

HETEROCYCLES, Vol. 75, No. 10, 2008, pp. 2429 - 2441. © The Japan Institute of Heterocyclic Chemistry  
Received, 8th April, 2008, Accepted, 19th May, 2008, Published online, 22nd May, 2008. COM-08-11408

## ALDOLISATION AND CARBOXYLATION REACTIONS FROM $\alpha$ -SILYL- $\beta$ -LACTAMS. A COMBINED THEORETICAL AND EXPERIMENTAL STUDY

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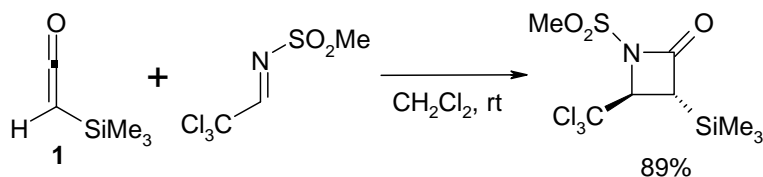
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**Abstract** - Treatment of  $\alpha$ -silyl- $\beta$ -lactam **3** with TBAF in the presence of an  
aldehyde or carbon dioxide leads, with total *trans* stereoselectivity, to the  
corresponding aldol or carboxy adducts **5-6**. Semiempirical calculations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

### INTRODUCTION

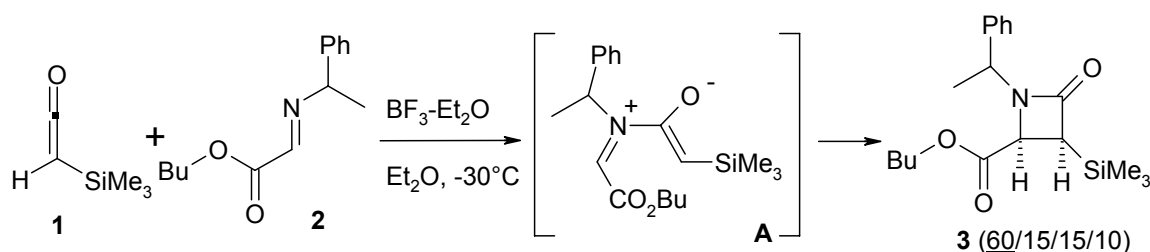
The Staudinger [2+2] cycloaddition between an imine and a ketene has been known since the beginning  
of the century<sup>1</sup> and is still widely used to prepare  $\beta$ -lactams.<sup>2</sup> Examples of the use of silylketenes<sup>3</sup> in  $\beta$ -  
lactam synthesis are rather scarce and involve an electron poor imine.<sup>4,5</sup> A typical example is due to  
Zaitseva and co-workers who prepared a *trans* silylated  $\beta$ -lactam from trimethylsilylketene (**1**) and  
phenylsulfonylchloraldimine (Scheme 1).<sup>5</sup> In all these examples, no Lewis acid is involved.



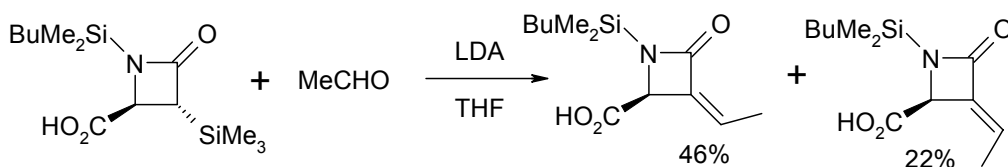
Scheme 1

We have already reported on the preparation of silylated  $\beta$ -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).<sup>6</sup> 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.<sup>7</sup>



The trimethylsilyl group of  $\alpha$ -silyl- $\beta$ -lactams can be removed by various fluoride anion vectors leading to the corresponding desilylated  $\beta$ -lactams,<sup>8</sup> or even to  $\alpha$ -deuterated  $\beta$ -lactams.<sup>9</sup> 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).<sup>10</sup>



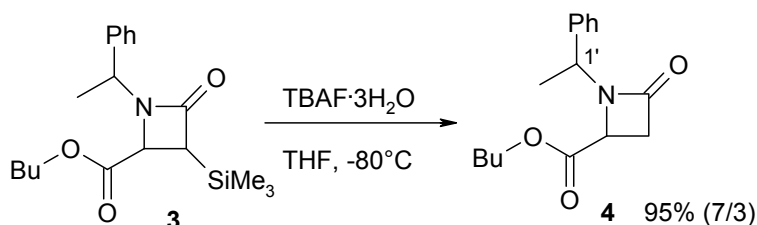
We would now like to report on a different, although related, aspect of the reactivity of  $\alpha$ -silylated  $\beta$ -lactams, the direct use of the trimethylsilyl group in base-free aldolization reactions,<sup>11</sup> a reactivity which is known in  $\beta$ -lactone chemistry.<sup>12</sup> A semiempirical study is also provided to try to account for the stereoselectivity of the aldolization reaction.

## RESULTS AND DISCUSSION

### Experimental study

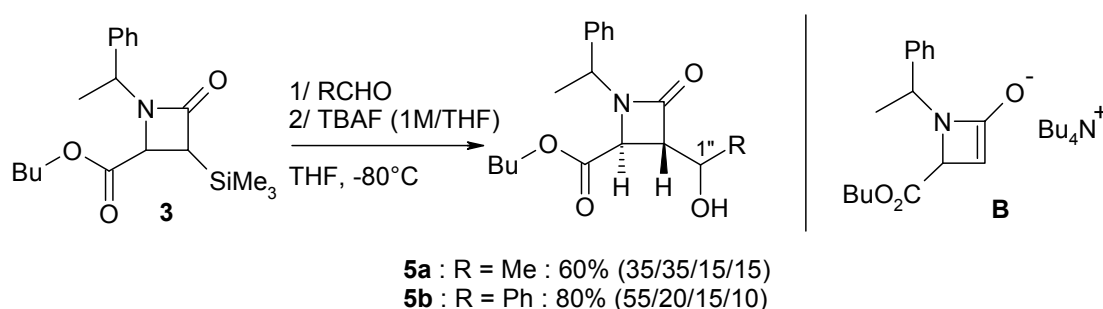
*Desilylation* : We started our study with the simple desilylation of  $\beta$ -lactam **3**, which was obtained as previously described from trimethylsilylketene (**1**) and imine **2** (Scheme 2). The reaction, performed with TBAF·3H<sub>2</sub>O (to provide a proton source), led to the corresponding 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.



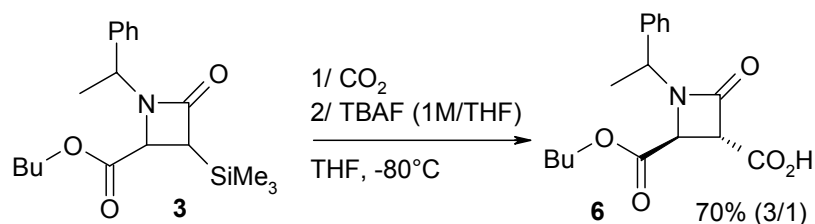
Scheme 4

*Aldolisation* : We then changed TBAF·3H<sub>2</sub>O 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**.



Scheme 5

*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.<sup>13</sup> 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).



Scheme 6

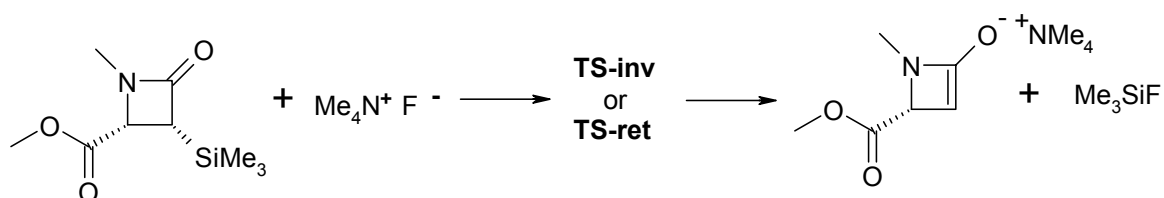
Various other attempts to trap the intermediate enolate with other electrophiles, such as methyl iodide, acetylchloride or *n*-butylglyoxylate, failed.

### 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<sup>14</sup> available in the AMPAC 8.16 package,<sup>15</sup> 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;<sup>16</sup> 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).



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, **TS-inv** and **TS-ret** (Figure 1) with close activation energies associated to them (12.45 vs 11.99 kcal/mol) (Table 1).

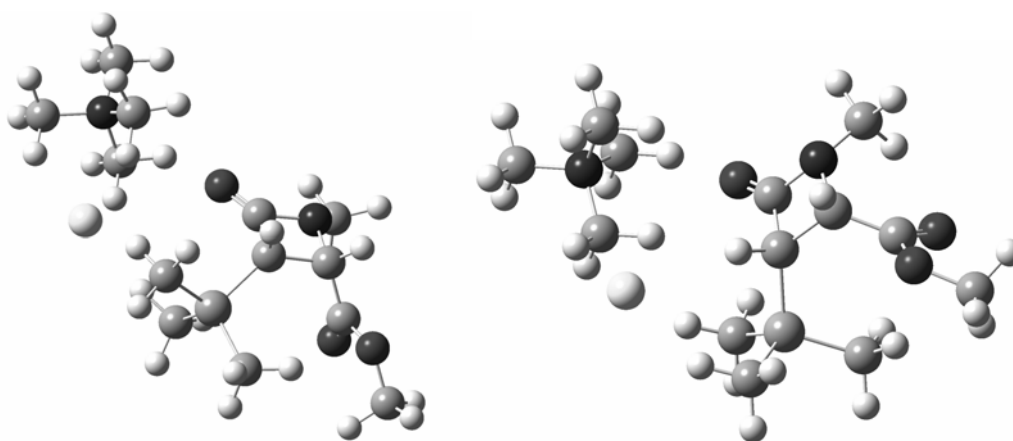


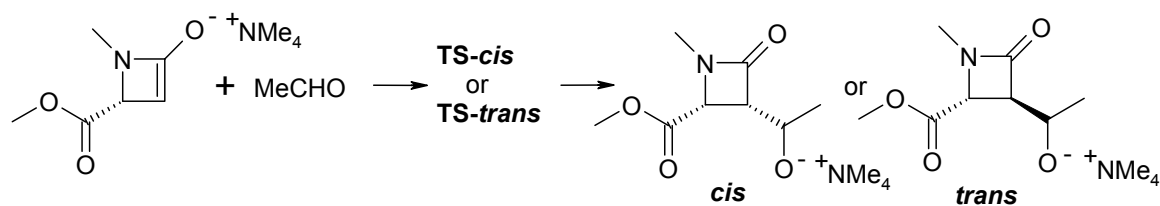
Figure 1. Structures of **TS-inv** (left) and **TS-ret** (right) (AM1-COSMO)

Transition States	$\Delta H_f$ (kcal/mol)	Activation Energy (kcal/mol)	d (C <sub>3</sub> -Si) (Å)	d (Si-F) (Å)	C <sub>3</sub> -Si-F (°)	C <sub>2</sub> -C <sub>3</sub> -Si-F (°)
<b>TS- inv</b>	-119.50	12.45	1.894	3.870	98.6	-35.0
<b>TS-ret</b>	-119.96	11.99	1.896	3.652	69.1	-93.8

Table 1. Main parameters of **TS-inv** and **TS-ret** (AM1-COSMO)

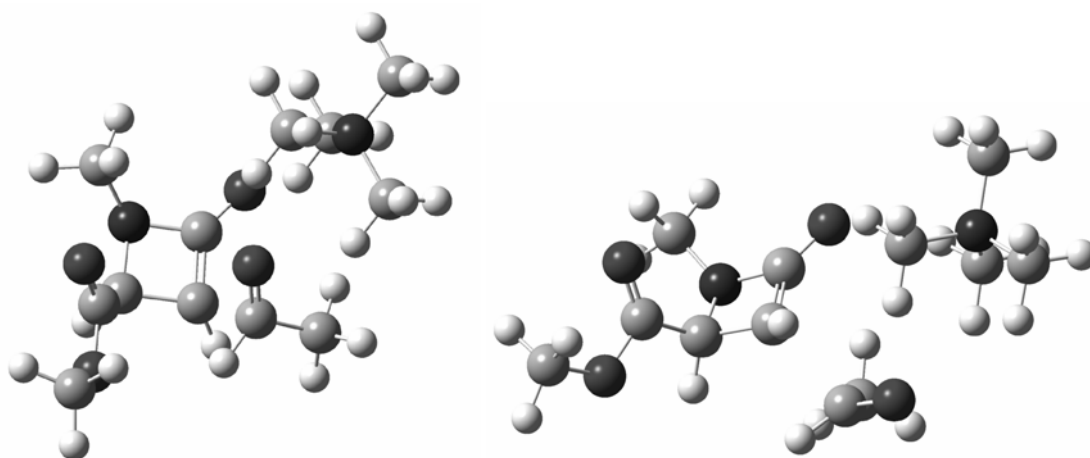
As can be seen from Table 1, the main difference between the two transition states is logically associated with the approach of the fluoride anion, particularly the C<sub>3</sub>-Si-F angle which is directly involved in the inversion vs retention competition. This angle variation appears in Figure 1 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,<sup>17</sup> or in the sigmatropic shift in allyl silanes.<sup>18</sup>

*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.



Scheme 8

Both paths, leading to the *cis* or *trans* diastereoisomer, were concerted, involving a single transition state, respectively **TS-*cis*** or **TS-*trans*** (Figure 2), but the *trans* isomer established itself as both the thermodynamic ( $\Delta E = -7.57$  kcal/mol) and the kinetic one ( $\Delta E_a = -1.68$  kcal/mol) (Table 2). These calculations are in agreement with the experimental observation, and indeed account for the exclusive obtention of the *trans* isomers.

Figure 2. Structures of **TS-*cis*** (left) and **TS-*trans*** (right) (AM1-COSMO)

Transition State	Method	$\Delta H_f$ (kcal/mol)	Activation Energy (kcal/mol)	$\Delta H_R$ (kcal/mol)	d (C <sub>3</sub> -C <sub>1</sub> ) (Å)	C <sub>3</sub> -C <sub>1</sub> -O (°)	O-C <sub>2</sub> -C <sub>3</sub> -H (°)
<b>TS-<i>cis</i></b>	AM1/COSMO	-90.81	13.96	-1.00	2.021	109.2	-56.2
<b>TS-<i>trans</i></b>	AM1/COSMO	-92.49	12.28	-8.57	2.138	109.0	42.0

Table 2. Main parameters of **TS-*cis*** and **TS-*trans*** (AM1-COSMO)

## CONCLUSION

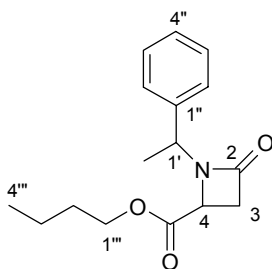
We have shown that a fluoride anion vector such as TBAF can promote an aldol or carboxylation reaction between  $\alpha$ -silyl- $\beta$ -lactam **3** and aldehydes (acetaldehyde and benzaldehyde) or carbon dioxide respectively. The reaction involves the formation of an enolate (through retention of 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  $\beta$ -lactam ring and therefore leads to the corresponding *trans*  $\beta$ -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/UV<sub>254</sub> pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm), then with KMnO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>/KOH in water with heating. Organic extracts were dried over MgSO<sub>4</sub> unless otherwise specified and evaporated at water pump using a Büchi rotary evaporator. Petroleum ether ("petrol", bp 40-60 °C) and diethyl ether (Et<sub>2</sub>O) 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 (Et<sub>2</sub>O) and tetrahydrofuran (THF) were distilled from Na/benzophenone and used fresh. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) was distilled from P<sub>2</sub>O<sub>5</sub>. 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<sup>-1</sup> 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 CHCl<sub>3</sub> ( $\delta$  = 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 ( $\delta$  = 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 <sup>13</sup>C 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.

#### *N*-(1'-Phenyl)ethyl-4-(*n*-butoxycarbonyl)-2-azetidinones **4**



To a stirred solution of 2-azetidinones **3** (55 mg, 0.158 mmol) in THF (0.5 mL) at  $-80\text{ }^{\circ}\text{C}$ , a solution of TBAF-3H<sub>2</sub>O (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 NH<sub>4</sub>Cl solution. Extraction was performed with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/Et<sub>2</sub>O, 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 <sup>1</sup>H NMR signal of proton H1') of diastereoisomers. IR (film):  $\nu = 1700$  (m), 1380 (m), 1350 (w), 1150 (w), 1110 (s), 910 (s), 730 (s) cm<sup>-1</sup>.

*major isomer*: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.38\text{--}7.28$  (5H, m, H2''-4''), 4.98 (1H, q,  $J = 7.1$  Hz, H1'), 4.10 (1H,  $\frac{1}{2}$  ABX<sub>2</sub>,  $J_{AB} = 10.7$  Hz,  $J_{AX} = 6.6$  Hz, H1'''), 4.05 (1H,  $\frac{1}{2}$  ABX<sub>2</sub>,  $J_{AB} = 10.7$  Hz,  $J_{BX} = 6.6$  Hz, H1'''), 3.84 (1H, dd,  $J = 5.4, 2.6$  Hz, H4), 3.07 (1H,  $\frac{1}{2}$  ABX,  $J_{AB} = 14.4$  Hz,  $J_{AX} = 5.4$  Hz, H3), 2.93 (1H,  $\frac{1}{2}$  ABX,  $J_{AB} = 14.4$  Hz,  $J_{BX} = 2.6$  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'''). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta = 171.3$  (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).

*minor isomer*: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.38\text{--}7.28$  (5H, m, H2''-4''), 4.68 (1H, q,  $J = 7.1$  Hz, H1'), 3.99 (1H,  $\frac{1}{2}$  ABX<sub>2</sub>,  $J_{AB} = 10.4$  Hz,  $J_{AX} = 6.7$  Hz, H1'''), 3.94 (1H,  $\frac{1}{2}$  ABX<sub>2</sub>,  $J_{AB} = 10.4$  Hz,  $J_{BX} = 6.8$  Hz, H1'''), 3.91 (1H, dd,  $J = 5.5, 2.6$  Hz, H4), 3.12 (1H,  $\frac{1}{2}$  ABX,  $J_{AB} = 14.4$  Hz,  $J_{AX} = 5.5$  Hz, H3), 2.92 (1H,  $\frac{1}{2}$  ABX,  $J_{AB} = 14.4$  Hz,  $J_{BX} = 2.6$  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'''). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$

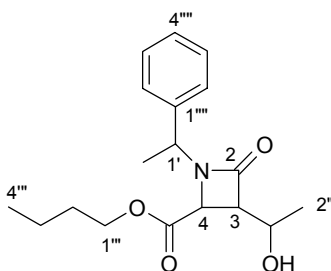


= 171.3 (0), 165.9 (0), 139.4 (0), 128.8 (1, 2C), 127.0 (1, 2C), 127.9 (1), 65.4 (2), 55.0 (1), 49.8 (1), 41.1 (2), 30.4 (2), 19.1 (2), 18.7 (3), 13.7 (3).

LRMS (CI mode):  $m/z = 382.2 [(M+H)^+, 24\%]$ , 279.2 (100), 79.0 (72).

HRMS (CI mode): found  $(M+H)^+ 382.2020$ .  $C_{23}H_{27}NO_4 + H$  requires 382.2018.

### ***N*-(1'-Phenyl)ethyl-4-(*n*-butoxycarbonyl)-3-[1''-(hydroxy)ethyl]-2-azetidiones **5a****



A solution of 2-azetidiones **3** (69 mg, 0.20 mmol) and acetaldehyde (40 mg, 0.88 mmol) in THF (2 mL) was cooled to  $-80\text{ }^{\circ}\text{C}$  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  $-40\text{ }^{\circ}\text{C}$  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 *in vacuo*. The residue was purified by column chromatography ( $\text{Et}_2\text{O}$ /petrol, 7/3) to give  $\beta$ -lactams **5a** (38 mg, 0.12 mmol, 60%) as a 35/35/15/15 (*trans/trans/trans/trans*) mixture (the ratio is determined based on the integration of the  $^1\text{H}$  NMR signal of proton H1') of diastereoisomers.

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

*2 major isomers*:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40\text{--}7.24$  (5H, m, H2'''-4'''), 4.99 and 4.97 (1H, q,  $J = 7.3$  Hz, H1'), 4.18 (1H, qd,  $J = 6.0, 3.7$  Hz, H1''), 4.09 (2H, t,  $J = 6.7$  Hz, H1'''), 3.98 (1H, d,  $J = 2.5$  Hz, H4) and 3.73 (1H, d,  $J = 2.7$  Hz, H4), 3.15 (1H, dd,  $J = 3.7, 2.6$  Hz, H3), 1.61 and 1.60 (3H, d,  $J = 7.3$  Hz, H2'), 1.60-1.48 (2H, m, H2'''), 1.38-1.24 (2H, m, H3'''), 1.27 (3H, d,  $J = 6.6$  Hz, H2'') and 1.22 (3H, d,  $J = 6.3$  Hz, H2''), 0.92 (3H, t,  $J = 7.4$  Hz, H4''') and 0.92 (3H, t,  $J = 7.3$  Hz, H4''').  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.4$  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).

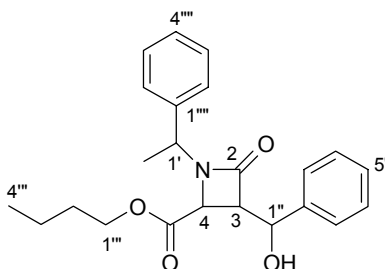
*2 minor isomers* (distinct signals):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40\text{--}7.24$  (5H, m, H2'''-4'''), 4.69 and 4.67 (1H, q,  $J = 7.4$  Hz, H1'), 4.25 (1H, qd,  $J = 6.0, 3.7$  Hz, H1''), 4.09 (2H, t,  $J = 6.6$  Hz, H1'''), 4.05 (1H, d,  $J = 2.4$  Hz, H4) and 3.81 (1H, d,  $J = 2.1$  Hz, H4), 3.14 (1H, dd,  $J = 3.7, 2.3$  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'').  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.0$  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.  $\text{C}_{18}\text{H}_{25}\text{NO}_4 + \text{H}$  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  $\text{Et}_2\text{O}$  (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 *in vacuo*. The residue was purified by chromatography (petrol/ $\text{Et}_2\text{O}$ , 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  $^1\text{H}$  NMR signal of protons H1' or H1'') of diastereomeric  $\beta$ -lactams **5b**.

IR (film):  $\nu = 3170$  (s),  $1740$  (s),  $1700$  (s),  $1200$  (m),  $1060$  (m),  $820$  (w),  $740$  (m),  $700$  (m)  $\text{cm}^{-1}$ .

*major isomer*:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40$ - $7.21$  (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,  $\frac{1}{2}$  ABX $_2$ ,  $J_{\text{AB}} = 13.0$  Hz,  $J_{\text{AX}} = 6.5$  Hz, H1'''), 3.84 (1H,  $\frac{1}{2}$  ABX $_2$ ,  $J_{\text{AB}} = 13.0$  Hz,  $J_{\text{BX}} = 6.5$  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''').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.2$  (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 1* (distinct signals):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40$ - $7.21$  (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''').

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.7$  (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):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40$ - $7.21$  (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''').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.9$  (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).

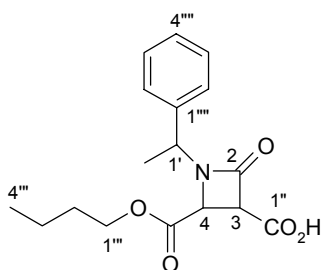
*minor isomer 3* (distinct signals):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40$ - $7.21$  (10H, m, H2''''-4''''+H3''-5''), 5.06 (1H, d,  $J = 5.5$  Hz, H1''), 4.56 (1H, q,  $J = 7.0$  Hz, H1'), 3.81 (2H, t,  $J = 6.6$  Hz, H1'''), 3.74 (1H, d,  $J = 2.3$  Hz, H4), 3.53 (1H, dd,  $J = 5.5, 2.3$  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''').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.4$  (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,  $\text{NH}_3$ ):  $m/z = 399$  [(M+ $\text{NH}_4$ ) $^+$ , 95%], 382 [(M+H) $^+$ , 14%].

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

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

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



Gaseous  $\text{CO}_2$ , dried by passing through a column of  $\text{CaCl}_2$  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  $\text{CO}_2$  solution cooled to  $-65$  °C. The resulting mixture was stirred for 2 h before being quenched with  $\text{H}_2\text{O}$  (10 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was dissolved in an aqueous  $\text{NaHCO}_3$  solution (pH=9) and extracted with  $\text{Et}_2\text{O}$ . 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<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The product, a 3/1 mixture (the ratio is determined based on the integration of the <sup>1</sup>H NMR signal of proton H1') of diastereomeric β-lactams **6**, was obtained as an orange oil (82 mg, 70%). IR (film): ν = 3011 (w), 1757 (s), 1733 (s), 1269 (m), 1194 (m) cm<sup>-1</sup>.

*major isomer*: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.71 (1H, broad singlet, 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'''). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): δ = 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): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 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''). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): δ = 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)<sup>+</sup>, 40%]; 337: [(M+NH<sub>4</sub>)<sup>+</sup>, 100%]; 342: [(M+Na)<sup>+</sup>, 25%]; 358: [(M+K)<sup>+</sup>, 15%]

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