

## One Step Synthesis of $\beta$ -lactams with Retro-Amide Side Chain.

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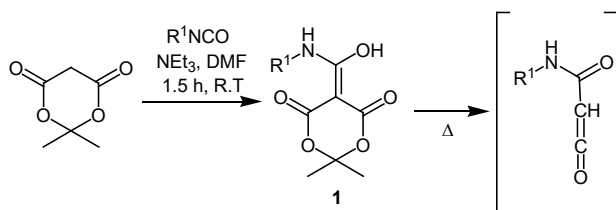
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**Abstract:** One pot synthesis for preparation of 1,4-disubstituted-2-oxo-azetidine-3-carboxylic acid amides was developed. 5-( $\alpha$ -N-substituted-amino- $\alpha'$ -hydroxy)methylene Meldrum's acids act as a source of ketenes that react with aldimines in boiling toluene to give  $\beta$ -lactams with retro-amid side chain.

**Key words:** lactams, cycloaddition, amides, ketenes, Meldrum acid

Compounds containing a  $\beta$ -lactam fragment are still a subject of unremitting interest to organic chemists. The main reason for this interest is clear, of course, due to their wide application as a chemotherapeutic. In almost seventy years since the first application of penicillin,  $\beta$ -lactam antibiotics are still the most commonly used drugs in bacterial infections. Although the biotechnological method of obtaining multiple antibiotics has been refined (1), there still remains a lot of work for organic chemists due to the need for modifications in the biotechnologically derived substrates – for example semisynthetic cefalosoryn (1), (2) or in the case of some  $\beta$ -lactam antibiotics like aztreonam (3), total chemical synthesis has proved to be more efficient. In addition  $\beta$ -lactams are valuable synthetic intermediates. The  $\beta$ -Lactam Synthone Method developed by Ojima uses  $\beta$ -lactams as the starting material for the synthesis of aminoacids (4), hydroxyacids (5), peptides (6). Also chiral  $\beta$ -lactams can be used for asymmetric induction (7).

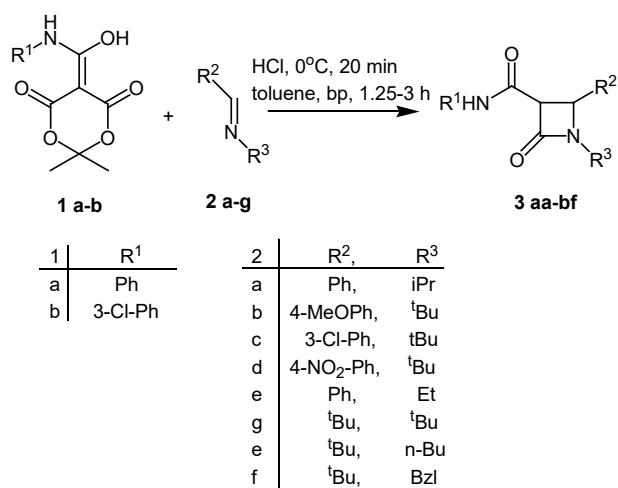
Despite the development of many unconventional ways to create a  $\beta$ -lactam system the Staudinger ketene-imine cycloaddition still remains the most popular method for the formation of four-membered lactams. Many methods for activation of carboxylic acid have been developed (8). One unusual method for the generation of ketenes is the thermal decomposition of Meldrum acid derivatives. Yamamoto used acyl ketenes formed in this way in reaction with aldimines for the preparation of monocyclic  $\beta$ -lactams (10). Almqvist tried without success to use a modification of this method for obtaining 6-acylpenams in cycloaddition reaction of ketenes with 2-thiazolines. Instead of the expected  $\beta$ -lactams they obtained bicyclic 1,3-oxazinones (11), (12). On the other hand 5-( $\alpha$ -N-substituted-amino- $\alpha'$ -methoxy)methylene Meldrum's acids or 5-( $\alpha$ -N-substituted-amino- $\alpha'$ -methylthio)methylene Meldrum's were explored as a source of ketenes (13) and also 5-( $\alpha$ -N-substituted-amino- $\alpha'$ -hydroxy)methylene Meldrum's acids **1** were used as a carbamoyl synthon for the preparation of malonic acid derivatives (14). **1** is simply prepared in the reaction of Meldrum acid with isocyanate in the presence of NEt<sub>3</sub> (14), (18). Thermal decomposition of **1** led to formation of carbamoyl ketenes which are able to react with various nucleophilic reagents, Scheme 1.



Scheme 1

In the course of the study we decided to check whether it is possible to obtain the  $\beta$ -lactam moiety with a retro-amide side chain by the reaction of carbamoylo ketenes generated from **1** with aldimines. The  $\beta$ -lactams containing retro-amide side chain are interesting as a unnatural inhibitors of  $\beta$ -lactamases (15). However, known methods for the preparation of  $\beta$ -lactams with inverted amide bond in the  $\beta$ -position which apply as a key step Wolff rearrangement (16) or Rapoport rearrangement of  $\beta$ -keto- $\beta$ -lactams (17) require multistep syntheses.

In this paper we present a one-step synthesis of  $\beta$ -lactams with a retro-amide side chain based on the reaction of **1** with aldimines.



Scheme 2

As a first experiment we performed a reaction of **1a** with benzylidene isopropylamine **2a** in benzene saturated with HCl. After purification we obtained 1,4-disubstituted-2-oxo-azetidone-3-carboxylic acid amides **3aa** with 54% yield. We chose benzene as a reaction medium based on the experiments of Yamamoto (10) where he generated acylketenes from acyl Meldrum acids. However, it turned out that **1** decomposes much more slowly than acyl Meldrum acids and the total disappearance of the substrate followed after 28 h. We optimized the temperature of the reaction and found the maximum yield in an acceptable reaction time when the reaction was carried out in toluene (Entry 3, Table 1). In addition, we have examined how stoichiometry affects the yield of reaction. Use of an excess of ketene precursor slightly decreased the yield, the use of equimolar or excess aldimine led to the maximum yield of  $\beta$ -lactam. Two-fold dilution of the reaction mixture also decreased the yield. A series  $\beta$ -lactams with retro-amide side chain were synthesised from **1a** and **1b** and aldimines by this one-step method; even highly hindered di-tert-butyl aldimine gave  $\beta$ -lactam **3bf** with good yield.

In the Staudinger ketene-imine cycloaddition *cis* or *trans*  $\beta$ -lactams may be formed; stereoselectivity of this process depends on several factors, such as substituents, temperature and solvent (8), (9). NMR spectra of prepared  $\beta$ -lactams with retro-amid side chain showed coupling constants for H-3, H-4 in the range 1.9-2.4 Hz in all presented models, what indicating the formation exclusively *trans* product.

In the course of our researches we encountered a limitation. If we tried to apply N-cyclohexyl or ethyl substituted **1** instead of an aryl substituted we did not observe formation of desired  $\beta$ -lactam; instead we obtain complicated mixtures of products.

Table 1 Synthesis of  $\beta$ -lactams with retro-amid side chain



Entry	3	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Solvent	Time (h)	Yield (%)
1	3aa	Ph	Ph	iPr	A	28	54
2	3aa	Ph	Ph	iPr	C	0,5	56
3	3aa	Ph	Ph	iPr	B	1,5	68
4 <sup>a</sup>	3aa	Ph	Ph	iPr	B	3	59
5 <sup>b</sup>	3aa	Ph	Ph	iPr	B	2	68
6	3ab	Ph	4-MeOPh	<sup>t</sup> Bu	B	1,5	56
7 <sup>b</sup>	3ab	Ph	4-MeOPh	<sup>t</sup> Bu	B	3	58
8	3ac	Ph	3-ClPh	<sup>t</sup> Bu	B	1,75	50
9	3ad	Ph	4-NO <sub>2</sub> Ph	<sup>t</sup> Bu	B	2,25	41
10	3ae	Ph	Ph	Et	B	1,5	56
11	3ag	Ph	<sup>t</sup> Bu	n-Bu	B	1,5	70
12	3ah	Ph	<sup>t</sup> Bu	Bzl	B	1,25	55
13	3ba	3-ClPh	Ph	iPr	B	1,5	58
14	3bf	3-ClPh	<sup>t</sup> Bu	<sup>t</sup> Bu	B	1,5	72

a) 2eq of **1a** was used b) 2eq of **2** was used  
Solvents A= benzene; B= toluene, C= ethylbenzene

Reagents were purchased from Sigma-Aldrich. Benzene, toluene and ethylbenzene were distilled from potassium under argon. Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck. Flash chromatography was performed using 40-63 microns of Zeochem silica gel. The 1H, 13C were recorded at Varian Gemini 200 and Varian Unity Plus 500. Melting points are uncorrected.

#### 5-( $\alpha$ -Phenylamino- $\alpha'$ -hydroxy)methylene Meldrum's acids (1a)

Was prepared according to literature procedure (18), and crystallized twice from AcOEt. Yield 89%; mp 105-107°C (lit. (18) mp (109-110°C). Spectral data in agreement with literature.

#### 5-( $\alpha$ -3-Chlorophenylamino- $\alpha'$ -hydroxy)methylene Meldrum's acids (1)

To a cooled to 0°C solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF(5 ml) was added Et<sub>3</sub>N (1.4 ml, 10 mmol). The mixture was stirred for 10 min and 3-chlorophenylisocyanate (0.767g, 5 mmol,) was added. The Stirring was continued for 15 min at 0°C and 1h at R.T. The reaction mixture was poured into 2 M HCl ice cooled aqueous solution (30 ml). The solid precipitate was filtered and washed with cold water. Crystallization from AcOEt/Hexan gave 0.939g 63% yield; mp 116-118 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.80 (s, 6 H), 7.25-7.28 (m, 1 H), 7.33-7.37 (m, 2 H), 7.58 (s, 1H) 11.20 (s, 1H), 16.05 (s, 1H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  26.56, 74.18, 105.65, 120.37, 122.45, 126.74.130.57, 135.25, 136.27, 164.44, 169.62, 171.25.

HRMS (ESI-): m/z [M – H<sup>+</sup>] - calcd for C<sub>13</sub>H<sub>12</sub>ClNO<sub>5</sub>: 297.0404; found: 269.0426.

#### 5-( $\alpha$ -cyclohexylamino- $\alpha'$ -hydroxy)methylene Meldrum's acids (1b)

To a solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF(5 ml) in glass ampoule was added Et<sub>3</sub>N (1.4 ml, 10 mmol). Cyclohexylisocyanate (0.751 g, 6 mmol,) was added, and ampoule was sealed. The ampoule was placed in the bath for 20 h at 40°C. The reaction mixture was poured into 2 M HCl ice cooled aqueous solution (30 ml). The solid precipitate was filtered and washed with cold water. Precipitate was dissolved in ethyl acetate (30ml) and dried with MgSO<sub>4</sub>, after cooling the solution the precipitate of DCU was removed by filtration. The solvent was removed under reduced pressure. Crystallization from AcOEt/Hexan gave 0.795g 60% yield; mp 103-104.5 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.28 (m, 1 H), 1.40 (m, 4 H), 1.64 (m, 1 H), 1.73 (m, 6 H), 1.78 (m, 2 H), 1.98 (m, 2 H), 3.81 (m, 1 H), 9.22 (s, 1 H), 14.91 (s, 1 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  24.59, 25.42, 26.51, 32.73, 50.09, 73.02, 104.77, 164.60, 169.42, 170.65.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>19</sub>NO<sub>5</sub>: 269.1262; found: 269.1266.

#### 5-( $\alpha$ -ethylamino- $\alpha'$ -hydroxy)methylene Meldrum's acids (1c)

To a solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF (5 ml) in glass ampoule was added Et<sub>3</sub>N (1.4 ml, 10 mmol). Ethylisocyanate (0.426 g, 6 mmol) was added, and ampoule was sealed. The ampoule was placed in the bath for 10 h at 40°C. The reaction mixture was poured into 2 M HCl ice cooled aqueous solution (30 ml). The solid precipitate was filtered and washed with cold water. Precipitate was dissolved in ethyl acetate (30 ml) and dried with MgSO<sub>4</sub>. The solvent was removed under reduced pressure. Crystallization from AcOEt/Hexan gave 0.706 g 65% yield; mp 72-74 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.30 (t, J=7.3 Hz, 3 H), 1.74 (s, 6 H), 3.49 (m, 2 H), 9.25 (brs, 1 H), 14.98 (s, 1 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  14.7, 26.4, 35.8, 104.2, 164.1.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>5</sub>: 215.0794; found: 215.0792.

#### Preparation of 1,4-disubstituted-2-oxo-azetidine-3-carboxylic acid amides 3. General procedure.

A cooled to 0 °C solution of 1 (2 mmol) and aldimine 2 (2 mmol) in toluene (10 ml) was saturated with HCl through 20 min. The resulting mixture was stirred and heated to reflux for time specified in Table 1. After completion of reaction the solvent was removed under vacuum, and the residue was purified as follows.

#### 1-Isopropyl-4-phenyl-2-oxo-azetidine-3-carboxylic acid phenylamide 3aa

Purification by flash column chromatography, (AcOEt/Hex, 1:3); mp 144-146 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.11 (d, J = 6.8 Hz, 3 H), 1.34 (d, J = 6.8 Hz, 3 H), 3.78 (h, J = 6.8 Hz, 1 H), 3.90 (d, J = 2.4 Hz, 1 H), 5.02 (d, J = 2.4 Hz, 1 H), 7.10 (t, J = 7.32 Hz, 1 H), 7.28-7.37 (m, 2 H), 7.38-7.76 (m, 5 H), 7.55 (d, J = 7.8 Hz, 2 H), 8.35 (s, 1 H).

<sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  20.3, 21.2, 46.0, 56.8, 63.0, 119.9, 124.5, 126.7, 128.8, 128.9, 129.0, 137.4, 137.9, 163.5, 165.0.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: 308.1525; found: 308.1501.

#### 1-Tert-butyl-4-(4-methoxy-phenyl)-2-oxo-azetidine-3-carboxylic acid phenylamide 3ab

Purification by flash column chromatography, (AcOEt/Hex, 1:3); mp 164-166 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.29 (s, 9 H), 3.80 (d, J = 2.4 Hz, 1 H), 3.83 (s, 3 H), 5.00 (d, J = 2.4 Hz, 1 H), 6.92 (d, J = 8.3 Hz, 2 H), 7.09 (t, J = 7.32 Hz, 1 H), 7.28 (t, J = 8.3 Hz, 2 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 7.8 Hz, 2 H), 8.45 (s, 1 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 28.4, 55.6, 55.6, 56.8, 63.0, 114.6, 120.0, 124.6, 128.2, 129.1, 131.2, 137.8, 160.1, 163.9, 165.5.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>: 352.1787; found: 352.1867.

#### 1-Tert-butyl-4-(3-chloro-phenyl)-2-oxo-azetidine-3-carboxylic acid phenylamide 3ac

Purification by flash column chromatography, (AcOEt/Toluene, 1:12); mp 207-208 °C

<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>):  $\delta$  = 1.22 (s, 9 H), 3.85 (d, J = 2.4 Hz, 1 H), 4.96 (d, J = 2.4 Hz, 1 H), 7.08 (t, J = 7.3 Hz, 1 H), 7.32 (t, J = 7.8 Hz, 2 H), 7.43-7.50 (m, 3 H), 7.51-7.60 (m, 2 H), 10.14 (s, 1 H).

<sup>13</sup>C NMR (50 MHz, DMSO-d<sub>6</sub>):  $\delta$  27.7, 54.4, 54.6, 63.6, 119.0, 123.6, 125.2, 126.6, 128.3, 128.7, 130.7, 133.4, 138.5, 142.7, 163.3, 164.0.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>: 356.1291; found: 356.1286.

1-Tert-butyl-4-(4-nitro-phenyl)-2-oxo-azetidine-3-carboxylic acid phenylamide 3ad

Purification by flash column chromatography, (AcOEt/Toluene, 1:8); mp 183-185 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.32 (s, 9 H), 3.77 (d, J = 1.9 Hz, 1 H), 5.13 (d, J = 1.9 Hz, 1 H), 7.14-7.21 (m, 1 H), 7.35 (t, J = 8.3 Hz, 2 H), 7.56 (d, J = 7.8 Hz, 2 H), 7.69 (d, J = 8.8 Hz, 2 H), 8.10 (brs, 1H), 8.30 (d, J = 8.8 Hz, 2 H).

<sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  28.2, 55.8, 62.7, 119.8, 124.3, 124.7, 127.4, 128.2, 129.0, 137.2, 146.7, 162.7, 164.9.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: 367.1532; found: 367.1528.

1-Ethyl-4-phenyl-2-oxo-azetidine-3-carboxylic acid phenylamide 3ae

Purification by flash column chromatography, (AcOEt/Hex, 1:3); mp 114-116 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.14 (t, J = 7.32 Hz, 3 H), 3.03 (h, J = 7.32 Hz, J = 6.83 Hz, 1H), 3.53 (h, J = 7.32 Hz, J = 6.83 Hz, 1H), 3.98 (d, J = 2.4 Hz, 1H), 5.09 (d, J = 2.4 Hz, 1 H), 7.07 (t, J = 7.32 Hz, 1H), 7.25 (m, 2H), 7.40 (m, 5H), 7.53 (d, J = 8.3 Hz, 2H), 8.78 (s, 1H).

<sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) = 13.2, 36.7, 57.5, 64.5, 120.4, 124.9, 127.1, 129.4, 129.6, 137.3, 138.1, 164.0, 165.5.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: 294.1367; found: 294.1351.

1-n-Butyl-4-tert-butyl-2-oxo-azetidine-3-carboxylic acid phenylamide 3ag

Purification by flash column chromatography, (AcOEt/Toluene, 1:6); mp 109-111 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  0.95 (t, J = 7.3 Hz, 2H), 1.08 (s, 9H), 1.33-1.38 (m, 2H), 1.58-1.65 (m, 2H), 3.01-3.06 (m, 1H), 3.58-3.64 (m, 1H), 3.72 (s, 1H), 3.84 (d, J = 1.9 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.8 Hz, 2 H), 7.56 (d, J = 7.8 Hz, 2 H), 8.32 (s, 1H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  13.5, 19.9, 26.0, 29.4, 32.5, 42.4, 55.2, 64.3, 119.7, 124.3, 128.8, 137.5, 164.0, 165.9.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: 302.1993; found: 302.2015.

1-Benzyl-4-tert-butyl-2-oxo-azetidine-3-carboxylic acid phenylamide 3ah

Purification by flash column chromatography, (AcOEt/Toluene, 1:6),

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.00 (ms 9 H), 3.78 (d, J = 2.4 Hz, 1 H), 3.81 (d, J = 2.4 Hz, 1 H), 4.18 (d, J = 15.6 Hz, 2 H), 4.88 (d, J = 15.6 Hz, 2 H), 7.13 (t, J = 7.3 Hz, 1 H), 7.25-7.30 (m, 2 H), 7.31-7.38 (m, 4 H), 7.58 (d, J = 7.8 Hz, 2 H), 8.33 (s, 1 H).



<sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 26.1, 32.4, 46.8, 55.5, 64.8, 119.9, 124.5, 127.9, 128.0, 128.9, 129.0, 135.1, 137.5, 163.8, 166.5.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 336.1838; found: 336.1872.

1-Isopropyl-4-phenyl-2-oxo-azetidine-3-carboxylic acid (3-chlorophenyl)amide 3ba

Purification by flash column chromatography, (AcOEt/Hex, 1:3), mp 145-147 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.13 (d, J = 6.8 Hz, 3 H), 1.35 (d, J = 6.8 Hz, 3 H) 3.75-3.80 (m, J = 6.8 Hz, 1 H), 3.87 (d, J = 2.4 Hz, 1 H), 4.98 (d, J = 2.4 Hz, 1 H), 7.11 (m, 1 H), 7.24-7.28 (m, 1 H), 7.36-7.42 (m, 2 H), 7.44-7.48 (m, 4 H), 7.74 (m, 1H) 8.16 (s, 1H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 20.6, 21.4, 46.4, 56.8, 63.4, 117.9, 120.1, 124.7, 126.9, 129.2, 129.3, 130.0, 134.8, 137.9, 138.9, 163.8, 165.3.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>2</sub>: 342.1135; found: 342.1130.

1-Tert-butyl-4-tert-butyl-2-oxo-azetidine-3-carboxylic acid (3-chlorophenyl)amide 3bf

Purification by flash column chromatography, (AcOEt/Hex, 1:3), mp 131-133 °C

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.11 (s, 9 H), 1.45 (s, 9 H), 3.58 (d, J = 2.4 Hz, 1 H), 3.95 (d, J = 2.4 Hz, 1 H) 7.09 (m, 1 H), 7.23 (t, J = 8.3 Hz, 1 H), 7.33 (m, 1 H), 7.75 (s, 1H), 8.42 (s, 1 H).

<sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 26.94, 29.0, 32.6, 55.0, 55.5, 65.2, 117.5, 119.7, 124.2, 129.7, 134.5, 138.8, 164.4, 165.9.

HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>: 336.1603; found: 336.1578.

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## References

- (1) Bruggink, A. Synthesis of β-lactam antibiotics: chemistry, biocatalysis and process integration. Kluwer Academic Publishers. 2001
- (2) a) DeMarinis, R. M.; Hoover, J. R.; Lam, L. L.; Uri, J. V.; Guarini, J. R.; Phillips, L.; Actor, P.; Weisbach, J. A. J. Med. Chem. 1976, 19, 754. b) Kariyone, K.; Harada, H.; Kurita, M. Takano, T. J. Antibiot. 1970, 23, 131. c) Ascher, G.; Ludescher, J.; Sturm, H.; Wieser, J. US Patent 5856474.
- (3) a) Curran, W. V.; Ross, A. A.; Lee, V. J. J. Antibiot. 1988, 41, 1418. b) Indelicato, J. M.; Fisher, J. W.; Pasini, C. E. J. Pharm. Sci. 1986. 75, 304.
- (4) Ojima, I.; Chen, H.-J. C.; Qiu, X. Tetrahedron 1988, 44, 5307.
- (5) Ojima, I.; Suga, S.; Abe, R.; Chem. Lett. 1980, 853.
- (6) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. J. Am. Chem. Soc. 1987, 109, 1798.
- (7) Ojima, I.; Pei, Y.; Tetrahedron Lett. 1990, 31, 977.
- (8) Gunda. I. G.; The organic chemistry of β-lactams, VCH: New York 1993
- (9) a) Jiao, L.; Liang, Y.; Xu, J. J. Am. Chem. Soc. 2006, 128, 6060-6069. b) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. J. Org. Chem. 2006, 71, 6983-6990.

- (10) Yamamoto, Y.; Watanabe, Y. *Chem. Pharm. Bull.*, 1987, 35, 1871-1878.
- (11) Emtenäs, H.; Soto, G.; Hultgren, S. J.; Marshall, G. R.; Almqvist, F. *Org. Lett.*; 2000, 2, 2065-2067.
- (12) Pemberton, N.; Emtenäs, H.; Boström, D.; Domaille, P. J.; Greenberg, W.A.; Levin, M. D.; Zhu, Z.; Almqvist, F.; *Org. Lett.*; 2005, 7, 1019-1021
- (13) (a) Shtaiwi, M.; Wenrup, C.; *J. Org. Chem.* 2002, 67, 858-8565. (b) Wentrup, C.; Rao, V. V. R.; Frank, W.; Fulloon, B. E.; Moloney D. W.; Mosandl, T.; *J. Org. Chem.* 1999, 64, 3608-3619. (c) Ye, F-Ch.; Chen, B-Ch.; Huang, X.; *Synthesis*, 1989, 4, 317-320.
- (14) (a) Lee, H. L.; Lee, J. P.; Lee, G. H.; Pak, Ch. S.; *Synlett.* 1996, 12, 1209-1210.
- (15) Adediran, S. A.; Lohier, J. F.; Cabaret, D.; Wakselman, M.; Pratt, R. F.; *Bioorg. Med. Chem. Lett.* 2006, 16, 869
- (16) (a) Lowe, G.; Wing Yeung, H.; *J. Chem. Soc. Perkin Tr. 1*; 1973, 2024. (b) Lowe, G.; Wing Yeung, H.; *J. Chem. Soc. Perkin Tr. 1*; 1973, 2907. (c) Corrie, J. E. T.; Hlubucek, J. R.; Lowe, G.; *J. Chem. Soc. Perkin Tr. 1*; 1977, 1421. (d) Gerstenberger, B. S.; Lin, J.; Mimieux, Y. S.; Brown, L. E.; Oliver, A. G.; Konopelski, J. P.; *Org. Lett.*; 2008, 10, 369.
- (17) (a) Bender, D. R.; Bjeldanes, L.F.; Knapp, D. R.; Rapoport, H.; *J. Org. Chem.* 1975, 40, 1264. (b) Adediran, S. A.; Lohier J. F.; Cabaret, D.; Wakselman, M.; Pratt, R. F.; *Bio. Med. Chem. Lett.* 2006, 16, 869.
- (18) Mukhopadhyaya, J. K.; Sklenák, S.; Rapoport, Z. *J. Am. Chem. Soc.* 2000; 122, 1325-1336.

