ALDOLISATION AND CARBOXYLATION REACTIONS FROM 
α-SILYL-β-LACTAMS. A COMBINED THEORETICAL AND 
EXPERIMENTAL STUDY

Sabrina Parat,a Béatrice Pelotier,a Lycia Fournier,a Michel Rajzmann,a 
Philip J. Kocienski,b and Jean-Marc Ponsa,*

a) Institut des Sciences Moléculaires de Marseille (ISM2), Aix-Marseille 
Université, UMR-CNRS 6263, Campus de St-Jérôme, service 532, F-13397 
Marseille Cedex 20, France. E-mail: jean-marc.pons@univ-cezanne.fr 
b) Department of Chemistry, University of Leeds, Leeds LS2 9JT, United 
Kingdom.

Abstract - Treatment of α-silyl-β-lactam 3 with TBAF in the presence of an 
aldehyde or carbon dioxide leads, with total trans stereoselectivity, to the 
corresponding aldol or carboxy adducts 5-6. Semiempirical calculations account 
for this result.

INTRODUCTION
The Staudinger [2+2] cycloaddition between an imine and a ketene has been known since the beginning of the century1 and is still widely used to prepare β-lactams.2 Examples of the use of silylketenes3 in β-
lactam synthesis are rather scarce and involve an electron poor imine.4,5 A typical example is due to 
Zaitseva and co-workers who prepared a trans silylated β-lactam from trimethylsilylketene (1) and 
phenylsulfonylchloraldimine (Scheme 1).5 In all these examples, no Lewis acid is involved.

![Scheme 1]

We have already reported on the preparation of silylated β-lactams 3 from trimethylsilylketene (1) 
through Lewis acid-promoted [2+2] cycloaddition reactions, and established, after both experimental and
theoretical studies, that the reaction path involves a classical Staudinger mechanism: attack by the lone pair of the nitrogen atom of the imine on the central carbon atom of the ketene and subsequent conrotatory electrocyclization of the resultant zwitterionic intermediate A to give $\beta$-lactam 3 as a mixture of four diastereomers (cis/cis/trans/trans : 60:15:15:10) (Scheme 2). This mechanism proved to be different to the one postulated for the formation of $\beta$-lactones from silylketenes which involves a nucleophilic attack of the silylketene on the aldehyde, activated by the Lewis acid.

The trimethylsilyl group of $\alpha$-silyl-$\beta$-lactams can be removed by various fluoride anion vectors leading to the corresponding desilylated $\beta$-lactams, or even to $\alpha$-deuterated $\beta$-lactams. Another more interesting reaction is the Peterson olefination which can be observed when these silylated $\beta$-lactams react with aldehydes or ketones in the presence of a base, typically LDA (Scheme 3).

We would now like to report on a different, although related, aspect of the reactivity of $\alpha$-silylated $\beta$-lactams, the direct use of the trimethylsilyl group in base-free aldolization reactions, a reactivity which is known in $\beta$-lactone chemistry. A semiempirical study is also provided to try to account for the stereoselectivity of the aldolization reaction.

RESULTS AND DISCUSSION
Experimental study
Desilylation: We started our study with the simple desilylation of $\beta$-lactam 3, which was obtained as previously described from trimethylsilyketene (1) and imine 2 (Scheme 2). The reaction, performed with TBAF$\cdot$H$_2$O (to provide a proton source), led to the corresponding desilylated $\beta$-lactam 4 in excellent yield as a 7:3 mixture of two diastereomers (Scheme 4). This ratio is consistent with the 60:15:15:10 ratio...
of the starting lactam 3 and provides interesting information on the stereoselectivity induced at the C4 carbon atom by the C1’ carbon of the imine during the cycloaddition step.

\[
\begin{array}{c}
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\end{array}
\xrightarrow{TBAF-3\text{H}_2\text{O}}
\begin{array}{c}
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\end{array}
\]

Scheme 4

**Aldolisation** : We then changed TBAF•3H₂O for a THF solution of TBAF, which was dried over molecular sieves to prevent protonation, and performed the reaction in the presence of an aldehyde (acetaldehyde and benzaldehyde) (Scheme 5). In both cases, the facial stereoselectivity associated with the intermediate enolate B is high since only trans β-lactam diastereomers 5a,b were obtained (this can easily be established based on both the chemical shifts and the coupling constants of the two C3-H and C4-H proton atoms of the ring). This stereoselectivity is consistent with observations made on the β-lactone version of the reaction and most probably results from steric interactions. As for the stereoselectivity associated with the aldehyde (formation of the new stereogenic center C1”), the result was less clearcut. Indeed, no induction was observed with acetaldehyde, resulting in a 35:35:15:15 ratio of diastereoisomeric lactams 5a, while a modest one occurred with benzaldehyde as shown by the 55:20:15:10 ratio obtained for lactams 5b.

\[
\begin{array}{c}
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\end{array}
\xrightarrow{1/ \text{RCHO} \quad 2/ \text{TBAF (1M/THF)}}
\begin{array}{c}
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\text{Bu}^\circ\text{O} & \text{O} & \text{Bu}^\circ\text{O} \\
\text{N} & \text{SiMe}_3 & \\
\text{Ph} & & \\
\text{Ph} & & \\
\end{array}
\]

**Carboxylation** : We also managed to perform a carboxylation reaction under conditions analogous to the carboxylation of the β-lactone ring in our total synthesis of antibiotic 1233A. The two diastereomers of β-lactam 6, obtained as a 3:1 ratio similar to the one obtained in the desilylation reaction, were also both trans with respect to the β-lactam ring (Scheme 6).
Various other attempts to trap the intermediate enolate with other electrophiles, such as methyl iodide, acetyl chloride or \( n \)-butyl glyoxylate, failed.

**Theoretical study**

We have studied the two steps of the aldolisation reaction: (1) the formation of the intermediate enolate, focusing on the competition between inversion vs retention of configuration on the silicon atom, and (2) the nucleophilic attack of the formed enolate on the carbonyl group, focusing on the competition between cis vs trans stereochemistry, with respect to the ring.

**Methodology:** Calculations of both studies were performed at the semiempirical level with the AM1 method available in the AMPAC 8.16 package, on models very close to the ones involved in the experimental studies and using COSMO solvation model. All stationary points (minima and transition states) were characterized by the calculation of the normal modes of the optimized structures. Transition states were determined by a calculation with the CHAIN algorithm; connections between these, the reactants and the products were checked by the intrinsic reaction coordinate (IRC) method.

**Enolate formation:** The following \( \beta \)-lactam model, involving a cis relative stereochemistry on the ring (which is the major one) was chosen to study the first step of the reaction, i.e. the formation of the intermediate enolate (Scheme 7).

Both paths, involving inversion and retention of configuration of the silicon atom, were investigated; they proved to be very close. The step was found to be exothermic (\(-56.86\) kcal/mol), mainly because of the formation of the very strong Si-F bond, and both reaction paths proved to be concerted, involving in each
case a single transition state, \textbf{TS-inv} and \textbf{TS-ret} (Figure 1) with close activation energies associated to them (12.45 vs 11.99 kcal/mol) (Table 1).

![Figure 1. Structures of TS-inv (left) and TS-ret (right) (AM1-COSMO)](image)

<table>
<thead>
<tr>
<th>Transition States</th>
<th>(\Delta H_f) (kcal/mol)</th>
<th>Activation Energy (kcal/mol)</th>
<th>d (C\textsubscript{3}-Si) (Å)</th>
<th>d (Si-F) (Å)</th>
<th>C\textsubscript{3}-Si-F (°)</th>
<th>C\textsubscript{2}-C\textsubscript{3}-Si-F (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS-inv</td>
<td>-119.50</td>
<td>12.45</td>
<td>1.894</td>
<td>3.870</td>
<td>98.6</td>
<td>-35.0</td>
</tr>
<tr>
<td>TS-ret</td>
<td>-119.96</td>
<td>11.99</td>
<td>1.896</td>
<td>3.652</td>
<td>69.1</td>
<td>-93.8</td>
</tr>
</tbody>
</table>

Table 1. Main parameters of \textbf{TS-inv} and \textbf{TS-ret} (AM1-COSMO)

As can be seen from Table 1, the main difference between the two transition states is logically associated with the approach of the fluoride anion, particularly the C\textsubscript{3}-Si-F angle which is directly involved in the inversion vs retention competition. This angle variation appears in Figure 1 although both transition states are rather early ones. Finally, although the preference for the retention pathway is only small (\(\Delta E_a = 0.46\) kcal/mol), it is in agreement with the behaviour of the silyl group in the 1,3-shift involved in the formation of silylketenes\textsuperscript{17} or in the sigmatropic shift in allyl silanes.\textsuperscript{18}

\textit{Aldolisation reaction:} We then investigated the reaction between the obtained enolate and acetaldehyde with emphasis on the cis vs trans competition around the four-membered ring (Scheme 8). Acetaldehyde was chosen in order to minimize the influence of the facial selectivity on the aldehyde since no selectivity at all was observed experimentally with this aldehyde.
Both paths, leading to the \textit{cis} or \textit{trans} diastereoisomer, were concerted, involving a single transition state, respectively \textbf{TS-\textit{cis}} or \textbf{TS-\textit{trans}} (Figure 2), but the \textit{trans} isomer established itself as both the thermodynamic ($\Delta E = -7.57 \text{ kcal/mol}$) and the kinetic one ($\Delta E_a = -1.68 \text{ kcal/mol}$) (Table 2). These calculations are in agreement with the experimental observation, and indeed account for the exclusive obtention of the \textit{trans} isomers.

![Figure 2. Structures of TS-\textit{cis} (left) and TS-\textit{trans} (right) (AM1-COSMO)](image)

<table>
<thead>
<tr>
<th>Transition State</th>
<th>Method</th>
<th>$\Delta H_f$ (kcal/mol)</th>
<th>Activation Energy (kcal/mol)</th>
<th>$\Delta H_R$ (kcal/mol)</th>
<th>d (C3-C1) (Å)</th>
<th>C3-C1-O (°)</th>
<th>O-C2-C3-H (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS-\textit{cis}</td>
<td>AM1/COSMO</td>
<td>-90.81</td>
<td>13.96</td>
<td>-1.00</td>
<td>2.021</td>
<td>109.2</td>
<td>-56.2</td>
</tr>
<tr>
<td>TS-\textit{trans}</td>
<td>AM1/COSMO</td>
<td>-92.49</td>
<td>12.28</td>
<td>-8.57</td>
<td>2.138</td>
<td>109.0</td>
<td>42.0</td>
</tr>
</tbody>
</table>

Table 2. Main parameters of \textbf{TS-\textit{cis}} and \textbf{TS-\textit{trans}} (AM1-COSMO)
CONCLUSION

We have shown that a fluoride anion vector such as TBAF can promote an aldol or carboxylation reaction between α-silyl-β-lactam 3 and aldehydes (acetaldehyde and benzaldehyde) or carbon dioxide respectively. The reaction involves the formation of an enolate (through retention of configuration of the silicon atom as predicted by semiempirical calculations) as its first step. The second step, the condensation, is, in both cases (aldolisation and carboxylation), totally trans stereoselective with respect to the β-lactam ring and therefore leads to the corresponding trans β-lactam. This selectivity is accounted for by semiempirical calculations.

EXPERIMENTAL

All reactions were magnetically stirred and were monitored by Thin Layer Chromatography (TLC) using Macherey-Nagel Düren Alugram Si G/UV254 pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm), then with KMnO4/K2CO3/KOH in water with heating. Organic extracts were dried over MgSO4 unless otherwise specified and evaporated at water pump using a Büchi rotary evaporator. Petroleum ether ("petrol", bp 40-60 °C) and diethyl ether (Et2O) for chromatography were distilled before use. Column chromatography was performed on Merck silica gel 60 (0.04-0.063 mm, 230-400 mesh) and run under low pressure. When appropriate, solvents and reagents were dried by distillation from the usual drying agent prior to use. Diethyl ether (Et2O) and tetrahydrofuran (THF) were distilled from Na/benzophenone and used fresh. Dichloromethane (CH2Cl2) was distilled from P2O5. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates. Absorptions are reported as values in cm⁻¹ and defined as either strong (s), medium (m) or weak (w). Proton NMR spectra were recorded in Fourier Transform mode on a Bruker AC 400 (400 MHz) or Bruker DRX 500 (500 MHz) spectrometer in chloroform-ᵈ. Chemical shifts are reported in ppm relative to residual CHCl3 (δ = 7.26). Multiplicities are described using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quint) quintet, (sext) sextet, (sept) septuplet, (m) multiplet, (br) broad. Carbon-13 NMR spectra were recorded on a Bruker AC 200 (50.3 MHz), Bruker AC 300 (75.4 MHz) or Bruker AC 400 (100.6 MHz) spectrometer in chloroform-ᵈ. Chemical shifts are reported in ppm relative to the solvent (δ = 77.1). Multiplicities were determined using the Distortionless Enhancement by Polarization Transfer (DEPT) spectral editing technique. C-H coupling is indicated by an integer 0-3 in parenthesis following the ¹³C chemical shift value denoting the number of coupled protons. Mass spectra were run on a VO 70-250-SE or JEOL MStation JMS-700 spectrometer. Ion mass/charge (m/z) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and where shown, the proposed signal assignment. All compounds submitted for mass spectral analysis were purified by either...
distillation or column chromatography and estimated to be at least 95% pure by NMR and thin layer chromatography.

\[ \text{N-(1'-Phenyl)ethyl-4-} (n\text{-butoxycarbonyl)-2-azetidinones 4} \]

To a stirred solution of 2-azetidinones 3 (55 mg, 0.158 mmol) in THF (0.5 mL) at -80 °C, a solution of TBAF-3H₂O (55 mg, 0.174 mmol) in THF (0.5 mL) was added. Once the addition was completed, the solution was stirred for a further 30 min. at the same temperature. Hydrolysis was then carried out with an aqueous NH₄Cl solution. Extraction was performed with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated \textit{in vacuo}. The residue was purified by column chromatography (petrol/Et₂O, 1/1) to give 2-azetidinones 4 (41 mg, 0.150 mmol, 95%) as a 7/3 mixture (the ratio is determined based on the integration of the ¹H NMR signal of proton H1') of diastereoisomers. IR (film): ν = 1700 (m), 1380 (m), 1350 (w), 1150 (w), 1110 (s), 910 (s), 730 (s) cm⁻¹.

\textit{major isomer:} ¹H NMR (400 MHz, CDCl₃): δ = 7.38-7.28 (5H, m, H2"-4"), 4.98 (1H, q, J = 7.1 Hz, H1'), 4.10 (1H, ½ ABX₂, JₐB = 10.7 Hz, JₐX = 6.6 Hz, H1"'), 4.05 (1H, ½ ABX₂, JₐB = 10.7 Hz, JₐX = 6.6 Hz, H1'"), 3.84 (1H, dd, J = 5.4, 2.6 Hz, H4), 3.07 (1H, ½ ABX, JₐB = 14.4 Hz, JₐX = 5.4 Hz, H3), 2.93 (1H, ½ ABX, JₐB = 14.4 Hz, JₐX = 5.4 Hz, H3), 1.60 (3H, d, J = 7.1 Hz, H2'), 1.57 (2H, br. quint, J = 7.0 Hz, H2'"), 1.35 (2H, br. sext, J = 7.5 Hz, H3"'), 0.94 (3H, t, J = 7.4 Hz, H4''). ¹³C NMR (50.3 MHz, CDCl₃): δ = 171.3 (0), 165.9 (0), 139.4 (0), 128.8 (1, 2C), 127.2 (1, 2C), 128.0 (1), 65.5 (2), 52.8 (1), 50.1 (1), 41.2 (2), 30.4 (2), 19.1 (2), 18.5 (3), 13.7 (3).

\textit{minor isomer:} ¹H NMR (400 MHz, CDCl₃): δ = 7.38-7.28 (5H, m, H2"-4"), 4.68 (1H, q, J = 7.1 Hz, H1'), 3.99 (1H, ½ ABX₂, JₐB = 10.4 Hz, JₐX = 6.7 Hz, H1"'), 3.94 (1H, ½ ABX₂, JₐB = 10.4 Hz, JₐX = 6.8 Hz, H1'"), 3.91 (1H, dd, J = 5.5, 2.6 Hz, H4), 3.12 (1H, ½ ABX, JₐB = 14.4 Hz, JₐX = 5.5 Hz, H3), 2.92 (1H, ½ ABX, JₐB = 14.4 Hz, JₐX = 5.5 Hz, H3), 1.76 (3H, d, J = 7.1 Hz, H2'), 1.56 (2H, br. quint, J = 7.0 Hz, H2'"), 1.29 (2H, br. sext, J = 7.5 Hz, H3"'), 0.92 (3H, t, J = 7.4 Hz, H4''). ¹³C NMR (50.3 MHz, CDCl₃): δ
LRMS (CI mode): \( m/z = 382.2 \ [\text{M+H}^+], 24\% \), 279.2 (100), 79.0 (72).
HRMS (CI mode): found (M+H)+ 382.2020. \( \text{C}_{23}\text{H}_{27}\text{NO}_4 + \text{H} \) requires 382.2018.

\[ \text{N-(1'-Phenyl)ethyl-4-(n-butoxycarbonyl)-3-[1''-(hydroxy)ethyl]-2-azetidinones 5a} \]

A solution of 2-azetidinones 3 (69 mg, 0.20 mmol) and acetaldehyde (40 mg, 0.88 mmol) in THF (2 mL) was cooled to -80 °C under argon. A solution of TBAF (1 M in THF, 0.22 mL, 0.22 mmol) was then added very slowly and the resulting mixture was allowed to warm slowly to -40 °C over 3 h. Water (5 mL) and \( \text{Et}_2\text{O} \) (5 mL) were added and extraction was carried out with \( \text{Et}_2\text{O} \) (3 x 5 mL). The organic phases were washed with brine (3 mL), dried and concentrated \textit{in vacuo}. The residue was purified by column chromatography (\( \text{Et}_2\text{O}/\text{petrol} \), 7/3) to give \( \beta \)-lactams 5a (38 mg, 0.12 mmol, 60%) as a 35/35/15/15 (\textit{trans}/\textit{trans}/\textit{trans}/\textit{trans}) mixture (the ratio is determined based on the integration of the \( ^1\text{H} \) NMR signal of proton H1').

IR (film): \( \nu = 3430 \) (s), 1750 (s), 1490 (m), 1370 (s), 1190 (s), 1060 (m), 760 (m), 700 (s) cm\(^{-1}\).

2 major isomers: \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.40-7.24 \) (5H, m, H2''''-4'''''), 4.99 and 4.97 (1H, q, \( J = 7.3 \text{ Hz, H1''} \)), 4.18 (1H, qd, \( J = 6.0, 3.7 \text{ Hz, H1''''} \)), 4.09 (2H, t, \( J = 6.7 \text{ Hz, H1''''} \)), 3.98 (1H, d, \( J = 2.5 \text{ Hz, H4} \)) and 3.73 (1H, d, \( J = 2.7 \text{ Hz, H4} \)), 3.15 (1H, dd, \( J = 3.7, 2.6 \text{ Hz, H3} \)), 1.61 and 1.60 (3H, d, \( J = 7.3 \text{ Hz, H2''} \)), 1.60-1.48 (2H, m, H2''''), 1.38-1.24 (2H, m, H3''''), 1.27 (3H, d, \( J = 6.6 \text{ Hz, H2''''} \)) and 1.22 (3H, d, \( J = 6.3 \text{ Hz, H2''''} \)), 0.92 (3H, t, \( J = 7.4 \text{ Hz, H4''''} \)) and 0.92 (3H, t, \( J = 7.3 \text{ Hz, H4''''} \)). \( ^{13}\text{C} \) NMR (50.3 MHz, CDCl\(_3\)): \( \delta = 171.4 \) and 171.0 (0), 167.4 and 167.3 (0), 139.4 and 139.3 (0), 128.7 (1, 2C), 127.3 (1, 2C), 127.0 (1), 65.9 and 65.8 (1), 65.5 (2), 61.7 and 60.7 (1), 53.4 (1), 52.5 and 52.4 (1), 30.5 (2), 21.2 and 21.1 (3), 19.0 (2), 18.6 and 18.5 (3), 13.7 (3).

2 minor isomers (distinct signals): \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.40-7.24 \) (5H, m, H2''''-4'''''), 4.69 and 4.67 (1H, q, \( J = 7.4 \text{ Hz, H1''} \)), 4.25 (1H, qd, \( J = 6.0, 3.7 \text{ Hz, H1''''} \)), 4.09 (2H, t, \( J = 6.6 \text{ Hz, H1''''} \)), 4.05 (1H, d, \( J = 2.4 \text{ Hz, H4} \)) and 3.81 (1H, d, \( J = 2.1 \text{ Hz, H4} \)), 3.14 (1H, dd, \( J = 3.7, 2.3 \text{ Hz, H3} \)), 1.76 and 1.75
(3H, d, J = 7.4 Hz, H2'), 1.60-1.48 (2H, m, H2''), 1.38-1.24 (2H, m, H3''), 1.33 (3H, d, J = 6.3 Hz, H2'') and 1.25 (3H, d, J = 6.1 Hz, H2''), 0.91 (3H, t, J = 7.2 Hz, H4'') and 0.90 (3H, t, J = 7.4 Hz, H4''). 13C NMR (50.3 MHz, CDCl3): δ = 171.0 and 170.7 (0), 140.4 (0), 128.7 (1, 2C), 128.7 (1, 2C), 65.4 and 65.3 (2), 64.0 and 63.8 (1), 61.6 and 60.6 (1), 55.2 and 53.0 (1), 52.6 and 51.9 (1), 30.4 (2), 21.3 (3), 20.1 and 20.0 (3).

LRMS (CI mode): m/z = 320.2 [(M+H)+, 100%], 216.1 (8), 105.1 (12).

HRMS (CI mode): found (M+H)+ 320.1863. C18H25NO4 + H requires 320.1862.

N-(1'-Phenyl)ethyl-4-(n-butoxycarbonyl)-3-[1''-(hydroxy)benzyl]-2-azetidinones 5b

A solution of 2-azetidinones 3 (52 mg, 0.15 mmol) and benzaldehyde (36 mg, 0.34 mmol) in THF (2 mL) was cooled to -80 °C under argon. A solution of TBAF (1 M in THF, 0.17 mL, 0.17 mmol) was then added very slowly and the resulting mixture was allowed to warm slowly to -40 °C over 3 h. Water (5 mL) and Et2O (5 mL) were added and extraction was carried out with Et2O (3 x 5 mL). The organic phases were washed with brine (3 mL), dried and concentrated in vacuo. The residue was purified by chromatography (petrol/Et2O, 1/1) to give alcohol (46 mg, 0.12 mmol, 80%) as a 55/20/15/10 (trans/trans/trans/trans) mixture (the ratio is determined based on the integration of the 1H NMR signal of protons H1' or H1'') of diastereoisomeric β-lactams 5b.

IR (film): ν = 3170 (s), 1740 (s), 1700 (s), 1200 (m), 1060 (m), 820 (w), 740 (m), 700 (m) cm⁻¹.

major isomer: 1H NMR (400 MHz, CDCl3): δ = 7.40-7.21 (10H, m, H2''''-4''''+H3''-5''), 5.17 (1H, d, J = 3.1 Hz, H1''), 4.94 (1H, q, J = 7.1 Hz, H1''), 4.07 (1H, d, J = 2.3 Hz, H4), 3.86 (1H, ½ ABX2, JAB = 13.0 Hz, JAX = 6.5 Hz, H1''), 3.84 (1H, ½ ABX2, JAB = 13.0 Hz, JBX = 6.5 Hz, H1''), 3.44 (1H, dd, J = 3.1, 2.3 Hz, H3), 1.56 (3H, d, J = 7.1 Hz, H2''), 1.48-1.15 (2H, m, H2'''), 1.15-1.00 (2H, m, H3'''), 0.80 (3H, t, J = 6.9 Hz, H4''). 13C NMR (100.6 MHz, CDCl3): δ = 171.2 (0), 167.5 (0), 141.2 (0), 139.3 (0), 128.6 (1, 2C), 128.4 (1, 2C), 127.8 (1, 2C), 127.3 (1, 2C), 125.6 (1, 2C), 69.0 (1), 65.1 (2), 61.6 (1), 52.7 (1), 51.9 (1), 30.2 (2), 18.8 (2), 18.7 (3), 13.6 (3).

minor isomer I (distinct signals): 1H NMR (400 MHz, CDCl3): δ = 7.40-7.21 (10H, m, H2''''-4''''+H3''-5''), 4.96 (1H, d, J = 7.0 Hz, H1''), 4.66 (1H, q, J = 7.0 Hz, H1''), 4.09 (1H, d, J = 2.3 Hz, H4), 3.89 (2H, t, J =...
6.7 Hz, H1''), 3.53 (1H, dd, J = 7.0, 2.3 Hz, H3), 1.71 (3H, d, J = 7.0 Hz, H2''), 1.48-1.15 (2H, m, H2'''), 1.15-1.00 (2H, m, H3'''), 0.92 (3H, t, J = 7.4 Hz, H4'').

$^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 170.7 (0), 69.0 (1), 65.0 (2), 60.8 (1), 55.1 (1), 51.3 (1), 30.2 (2), 20.3 (2), 20.2 (3), 13.6 (3).

**minor isomer 2** (distinct signals): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.40-7.21 (10H, m, H2''''-4''''+H3''-5''), 5.22 (1H, d, J = 2.9 Hz, H1''), 4.88 (1H, q, J = 7.1 Hz, H1'), 3.98 (2H, t, J = 6.6 Hz, H1'''), 3.69 (1H, d, J = 2.3 Hz, H4), 3.44 (1H, dd, J = 2.9, 2.3 Hz, H3), 1.50 (3H, d, J = 7.0 Hz, H2'), 1.48-1.15 (2H, m, H2''''), 1.15-1.00 (2H, m, H3'''), 0.86 (3H, t, J = 7.2 Hz, H4''). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 170.9 (0), 71.5 (1), 65.4 (2), 61.5 (1), 53.1 (1), 52.3 (1), 30.3 (2), 18.9 (2), 18.4 (3), 13.7 (3).

**minor isomer 3** (distinct signals): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.40-7.21 (10H, m, H2''''-4''''+H3''-5''), 5.06 (1H, d, J = 5.5 Hz, H1''), 4.56 (1H, q, J = 7.0 Hz, H1'), 3.81 (2H, t, J = 6.6 Hz, H1'''), 3.74 (1H, d, J = 2.3 Hz, H4), 3.53 (1H, dd, J = 5.5, 2.3 Hz, H3), 1.60 (3H, d, J = 7.0 Hz, H2'), 1.48-1.15 (2H, m, H2''''), 1.15-1.00 (2H, m, H3'''), 0.85 (3H, t, J = 7.2 Hz, H4''). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 170.4 (0), 71.5 (1), 65.2 (2), 61.5 (1), 55.0 (1), 52.63 (1), 29.7 (2), 19.6 (3), 18.9 (2), 13.8 (3).

LRMS (CI mode, NH$_3$): m/z = 399 [(M+NH$_4$)$^+$, 95%], 382 [(M+H)$^+$, 14%].

LRMS (CI mode): m/z = 276.2 [(M+H)$^+$, 100%].

HRMS (CI mode): found (M+H)$^+$ 276.1598. C$_{16}$H$_{21}$NO$_3$ + H requires 276.1600.

**N-(1'-Phenyl)ethyl-4-(n-butoxycarbonyl)-3-[1''-carboxy]-2-azetidinones 6**

Gaseous CO$_2$, dried by passing through a column of CaCl$_2$ was bubbled through TBAF (1M in THF, 0.7 mmol, 0.7 mL) diluted in anhydrous THF (10 mL) at -78 °C for 10 min. A solution of 2-azetidinones 3 (126 mg, 0.36 mmol) in THF (2 mL) was then added dropwise to the CO$_2$ solution cooled to -65 °C. The resulting mixture was stirred for 2 h before being quenched with H$_2$O (10 mL). The aqueous phase was extracted with Et$_2$O (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was dissolved in an aqueous NaHCO$_3$ solution (pH=9) and extracted with Et$_2$O. The aqueous phase was then slowly acidified to pH=3 with 1 M...
HCl and extracted with EtOAc. The combined organic layers were then dried over Na$_2$SO$_4$ and concentrated in vacuo. The product, a 3/1 mixture (the ratio is determined based on the integration of the $^1$H NMR signal of proton H1') of diastereomeric β-lactams 6, was obtained as an orange oil (82 mg, 70%).

IR (film): $\nu = 3011$ (w), 1757 (s), 1733 (s), 1269 (m), 1194 (m) cm$^{-1}$.

**major isomer:** $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.71$ (1H, broad singulet, OH), 7.31 (5H, m, H2‴-4‴), 4.96 (1H, q, $J = 7.0$ Hz, H1′), 4.18 (1H, d, $J = 2.3$ Hz, H4), 4.09-4.03 (3H, m, H3 and H1‴), 1.64 (3H, d, $J = 7.0$ Hz, H2″), 1.56 (2H, m, H2‴), 1.30 (2H, m, H3‴), 0.91 (2H, m, H4‴). $^{13}$C NMR (75.4 MHz, CDCl$_3$): $\delta = 177.3$ (0), 169.5 (0), 161.3 (0), 138.6 (0), 128.9 (1, 2C), 128.2 (1), 127.3 (1, 2C), 66.0 (2), 57.4 (1), 53.8 (1), 53.6 (1), 30.4 (2), 19.0 (2), 18.7 (3), 13.7 (3).

**minor isomer** (distinct signals): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 4.76$ (1H, q, $J = 7.0$ Hz, H1′), 4.23 (1H, d, $J = 2.3$ Hz, H4), 1.77 (3H, d, $J = 7.0$ Hz, H2″). $^{13}$C NMR (75.4 MHz, CDCl$_3$): $\delta = 169.0$ (0), 139.4 (0), 128.1 (1), 127.0 (1, 2C), 65.9 (2), 55.4 (1), 52.9 (1), 14.2 (3).

LRMS (CI mode): $m/z = 320$: [(M+H)$^+$, 40%]; 337: [(M+NH$_4$)$^+$, 100%]; 342: [(M+Na)$^+$, 25%]; 358: [(M+K)$^+$, 15%]

**REFERENCES**


15. AMPAC Version 8.16, Semichem, Inc., PO Box 1649, Shawnee KS 66222.

