Organic & Biomolecular Chemistry

REVIEW

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 10134

Biologically active γ-lactams: synthesis and natural sources

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Received 22nd June 2016,
Accepted 5th October 2016

DOI: 10.1039/c6ob01349j

www.rsc.org/obc

The γ-lactam moiety is present in a large number of natural and non-natural biologically active compounds. The range of biological activities covered by these compounds is very broad. Functionalized γ-lactams are thus of high interest and have great potential in medicinal chemistry. This review provides a description of the title compounds by focusing on their synthesis, natural sources and biological activities.

1 Introduction

The γ-lactam ring, also known as γ-butyrolactam, pyrrolidin-2-one, azolidin-2-one or 2-oxopyrrolidine, is part of the core structure of a large number of natural and non-natural compounds covering a broad spectrum of biological activities. Accordingly, γ-lactams are of primary interest in medicinal chemistry and many synthetic strategies have been disclosed to access this structural moiety.

The interest in this scaffold started with the observation of the increasing bacterial resistance toward traditional β-lactam antibiotics. To overcome this resistance issue it was necessary to move away from the β-lactam core. Knowing that a suitable activated amide bond is essential for the activity (but not the β-lactam ring), the attention turned naturally to γ-lactams and their analogues, and more specifically to bicyclic γ-lactams such as penem derivatives.

It is in 1986 that the first γ-lactam analogues of penicillins active as antibiotics were reported, independently, by Baldwin *et al.* and researchers from Eli Lilly.[1–4] According to Baldwin, who developed compound A (Fig. 1), the increase in reactivity, and thus the biological activity, of γ-lactam analogues of penems can be accounted for by the delocalization of the lactam nitrogen lone pair into the olefin π system (and stabilization by an electron withdrawing group X).[5]

Eli Lilly's group agreed with this assumption and performed additional molecular modeling studies on compounds B.[6] The results showed that bicyclic γ-lactams bearing an acylamino

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G. G. Muccioli

Giulio Muccioli studied pharmacy at the Université catholique de Louvain (Belgium) and received his Ph.D. in 2005 under the guidance of Prof. Didier Lambert. After a postdoctoral stay in Prof. Nephi Stella's lab at the University of Washington (Seattle, USA) he returned to the Université catholique de Louvain as an F.R.S.-FNRS Research Fellow (2007–2008). Since 2008 he has been a professor and leading a research group within the Louvain Drug Research Institute (Université catholique de Louvain). His research interests encompass the study of bioactive lipids in the context of inflammatory diseases, from their quantification to the study of their therapeutic potential.

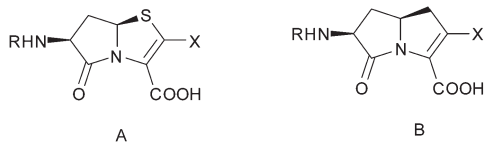


Fig. 1 First γ-lactam structures showed to possess a biological activity (in A: X = CO_2Ph; in B: X = CO_2Me, CN).

side chain at C7 instead of C6 and in a β orientation are conformational analogues of β-lactam antibiotics. The decrease in activity resulting from the lower ring strain of the γ-lactam ring compared to β-lactam could be offset by the acylamino side chain.

Due to low but detectable levels of antibacterial activity, these two compounds did not eventually go on the market. Yet, they inspired many chemists to design new biologically active compounds possessing a γ-lactam ring and develop efficient routes toward these compounds.[7] Accordingly, a very large number of pharmaceutically active γ-lactams have since been reported, including antibiotics, anti-inflammatory, cytotoxic and antitumor compounds. Several natural compounds have also been found to possess this structural moiety.

In this review, we focus exclusively on non-aromatic γ-lactam compounds possessing an actual biological activity.[8,9] In the first part, the different approaches developed for their synthesis are described.[10] Several strategies involve the construction of the γ-lactam heterocycle, through a cyclization or an annulation reaction. The γ-lactam ring can also be formed by the modification of a pre-existing five-membered ring *via* a reduction or an oxidation process. In the second part of this review, we will discuss about γ-lactams which are non-synthetic but have been extracted from a natural source.

R. Robiette

Raphaël Robiette studied chemistry at the Université catholique de Louvain (Belgium) and received his Ph.D. in 2003 under the guidance of Prof. Jaqueline Marchand-Brynaert. He then carried out postdoctoral studies with Prof. Michael Jung, University of California at Los Angeles (2003–2004), and then with Profs Varinder Aggarwal and Jeremy Harvey, University of Bristol (2004–2005). In 2005, he returned to Belgium as an F.R.S.-FNRS Research Fellow at the Université catholique de Louvain. In 2009, he was promoted to Chercheur Qualifié of the F.R.S.-FNRS and Professor. His research interests lie in the fields of organic, physical–organic and medicinal chemistry.

2 Synthesis of the γ-lactam core

Many synthetic approaches have been developed for the preparation of γ-lactam structures.[11–13] The most intuitive method, and the most widely used, is the cyclization by amide formation between a carboxylic group and an amine or an amine precursor (Fig. 2). The construction of the γ-lactam ring can also be performed by ring-closing an aliphatic amide either by *N*-alkylation or by C–C bond formation. Beside these cyclization strategies, several (3 + 2) and (4 + 1) cycloaddition/annulation reactions leading to the γ-lactam core have also been devised.

2.1. Cyclization

2.1.1. *Via* amide bond formation

2.1.1.1. From amino acid derivatives. In 1964, Jenkins *et al.* elaborated the synthesis of a substituted γ-lactam named doxapram (**3**) (Scheme 1).[14] Pyrrolidine **1** was *in situ* transformed into an acyl bromide and subsequent intramolecular addition of the tertiary amine onto this later followed by opening of the pyrrolidine ring by bromide led to pyrrolidinone **2**. A single

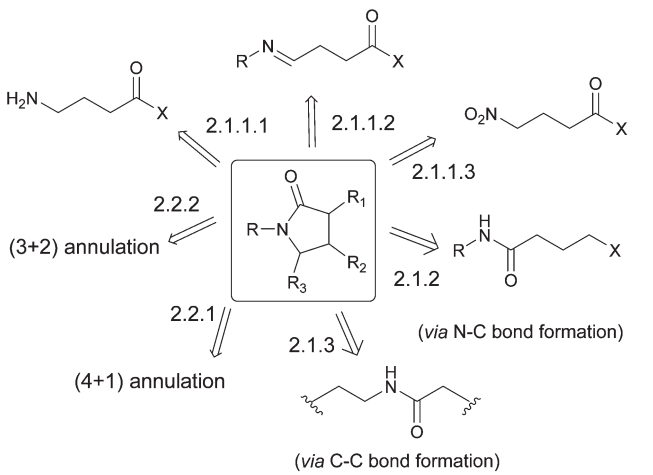
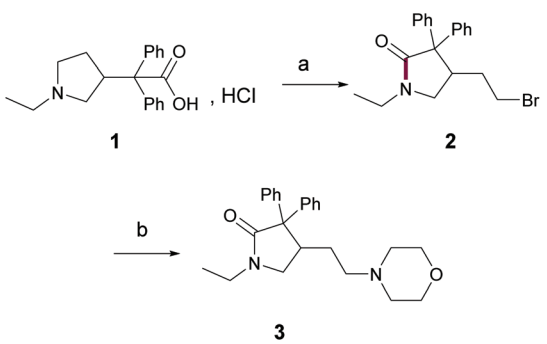


Fig. 2 Overview of synthetic strategies to build the γ-lactam core (X = leaving group).



Scheme 1 Synthesis of doxapram **3**. (a) PBr_3, CH_2Cl_2, reflux, 13 h, 15%; (b) morpholine, EtOH, 90–120 °C, 8 h, 73%.

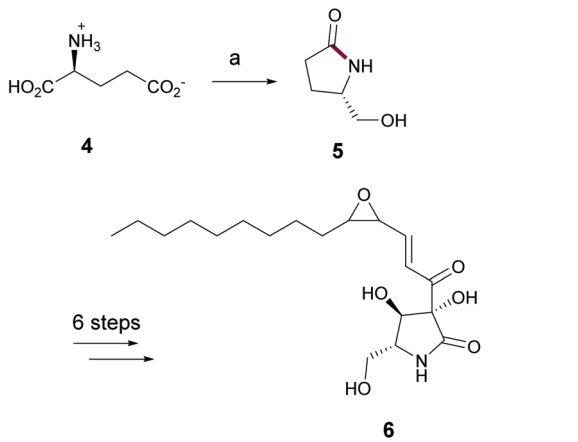
step, substitution of the bromide atom by morpholine, completed the synthesis of doxapram. This compound is a respiratory stimulant which increases the rate and depth of breathing by activating chemoreceptors the carotids (the activation encourages breathing deeper).[15]

Starting from L-glutamic acid, Williams *et al.* performed, in 1999, the condensation of an amine with a carboxylic acid to access, after reduction, γ-lactam **5** (Scheme 2).[16] This was the first step in the total synthesis of (+)-pramanicin **6**. Thanks to their work, the stereochemistry of naturally occurring pramanicin could be established. (−)-Pramanicin, the natural compound, exhibits antimicrobial and antibacterial activity (see section 4.1.7).[17]

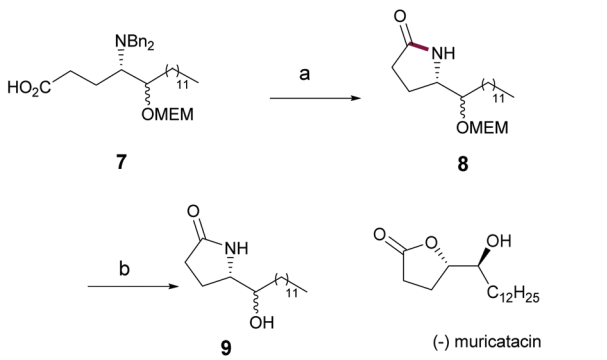
The group of Pérez-Encabo published the synthesis of two aza-analogues of muricatacin using a similar strategy.[18] Muricatacin is a natural hydroxy lactone with antiproliferative activity against several human cell lines (K562, HeLa, HL60).[19] The two aza-analogue compounds synthesized were the *syn* and *anti* 5-(α-hydroxy)-substituted γ-lactams (**9**) (Scheme 3). In both cases, the quantitative deprotection of the amine group in **7** by hydrogenolysis furnished the free amino-alcohol which then ring-closed in the presence of DCC and 4-pyrrolidinopyridine leading to γ-lactam **8** in a reasonable yield. Final deprotection of the alcohol function allowed obtaining *syn* and *anti* **9**. Cavé's group showed that these compounds possess interesting cytotoxic activity on a keratin-forming tumor cell line HeLa (KB cells, *in vitro* assays, EC_{50} = 2.7 to 7.2 μg mL^{-1}), in the same range as muricatacin itself.

Furthermore, in 2000, Yocum *et al.* used Ohfune's methodology[20] (reaction of an amine and a base without heating) for producing new matrix metalloproteinase-13-inhibitors (MMP-13 inhibitors) (Scheme 4). In fact, by studying the structure of the known inhibitors and by analyzing the X-ray crystal structure of MMPs (MMP-13 in particular), the authors established that 5 (or 6)-membered peptides could fit the active site. This structure based approach led to compound **12**, a potent inhibitor of MMP-13 with an IC_{50} of 7 nM.[21] According to the authors, the conformational rigidity given by the γ-lactam ring could explain the higher selectivity of **12** compared to acyclic compounds. This study should pave the way for the development of inhibitors of other MMPs.

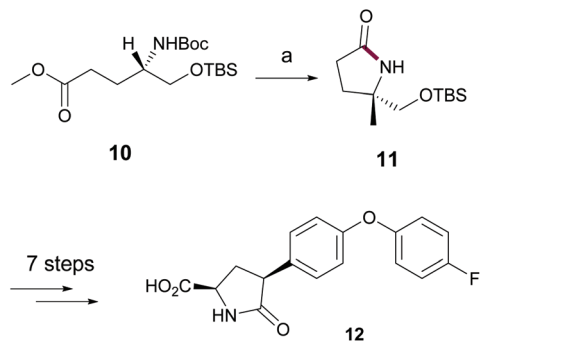
In 2008, Różalski *et al.* performed an intramolecular condensation between the *tert*-butylic ester and the primary amine groups of **13** upon heating at reflux of methanol in the presence of sodium carbonate (Scheme 5).[22] The aim was to produce analogues of α-methylene-γ-lactones, known to have a



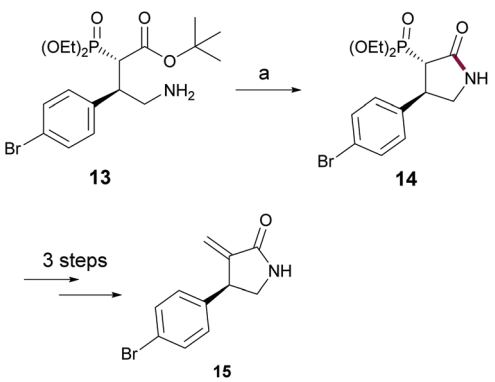
Scheme 2 Synthesis of (+) pramanicin **6**. (a) (i) H_2O, reflux; (ii) MeOH, $SOCl_2$ cat.; (iii) $NaBH_4$, EtOH, 81%.



Scheme 3 Synthesis of **9**. (a) (i) H_2, $Pd(OH)_2/C$, MeOH, r.t., 2 h; (ii) DCC, 4-pyrrolidinopyridine, CH_2Cl_2, r.t., 5 h, 55% (*syn* isomer) or 74% (*anti* isomer); (b) $TiCl_4$, CH_2Cl_2, 0 °C, 4 h, 93% (*syn* isomer) or 70% (*anti* isomer).



Scheme 4 Synthesis of **12**. (a) NaH, Et_2O, r.t., 16 h (yield not reported).

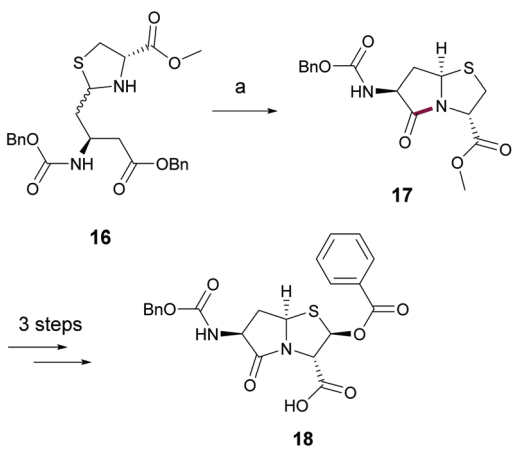


Scheme 5 Synthesis of **15**. (a) Na_2CO_3, MeOH, reflux, 4 h, 70%.

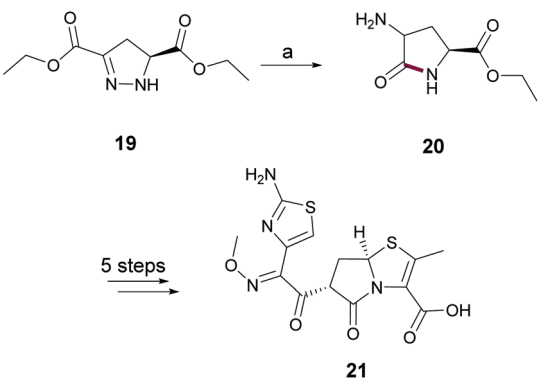
cytotoxic activity against leukemia cells. Accordingly, the synthesized compounds were evaluated against two human leukemia cell lines (HL-60 and NALM-6). They displayed very low cytotoxic activity: IC_{50} of the more active compound (**15**) is 433 μM (IC_{50} of carboplatin, the reference compound, is 0.7 μM). The authors were the first to report that N-analogues of α-methylene-γ-lactones are less efficient. Nevertheless, they described a simple and very diastereoselective method for obtaining phosphoryl-γ-lactams.

A related method involving a thiazolidine and a benzylic ester group *via* reflux of pyridine was also used by Lee in 1986 (Scheme 6).[1] The bicyclic lactam **18** designed, as an analogue of penem, showed weak but real antibacterial activity against Gram positive and negative bacteria (data not available).[1]

γ-Lactam analogues of penems and carbapenems have been subjected to intensive studies at the end of the 80s due to their structural homology with β-lactam antibiotics which act by acylating enzymes involved in bacterial cell wall synthesis. It turned out that they are mostly devoid of activity. Only a few compounds exhibited biological activity; among them, a penem analogue, **21** (Scheme 7).



Scheme 6 Synthesis of **18**. (a) Pyridine, reflux, 14 h, 45%.

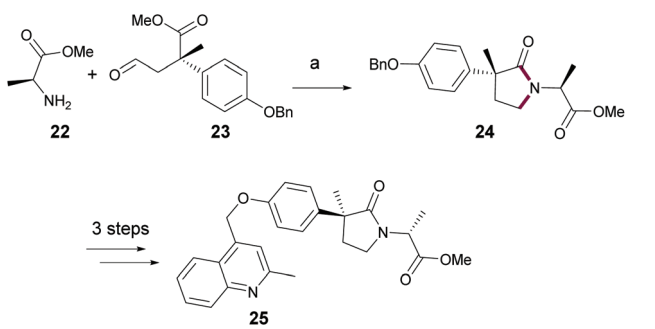


Scheme 7 Synthesis of **21**. (a) Ra-Ni, EtOH, 60–115 °C, 6 h, 88%.

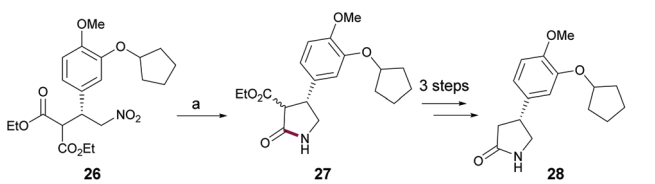
Boyd *et al.* investigated the effect of the presence of the 2-amino-thiazol-4-yl-methoximino-acetamido substituent at the alpha position of the carbonyl, known to enhance biological activity in β-lactam systems. Reductive cleavage of pyrazoline **19** with RANEY® nickel gives a diamino ester which cyclizes spontaneously into two diastereoisomers aminopyrrolidinones **20** (Scheme 7).[2] Compound **21** displayed low but demonstrable activity against three organisms: Minimum Inhibitory Concentration (MIC) values equal 4.0, 8.0, and 32.0 μg ml^{-1} against *Streptococcus pyogenes* (C0203), *S. pneumoniae* (PARK) and *Staphylococcus aureus* (X1.1) respectively. Interestingly, **21** is active against *S. aureus* X1 but inactive towards its L-form, *S. aureus* X680. This last result is consistent with a mechanism of action based on the cell wall inhibition type.[6]

2.1.1.2. From an imine. The group of Decicco reported the formation of a γ-lactam from an imine by a one-pot reduction/cyclization process.[23] The imine was formed *in situ* by condensation of **22** and **23** (Scheme 8). After reduction and cyclization, a 1 : 1 mixture of diastereoisomers was obtained. These two isomers could however be easily separated by chromatography. This strategy allowed eventually the synthesis of functionalized γ-lactam **25** which is a potent TNFα converting enzyme (TACE) inhibitor (K_i = 0.56 nM). This compound showed a very good selectivity for TACE (from >2000 to >200 fold) relative to ten classes of MMPs.

2.1.1.3. From a nitro group. Barnes group reported, in 2002, the reduction of γ-nitroester **26** into a γ-aminoester which, *in situ*, cyclizes to give γ-lactam **27**, an intermediate in the synthesis of (*R*)-rolipram (Scheme 9).[24] RANEY® nickel was chosen to perform the hydrogenation in very good yields and



Scheme 8 Synthesis of **25**. (a) (i) Zn, AcOH, reflux; (ii) separation, 80% (for both isomers).



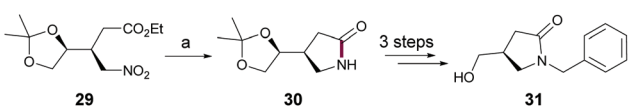
Scheme 9 Synthesis of (*R*)-rolipram (**28**). (a) Ra-Ni/H_2, H_3PO_4, THF, 50 °C, not purified and yield not reported.

no purification was needed at the end of this step. It is interesting to note that in the presence of hydrochloric or triflic acid, the reaction was slower and by-products were formed. The reaction rate was also slowed down when using more than 20 mol% of phosphoric acid (due to the competitive reaction between the acid and nickel). (*R*)-Rolipram **28**, obtained in 92% yield from **26**, is a potent inhibitor of phosphodiesterase (PDE) of type IV exhibiting antidepressant and anti-inflammatory activity.[25]

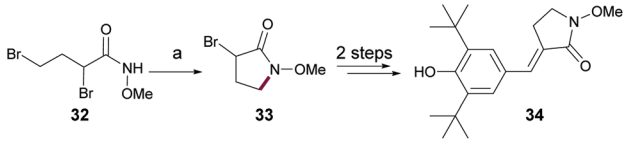
Two years later, Costa *et al.* used a similar approach to obtain γ-lactam **30** from γ-nitroester **29** (Scheme 10).[26] An excess of ammonium formate and a long reaction time are required to reduce entirely the nitro group. This palladium-catalyzed cyclization reaction is a key step in the synthesis of (*S*)-WEB-1868 (**31**), a cognitive enhancer,[27] also called a nootropic compound.[28]

2.1.2. Intramolecular *N*-alkylation of an amide. Katayama *et al.* showed that intramolecular cyclization of γ-bromo-amide **32** in the presence of a strong base affords the corresponding *N*-methoxy substituted γ-lactam **33** (Scheme 11).[29] Using this strategy, they synthesized **34** which shows *in vivo* inhibitory activity on adjuvant-induced arthritis (assays on rats). Furthermore, it is well absorbed in the gastrointestinal tract and is less ulcerogenic than other commercially available anti-inflammatory drugs, compound **34** having thus a potent anti-inflammatory activity.

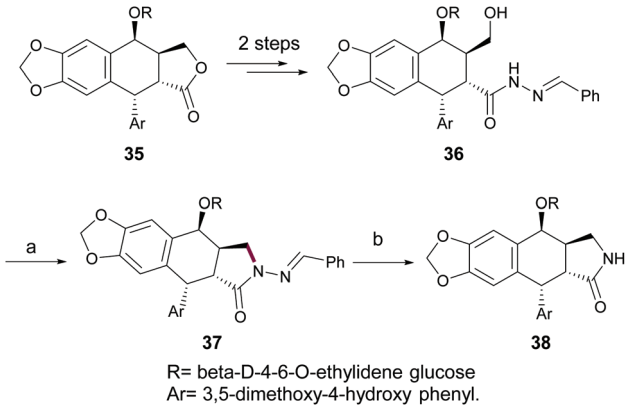
In 1989, Doyle *et al.* were the first to report a cyclization strategy using the Mitsunobu reaction to obtain a γ-lactam ring.[30] The strategy was used to convert etoposide **35**, an anti-tumor lactone marketed as Vepesid®, into the corresponding lactam **38** (Scheme 12). Interestingly, the Mitsunobu reaction of hydrazine derivatives (**36**) proceeds with an excellent yield whereas direct conversion of lactone **37** into γ-lactam **38** using ammonia remained unsuccessful. γ-Lactam **38** shows a weak activity against P388 leukemia *in vivo*. The antitumor activity was expressed as % T/C *i.e.* the percentage of median survival time of the drug-treated group to that of the control group. It equals 185% for a dose of 160 mg kg^{-1}. In comparison, it is 235% for etoposide with a smaller dose of 100 mg kg^{-1} demonstrating that lactone analogues are more active.



Scheme 10 Synthesis of **31**. (a) NH_4HCO_2, Pd–C 10%, MeOH, r.t., 4 d, 85%.



Scheme 11 Synthesis of **34**. (a) NaH, 2 h, 0 °C, 75%.

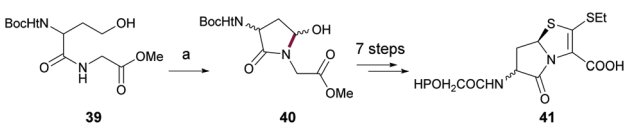


Scheme 12 Synthesis of **38**. (a) DEAD, PPh_3, THF, 25 °C, 20 min, 90%; (b) Ra-Ni, EtOH, reflux, 68%.

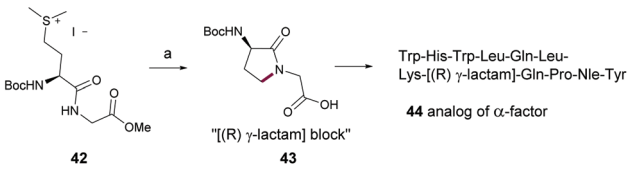
Furthermore, lactam **38** was also evaluated in *in vitro* cytotoxicity assay against multiple human and murine tumor cell lines and appeared to be more active than etoposide in two cell-lines at an equivalent dose.[31]

Another interesting method to access the γ-lactam core from a linear amide is the Swern oxidation of a primary alcohol into an aldehyde which spontaneously undergoes cyclization to form the desired heterocycle. This method was used by Ghosez *et al.* in 1993 to obtain an intermediate γ-lactam **40** (3 : 1 mixture *cis*/*trans*) and finally furnish **41**, an homolog of penems (Scheme 13).[32] Biological evaluations have revealed a weak antibacterial activity (MIC = 320 μg ml^{-1} against *S. aureus*) for **41**.

In 1998, Naider's group synthesized a "γ-lactam building block" from acyclic amino acid **42** (Scheme 14).[33] Basic conditions were required to afford the subsequent cyclization into the five membered ring. The strategy was to obtain a constrained analog of Pro-Gly residues in *Saccharomyces cerevisiae* α-factor. Compound **44** was found to be equally active as the wild one and helped in the understanding of the mechanism of action.



Scheme 13 Synthesis of **41**. (a) $(COCl)_2$, Et_3N, DMSO, –70 °C to 0 °C, 74%.



Scheme 14 Synthesis of **44**. (a) (i) NaH, CH_2Cl_2/DMF, 0 °C, 2,5 h; (ii) CH_3COOMe, water, r.t., 16 h, 98%.

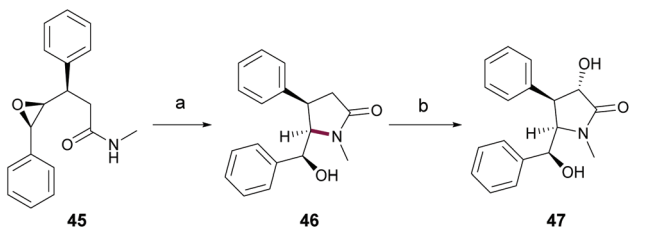
In 2013, Huang *et al.* performed the intramolecular epoxide ring opening reaction by an amide moiety to access the γ-lactam core (Scheme 15).[34] The base (*t*BuOK) deprotonates the amide which then undergoes S_N2 type reaction onto the epoxide. The reaction proved to be straightforward and provides the corresponding γ-lactam in high yield. Using this strategy, a single stereoisomer of a natural compound, (−)-clausenamide (**47**), was obtained in 6 steps. Interestingly, when extracted from nature, clausenamide is found as a racemate (see section 4.2.1). The total synthesis of a single enantiomer was thus really important because the (+)-clausenamide proved to have no activity whereas the (−)-clausenamide has strong potential in the treatment of Alzheimer's disease (human clinical trials are in progress in China). In fact, it was shown that (−)-clausenamide increased the population spike amplitude (PSA) by 58.1% that is to say was able to induce basal synaptic transmission and thus play a role in learning and memory. The synthesis and the study of other diastereoisomers of clausenamide showed to be also promising antidementia drugs.[35] Indeed, they exert a significant neuroprotective effect against β-amyloid in cellular models and potentiate synaptic transmission in the dentate gyrus of rats.

2.1.3. *Via* C–C bond formation. In 1989, Danishefsky *et al.* reported the Dieckmann condensation of a β-keto amide ester to access the γ-lactam core of equisetin **49**.[36] The cyclization takes place quite rapidly (30 min) and provides the desired compound in a quantitative yield. Equisetin is a natural compound showing a broad range of biological activities (see section 4.1.5 for further details) (Scheme 16).

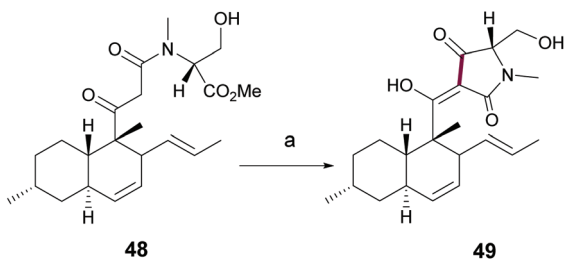
A Dieckmann condensation strategy was also used in 1998 by Corey in the enantioselective synthesis of lactacystin **52**, a 20S proteasome inhibitor (see section 4.3.4) (Scheme 17).[37] γ-Lactam **51** was obtained as a 1 : 1 mixture of two diastereoisomers. Corey was the first author to report the total synthesis of lactacystin, in 1992.[38] He inspired the group of Smith for their total synthesis of this γ-lactam.[39,40]

In 1993, Ninomiya's group reported a radical reaction to close the γ-lactam ring (Scheme 18).[41] Starting from the *N*-allyl-*N*-benzylcinnamamide, they performed a smooth thiyl radical addition–cyclization in the presence of a disulphane, furnishing a 1 : 1 mixture of *cis*/*trans* diastereoisomers of **54**. Nine other steps were necessary to access the racemic natural product anantine **55**. The same synthesis was applied to obtain one of its regioisomers, the racemic isoanantine. Both exhibit cytotoxic, antitumor and anti-inflammatory activities (see section 4.2.2).[42]

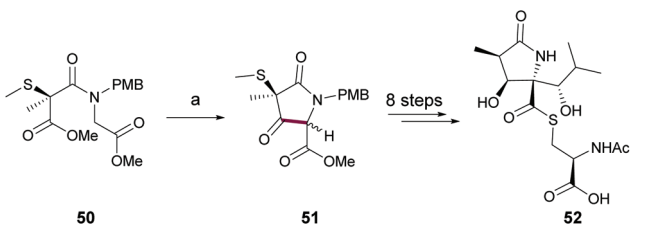
Kozikowski *et al.* used Kagan's reagent to perform the ring closure of a bioactive compound involved in Protein Kinase C (PKC) modulation.[43] Samarium iodide-mediated ring closure of **56** provides γ-lactam **57** as a single diastereoisomer in a good yield (Scheme 19). This step was used in the synthesis of **58** which was developed *via* a structure-based design study aiming at finding new mimics of indolactam. Indolactam is able to activate PKC, this latter being involved in various biological effects (such as apoptosis and neuronal plasticity).



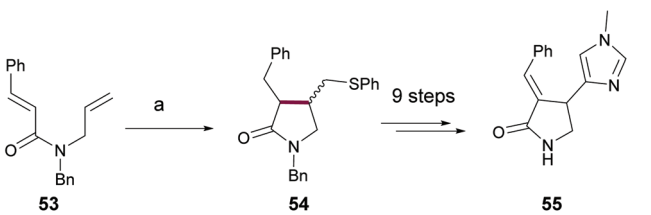
Scheme 15 Synthesis of (−)-clausenamide **47**. (a) *t*BuOK (1 eq.), *t*BuOH, 45 °C, 3 h, 88%; (b) LDA, Davis oxidant, THF, −78 °C, 80%.



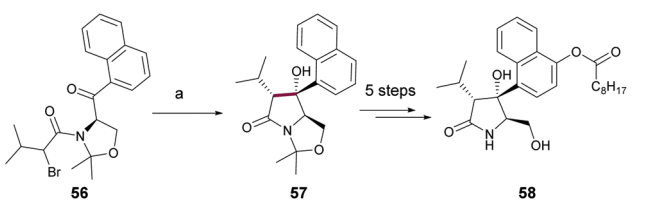
Scheme 16 Synthesis of equisetin **49**. (a) NaH, CH_2Cl_2, 0 °C to r.t., 30 min, 100%.



Scheme 17 Synthesis of lactacystin **52** by Dieckmann condensation. (a) LDA, THF, −78 °C to 0 °C, 2 h, 93%.



Scheme 18 Synthesis of (±)-anantine **55**. (a) *hν*, $(PhS)_2$, PhSH, 71%.



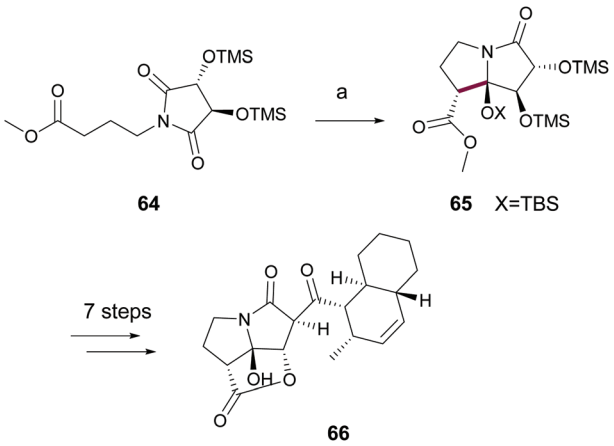
Scheme 19 Synthesis of **58**. (a) SmI_2, $FeCl_3$, THF–HMPA, r.t., 91%.

Compound **58** was thus evaluated as an inhibitor of phorbol 12,13-dibutyrate binding from a recombinant PKCα. The K_i value of 296 nM shows that compound **58** is active and could be a promising hit in PKC modulation's area.

Gu *et al.* reported, in 2001, the enantioselective synthesis of (−)-dysibetaine **61**, a natural compound extracted from the marine sponge *Dysidea herbacea*. The key step of the synthesis involves the formation of the γ-lactam core *via* intramolecular alkylation of amide **59** which yields pyrrolidinone **60** as a mixture of diastereomers easily separable in the next step of the synthesis (Scheme 20).[44] The synthesis of dysibetaine **61** (but also of 3 other stereoisomers) was accomplished in five more steps from **60**. Dysibetaine showed an interesting feature because three years earlier, Tagawa's group found that it was probably active against glutamate receptors in the CNS[45] (because of its structural proximity with dysiherbaine non-*N*-methyl-D-aspartic acid type glutamate receptor agonist) (see section 4.4.2).

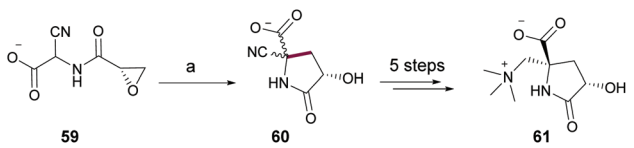
Transition metal-catalyzed reactions can also be applied to the formation of a γ-lactam ring.[46] For example, Jung *et al.* reported the rhodium-catalyzed intramolecular C–H insertion of *N*-benzylated-α-diazo-α-(phenylsulfonyl)acetamide **62** leading to γ-lactam **63** (Scheme 21).[47] Reduction of **63** by lithium provided (*R*)-rolipram **28** which is a selective inhibitor of phosphodiesterase (PDE) type IV, anti-inflammatory agent and antidepressant.[25] Interestingly, both enantiomers are active with an IC_{50} of 1 μM. Numerous enantioselective syntheses of rolipram were however reported,[24,48–54] including the one of Barluenga *et al.* using an oxidation followed by an ester hydrolysis–decarboxylation–carbonyl deprotection sequence (see section 2.2.2).[55]

Danishefsky *et al.* showed that cyclization of an imide with a methyl ester in the presence of a base was very effective to access the γ-lactam core of UCS1025A[56] (even if a 10 : 1 mixture of diastereoisomers was obtained, Scheme 22). The latter is a natural compound reported to possess antimicrobial and antiproliferative activities against cancer cell lines (see section 4.1.6).[57] More specifically, **66** is believed to act by inhibiting telomerase enzyme and thus could be a possible antitumor agent.

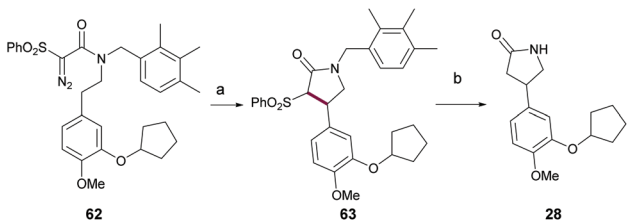


Scheme 22 Synthesis of UCS 1025 A **66**. (a) TBSOTf, iPr2NEt, CH_2Cl_2, −78 °C to r.t., 79%.

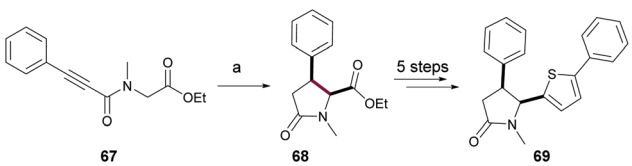
In 2005, Cook *et al.* reported an interesting intramolecular Michael addition to access the γ-lactam core of 17β-HSD-type 2 inhibitors (Scheme 23).[58] This quite atypical strategy was inspired by the work of W. Hartwig[59] on his search for 17β-HSD-type 2 inhibitors (IC_{50} of the best compound is 5.0 μM). In this study, the authors used an intermolecular Michael addition yielding the desired core in a good yield (68%) but a low *cis*/*trans* ratio (2 : 1). Cook *et al.* succeeded in performing the intramolecular 5-*endo*-dig cyclization of alkyne–amide **67** in the presence of LiHMDS followed by a hydrogenation step, providing **68** in an improved 10 : 1 *cis*/*trans* ratio. The authors specified that a purge with argon prior to the basic treatment of the reaction was essential to avoid side-product formation (degradation or oxidation of the desired product). Five further steps allowed obtaining compound **69**. Biological assays showed that this latter is a potent 17β-HSD-type 2 inhibitor (with an IC_{50} of 0.1 μM)[60] and that a *cis* configuration is required for the activity. Inhibition of 17β-HSD-type 2 enzyme (an estradiol degrading enzyme) maintains levels of this hormone in bones, estradiol having a positive effect on the bone mineral density. A novel route is thus opened to treat osteoporosis.



Scheme 20 Synthesis of (−)-dysibetaine **61**. (a) NaOEt, THF, 60 °C, 12 h, 58%.



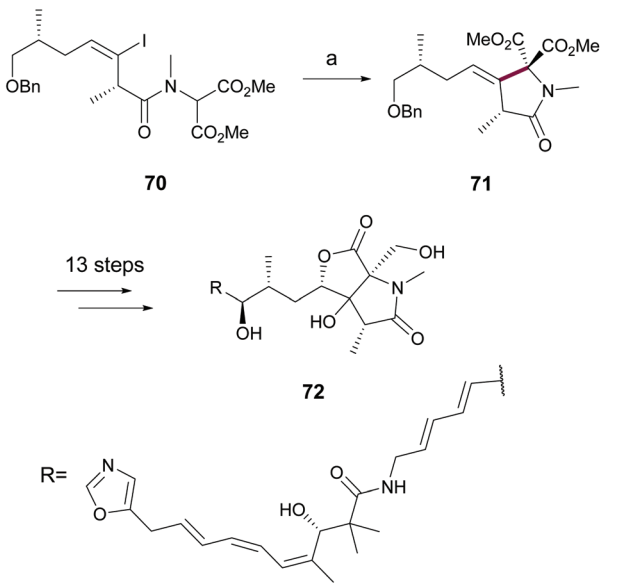
Scheme 21 Synthesis of (±)-rolipram **28** by intramolecular C–H insertion. (a) Cat. $Rh_2(OAc)_4$, DCE, reflux, 75%; (b) Li, NH_3, −78 °C, 90%.



Scheme 23 Synthesis of **69**. (a) (i) $LiN(SiMe)_3$, THF, 0 °C, 2 h, 70%; (ii) H_2, Pd/C, 100%.

In 2007, Hatakeyama *et al.* performed a stereoselective cyclization of a substituted amide into a γ-lactam moiety using palladium catalysis (Scheme 24).[61] The aim of this work was to obtain the natural compound neooxazolomycin **72** in an enantiopure form and *via* a robust synthesis (convergent synthesis). In fact, this natural compound had already been built by the group of De Vita[62] but without any stereocontrol of the bicyclic core. Neooxazolomycin, isolated in 1985 from a broth of *Streptomyces* sp. by the group of Uemura, is a potent antibacterial and antiviral agent (see section 4.3.5).[63]

Salinosporamide A has been the target of many research groups over the last decade, and several strategies have been disclosed to access its γ-lactam core.[64] This natural compound and its analog cinnabaramide A (see sections 4.3.2 and 4.3.3) are very potent 20S proteasome inhibitors at the sight of their



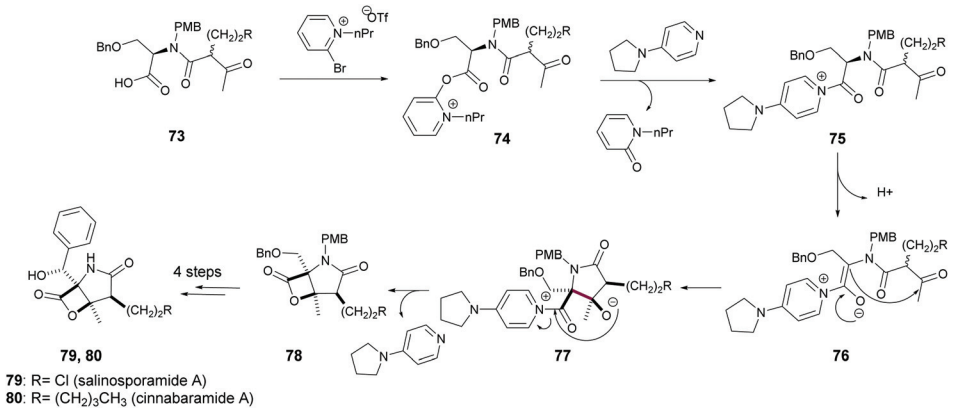
Scheme 24 Synthesis of neooxazolomycin **72**. (a) $Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%), nBu_4NBr, K_2CO_3, DMF/H_2O, 70 °C, 84%.

IC$_{50}$ of 1 and 10 nM, respectively (IC$_{50}$ of the potent and selective irreversible proteasome inhibitor lactacystin is 259 nM). Both compounds are therefore promising molecules to treat cancer.[65] Romo's group synthetic strategy toward these natural compounds consists of a bis-cyclization process which allows the simultaneous construction of γ-lactam and fused β-lactone (Scheme 25).[66] The proposed mechanism for this transformation involves the activation of the carboxylic acid function as pyridone ester (**74**) thanks to the Mukaiyama reagent. Transacylation then takes place with 4-pyrrolidinopyridine, followed by deprotonation by Hünig's base leading to ammonium enolate **76**. This latter undergoes aldol-lactonization *via* **77** to provide the desired skeleton. The main advantage of this synthesis lies in its shortness (despite the fact that racemic compounds are obtained).

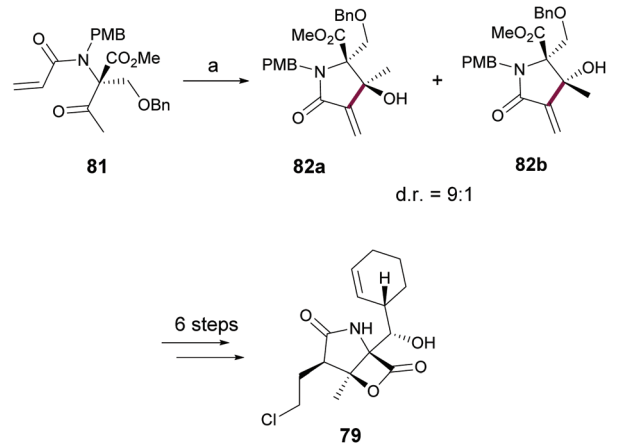
Another strategy for preparing (−)-salinosporamide A involves an intramolecular Morita–Baylis–Hillman reaction. Corey *et al.* used this methodology to transform keto amide ester **81** into γ-lactam **82** (Scheme 26).[67] Two diastereomers are formed in C4 with a diastereomeric ratio in favor of the one leading to (−)-salinosporamide A.

The same group published one year later a new synthesis for this natural compound. Indeed, in order to synthesize a new series of molecules based on the salinosporamide A skeleton, they developed a keto-amide cyclization promoted by a titanium complex as the key step to form the γ-lactam core (Scheme 27).[68] The Kulinkovich reagent (bis-ethoxytitanacyclopropane) promoted the intramolecular carbo-titanation of the acrylamide **83**, which leads to heterocycle **84** in an excellent yield and stereoselectivity (only one stereoisomer could be detected).[69,70]

Another strategy toward γ-lactams is the ring-closing metathesis.[71] Han and Carafa used this methodology in 2011 in their synthesis of **87**, a histone deacetylase inhibitor (HDAC), which is an anti-cancer agent (Scheme 28).[72,73] In their previous work, they developed δ-lactams with good potency in HDAC inhibition. After QSAR studies they however went on with the synthesis of a series of γ-lactams. All the compounds

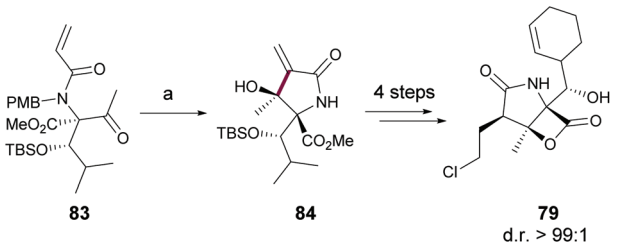


Scheme 25 Synthesis of (±)-salinosporamide A **79** and (±)-cinnabaramide A **80** by the bis-cyclisation process. (a) Modified Mukaiyama reagent, i-Pr_2NEt, 4-pyrrolidinopyridine, CH_2Cl_2, 0 °C, 45%.



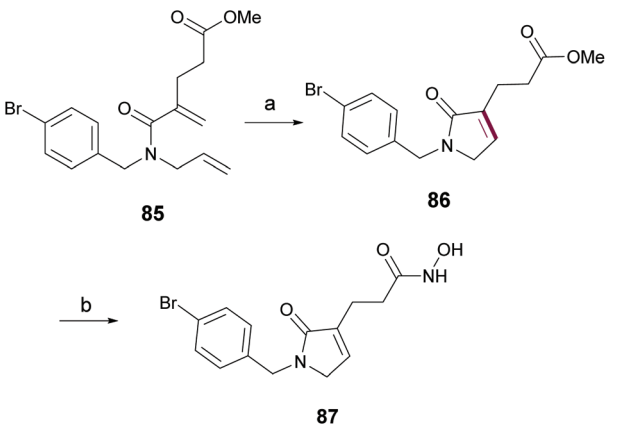
81 82a 82b 79

Scheme 26 Synthesis of (–)-salinosporamide **79** by intramolecular Morita–Baylis–Hillman reaction. (a) (i) Quinuclidine, DME, 0 °C, 7 d, 90%; (ii) $BrCH_2Si(CH_3)_2Cl$, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min, 95%.



83 **84** **79**

Scheme 27 Synthesis of (–)-salinosporamide A **79** by keto-amide cyclization promoted by a Ti complex. (a) (i) $Ti(Oi\text{-}Pr)_4$, C_5H_9MgCl, *t*-BuOMe, –40 °C, 30 min, I_2, –40 °C, 2 h, 0 °C, 2 h; (ii) Et_3N, CH_2Cl_2, r.t., 30 min, 85% (dr > 99 : 1).



85 **86** **87**

Scheme 28 Synthesis of **87**. (a) Grubb's catalyst (2nd generation), CH_2Cl_2, reflux, 12 h, 30%; $KONH_2$, MeOH, 0 °C (yield not reported).

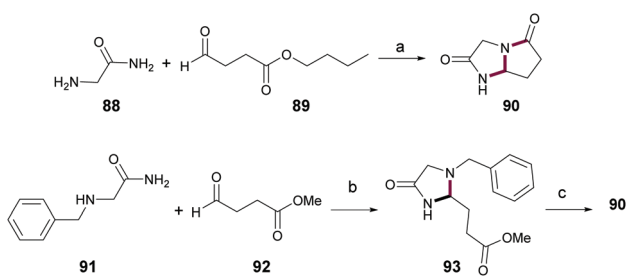
were evaluated as HDAC inhibitors and in cancer cell growth inhibition. One of the most active compounds (**87**, IC_{50} = 16.6 nM) shows good inhibition activities on 7 human cancer cell lines and exhibits promising pharmacokinetic characteristics in view of the results obtained with the preADME program. Thanks to the docking study, the authors showed that the γ-lactam core fitted better than the δ-lactam one in the narrow tunnel of the active site.

2.2. Annulation

2.2.1. (4 + 1) annulation. The first application of a (4 + 1) annulation strategy to the synthesis of a biologically active γ-lactam was reported by Dorigotti *et al.* in 1993.[74] Using an aldehyde as a one-atom unit and an α-aminoamide (glycinamide) as a four-atom unit, they synthesized 1-azabicyclo[3.3.0] octan-3,8-diones **90** upon simple basic refluxing water treatment (Scheme 29). The yield of **90** was however low (23%). Carrying out the reaction in two steps from benzyl protected α-aminoamide **91** and aldehyde **92** was more efficient. Indeed, after deprotection, the obtained corresponding aminal **93** cyclizes to provide the bicyclic lactam **90** in 80% overall yield. Compound **90** is reported to be a potent cognition enhancer[74] which can be seen as a structural analog of oxiracetam,[75] a well-known very potent and safe cognition enhancer. Despite the fact that the mechanism of action is still unknown, the results showed that the γ-lactam core is essential for the biological activity.

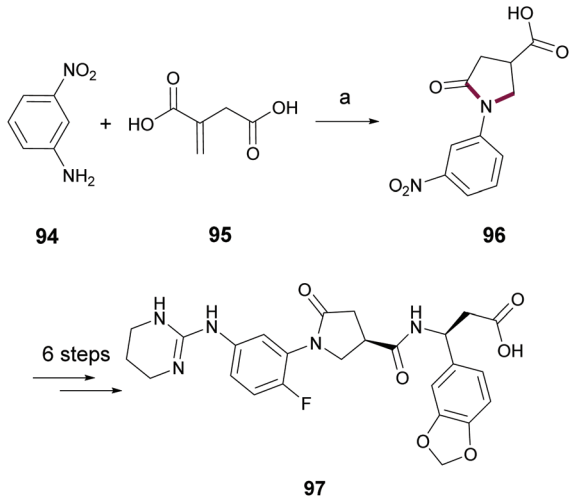
In 2004, Dominguez *et al.* used a (4 + 1) annulation reaction as the first step of the synthesis of *N*-aryl-γ-lactams.[76] In this case, the γ-lactam core is obtained from the condensation of 3-nitroaniline **94** (one-atom unit) with itaconic acid **95** (four-atom unit) under neat conditions at a high temperature (110 °C) (Scheme 30). A racemate was obtained but the two enantiomers were separated later in the synthesis by the use of Evans' chiral auxiliary. As γ-lactam derivatives seem to mimic a specific dipeptide able to interact with a specific integrin receptor, a series of compounds was prepared and tested as $\alpha_v\beta_3$ integrin antagonists *via in vitro* competitive electrochemiluminescence binding assays. This SAR study allowed the authors to identify compound **97** as the most selective and potent $\alpha_v\beta_3$ antagonist (K_i = 0.1 nM, 1*R*2*S*), which could open up a new route to osteoporosis treatment.[77] The diastereoisomer 1*R*2*R* was not active.

Another interesting strategy is the ring opening–ring closure (RORC) lactamization developed by Bouillon *et al.* between a saturated lactone and an aminoloquinoline



88 **89** **90** **91** **92** **93**

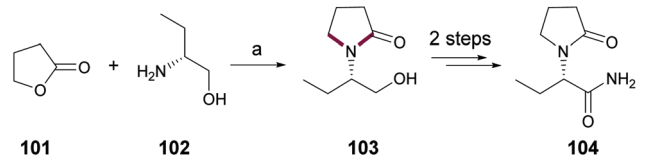
Scheme 29 Synthesis of **90**. (a) NaH 10%, H_2O, reflux, 20 h, 23%; (b) MeOH, reflux, 3 h, 85%; (c) ammonium formate, Pd/C 5%, MeOH–H_2O, reflux, 3 h, 81%.



Scheme 30 Synthesis of **97**. (a) Neat, 110 °C, 8 h, 70%.

derivative (Scheme 31).[78] This (4 + 1) annulation reaction allowed the synthesis of compound **100** which exhibits a good *in vitro* antimalarial activity against *P. falciparum* clones (IC_{50} = 87 nM for 3D7 clones) and no relevant cytotoxicity.[79] This recent work was inspired by the structure of codinaeopsin which showed antimalarial activity (see section 4.1.1)

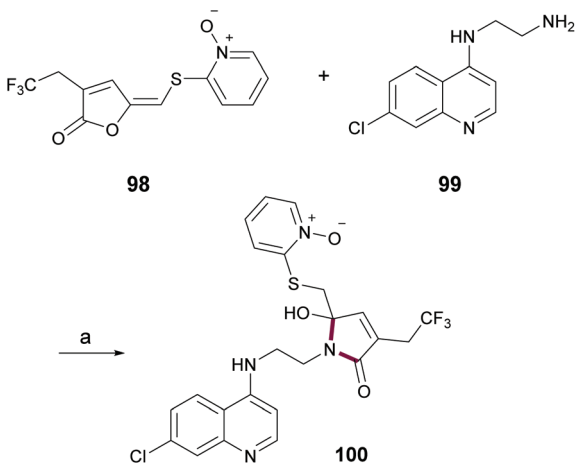
In 2010, Bandichhor *et al.* went on to develop a facile and green synthesis of levetiracetam **104**.[80] The first step consisted of the condensation of γ-butyrolactone **101** and (*S*)-amino butanol (**102**) at high temperatures and under neat conditions to provide the γ-lactam core **103** (Scheme 32). The target molecule was then obtained after two more steps. The synthesis is considered as green not only because of the solvent-free first step but also because no protection/deprotection sequence is used and no side products are generated. Commercially delivered under the name Keppra®, levetiracetam is one of the main anticonvulsant drugs used to treat epilepsy.[81]



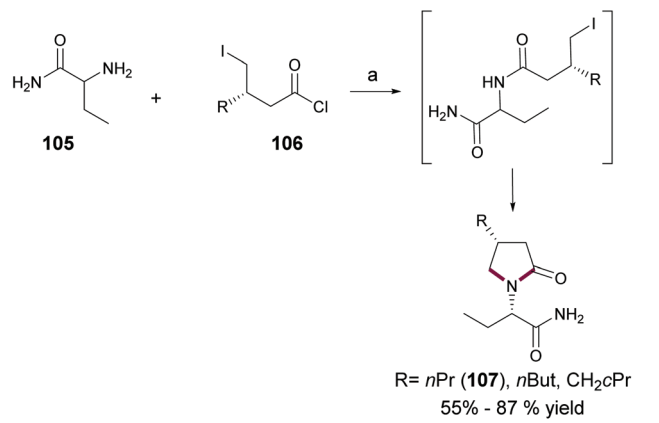
Scheme 32 Synthesis of levetiracetam **104**. (a) Neat, 225 °C, 10 h, 93%.

Along the same lines, Michel *et al.* reported, in 2004, the alkylation/cyclization of 4-butanoyl chloride with amino acids to produce a series of levetiracetam analogues (Scheme 33).[82] The synthetic pathway furnishing the most active structure (**107**; R = *n*Pr) involves the use of a phase-transfer catalyst at low temperatures to avoid racemization. The authors found that this compound is ten times more potent than levetiracetam (assays on mice) and shows significant efficiency in several animal models of epilepsy.[83] Named brivaracetam, it entered phase II clinical trials in 2003 where it appeared to be well tolerated and potent in the treatment of partial seizures. It consequently entered in phase III clinical trials in 2007 in order to evaluate the efficacy, safety and tolerability of adjunctive drugs in patients with partial-onset seizures and uncontrolled partial-onset seizures.[84,85] UCB announced in January 2015 that brivaracetam would be reviewed in the US and in Europe as an adjunctive for the treatment of partial-onset seizures in patients with epilepsy. In November 2015, the European Medicines Agency's Committee for Medicinal Products for Human Use approved the use of brivaracetam for people with epilepsy. In fact, phase III studies revealed that it significantly reduces the frequency of seizures in patients aged 16 years and older with uncontrolled partial-onset seizures. This molecule will be marketed as Briviact® once finally approved by the European Commission. It is the perfect example of discovery of a new drug by optimization of pharmacodynamics at a molecular target.

In 2011, Patel *et al.* reported the synthesis of TACE inhibitors possessing a structure close to IK682.[86,87] The key step of their synthesis consisted of the (4 + 1) annulation between



Scheme 31 Synthesis of **100**. (a) THF/MeOH, r.t., 43%.



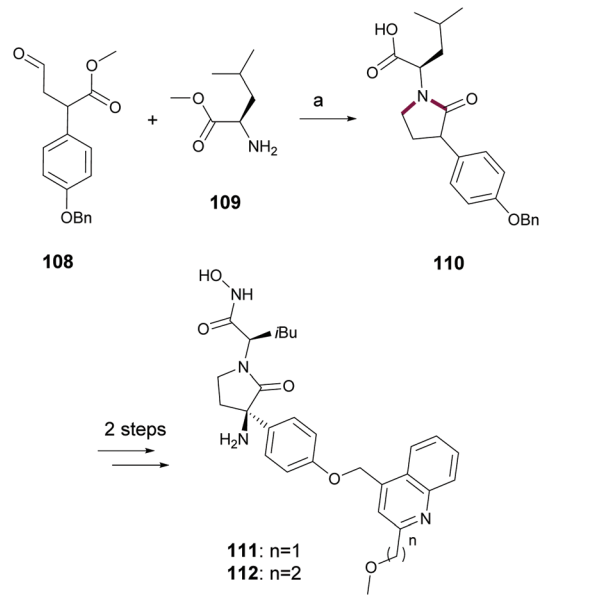
Scheme 33 Synthesis of brivaracetam **107**. (a) KOH, Na_2SO_4, *n*-BuNBr, CH_2Cl_2, –5 °C, 16 h, 55%.

protected amino acids and aldehydes under reductive amination conditions to give the desired γ-lactam core of **110** (Scheme 34).[88] After numerous inhibition assays towards TACE and various MMP enzymes, compounds **111** and **112** were found to be potent and selective TACE inhibitors exhibiting an IC_{50} value of 11 nM and 13 nM respectively. Pharmacokinetics parameters were also analyzed and demonstrated that **112** has a better bioavailability than **111**. Inhibition of TACE could offer a promising therapeutic approach for the treatment of inflammatory diseases.

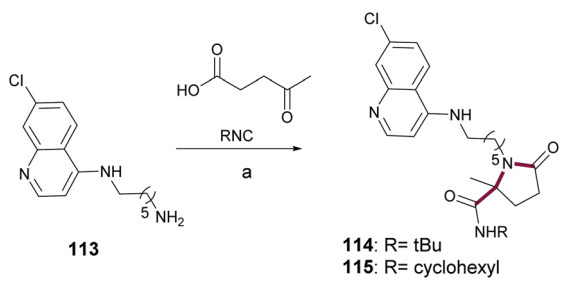
Chibale's group demonstrated, in 2006, that the Ugi four centers three components reaction (U-4C-3CR) was effective to access the γ-lactam moiety (Scheme 35).[89] Using this strategy, a large library of heterocyclic compounds was created without apparent problems of conversion. Particular efforts were made to purify this huge amount of compounds and finally the "catch and release" protocol[90] gave excellent results. Among all synthesized compounds, **114** and **115** showed particular interest. Indeed, obtained from the reaction between diamine, levulinic acid and *tert*-butylisocyanide, they show a comparable activity against cultures of P. *falciparum* parasite to chloroquine, the reference drug used in the treatment of malaria. Indeed, the authors obtained IC_{50} values of 0.18 μM and 0.27 μM for **114** and **115** respectively, compared to the 0.24 μM of chloroquine.

In 1998, Smith's medicinal chemists designed, synthesized and evaluated a series of γ-lactam analogs of clavamycin D in order to find new compounds able to enhance the peripheral insulin sensitivity.[91] Their synthetic strategy was based on the reaction between a keto-acid and an amino-alcohol, and allowed obtaining compound **118** in a moderate yield (Scheme 36). *In vitro* and *in vivo* tests showed that **118** was the most active compound among those synthesized. The *in vitro* stimulation of glucose utilization's test gave a good result with an EC_{50} value of 6.8 μM. The *in vivo* test evaluating the hypoglycemic activity revealed that **118** improved significantly glucose metabolism in insulin-resistant animals and diabetic animals. Its potency and efficacy (for one *in vivo* model) was equivalent to those of troglitazone (launched in 1997 as a potent antidiabetic but withdrawn from the market in 2000 because of hepatotoxicity problems) and metformin, the worldwide reference compound in antidiabetic medication (type 2 diabetes). Compound **118** has a potential valuable effect in the treatment of type 2 diabetes.

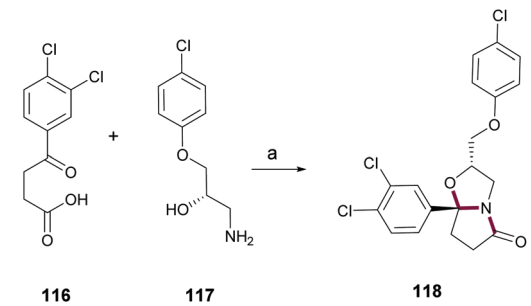
2.2.2. (3 + 2) annulation. Carr *et al.* were the first to report the use of a (3 + 2) strategy for the synthesis of a biologically active γ-lactam.[92] The key reaction of their synthesis consists of a 1,3-dipolar cycloaddition between an enone and an iminium ylide bearing a dithiolane group (Scheme 37); subsequent deprotection of this latter function furnishes the γ-lactam functionality. This methodology appeared to be a fast



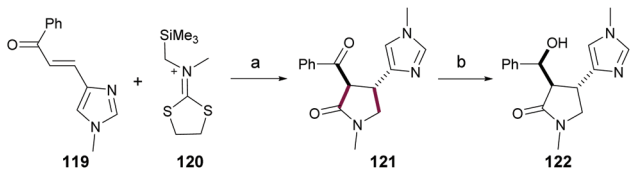
Scheme 34 Synthesis of **111** and **112**. (a) $NaBH(OAc)_3$, DIPEA, DME, 85 °C, 14 h, 95%.



Scheme 35 Synthesis of **114–115**. (a) (i) Isocyanide, MeOH, r.t., 18 h; (ii) MP-TsOH, 1 h; (iii) filter, wash; (iv) 3% NH_3/MeOH, 73%.



Scheme 36 Synthesis of **118**. (a) PTSA, toluene, reflux, 16 h, 44% (obtained from enantiopure amino-alcohol in this case).



Scheme 37 Synthesis of cynometrine **122**. (a) (i) CsF; (ii) SO_2Cl_2, SiO_2, H_2O, 60%; (b) $NaBH_4$, 0 °C, 74%.

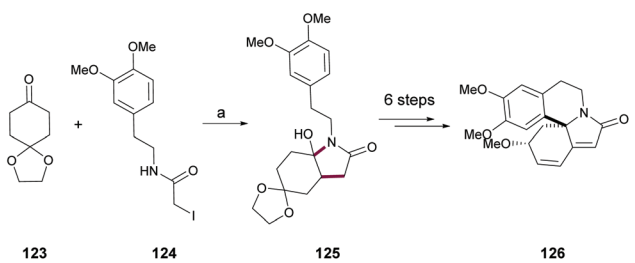
regio- and stereoselective method to access this five-membered ring. It was valued in the total synthesis of a natural analgesic compound named cynometrine (see section 4.2.3).[93]

In 2006 Zhang *et al.* accomplished the total synthesis of erysothramidine 2 (**126**), a natural compound bearing a tetracyclic system (see section 4.2.4).[94] The γ-lactam ring of this compound was built *via* a (3 + 2) annulation. In this case, the two-atom unit is an (*in situ* formed) enolate and the three-atom unit is an α-iodo amide (Scheme 38). The erythrinane skeleton of erysothramidine 2 is responsible for its sedative, hypotensive, neuromuscular blocking and CNS activities.[95]

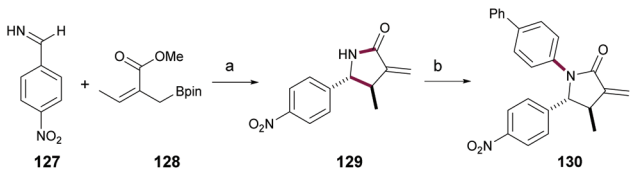
Later, most (3 + 2) strategies toward γ-lactams turned to the use of an imine group as a two-atom unit. In 2008, Hall *et al.* reported for instance the synthesis of **130** using a tandem allylation/lactamization to obtain an α-*exo*-methylene-γ-lactam nucleus from 2-alkoxycarbonyl allylboronate **128** and an imine (Scheme 39).[96] The reaction is quite general, working with various aromatic and aliphatic imines. The imine allylboration reaction is diastereospecific.[97] Compound **130** was evaluated as a homoserinetransacetylase inhibitor (IC_{50} = 140 μM). By comparison, the best known inhibitor (a quinolone) has an IC_{50} value of 4.50 μM. α-Methylene-γ-lactams are thus a potential new class of inhibitors.

A similar strategy was used by Roy *et al.* in their synthesis of **134**.[98] Treatment of a methyl imine (**133**) with an organozinc reagent (formed *in situ* from an allyl bromide) allowed generating an α–β-unsaturated γ-lactam intermediate **133** (Scheme 40). Biological testing revealed that compound **134** is an alpha 7 nicotinic acetylcholine receptor agonist (pEC_{50} = 8.0). In fact, it displays good selectivity, potency and pharmacokinetic properties.

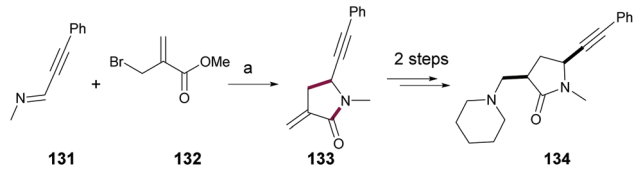
In 2012, Zhang *et al.* reported the synthesis of the 2-pyrrolidinone core of **139**, a novel antitumor compound, by the (3 + 2)



Scheme 38 Synthesis of erysothramidine 2 **126**. (a) LDA, THF, −78 °C, 1 h, 87%.



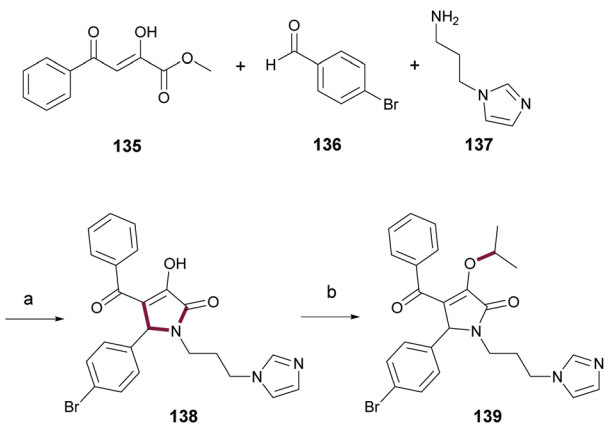
Scheme 39 Synthesis of **130**. (a) EtOH, 70 °C, 4 h, 63%; (b) CuI, 4-iodobiphenyl, *N*-*N*′-dimethylethylenediamine, K_3PO_4, dioxane, 110 °C, 16 h, 29%.



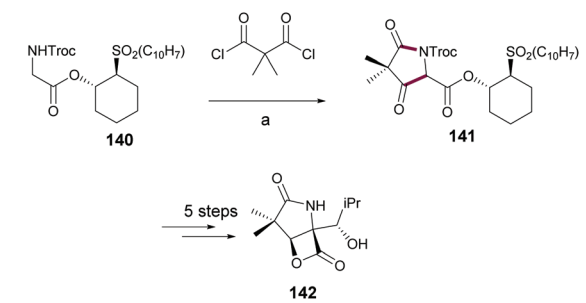
Scheme 40 Synthesis of **134**. (a) (i) Bromide, Zn in THF, r.t., 20 min, (ii) imine, r.t., 3.5 h, 80%. *cis*/*trans* ratio = 3/1.

annulation reaction between an imine and a methyl pyruvate derivative (Scheme 41).[99,100] Compound **139** was evaluated as a novel inhibitor of p53–MDM2 protein–protein interaction and systematically compared with nutlin-3a, one of the most potent inhibitors of the p53–MDM2 interaction. For example, the MDM2 binding affinity value was comparable to the reference nutlin-3a; the *in vitro* antiproliferative activity against the A549 cell line was better in the case of **139** and no toxicity or drug related death was observed in the nude mice. γ-Lactam inhibitors are thus novel antitumor hits.

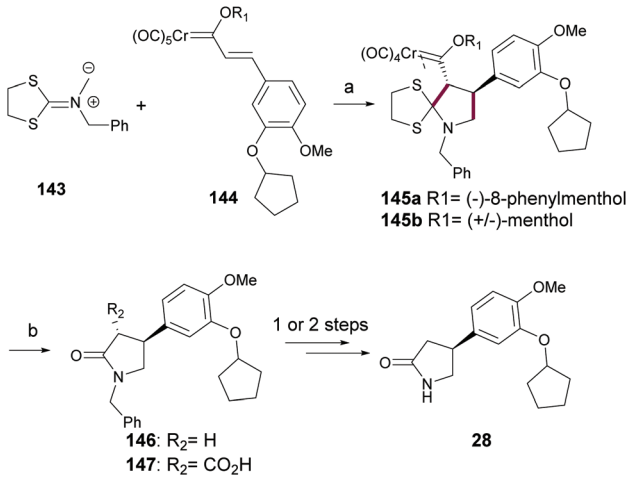
Corey *et al.* used also a (3 + 2) annulation reaction in their total synthesis of (−)-7-methylomuralide (**142**), which is structurally close to omuralide, a precursor of lactacystin (see section 4.3.4) (Scheme 42).[101] The key step of their synthesis is



Scheme 41 Synthesis of **139**. (a) 1,4-Dioxane, r.t., 12 h, 40%; (b) PPh_3, DIAD, iPrOH, THF, r.t., 12 h, 41%.



Scheme 42 Synthesis of (−)-methylomuralide **142**. (a) LiHMDS, THF, −78 °C, 15 min, 89%.



Scheme 43 Synthesis of (+)-rolipram **28** by (3 + 2) annulation. (a) CsF, THF, −50 °C, 58% (**145a**, dr > 95 : 5) 67% (**145b**, dr = 1 : 1); (b) *hv*, LiOH, 1,4 dioxane/H_2O (3 : 1), reflux, 15% (**146** er = 92 : 8 (*R*/*S*)) 35% (**147**). Pour **28**, er = 91 : 9 (*S*/*R*).

the condensation, under basic conditions, of the α-amino ester **140** and dimethylmalonyl dichloride to obtain the desired 5-membered ring in a good yield (Scheme 42). Lactacystin is a potent 20S proteasome inhibitor (IC_{50} value of 259 nM).

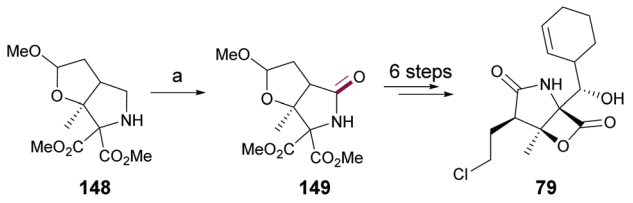
Barluenga *et al.* performed the synthesis of (+) rolipram **28** in 2001 (Scheme 43).[55] In this synthesis, compound **145** results from a (3 + 2) cycloaddition involving an azomethine ylide (**143**) and a menthol derived carbene (**144**). The cycloadduct formed is then subjected to an ester-hydrolysis–decarboxylation–carbonyl deprotection sequence. More precisely, photochemical oxidation of intermediate **145** and then basic hydrolysis allowed the dithiolane hydrolysis, furnishing *N*-benzylpyrrolidin-2-one **146** and variable amounts of **147**, the *N*-benzylpyrrolidin-2-one bearing the carboxylic acid at C3.

3. Redox approaches

In this section, we considered the synthesis of biologically active γ-lactam compounds starting from a building block which already includes a five-membered ring (*i.e.* a masked γ-lactam).

The oxidation of pyrrolidine derivatives is a widely used approach toward the γ-lactam core. Fukuyama's group applied this strategy to the synthesis of (−)-salinosporamide A **79** (see section 4.3.2).[102] Ruthenium mediated oxidation of pyrrolidine **148** at low temperatures allowed these researchers to obtain γ-lactam **149** in a good yield, without oxidation of the cyclic acetal (the electron-withdrawing diester moiety showed to be crucial for chemoselectivity) (Scheme 44).

The same strategy was used by Thomas *et al.* to access the core of KSM-2690B, a natural compound of the (neo)oxazolomycin's family (see section 4.3.5).[63,103] Oxidation of the pyrrolidine ring **150** with ruthenium tetroxide in a biphasic media

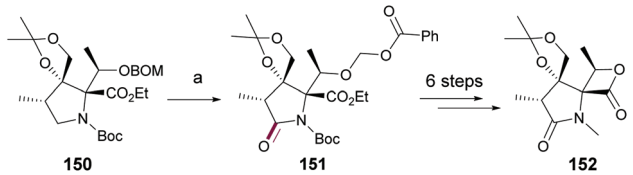


Scheme 44 Synthesis of (−)-salinosporamide A **79** *via* oxidation of a pyrrolidine ring. (a) RuO_2, $NaIO_4$, phosphate buffer, 0 °C, 85%.

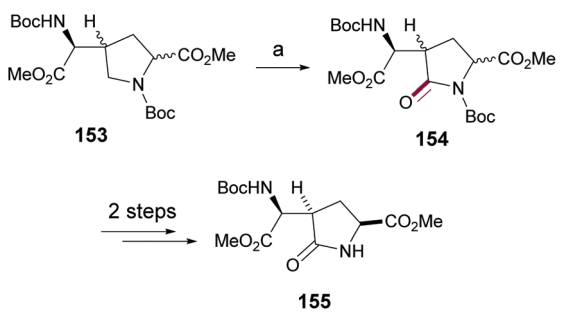
afforded the desired γ-lactam moiety which underwent further oxidation at the benzylic position leading to deprotection of the BOM protecting group (Scheme 45).[104] KSM-2690B's core **152** was obtained in a total of 20 steps. The biologically active compound, bearing five olefins and a terminal oxazole, showed antimicrobial activity against several Gram-positive bacteria and cytotoxic activity against human bladder carcinoma T24 cells.[105]

Denis *et al.* developed an efficient synthesis of penmacric acid where the γ-lactam moiety was introduced by oxidation of a proline derivatives.[106] The use of ruthenium chloride hydrate yielded the fully protected pyroglutamic acid derivatives **154** as a separable 1 : 1 mixture of diastereoisomers (Scheme 46). Two more steps provided the target molecule, penmacric acid **155**, which is a natural biologically active compound (see section 4.2.6). This latter finds applications in food[107] or as an anti-inflammatory agent.[108]

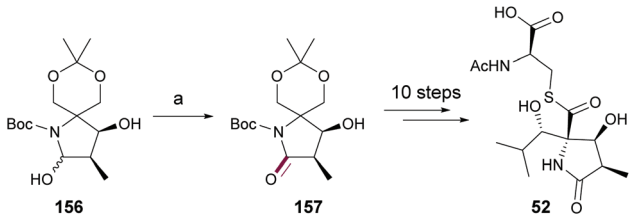
In 2004, Hatakeyama's group revisited the (+)-lactacystin synthesis performed by Corey (see section 2.1.3). The authors developed a new and concise strategy toward this natural product (see section 4.3.4) *via* Kang's intermediate (**157**) (Scheme 47).[109] The γ-lactam moiety was introduced by oxi-



Scheme 45 Synthesis of **152**. (a) RuO_4, aq. $NaIO_4$, EtOAc, 66%.



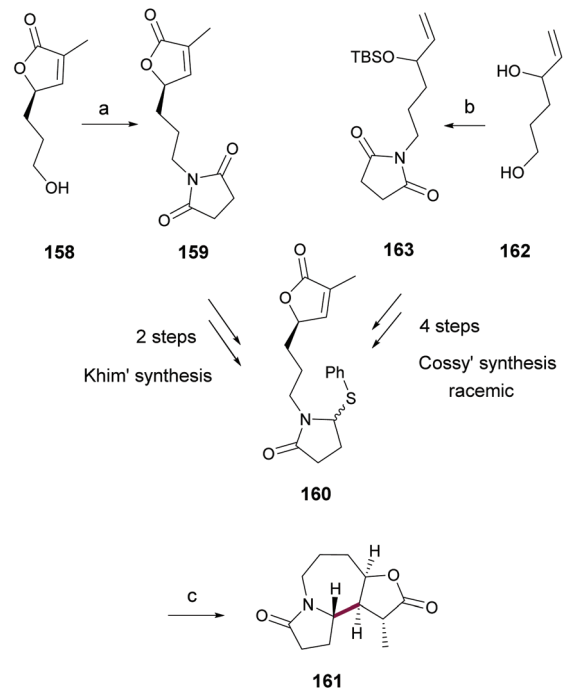
Scheme 46 Synthesis of penmacric acid **155**. (a) $NaIO_4$, $RuCl_3/H_2O$, $CCl_4/CH_3CN/H_2O$ (3/3/4), 36 h, 89%.



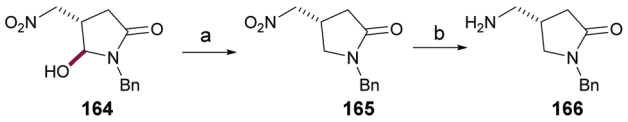
Scheme 47 Synthesis of (+) lactacystin **52** *via* Kang's intermediate. (a) PDC, CH_2Cl_2, r.t., 60%.

dation of the hemiaminal **156** using pyridinium dichromate.[110] This strategy allowed achieving the total synthesis of (+)-lactacystin in 16 steps and purification by column chromatography was needed only from the seventh step. (+)-Lactacystin causes a transient increase of the intracellular cyclic adenosine monophosphate (cAMP) level in Neuro 2A cells and morphological changes including neuritogenesis but is also a 20S proteasome inhibitor.[111]

Besides oxidation of pyrrolidine, imide reduction of succinimide derivatives has also been exploited for preparing a γ-lactam moiety. Both Khim,[112] in 2004, and Cossy,[113] in 2005, reported the synthesis of 9,10-*epi*-stemoamide (**161**) from a succinimide derivative using a reduction/alkylation strategy to install the γ-lactam ring (Scheme 48). Stemoamide derivatives are used in traditional Chinese medicine to treat respiratory diseases or as insecticides (see section 4.2.6).[114] The synthesis of other compounds of this family was reported later in the literature.[115–117]



Scheme 48 Synthesis of **161**. (a) Succinimide, PPh_3, DEAD, THF, r.t., 92%; (b) succinimide, DIAD, PPh_3, THF, 91%; (c) (i) *n*-Bu_3SnH, AIBN, benzene, reflux, 24 h; (ii) K_2CO_3, MeOH, r.t., 74% for two steps.



Scheme 49 Synthesis of **166**. (a) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to r.t., 14 h, 52%. (b) Pd/C, H_2, THF, r.t., 8 h, 95%.

Deoxygenation of pyrrolidinones can be another strategy to access the γ-lactam core. Indeed, Yamashita's group accomplished the first enantioselective synthesis of (*S*)-nebracetam **166**, a nootropic compound, by deoxygenation of **164** (Scheme 49).[118] Subsequent reduction by hydrogenation in the presence of Pd/C resulted in (*S*)-nebracetam. This compound is known to enhance cholinergic neurotransmission and to reduce dopamine and serotonin uptake.[119]

4. Natural compounds containing a γ-lactam moiety

Nature has always been an excellent source of pharmaceutical agents: natural compounds can be directly used such as in traditional medicine or inspire chemists in the total or semi-synthesis of analogues with improved biological properties. As we will discuss below, γ-lactam is a key structural feature in a large number of biologically active natural compounds.

The diversity of natural sources of γ-lactam is reflective of the spectrum of biological activities displayed. In fact, this motif can be found in organisms such as bacteria, fungi, plants or even animals. Accordingly, structural features of natural γ-lactams are also wide.

Some specific structural motifs are nonetheless found in many natural γ-lactams suggesting common biochemical pathways. However, very little is reported on the biosynthesis of γ-lactams.[120–122] But one can conjecture that glutamic acid, glutathione,[121] proline and γ-aminobutyric acid (GABA)[123] are the main precursor compounds of γ-lactams in living cells.

In this section we will discuss natural γ-lactam compounds, selected on the basis of their frequency of occurrence in the literature and of data availability, classified according to their origin.

4.1. γ-Lactams from fungi

Among fungal bioactive metabolites containing γ-lactams (Fig. 3), a large proportion of them is based on a decalin motif suggesting a common origin; the polyketide (PKS) non-ribosomal peptide synthase (NRPS) pathway being often quoted.[124,125]

4.1.1. Codinaeopsin and ascosali pyrrolidinone A. Codinaeopsin and ascosali pyrrolidinone A have a very closely related structure built around a decalin core and a γ-lactam ring (see Fig. 3). Both are active against *P. falciparum* and thus have an antimalarial activity. The latter was isolated by Osterhage *et al.* in 2000 from *Ascochyta salicornae*, a marine fungus and exhibits an IC_{50} value of 1.72 μM (NF54 strain).[126]

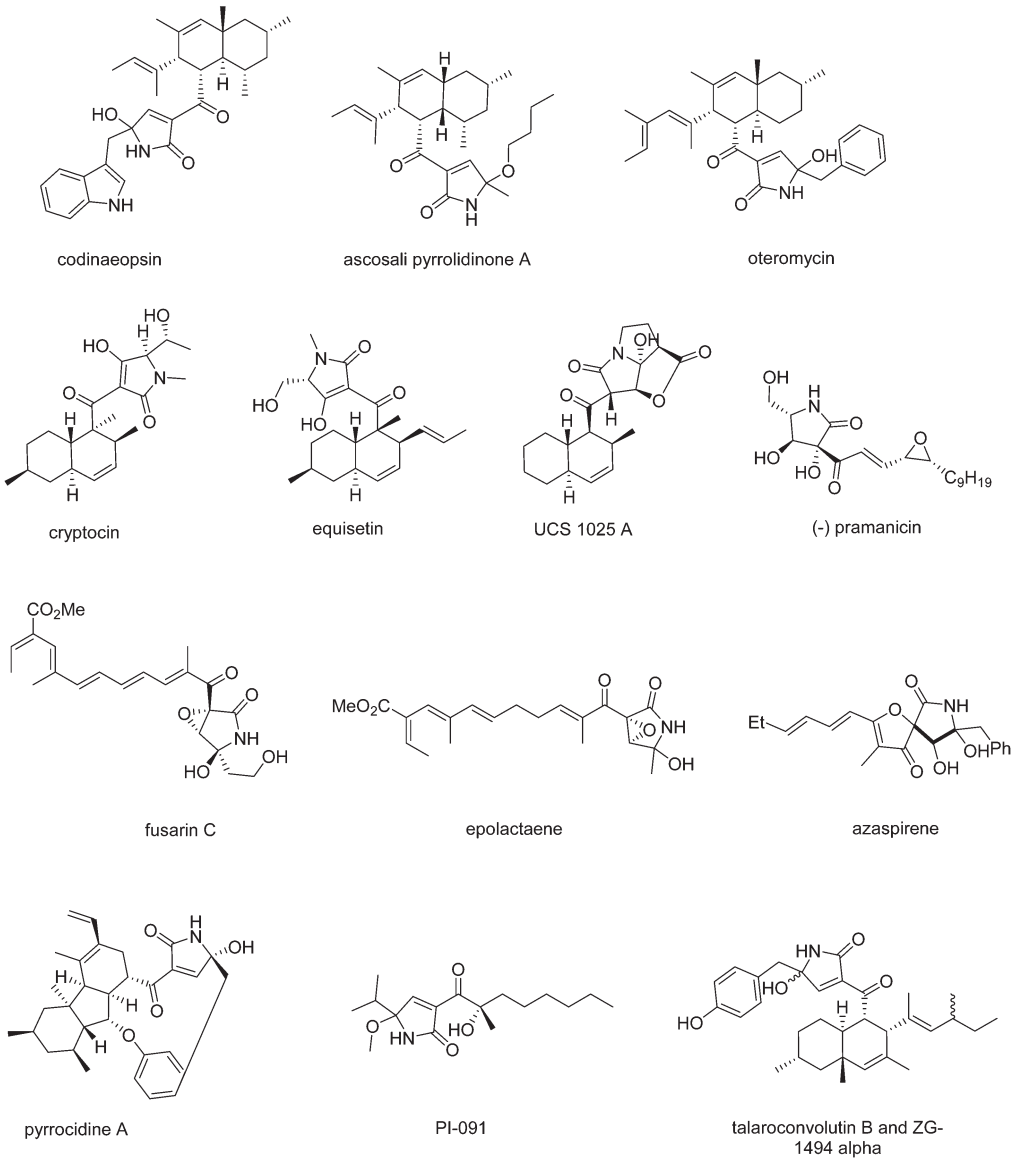


Fig. 3 Structure of naturally occurring γ-lactams derived from fungi.

Furthermore, it inhibits tyrosine kinase p53. It is worth noting that its development as a therapeutic tool will not go further because of its cytotoxicity (effect on rat skeletal muscle myoblast cells). Codinaeopsin[127] (stereochemistry at C2 is arbitrary) was discovered later, in 2008, in a fungal extract of a tree (*Vochysia guatemalensis*). Thanks to a high output screening, Kontnik *et al.* found that it is active against the 3D7 strain of *P. falciparum* with an IC_{50} value of 4.7 μM.

4.1.2. Oteromycin. Isolated from fungus strains MF5810 and MF5811, oteromycin was subjected to a biological testing in 1991. Singh *et al.* found that it was a novel antagonist of the endothelin receptor type B (ET_B implicated in vasoconstriction and vasodilatation) with an IC_{50} value of 2.5 μM.[128] In addition, the team of Hazuda discovered its activity as a HIV-1 integrase inhibitor.[129] The mode of action has however yet to be identified.

4.1.3. ZG-1494 alpha and talaroconvolutin. Thanks to Piggott's screening program aiming at developing new PAF acetyltransferase inhibitors, the *trans* decalin derivative ZG-1494α has been showed to have an IC_{50} of 40 μM.[130,131] Binding assays for PAF, histamine and glucocorticoid receptor binding indicated a promising anti-inflammatory activity (IC_{50} = 3 μM). This natural compound has been extracted from a culture broth of *Penicillium rubrum*.

On the other hand, talaroconvolutin B, extracted from *Talaromyces convolutes* (fungus present on barley grains) by Suzuki *et al.*, exhibits antifungal activity against *A. fumigatus*, *A. niger*, and *C. albicans* (between 9 and 15 μg of organisms per disk; using amphotericin as a positive control).[132]

Because the stereochemistry at C5 and C26 has not been determined, talaroconvolutin B and ZG-1494 alpha may be stereoisomers at either position or both.[130]

4.1.4. Cryptocin. Cryptocin, a tetramic acid derived from the endophytic *fungus Cryptosporiopsis* cf. *quercina*, is inactive against human pathogenic fungi but active against numerous plant pathogenic ones (MIC values below 1 μg ml^{-1}).[133] Interestingly, *Pyriculariaoryzae*, responsible for rice blast (one of the most economically important plant pathogenic fungi in the world) is particularly sensitive (MIC = 0.39 μg ml^{-1}), making cryptocin a serious candidate for fungicide development.

4.1.5. Equisetin. Discovered in 1974, equisetin was isolated from the fungus *Fusarium pallidoroseum*. Its chemical structure was identified by Laugal[134] in 1979 and completely characterized in 1989 by Lynn.[135] This natural compound shows a very broad range of biological activities.[136] At first it was known as an antibiotic: it is active against *Staphylococcus aureus* and *erythraea* (with respective MIC < 1.25 μg and <2.5 μg), as well as against *Bacillus subtilis*. Then, other significant activities were discovered such as cytotoxic[137] and phytotoxic activities.[138] It is also a potent inhibitor of mitochondrial ATPases and HIV-integrase (IC_{50} values between 7 and 20 μM).[129]

4.1.6. UCS 1025 A. *trans*-Decalin UCS 1025 A was isolated from the fungus *Acremonium* sp. by West *et al.* It proved to be an antitumor antibiotic on various cell lines (IC_{50} = 21 to 58 μM) as well as a telomerase inhibitor[124,130,132] making it a potential chemotherapeutic agent. The structure of UCS 1025 A (Fig. 3) was elucidated by NMR and crystallographic studies.[57] Finally, its total synthesis was reported by Danishefsky in 2005 (see section 2.1.3)

4.1.7. (−)-Pramanicin. Pramanicin is a natural γ-lactam isolated from fungi which do not possess a decalin core. It was extracted and isolated in 1994 by Schwartz *et al.* from a lactose-containing liquid fermentation (or a corn-based solid) of a sterile fungus growing in grass.[17] Its stereochemistry was determined by Barrett five years later, in 1999.[16] MIC tests revealed that pramanicin has a good antimicrobial activity against *Candida parapsilosis* (MIC = 4 μM), and *Cryptococcus neoformans* (MIC = 0.062 μM) and also a good antibacterial activity against *Bacillus subtilis* (MIC = 4 μM).

4.1.8. Fusarin C. Fusarin C is a polyketide produced mainly by the entomopathogenic fungus *Metarhizium anisopliae*. Its chemical structure was elucidated in 1984 and consists of a polyenic chromophore with a substituted 2-pyrrolidone (see Fig. 3).[139]

In addition, its biological activities are wide and also opposed. For example, it not only stimulates human breast adenocarcinoma MCF-7 cell line growth but also decreases the viability of colorectal cancer Caco 2 human cells (IC_{50} = 5.6 μM).[140,141] These opposite effects could be due to the presence of alpha and beta estrogen receptors in those cell lines. In fact, fusarin C is an estrogenic agonist. From 20 μM, cells are inhibited with an IC_{50} value of 46.8 μM but above 20 μM and up to 100 nM, there is an induction.

Another natural analogue (with Z olefins) called NG-391 exhibits also mutagenic properties.[142]

4.1.9. Epolactaene. Isolated from a fungal strain of a marine sediment in Japan (*Penicillium* sp.), epolactaene possesses several biological activities. In particular, it is known as a neuritogenic compound and apoptosis inducer.[143] It induces neurite outgrowth in human neuroblastoma SH-SY5Y cells, which lack significant TRK family mRNA. It constitutes also a rare example of a natural molecule able to bind and inhibit Hsp60 chaperone activity, the latter playing an important role in the folding, translocated and stress denatured proteins.[144] The diastereoselective total synthesis of epolactaene was accomplished in 2002.[145] Recently, Kuramochi reported disulfide formation *via* reactions of epolactaene with several thiols.[146] Given the crucial role of disulfide bridges in stabilizing protein structures and hence in protein function, epolactaene could be a promising new drug.

4.1.10. Azaspirene. Azaspirene was isolated in 2002 from the fungus *Neosartorya* sp. and is composed of a highly oxygenated azaspirocyclic system and two hydroxyl groups at C8 and C9 positions. Its total synthesis was performed by Hayashi and co-workers in 2002.[147]

Azaspirene is an angiogenesis inhibitor candidate. In fact, it was shown to inhibit the endothelial migration induced by the vascular endothelial growth factor (ED_{100} = 27.1 μM).[148]

Besides, azaspirene shares the same core as pseurotin A (IgE inhibitor production)[149] and synerazol (antifungal and antibiotic).[150] Based on genome sequencing and feeding experiments, Turner *et al.* showed that the biosynthesis of these γ-lactams starts from phenylalanine in the human pathogen *Aspergillus fumigatus.*[120]

4.1.11. Pyrrocidine A. In 2002, the team of He elucidated the chemical structure of pyrrocidine A, extracted and isolated from the fungal endophyte *Acremonium zeae.*[151] This compound exhibits a unique 13-membered macrocycle containing phenyl, ether, ketone and pyrrolidinone function patterns (see Fig. 3). Displaying MIC values of 0.25–2 μg ml^{-1} against *Staphylococcus aureus* (including two resistant strains), it is a potent antibiotic towards Gram-positive bacteria. This work was pursued in 2008 by the group of Wicklow, working in the field of agrochemistry,[152] in which pyrrocidine A was utilized against maize pathogen with testing on different strains. The most sensitive are *S. maydis*, *F. graminearum*, and *C. michiganense* subsp. *nebraskaense*, each of which is a seed-borne pathogen responsible for severe seedling blights and vascular wilts of maize.

4.1.12. PI-091. Taisho Pharmaceutical Co. isolated PI-091 from *Paecilomyces* sp. F-3430, during a screening aiming at finding new natural platelet aggregation inhibitors. They found that it exhibits arachidonic acid-induced platelet aggregation-inhibitory activity in rabbits with an IC_{50} value equal to 120 μM.[153] The total synthesis of PI-091 was performed in 1996 and furnished this latter as found in nature, *i.e.* as a 1 : 1 diastereoisomeric mixture at the γ-ketal carbon.[154]

4.2. γ-Lactams from plants

4.2.1. Racemic clausenamide. Clausenamide (Fig. 4) was isolated from a traditional Chinese plant called *Clausena lansium*. Although it was isolated as a racemic mixture, only (−)-clausenamide shows biological activities: it improves

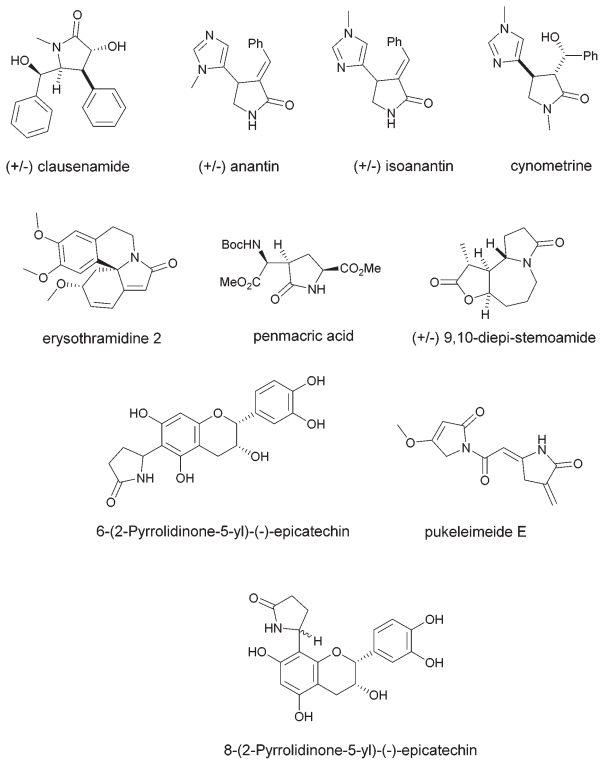


Fig. 4 Structure of naturally occurring γ-lactams of plant origin.

learning and memory capacities in amnesia animal models (enhancing synaptic transmission) by enabling the CaMKII α-CREB signal pathway activation *via* intracellular calcium release.[155,156]

Based on these improving cognition and anti-Alzheimer's disease pathogenesis properties,[157] clinical trials of (−)-clausenamide for Alzheimer's disease patients started in China and it entered in phase II in 2015.

4.2.2. Anantin and isoanantin. Anantin and isoanantin belong to the very small family of natural α-methylene-γ-lactams. They were isolated from the leaves of an African plant named *Cynometra* which was traditionally used to treat cough and pain.[158] Both compounds, like most α-methylene-γ-lactams, exhibit cytotoxic, antitumor and anti-inflammatory activities.[42]

4.2.3. Cynometrine. The γ-lactam alkaloid cynometrine was found in the stem bark of *Cynometra hankei*[93] which is used in traditional African medicine as an antitussive and analgesic (for dental pain and rheumatism).[159] Cynometrine belongs to the same family as anantin and isoanantin. Other alkaloids were discovered at the same time: isocynometrine and isonaritine.[158]

4.2.4. Flavan-3-ol derivatives. 6-(2-Pyrrolidinone-5-yl)-(−) epicatechin and its regioisomer with the γ-lactam substituent in position 8, possessing a flavan-3-ol feature, were isolated in 1991 from the roots of *Actinidia arguta*, an Asian fruit.[160] These compounds were tested as an inhibitor of the formation of advanced glycation end products (AGEs) which are over-produced in diabetes. Actually, *in vitro* tests revealed that these flavan-3-ol derivatives are more potent (IC_{50} values are 36 μM and 48 μM, respectively) than the glycation inhibitor taken as a reference, aminoguanidine (IC_{50} = 961 μM).

4.2.5. Erysothramidine 2. Erysothramidine 2 belongs to a class of structurally diverse products isolated from tropical and sub-tropical *Erythrina* genus plants, used in indigenous medicines. These alkaloids possess a wide range of biological activities including anticonvulsive, sedative, and hypnotic properties.[95] Recently, Wink *et al.* reported it as a neuromuscular blocking agent.[161]

4.2.6. Penmacric acid. Penmacric acid was isolated by two independent teams[162,163] in 1975 from *Pentaclethra macrophylla*, an African leguminous tree. It has an interesting structure composed of a pyroglutamic acid linked to a glycine *via* a carbon–carbon bond. This natural compound could find applications as an anti-inflammatory agent, knowing that the extracts of the plant show significant anti-inflammatory activity against acute inflammation[108] (78% inhibition of oedema in rat hind paw, 3 h after the administration). It could also find application in food, by being a potential nutritive component in cereal mixture based food.[107]

4.2.7. Stemoamide. This alkaloid was isolated in 1992 from *Stemona tuberosa* Lour, a Chinese traditional medicine also called "wild asparagus" used as an anticough agent and also for the treatment of respiratory diseases such as asthma and tuberculosis.[164] This explains why extracts of *Stemona tuberosa* are employed in China and Japan in traditional medicine in the case of respiratory disorders or helminth infection.[165,166]

4.2.8. Pukeleimide E. Pukeleimide E is an α-methylene-γ-lactam which was isolated from a marine blue green alga named *Lyngbya majuscula*.[42] As other α-methylene-γ-lactams, it is a cytotoxic agent but is about ten times less toxic than the corresponding lactone. It also shows activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes.*[167]

4.3. γ-Lactams from bacteria sources

4.3.1. Lajollamycin. Lajollamycin was isolated from sediments found in the US: the marine actinomycete *Streptomyces nodosus* (Fig. 5).[168] This nitro-tetraene-spiro-β-lactone-γ-lactam was evaluated as an antimicrobial agent against a variety of bacteria (both drug sensitive and resistant micro-organisms).[168] The MIC values ranged from 1.5 to 20 μM demonstrating a good antibiotic effect. Furthermore, lajollamycin inhibited murine melanoma's growth with an EC_{50} value of 9.6 μM (B16-F10 cell line).

4.3.2. Salinosporamide A. Salinosporamide A bears a quite unusual γ-lactam-β-lactone core (see Fig. 5). It was isolated from a marine bacterium, *Salinispora tropica*, by Fenical *et al.*[169,170] Due to its structural similarity with the proteasome inhibitor omuralide (see section 4.3.4), it was directly tested as a 20S proteasome inhibitor, showing a very promising activity.[171] In fact, it exhibits an IC_{50} value of 1.3 nM by inhibiting the proteasomal chymotrypsin-like proteolytic activity in a 20S purified proteasome. This result suggests that it is 35

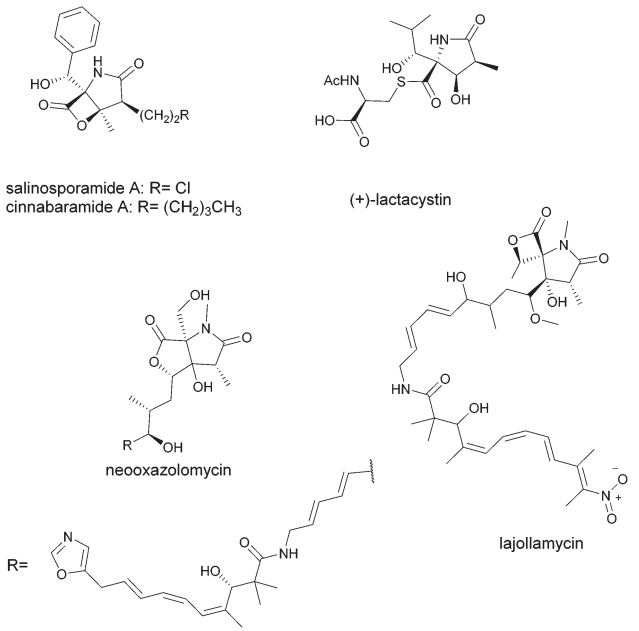
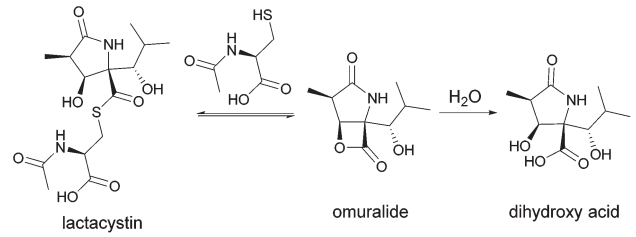


Fig. 5 Structure of naturally occurring γ-lactams from bacteria sources.



Scheme 50 Hydrolysis of lactacystin into omuralide.

times more potent than omuralide. It was showed to be also very active against one colon cancer cell line (HCT-116) in the range of 10 nM (*in vitro* assays). Furthermore, salinosporamide A is found to inhibit in a potent and very selective manner the growth of a broad range of NCI's 60 cell lines. For example, it is active against NCI-H226 non-small cell lung cancer, SF-539 CNS cancer, SK-MEL-28 melanoma, and MDA-MB-435 breast cancer with GI_{50} values <10 nM. It is currently in the phase I clinical trial for the treatment of cancer. Many groups reported the stereoselective synthesis of this compound (see sections 2 and 3)[66,102,172] allowing for interesting SAR studies.[173]

4.3.3. Cinnabaramide A. Cinnabaramide A was isolated from a soil bacteria strain (*Streptomyces*) and has a structure closely related to salinosporamide A. It also shares its biological activities.[174] Indeed, it is a potent and selective inhibitor of 20S proteasome (IC_{50} = 1 nM) and is very active against HCT-116 cell lines. Nevertheless, cinnabaramide A did not show activity against trypsin or chymotrypsin up to 100 μM.

4.3.4. Lactacystin. Lactacystin was isolated from a *Streptomyces* strain, characterized and crystallized by Omura *et al.* in 1991.[111] Several total syntheses of this natural compound were reported (see sections 2.1.3 and 3).[37,39,109,110,175] Lactacystin is a cell-permeable and irreversible 20S proteasome inhibitor (IC_{50} = 259 nM); this latter being called the "multicatalytic proteinase complex" regulating intracellular protein degradation (removal of damaged/mutated proteins, or proteins involved in cell growth and metabolism for example).[175]

Interestingly, Dick showed, in 1996, that lactacystin hydrolyzes in aqueous solution into clasto-lactacystin β-lactone (known as omuralide; Scheme 50) and finally into a dihydroxy acid.[176] The thiol ester function is indeed reactive enough to allow spontaneous conversion to the β-lactone. It has in fact been proved that omuralide is the sole inhibitory species. The inhibitory mechanism is believed to involve covalent binding to the active site N-terminal threonine residue in some of the β-subunits of the proteasome.

4.3.5. Neooxazolomycin. Neooxazolomycin is a biologically active natural product featuring a fused γ-lactam-γ-lactone core (see Fig. 5). It was isolated from several strains of *Streptomyces* sp., in 1985, and showed a strong *in vivo* antitumor activity[177] as well as antiviral activities against influenza, herpes simplex type I and vaccinia.[178] Its original structure inspired many chemists in developing total or a part of its synthesis (see section 2.1.3).[61,62,179]

4.4. γ-Lactams from animal sources

4.4.1. Pyroglutamic acid. The cyclic lactam of glutamic acid, known for over a century but poorly understood, could play a role in the treatment of neurodegenerative disorders, if considered as an analogue or reservoir of glutamate. For example, it prevents amnesia in rats and improves learning in age-associated and alcohol induced memory loss in humans.[121] Moreover, it can have a role in osmoprotection.[121]

Pyroglutamic acid, also present in plant tissues, is sold as a "smart drug" for improving blood circulation in the brain.

4.4.2. Dysibetaine. Dysibetaine was extracted and isolated from the marine sponge *Dysidea herbacea*. When this α,α-disubstituted-α-amino acid derivative is injected intracerebrally in mice, it induces scratching. Scratching is usually considered as an early sign of convulsion, indicating that dysibetaine can have an impact on glutamate receptors in the CNS.[44,45]

5. Conclusion

The interest in γ-lactams originates from its analogy to the β-lactam core. This review clearly demonstrates that nowadays the interest in γ-lactams is well beyond their analogy with their β-lactam analogues. The γ-lactam motif was indeed found in many natural compounds from bacteria, plants, fungi or even animal sources, covering a large variety of structures and biological activities. Several non-natural γ-lactam compounds have also been developed and shown to possess interesting pharmacological properties.

Many synthetic approaches have been developed for the preparation of γ-lactam structures. The most widely used

methodology involves the cyclization by amide formation but other ring-closing strategies, by *N*-alkylation or C–C bond formation, have been reported. In recent years, a series of (3 + 2) and (4 + 1) annulation reactions were also developed to access the γ-lactam core in a more convergent manner. These synthetic methodologies are very important to fully exploit the potential of this scaffold in medicinal chemistry. Several challenges are however likely to be addressed in the future development of new efficient synthesis of γ-lactams. For example, although a limited number of stereoselective syntheses have been reported, developments of general enantioselective catalytic methodologies remain highly desirable.

γ-Lactams thus represent an important class of compounds both from a synthetic and biological point of view and one can expect an increase in the number of drugs on the market containing a γ-lactam core in the next few years.

Acknowledgements

R. R. is a Chercheur qualifié of the Fond de la Recherche Scientifique de Belgique (F.R.S.-FNRS).

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