

Preparation of bicyclic β -lactam and bicyclic 1,3-oxazinone scaffolds using combined cycloaddition and metathesis processes

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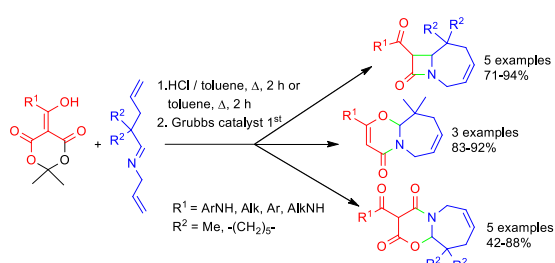
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Abstract

A simple, efficient two-step method for the preparation of heterobicyclic compounds was developed. Starting from 5-acyl or 5-carbamoyl-2,2-dimethyl-1,3-dioxo-4,5-dione bicyclic scaffolds of 1-azabicyclo[5.2.0]non-3-en-9-one, 6,9,10,10a-tetrahydro-4*H*-[1,3]oxazino[3,2-*a*]azepin-4-one, and 6,9,10,10a-tetrahydro-2*H*-[1,3]oxazino[3,2-*a*]azepine-2,4(3*H*)-dione were prepared using cycloaddition of thermally generated ketenes to aldimines with unsaturated side chains, followed by metathesis. The method was applied to ring closing metathesis (RCM) of different heterocyclic substrates to demonstrate its versatility.

Graphical Abstract



KEYWORDS: ketene, cyclization, Meldrum's acid, β -lactam, pilicide

INTRODUCTION

Small heterocycles as β -lactams have a well-established position in organic and medicinal chemistry mainly because of their chemotherapeutic antimicrobial properties.^[1] Seventy years after the first medical use of penicillin^[2] and more than a century after the synthesis of β -lactams by Staudinger,^[3] β -lactams are still an interesting target for organic chemists. Although the core of most of the currently used β -lactams is produced with fine biotechnology methods, often chemical modifications are required, e.g. for semisynthetic cephalosporins.^[4] Further, fully synthetic β -lactam antibiotics such as aztreonam are applied in medicinal practice.^[5] In contrast, medical applications of β -lactams are not restricted to antimicrobial activity, the derivatives of azetidinones find application in the therapy of atherosclerosis. Fully synthetic ezetimibe^[6] and other cholesterol transporter NPC1L1 inhibitors (AZD 4121^[7] Astra Zeneca, AVE5530^[8] Sanofi-Aventis, and SCH-48461^[9]) are effective drugs to treat hypercholesterolemia. All these facts confirm the necessity to study and develop new methods for preparation and modification of β -lactam rings.

From the chemical point of view, the formation of azetidone rings may proceed in two ways, namely, cyclization or cycloaddition. In the case of cyclization, four approaches are possible with the formation of new bonds between N1–C2 and C4–N1, the most popular of these are the cyclization of β -aminoacids^[10] and the natural biosynthesis of azetidinone antibiotics. In contrast, ring closing between C2–C3 and C3–C4 atoms are less common. Among the cycloaddition methods, the most popular ones are ester enolate-imine cyclocondensation,^[11] Kinugasa's nitrene addition to copper acetylide,^[12] vinyl ether addition to isocyanates,^[13] and the classical Staudinger ketene addition to imines.^[14]

Recently, we focused our research efforts on the synthesis of β -lactam rings by using a modification of the Staudinger method based on an alternative method of ketene

generation.^[15] In 1987, Yamamoto initiated the use of 5-acyl Meldrum' acid as an alternative source of ketenes for β -lactam preparation.^[16] Further, Almquist and co-workers tried to use such a method with the intention of 6-acylpenam synthesis^[17] however, instead they obtained 1,3-oxazinones.^[18] Nevertheless, these unwanted results led Almquist to develop a new synthesis method for 2-pyridones, bicyclic rigid compounds – pilicides active against uropathogenic bacteria.^[19]

Inspired by the Almquist trials approach, we worked on developing one- or two-step synthesis method for bicyclic scaffolds with β -lactam moiety and a second major hetero ring (Figure 1). Bearing in mind that such a compound may be a new potentially anti-uropathogenic type of pilicide.

DISCUSSION

Our approach to the synthesis of such a heterobicyclic species is based on the two following assumptions: the first, under certain thermal conditions, 5-[(N-aryl/N-alkylamino/alkyl/aryl)(hydroxyl)methylene]-2,2-dimethyl-1,3-dioxo-4,6-diones (**1**, **2**, and **3**) form ketenes **4**, which can react with unsaturated aldimines **5a**, and **b** to form four- or six-membered heterocyclic products. The relationship between the constitution of substrates **1**, **2**, and **3**, reaction conditions, and the size of the formed heterocyclic ring has already been reported.^[20] Therefore, we expected the formation of three types of heterocyclic products **6**, **7**, and **8** in this step (Scheme 1). In the second step, we planned to exploit a metathesis reaction to rapidly form the second heterocyclic ring.

The first step of our synthesis required the cycloaddition of the formed ketenes (**4a** or **4b**) to aldimines (**5a**, and **b**) possessing unsaturated side chains. We anticipated it to be a possible source of the side reaction, the cycloaddition of ketene to a C=C double bond. Therefore, at the beginning, we performed the control experiment where 5-

[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione (**1a**) was heated to reflux in cyclohexene (neat) saturated with gaseous HCl, a typical condition for an efficient and rapid formation of carbamoylketenes (Scheme 2). Surprisingly, but fortunately, despite the large excess of π -nucleophile, after the reaction workup, we did not observe any product of the carbamoylketene addition to alkene.

Apart from the above, we know from previous research that aldimine subjected to a cycloaddition with ketene generated from Meldrum's acids should not contain acidic α -protons; otherwise, the process is considered a failure.^{[15d], [21]} Therefore, for our purposes, we used aldimines with quaternary carbon in the aldehyde moiety **5a** and **b**.

As a first, we performed a series of experiments between 5-[hydroxy(arylamino)methylene]-2,2-dimethyl-1,3-dioxo-4,6-diones (**1a–d**) and aldimines (**5a** and **b**) in boiling toluene previously saturated with gaseous HCl. From the reaction mixture, we isolated the required β -lactams (**6aa–db**) (Table 1), however with the yield not exceeding 60%. A similar reaction conducted with imines not containing an unsaturated moiety led to higher yields of β -lactams.^[15a, d] A possible explanation for the relatively low yields is tautomerization in the highly acidic conditions of aldimine to a conjugated system^[22] (Scheme 3), which, as we know from previous, independent experiments does not add to ketenes at all.

The NMR spectra of prepared β -lactams (**6aa–db**) showed coupling constants for H3 and H4 in the range of 2.4–2.6 Hz, which indicates the exclusive formation of *trans* product.

Some problems we experienced with the reactivity of 5-[hydroxy(aryl/alkyl)methylene]-2,2-dimethyl-1,3-dioxo-4,6-diones (**2**) with aldimines (**5**). Based on our previous study^[15a, b, d] and the Watanabe works,^{[16], [20a]} we expected the formation of β -lactams (**6**) in the reaction of (**2a–c**) with aldimine in the presence of HCl, and the formation of 2*H*-1,3-oxazin-4(3*H*)-ones (**7**) in the absence of HCl. But, as a result of the reaction of (**2a–c**) with aldimine (**5a**) in the

presence of HCl, we did not obtain β -lactams, but only *2H*-1,3-oxazin-4(*3H*)-ones (**7aa–ca**) in trace amounts. Fortunately, the reaction of (**2a–c**) with aldimines in the absence of HCl gave a better yield of racemic (**7aa–ca**) (Table 2).

As the last substrate for further metathesis, we decided to prepare 5-carbamoyl-1,3-oxazine-4,6-diones (**8**). In the reaction of 5-[hydroxy(alkylamino)methylene]-2,2-dimethyl-1,3-dioxo-4,6-diones (**3a–b**) with aldimines (**5a** and **b**) without the addition of HCl, we prepared (**8aa–bb**) with good yields (Table 3). But, when we tried to prepare aryl analogs of **8** under identical conditions, we experienced substantial problems. It was difficult to finally purify and unambiguously characterize the obtained products with NMR, which we attributed to existence in equilibrium of four tautomeric forms of highly acidic 3-allyl-*N*-aryl-4,6-dioxo-1,3-oxazine-5-carboxylicamides. (Scheme 4)

We wanted to carry out the second cyclization step with RCM metathesis. In chemical literature, a few examples of the use of the RCM procedure for the formation of bicyclic β -lactams have been reported, but in most examples, were used as substrates 3-unsubstituted or fully protected β -lactams.^[23] In our case, we planned to use for metathesis substrates with a reasonably acidic and nucleophilic malonoamide moiety, which could disrupt the RCM process.

Moreover, in chemical literature, thus far, no example of RCM with *2H*-1,3-oxazin-4(*3H*)-ones (**7**) and 1,3-oxazine-5-carbamoyl-4,6-diones (**8**) as substrates has been reported.

As our first experiment, we performed a trial metathesis cyclization using 1-allyl-2-(2-methylpent-4-en-2-yl)-4-oxo-*N*-phenylazetidine-3-carboxamide (**6aa**) in dichloromethane as a solvent in the presence of 10% mol% of a first-generation Grubbs catalyst. The result was 71% yield of bicyclic *trans* β -lactam **9aa**. Encouraged by the initial experimental success, we

performed a further metathesis cyclization. The obtained yields of bicyclic β -lactams were high, and in two cases, they were almost quantitative (Table 4, Entries 2 and 3).

The next synthetic challenge was connected with the ring closing metathesis of 2*H*-1,3-oxazin-4(3*H*)-ones (**7aa–cb**); these substrates contain an additional C=C double bond, which may interact with the Grubbs catalyst and disrupt the essential metathesis process.

The performed experiments have shown no influence of the conjugated C=C double bond on the process used. The results are presented in Table 5.

The last and the most demanding set of substrates for the metathesis 5-carbamoyl-1,3-oxazine-4,6-diones (**8aa–bb**) also provided desired products **11aa–bb**. (Table 6)

The positive results of metathesis for three different types of substrates prompted us to check the reactivity of precursors with a triple C–C bond in the enyne metathesis process.^[24] Aldimine **12** containing a triple bond was prepared in the usual manner from 2,2-dimethylpent-4-enal and propargylamine.^[25] We planned to use for the enyne synthesis, β -lactams and/or 5-carbamoyl-1,3-oxazine-4,6-diones with unsaturated side chains. But, an attempt to prepare β -lactams with a triple bond in the side chain via the reaction of arylcarbamoyl Meldrum's acid (**1a** and **b**) and aldimine (**12**) was unfeasible. Yields below 8% excluded this process from practical application.

In contrast, for **13a** and **b**, the obtained yields of the metathesis precursors was sufficient and allowed us to move to the next step. We prepared two examples of 6,9,10,10a-tetrahydro-2*H*-[1,3]oxazino[3,2-*a*]azepine-2,4(3*H*)-diones (**14a** and **b**). (Table 7)

In conclusion, we developed a simple and convenient two-step method for the synthesis of bicyclic heterocycle scaffolds 1-azabicyclo[5.2.0]non-3-en-9-one (**9**), 6,9,10,10a-tetrahydro-4*H*-[1,3]oxazino[3,2-*a*]azepin-4-one (**10**), and 6,9,10,10a-tetrahydro-2*H*-[1,3]oxazino[3,2-

a]azepine-2,4(3*H*)-diones (**11** and **14**) via the a combination of [2+2] or [4+2] cycloaddition and metathesis process. The applied approach based on 5-acyl/carbamoyl Meldrum's acid as the key substrate proved to be a universal and fast tool for the preparation of various wide - scope heterocyclic scaffolds.

SUPPORTING INFORMATION

Full experimental details, copies of ¹H and ¹³C NMR spectra of synthesized compounds can be found via the "Supplementary Content" section of this article's webpage.

EXPERIMENTAL

General Procedure for the Preparation of 3-carbamoyl-azetidin-2-ones 6aa–db.

To a solution of **1a–d** (1 mmol) in dry toluene (5 ml) was added aldimines **5a** and **b** (1.5 mmol). The reaction mixture was cooled to 0°C and saturated with dry HCl for 20 min. The resulting mixture was stirred and heated to reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified as specified below.

1-Allyl-2-(1-allylcyclohexyl)-N-(4-fluorophenyl)-4-oxoazetidine-3-carboxamide (6db)

Purification by flash chromatography (EtOAc/Hex 1:3, SiO₂). Yellow oil; yield: 195mg, 53%. IR (neat, ATR): 3289 (br), 3078 (m), 2931 (s), 1735 (vs), 1684 (s), 1508 (vs), 1214 (s), 994 (w), 918 (m), 738 (m) cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 8.64 (s, 1 H), 7.50-7.45 (m, 2 H), 6.99-6.93 (m, 2 H), 5.95-5.71 (m, 2 H), 5.34-5.30 (m, 1 H), 5.29-5.27 (m, 1 H), 5.15-5.03 (m, 2 H), 4.26 (ddt, *J* = 15.9, 5.1, 1.5 Hz, 1 H), 4.21 (d, *J* = 2.5 Hz, 1 H), 4.00 (d, *J* = 2.5 Hz, 1 H), 3.74-3.65 (m, 1 H), 2.33-2.19 (m, 2 H), 1.66-1.23 (m, 10 H). ¹³C-NMR (100 MHz, CDCl₃): δ = 166.2, 163.8, 159.4 (d, *J* = 242.0 Hz), 133.7, 133.6 (d, *J* = 2.8 Hz), 131.3, 121.5 (d, *J* = 7.8 Hz), 119.1, 118.4, 115.4 (d, *J* = 22.4 Hz), 62.7, 55.0, 45.6, 37.7, 37.3, 31.9, 31.6,

25.7, 21.1, 20.9. HR-MS (ESI+): m/z $[M + Na]^+$ calcd for $C_{22}H_{27}FN_2O_2Na$: 393.1954; found: 393.1940.

General Procedure for the Preparation of 2H-1,3-oxazin-4(3H)-ones 7aa–ca.

To a solution of **2a–c** (1 mmol) in dry toluene (5 ml) was added aldimine **5a** (1.5 mmol). The resulting mixture was stirred and heated to reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified as specified below.

3-Allyl-6-methyl-2-(2-methylpent-4-en-2-yl)-2H-1,3-oxazin-4(3H)-one (7aa)

Purification by flash chromatography (EtOAc/Hex 2:5, SiO₂). Yellow oil; yield: 70 mg, 30%.

IR (neat, ATR): 3289 (br), 3078 (m), 2931 (s), 1735 (vs), 1684 (s), 1553 (s), 1508 (vs), 994 (w), 918 (m), 738 (m) cm^{-1} . ¹H-NMR (400 MHz, CDCl₃): δ = 5.85-5.73 (m, 2 H), 5.22-5.15 (m, 2 H), 5.14-5.06 (m, 2 H), 5.12 (bs, 1 H), 5.00-4.93 (m, 1 H), 4.98 (s, 1 H), 3.25 (ddt, J = 16.1, 6.8, 1.0 Hz, 1 H), 2.20-2.07 (m, 2 H), 1.94 (d, J = 0.8 Hz, 3 H), 0.98 (s, 3 H), 0.95 (s, 3 H). ¹³C-NMR (100 MHz, CDCl₃): δ = 164.8, 162.7, 133.5, 132.7, 118.6, 117.0, 99.1, 93.2, 48.6, 43.9, 42.9, 23.2, 23.1, 19.3. HR-MS (ESI+): m/z $[M + Na]^+$ calcd for $C_{14}H_{21}NO_2Na$: 258.1470; found: 258.1459.

General Procedure for the Preparation of 5-carbamoyl-1,3-oxazine-4,6-diones 8aa–bb and 13a and b.

To a solution of **3a–b** (1 mmol) in dry toluene (5ml) was added aldimine **5a**, **b**, or **12** (1.5 mmol). The resulting mixture was stirred and heated to reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified as specified below.

3-Allyl-N-ethyl-2-(2-methylpent-4-en-2-yl)-4,6-dioxo-1,3-oxazinane-5-carboxamide (8aa)

Purification by flash chromatography (EtOAc/Hex 1:5 SiO₂). Yellow oil; yield: 200 mg, 65%. IR (neat, ATR): 3078 (m), 2975 (s), 1661 (vs), 1509 (s), 1416 (s), 996 (w), 915 (m), 813 (m) cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 15.10 (d, *J* = 1.1 Hz, 1 H), 9.75 (s, 0.15 H), 8.91 (s, 0.85 H), 5.85-5.73 (m, 2 H), 5.27-5.25 (m, 1 H), 5.24-5.21 (m, 1 H), 5.16-5.14 (m, 1 H), 5.13-5.08 (m, 1 H), 4.96 (s, 0.15 H), 4.91 (s, 0.85 H), 4.84 (ddt, *J* = 16.4, 4.2, 1.8 Hz, 1 H), 3.46-3.36 (m, 3 H), 2.21 (dd, *J* = 13.5, 7.5 Hz, 1 H), 2.09 (dd, *J* = 13.5, 7.5 Hz, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H) 0.98 (s, 3 H), 0.97 (s, 3 H). ¹³C-NMR (100 MHz, CDCl₃, major tautomer): δ = 170.6, 170.0, 165.5, 133.2, 131.8, 118.9, 117.6, 91.0, 75.4, 48.8, 43.8, 42.3, 34.7, 22.8, 22.2, 14.6. HR-MS (ESI+): *m/z* [M + Na]⁺ calcd for C₁₆H₂₄N₂O₄Na: 331.1634; found: 331.1649.

General Procedure for Ring Closing Metathesis

To a solution of **6aa–db**, **7aa–ca**, **8aa–bb**, or **13a** and **b** (0.1 mmol) in dry DCM (3 ml) was added Grubbs catalyst 1st generation 10% mol%. The resulting mixture was stirred at room temperature for 24 h, in argon atmosphere. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified as specified below

N-(3-Chlorophenyl)-6,6-dimethyl-9-oxo-1-azabicyclo[5.2.0]non-3-ene-8-carboxamide (9ba)

Purification by flash chromatography (EtOAc/Hex 1:2, SiO₂). Yellow oil; yield: 29.8 mg, 94%. IR (neat, ATR): 3313 (br), 2965 (s), 1738 (vs), 1686 (s), 1601 (s), 1594 (s), 778 (m) cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 8.35 (s, 1 H), 7.63 (t, *J* = 2.0 Hz, 1 H), 7.24-7.19 (m, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.00-6.97 (m, 1 H), 5.64-5.57 (m, 1 H), 5.52-5.47 (m, 1 H), 4.27 (dd, *J* = 18.0, 5.7 Hz, 1 H), 3.82 (d, *J* = 2.3 Hz, 1 H), 3.73 (d, *J* = 2.4 Hz, 1 H), 3.63-3.54 (m, 1 H), 2.14-2.12 (m, 2 H), 1.04 (s, 3 H), 0.90 (s, 3 H). ¹³C-NMR (100 MHz, CDCl₃): δ = 164.0, 163.9, 138.5, 134.6, 129.8, 128.7, 124.5, 124.1, 119.9, 117.7, 65.7, 56.3, 41.6, 40.6, 35.3, 27.1, 20.6.

REFERENCES

- [1] (a) Dougherty, T. J.; Pucci, M. J. *Antibiotic Discovery and Development*, Springer: New York, **2012**. (b) Morin, R. B.; Gorman, M. *Chemistry and Biology of β -Lactam Antibiotics*, Academic Press: New York, **1982**.
- [2] Torok, M. E.; Moran, E.; Cooke, F. *Oxford Handbook of Infectious Diseases and Microbiology*, 1st ed., Oxford University Press, **2009**.
- [3] Staudinger, H. Zur Kenntniss der Ketene. Diphenylketen. *Justus Liebigs Ann. Chem.* **1907**, 356, 51-123.
- [4] Bruggink, A. *Synthesis of β -lactam antibiotics: chemistry, biocatalysis and process integration*, Kluwer Academic Publishers, **2001**.
- [5] a) Curran, W. V.; Ross, A. A.; Lee, V. J. N-azamonobactams. 1. The synthesis of some 3-substituted N-azamonobactam derivatives. *J. Antibiot.* **1988**, 41, 1418-1429. b) Indelicato, J. M.; Fisher, J. W.; Pasini, C. E. Intramolecular nucleophilic amino attack in a monobactam: synthesis and stability of (2S,3S)- 3-[(2R)-2-amino-2-phenylacetamido]-2-methyl-4-oxo-1-azetidinesulfo-nic acid. *J. Pharm. Sci.* **1986**, 75, 304-306.
- [6] a) Gupta, E. K.; Ito, M. K. Ezetimibe: the first in a novel class of selective cholesterol-absorption inhibitors. *Heart Dis.* **2002**, 4, 399-409. b) Clader, J. W. The discovery of ezetimibe: a view from outside the receptor. *J. Med. Chem.* **2004**, 47, 1-9. c) Rosenblum, S. B.; Huynh, T.; Afonso, A. ; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A. Discovery of 1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): a designed, potent, orally active inhibitor of cholesterol absorption. *J. Med. Chem.* **1998**, 41, 973-980.

- [7] Karlsson, S.; Sorensen, J. H.; Selection and Development of a Route for Cholesterol Absorption Inhibitor AZD4121. *Org. Process Res. Dev.* **2012**, *16*, 586-594.
- [8] Kramer, W.; Corsiero, D.; Girbig, F.; Jähne, G. Rabbit small intestine does not contain an annexin II/caveolin 1 complex as a target for 2-azetidinone cholesterol absorption inhibitors. *Biochim. Biophys. Acta* **2006**, *1*, 45-54.
- [9] Salisbury, B. G.; Davis, H. R.; Burrier, R. E.; Burnett, D. A.; Boykow, G. Caplen, M. A.; Clemmons, A. L.; Compton, D. S.; Hoos, L. M.; McGregor, D. G.; Schnitzer-Polokoff, R.; Smith, A. A.; Weig, B. C.; Zilli, D. L.; Clader, J. W.; Sybertza, E. J. Hypocholesterolemic activity of a novel inhibitor of cholesterol absorption, SCH 48461. *Atherosclerosis*, **1995**, *115*, 45-63.
- [10] (a) Grieco, P. A; Flynn, D. L.; Zelle, R. E. Beta.-Lactam antibiotics: a formal stereocontrolled total synthesis of (+,-)-thienamycin. *J. Am. Chem. Soc.* **1984**, *106*, 6414-6417. (b) Kametani, T.; Chu, S. D.; Honda, T. Asymmetric Synthesis of 4-Acetoxy-3-hydroxyethylazetidin-2-one, a Key Intermediate for the Preparation of Penem and Carbapenem Antibiotics. *Heterocycles* **1987**, *25*, 241-244. (c) Ito, K.; Iida, T.; Fujita, T.; Tsjui, S. A Simple Method for the Synthesis of Amides by Use of 2,2'-Dibenzothiazolyl Disulfide as an Oxidant. *Synthesis* **1981**, *4*, 287-288. (d) Palomo, C.; Azipurua, J. M.; Urchegui, R.; Iturburu, M.; Ochoa de Retana, A.; Cuevas, C. A convenient method for .beta.-lactam formation from .beta.-amino acids using phenyl phosphorodichloridate reagent. *J. Org. Chem.* **1991**, *56*, 2244-2247.
- [11] (a) Gilman, H.; Speeter, M. The Reformatsky Reaction with Benzalaniline. *J. Am. Chem. Soc.* **1943**, *65*, 2255-2256. (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L.R. Efficient and practical asymmetric synthesis of the taxol C-13 side chain, N-benzoyl-(2R,3S)-3-phenylisoserine, and its analogs via chiral 3-hydroxy-4-aryl-.beta.-lactams through

chiral ester enolate-imine cyclocondensation. *J. Org. Chem.* **1991**, *56*, 1681-1683. (c) Hart, D. J.; Ha, D-C. The ester enolate-imine condensation route to β -lactams. *Chem. Rev.* **1989**, *89*, 1447-1465. (d) Ojima, I.; Habus, I. Asymmetric synthesis of β -lactams by chiral ester enolate - imine condensation. *Tetrahedron Lett.* **1990**, *31*, 4289-4292. (e) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y.; Sun, C.; Brigaud, T. New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of β -lactam synthon method. *Tetrahedron* **1992**, *48*, 6985-7012. (f) Ojima, I.; Habus, I.; Zhao, M. Efficient and practical asymmetric synthesis of the taxol C-13 side chain, N-benzoyl-(2R,3S)-3-phenylisoserine, and its analogs via chiral 3-hydroxy-4-aryl- β -lactams through chiral ester enolate-imine cyclocondensation. *J. Org. Chem.* **1991**, *56*, 1681-1683. (g) Ojima, I.; Slater, J. S.; Kuduk, S. D.; Takeuchi, C. S.; Gimi, R. H.; Sun, C. M.; Park, Y. H.; Pera, P.; Veith, J. M.; Bernacki, R. J. Syntheses and Structure–Activity Relationships of Taxoids Derived from 14 β -Hydroxy-10-deacetylbaccatin III *J. Med. Chem.* **1997**, *40*, 267-278.

[12] (a) Kinugasa, M.; Hashimoto, S. The reactions of copper(I) phenylacetylide with nitrones. *J. Chem. Soc. Chem. Commun.* **1972**, *8*, 466-467. (b) Stecko, S.; Furman, B.; Chmielewski, M. Kinugasa reaction: an ‘ugly duckling’ of β -lactam chemistry *Tetrahedron* **2014**, *70*, 7817-7844.

[13] Chmielewski, M.; Kałuzna, Z.; Abramski, W.; Belzacki, C. Stereocontrolled entry to 1-oxapenams and 1-oxacephems from carbohydrates. *Tetrahedron Lett.* **1987**, *28*, 3035-3038.

[14] (a) Kamath, A.; Ojima, I. Advances in the chemistry of β -lactam and its medicinal applications. *Tetrahedron* **2012**, *68*, 10640-10664. (b) Mendez, L.; Mata, E. G. Synthesis of Multicyclic β -Lactam Derivatives via Solid-Phase-Generated Ketenes. *J. Comb. Chem.* **2010**, *12*, 810-813. (c) Jiao, L.; Zhang, Q.; Liang, Y.; Zhang, S.; Xu, J. A Versatile Method for the Synthesis of 3-Alkoxy-carbonyl β -Lactam Derivatives *J. Org. Chem.* **2006**, *71*, 815-818. (d)



Xu, J. Synthesis of β -lactams with π electron-withdrawing substituents. *Tetrahedron* ~~Synthesis of β lactams with π electron withdrawing substituents.~~ **2012**, 68, 10696-10747. (e)

Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. The Development of the First Catalyzed Reaction of Ketenes and Imines: Catalytic, Asymmetric Synthesis of β -Lactams. *J. Am. Chem. Soc.* **2002**, 124, 6626-6635. (e) McKittrick, B. A.; Ma, K.; Huie, K.; Yumibe, N.; Davis, H.; Clader, J. W.; Czarnecki, M.; McPhail A. T. Synthesis of C3 Heteroatom-Substituted Azetidiones That Display Potent Cholesterol Absorption Inhibitory Activity. *J. Med. Chem.* **1998**, 41, 752-759. (f) Li, B.; Wang, Y.; Du, D. M.; Xu, J. Notable and Obvious Ketene Substituent-Dependent Effect of Temperature on the Stereoselectivity in the Staudinger Reaction. *J. Org. Chem.* **2007**, 72, 990-997. (g) Nahmany, M.; Melman, A. Simple Approach to β -Lactam Derivatives from N-Acylimidazoles. *J. Org. Chem.* **2006**, 71, 5804-5806.

[15] (a) Janikowska, K.; Pawelska, P.; Makowiec, S. One-Step Synthesis of β -Lactams with Retro-Amide Side Chain. *Synthesis*, **2011**, 1, 69-72. (b) Zakaszewska, A.; Najda, E.; Makowiec, S. The stereoselective formation of β -lactams with acyl ketenes generated from 5-acyl-Meldrum's acids. *New. J. Chem.* **2016**, 40, 6546-6549. (c) Zakaszewska, A.; Najda-Mocarska, E.; Makowiec, S.; Evidence for an umpolung type of [2+2] cycloaddition of 2-carbamoyl ketenes. *New. J. Chem.* **2017**, 41, 6067-6070. (d) Zakaszewska, A.; Najda-Mocarska, E.; Makowiec, S. A new approach to the stereoselective synthesis of trans-3-carbamoyl- β -lactam moieties *New. J. Chem.* **2017**, 41, 2479-2489.

[16] Yamamoto, Y.; Watanabe, Y. 1,3-Oxazines and Related Compounds. XIV. Facile Synthesis of 2,3,6-Trisubstituted 2,3-Dihydro-1,3-oxazine-5-carboxylic Acids and 1,4-Disubstituted 3-Acyl- β -lactams from Acyl Meldrum's Acids and Schiff Bases *Chem. Pharm. Bull.* **1987**, 35, 1871-1878.

[17] Emtenäs, H.; Soto, G.; Hultgren, S. J.; Marshall, G. R.; Almqvist, F. Stereoselective synthesis of optically active beta-lactams, potential inhibitors of pilus assembly in pathogenic bacteria. *Org. Lett.* **2000**, *2*, 2065-2067.

[18] Pemberton, N.; Emtenäs, H.; Boström, D.; Domaille, P. J.; Greenberg, W. A.; Levin, M. D.; Zhu, Z.; Almqvist, F. Cycloaddition of delta2-thiazolines and acyl ketenes under acidic conditions results in bicyclic 1,3-oxazinones and not 6-acylpenams as earlier reported. *Org. Lett.* **2005**, *7*, 1019-1021.

[19] (a) Emtenäs, H.; Alderin, L.; Almqvist, F. An enantioselective ketene-imine cycloaddition method for synthesis of substituted ring-fused 2-pyridinones. *J. Org. Chem.* **2001**, *66*, 6756-6761. (b) Pemberton, N.; Aberg, V.; Almstedt, H.; Westermark, A.; Almqvist, F. Microwave-assisted synthesis of highly substituted aminomethylated 2-pyridones. *J. Org. Chem.* **2004**, *69*, 7830-7835. (c) Emtenäs, H.; Carlsson, M.; Pinkner, S. J.; Hultgren S. J.; Almqvist, F. Stereoselective synthesis of optically active bicyclic beta-lactam carboxylic acids that target pilus biogenesis in pathogenic bacteria. *Org. Biomol. Chem.* **2003**, *1*, 1308-1314. (d) Chorell, E.; Pinkner, J. S.; Phan, G.; Edvinsson, S.; Buelens, F.; Remaut, H.; Waksman, G.; Hultgren, S. J.; Almqvist, F. Design and Synthesis of C-2 Substituted Thiazolo and Dihydrothiazolo Ring-Fused 2-Pyridones: Pilicides with Increased Antivirulence Activity. *J. Med. Chem.* **2010**, *53*, 5690-5695. (e) Emtenäs, H.; Pinkner, S. J.; Jones, M. J.; Jakobsson, L.; Hultgren, S. J.; Almqvist, F. Functionalization of bicyclic 2-pyridones targeting pilus biogenesis in uropathogenic *Escherichia coli*. *Tetrahedron Lett.* **2007**, *48*, 4543-4546.

[20] (a) Yamamoto, Y.; Watanabe, Y.; Ohnishi, S. 1, 3-Oxazines and Related Compounds. XIII. Reaction of Acyl Meldrum's Acids with Schiff Bases Giving 2, 3-Disubstituted 5-Acyl-3, 4, 5, 6-tetrahydro-2H-1, 3-oxazine-4, 6-diones and 2, 3, 6-Trisubstituted 2, 3-Dihydro-1, 3-



oxazin-4-ones. *Chem. Pharm. Bull.* **1987**, *35*, 1860-1870. (b) Makowiec, S.; Najda, E.; Janikowska, K. Thermal Decomposition of Carbamoyl Meldrum's Acids: A Starting Point for the Preparation of 1,3-Oxazine Derivatives. *J. Heterocycl. Chem.* **2015**, *52*, 205-210.

[21] Punda, P.; Makowiec, S. One-Step Formation of N-Alkenyl-malonamides and N-Alkenyl-thiomalonamides from Carbamoyl Meldrum's Acids. *Synth. Commun.* **2013**, *43*, 1362-1367.

[22] (a) De Kimpe, N.; De Smaele, D.; Hofkens, A.; Dejaegher, Y.; Kesteleyn, B. Synthesis of 3-alkenylamines, 4-alkenylamines and 3-allenylamines via a transamination procedure. *Tetrahedron* **1997**, *53*, 10803-10816. (b) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. Formation and isomerization of 2-azaallyllithium reagents in deprotonations of N-benzyl ketimines containing α -protons. *J. Org. Chem.* **1985**, *50*, 4549-4553.

[23] (a) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D.; β -, γ - and δ -Lactams as conformational constraints in ring-closing metathesis. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695-1702. (b) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A. Enyne metathesis for the facile synthesis of highly functionalised novel bicyclic β -lactams. *Chem. Commun.* **1997**, *15*, 1375-1376. (c) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. Tandem Ireland-Claisen Rearrangement Ring-Closing Alkene Metathesis in the Construction of Bicyclic β -Lactam Carboxylic Esters. *J. Org. Chem.* **2000**, *65*, 3716-3721. (d) Watson, K. D.; Carosso, S.; Miller, M. J. New and Concise Syntheses of the Bicyclic Oxamazin Core Using an Intramolecular Nitroso Diels-Alder Reaction and Ring-Closing Olefin Metathesis. *Org. Lett.* **2013**, *15*, 358-361. (e) Desroy, N.; Robert-Peillard, F.; Toueg, J.; Duboc, R.; Hénaut, Ch.; Rager, M-N.; Savignac, M.; Genêt, J-P. An Efficient Route to 4/5/6 Polycyclic β -Lactams. *Eur. J. Org. Chem.* **2004**, *23*, 4840-4849. (f) Woźnica,

M.; Masnyk, M.; Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M.; Frelek, J. Structure–Chiroptical Properties Relationship of Carbapenams by Experiment and Theory. *J. Org. Chem.* **2010**, *75*, 7219-7226.

[24] (a) Katz, T.J.; Sivavec, T. M. Metal-catalyzed rearrangement of alkene-alkynes and the stereochemistry of metallacyclobutene ring opening. *J. Am. Chem. Soc.* **1985**, *107*, 737-738. (b) Kim, S. H.; Bowden, N.; Grubbs, R. H. Catalytic Ring Closing Metathesis of Dienes: Construction of Fused Bicyclic Rings. *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802. (c) Stragies, R.; Schuster, M.; Blechert, S. A Crossed Yne–Ene Metathesis Showing Atom Economy. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518-2520.

[25] Boyer, N.; Gloanec, P.; Nanteuil, G.; Jubault, P.; Quiriona, J. Ch. Chemoselective and stereoselective synthesis of gem-difluoro- β -aminoesters or gem-difluoro- β -lactams from ethylbromodifluoroacetate and imines during Reformatsky reaction. *Tetrahedron* **2007**, *63*, 12352-12366.