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PACTAMYCIN: A COMPREHENSIVE REVIEW OF ITS BIOLOGICAL ACTIVITY, BIOSYNTHESIS, AND SYNTHETIC STRATEGIES IN THE FIGHT AGAINST ANTIBIOTIC RESISTANCE

Ghassan Shannan[1], Zeina S. Malek[2] and Nasser Thallaj[3]*

[1]BSc, PhD, Head of Biochemistry Department, Al Rasheed University for Science and Technology, Damascus, Syria.
[2]PhD. Physiology Professor. Faculty of Dentistry, Syrian Private University, Damascus, Syria.
[3]Pharmaceutical Chemistry and Drug Quality Control Department, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria.

***Corresponding Author: Prof. Dr. Nasser Thallaj**
Pharmaceutical chemistry and drug quality control Department, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria.

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ABSTRACT
Pactamycin, an aminocyclopentitol antibiotic, has garnered significant attention due to its dual efficacy as an antimicrobial and antitumor agent. Initially isolated from *Streptomyces pactum var. pactum* during the "Golden Age" of antibiotics in the 1960s, pactamycin exhibits potent activity against both Gram-positive and Gram-negative bacteria, positioning it as a promising candidate in the fight against antibiotic resistance. Its complex structure, characterized by a cyclopentane core with multiple stereogenic centers and a triamino motif, poses challenges for synthetic chemists aiming to produce this compound and its analogues. Recent advances in understanding the biosynthesis of pactamycin have revealed that it is assembled from three distinct cyclic fragments derived from glucose and acetic acid through independent metabolic pathways. This has provided insights for engineering new derivatives with enhanced biological properties. Structure-activity relationship (SAR) studies have identified critical features influencing biological activity, leading to derivatives with improved selectivity and reduced cytotoxicity. The emergence of nitrene chemistry has facilitated innovative synthetic methodologies, allowing for the efficient generation of pactamycin analogues through controlled C-H amination and aziridination reactions. This article explores the biological structures and activities of pactamycin, its biosynthetic pathways, mechanisms of action, and recent synthetic advancements. By synthesizing knowledge from various disciplines, we aim to provide a comprehensive overview of pactamycin's significance in contemporary medicinal chemistry and its potential role in addressing urgent health challenges, including antibiotic resistance and cancer treatment. As researchers continue to explore the therapeutic potential of pactamycin, its study exemplifies the vital intersection of natural product chemistry and synthetic innovation in the quest for new drugs.

KEYWORDS: Pactamycin; Antibiotic; Antitumor; Biosynthesis; Structure-activity relationship (SAR); Nitrene chemistry; Antibiotic resistance.

INTRODUCTION
Pactamycin, a member of the aminocyclopentitol family, stands out as a remarkable compound with significant biological activity, particularly in the fields of antimicrobial and antitumor research. Discovered during the "Golden Age" of antibiotics in the early 1960s, pactamycin was isolated from the fermentation of *Streptomyces pactum var. pactum*, a bacterium renowned for its rich biosynthetic capabilities.[1] This period marked a pivotal moment in pharmaceutical history, as researchers evaluated a plethora of microbial metabolites, leading to the identification of numerous biologically active molecules.[2] The exploration of *Streptomyces* species has been particularly fruitful, yielding a wide array of antibiotics that continue to form the backbone of modern medicine.[3]

Initially recognized for its potent antitumor properties, pactamycin demonstrated significant antibiotic efficacy against both Gram-positive and Gram-negative bacteria.[4] This dual action positions pactamycin as a versatile candidate in the ongoing battle against antibiotic resistance, a pressing global health challenge exacerbated by the overuse and misuse of existing antibiotics.[5] As bacterial pathogens evolve and develop resistance mechanisms, the need for new therapeutic

agents has never been more urgent, making the exploration of compounds like pactamycin critical.[6]

The structural complexity of pactamycin is remarkable, featuring a cyclopentane core adorned with multiple stereogenic centers and a triamino motif. [7]This intricate architecture not only influences its biological activity but also poses challenges for synthetic chemists aiming to produce this compound and its analogues.[8] The process of elucidating the structure of pactamycin involved extensive chemical degradation studies and advanced techniques such as X-ray crystallography and NMR spectroscopy.[9] These efforts culminated in the establishment of its absolute stereochemistry, further illuminating the intricate relationship between its structure and biological function.[10]

The biosynthesis of pactamycin has been a subject of extensive investigation, revealing that it is constructed from three distinct cyclic fragments derived from independent metabolic pathways. [11]Specifically, the cyclopentitol core originates from glucose, while the 6-methylsalicylate and aminoacetophenone components come from acetic acid and glucose, respectively.[12] The incorporation of methyl groups into the structure occurs through S-adenosyl(L)methionine (SAM), a common methyl donor in biological systems. Understanding the biosynthetic pathway not only sheds light on the natural production of pactamycin but also provides insights for the engineering of new analogues with enhanced properties.[13]

Recent years have seen a resurgence of interest in pactamycin due to its promising biological activities and the potential for developing novel therapeutic agents.[14] Researchers are increasingly focused on structure-activity relationship (SAR) studies to identify critical features of pactamycin that influence its activity. Insights gained from these studies have led to the identification of derivatives with improved selectivity and reduced cytotoxicity.[15] For instance, the removal of specific functional groups has been shown to enhance the antiprotozoal activity of certain analogues while diminishing their antibacterial properties, highlighting the delicate balance between efficacy and safety in drug design.[16]

Moreover, advances in synthetic methodologies, particularly in the realm of nitrene chemistry, have opened new avenues for generating pactamycin analogues.[17] Nitrenes, the nitrogen counterparts of carbenes, are highly reactive species that can insert into various chemical bonds, including C-H and C=C bonds.[18] The ability to utilize transition metal catalysis to mediate nitrene transfers has significantly enhanced the synthetic toolbox available to chemists.[19] These developments have allowed for the efficient synthesis of pactamycin and its derivatives, enabling researchers to explore the structure-activity landscape more comprehensively.[20]

The ongoing synthesis of pactamycin and its analogues underscores the intricate interplay between natural product chemistry, medicinal chemistry, and synthetic biology. Recent strategies have employed both partial and total synthesis approaches, each with its own set of challenges and opportunities.[21] From stereoselective functionalization of the cyclopentane core to linear construction methods, researchers are continually refining their techniques to achieve successful syntheses with higher yields and greater efficiency.[22]

As the understanding of pactamycin continues to evolve, so too does the potential for its application in the treatment of various diseases.[23] Its multifaceted biological activities, coupled with innovative synthetic strategies, position pactamycin as a key player in the development of next-generation therapeutics.[24] The lessons learned from its study will undoubtedly inform future research endeavors aimed at combating antibiotic resistance and developing effective treatments for cancer and other diseases.[25]

In this article, we will explore the biological structures and activities of pactamycin, delve into its biosynthetic pathways, examine its mechanisms of action, and highlight the recent advancements in synthetic methodologies that enable the creation of novel analogues.[26] By synthesizing knowledge from various disciplines, we aim to provide a comprehensive overview of pactamycin's significance in contemporary medicinal chemistry and its potential role in addressing some of the most pressing health challenges of our time.[27]

A. Biological Structures and Activities

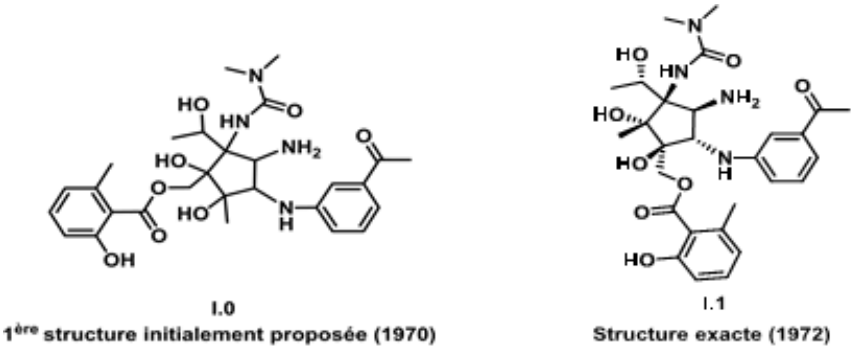
1. Pactamycin and the Family of Polyamine Aminocyclopentitols

The majority of antibiotics in use today were discovered during the "Golden Age" of antibiotics, spanning from the 1940s to the 1970s. During this period, the evaluation of metabolites from various bacteria and fungi led to the identification of 12,000 biologically active molecules, resulting in 160 candidates for clinical trials. More than half of these natural products were derived from a single genus, *Streptomyces*.[28]

Pactamycin and one of its secondary metabolites were isolated in 1961 through the fermentation of *Streptomyces pactum*var. *pactum* by researchers from Upjohn, achieving a notable yield of 216 µg/mL from the fermentation process. Initially recognized for its antitumor properties, pactamycin also exhibited significant antibiotic activity against both Gram-positive and Gram-negative strains.[29]

In 1970, researchers from Upjohn proposed the first structure (I.0) of pactamycin based on their chemical degradation studies.[30] Two years later, this structure was revised (I.1), and its absolute relative stereochemistry was determined using X-ray crystallography on a pactamycin derivative. By 1978, the 13C NMR spectra

of this derivative and pactamycin were published, confirming the earlier structural attributions **Schema 1**.

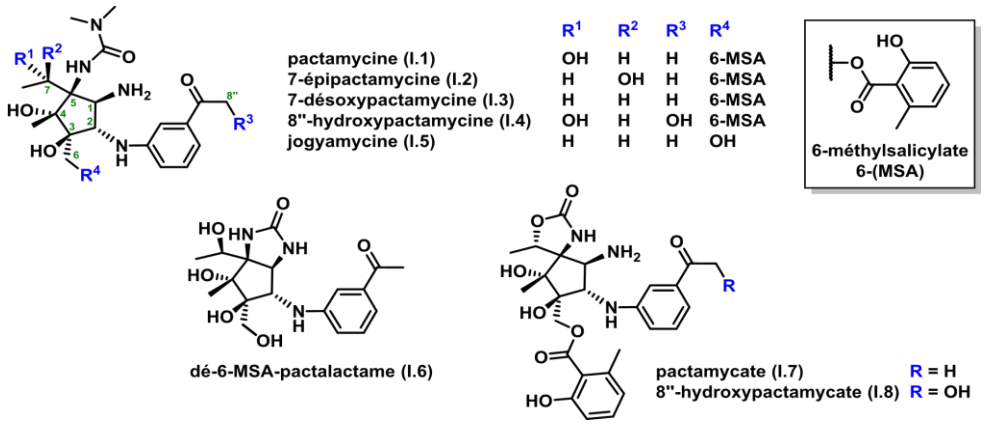


Schema 1: 1st proposed structure of pactamycin.

Pactamycin is a compound from the aminocyclopentitol family, characterized by a complex structure featuring a cyclopentane core with substitutions on each carbon and six adjacent stereogenic centers, including a triamino motif. This complexity likely makes it the most intricate metabolite among the natural aminocyclopentitols described to date.[31]

In chemical degradation studies, researchers have identified and characterized two novel derivatives of pactamycin: pactamycate I.7, which is crystalline, and de-6-MSA-pactalactam I.6, the first isolated derivative lacking the characteristic salicylic unit of pactamycin.

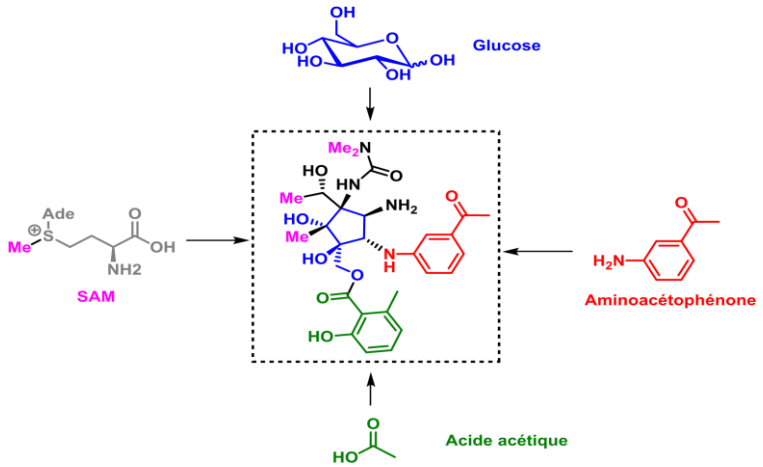
Further derivatives were identified in the 1980s, including 7-epipactamycin I.2, 7-deoxypactamycin (initially referred to as cranomycine) I.3, 8''-hydroxypactamycin I.4, and 8''-hydroxypactamycate I.4.11 The most recent derivative discovered is 7-deoxy-de-6-MSA-pactamycin I.5 (also known as jogyamycine), isolated in 2012 from cultures of Streptomyces sp. a-WM-JG-16.2 by a research team. Biological evaluations of these various compounds have revealed significant variability in their biological activities and selectivities, depending on the substitutions present on the cyclopentane structure **Schema2**.



Schema 2: Structure of natural pactamycin analogues.

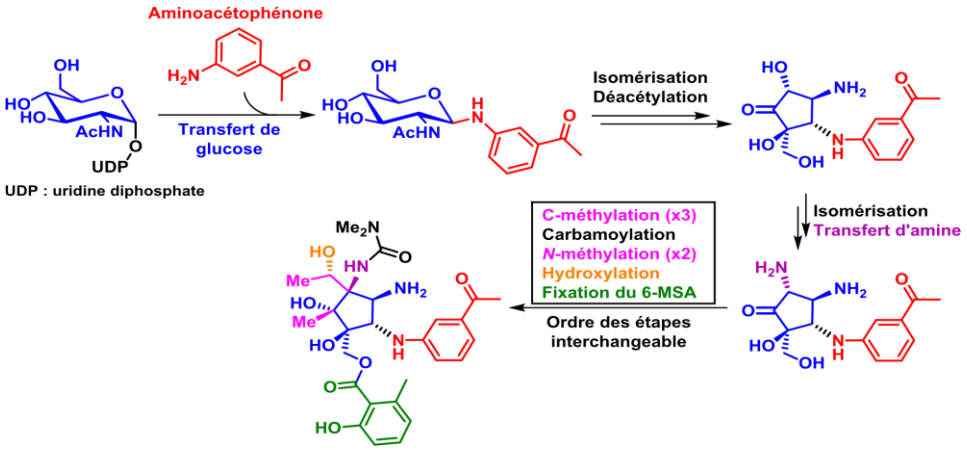
2. Biosynthesis

From a biosynthetic perspective, research conducted in the 1980s demonstrated that pactamycin is formed through the assembly of three cyclic fragments, originating from independent biosynthetic pathways. The cyclopentitol, which serves as the central core of the molecule, is derived from glucose.[32] The 6-methylsalicylate portion comes from acetic acid, involving polyketide synthase (PKS) enzymes, while the aminoacetophenone component also originates from glucose. Additionally, the introduction of the two methyl groups attached to the urea and the two methyl groups decorating the cyclopentane core occurs via S-adenosyl(L)methionine (SAM).[33] These findings were made possible through incubation experiments with isotopically labeled compounds. However, some uncertainties remain regarding the mechanisms of incorporation and the sources of certain atoms within the aromatic cycle of the aminoacetophenone motif **Schema 3**.



Schema 3: Biosynthesis of pactamycin considered.

Starting in 2010, independent research teams investigated the genetic sequences involved in the biosynthesis of pactamycin. Based on their respective studies, they proposed a biosynthetic pathway that aligns with the conclusions drawn from earlier isotopic labeling experiments. Additionally, further details were provided regarding the construction of the cyclopentitol core from glucose **Schema 4**.

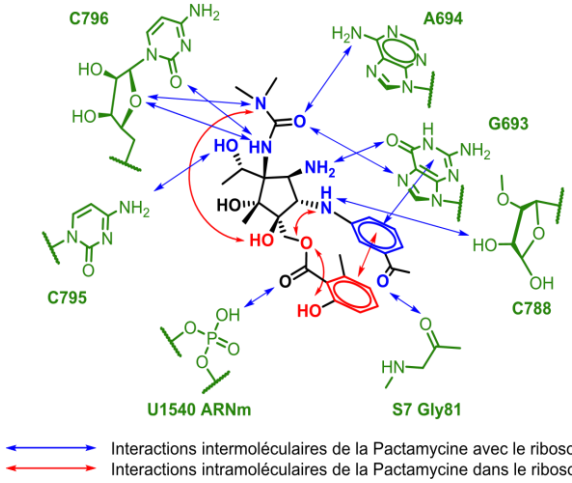


Schema 4: Revised biosynthesis of pactamycin by Kudo and Mahmud.

3. Mécanisme d'action et propriétés biologiques

Pactamycin exhibits a wide range of biological activities, including in vitro efficacy against both Gram-positive and Gram-negative bacteria, positioning it as a potential candidate in the search for a new class of antibiotics to address the growing issue of antibiotic resistance. In addition to its antimicrobial properties, pactamycin also demonstrates promising antitumor effects, which may be valuable for developing complementary cancer treatments alongside existing chemical and biological therapies. Recently, it has been found to possess noteworthy antiprotozoal properties as well. Despite these impressive biological activities, its high cytotoxicity and lack of selectivity currently hinder its development as a therapeutic agent.[34]

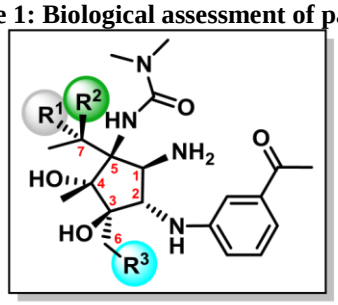
From a mechanistic perspective, X-ray diffraction analysis of the complex formed between the ribosome from *Thermus thermophilus* and pactamycin has revealed key interactions. Pactamycin mimics a dinucleotide, interacting with the small subunit (30S) of the ribosome, which plays a critical role in the action of many antibiotics. These interactions result in the inhibition of mRNA translocation at the E site, consequently disrupting protein synthesis **Schema 5**.



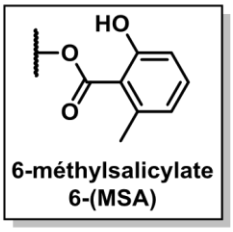
Schema 5: Key interactions between pactamycin and the 30S subunit of the ribosome.

Although pactamycin exhibits high cytotoxicity, structure-activity relationship studies conducted on its natural derivatives have demonstrated that modifying the groups attached to the cyclopentane can lead to changes in selectivity toward various biological targets. Notably, the removal of the hydroxyl group at C7 significantly enhances the antiprotozoal and cytotoxic activity of 7-deoxypactamycin compared to pactamycin. Additionally, the absence of the 6-MSA unit increases the cytotoxic activity of jogyamycine against MCR-5 embryonic cells when compared to 7-deoxypactamycin **Table 1**.

Table 1: Biological assessment of pactamycin and its natural analogues.

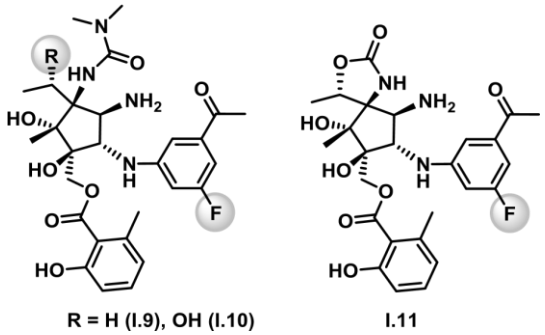


	R^1	R^2	R^3
pactamycine (I.1)	OH	H	6-MSA
7-désoxypactamycine (I.3)	H	H	6-MSA
jogyamycine (I.5)	H	H	OH



	IC_{50} (nM)		
	Activité antiprotozoaire		Cytotoxicité
Composés	P. f. K1	T. b. b. GUTat 3.1	MCR-5
pactamycine (I.1)	14,2	7,4	95
7-désoxypactamycine (I.3)	0,4	0,9	29,5
jogyamycine (I.5)	1,5	12,3	5,6

Concurrently, research conducted during the biosynthetic studies has provided valuable insights for the development of new analogs. Fluorinated analogs were synthesized through biosynthesis, particularly by employing feeding experiments, which involve incorporating an alternative precursor into the culture medium rather than the one typically utilized by the enzyme. This approach led to the synthesis of three fluorinated analogs using 3-amino-5-fluorobenzoic acid as a modified precursor. It is noteworthy that an attempt was made to use 3-amino-5-methylbenzoic acid; however, this experiment proved unsuccessful.[34] Despite the relative ease of implementation, feeding experiments are sensitive to steric hindrance, which limits the selection of available precursors. Only the fluorinated derivative I.10 underwent biological testing, yielding results comparable to the parent compound, pactamycin **Figure 1**.



R = H (I.9), OH (I.10) I.11

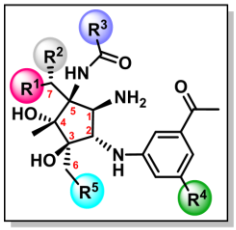
Figure 1: Fluorinated analogues of pactamycin obtained by biosynthesis.

Recent advancements in genetics have enabled researchers to generate non-natural analogs through targeted gene mutations, specifically by selectively repressing one or more genes involved in the biosynthesis of pactamycin. Key modifications include:

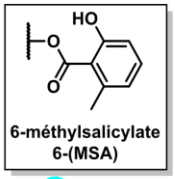
- Inactivation of the gene encoding type I polyketide synthase (ptmQ), resulting in the absence of the salicylate motif.
- Inactivation of the N-methyltransferase gene (ptmD), leading to the production of an unsubstituted urea.
- Inactivation of the ptmH gene, which is involved in C-methylation, causing the C7 carbon to become a methyl group (R1 = R2 = H).

Among the generated non-natural analogs, compounds I.12 and I.13 lack both the methyl and hydroxyl groups at C7, while I.12 also does not contain the MSA unit at C6. These two derivatives are the only ones tested in vitro.[35] They exhibit antimalarial activities comparable to those of the parent compound, pactamycin; however, they show no antibacterial activity and are 10 to 30 times less cytotoxic. Given their antimalarial properties and enhanced selectivity for this target, these compounds are highly promising **Table 2**.

Table 2: Pactammycin analogues.



	R^1	R^2	R^3	R^4	R^5
pactamycine (I.1)	Me	OH	NMe_2	H	MSA
I.12	H	H	NMe_2	H	OH
I.13	H	H	NMe_2	H	MSA



R^1 = H, Me R^2 = H, OH R^3 = NH_2, NMe_2 R^4 = H, F R^5 = OH, MSA

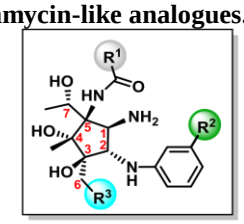
	IC_{50}				
	Activité antiprotozoaire		Antibactérien		Cytotoxicité
Composés	D6	Dd2	*S. aureus*	*P. aeruginosa*	HCT116
pactamycine (I.1)	24 nM	21 nM	10 µM	500 µM	100 nM
I.12	25 nM	25 nM	> 1 mM	> 1 mM	1-3 µM
I.13	30 nM	26 nM	> 1 mM	> 1 mM	1-3 µM

While genetic mutations allow for the creation of certain analogs, the structural modifications that can be achieved are limited. Chemical synthesis presents an alternative to enhance this diversity. The research groups led by Hanessian and Johnson have synthesized various analogs following the strategies used in their respective total syntheses, which will be discussed later.[36]

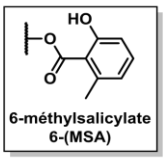
In Hanessian's approach, modulation focuses on substituting the urea at C5 and the meta position of the aniline at C2. Johnson's modifications target the alcohols at C6 and C7, the substituent at C4, and the nature of the aniline at C2.[36]

According to the findings from Hanessian's work, the salicylate unit does not appear to be critical for antiprotozoal or cytotoxic activity; however, there is a noticeable reduction in antibacterial activity for the compound de-6-MSA-pactamycin I.14 compared to pactamycin. The urea at C5 plays a significant role: its replacement with an oxazolidinone in pactamycate I.7 or substituting the dimethylamine of the urea with a piperidine (derivative I.15) results in a complete loss of activity. The presence of the urea is essential for activity, but the terminal secondary amine should not be overly bulky. Modifications at the meta position of the aniline component are better tolerated than those affecting the urea; for instance, the meta-fluorinated compound I.16 exhibits promising antiplasmodial activity while being less cytotoxic than its parent compound, de-6-MSA-pactamycin I.14 **Table 3**.

Table 3: Pactammycin-like analogues.

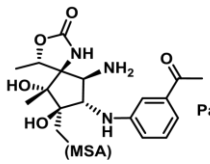


	R^1	R^2	R^3
pactamycine (I.1)	NMe_2	Acétyle	MSA
dé-6-MSA-pactamycine (I.14)	NMe_2	Acétyle	OH
I.15	Pipéridine	Acétyle	OH
I.16	NMe_2	F	OH



	IC_{50} (nM)					
	Activité antiprotozoaire		Cytotoxicité			
Composés	D6	Dd2	HCT116 (colorectale)	PC3 (prostate)	WI-38 (foie)	MDA-231 (sein)
pactamycine (I.1)	<2,5	<2,5	70	240	>1000	500
dé-6-MSA-pactamycine (I.14)	<2,5	<2,5	70	310	>1000	260
pactamycate (I.7)	>2500	>2500	>1000	>1000	>1000	>1000
I.15	>2500	2000	>1000	>1000	>1000	>1000
I.16	6,7	3,5	190	>1000	>1000	>1000

	MIC (mg/L)	
	Antibactérien	
Composés	*S. aureus*	*K. pneumoniae*
pactamycine (I.1)	0.12	32
dé-6-MSA-pactamycine (I.14)	2	8
pactamycate (I.7)	>128	>128
11C (I.15)	>128	>128
19B (I.16)	4	32

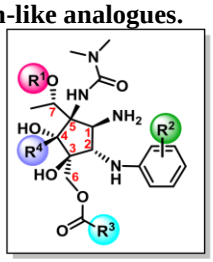


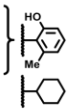
Pactamycate (I.7)

According to the findings from anticancer tests, replacing the methyl group at position 4 of pactamycin with an ethyl group (derivative I.17) results in a complete loss of activity.[37] In contrast, substituting it with a hydrogen atom (derivative I.18) significantly enhances anticancer activity, increasing it by approximately 20-fold in ovarian cancer cells. However, the cytotoxicity of compound I.18 is also higher than that of pactamycin. Modifying the aniline substitution, as seen in derivative I.19 where a fluorine atom replaces the acetyl group, generally leads to a reduction in both activity and cytotoxicity.[38] When the salicylate unit at C6 is replaced with another carboxylate (derivative I.20), selectivity is altered. Specifically, the anticancer activity of I.20 is less effective against lung and breast cancer cells compared to pactamycin but shows improved efficacy against ovarian cancer cells. Furthermore, I.20

exhibits approximately eight times lower cytotoxicity against human lung fibroblasts than pactamycin **Table 4**.

Table 4: Pactamycin-like analogues.



	R^1	R^2	R^3	R^4
pactamycine (I.1)	H	*m*-Ac		Me
I.17	H	*m*-Ac		Et
I.18	H	*m*-Ac		H
I.19	H	*m*-F		Me
I.20		*m*-Ac		Me

	EC_{50} (nM)			
Composés	A549 (cancer du poumon)	MDA-MB-231 (cancer du sein)	SK-OV-3 (cancer des ovaires)	MRC-5 (fibroblastes pulmonaires humains)
pactamycine (I.1)	160	124	129	53
I.17	non toxique	non toxique	non toxique	2063
I.18	32	50	7	6,5
I.19	141	556	434	314
I.20	175	1930	86	396

Based on the biological results obtained by various research teams, four main trends can be identified:

1. The salicylate motif does not appear to be essential for maintaining effective biological activity.[39]
2. The C5 urea component is necessary for activity (for instance, pactamycate is nearly non-toxic). However, excessive steric hindrance in this region diminishes biological activity. It is noteworthy that the pactamycin analogue with a free (primary) urea exhibits lower antibacterial activity compared to its parent compound, yet shows improved selectivity against Plasmodium, being 10 to 30 times less cytotoxic to humans.[40]
3. Increased steric hindrance at the C4 position correlates with reduced biological activity.[41]
4. Modifications to the aniline group at C2 and the hydroxyl groups at C6 and C7 allow for variations in both biological activity and selectivity.[42]

Structure-activity relationship studies conducted on previous pactamycin analogues have revealed that altering the substituents on the cyclopentane results in changes in selectivity towards different biological targets.[43] While genetic mutation facilitates the generation of a broader range of analogues, structural modifications remain constrained. Chemical synthesis presents a viable avenue to enhance this diversity, prompting organic chemists to seek a modular synthetic pathway for pactamycin and its natural analogues. A rapid strategy would enable structure confirmation and subsequent development of new analogues to deepen structure-activity relationship investigations. The following chapter will elaborate on various approaches documented in the literature, along with total syntheses and medicinal chemistry studies derived from them.[44]

Partial and Total Syntheses of Pactamycin-Jogyamycine and Analogues

For a long time, synthesizing pactamycin posed challenges that did not seem to attract the interest of organic chemists.[45] However, the focus on the biological activities of this compound during the 2000s led to renewed interest from synthetic chemists. The structural complexity of this target opens up various synthetic strategies.[46] We will outline the different partial and total syntheses, categorizing them by strategy type:

- Stereoselective functionalization of a cyclopentane through successive incorporation of various groups, guided by previously established centers.
- A linear construction of the functionalized carbon chain, followed by late-stage formation of the cyclopentane.

In 2007, an approach was published by a research group focusing on the stereoselective incorporation of oxygenated functional groups into the core of pactamycin in a linear manner around a commercially available cyclopentane, 2-methyl-cyclopentenone.[47] The initial step involved asymmetric reduction of the starting ketone using borane and a chiral oxazaborolidine, followed by hydroxyl protection, leading to the formation of an allylic alcohol. This enantioselective step enabled the stereoselective incorporation of additional substituents.[48] The quaternary stereogenic center at C4 was established through diastereoselective dihydroxylation of the vinyl derivative on the less hindered face, followed by a Swern oxidation to yield the carbonyl. Functionalization of the C3 center was achieved via a Wittig olefination/diastereoselective epoxidation sequence directed by the allylic alcohol at C4.[49] A protected homoallylic alcohol was obtained through β-deprotonation of the epoxide, leading to hydroxyl functionalization. The correct absolute configuration at C3 was introduced after epoxidation, directed by the hydroxyl group at C5, followed by oxidation, resulting in a Michael acceptor. An elegant cascade of carbamoylation and intramolecular aza-Michael addition facilitated the installation of the amino motif at C2, yielding a fused bicyclic compound. After activation as an enol triflate, a Stille coupling formed the C5-C7 bond.[50]

This strategy represents a significant advancement in constructing the pactamycin core, achieving functionalization at C2, C3, and C4, although epimerization of the amide at C2 remains necessary. The

Michael acceptor served as a platform for installing the diamino motif at C1 and C5. This complex strategy encompasses sixteen steps, including five stereoselective functionalizations, with an overall yield around 7%. One out of three nitrogen centers was successfully introduced **Figure 2**.

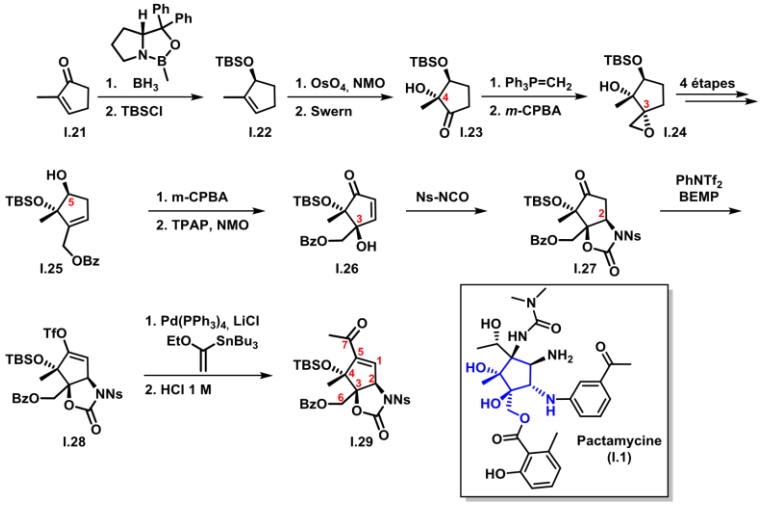


Figure 2: Approach to pactamycin.

In 2016, a research team developed a novel approach to synthesizing pactamycin, which included late-stage 1,3-dipolar cycloaddition steps that facilitate the construction of two contiguous stereocenters, followed by C(sp3)-H amination through catalytic nitrene insertion. The trans 1,2-diamino motif was established at the C1 and C2 positions of 2-cyclopenten-1-one via an asymmetric organocatalyzed aziridination using the diamine, resulting in a compound that was then subjected to regioselective ring opening with an azide. Concurrently, a selenide was introduced to yield an intermediate.[51]

In five steps, this selenide was converted into an iodinated vinyl intermediate, which underwent Meerwein-Ponndorf-Verley reduction to achieve the correct alcohol configuration at C3, followed by a Stille reaction to add a methyl group at C4. The contiguous stereocenters at C4 and C5 were established through regio- and diastereoselective 1,3-dipolar cycloaddition between the allylic alcohol and in situ generated acetonitrile oxide, resulting in isoxazoline. After a sequence of hydrogenolysis of the isoxazoline and protection of the diol at C3 and C4 to yield a carbonyl, the subsequent reduction and carbamoylation produced the corresponding carbamate. This compound was then involved in a late-stage intramolecular C-H amination via Rh2(OAc)4-catalyzed nitrene insertion, leading to the stereoselective installation of the tetrasubstituted amine center at C5 **Figure 3**.

The authors successfully established five of the six stereocenters present in pactamycin. This synthetic strategy comprises seventeen steps, achieving an overall yield of approximately 4.3% while successfully incorporating three amino centers within the cyclopentane framework.[52]

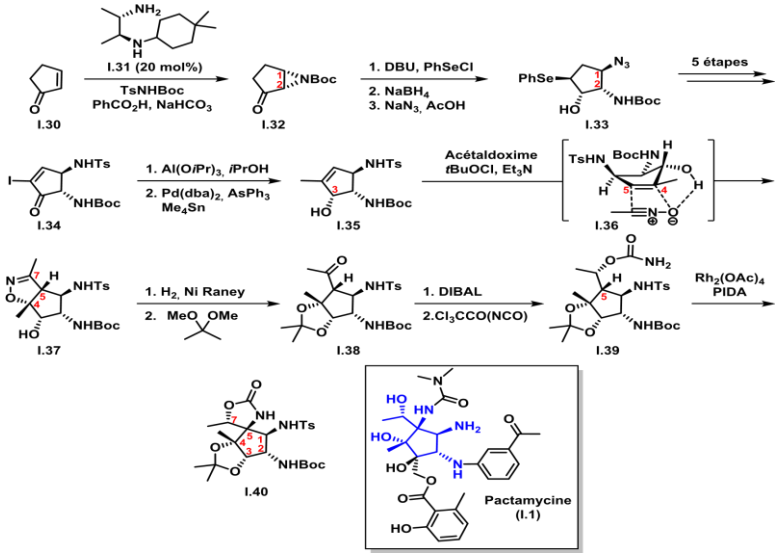


Figure 3: Approach to pactamycin.

The significant functional density at each center of pactamycin poses challenges for an iterative functionalization strategy of the cyclopentane. Consequently, most synthetic approaches focus on a linear construction of the functionalized carbon chain followed by cyclization.[53]

The first synthesis of the polysubstituted cyclopentane core was reported in 2005. Starting from commercially available diacetone-D-glucose, a chiral pool precursor, the trichloroacetamide was synthesized through a sequence of oxidation, Wittig reaction, and carbamoylation. This intermediate facilitates the creation of the stereocenter at C5 via a substrate-controlled Overman rearrangement, leading to the corresponding derivative. The correct configuration at C7 is subsequently achieved in two steps through the epimerization of an alcohol, which is isolated after oxidative cleavage of the vinyl derivative and methylation with a Grignard reagent.[54]

Following a sequence involving protection, deprotection, and oxidative cleavage of the resulting compound, the β-hydroxy aldehyde is obtained. This compound then undergoes diastereoselective addition of an acetylide, yielding the corresponding propargylic alcohol. After protecting the hydroxyl groups, the key step of the synthesis—a Pauson-Khand intramolecular reaction—leads to the formation of the cyclopentane **Figure 4**.

The initial approach successfully establishes the stereocenters at C5 and C7 and forms the cyclopentane through the Pauson-Khand reaction, although it contains only one of the three nitrogen functionalities. However, the resulting compound indicates that complex manipulations will be required to achieve total synthesis. The advanced tricyclic intermediate is obtained in twenty-one steps with an overall yield of 5.5%.[55]

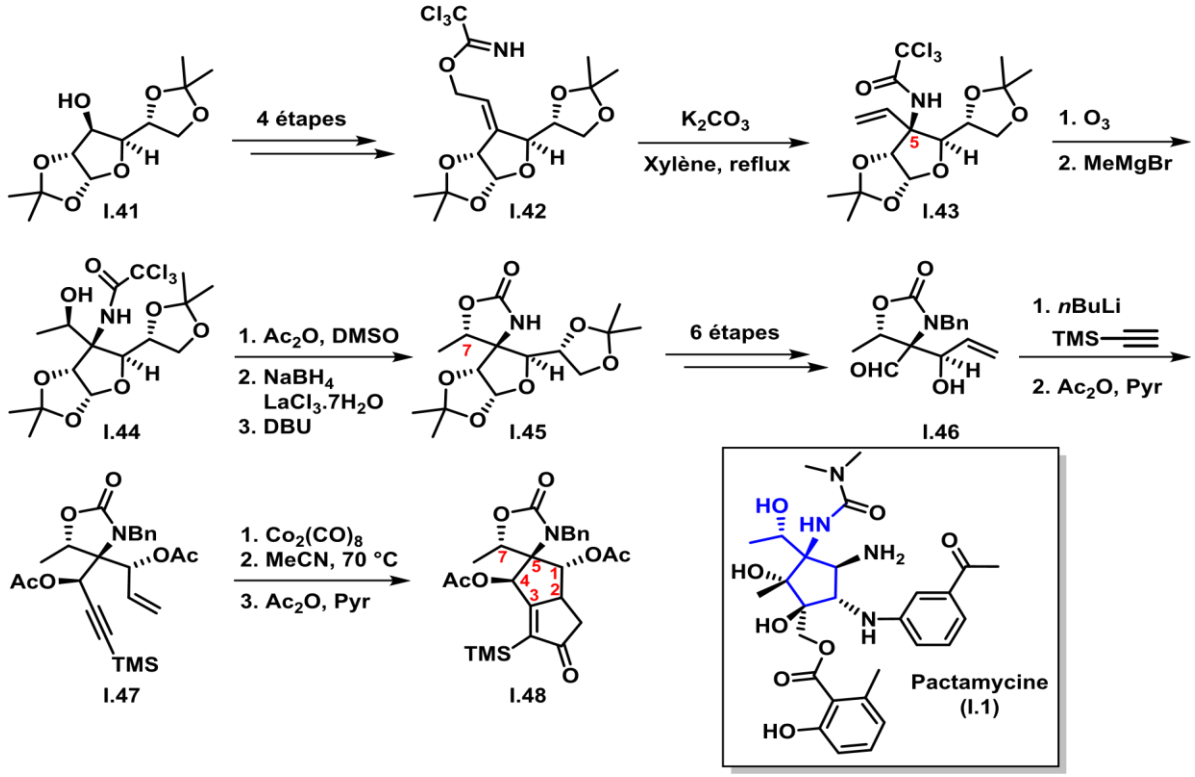


Figure 4: First approach to pactamycin.

A few years later, a research group modified the previous approach by substituting the Pauson-Khand reaction with a 1,3-dipolar cycloaddition to form the cyclopentane. Starting from the advanced enyne intermediate, hydroxyl groups were protected and the vinyl motif was transformed into a nitrone, leading to an intermediate. Following thermal cycloaddition and a spontaneous Baldwin rearrangement, the resulting aziridine was obtained. This cyclization method provides greater flexibility for the subsequent introduction of functionalities. In five steps, the diol was isolated **Figure 5**.

Despite achieving a more advanced functionalization than the previous approach, which included the installation of two nitrogen atoms, incorrect absolute configurations were introduced at the C2 and C3 centers, making them difficult to rectify. The second approach described requires a total of 29 steps and achieves an overall yield of 1.3%.[56]

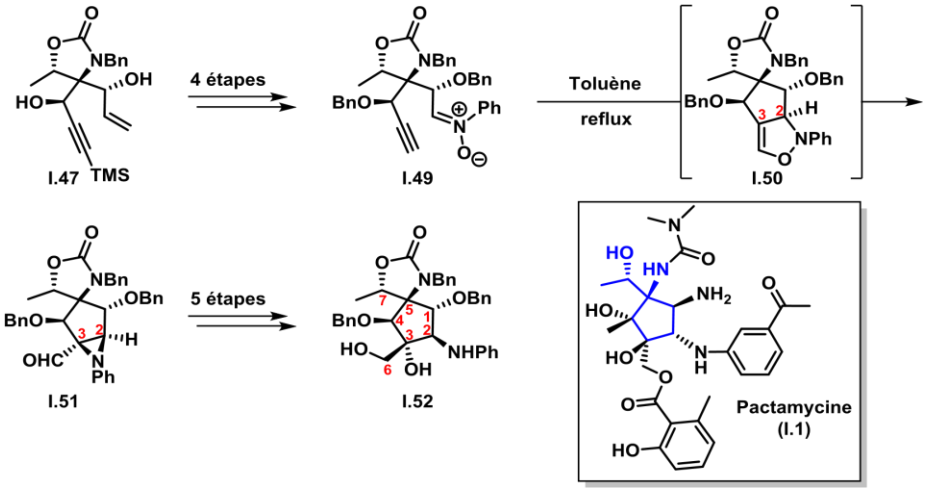


Figure 5: Second approach to pactamicin.

In 2017, a research group proposed a third synthetic approach starting from the intermediate described in the initial method. This synthetic pathway aims to produce ent-pactamycin, although the authors note the potential to begin with the other enantiomer of the starting material to access pactamycin.[57]

A series of protection and deprotection steps on the oxazolidinone intermediate enables the formation of the furanose derivative in six steps. The fused cyclopentane is then obtained through an intramolecular cycloaddition of an intermediate oxime, generated by treating the furanose with hydroxylamine in pyridine. Only one diastereomer is produced. Additional protection and deprotection steps yield the mesylate derivative, which, after N-O bond cleavage of the oxime via hydrogenolysis and treatment in a basic medium, provides an aziridine intermediate. Regioselective opening of this aziridine with an azide leads to the final compound, featuring the correct stereochemistry at C1 and C2.

This derivative incorporates all nitrogen atoms with the appropriate absolute configurations for the C-N bonds. A protected hydroxyl group and a hydroxymethyl chain are present at C3 and C4 to enable the quaternization of these centers, completing the total synthesis of ent-pactamycin **Figure 6**.

The third approach is more efficient than the previous ones, with a greater portion of the skeleton constructed, achieving an overall yield of 7.7% and a shorter synthesis comprising 22 steps.

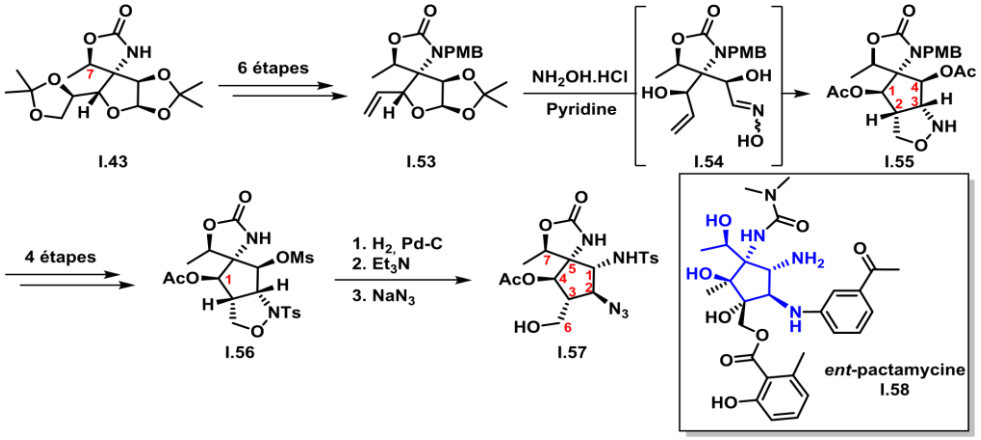


Figure 6: Approach to the synthesis of ent-pachamycin.

In 2016, a research group proposed a synthetic strategy to access jogyamycine, another natural product from the pactamycin family. The carbon skeleton of jogyamycine is constructed from a racemic homoallenic sulfamate, utilizing key steps of intramolecular aziridination and cyclization metathesis to form the cyclopentane.

The sulfamate alkene is synthesized through intramolecular aziridination of the corresponding precursor via a nitrene addition catalyzed by Rh2(OAc)4, followed by the opening of the resulting aziridine intermediate with water. An epoxidation reaction using DMDO, which induces a rearrangement, leads to the in situ formation of the imino alcohol. This intermediate undergoes alkylation with a Grignard reagent derived from ethyne. The resulting cyclic sulfamate is obtained with a diastereomeric ratio of 11.5:1, with a quaternized and stereodefined C5 center.[58]

After a series of transformations, the quaternary center at C4 is created through a diastereoselective addition (dr 20:1) to the carbonyl using an isopropenyl Grignard reagent, yielding the acyclic bis-vinyl precursor. Following cyclization metathesis, the functionalized cyclopentene is obtained, featuring an olefin between C2 and C3 for subsequent functionalization, and a hydroxyl group at C1 that can be converted to an amine via configuration inversion **Figure 7**.

This partial synthesis provides access, in fifteen steps and with an overall yield of 10%, to a cyclopentane intermediate containing two quaternary centers with the correct configuration and one of the three required nitrogen functionalities.

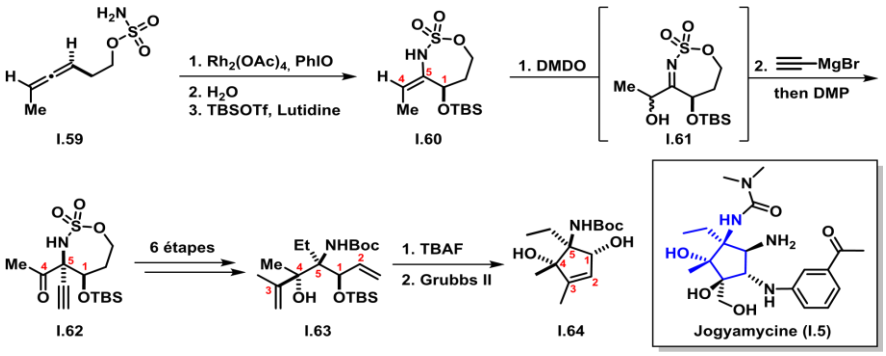


Figure 7: Approach to the synthesis of jogyamycin.

In 2012, a research group proposed a strategy utilizing a chiral pool, beginning with an oxazoline derived from L-threonine. This initial approach closely resembles that described by another researcher.

The quaternary center at C5 is constructed through a diastereoselective alkylation of an enolate formed from the oxazoline, using an iodinated derivative (dr > 20:1). The subsequent reduction of the ester to a ketone provides access to the vinyl derivative. The formation of cyclopentene begins with the ozonolysis of this vinyl compound, followed by an intramolecular aldol condensation between C3 and C4. A radical photobromination at the allylic position (r.d. > 20:1) is then performed, followed by substitution of the bromine with a benzoate to introduce an oxygen functionality at C2.[59]

Next, a sequence involving the reduction of the aldehyde, hydrolysis of the oxazoline, and acylation of the amine leads to the formation of the allylic alcohol. This intermediate undergoes a stereoselective epoxidation to yield a specific derivative. Notably, an incorrect configuration at carbon C7 was intentionally chosen at the start of the synthesis. The following step involves a cascade reaction that opens the epoxide, catalyzed by a Lewis acid, which restores the correct stereochemistry at this center through configuration inversion. During this cascade, the C3, C4, and C7 centers are established concurrently.

Ultimately, the triol is obtained after a 1,3 acyl transfer between the tertiary hydroxyl at C4 and the primary hydroxyl at C6. This transformation completes the installation of the missing stereogenic centers, leaving a hydroxyl group at C2 for the introduction of amino motifs at C1 and C2 **Figure 8**.

This partial synthesis involves thirteen steps and achieves an overall yield of 4%, with one of the three nitrogen functionalities present in the final intermediate.

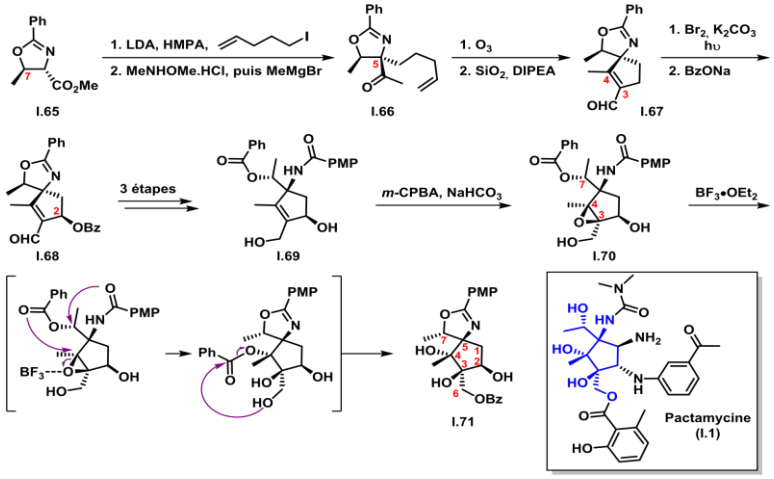


Figure 8: Approach to the synthesis of pactamycin.

In 2011, a research group reported the first total synthesis of pactamycin, employing a linear strategy that includes a series of stereocontrolled condensations, ultimately leading to the formation of a spiro oxazoline, which serves as a key intermediate in the synthesis.

The synthesis begins with the formation of the oxazoline derived from L-threonine from the chiral pool, which involves the inversion of configuration at C7. Following deprotonation and stereocontrolled condensation with a functionalized acrolein, the quaternary center at C5 is constructed, along with a partially functionalized C4 center. Subsequently, a sequence involving the transformation of an ester into a ketone, vinyl ozonolysis, and intramolecular Mukaiyama aldol condensation yields the cyclopentenone.[60]

The removal of the hydroxyl group at C3, followed by stereocontrolled epoxidation, facilitates the functionalization of the C2 and C3 centers. The nitrogen functionality at C1 is introduced through a sequence that includes stereoselective reduction, activation of the alcohol via triflation, and nucleophilic substitution with an azide. The quaternary center at C4 is established through a series of steps involving deprotection of the alcohol, oxidation, and stereocontrolled alkylation.

At this stage, the C3 center possesses an incorrect configuration. This is rectified through a Payne rearrangement promoted by zinc triflate, followed by solvolysis of the epoxide, yielding the acetylated compound. This intermediate undergoes a series of deprotection and protection steps of the primary alcohol at C7, followed by activation of the secondary alcohol at C2 as a triflate, leading to the formation of the epoxide through intramolecular nucleophilic substitution. This epoxide allows for the installation of the amino motif at C2 via regioselective opening with an aniline, while the urea at C5 is constructed after deprotecting the oxazoline, forming an isocyanate, and subsequent nucleophilic attack by dimethylamine. Finally, a series of functional modifications and deprotections culminate in the synthesis of pactamycin **Figure 9**.

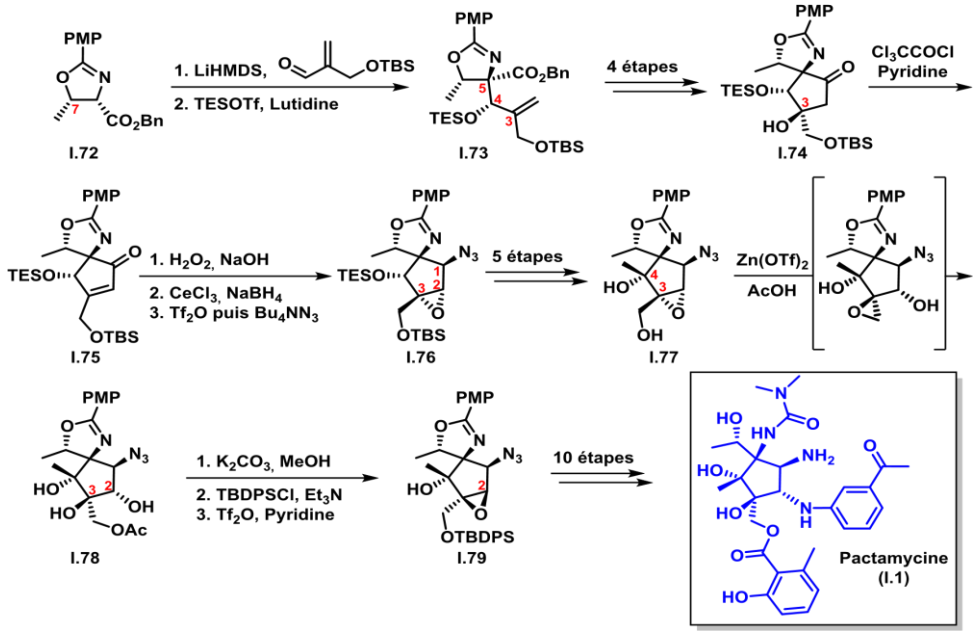


Figure 9: Total synthesis of pactamicin.

The total synthesis derived from L-threonine by the research group is entirely linear and involves thirty-two steps, achieving an overall yield of 1.1%.

In 2012, another research group published an elegant approach that included an early construction of the quaternary stereocenter C5, which bears the urea, and a late-stage formation of the cyclopentane. The compound is synthesized starting from commercially available methyl acetoacetate, where a rhodium-catalyzed N-H insertion of a carbene occurs on dimethylurea to create the initial product. The quaternary stereocenter at C5 is constructed next through a Tsuji-Trost allylation. Notably, in the presence of (R)-BINAP, this transformation can be carried out enantioselectively (though not optimized, with an enantiomeric ratio of 92:8). The synthesis continues with a desymmetrization step during the diastereoselective reduction of the ketone at C7 using L-selectride, followed by protection of the resulting alcohol to yield the ester **Figure 10**.

Transforming this ester into an enone in five steps allows for the installation of the C3 and C6 carbons. The quaternization at C4 is achieved through diastereoselective alkylation of the ketone, followed by metathesis to produce cyclopentene. The stereocenters at C2 and C3 are functionalized through a sequence of stereoselective dihydroxylation, oxidation, and protection, ultimately leading to the final cyclopentenone. This synthesis results in the

establishment of four stereogenic centers out of six, along with one of the three required nitrogen functionalities.

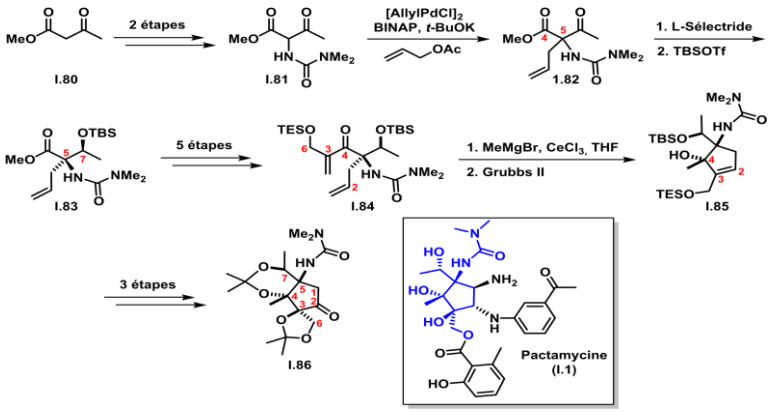


Figure 10: Approach to pactamycin synthesis.

This approach, comprising fifteen steps and achieving an overall yield of 5.0%, outlines the total synthesis published by the same research group a year later. An enantioselective Mannich reaction and a desymmetrization step facilitate the assembly of the carbon skeleton in five steps while ensuring effective stereocontrol during the installation of additional functional groups.[60]

As with the partial synthesis, the pronucleophile is synthesized in two steps from commercially available acetylacetone through carbene insertion on dimethylurea. The addition of this pronucleophile to an imine derived from cinnamaldehyde, via an enantioselective Mannich reaction (with an enantiomeric ratio of 98:2) catalyzed by a cinchonidine derivative, results in the formation of both the C5 and C1 centers, although the latter possesses the incorrect stereochemistry. The diketone is then desymmetrized through monoreduction of the ketone at C7 (dr > 10:1). Protection of the resulting alcohol followed by aldol condensation yields an intermediate.[61]

Notably, the incorrect configuration at C1 aids in controlling the desired configurations at the C5 and C7 centers. Following ozonolysis of the intermediate, treatment in a basic medium initiates intramolecular aldolization between C2 and C3 of the β-hydroxy ketone to form the cyclic core of pactamycin, while also inducing complete epimerization at C1 toward the desired diastereomer. A sequence of protection and diastereoselective epoxidation facilitates the functionalization of the C2 and C3 centers, and a diastereoselective Grignard addition constructs the quaternary stereogenic center at C4.[62]

The installation of the amino motif at C2 occurs through regioselective opening of the epoxide by 3-acetylaniline, followed by a sequence of deprotection, selective acylation, and hydrogenolysis, leading to the final product, pactamycin **Figure 11**.

This particularly notable approach allows for the synthesis of pactamycin in just fifteen steps, with an overall yield of 1.9%. To date, it represents the most efficient published strategy for this compound.[63]

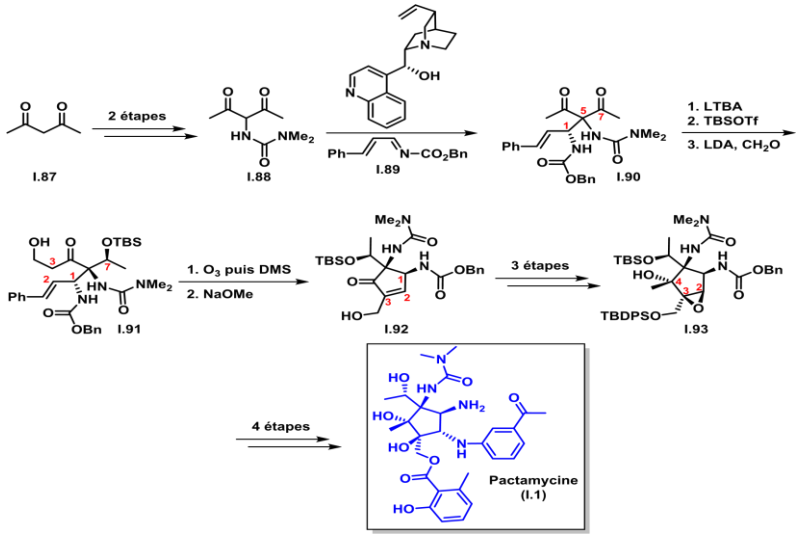


Figure 11: Total synthesis of pactamicin.

After successfully completing the first total synthesis of pactamycin in 2011, the research group focused on the preparation of analogues and their biological evaluation against various targets. Eight new analogues were synthesized using the strategy developed for the total synthesis. Derivatives of pactamycin with a de-6-methylsalicylate modification were created, featuring variations in the urea component achieved through the addition of different dialkylamines to the isocyanate function at C5. Additionally, various meta-substituted anilines were introduced at C2 through the opening of an epoxide **Figure 12**.

The researchers did not discuss the potential for modifying the nitrogen groups at C1, the hydroxyls at C6 and C7, or the alkyl group at C4, although the synthetic route they employed allows for these modifications to be considered.[64]

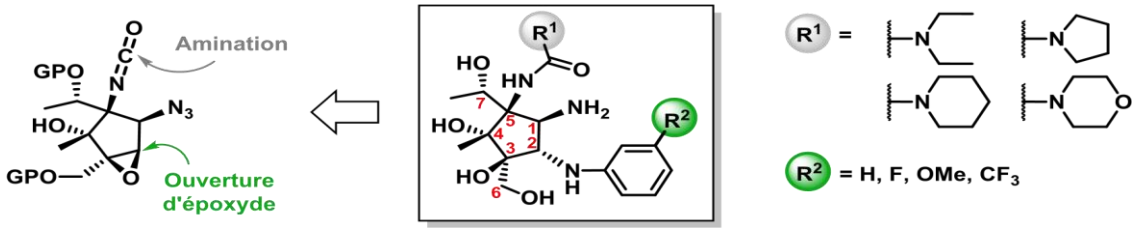


Figure 12: Pactamamycate-like analogues.

A few months after the total synthesis of pactamycin, another research group published findings on the synthesis of pactamycin analogues, employing the same strategy. Starting from an advanced intermediate, they performed modifications on the groups attached to the cyclopentane. This included the opening of an epoxide at C2 with various anilines, selective acylations of the hydroxyl groups at C6 and C7, and the addition of different nucleophiles to the carbonyl at C4.[65]

It is noteworthy that the variation of the dialkylamine component on the urea, through the late-stage nucleophilic attack of a dialkylamine on an isocyanate function—as seen in the previous strategy—appears incompatible. The generation of an isocyanate at this position inevitably leads to intramolecular nucleophilic attack by the amine (either free or protected) at C1 or the hydroxyl at C7. Additionally, steric hindrance significantly restricts the modulation of the nucleophile added to the carbonyl at C4 **Figure 13**.

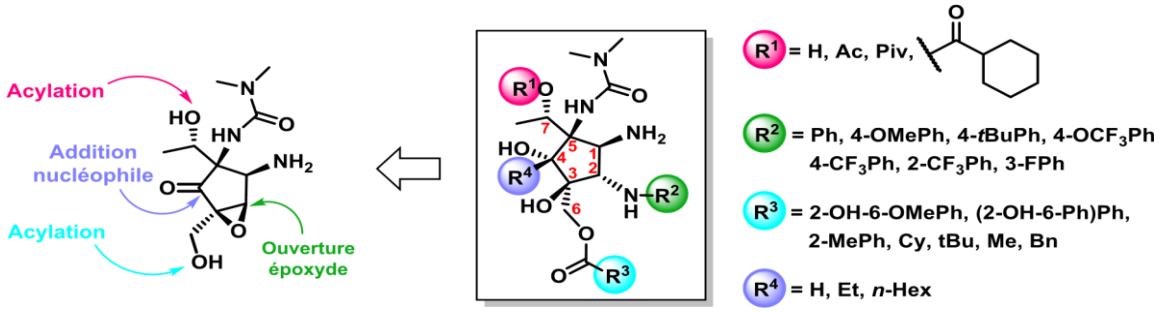


Figure 13: Pactammycin-like analogues.

Access to pactamycin analogues is of considerable importance due to their exceptional biological properties. Although bioengineering offers certain efficacy and ease of implementation, it does not allow for controlled and specific modulation of the various functional groups. This highlights the need for the development of complementary synthetic strategies to enhance molecular diversity and improve the understanding of structure-activity relationships.[66]

The synthesis of these polyazole compounds presents a challenge for organic chemists, who have a wide range of reactions available for creating C-N bonds. These include reductive amination of carbonyl compounds, nucleophilic substitution, hydroamination of alkenes, and, with the rise of organometallic chemistry in recent decades, allylic amination and Buchwald-Hartwig coupling. However, a drawback of these methods is their requirement for prefunctionalized substrates **Figure 14**.

In this context, organic chemists have leveraged the growth of transition metal catalysis since the 1960s to develop highly controlled methods for the direct conversion of C-H bonds to C-N bonds. In particular, nitrene chemistry has proven very useful for incorporating nitrogen functionalities into carbon skeletons. While C-H aminations can also be carried out via radical pathways, enzymatic methods, or organocatalysis, these approaches will not be discussed in this manuscript.[67]

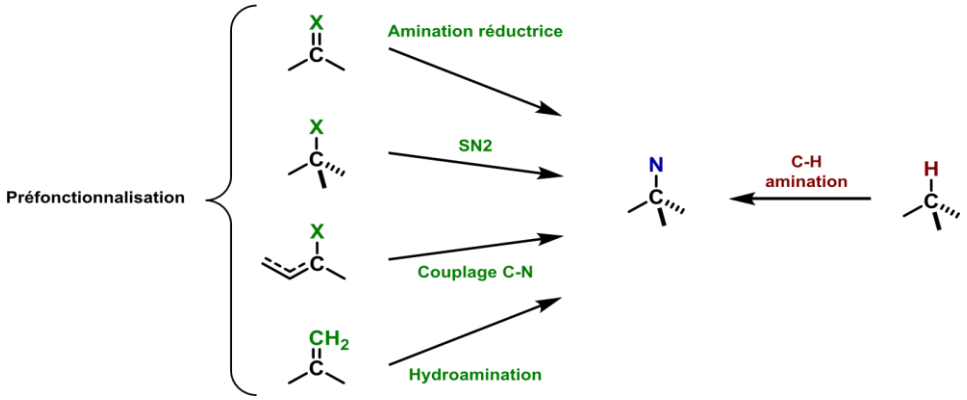


Figure 14: Reactions for the formation of C-N bonds.

II. STRATEGY

A. Nitrene Chemistry

Nitrènes, the nitrogen analogues of carbenes, are neutral monovalent compounds of nitrogen characterized by having six valence electrons. Their existence was first proposed in 1891 during the study of the Lossen rearrangement. Due to their electron deficiency and limited bonding, nitrènes can insert into various types of bonds, including C=C (aziridination), C-H (amination), and more formally, C-CO (rearrangement) **Figure 15**.

Nitrènes exist in two distinct states depending on the orbitals occupied by their two unpaired electrons:

- A triplet state, which is the most stable, where the two electrons occupy different orbitals. This configuration imparts a radical character to the nitrène, often complicating stereoselective reactions.
- A singlet state, where the two electrons are paired. In this state, the nitrène tends to react through concerted, stereospecific processes.

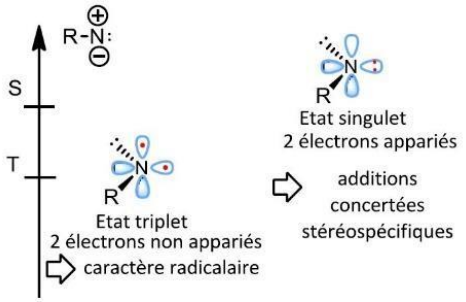


Figure 15: The two states of nitrene.

The synthetic chemistry of nitrènes began to see significant developments in the 1950s, following the work of several researchers who reported the generation of various classes of nitrènes under thermal or photochemical conditions for addition to alkenes or C-H insertion. However, the yields and selectivities of these reactions remained moderate due to the high reactivity and lack of selectivity of the generated free nitrènes, which tend to relax to the more thermodynamically stable triplet state.[68-72]

The emergence of organometallic chemistry has facilitated better control over their reactivity. This was first demonstrated by researchers in the 1960s, who showed that copper complexes could mediate the transfer of nitrènes.[70-76]

Nitrènes can be generated from various precursors, such as azides, N-sulfonyloxycarbamates, or haloamines; however, iminoiodanes have yielded the best results and have led to significant advancements in this field. These hypervalent iodine reagents are particularly useful for aziridination and C-H amination reactions catalyzed by transition metals **Figure 16**.

Initial reports of their application were described by researchers, illustrating the reactivity of these oxidizing entities in the aziridination of olefins and the amination of C(sp3)-H bonds.

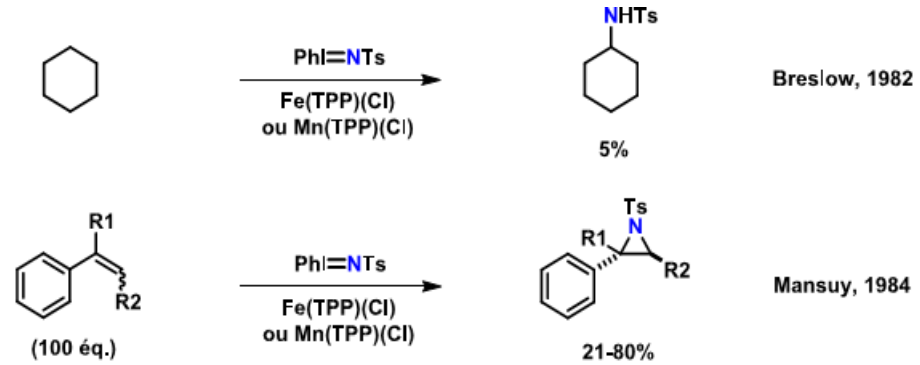


Figure 16: Early developments in metallocatalysed nitrene insertion reactions in the presence of iminoiodanes.

Despite their intriguing reactivity, iminoiodanes have several drawbacks: they are unstable compounds that are challenging to isolate and characterize properly. Their in situ formation was first reported in the early 2000s, both by researchers in the context of C(sp3)-H amination reactions and by another group for aziridination reactions involving olefins **Figure 17**.

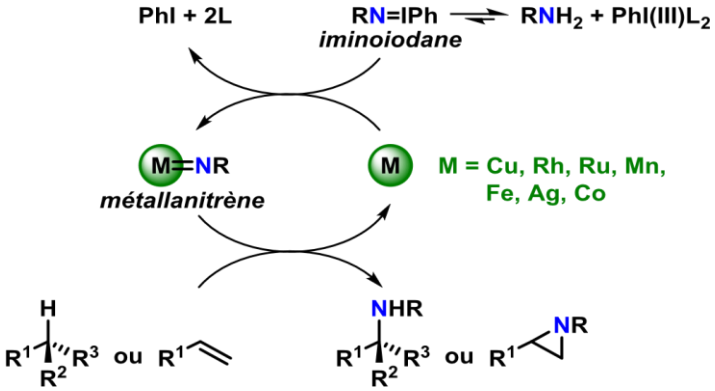


Figure 17: General mechanism of catalytic reactions of C-H amination and aziridination by insertion of nitrenes.

One researcher described intermolecular C-H amination at the benzylic position catalyzed by a ruthenium complex, using a sulfonamide and $PhI(OAc)_2$. Another developed an intramolecular amination of carbamates and sulfamates catalyzed by a binuclear rhodium(II) complex in the presence of $PhI(OAc)_2$. Additionally, other researchers formulated intra- and intermolecular aziridination reactions of olefins using sulfamates and sulfonamides, catalyzed by a copper(I) complex in the presence of iodosobenzene **Figure 18**.

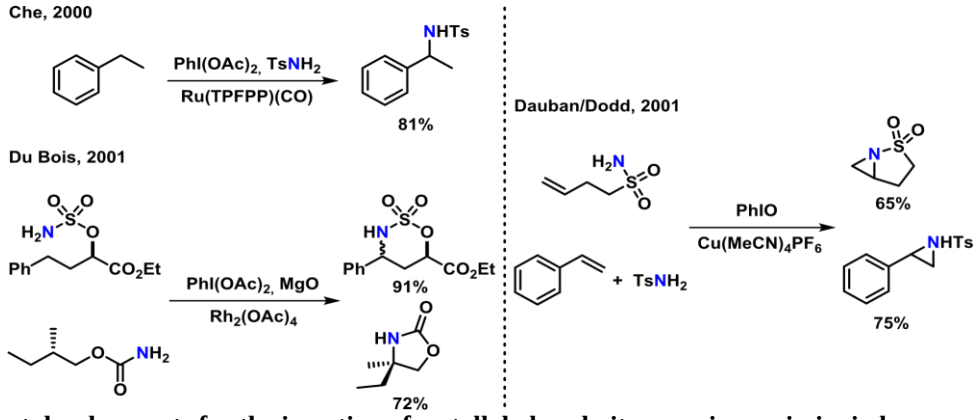


Figure 18: First developments for the insertion of metallokalyzed nitrene using an iminoiodane generated *in situ.*

These studies have enhanced the reproducibility of reaction yields and expanded the range of nitrène precursors available. In addition to sulfonamides, sulfamates, carbamates, ureas, guanidines, and carbamimidates have also been utilized. Various metal complexes derived from rhodium, silver, ruthenium, manganese, copper, iron, and cobalt can catalyze these reactions. This advancement has led to the development of efficient methodologies for aziridination and C-H amination that are chemoselective and diastereoselective. Furthermore, the use of sulfonimidamides, which are chiral nitrogen analogues of sulfonamides, in combination with a chiral rhodium complex, has resulted in highly stereoselective intermolecular reactions.[76-80]

For intramolecular C(sp3)-H amination reactions, two common types of nitrène precursors are used in total or multi-step synthesis: carbamates, whose β-insertion leads to the formation of oxazolidinones, and sulfamates, which allow for γ-amination to form six-membered rings. Regarding reactivity, the electron-deficient nature of the nitrène directs the amination reaction toward electron-rich C(sp3)-H bonds. Consequently, functionalization tends to occur preferentially at tertiary or benzylic positions, as well as at the α position of ethers, although it can still occur at less activated secondary positions. The chemoselectivity of C-H amination reactions is generally good, except in the case of allylic amination, where aziridination of the olefin may be highly competitive **Figure 19**.

However, both chemoselectivity and regioselectivity can be modulated by the nature of the ligands attached to the metal. For instance, the results of amination reactions involving unsaturated sulfamates show that intramolecular C(sp3)-H amination is favored when dirhodium complex ligands are of the carboxamidate type, despite the unfavorable formation of a five-membered ring. In contrast, aziridination is favored when the ligands are of the carboxylate type. Recently, similar

chemoselectivity favoring C(sp3)-H amination was reported in intramolecular C-H amination catalyzed by a manganese complex.[80-83]

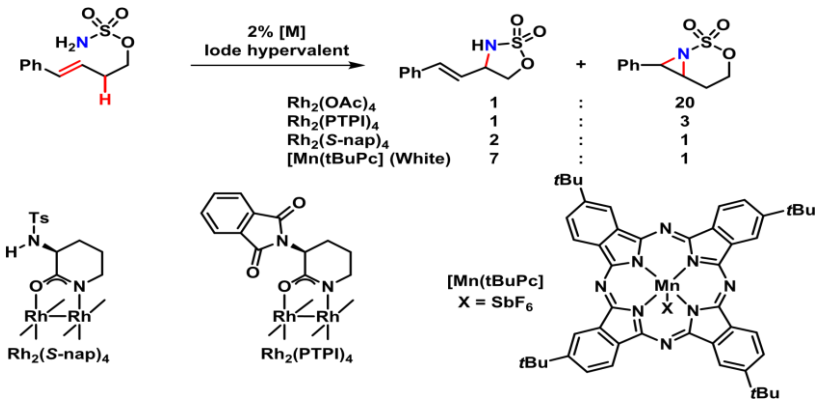
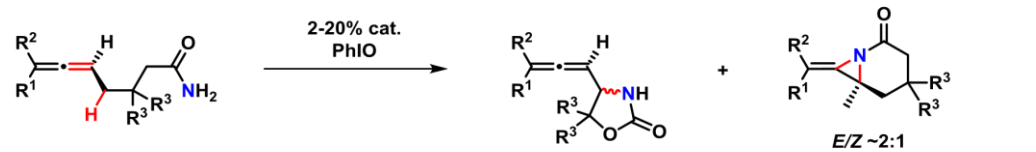


Figure 19: Chemioselectivity of nitrene insertion modulated by the nature of the metal complex.

Very recently, a methodology for the intramolecular amination of homoallenic carbamates was developed, with chemoselectivity controlled by the geometry of the complex. Using the same metal, silver, and the same ligand, phenanthroline, it is possible to achieve either C-H amination or aziridination. The modulation of this chemoselectivity is dependent on the structure of the complex, which varies according to the metal-to-ligand ratio: a metal-to-ligand ratio of 1:1.25 favors insertion, while a ratio of 1:3 promotes aziridination **Figure 20**.



I.94 a (R^1, R^2=Me, R^3=H) I.95 a (R^1, R^2=Me, R^3=H) I.96 a (R^1, R^2=Me, R^3=H)
I.94 b (R^1=C_5H_{11}, R^2=H, R^3=Me) I.95 b (R^1=C_5H_{11}, R^2=H, R^3=Me) I.96 b (R^1=C_5H_{11}, R^2=H, R^3=Me)

Substrat	Cat.	I.95	I.96
I.94 a	$Rh_2(esp)_2$	35%	14%
I.94 b	$Rh_2(esp)_2$	5%	80%
I.94 a	AgOTf/phén (1:1,25)	79%	<4%
I.94 b	AgOTf/phén (1:1,25)	79%	13%
I.94 a	AgOTf/phén (1:3)	<1%	81%
I.94 b	AgOTf/phén (1:3)	<1%	76%

Figure 20: Chemioselectivity of nitrene insertion modulated according to the nature of the metal complex.

In this context, we have proposed a new synthetic route aimed at developing a versatile platform for the preparation of pactamycin and/or jogamycin, along with novel analogues. Catalytic nitrène transfers are expected to facilitate access to the triamine motif present in the cyclic core of these molecules through aziridination, leading to the formation of the trans-1,2-diamine motif, followed by a late-stage C(sp3)-H amination.[84]

CONCLUSION

Pactamycin and its analogues represent a significant class of compounds with notable biological activities, particularly in the realms of antimicrobial and antitumor efficacy. The exploration of pactamycin has its roots in the "Golden Age" of antibiotics, highlighting the importance of natural products derived from microbes, specifically the Streptomyces genus. As researchers continue to unravel the complex biosynthetic pathways that lead to these intricate molecules, our understanding of their structure-activity relationships (SAR) has deepened, paving the way for the development of more effective therapeutic agents. The progressive elucidation of pactamycin's structure, from its initial identification to the determination of its absolute stereochemistry, illustrates the intricate relationship between structure and biological function. The discovery of various derivatives has underscored the vast potential of modifying the cyclopentane core to enhance selectivity and reduce cytotoxicity. Notably, the ongoing research into the biosynthesis of pactamycin has revealed the assembly of its tricyclic structure from distinct biosynthetic precursors, emphasizing the complex interplay of metabolic pathways in natural product synthesis.

As the issue of antibiotic resistance continues to escalate, pactamycin emerges as a promising candidate for the development of novel antibiotic therapies. Its ability to inhibit both Gram-positive and Gram-negative bacteria places it at the forefront of the search for new antimicrobial agents. Furthermore, its antitumor and antiprotozoal properties add another layer of utility, suggesting that pactamycin could serve as a multifaceted therapeutic agent in oncology and infectious disease treatment.

Recent advances in synthetic methodologies, particularly those employing nitrene chemistry, have opened new avenues for the generation of pactamycin analogues. The ability to modulate chemoselectivity and regioselectivity through careful manipulation of reaction conditions and metal-ligand complexes has been instrumental in enhancing the repertoire of available derivatives. This flexibility in synthetic strategy allows for the systematic exploration of the structure-activity landscape, enabling researchers to design analogues with tailored biological properties. The insights gained from structure-activity relationship studies have highlighted critical features of the pactamycin skeleton, such as the necessity of the urea moiety and the impact of steric factors on biological activity. These findings not only inform the design of new analogues but also facilitate a better understanding of the molecular basis for their activity, guiding future therapeutic development.

The challenges associated with the synthesis of pactamycin underline the complexity inherent in producing such biologically active compounds. The innovative strategies developed by various research teams showcase the potential for achieving total syntheses through diverse approaches, including stereoselective functionalization and linear construction of the carbon framework. As synthetic methods continue to evolve, the prospect of accessing a wider array of pactamycin derivatives becomes increasingly feasible, further enhancing our ability to combat pressing health challenges.

The ongoing research into pactamycin and its analogues signifies a critical intersection of natural product chemistry, medicinal chemistry, and synthetic biology. The combination of biological evaluation, biosynthetic understanding, and innovative synthetic strategies holds great promise for the future of antibiotic development and the fight against antibiotic resistance. As we continue to explore the potential of these compounds, the lessons learned from pactamycin will undoubtedly inform the design and development of the next generation of therapeutic agents. The journey from natural product discovery to therapeutic application remains a dynamic and rewarding field, with pactamycin standing as a testament to the enduring impact of natural products in modern medicine.

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