethoxy lactams from oxazolidine-2,4-diones. A solution of the oxazolidine-2,4-dione in ethanol (0.1 M) was cooled at 0 °C and NaBH₄ (2 equiv) was added portionwise. During the reaction time every 15 min a few drops of ethanolic 2 M H₂SO₄ were added. After TLC indicated complete consumption of starting material (ca. 2 h) the reaction mixture was acidified to pH<2 and stirred overnight. The solvent was removed and the residue taken up in CH₂Cl₂. The solution was filtrated over Celite®, washed with water (2 x), brine, dried (MgSO₄) and concentrated in vacuo to give the product.
**Synthesis via a cyclic N-acyliminium ion**

**C: Preparation of amino-alcohols from oxazolidinones.** To a solution of the oxazolidinone in ethanol (0.2 M) was added aqueous 2 N NaOH (same volume as ethanol) and the mixture was heated at reflux until TLC indicated complete consumption of starting material (ca. 1–2 h). The reaction mixture was cooled to rt and pieces of dry ice were added. The volatiles were removed to afford a white solid from which the product was extracted with hot EtOAc (5 ×). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to give the product.

**D: tert-Butoxycarbonylation of amines.** To a solution of the amine in CH₂Cl₂ (0.2 M) Et₃N (2 equiv) was added, followed by Boc₂O (1.25 equiv). The solution was stirred overnight at rt. The reaction mixture was washed with water. The aqueous layer was extracted with CH₂Cl₂ (3 ×). The combined organic layers were dried (MgSO₄) and concentrated to yield the N-Boc protected amine. The product was purified using flash chromatography.

**E: Procedure for the Swern oxidation of alcohols to aldehydes.** To a solution of oxalyl chloride (2 equiv) in CH₂Cl₂ (0.2 M) at −78 °C was added DMSO (4 equiv). The mixture was stirred for 5 min, then the alcohol was added as a solution in CH₂Cl₂ (0.2 M). After being stirred for 20 min, the reaction mixture was treated with Et₃N (6 equiv) and was allowed to warm to −40 °C over 30 min. Water was added and the layers were separated. The aqueous layer extracted with CH₂Cl₂ (3 ×). The combined organic layers were dried (MgSO₄) and concentrated to yield the aldehyde which was used in the next reaction without purification.

**F: Procedure for the oxidation of aldehydes to acids using NaClO₂.** The aldehyde was dissolved in a mixture of *tert*-butanol and 2-methyl-2-buten 1:1 (1.0 M). An aqueous solution of NaH₂PO₄ (pH~3.6) (half the volume of the organic solvents) was added and the mixture was cooled on ice. NaClO₂ (1.4 equiv) was added while stirring vigorously. After TLC indicated complete consumption of starting material the layers were separated and the water layer extracted with CH₂Cl₂ (3 ×). The combined organic layers were dried (MgSO₄) and concentrated to yield the acid which was used without purification.

3-Cyclohex-3-enylmethyloxazolidine-2,4-dione (19). According to general procedure A, (±)-cyclohex-3-ene-1-methanol 16 (6.0 g, 53.6 mmol) was coupled to oxazolidine-2,4-dione to afford the product 19 (9.2 g, 47 mmol, 88%) as a colourless oil after flash chromatography (EtOAc/P E 1:4): IR (CHCl₃) ν 1753, 1737, 1444, 1417; ¹H NMR (400 MHz) δ 5.70–5.59 (m, 2 H, CH=CH), 4.70 (s, 2 H, OCH₂), 3.49 (d, J = 7.0 Hz, 2 H, NCH₂), 2.12–2.00 (m, 4 H), 1.80–1.69 (m, 2 H), 1.33–1.23 (m, 1 H); ¹³C NMR (100 MHz) δ 170.6 (C=O), 156.0 (NC=O), 126.9 (=CH), 124.8 (=CH), 67.6 (OCH₂), 45.3
(NCH₂), 32.2 (CH), 28.9, 25.9, 24.1 (3×CH₂); HRMS calculated for C₁₀H₁₃NO₃ 195.0896, found 195.0908.

(S)-3-(4-Methylcyclohex-3-enylmethyl)oxazolidine-2,4-dione (20). According to general procedure A, (S)-(4-methylcyclohex-3-enyl)methanol 17 (5.0 g, 39.9 mmol) (ee 93%) was coupled to oxazolidine-2,4-dione to afford the product 20 (7.0 g, 33.6 mmol, 84%) as a colourless solid after flash chromatography (EtOAc/PE 1:4); mp 56–61 °C; [α]D -52.2 (c 1.0, CHCl₃); IR (film) ν 2915, 1818, 1737, 1445, 1417; ¹H NMR (400 MHz) δ 5.32 (br s, 1 H, =CH), 4.70 (s, 2 H, OCH₂), 3.48 (d, J = 6.7 Hz, 2 H, NCH₂), 2.10–1.96 (m, 4 H), 1.74–1.69 (m, 2 H), 1.63 (s, 3 H, CH₃), 1.35–1.28 (m, 1 H, CH); ¹³C NMR (100 MHz) δ 170.6 (C=O), 156.0 (NC=O), 133.8 (C=CH), 118.8 (C=CH), 67.6 (OCH₂), 45.2 (NCH₂), 32.0 (CH), 29.1, 29.0, 26.3 (3×CH₂), 23.2 (CH₃); HRMS calculated for C₁₁H₁₃N₃O, 209.1052, found 209.1056. In a similar experiment racemic material was produced: mp 57–62 °C.

(S)-3-[(Dimethylphenylsilyl)methyl]cyclohex-3-enylmethyl)oxazolidine-2,4-dione (21). According to general procedure A, the alcohol 18 (4.00 g, 15.4 mmol) (ee 93%) was coupled to oxazolidine-2,4-dione to afforded the product 21 (4.72 g, 13.7 mmol, 89%) as a yellowish solid after flash chromatography (EtOAc/PE 3:1); mp 83 °C; [α]D -43 (c 2.0, CH₂Cl₂); IR (film) ν 2912, 1818, 1737, 1443, 1416, 1247; ¹H NMR (400 MHz) δ 7.51–7.48 (m, 2 H, Ar-H), 7.35–7.26 (m, 3 H, Ar-H), 5.155 (s, 1 H, =CH), 4.69 (s, 2 H, OCH₂), 3.45 (d, J = 7 Hz, 2 H, NCH₂), 2.08–1.58 (m, 8 H), 1.22 (m, 11 H), 0.28 (s, 6 H, Si(CH₃)₂); ¹³C NMR (100 MHz) δ 170.6 (C=O), 156.0 (NC=O), 139.1 (Ar), 134.8 (C=CH) 133.5, 128.8, 127.6 (3×Ar-H), 117.3 (C=CH), 67.6 (OCH₂), 45.3 (NCH₂), 32.0 (CH), 30.0, 29.3, 26.6, 26.5 (4×CH₂), -2.9 (Si(CH₃)); HRMS calculated for C₁₆H₂₅N₃O₅Si 343.1604, found 343.1620. In a similar experiment racemic material was obtained as a white solid: mp 72–75 °C.

3-Cyclohex-3-enylmethyl-4-ethoxyoxazolidin-2-one (22). According to general procedure B, the oxazolidine-2,4-dione 19 (9.0 g, 46 mmol) of transformed into the ethoxylactam 22. This ethoxylactam was purified using flash chromatography (EtOAc/PE 1:4) yielding a colourless oil (6.86 g, 28.7 mmol, 93%) (1:1 mixture of diastereomers); IR (film) ν 2912, 1755, 1423, 1235; ¹H NMR (400 MHz) δ 5.69–5.57 (m, 2 H, CH=CH), 5.10–5.07 (m, 1 H, NCH), 4.31–4.26 (m, 1 H, OCH/H), 4.19 (dd, J = 10.2, 1.6 Hz, 1 H, OCH/H), 3.52–3.38 (m, 2 H, OCH₂CH₃), 3.37–3.30 (m, 1 H, NCH/H), 3.05 (dddd, J = 14.0, 6.3, 5.4 Hz, 1 H, NCH/H), 2.12–1.89 (m, 4 H), 1.78–1.70 (m, 2 H), 1.34–1.23 (m, 1 H), 1.20 (dt, J = 7.0, 1.5 Hz, 3 H, OCH₂CH₃); ¹³C NMR (100 MHz) δ 157.7 & 157.6 (C=O), 127.1 & 126.8 (=CH), 125.3 & 125.2 (=CH), 85.2 & 85.1 (NCH), 67.5 & 67.4 (OCH₂), 60.8 & 60.6 (OCH₂CH₃), 46.8 & 46.4 (NCH₂), 32.2 (CH), 29.3 & 29.1 (CH₂), 26.3 & 25.9 (CH₂), 24.4 & 24.2 (CH₂), 15.0 (OCH₂CH₃); HRMS calculated for C₁₀H₁₉NO₃ 223.1363, found 225.1362.
(3S)-4-Ethoxy-3-(4-methylcyclohex-3-enylmethyl)oxazolidin-2-one (23). According to general procedure B, the oxazolidine-2,4-dione 20 (6.5 g, 31.1 mmol) was transformed into the ethoxylactam 23. This ethoxylactam was purified using flash chromatography (EtOAc/PE 1:4) yielding a colourless oil (6.86 g, 28.7 mmol, 93%) (1:1 mixture of diastereomers): [α]D -43.1 (c 1.5, CHCl3); IR (film) ν 2913, 1751, 1237, 1094; 1H NMR (400 MHz) (assignment with aid of COSY) δ 5.28 (s, 1 H, =CH), 5.05 (d, J = 6.0, 1.8 Hz, 1 H, NCH), 4.27–4.22 (m, 1 H, OCH/H), 4.14 (dd, J = 10.2, 1.5 Hz, 1 H, OCH/H), 3.48–3.34 (m, 2 H, OCH2CH3), 3.30 (t, J = 8.5 Hz, 1/2 H, NCHH), 3.26 (t, J = 8.6 Hz, 1/2 H, NCHH), 3.01 (dd, J = 10.9, 6.4 Hz, 1/2 H, NCHH), 2.99 (dd, J = 10.7, 6.2 Hz, 1 H, NCH/H), 2.05–1.79 (m, 6 H), 1.73–1.62 (m, 2 H), 1.58 (s, 3 H, CH3), 1.29–1.20 (m, 1 H, CH), 1.18–1.14 (t, J = Hz, 3 H, CH2C/H); 13C NMR (100 MHz) δ 157.7 & 157.6 (C=0), 134.0 & 133.8 (C=CH), 119.3 & 119.2 (C=CH), 85.2 & 85.1 (NCH), 67.6 & 67.5 (OCH2), 61.0 & 60.9 (OCH2CH3), 46.8 & 46.2 (NCH2), 32.0 (CH), 29.4 & 29.3, 29.2 & 29.0, 26.7 & 26.3 (3 × CH3), 23.3 (CH3), 15.0 (OCH2CH3); HRMS calculated for C13H21NO3, 239.1512, found 239.1512.

(3S)-Acetic acid-3-{4-[(dimethylphenylsilanyl)methyl]cyclohex-3-enylmethyl}-2-oxooxazolidin-4-yl-ester (24). To an ice-cooled solution of the oxazolidinedione 21 (1.88 g, 5.48 mmol) in MeOH (50 mL) was added NaBH4 (0.41 g, 11 mmol). The mixture was allowed to warm to rt and left stirring for 2.5 h. The reaction was quenched by the addition acetone and stirring was continued for 1 h. After evaporation of the solvent in vacuo the residue was taken up CH2Cl2 and the remaining inorganic salts were removed by filtration through Celite®. The organic solution was washed with water. The aqueous layer was extracted with CH2Cl2 (2 ×). The combined organic layers were dried (MgSO4) and concentrated in vacuo, yielding (3S)-3-{4-[(Dimethylphenylsilanyl)methyl]cyclohex-3-enylmethyl}-4-hydroxyoxazolidin-2-one (1.89 g, 100%) as a white solid (1:1 mixture of diastereomers): mp 100 °C; [α]D -49 (c 2.0, CH2Cl2); IR (film) ν 3354, 2952, 2911, 1732, 1427, 1247; 1H NMR (400 MHz) δ 7.52–7.48 (m, 2 H, Ar-H), 7.35–7.26 (m, 3 H, Ar-H), 5.22, 5.18 (s, 2 H, NCHO & =CH), 4.69 (br s, 1 H, OH), 4.34 (dd, J = 10.0, 5.9 Hz, 1 H, OCH/H), 4.15 (d, J = 10.0 Hz, 1 H, OCH/H), 3.23–3.17 (m, 2 H, NCH2), 2.20–1.63 (m, 6 H), 1.65 (s, 2 H, SiCH2) 1.22 (m, 1 H), 0.29 & 0.30 (s, 6 H, Si(CH3)2); 13C NMR (100 MHz) δ 158.4 & 158.3 (C=O), 139.5 (Ar), 135.0 & 134.8 (C=CH), 133.5, 128.8, 127.6 (3 × Ar-H), 117.8 & 117.7 (C=CH), 79.9 & 79.8 (NCHO), 70.8 (OCH2), 46.2 & 45.7 (NCH2), 31.9 (CH), 30.4 & 30.1, 29.7 & 29.5, 27.0 & 26.7, 26.6 & 26.5 (4 × CH3), -2.8 (Si(CH3)); HRMS calculated for C19H27NO3Si 345.1760, found 345.1765. (In a similar experiment racemic material was obtained as a colourless oil.) To a solution of this hydroxyoxazolidinone (3.9 g, 10.1 mmol) in CH2Cl2 (120 mL) pyridine (3.6 mL, 45 mmol), acetic acid anhydride (1.6 mL, 17 mmol) and DMAP (120 mg, 1 mmol) were added. After stirring for 5 h at ambient temperature, the reaction mixture was poured into water. The water layer was extracted with CH2Cl2 (4 ×). The combined organic layers were dried (MgSO4) and concentrated in vacuo. Residual pyridine was
removed by azeotropic distillation with toluene. The product 24 (4.35 g, 10.9 mmol, 97%) was obtained as a colourless oil (1:1 mixture of diastereomers): [α]_D^2914 = -36.0 (c 1.9, CH_2Cl_2); IR (film) ν 2914, 1770, 1746, 1236; 'H NMR (400 MHz) δ 7.51-7.48 (m, 2 H, Ar-H), 7.35-7.26 (m, 3 H, Ar-H), 6.21 (d, J = 6.0 Hz, 1 H, NCH), 5.16 (s, 1 H, =CH), 4.43 (dd, J = 10.9, 6.0 Hz, 1 H, OCHH), 4.20 (d, J = 11 Hz, 1 H, OCHH), 3.33 (m, 1 H, NCHH), 3.02 (m, 1 H, NCHH), 2.10 (s, 3 H, CH_3), 2.09-1.58 (m, 6 H), 1.66 (s, 2 H, SiCH_2), 1.30-1.16 (m, 1 H) HRMS calculated for C_{21}H_{26}NO_4Si 387.1866, found 387.1846. In a similar experiment racemic material was obtained as a white solid: mp 49-50 °C.

A summary of the cyclisations of 3-Cyclohex-3-enylmethyl-4-ethoxyoxazolidin-2-one (22) and spectral data of the products (25, 26, 28, 32, 33). 3-Cyclohex-3-enylmethyl-4-ethoxy-oxazolidin-2-one 22 was dissolved in HCOOH and stirred at different temperatures (rt, 100 °C) and 3-Cyclohex-3-enylmethyl-4-ethoxy-oxazolidin-2-one 22 was dissolved in saturated NaI in HCOOH (1 g/mL) and stirred at rt. 'H NMR (400 MHz, CDCl_3) spectra of the crude concentrated reaction mixture revealed the product ratio (vide supra). After flash chromatography (twice with EtOAc/PE 1:2) most of the products were obtained in pure form. However, two of the products (25 and 28) were identified by deriving characteristic signals from the NMR spectra of mixtures of the compound as the major component together with a minor known component (25 from a mixture of 25 and 26; 28 from a mixture of 27 and 28). Whereas the cyclisation product 4-Oxa-6-azatricyclo[6.3.1.0^{3,6}]dodec-10-en-5-one 27 was syntheised in pure form from the 11-iodo-compound 32 in an independent experiment. Formic acid 5-oxo-4-oxa-6-azatricyclo[6.3.1.0^{3,6}]dodec-11-yl ester (25): 'H NMR (400 MHz) (characteristic signals) δ 3.50 (s, 1 H, H-11), 4.39 (t, J = 8.9 Hz, 1 H, OCHH), 3.17 (dd, J = 12.5, 3.9 Hz, 1 H, NCH). Formic acid 5-oxo-4-oxa-6-azatricyclo[6.3.1.0^{3,6}]dodec-10-yl ester (26): white solid; mp 136 °C; IR (KBr) ν 2936, 1755, 1708, 1453, 1431, 1185; 'H NMR (400 MHz) δ 5.78-5.60 (m, 2 H, CH=CH), 4.36 (t, J = 8.9 Hz, 1 H, OCHH), 4.14 (dd, J = 9.1, 2.3 Hz, 1 H, OCHH), 3.93 (m, 1 H, NCH), 3.60 (d, J = 12.9 Hz, 1 H, NCHH), 3.08 (dd, J = 13.0, 7.0 Hz, 1 H, NCH).
**Synthesis ... via a cyclic N-acyliminium ion**

\[ J = 12.9, 3.1 \text{ Hz, } 1 \text{ H, } NCH} \]

11-Iodo-4-oxa-6-azatricyclo[6.3.1.0\text{2}3]dodecan-5-one (32): yellowish solid; mp 202 °C; IR (KBr) ν 2931, 1732, 1439, 1283; \(^1\)H NMR (400 MHz) δ 5.04 (s, 1 H, H-11), 4.40 (t, \( J = 9.3 \) Hz, 1 H, OCH\(_2\)), 4.22 (dd, \( J = 9.2, 7.2 \) Hz, 1 H, OCH\(_2\)), 3.97 (ddd, \( J = 9.2, 7.2, 3.6 \) Hz, 1 H, NCH\(_2\)), 3.80 (d, \( J = 13.2 \) Hz, 1 H, NCH\(_3\)), 3.19 (ddd, \( J = 13.2, 4.1, 2.0 \) Hz, 1 H, NCH\(_2\)), 2.64 (br d, \( J = 13.7 \) Hz, 1 H), 2.16–2.05 (m, 2 H), 2.04–1.94 (m, 3 H), 1.70 (t, \( J = 12.0 \) Hz, 2 H); \(^1\)C NMR (100 MHz) δ 156.3 (C=O), 64.1 (OCH\(_2\)), 57.1 (NCH), 47.0 (NCH\(_2\)), 38.5 (C-11), 31.7 (CH\(_2\)), 30.8 (C-1), 29.2, 26.8 (2 × CH\(_3\)), 26.3 (C-8); HRMS (FAB) calculated for C\(_{10}\)H\(_{14}\)NO\(_2\)I[M+H]\(^+\) 308.0147, found 308.0157.

10-Iodo-4-oxa-6-azatricyclo[6.3.1.0\text{2}3]dodecan-5-one (33): white solid; mp 152 °C; IR (KBr) ν 2917, 1741, 1478, 1426; \(^1\)H NMR (400 MHz) δ 4.58 (sept, \( J = 5.5 \) Hz, 1 H, H-10), 4.37 (t, \( J = 8.9 \) Hz, 1 H, OCH\(_2\)), 4.13 (t, \( J = 8.6 \) Hz, 1 H, OCH\(_2\)), 3.97 (dt, \( J = 8.8, 2.9 \) Hz, 1 H, NCH\(_2\)), 3.76 (d, \( J = 13.2 \) Hz, 1 H, NCH\(_3\)), 3.11 (ddd, \( J = 15.9, 4.4, 2.6 \) Hz, 1 H, NCH\(_2\)), 2.61 (br d, \( J = 11.0 \) Hz, 1 H), 2.51 (br d, \( J = 13.3 \) Hz, 1 H), 2.39–2.27 (m, 2 H), 2.00–1.95 (m, 1 H), 1.88 (s, 1 H, H-8), 1.82–1.78 (m, 2 H); \(^1\)C NMR (100 MHz) δ 156.2 (C=O), 64.8 (OCH\(_2\)), 56.9 (NCH), 45.8, 45.2, 39.4 (3 × CH\(_2\)), 32.6 (C-10), 31.4 (CH\(_3\)), 30.4 (C-1), 23.9 (C-8); HRMS calculated for C\(_{10}\)H\(_{14}\)NO\(_2\)I[M+H]\(^+\) 307.0069, found 307.0067.

4-Oxa-6-azatricyclo[6.3.1.0\text{2}3]dodec-10-en-5-one (27). A solution of the 11-iodo-compound 32 (343 mg, 1.1 mmol) and DBU (420 µL, 2.8 mmol) in toluene (4 mL) was refluxed for 2 h. The reaction mixture cooled to rt and aqueous 0.1 N HCl was added. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (4 x). The organic layers were washed with aqueous saturated NaHCO\(_3\), dried (MgSO\(_4\)) and concentrated to give the product 27 (195 mg, 1.1 mmol, 100%): mp 72 °C; IR (film) ν 2916, 1746, 1426, 1260, 1218; \(^1\)H NMR (400 MHz) (assignment with aid of COSY) δ 5.94 (dt, \( J = 9.9, 3.4 \) Hz, 1 H, H-10), 5.75–5.70 (m, 1 H, H-11), 4.24 (t, \( J = 8.7 \) Hz, 1 H, OCH\(_2\)), 3.98 (ddd, \( J = 8.8, 4.2 \) Hz, 1 H, OCH\(_2\)), 3.84–3.80 (m, 2 H, NCH + NCH\(_2\)), 3.12 (ddd, \( J = 13.4, 3.6, 1.0 \) Hz, 1 H, NCH\(_2\)), 2.36 (m, 1 H, H-9), 2.27 (br s, 1 H, H-1), 2.11 (d, \( J = 9.1 \) Hz, 1 H, H-9), 1.99 (br s, 1 H, H-8), 1.90–1.83 (m, 1 H, CHCHHCH), 1.71 (d, \( J = 12.8 \) Hz, 1 H, CHCHHCH); \(^1\)C NMR (100 MHz) δ 157.8 (C=O), 132.7 (=CH), 122.6 (=CH\(_3\)), 64.7 (OCH\(_2\)), 57.0 (NCH), 48.7 (NCH\(_2\)), 31.5 (CH\(_2\)), 31.3 (C-1), 28.2 (CH\(_3\)), 26.1 (C-8); HRMS (FAB) calculated for C\(_{10}\)H\(_{14}\)NO\(_2\)I[M+H]\(^+\) 180.1025, found 180.1025.

3-Cyclohex-3-enylmethy1-3//-oxazol-2-one (29). A solution of the oxazolidine-2,4-dione 19 (1.2 g, 6.3 mmol) in methanol (70 mL) was cooled to 0 °C and NaBH\(_4\) (2 equiv) was added portionwise (480 mg, 12.6 mmol). After 2 h the reaction was quenched with acetone (20 mL). The volatiles were removed in vacuo and the residue taken up in CH\(_2\)Cl\(_2\). The solids were filtered off over a path of Celite\. The resulting clear solution was washed with water and the aqueous layer was extracted with
Chapter 4

CH₂Cl₂ (2 x). The combined organic solutions were dried (MgSO₄) and concentrated to afford 3-Cyclohex-3-enylmethyl-4-hydroxyoxazolidine-2-one as a colourless oil (1.20 g, 6.3 mmol, 100%) (1:1 mixture of diastereomers): IR (film) ν 3348, 2912, 1718, 1437, 1245; ¹H NMR (400 MHz) δ 5.65–5.57 (m, 2 H, CH=CH), 5.40 (br s, 1 H, OH), 5.25 (d, J = 4.2 Hz, 1 H, CHO₂H), 4.33 (dt, J = 6.2, 1.6 Hz, 1 H, OCH₂H), 4.11 (dd, J = 10.0, 1.8 Hz, 1 H, OCH₂H), 3.24–3.12 (m, 2 H, NCH₂), 2.09–1.92 (m, 4 H), 1.73–1.69 (m, 2 H), 1.30–1.17 (m, 1 H); ¹³C NMR (100 MHz) δ 158.5 & 158.4 (C=O), 127.0 & 126.9 (CH), 125.3 & 125.2 (CH), 70.7 (OCH₂), 46.2 & 45.8 (NCH₂), 32.0 & 31.9 (CH), 26.2 & 25.8 (CH₂), 24.4 & 24.2 (CH₂); HRMS calculated for C₁₀H₁₃NO 197.1052, found 197.1051.

A solution of this hydroxy-oxazolidone (109 mg, 0.55 mmol) in CH₂Cl₂ (10 mL) was treated with thionylchloride (85 µL, 1.1 mmol) and refluxed for 1 h. The reaction mixture was cooled to rt and concentrated to afford the oxazolone 29 (98 mg, 0.55 mmol, 100%) as a colourless oil: IR (film) ν 3023, 2911, 1749, 1409; ¹H NMR (400 MHz) δ 6.75 (s, 1 H, CH=CHO), 6.50 (s, 1 H, =CH=CHO), 5.61–5.53 (m, 2 H, CH=CH), 3.45–3.30 (m, 2 H, NCH₂), 2.09–1.89 (m, 4 H), 1.71–1.59 (m, 2 H), 1.30–1.18 (m, 1 H); ¹³C NMR (100 MHz) δ 156.5 (C=O), 127.3, 126.9, 124.8, 116.2 (4 x =CH), 49.1 (NCH₂), 33.3 (CH), 28.7, 25.6, 24.1 (3 x CH₂); HRMS calculated for C₁₀H₁₃NO 179.0946, found 179.0948.

(1R,2S,8R)-11-Methyl-4-oxa-6-azatricyclo[6.3.1.0²⁶]dodec-10-en-5-one (34). A solution of the ethoxy-oxazolidin-2-one 23 (6.86 g, 28.7 mmol) in HCOOH (50 mL) was stirred overnight at rt. The reaction mixture was concentrated in vacuo. The resulting residue was subjected to flash chromatography (EtOAc/ PE 1:2) to yield the pure bicyclic product (3.99 g, 20.7 mmol, 72%) as colourless crystals after recrystallisation from ether; mp 126–128 °C; [α]D –84.9 (c 1.4, CHCl₃); IR (film) ν 2889, 1745, 1431; ¹H NMR (400 MHz) δ 5.57 (s, 1 H, =CH) 4.18 (t, J = 8.7 Hz, 1 H, OCH₂H), 4.09 (dd, J = 8.9, 4.5 Hz, 1 H, OCH₂H), 3.82–3.78 (m, 1 H, NCH), 3.76 (d, J = 13.1 Hz, 1 H, NCH₂H), 3.06 (dd, J = 13.1, 2.6 Hz, 1 H, NCH₂H), 2.32–2.26 (m, 1 H, H–9), 2.15–2.14 (d, J = 2.9 Hz, 1 H, H–1), 2.06 (d, J = 9.3 Hz, 1 H, H–9), 1.92 (br d, J = 3.2 Hz, 1 H, H–8), 1.79–1.67 (m, 1 H, CHCH₂HCH), 1.76 (s, 3 H, CH₃), 1.72 (dt, J = 15.4, 2.5 Hz, 1 H, CHCH₂HCH); ¹³C NMR (100 MHz) δ 157.9 (C=O), 130.3 (C=CH), 126.2 (C=CH), 65.2 (OCH₂), 57.7 (NCH), 48.8 (NCH₂), 36.2 (C–1), 31.3 (CH₂), 29.4 (CH₂), 25.2 (CH₂), 25.1 (C–5); HRMS calculated for C₁₁H₁₅NO₂ 193.1103, found 193.1110. In a similar experiment racemic material was obtained: mp 111–112 °C.

Crystallographic data of 34.

Monoclinic, P2₁/a, a = 10.4102(5), b = 7.8193(15), c = 12.7261(7)Å, β = 107.573(5)°, V = 987.6(2) Å³, Z = 4, D₀ = 1.30 g cm⁻³, λ(CuKα) = 1.5418Å, μ(CuKα) = 7.2 cm⁻¹, F(000) = 416. Final R = 0.070 for 1962 observed reflections.
Cyclisation of 24 with $\text{BF}_3\cdot\text{OEt}_2$. A solution of 24 (4.35 g, 10.8 mmol) in CH$_2$Cl$_2$ (100 mL) was treated with boron trifluoride diethyl etherate (5.3 mL, 43 mmol) at -35 °C. After stirring for 30 min, aqueous saturated NaHCO$_3$ was added. The mixture was allowed to warm to rt, the layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (4 ×). The combined organic layers were dried (MgSO$_4$) and concentrated. Purification using flash chromatography (EtOAc/PE 1:1), afforded two fractions. The first fraction consisted of the minor axial product (209 mg, 1.1 mmol, 10%) as a white solid: ($1R,2R,8S$)-11-Methylene-4-oxa-6-azatricyclo[6.3.1.0$^{2,6}$]dodecane-5-one (36): mp 59–63 °C; [α]$_D$$^+$48.5 (c 1.0, CHCl$_3$); IR (KBr) v 2925, 1747, 1418; $^1$H NMR (400 MHz) (assignment with aid of COSY and HETCOR) δ 4.67 (s, 1 H, CH=CH), 4.66 (s, 1 H, =CHH), 4.50 (t, J = 8.0 Hz, 1 H, OCHH), 4.06 (dd, J = 13.7, 10.0 Hz, 1 H, NCHH) 3.89 (t, J = 8.0 Hz, 1 H, OCHH), 3.86–3.81 (m, 1 H, H–2), 2.95 (d, J = 13.6 Hz, 1 H, NCHH), 2.44 (dt, J = 13.6, 6.0 Hz, 1 H, H–10), 2.37 (s, 1 H, H–1), 2.30 (d, J = 8.9 Hz, 1 H, H–8), 2.22 (d, J = 13.4 Hz, 1 H, H–10), 1.75 (d, J = 13.2 Hz, 1 H, CHCHHCH), 1.68–1.57 (m, 2 H, H–9), 1.47 (d, J = 13.2 Hz, 1 H, CHCHHCH); $^{13}$C NMR (100 MHz) δ 157.0 (C=O), 149.4 (C=CH$_2$), 108.5 (C=CH$_2$), 69.1 (CH$_2$O), 56.1 (NCH), 46.2 (NCH$_2$), 40.3 (C–1), 32.5, 26.9, 26.4 (3 x CH$_2$), 24.5 (C–8); HRMS calculated for C$_{19}$H$_{15}$NO$_2$ 193.1098, found 193.1100.

The second fraction consisted of the major equatorial product (1.51 g, 7.8 mmol, 72%) as white crystals: (1$R$,2$S$,8$S$)-11-Methylene-4-oxa-6-azatricyclo[6.3.1.0$^{2,6}$]dodecane-5-one (35): mp: 66–68 °C; [α]$_D$$^+$84.0 (c 1.9, CHCl$_3$); IR (film) v 2924, 2860, 1738; $^1$H NMR (400 MHz) (assignment with
aid of COSY and HETCOR) δ 4.90 (s, 1 H, =CHH), 4.70 (s, 1 H, =CHH), 4.31 (t, J = 7.6 Hz, 1 H, OCH₃H), 4.00 (t, J = 7.7 Hz, 1 H, OCH₃H), 3.95 (dt, J = 7.8, 3.2 Hz, 1 H, H-2), 3.80 (d, J = 13.0 Hz, 1 H, NCH₃H), 3.22-3.16 (m, 1 H, NCH₃H), 2.34 (m, 1 H, H-1), 2.26 (m, 2 H, H-10), 1.93 (m, 1 H, H-8), 1.90-1.81 (m, 3 H, CHCH₂CH and H-9), 1.73-1.62 (m, 1 H, H-9); ¹³C NMR (100 MHz) δ 156.6 (C=O), 145.8 (C=CH₂), 112.5 (C=CH₂), 65.3 (CH₂O), 56.7 (NCH), 46.3 (NCH₂), 40.0 (C-1), 33.0 (CHCH₂CH), 31.3 (C-9), 30.3 (C-10), 26.3 (C-8); HRMS calculated for C₁₁H₁₅NO₂ 193.1098 found 193.1101. In a similar experiment racemic products were obtained. The minor axial product as a colourless oil and the major equatorial product as a white solid: mp 100–102 °C.

Crystallographic data of 35.
Orthorhombic, P₂₁₂₁, a = 6.2387(6), b = 10.1721(15), c = 15.276(2) Å, V = 969.4(2) Å³, Z = 4, Dₐ = 1.32 gcm⁻³, λ(MoKα) = 0.71073 Å, μ(MoKα) = 0.9 cm⁻¹, F(000) = 416, Final R = 0.058.

| Table 4.5 Bond distances of the non-hydrogen atom(Å) of 35 (standard deviations) |
|---------------------------------|-----------------|-----------------|-----------------|
| C(1)-C(2)                       | 1.543(3)        | C(4)-O(1)       | 1.365(3)        | C(6)-C(11)      | 1.530(4)        |
| C(1)-C(11)                      | 1.539(4)        | C(4)-O(2)       | 1.218(3)        | C(7)-C(8)       | 1.534(4)        |
| C(1)-C(9)                       | 1.512(3)        | C(4)-N(1)       | 1.331(3)        | C(8)-C(9)       | 1.518(4)        |
| C(2)-C(3)                       | 1.530(4)        | C(5)-N(1)       | 1.462(3)        | C(9)-C(10)      | 1.328(3)        |
| C(2)-N(1)                       | 1.456(3)        | C(5)-C(6)       | 1.531(3)        |                |                |
| C(3)-O(1)                       | 1.450(3)        | C(6)-C(7)       | 1.532(3)        |                |                |

| Table 4.6 Bond angles of the non-hydrogen atoms (°) of 35 (standard deviations) |
|---------------------------------|-----------------|-----------------|-----------------|
| C(1)-C(2)-C(3)                  | 117.4(2)        | C(2)-C(1)-C(11) | 106.8(2)        | N(1)-C(5)-C(6)  | 111.3(2)        |
| C(1)-C(2)-N(1)                  | 110.4(2)        | C(2)-C(1)-C(9)  | 114.0(2)        | C(5)-C(6)-C(7)  | 113.8(2)        |
| C(1)-C(11)-C(6)                 | 109.1(2)        | C(3)-O(1)-C(4)  | 109.6(2)        | C(5)-C(6)-C(11)| 110.1(2)        |
| C(1)-C(9)-C(8)                  | 117.1(2)        | C(3)-C(2)-N(1)  | 101.2(2)        | C(6)-C(7)-C(8)  | 113.4(2)        |
| C(1)-C(9)-C(10)                 | 121.4(2)        | O(1)-C(4)-O(2)  | 121.5(2)        | C(7)-C(8)-C(9)  | 112.8(2)        |
| C(2)-C(3)-O(1)                  | 105.7(2)        | O(1)-C(4)-N(1)  | 109.9(2)        | C(7)-C(6)-C(11)| 108.9(2)        |
| C(2)-N(1)-C(4)                  | 113.4(2)        | C(4)-N(1)-C(5)  | 125.4(2)        | C(8)-C(9)-C(10)| 121.5(2)        |
| C(2)-N(1)-C(5)                  | 120.2(2)        | N(1)-C(4)-O(2)  | 128.6(2)        | C(9)-C(1)-C(11)| 110.0(2)        |

(1R,2S,5R)-(8-Methyl-3-azabicyclo[3.3.1]non-7-en-2-yl)methanol (38). According to general procedure C, the oxazolidinone 34 (1.70 g, 8.8 mmol) was converted into the amino-alcohol 38 (1.34 g, 8.0 mmol, 91%): Yellowish oil; [α]D = -23.2 (c 1.9, CHCl₃); IR (film) v 3276, 2916; ¹H NMR (400 MHz, CD₃OD) δ 5.47 (s, 1 H, =CH), 3.44 (dd, J = 10.6, 4.7 Hz, 1 H, OCHH), 3.29 (dd, J = 10.4, 8.6 Hz, 1 H, OCHH), 2.82–2.78 (m, 2 H, NCH₃), 2.72 (s, 1 H, NCH), 2.12–2.07 (m, 1 H), 1.86 (s, 1 H, H–1), 90
Synthesis... via a cyclic N-acyliminium ion

1.67-1.44 (m, 4 H), 1.58 (s, 3 H, CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 133.4 (C=CH), 124.9 (C=CH), 65.0 (OCH₂), 61.8 (NCH), 54.0 (NCH₂), 36.8 (C-1), 31.7, 31.6 (2 x CH₂), 26.6 (C-5), 24.5 (CH₂); HRMS calculated for C₁₀H₁₇NO 167.1310, found 167.1301.

(1S,2S,5S,11R)-11-methyl-4-oxa-6-azatricyclo[6.3.1.0²⁶]dodecan-5-one (39). A Parr apparatus was charged with a solution of 34 (163 mg, 0.84 mmol) in ethanol (5 mL) and Pd/C (25 mg) was added. The reaction mixture was degassed and placed under a H₂ atmosphere (40-50 psi) with shaking for 16 h. After filtration over Celite® the reaction mixture was concentrated in vacuo to give the product 39 as colourless crystals (168 mg, 0.861 mmol, 100%); mp 76-86 °C; [α]D +33.7 (c 0.5, CHCl₃); IR (film) ν 2922, 1751, 1461, 1433, 1245; ¹H NMR (400 MHz) δ 4.46 (dd, J = 9.1, 4.6 Hz, 1 H, OCH₂), 4.25 (t, J = 9.2 Hz, 1 H, OCHF), 3.96 (dt, J = 9.3, 3.8 Hz, 1 H, NCH), 3.74 (d, J = 13.2 Hz, 1 H, NCH₂), 3.16 (dd, J = 13.2, 4.1, 1.9 Hz, 1 H, NCH₂), 1.94-1.74 (m, 3 H), 1.78-1.74 (m, 2 H), 1.73-1.69 (m, 1 H), 1.68-1.60 (m, 1 H), 1.56-1.42 (m, 2 H), 1.14 (d, J = 7.4 Hz, 3 H, CH₃); ¹³C NMR (100 MHz) δ 157.0 (C=O), 65.0 (OCH₂), 59.0 (NCH), 46.8 (NCH₂), 35.7 (CH), 35.2, 31.3, 28.7 (3 x CH₂), 26.5 (C-8), 21.6 (CH₃); HRMS calculated for C₁₇H₉NO 195.1260, found 195.1262.

(1S,2S,5S,8R)-(8-methyl-3-azabicyclo[3.3.1]non-2-yl)methanol (40). According to general procedure C, the oxazolidinone 39 (82.2 mg, 0.42 mmol) was converted into the amino-alcohol 40 (59.0 mg, 0.35 mmol, 83%); [α]D +13.3 (c 0.8, CHCl₃); IR (film) ν 3330, 2912, 1457, 1037; ¹H NMR (400 MHz) δ 3.79 (t, J = 10.7 Hz, 1 H, OCHH), 3.63 (dd, J = 10.8, 3.0 Hz, 1 H, OCHH), 3.24 (br s, 2 H, OH & NH), 3.14-2.99 (m, 3 H, NCH+NCH₂), 2.04-1.69 (m, 7 H), 1.61-1.54 (m, 2 H), 0.98 (d, J = 7.0 Hz, 3 H, CH₃); ¹³C NMR (100 MHz) δ 66.3 (OCH₂), 64.8 (NCH), 52.5 (NCH₂), 38.0 (CH₂), 37.1 (CH), 37.0 (CH), 31.6 (CH₂), 31.4 (CH₂), 28.3 (CH), 22.0 (CH₂); HRMS calculated for C₁₉H₁₉NO 169.1466, found 169.1460.

(1R,2S,5R)-4-Hydroxymethyl-6-methyl-3-azabicyclo[3.3.1]non-6-ene-3-carboxylic acid tert-butyl ester (41). According to general procedure D, the amine 38 (1.8 g, 10.8 mmol) was treated with Boc₂O. The product was purified by flash chromatography (EtOAc/PE 1:3) to yield the pure N-Boc protected compound 41 (2.5 g, 9.4 mmol, 87%) as a colourless oil: [α]D -39.4 (c 3.3, CHCl₃); IR (film) ν 3500, 2913, 1681, 1430, 1161; ¹H NMR (400 MHz) (rotamers) (assignment with aid of COSY) δ 5.49 (d, J = 1.3 Hz, 1 H, =CH), 4.25 (t, J = 11.3 Hz, 1 H, OCHH), 3.99 (dd, J = 13.5, 3.1 Hz, 1 H, NCHH), 3.58 (dd, J = 11.5, 4.5 Hz, 1 H, OCHH), 3.50 (br d, J = 10.7 Hz, 1 H, NCH), 3.03 (dd, J = 10.4, 3.1 Hz, 1 H, NCHH), 2.23 (dt, J = 18.4, 3.0 Hz, 1 H, H-8), 2.13 (s, 1 H, H-5), 2.06 (d, J = 19.1 Hz, 1 H, H-8), 1.94 (t, J = 3.1 Hz, 1 H, H-1), 1.74 & 1.73 (s, 3 H, CH₃), 1.70-1.66 (m, 2 H, CHCH₂CH), 1.44 (s, 9 H, C(CH₃)₃); ¹³C NMR (50 MHz) δ 155.4 (C=O), 133.2 (C=CH), 124.2...
(1R,2S,5R)-4-Formyl-6-methyl-3-azabicyclo[3.3.1]non-6-ene-3-carboxylic acid tert-butyl ester (42). According to general procedure E, the alcohol 41 (1.90 g, 7.1 mmol) was submitted to the Swern oxidation to yield the aldehyde 42 (1.85 g, 7.0 mmol, 98%) as a slightly yellowish oil: $\alpha_d$ -111.4 (c 10.4, CHCl$_3$); IR (film) v 2916, 1730, 1682, 1410, 1367, 1162; $^1$H NMR (400 MHz) (rotamers) $\delta$ 9.51 (d, $J = 2.1$ Hz, 1 H, CHO), 5.48 (d, $J = 1.4$ Hz, 1 H, =CH), 4.30–3.80 (br s, 1 H), 3.51 (br s, 1 H), 3.04–3.00 (m, 1 H), 2.63 (s, 1 H), 2.33 (br d, $J = 20.0$ Hz, 1 H), 2.10 (br d, $J = 17.7$ Hz, 1 H), 1.99 (s, 1 H), 1.81–1.77 (m, 1 H), 1.70 (s, 3 H, CH$_3$), 1.66 (dt, $J = 12.3$, 2.9 Hz, 1 H), 1.41 & 1.39 (s, 9 H, C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz) (rotamers) $\delta$ 195.6 (HC=O), 145.0 (NC=O), 68.3 (NCH), 52.8 (NCH$_2$), 45.7, 31.2 (2 x CH$_2$), 28.0 & 27.8 (C(CH$_3$)$_3$), 24.8, 8.5 (C-1+CH$_3$) (4 carbon signals not observed); $^1$H NMR (400 MHz, CD$_6$D$_6$, 340K) $\delta$ 9.59 (s, 1 H, CHO), 5.33 (s, 1 H, =CH), 3.91 (d, $J = 13.1$ Hz, 1 H, NCHH), 3.21 (s, 1 H, NCH), 2.71 (dd, $J = 13.2$, 3.2 Hz, 1 H, NCHH), 2.51 (s, 1 H, H–5), 2.05 (d, $J = 18.5$ Hz, 1 H, H–8), 1.95 (d, $J = 18.5$ Hz, 1 H, H–8), 1.73 (s, 3 H, CH$_3$), 1.53–1.37 (m, 3 H), 1.33 (s, 9 H, C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CD$_6$D$_6$, 340 K) $\delta$ 194.9 (HC=O), 134.4 (C=CH), 125.8 (C=CH), 81.5 (C(CH$_3$)$_3$), 70.0 (NCH), 53.9 (NCH$_2$), 36.3 (C–5), 32.6, 32.5 (2 x CH$_2$), 29.2 (C(CH$_3$)$_3$), 28.1, 25.3 (C–1 + CH$_3$), (NC=O not observed); HRMS calculated for C$_{15}$H$_{23}$N$_0$ 267.1834, found 267.1841.

(1R,2S,5R)-8-Methyl-3-azabicyclo[3.3.1]non-7-ene-2,3-dicarboxylic acid 2-methyl ester 3-tert-butyl ester (43). According to general procedure F, the aldehyde 42 (1.07 g, 4.0 mmol) was oxidised to the corresponding acid using NaClO$_2$. After work up the crude acid was taken up in ether and treated with CH$_2$N$_2$ until the yellow colour persisted. The solution was concentrated and the residue was applied to flash chromatography (EtOAc/PE 1:4) to afford the methyl ester 43 (1.0 g, 3.4 mmol, 85%) as a colourless oil: $\alpha_d$ -103.8 (c 3.4, CHCl$_3$); IR (film) v 2928, 1748, 1697, 1397, 1165; $^1$H NMR (400 MHz) (rotamers) $\delta$ 5.48 (s, 1 H, =CH), 4.18 (br d, $J = 5.4$ Hz, 1 H, NCH), 3.69 (s, 3 H, OCH$_3$), 3.29 (br s, 1 H, NCHH), 2.63 (s, 1 H, H–1), 2.21–2.18 (m, 2 H, H–5 + H–6), 1.90 (d, $J = 12.2$ Hz, 1 H, H–6), 1.64 (s, 3 H, CH$_3$), 1.61–1.51 (m, 1 H, CHCHHCH), 1.47–1.41 (m, 1 H, CHCH/HCH), 1.40 (s, 9 H, C(CH$_3$)$_3$), (H–4 not observed); $^1$H NMR (400 MHz, CD$_6$D$_6$, 340K) (assignment with aid of COSY and HETCOR) $\delta$ 5.32 (s, 1 H, =CH), 4.19 (d, $J = 6.9$ Hz, 1 H, NCH), 3.75 (dd, $J = 13.2$, 8.0 Hz, 1 H, NCHH), 3.45 (s, 3 H, OCH$_3$), 3.34 (dd, $J = 13.5$, 4.4 Hz, 1 H, NCHH), 2.47 (s, 1 H, H–1), 1.93 (d, $J = 18.1$ Hz, 1 H, H–6), 1.83 (br s, 1 H, H–5), 1.73–1.65 (m, 1 H, H–6), 1.68 (s, 3 H, CH$_3$), 1.47–1.44 (m, 1 H, CHCH/HCH), 1.40 (s, 9 H, C(CH$_3$)$_3$), 1.37–1.26 (m, 1 H, CHCH/HCH); $^{13}$C NMR (100 MHz, CD$_6$D$_6$, 340 K) $\delta$ 171.9 (C=O), 155.0 (NC=O), 135.1. (C=CH), 124.7 (C=CH), 80.2 (C(CH$_3$)$_3$), 61.2 (NCH), 51.2 (OCH$_3$), 48.5 (NCH$_2$), 36.2 (C–1), 33.2 (C–6), 29.8 (CHCH$_2$CH), 29.0
(C(CH₃)₃), 26.7 (C-5), 24.4 (CH₃); HRMS calculated for C₁₆H₂₅NO₄ 295.1783, found 295.1774.

(1R,2S,5R)-8-Methyl-3-azabicyclo[3.3.1]non-7-ene-2-carboxylic acid methyl ester HCl salt (44). The N-Boc protected amino ester 43 (139 mg, 0.47 mmol) was dissolved in methanolic 3 N HCl (5 mL). After 1 h the volatiles were removed to obtain the HCl salt of the amino ester 44 (109 mg, 0.47 mmol, 100%) as a colourless oil: [α]D +12.2 (c 5.4, CH₃OH); IR (film) ν 3387, 1743, 1272; ¹H NMR (400 MHz) δ 10.94 (br s, 1 H, NH), 7.86 (br s, 1 H, NH), 5.82 (s, 1 H, =CH), 3.97 (br s, 1 H, NCH), 3.81 (s, 3 H, OCH₃), 3.73 (d, J = 11.1 Hz, 1 H, NCH₃), 3.22 (d, J = 10.9 Hz, 1 H, NCHH), 2.79 (s, 1 H, H-1), 2.54 (d, J = 18.7 Hz, 1 H, CHH), 2.37 (d, J = 19.0 Hz, 1 H, CHH), 2.21 (s, 1 H, H-5), 1.91–1.81 (m, 2 H, CH₂), 1.56 (s, 3 H, CH₃); ¹³C NMR (100 MHz) δ 168.1 (C=O), 129.1 (C=CH), 128.9 (C=CH), 58.0 (NCH), 52.8 (OCH₃), 50.3 (NCH₂), 35.1 (C-1), 30.2, 29.4 (2 × CH₂), 23.8, 23.0 (CH + CH₃); HRMS calculated for C₁₆H₂₅NO₄ 295.1774, found 295.1774.

(2S,3R,4R,5S,7S)-4-Hydroxy-4-methyl-1-azatricyclo[3.3.1.1₃,₂]decane-2-carboxylic acid methyl ester HCl salt (45b). Paraformaldehyde (220 mg, 5.6 mmol) was dissolved in boiling HCOOH (10 mL). After the solution had cooled to rt it was added to the N-Boc-protected bicyclic amino ester 43 (548 mg, 1.86 mmol). Stirring was continued overnight. The volatiles were removed in vacuo. The residue consisted of the formic acid salt of the adamantane 45a (582 mg, 1.91 mmol, 103%) as a colourless oil. The ¹H NMR spectrum showed the adamantane as the formic acid salt together with some minor impurities such as formic acid and formaldehyde residues: [α]D +24.7 (c 4.7, CHCl₃); ¹H NMR (400 MHz) (assignment with aid of COSY, HETCOR and NOE) δ 8.09 (s, 1 H, C(OH)), 4.30 (d, J = 12.5 Hz, 1 H, NC^HH), 4.20 (s, 1 H, NCH), 3.75 (s, 3 H, OCH₃), 3.51 (d, J = 11.8 Hz, 1 H, NC^HH), 3.45 (d, J = 12.6 Hz, 1 H, NC^HH'), 3.28 (d, J = 12.6 Hz, 1 H, NC^HH), 2.60 (s, 1 H, H-3), 2.14 (s, 1 H, H-5), 2.08–2.03 (m, 2 H, CH₂), 1.99 (s, 2 H, CH₂), 1.90 (s, 1 H, H-7), 1.44 (s, 3 H, CH₃); ¹³C NMR (100 MHz) δ 168.1 (C=O), 160.1 (HC=O), 70.1 (C-4), 62.9 (NCH), 57.8 (NCH₂), 52.7 (OCH₃), 49.1 (NCH), 39.9 (C-3), 36.3 (C-5), 31.9 (CH₃), 30.9 (CH₂), 26.1 (CH₃), 24.6 (C-7); A portion of the crude formic acid salt of adamantane 45a (111 mg, 19% of the crude) was dissolved in methanol and applied on a DOWEX column (2 g). After washing the column with methanol, it was eluted with dry methanolic 6 N HCl. The solvent was removed in vacuo to afford the pure HCl salt of the adamantane 45b (64 mg, 0.247 mmol, 70%) as a amorphous solid: mp 72 °C (dec.); [α]D +35.3 (c 0.94, CH₃OH); IR (film) ν 3457, 3194–2300, 1749, 1606, 1388, 1304, 1125; ¹H NMR (400 MHz, CD₃OD) δ 4.36 (s, 1 H, NCH), 4.28 (d, J = 12.2 Hz, 1 H, NC^HH), 3.80 (s, 3 H, OCH₃), 3.58 (d, J = 12.0 Hz, 1 H, NC^HH), 3.49 (d, J = 12.0 Hz, 1 H, NC^HH), 3.47 (d, J = 11.6 Hz, 1 H, NC^HH), 2.57 (s, 1 H, H-3), 2.16 (s, 1 H, H-5), 2.14–2.09 (m, 2 H, CH₂), 2.06 (s, 2 H, CH₂), 1.87 (s, 1 H, H-7), 1.42 (s, 3 H, CH₃); ¹³C NMR (400 MHz, CD₃OD) δ 170.0 (C=O), 72.6 (C-4), 64.4 (NCH),
Chapter 4

59.1 (NCH$_3$), 53.2 (OCH$_3$), 50.6 (NCH$_3$), 41.6 (C–3), 37.8 (C–5), 32.2 (CH$_2$), 31.3 (CH$_2$), 26.2 (CH$_3$), 25.8 (C–7). HRMS (FAB) calculated for C$_{12}$H$_{20}$NO$_3$ [M+H]$^+$ 226.1444, found 226.1453.

4.10 References and notes


7. (a) Yokomatsu, T.; Yuasa, Y.; Shibuya, S. Heterocycles 1992, 33, 1051. (b) See also [4a].


Synthesis ... via a cyclic N-acyliminium ion


