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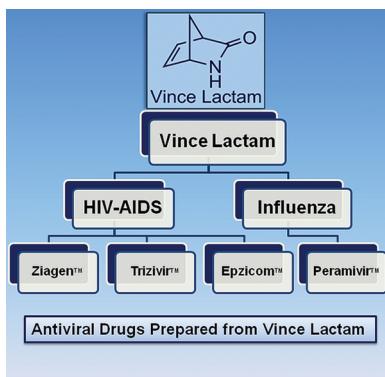
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2-Azabicyclo[2.2.1]hept-5-en-3-one: Chemical Profile of a Versatile Synthetic Building Block and its Impact on the Development of Therapeutics

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1. INTRODUCTION

Replacement of the furanoyl oxygen with a methylene unit in the ribose sugar in nucleosides¹ and nucleotides² prompted the rise of a new nucleoside class with very distinct structural, chemical, and medicinal properties.³ This class of compounds was named carbocyclic nucleosides.^{4,5} The therapeutic properties of carbocyclic nucleosides⁶ were identified early with the detection of significant antibiotic activity of aristeromycin (2, Figure 1)^{7,8} and subsequently the antitumor activity of neplanocin A⁹ (3, Figure 1).¹⁰ The significance of carbocyclic

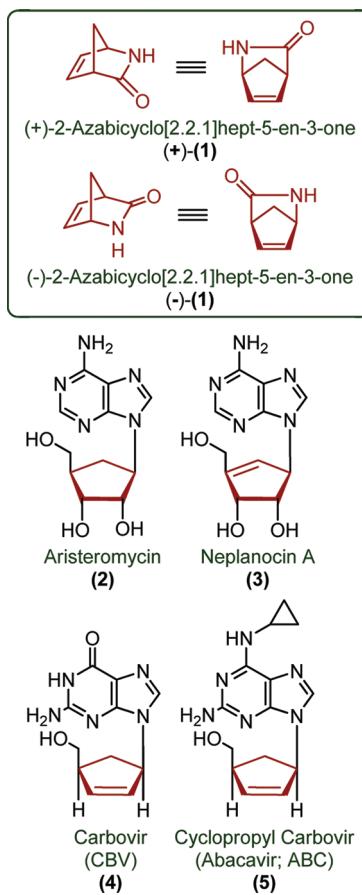
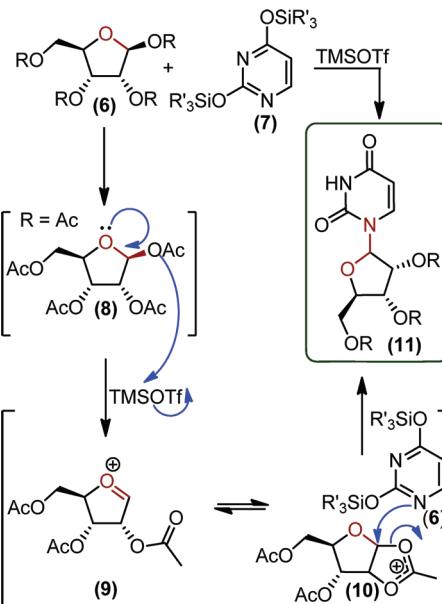


Figure 1. Structures of 2-azabicyclo[2.2.1]hept-5-en-3-one, aristeromycin, neplanocin A, carbovir, and abacavir with carbocyclic sugar moiety.

nucleosides in medicinal chemistry attracted higher attention with the disclosure of the antiviral activity of carbovir (CBV 4, Figure 1)¹¹ and its commercial form, abacavir (ABC 5, Figure 1).¹² The development of abacavir as an essential component of HAART (highly active antiretroviral therapy) for HIV–AIDS,¹³ cemented the status of carbocyclic congeners as a nucleosidic class of prime significance in medicinal chemistry.¹⁴

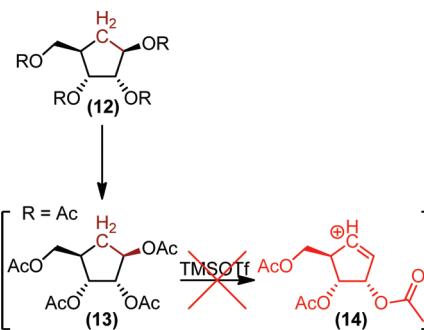
While the replacement of furanoyl oxygen by a methylene unit afforded stability against hydrolysis of the pseudo-glycosidic bond (carbocyclic sugar–nucleobase) of the nucleosides,¹⁵ it also presented a challenge of developing a universal protocol for their preparation. Lewis acid catalyzed glycosylation¹⁶ of silylated nucleic bases, developed by Vorbruggen,¹⁷ to form the nucleoside product (11, Scheme 1) with the hemi–aminal glycosidic bond (ribose sugar–nucleobase) could no longer be utilized (Scheme 2).¹⁸

Scheme 1. Mechanistic Favorability of Glycosylation with Ribose Sugar under Vorbruggen Conditions



For the preparation of carbocyclic nucleoside analogues, various strategies, such as Mitsunobu reaction,¹⁹ oxirane ring cleavage,²⁰ Michael addition on olefinic bonds,²¹ labile leaving group displacement,²² and transition metal mediated reactions,^{23,24} were tried. Although successful in furnishing the targeted compounds, none of these methods offered a universal

Scheme 2. Divergent Reactivity of Carbocyclic Sugar Substrate in Vorbruggen Glycosylation Conditions



approach to provide access to this exciting class of compounds. Moreover, preparation of 2'- and 3'-substituted carbocyclic analogues was a cumbersome process²⁵ owing to the lack of a general intermediate which could be diversified into various analogues. A protocol amenable to industrial as well as academic implications was deemed highly desirable.²⁶

The bicyclic γ -lactam, 2-Azabicyclo[2.2.1]hept-5-en-3-one, (1, Figure 1) provided the ideal means to address the challenge of devising a synthetic strategy with broader applicability. The bicyclic system furnishes a high strain on the ring²⁷ and increases the ground state energy of the molecule.²⁸ The presence of amide bond furnished an ideal prospect to open the heterocyclic ring of the bicyclic framework and provide a cyclopentane ring template.²⁹ The presence of olefinic bond in the second five membered ring, allowed the molecule to undergo various transformations such as epoxidation,^{30,31} aziridination,³² fluorination,³³ hydroxylation,³⁴ selenylation,³⁵ cyclopropylation,³⁶ etc. Along with conferring the means to access various carbocyclic nucleosides, the use of 2-azabicyclo[2.2.1]hept-5-en-3-one also provided an added venue for introducing stereospecificity in the final carbocyclic sugar analogue.³⁷ These favorable structural characteristics led to the recognition of 2-azabicyclo[2.2.1]hept-5-en-3-one as a molecular template of high significance.³⁸

1.1. History

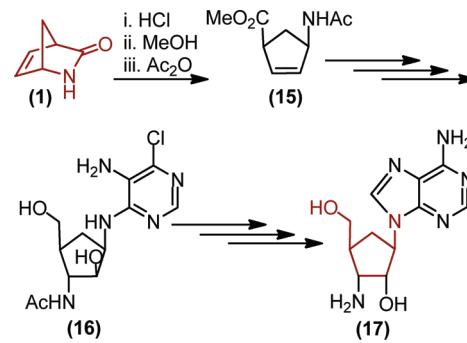
Interest in 2-azabicyclo[2.2.1]hept-5-en-3-one originated from the focus of our initial research efforts on nucleoside and nucleotide chemistry.³⁹ In 1971, we reported the first example of an acyclonucleoside (acycloadenosine) in which the sugar of the nucleoside was replaced with a 2-hydroxyethoxymethyl functionality.⁴⁰ Significant anti-herpes activity of acycloadenosine prompted the investigation of the replacement of adenine with other purine and pyrimidine nucleobases.⁴¹ Subsequent testing showed that acycloguanosine had noteworthy traits to be explored as a commercially viable candidate for activity against Herpes Simplex Virus (HSV).⁴² Consequently, acycloguanosine was developed as an anti-herpes drug by Burroughs-Welcome and marketed as acyclovir.⁴³ We continued our work on the synthesis and development of nucleosides with modified sugar moieties.⁴⁴

Structural comparisons of the natural and carbocyclic sugar moieties of nucleosides, expectedly revealed comparable bond distances and bond orientations.⁴⁵ However, noticeable differences were observed on studying their structural behaviors in solution.⁴⁶ In ribose nucleotides and nucleosides, a combination of gauche interactions of furan oxygen with 2'-OH and 3'-OH groups⁴⁸ and the anomeric effect,⁴⁹ prompts the sugar ring in solution to exist in an equilibrium between the northern (2'-exo/3'-endo) and the reversed southern (2'-endo/3'-exo) conformations.⁵⁰ In the solid state, however, one of the two conformations assumes more favorability and exists as the more predominant conformation.⁵¹ Similar major subsistence of one conformation over another is observed when the nucleotide (or nucleoside) undergoes binding with its target enzyme.⁵²

Interestingly, the absence of the furanosyl oxygen in carbocyclic sugar analogues forces the cyclopentane ring to espouse an uncharacteristic 1'-exo conformation.⁵³ This acquired conformation of carbocyclic sugars is very distinct from the usual northern/southern conformations.⁵⁴ Envisioning a diminished toxicity and drug-resistance, we sought to exploit the structural incongruity to the natural nucleosides,⁵⁵ along with the added stability of carbocyclic sugars, against

hydrolytic cleavage of glycosidic bond.⁵⁶ Retrosynthetic analysis of the targeted compounds steered us toward using a cyclic lactam to achieve our target. We envisaged ring-opening hydrolysis⁵⁷ followed by a series of chemical transformations, leading to the desired carbocyclic nucleoside compounds (Scheme 3).⁵⁸ We identified the bicyclic lactam 2-

Scheme 3. First Example of the Use of 2-Azabicyclo[2.2.1]hept-5-en-3-one in the Synthesis of Nucleosides



azabicyclo[2.2.1]hept-5-en-3-one as a potential precursor to our synthetic plans directed toward the development of a universal approach for preparing carbocyclic nucleosides.⁵⁹ Our subsequent research efforts were heavily directed toward the preparation and development of drug molecules with a carbocyclic sugar to limit the toxicity and instability of compounds while retaining the ability to interfere with various enzymes engaged in DNA and RNA synthesis.⁶⁰

Initially, we were able to translate our experience with non-classical nucleosides (acycloadenosine, acyclovir, etc.) to the removal of the nephrotoxic side-effect of the known antitumor, anti-trypnasomal antibiotic, puromycin.⁶¹ Incorporation of the carbocyclic sugar scaffold maintained the desirable inhibition of protein synthesis but without any toxic side effects.⁶² An expansion of this work led to the synthesis of anti-herpes agent carbocyclic arabinosyladenine (*C*-araA).⁶³ The preparative protocols for obtaining these carbocyclic medicinal compounds eventually led to our use of 2-azabicyclo[2.2.1]hept-5-en-3-one as an integral synthetic component for the preparation of similar non-classical nucleosides. Our continued research efforts came to fruition when several of our carbocyclic nucleosides inhibited the replication of HIV in T-cells and one such compound, abacavir, was developed by GlaxoSmithKline (GSK) as a commercial drug, Ziagen.⁶⁴

1.2. Significance and Major Effects on Medicinal and Synthetic Organic Chemistry

A recent study reported that about 40% of all marketed drugs come from natural products or their derivatives, and the remaining 60% are synthetically obtained.⁶⁵ Amidst the controversies surrounding the cost of research and development⁶⁶ of the predominantly synthetic base of pharmaceuticals,⁶⁷ there subsists a consensus that the amount is not trivial.⁶⁸ For any given drug, the costs associated from discovery to market-release can reach several billion U.S. dollars.⁶⁹ Only 63% of all new drug candidates in phase I advance to phase II testing. Further, only 21% are able to make it to phase III trials. After completion of phase III, 12% candidates proceed to the new drug applications or license approval filing and finally 9% candidates are approved as drugs and only 3% out of them ever

become commercially viable. With such disappointing numbers governing the process of drug discovery and development, it is undeniably noteworthy that a single compound can be deemed integral to the preparation of several distinct pharmaceutically relevant compounds.³⁸ Apart from the well-known antiviral agents carbovir/abacavir⁷¹ the 2-azabicyclo[2.2.1]hept-5-en-3-one lactam has also been utilized in the synthesis of neuraminidase inhibitor⁷² intravenous antiviral peramivir (PRV).^{73,74} Because of the public health concerns during the 2009 H1N1 influenza pandemic,⁷⁵ peramivir was authorized for emergency use by the United States government in spite of not having the approval of the FDA.⁷⁶ These potent antivirals are believed to have sold enough units to generate several billion U.S. dollars as revenue for their inventors and developers.⁷⁷ Since the unveiling of abacavir, GSK has reported 7.12 billion dollars in sales of the drug.⁷⁸ Furthermore, the lactam has also been utilized by various research groups around the world to develop new and effective therapies for various diseases. Some examples of such efforts include Merck's compound (MK-0812)⁷⁹ as a potent and selective chemokine antagonist⁸⁰ (CCR2),⁸¹ AstraZeneca's development of piperidinium compounds⁸² as muscarinic acetylcholine receptor agonists^{83,84} for chronic obstructive pulmonary disease (COPD),⁸⁵ Glenmark Pharmaceutical's dipeptidylpeptidase-4 (DPP-4) inhibitor⁸⁶ as an anti-diabetic drug candidate, melogliptin,⁸⁷ etc.

The volume of research focused on the preparation of a compound is directly proportional to the commercial interests related to that compound. The important target compounds of

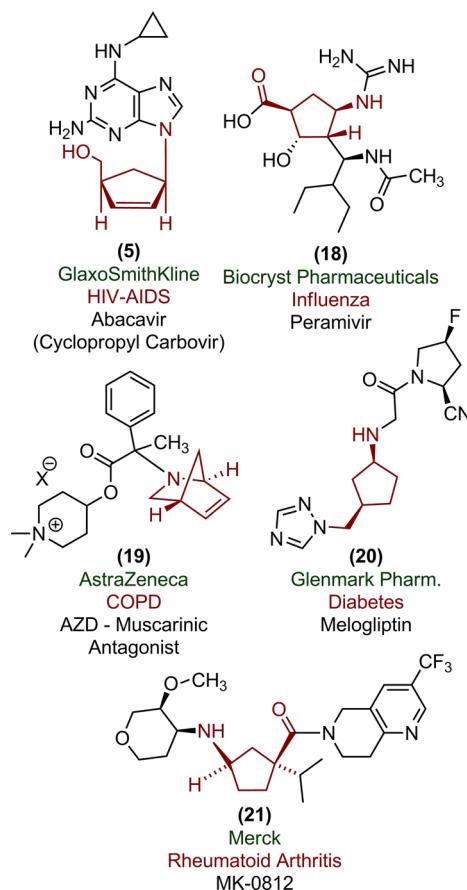


Figure 2. Structures of abacavir, peramivir, and other clinical candidates prepared from 2-azabicyclo [2.2.1]hept-5-en-3-one.

commercial pertinence have rendered 2-azabicyclo [2.2.1]hept-5-en-3-one as a highly desirable compound and today it is prepared at metric tons scale in the industry. It is commercially available from about 250 vendors worldwide⁸⁸ and is usually known by its general name "Vince lactam" coined by Chemical and Engineering News in 2003.⁸⁹ Vince lactam has been cited more than 2000 times⁹⁰ in the literature and has had more than 120 patents filed with products or processes related to it.⁹¹ For a more detailed quantitative analysis, we used SciFinder database for searching articles and reports related to Vince lactam. The numbers of hits were sorted chronologically and categorized by year. To obtain information about the progression of reports related to Vince lactam, the cumulative number of hits in SciFinder was plotted against the corresponding year (Figure 3). The line-graph in Figure 3

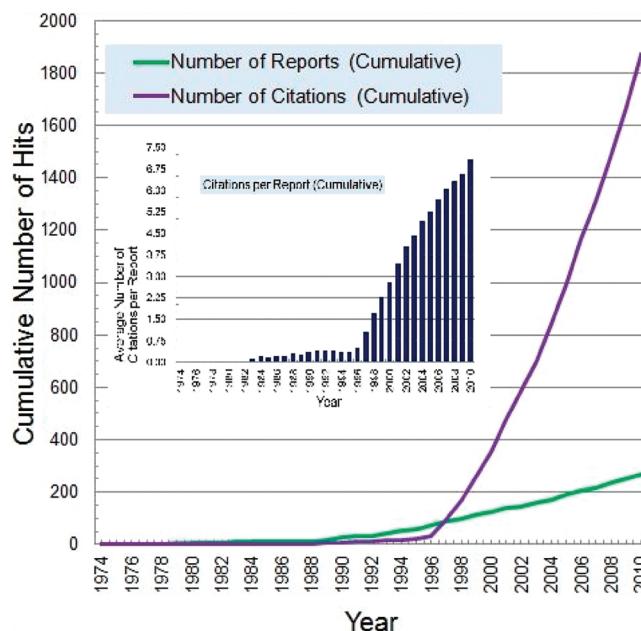


Figure 3. Chronological progression of the number of reports with Vince lactam and number of reports citing Vince lactam.⁹²

represents the noteworthy fact that although the lactam was known for about 20 years, it was only in 1996 that the number of reports pertaining to it saw a Cambrian explosion. The timeline corresponds to our disclosure of the abacavir synthesis starting from azabicyclo[2.2.1]hept-5-en-3-one. A bar graph depicting an increase in number of citations of Vince lactam related reports as a function of time (years) is also included (Inset, Figure 3). Again, the precipitous increase in number of citations around 1996–1997 corresponds to the approval of abacavir for the treatment of AIDS–HIV.

Herein, we present a comprehensive account of the structural attributes and the progressive development of various methods of preparation of Vince lactam and the resolution of its stereoisomers.⁹³ Starting from the initial reports in mid-seventies, literature related to Vince lactam is discussed up to the most recent developments in 2011. Reference to proprietary information in patents has been avoided.⁹⁴ Within the context of its application toward the preparation of various medicinal agents, diverse chemical and biochemical modifications that this compound has been subjected to, are also discussed. Finally, the applications of Vince lactam in the development of therapeutics including both nucleoside and

non-nucleoside compounds are presented. The vast impact of this lactam upon diverse areas, such as metathesis, methodology development, organic synthesis, etc., which underscore the worthiness of this compound for being reviewed via this forum, are also discussed.

2. STRUCTURAL ATTRIBUTES AND SYNTHESIS OF VINCE LACTAM

2.1. Structural Attributes of Vince Lactam

The molecular structure of Vince lactam has been studied by various groups. Elucidation of the crystal structure of Vince lactam by Suchod et al. represents a prominent effort among them.⁹⁵ While resolving the racemic mixture of the lactam via preferential crystallization,⁹⁶ the authors discovered the proclivity of the lactam to crystallize as a conglomerate.⁹⁷ Furthermore, the super saturated solution of the lactam displayed oscillatory crystallization.⁹⁸ These intriguing observations led to the preparation of crystals of the lactam,⁹⁹ which were suitable for performing diffraction studies (Figure 4).¹⁰⁰

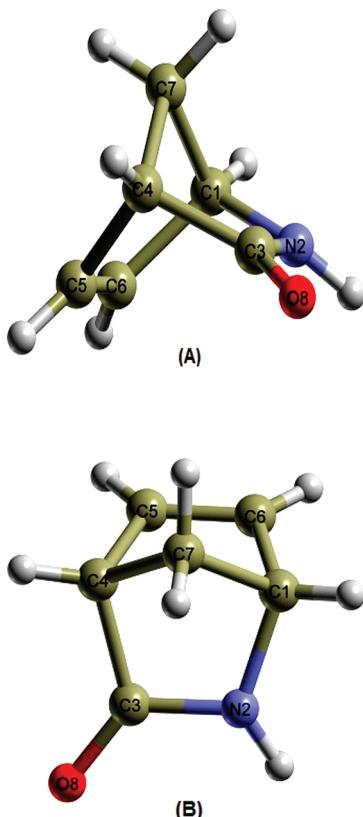


Figure 4. Ball and stick representations of the crystal structure of Vince lactam from two different perspectives (A and B).¹⁰¹

The translucent white crystals revealed that the molecule sits in an orthorhombic crystal system.¹⁰² The crystal lattice is afforded stability by the intermolecular hydrogen bonding between the carbonyl group and the amine functionalities of neighboring molecules. The distance between oxygen and nitrogen atoms involved in hydrogen bond formation is 2.885 Å. Within the molecule, the bond length between C(5)—C(6) and N(2)—C(3) atoms are 1.302 Å and 1.333 Å respectively. The oxygen lone pair orbital lies in the plane of the amide group. The dihedral angle for the amide functionality is 5.4 degrees and the nitrogen lone pair orbital assumes a position

orthogonal to the oxygen lone pair orbital. This arrangement results in maximum overlap between the nitrogen lone pair orbital and the π orbital of the carbonyl group (π_{CO}) while keeping conjugation between nitrogen and oxygen lone pair orbitals to a minimum.¹⁰³ These characteristics make the lactam a structurally stable molecule. Conversely, the presence of unsaturated C(sp²) hydrogen atoms along with the heteroatomic —NH and —CO functionalities allow for it to undergo various chemical transformations under suitable reaction conditions. The rigid bicyclic framework allows stereo-defined construction of optically active molecules. Overall, these features impart highly desirable characteristics to the reactivity profile of the lactam and render it an ideal candidate to be exploited as a synthetic building block.¹⁰⁴

Table 1. Selected Bond Lengths of Vince Lactam^a

S. No.	Atom(1)	Atom(2)	Distance (Å)
1	C(1)	N(2)	1.476(3)
2	C(1)	C(6)	1.513(3)
3	C(1)	C(7)	1.529(3)
4	C(3)	O(8)	1.232(2)
5	C(3)	C(4)	1.523(2)
6	C(4)	C(5)	1.514(2)
7	C(4)	C(7)	1.532(3)
8	C(5)	C(6)	1.302(3)
9	N(2)	C(3)	1.333(2)

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Availability of fundamental knowledge about Vince lactam, along with increasing significance of the amide group, especially in biological systems such as peptides and proteins, prompted different groups to study electronic behavior of amides

Table 2. Selected Bond Angles of Vince Lactam^a

S. No.	Atom(1)	Atom(2)	Atom(3)	Angle(deg)
1	C(1)	C(7)	C(4)	91.4(1)
2	C(1)	C(6)	C(5)	106.8(2)
3	C(1)	N(2)	C(3)	108.3(1)
4	C(3)	C(4)	C(5)	104.7(1)
5	C(4)	C(3)	O(8)	127.1(2)
6	C(4)	C(5)	C(6)	107.3(2)
7	C(3)	C(4)	C(7)	99.5(1)
8	C(5)	C(4)	C(7)	99.5(1)
9	C(6)	C(1)	C(7)	99.6(2)
10	N(2)	C(3)	O(8)	128.0(1)
11	N(2)	C(3)	C(4)	104.9(1)
12	N(2)	C(1)	C(7)	98.5(1)
13	N(2)	C(1)	C(6)	107.4(2)

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including lactams via various techniques including photo-electron spectroscopy etc.¹⁰⁵ Novak and Kovac realized the inherent challenges in studying various classes of lactams, such as *N*-vinyl lactams.¹⁰⁶ Although contribution of both inductive as well as resonance effects was indisputable, a quantitative analysis independent of effect of one moiety over another for such species had eluded the researchers. Various factors, such as (i) conjugation between amide and exocyclic C=C bond and (ii) the propensity of exocyclic C=C bond to acquire a twisted conformation,¹⁰⁷ along with (iii) relative conformational flexibility in bigger ring systems¹⁰⁸ (5, 6, and 7 member lactam ring systems), were deemed accountable for this lability. The authors realized that Vince lactam could be a candidate for comparison with related bicyclic ring systems to discern the aforementioned effects. A comparison of Vince lactam with norbornene (22, Chart 1) quantified the congruity of the C=C

Chart 1. Comparison of Electronic Properties of Vince Lactam and Other Related Bicyclic Molecules

	Ionization Energy (eV)		
	n_N	n_O	$\pi_{(C=C)}$
(1)	9.1	9.4	10.5
(22)	—	—	9.0
(23)	8.6	—	9.4
(24)	—	8.9	10.1

bond distances.¹⁰⁹ Further extension of a comparison of structural traits of the lactam to related molecules led the authors to notice the trans-annular conjugation¹¹⁰ between the two π orbitals of norbornadiene.¹¹¹ The possibility of a similar trans-annular interaction between the amide and $\pi[C(5)=C(6)]$ orbitals, with the absence of a functional group capable of direct conjugation between C=C and the amide functionality was considered. Vince lactam was chosen as an ideal molecular system to investigate the electronic structural effects of amides by the means of spectroscopy.¹⁰⁶ Photo-electron spectroscopy¹¹² along with ab initio calculations¹¹³ provided enough data to analyze the orbital energies of the structure and perform a comparative analysis with other compounds of similar structural features.¹¹⁴ As evident from the data presented in chart 1, the nitrogen and oxygen lone pairs on the lactam have higher ionization energies than the corresponding cyclic amine azanorbornene¹¹⁵ (23, Chart 1) and the bicyclic molecule norcamphor¹¹⁶ (24, Chart 1). The $\pi(C-C)$ energy values provide information about the effect of the amide bond. In the absence of any trans-annular moiety to assert an electronic effect (Norbornene, 22, Chart 1), the ionization energy of the double bond assumes the least numerical value. The ionization value increases with the presence of nitrogen (23, Chart 1) and carbonyl functionalities (24, Chart 1). These ionization energy values also indicate toward a stabilization of the C=C by 0.43 eV in case of the amine, and 1.12 eV when in conjugation with the carbonyl

group. The 3-fold increase is not surprising given the higher electronegativity of oxygen as compared to a nitrogen atom. For Vince lactam, this value was determined to be 1.55 eV which is in agreement with the additive effect of carbonyl (−CO) and amine (−NH) groups (1.53 eV). This was also deemed indicative of the stabilization of the molecule being a contributory effect, rather than being an exclusive function of the amide group in isolation. Additive nature of the electrostatic inductive effects lends support to the hypothesis. The authors also concluded that −NH and −CO groups exert stronger inductive effects on each other, compared to their respective inductive effects on the C=C functionality. Higher polarizability of the double bond electron density as compared to the more localized lone pair electronic distribution on nitrogen and oxygen atoms of the −NH and −CO groups is responsible for this effect.

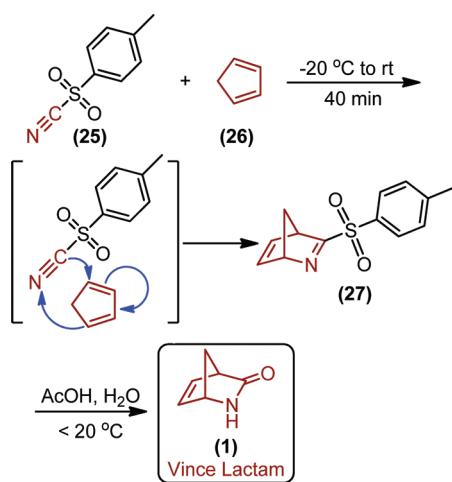
2.2. Methods of Preparation

The preparative route for Vince lactam has witnessed numerous improvements over the years. The synthetic protocol for the lactam has evolved with major developments incorporating several variations of Diels–Alder cycloaddition reaction, and diverse techniques for the resolution of the stereoisomers of Vince lactam.

2.2.1. Diels–Alder Cycloaddition of Tosyl Cyanide with Cyclopentadiene.

The initially reported preparation of Vince lactam as an intermediate for the preparation of 2-azabicyclohepta-2,5-dienes involved the Diels–Alder cycloaddition reaction.¹¹⁷ The initial use of nitriles in the role of dienophiles, did not allow for the aromatization of the cycloaddition product. The lactam was synthesized in 61% yield in a two step process. The process was part of a four step synthetic scheme culminating with amino acids as the final products. However, since the focus of the research was neither on the lactam, nor on its potential as a synthetic entity, the procedure suffered from severe limitations. Prominent among them included, the toxicity of the tosyl cyanide reagent, and the lack of a viable detailed preparative protocol.¹¹⁸ In our work focused on the development of carbocyclic analogues of 9- β -D-arabinofuranosyladenosine (*araA*), puromycin, and other nucleosides, we had identified Vince lactam as a prospective means of achieving the preparation of numerous carbocyclic nucleosides. Particular attention was given to the presence of heterocyclic moiety and the hydroxymethyl functionality disposed in cis orientation to each other. However, precedence was given to streamline the preparative process and make the starting material accessible in optimal amounts. Lack of details in reported literature for the preparation of tosyl cyanide (25, Scheme 4) led us to develop a protocol which was amenable to scaling up to larger quantities of the final product. Diminishing the possibility of accidental exposure to toxic effects was also given due consideration. The nitrile starting material for the synthesis of Vince lactam was prepared via the bubbling of cyanogen chloride through 1 M aqueous solution of sodium salt of 4-methylbenzenesulfinate. The tosyl cyanide product was consistently obtained as a white solid in nearly quantitative yields at reaction scales as large as 500 g. The newly prepared dienophile was utilized in cycloaddition with freshly prepared cyclopentadiene monomer (26, Scheme 4) obtained from thermolysis of the commercially available dicyclopentadiene dimer. With careful temperature management during both the reaction, and the work-up, we were able to synthesize the desired compound with 72% yield. Comparatively, the known

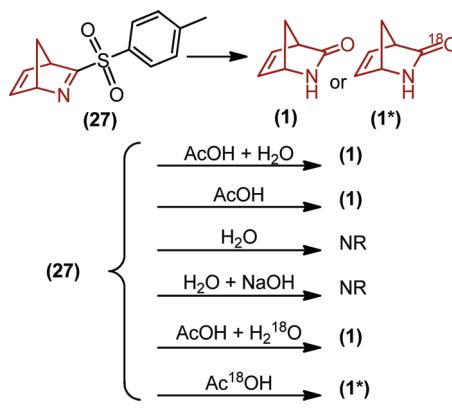
Scheme 4. One-Pot Diels–Alder Cycloaddition for the Preparation of Vince Lactam



procedures as reported in the literature at the time,¹¹⁸ furnished the lactam in low yields (30%) in our hands. Our modifications to the protocol helped prepare the lactam at scales as large as 200 g. This proved to be a highly beneficial development and led to the preparation of carbocyclic nucleosides for the first time via a simple and high yielding preparative route which allowed for stereospecific modifications to be introduced on the cyclopentyl ring. These developments prompted an increase in the interest of research community in the lactam and the chemistry related to it, and subsequently led to the rapid acceptance of carbocyclic nucleoside as medicinal agents of high efficacy. It is noteworthy that this preparative protocol was performed without the use of any special equipment in our academic laboratorial settings.

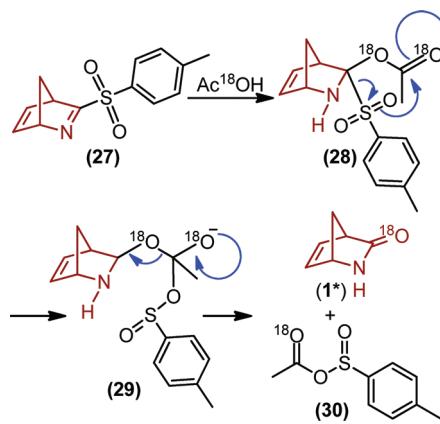
Later, Whiting and co-workers performed mechanistic investigation on the Diels–Alder reaction of tosyl cyanide and cyclopentadiene via labeling experiments.¹¹⁹ Their observations (Scheme 5) led them to propose the formation

Scheme 5. Mechanistic Investigation via Labeling Studies



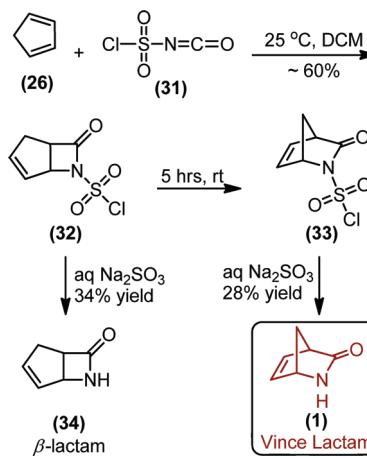
of tetrahedral intermediate 28, during the hydrolysis (Scheme 6). The proposal included the rearrangement of intermediate 28, to furnish the desired lactam along with the acetyl tosyl sulfinate (30) side-product. The dynamic ability of a sulfur atom to undergo redox transformation from S^(VI) to S^(IV) oxidation state was credited for the observed reactivity patterns and the formation of the γ -lactam rather than C–N bond cleavage, or other side reactions during the synthesis.

Scheme 6. Hydrolysis during the Preparation of Vince Lactam



2.2.2. Use of Chlorosulfonyl Isocyanate as the Dienophile in Diels–Alder Cycloaddition for the Preparation of Vince Lactam. Meanwhile, the interest in cycloaddition reactions had implored various research groups to study these transformations with a number of distinct diene substrates.¹²⁰ One such intriguing case was the 1,2-cycloaddition of 1,3-butadienes and chlorosulfonyl isocyanate leading to the formation of N-chlorosulfonyl β -lactams. The susceptibility of the prepared β -lactams to undergo rearrangement, leading to the formation of thermodynamically more stable 1,4-addition products was also explored.¹²¹ Malpass et al. followed the works of Durst and O’Sullivan,¹²² and Bestian,¹²³ in studying the performance of the dienophile isocyanate with homoannular 1,3-dienes.¹²⁴ Malpass and co-workers were studying the mechanism of rearrangement of 1,2-cycloaddition product into the 1,4-cycloaddition product. They were able to achieve 60 \pm 5% yields of the N-chlorosulfonyl β -lactam (32, Scheme 7) from the 1,2-cyclization of cyclopentadiene (26)

Scheme 7. Preparative Distinction between Formed β -Lactam and γ -Lactam

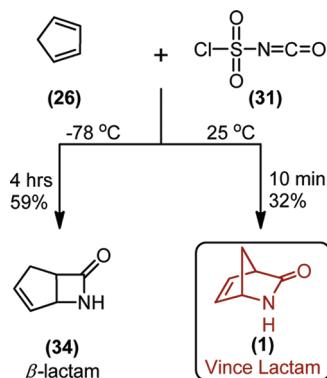


and chlorosulfonyl isocyanate (31). Immediate hydrolysis of the N-substituted β -lactam (32), by treating the reaction mixture with aqueous solution of sodium sulfite, afforded the β -lactam product (34) in 34% yield. However, allowing the reaction mixture to stir at room temperature, led to the rearrangement of the unstable β -lactam (32) into the γ -lactam (33). Treatment of the reaction mixture with aqueous sodium

sulfite solution after allowing it to stir at room temperature for 5 h afforded the Vince lactam (**1**) in 28% isolated yield.

Later, while working on the preparation and bioactivity of carbocyclic 2',3'-didehydro-2',3'-dideoxy-2-amino-6-substituted purines (carbovir)^{71a,f25} and related phosphonate analogs,¹²⁶ we revisited the Malpass method and reported upon unambiguous delineation of kinetic and thermodynamic preparative protocols. We observed that at ambient temperatures, formation of the γ -lactam was highly favored. We were able to isolate and characterize the γ -lactam (**1**, Scheme 8).

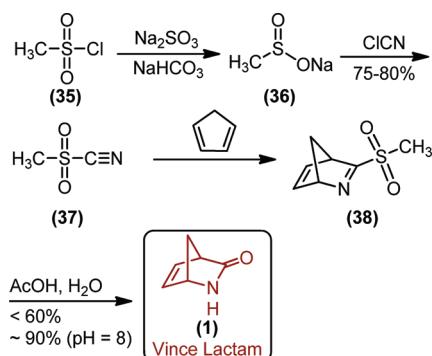
Scheme 8. Thermodynamic Effect in the Cyclization Product



within 10 min of addition of the reagents. To obtain the β -lactam, the temperature of the reaction had to be lowered considerably. While at sub-zero temperatures (-5 to -10 °C), a mixture of both the products was obtained, at -78 °C, the β -lactam was obtained as the sole product.

2.2.3. Diels–Alder Cycloaddition of Methanesulfonyl Cyanide with Cyclopentadiene. Increasing popularity and usefulness of Vince lactam encouraged researchers at Lonza AG to explore more user-friendly protocols for the synthesis of lactam at bigger scale.¹²⁷ Griffiths and Previdoli revisited the chlorosulfonyl isocyanate Diels–Alder protocol but were discouraged by the low yields and excessive use of solvent. They contemplated using the tosyl cyanide and cyclopentadiene approach but were aware of the difficulties in handling tosyl cyanide. Finally, the synthesis was modified by utilizing methanesulfonyl cyanide (**37**, Scheme 9) as the starting dienophile. **37** was prepared via the conversion of methanesulfonyl chloride (**35**) to methanesulfinate (**36**), followed by the addition of cyanogen chloride. **37** was obtained in 75–80% yield.¹²⁷

Scheme 9. Alternate Synthetic Procedure for the Preparation of Vince Lactam at Industrial Scale

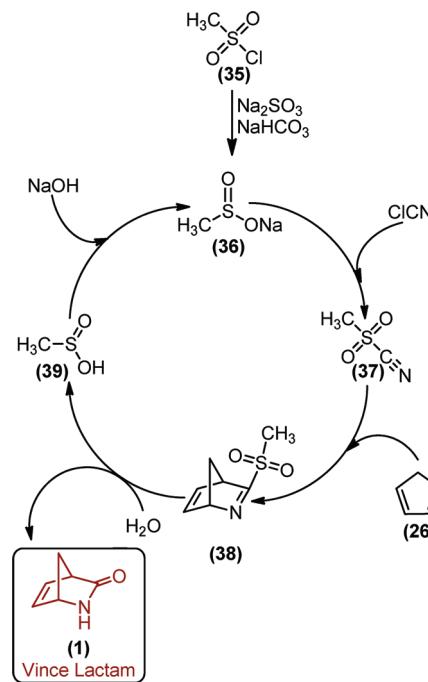


Cycloaddition of (**37**) with cyclopentadiene was studied and the progress of the reaction monitored. Although the reaction proceeded at room temperature, yields better than 60% were not attained. The tendency of unreacted **37** to undergo hydrolysis during the addition of acetic acid in last step was deemed responsible and the protocol modified accordingly. Using controlled amount of glacial acetic acid along with maintaining pH = 8 during work-up helped achieve reproducible yields as high as 90%.

2.2.4. One-Pot Procedure for the Preparation of Vince Lactam

Lactam. Despite the remarkable improvement in obtained yields, the methanesulfonyl cyanide method suffered from the drawback of not being viable for scaling up to multi kilogram levels, as aspired by the authors. Preparation of **37** could only be performed at an efficiency of 20 g/L reactor volume. Griffith and Previdoli envisioned a one-pot procedure for the synthesis of Vince lactam. The method was considered a more suitable option for the industrial preparation of the desired compound

Scheme 10. One-Pot Procedure for the Preparation of Vince Lactam at Industrial Scale



(Scheme 10).¹²⁷ For the success of this scale-up process, the following prerequisites were identified:

- Minimizing the hydrolysis of **37**, thus limiting the direct formation of methane sulfenic acid (**39**), by maintaining a competitive rate of formation of **38** from **37**.
- Clean hydrolysis of **38** to provide **39** and the desired product, Vince lactam (**1**).
- Regeneration of **36**, followed by **37**, from the side product **39**.

The authors were able to satisfy all the conditions and optimize the procedure to obtain the final product in 67% yield with excellent purity. Fifteen degrees Celsius was reported as the ideal reaction temperature for the successful preparation of Vince lactam at industrial scale via one-pot procedure. Maintaining pH = 5, in a binary solvent system of water and

dichloromethane was also considered crucial to the success of the process. The procedure made it possible to achieve productivity as high as 105 g/L of the product.

2.3. Bioenzymatic and Chemical Means for the Preparation and Resolution of the Distinct Stereoisomers of Vince Lactam

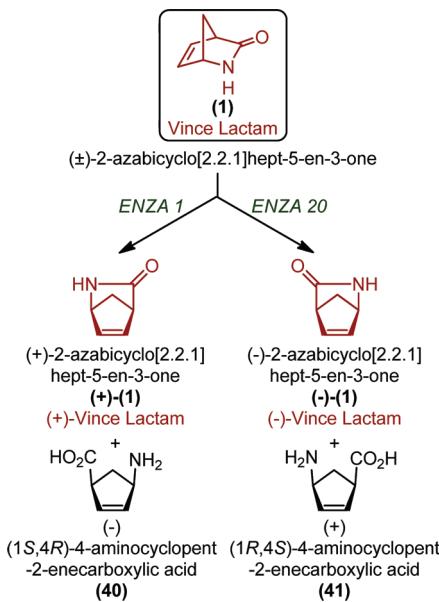
Numerous racemic carbocyclic ribofuranosyl compounds are known to display therapeutic characteristics.¹²⁸ The significance of enantiomeric purity in determining the bioactivity of the molecule has consistently pressed researchers to maintain the structural integrity of a molecule. Such circumspection often led to achieving the maximum therapeutic potential with minimum side effects, for a given compound.¹²⁹ Once it was established that the antiviral activity of carbovir was due to the (−) isomer of the compound,^{130,131} persistent efforts have been directed toward achieving either high efficiency synthesis of Vince lactam in a stereospecific manner, or to resolve the racemic mixture produced from the usual synthetic methods.

This endeavor assumed extra significance due to the inherent shortcomings in the procedure being utilized to synthesize carbovir at the time. It included starting from the previously mentioned natural product aristeromycin¹³² and allowed the formation of only one enantiomer.¹³³ Although the stereospecific synthesis of aristeromycin had been worked out,¹³⁴ the overall synthetic protocol was considered cumbersome,¹³⁵ and unworthy of being developed for further applications, especially in industrial processes.¹³⁶

2.3.1. Biocatalytic Enzymatic Processes for the Resolution of Stereoisomers of Vince Lactam. The most often utilized means of resolving the enantiomers for the preparation of carbocyclic nucleoside compounds of prominent medicinal relevance,¹³⁷ is the enzymatic kinetic resolution of the racemic mixture.¹³⁸ The development of methodologies related to the lactam have received scrupulous attention from researchers from biotech companies, such as Enzimatix, Ltd. (Cambridge, U.K.). Pioneering work by Evans and co-workers (including Taylor, Roberts, and McCague) led to significant advances in the bioenzymatic resolution of stereoisomers of Vince lactam. They recognized the need for larger quantities of the racemic lactam from our synthetic scheme for the preparation of carbovir¹³⁰ and set out to find microbial entities suitable for providing both the enantiomers of the lactam. To that end, they reported whole cell preparations of microbial strains from environmental sources (soil and sewage samples etc.) and utilized them as biocatalysts for the desired resolution of the lactam.¹³⁹ The efficiency of the system was improved by developing the mutant strains of the microbes which over-express γ -lactamase. Hydrolysis of one enantiomer not only provided the other enantiomer intact but also unlocked the prospect of chemically modifying the optically active amino acids (**40** and **41**, Scheme 11) to convert them into substrates, for the preparation of nucleosides with the desired stereospecificity. The authors made significant advances in the exploration and development of subsequent chemistry required to attain the desirable enantiomers of the product.¹⁴⁰

Scheme 12 represents a general synthetic pathway to illustrate the formation of various conformations of the desired molecule, following the biocatalyzed resolution of the racemic Vince lactam. For instance: Action of ENZA-1 on the racemic mixture hydrolyzes the (−) isomer to furnish optically pure stereoisomer (+)-(1) of the lactam. The hydrolyzed product (**40**) of the racemic mixture, was subjected to hydrogenation to

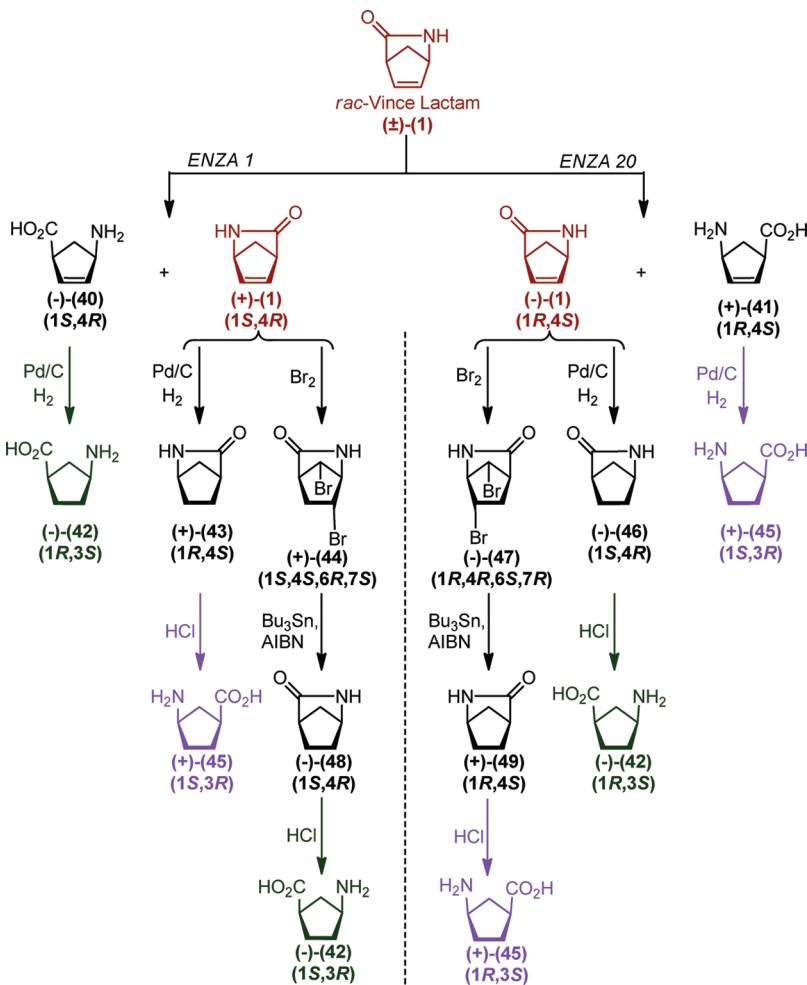
Scheme 11. Bioenzymatic Resolution of Vince Lactam



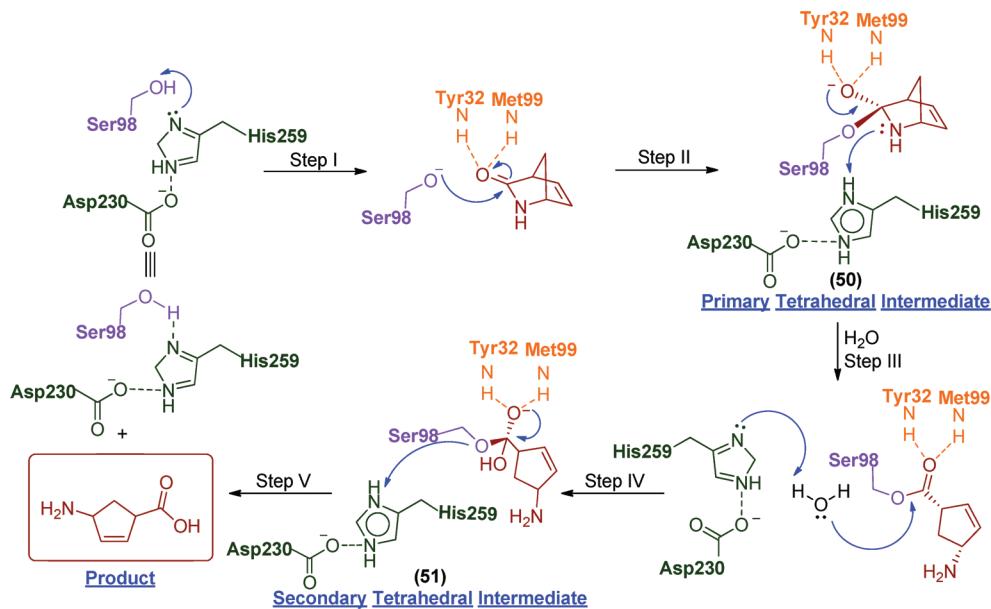
obtain the cyclopentane amino acid in the desirable conformation (**42**, Scheme 12). Meanwhile, the resolved lactam (+)-(1) was also subjected to hydrogenation and the resulting reduced lactam (**43**, Scheme 12) was hydrolyzed to obtain **45**, the geometrically inverse stereoisomer of **42**. Inversion of the resolved lactam was also achieved. A sample of optically pure compound was brominated to obtain the dibromo intermediate (**44**), which underwent rearrangement in the presence of tributyltin and AIBN.¹⁴¹ The bromonium ion intermediate encouraged the inversion of the cyclopentane structure and hence the formation of the opposite enantiomer of cyclopentane amino acid was obtained on hydrolysis of **48**. Desired chirality in the final product was attained on performing similar transformations on various adducts and derivatives of Vince lactam.^{139,141}

Later, Littlechild continued the work and reported on the crystal structure elucidation of a (−) γ -lactamase enzyme from an *Aurobacterium* species.¹⁴² The structure was solved in both free noncomplexed form, and in complexation with a ligand. Elucidation of the mechanism of action of the enzyme indicated that the (−) γ -lactamase follows a mechanism similar to other α/β hydrolase enzymes.¹⁴³ The mechanism (Scheme 13) entails the activation of serine residue (**Ser98**) via deprotonation by a histidine residue (**His259**), represented by step-I in scheme 13. The carbonyl oxygen of the lactam interacts with a positively charged oxyanion opening formed by nitrogen atoms of **Tyr32** and **Met99** amino acid residues, and acquires susceptibility toward the attack from the activated serine residue (**Ser98**). Complexation of **Ser98** with the lactam carbonyl carbon forms the primary tetrahedral intermediate (Step II). **His259** releases a proton to nitrogen atom on the lactam resulting in the collapse of the tetrahedral complex intermediate (Step III). **His259** maintains a central role to the progress of the reaction by deprotonating a molecule of water. The hydroxyl anion thus released, attacks the carbonyl carbon of the lactam and forms the secondary tetrahedral intermediate at that carbon (Step IV). Next, **Ser98** abstracts a proton from **His259** leading to a collapse of the second tetrahedral intermediate and consequently releasing the cyclopentene amino acid product of the (−) isomer of the lactam (Step

Scheme 12. Biocatalytic Resolution of Vince Lactam Followed by Various Chemical Transformations to Obtain the Desired Stereoisomers of Synthetic Intermediates



Scheme 13. Proposed Mechanistic Pathway for the Biocatalytic Hydrolysis of Vince Lactam



V). The well-known preference of the hydrolase enzymes to attack a substrate from *si* face rather than *re* face was studied in the system via molecular modeling of the two tetrahedral

intermediates. These studies revealed that the complexes modeled on *re* face for both the isomers of the racemate were highly unfavorable. Furthermore, the unpropitious steric

Table 3. Bioenzymatic Resolution of Vince Lactam and Its Derivatives^a

S. No.	Enzyme (Name/Strain)	Reaction Substrate → Product	Yield (%)	ee (%)
1 ¹³⁹	ENZA - 1 (<i>Rhodococcus equi</i>)	A → B + D	45	>98
2 ¹³⁹	ENZA - 20 (<i>Pseudomonas solanacearum</i>)	A → C + E	45	>98
3 ¹⁵²	ENZA - 22 (<i>Pseudomonas fluorescens</i>)	A → B + D	-	93
4 ¹⁵²	ENZA - 25 (<i>Aurobacterium species</i>)	A → C + E	-	91
5 ¹⁴⁴	Lipase PS (<i>Pseudomonas cepacia</i>)	F → G + H	38	94
6 ¹⁴⁴	Lipase AK (<i>Pseudomonas fluorescens</i>)	F → G + H	31	89
7 ¹⁴⁴	Lipase AY (<i>Candida rugosa</i>)	F → G + H	5	26
8 ¹⁵³	Lipase PS - On Diatomite (<i>Pseudomonas cepacia</i>)	F → G + H	43	93
9 ¹⁵³	Lipase PS - On Toyonite-200P (<i>Pseudomonas cepacia</i>)	F → G + H	39	86
10 ^{154,155}	Porcine Liver Esterase	I → J	74	≥ 99
11 ¹⁵⁴	Porcine Liver Esterase	I → K → L	-	50
12 ^{156,157}	Savinase (<i>Bacillus lentus</i>)	M → N	84	>99
13 ¹⁵⁶	Savinase (<i>Bacillus lentus</i>)	P → Q	50	>99
14 ¹⁵⁸	γ-Lactamase (<i>Sulfolobus solfataricus</i>)	A → B	100	>99

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hindrance on the *si* face of the (−)-γ-lactam, allowed only the possibility of attack from *si* face of the carbonyl of (−)-γ-lactam. This preferential approach of the enzymes, imparts the desirable stereoselectivity in the resolution of the two isomers.¹⁴²

In separate work, Hongo et al. studied Lipase enzymes for similar resolution of racemic mixtures.¹⁴⁴ Lipase enzymes have found more applications in organic synthesis owing to their easy commercial availability, less cost and no prerequisites of a coenzyme to be required for its activity.¹⁴⁵ The lipase enzymes act by mediating the transesterification reaction in an enantioselective manner.¹⁴⁶ Transesterification is a potent organic transformation utilized widely in organic synthesis.¹⁴⁷ Many impactful advances in molecular catalysis have been reported in recent years.¹⁴⁸ Although transesterification with molecular catalysts now allows the use of secondary¹⁴⁹ and

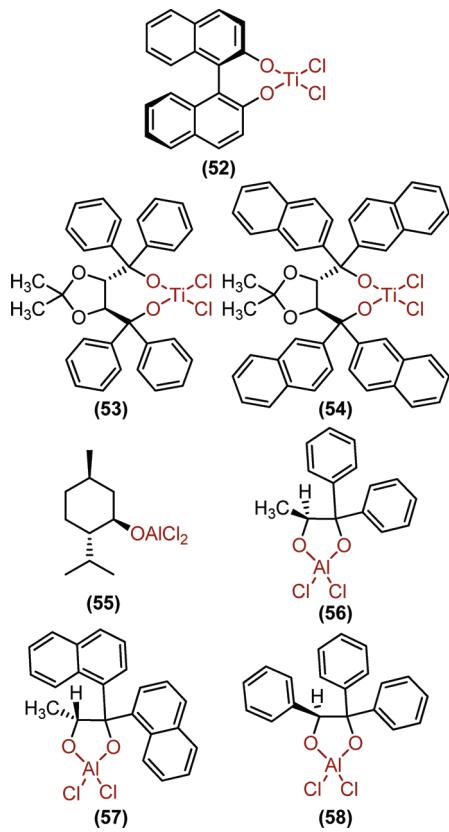
tertiary alcohols¹⁵⁰ as well as phosphorus esters as substrates,¹⁵¹ enzymatic resolution of alcohols remains a cornerstone of the methodology. To discourage the formation of cyclopentane amino acid, and to make the lactam more suitable substrate for the transesterification reaction, *N*-hydroxymethyl group was installed on the lactam. The transesterification of the substrate furnished preferential formation of the acyl derivative of one enantiomer. Thus, facilitating the separation of the two isomers by significantly altering the chemical and physical properties of the acylated product as compared to the unreacted *N*-hydroxymethyl isomer of the substrate. Conversion of the acylated stereoisomer back into the hydroxymethyl compound was followed by deprotection of both the enantiomers. Treatment of the *N*-hydroxymethyl-protected enantiomers with ammonium hydroxide in methanol furnished the optically pure bicyclic lactams. A summary of several enzymes, studied

by various research groups for the resolution of Vince lactam, are presented in table 3.

2.3.2. Chemical Methods Utilized for Obtaining Stereospecific Forms of Vince Lactam

Various chemical approaches¹⁶⁰ have been explored as alternative means of obtaining the optically pure enantiomers of Vince lactam. One such approach involves the use of an optically active catalyst for the induction of chirality in the molecule. Chiral Lewis acids are known to stimulate the construction of optically active centers in substrate molecules.¹⁶¹ Katagiri and co-workers reported the first application of this system to the asymmetric preparation of Vince lactam in Diels–Alder reaction.^{162,163} Various titanium,¹⁶⁴ and aluminum¹⁶⁵ chiral Lewis acids were analyzed. Titanium catalyst (52, Scheme 14)¹⁶⁶ provided the cyclization

Scheme 14. Chiral Lewis Acid Catalysts for the Preparation of Pure Enantiomers of Vince Lactam



product lactam in 48% yield. However, the product was obtained in very poor enantiomeric excess (2.8%). Titanium complexes 53¹⁶⁷ and 54¹⁶⁸ displayed similar reactivity by failing to generate chiral products. Presumably, the attenuated coordination between the Lewis acid and the dienophile sulfonyl moiety, led to the failure in adequate promotion of the reaction by the catalyst. Titanium complexes were subsequently replaced by aluminum Lewis acid catalysts. Koga's catalyst (55)¹⁶⁹ along with a series of aluminum complexes (56–58)¹⁷⁰ based on Kagan's catalyst^{171,172} were studied. After optimization of the reaction conditions, the synthesis of (+)-(1) was achieved in moderate yields of 45%. The product was obtained in enantiomeric excess up to 25.6% in the reaction catalyzed by the aluminum complex 56.

Fernandez et al. diverged from these catalytic methods for the enantioselective synthesis of Vince lactam and instead,

relied on chiral synthesis. They made use of chiral sulfonyl chlorides in Diels–Alder reaction to generate the asymmetric product.¹⁷³ To that end they prepared neomenthylsulfonyl cyanide and menthylsulfonyl cyanide and tested them in Diels–Alder reaction with cyclopentadiene. After a thorough analysis of the reaction mixture it was concluded that the neomenthylsulfonyl congener provided 11% ee of 1S isomer of the lactam, while the methylsulfonyl analogue furnished 12% ee of the 1R isomer of the lactam.

2.3.3. Resolution of Racemic Vince Lactam by Recrystallization Methods

Along with chemical and biological methods, the process of preferential crystallization (entrainment) has also been utilized to resolve the racemic Vince lactam. As mentioned in section 2.1, the discovery that the lactam crystallized as a conglomerate,⁹⁵ intrigued Collet et al. Conglomerate crystallization for resolution of racemic mixtures represents a very cost effective and attractive option.¹⁷⁴ However, the attempts to perform this ‘routine’ process, revealed the display of an usual behavior by the supersaturated solution of the lactam.¹⁷⁵ The supersaturated solution was prepared by dissolution of Vince lactam in 1:9 (w/w) binary mixture of isopropanol and diisopropyl ether. On attempts to seed the crystallization, it was discovered that the crystallization of the enantiomers of the lactam proceeds in an oscillating manner. It was observed that one enantiomer of the substrate in the super saturated solution, starts crystallizing and continues to do so until it reaches its maxima. From which point onward, the other enantiomer of the compound starts crystallizing spontaneously and continues to do so until it reaches its threshold. Once the second enantiomer reaches its maxima, crystallization of the first enantiomer recommences. The process persists with such oscillating behavior until the solution reaches its solubility equilibrium. Analysis of various factors assisted the authors in drawing the conclusion that one enantiomer helps in solubilization of the second, and while the first enantiomer is crystallizing, the concentration of the second isomer reaches the level of supersaturation. Beyond the point of supersaturation, the second isomer starts crystallizing. Moreover, the two enantiomers are inclined to grow on the surface of each other.¹⁷⁶ The process could be modified to isolate the desired stereoisomer with enantiomeric excess of up to 90% via seeding the solution with the preferred enantiomer and removal of the freshly formed crystals prior to the system undergoing oscillatory phenomenon. However, it was concluded that the process was very difficult to implement in industrial settings. The phenomenon, though observed in few other compounds,¹⁷⁷ is largely rare, and development of such a method would have very specific applications.

A thematically similar attempt of resolving the racemic mixture of Vince lactam was attempted by Toda et al.¹⁷⁸ It was conceptualized that one enantiomer of the lactam might be more inclined to form a host–guest inclusion complex with certain molecules. The alkaloid brucine has a history of being utilized for various functionalities which include carbocyclic compounds as well as amides.¹⁷⁹ On incubation with Vince lactam for 6 h at room temperature, the inclusion complex was obtained as colorless prism crystals with ee of 36%. After performing recrystallization of the crude complex four times, the product was purified via distillation, to furnish (−)-(1) in poor yield (13%) but with high enantiomeric excess of 92%. X-ray diffraction studies were performed on the crystals of the complex. The (−)-(1) isomer was shown to be able to place itself between channel type cavities in the layers of host

molecules while (+)-(1) was unable to fit itself in the molecular structure leading to the excellent enantioselectivity as observed in the host–guest inclusion complex method for the resolution of Vince lactam.

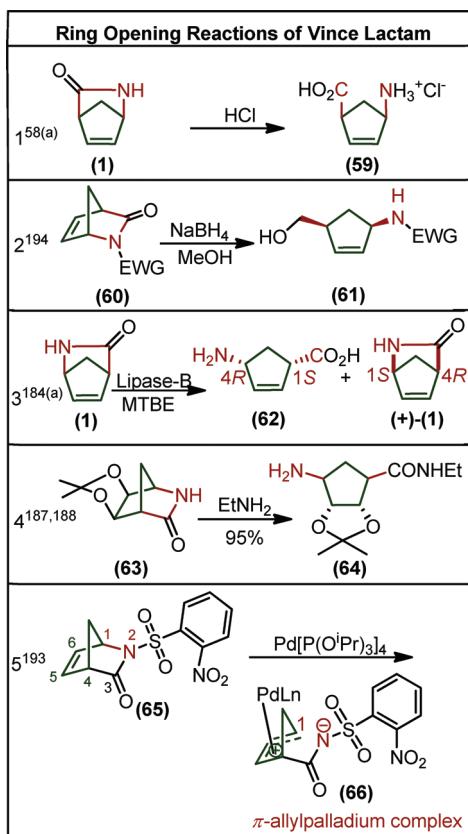
3. REACTIVITY PROFILE OF VINCE LACTAM

Because of the extensive use in medicinal chemistry and organic synthesis, Vince lactam is often subjected to certain structural modulations and chemical transformations. Some examples of these transformations include ring-opening, epoxidation of double bond, fluorination, methylation, etc. The utilization of these reactions to achieve the target and examples of unusual or interesting reactivity characteristics displayed by the lactam are worthy of note.

3.1. Ring-Opening Reactions of Vince Lactam

In our initial synthesis protocols, we reported hydrolysis of the amide bond of Vince lactam under acidic conditions.⁵⁸ Use of 2 N hydrochloric acid at room temperature furnished the 4-aminocyclopent-2-ene carboxylic acid hydrochloride salt in optimum yields (entry 1, Table 4). Later, we adopted a synthetic protocol which obviated the requirement to isolate the cyclopentane amino acid.¹⁸⁰ Other research groups continued to study the opening of the ring of Vince lactam

Table 4. Various Methods for the Ring-Opening of Vince Lactam and Its Derivatives^a



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in diverse systems. The utilization of retrograde aldol reaction toward the synthesis of carbocyclic C-nucleosides from norcamphor intermediate was reported.¹⁸¹ The authors contemplated the use of the similar reaction conditions (NaBH_4 , K_2CO_3 , methanol) for the preparation of carbocyclic N-nucleosides, but realized that the scope of the requisite C–N bond cleavage via sodium borohydride in cyclic amide congeners was limited to only imides on five membered ring.¹⁸² The lactam precursors (Vince lactam and dihydro Vince lactam) are stable to the reduction by NaBH_4 and hence the rings do not open under the given conditions. However, introduction of electron withdrawing groups on the nitrogen imparts lability to the C–N bond of the lactam, and renders them more susceptible to react with NaBH_4 , and furnish amino alcohol in excellent yields (entry 2, Table 4). Reaction of lactam precursors with various chlorides (tosyl chloride, methylcarbamoyl chloride, and ethyl chloroformate) furnished the corresponding N-protected lactam precursors. The protocol was utilized to achieve the stereospecific synthesis of uridine carbocyclic nucleoside derivatives.¹⁸³

In section 2.3, we detailed the bioenzymatic resolution of the enantiomers of the lactam, leading to the desired enantiomer of the compound, along with ring-opened cyclopentane product. However, if the targeted molecule is cyclopentane amino-alcohol rather than the intact lactam, the bioenzymatic ring-opening of lactam can be regarded as a corollary of the methodology. In an elegant work, Fulop et al. reported a very felicitous illustration of such a requirement being fulfilled by the bio-catalytic approach.¹⁸⁴ Vince lactam was subjected to hydrolysis by enzyme lipase B from *Candida antarctica*¹⁸⁵ to provide the required amino acid (−)-(62) along with the (+)-isomer of the Vince lactam (entry 3, Table 4) in highly enantioselective process (both (−)-(62) and (+)-(1) isolated with $ee > 99\%$). The authors utilized this method for the stereospecific preparation of carbocyclic amino alcohols. These amino alcohols were further subjected to carbamoyl protection, esterification, epoxidation, and oxirane ring-opening to obtain the stereoisomers of functionalized azidocarbocyclic amino-alcohols¹⁸⁶ for their potential use in the preparation of carbocyclic azidonucleosides, such as puromycin.⁶¹

Chen et al. had reported preparing protected 4-amino-N-ethyl-2,3-dihydroxy cyclopentane-carboxamide (entry 4, Table 4) via the reaction of acetonide protected Vince lactam with neat ethylamine under very extreme conditions (140°C , steel bomb).¹⁸⁷ Later, Bannister et al., at Chiroscience, Ltd., repeated the procedure under similar conditions (140°C , 250 psi, 15–20 h) and prepared the desired product in 80–90% yield at kilogram scale.¹⁸⁸ However, their need of the material necessitated the modification of the process to make it amenable to a standard pilot plant. After careful optimization of the process, the preparation of the required compound as a benzoate salt under relatively mild conditions (reflux in THF, 24 h, 80% yield) was achieved.¹⁸⁹ The reaction proceeds with catalytic amount of ethylamine (5 mol %). Ethylammonium benzoate serves as the stoichiometric contributor for ethylamine. The product precipitates out on cooling the reaction to room temperature, making this process very suitable for implementation in a pilot plant.

In other related studies, Ponticelli and co-workers have underscored the studies on the ring-opening of Vince lactam via nitrogen nucleophiles in a recently revealed elegant report.¹⁹⁰ The products thus obtained were further functionalized into useful synthetic units.¹⁹¹ Significant advances in metal catalyzed

synthesis of carbocyclic nucleosides have also been described. Palladium has been studied for ring-opening of the lactam.¹⁹² In the application of Trost's chemistry to Vince lactam, presence of an electron withdrawing group on the nitrogen of the lactam was deemed essential.¹⁹³ On reaction with the palladium source, the lactam forms a π -allyl palladium complex (entry 5, Table 4) with the metal center. Preferential approach of the metal center from the exo-side of the lactam leads to an increase in the ring strain. Interestingly, the ring undergoes cleavage from C(1)—N(2) bond rather than the usual N(2)—C(3) bond with N-sulfonyl group acting as an intramolecular leaving group. The 2-azabicyclo[2.2.2]oct-5-en-3-one congener failed to undergo any reaction with 6-chloropurine in presence of the metal catalyst. The failure in formation of the six membered ring, corresponding to the five membered ring with Vince lactam as substrate, proved the inherent ring strain of the lactam as a characteristic, indispensable to its observed reactivity profile.

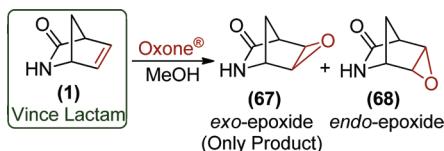
3.2. Modification of the Double Bond on Vince Lactam

The presence of C(5)=C(6) double bond in the structure of Vince lactam provides a suitable template for the introduction of various functionalities on the molecules. It can be exploited to modulate the reactivity of the synthetic intermediates (for example, introduction of acetonide protecting group: 63, Table 4), or to incorporate a specific functional group in the final carbocyclic structure (For example, the inclusion of fluoro group as depicted in Scheme 29). These transformations helped elaborate the versatility of Vince lactam and further established it as a valuable synthetic precursor.

3.2.1. Epoxide Formation and Opening of the Oxirane Ring on Vince Lactam. In our initial report with the preparation of carbocyclic nucleosides via the use of Vince lactam, we presented epoxidation of the double bond in the acetoxyamino cyclopentene ester obtained from the hydrolysis of the lactam. We utilized *m*-perchlorobenzoic acid (*m*CPBA) to achieve the requisite oxirane formation (2 h, reflux in CCl_4).⁵⁸ Several groups have studied the epoxidation of Vince lactam in its bicyclic form prior to opening the ring.

Legraverand and Bisagni presented the epoxidation of Vince lactam induced via potassium peroxymonosulfate (Oxone).¹⁹⁵ The transformation required assiduous control of the pH of the reaction medium. While, the formation of exo-epoxide product was observed in good yields, endo-epoxide product formation was not detected (Scheme 15). Furthermore, no epoxidation

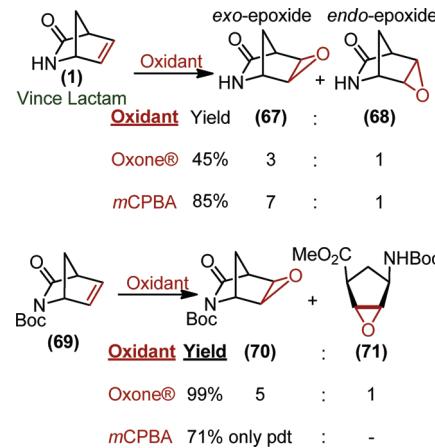
Scheme 15. Oxone-Promoted Preparation of exo-Epoxide of Vince Lactam



product formation was observed on utilizing *m*CPBA as reagent. However, the experiments were later repeated by Cullis and Dominguez.¹⁹⁶ Contrary to the observations reported by Legraverand and Bisagni, formation of the endo-product was recorded, on employing Oxone for epoxidation. Their experiments resulted in formation of a mixture of exo- and endo-products in the ratio of 3:1 (exo/endo). The epoxides were isolated in a modest yield of 45% (Scheme 16).

16). Also contrary to the claims by Legraverand and Bisagni, epoxide formation with *m*CPBA was noted by Dominguez and

Scheme 16. Epoxidation of Vince Lactam by *m*CPBA: Selective Formation of exo-Epoxide over endo-Epoxide



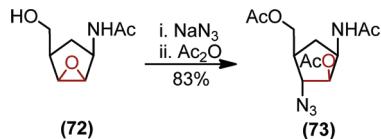
Cullis. Not only did the reaction proceed to form the epoxide product with *m*CPBA, it furnished better yields and much improved selectivity (exo/endo = 7:1). The contradictory observations were assigned to incidental factors such as variable pH in Legraverand/Cullis experiments, which could have led to opening of the ring. The polar product thus formed would not have dissolved in dichloromethane, the solvent of choice for extraction of the product. Furthermore, the discrepancy in selectivity in facial approach in the epoxidation of the lactam was explicated by inadvertent removal of the endo-epoxide during purification by crystallization in Legraverand/Cullis experiments.

Lack of formation of facially distinct products with 1, prompted the exploration of the epoxidation of N-protected analogues of Vince lactam. While Katagiri et al. had presented their protocol for the N-protected Vince lactam to cleave the C—N bond by NaBH_4 , for which the presence of electron withdrawing group on nitrogen of the lactam was a necessity,¹⁹⁴ Rapoport and co-workers also helped lay down the groundwork for these studies by utilizing N-protected Vince lactam analogues in their preparation of carbocyclic nucleosides via trans-annular alkylation.¹⁹⁷ Taylor et al. had also reported N-protection of Vince lactam in their studies pertaining to bioenzymatic activity for resolution of the stereoisomers of the lactam.¹⁵² Indeed, excellent selectivity was achieved with *m*CPBA as the oxidant. Formation of the exo product (70, Scheme 16) of the Boc-protected Vince lactam (69) was observed. Katagiri et al. had attained similar results with *m*CPBA in their studies.¹⁹⁸ However, with Legraverand conditions using Oxone, a mixture of the desired Vince lactam oxirane along with the ring opened cyclopentane side product (71, Scheme 16) was obtained.

After obtaining easy access to the epoxides of Vince lactam, Cullis and Dominguez decided to address reductive ring-opening of the obtained epoxides and attempted to provide a versatile regioselective route for the synthesis of 2'- and 3'-deoxyribose carbocyclic nucleosides.¹⁹⁶ In our initial studies, we had utilized sodium azide for the oxirane ring-opening.⁵⁸ We had focused our attention on the hydrolyzed lactam product *N*-4-(hydroxymethyl)-6-oxabicyclo[3.1.0]hexan-2-yl)acetamide

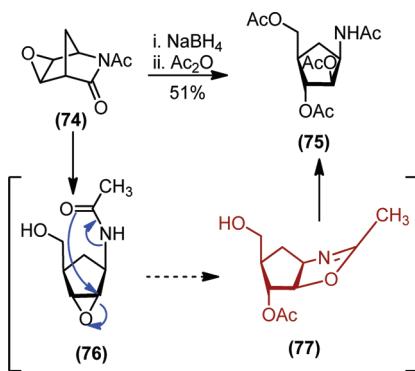
(72, Scheme 17) owing to its usefulness in the synthesis of targeted nucleosides.

Scheme 17. Epoxide Ring-Opening by Sodium Azide



Katagiri et al. reported a one-pot procedure for opening both the lactam ring, and the epoxide ring, by the use of NaBH_4 ($\text{K}_2\text{CO}_3\text{-NaBH}_4\text{/MeOH}$).¹⁹⁹ Further development of the methodology, and the mechanistic rationale for the favorability of formation of compounds with regio and stereo preference of one compound over its other isomers (Scheme 18) was

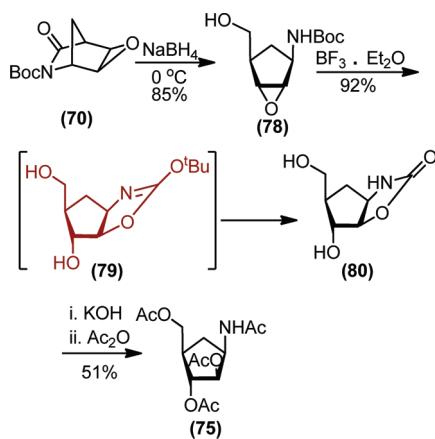
Scheme 18. Reductive Epoxide Opening



presented later.¹⁹⁸ The proposed mechanism included the formation of an oxazoline intermediate (77, Scheme 18). Formation of this key intermediate is facilitated by the presence of the acyl group on the nitrogen (76, Scheme 18).

The sequential two-step ring-opening of the two heterocyclic rings was also studied. Selective cleavage of only the more labile bond (C–N) of Boc-protected lactam (70, Scheme 19) was achieved by cooling the reaction mixture to 0°C , prior to the addition of NaBH_4 . The intact oxirane ring was opened via the use of $\text{BF}_3\text{-Et}_2\text{O}$ in acetonitrile at room temperature. The oxazoline intermediate (79, Scheme 19) was isolated and characterized providing credence to the proposal of existence of

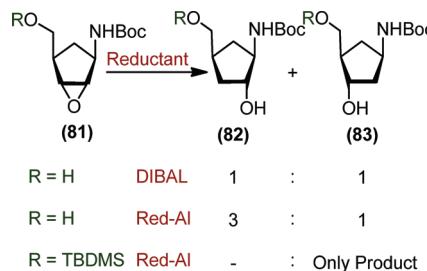
Scheme 19. Sequential Two Step Ring-Opening



similar intermediate (77, Scheme 18) in the acyl protected lactam.

Later, Culles and Dominguez reported the utilization of numerous reducing agents for the analysis of this transformation and confirmed the higher lability of the C–N bond of the lactam relative to the C–O bonds in the epoxide ring.¹⁹⁶ On comparison of DIBAL and Red-Al reducing agents, the steric demands exerted by the bulky Red-Al were observed to provide an impetus to the reaction for achieving better stereocontrol on the outcome (Scheme 20).¹⁹⁶ Indeed, on

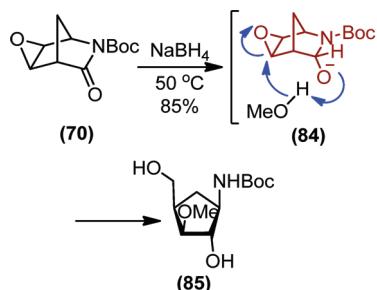
Scheme 20. Reductive Opening of Epoxide with Aluminum Reducing Agents



introduction of further steric encumbrance in the path of the reducing agent by incorporating the structurally encumbering TBDMS group on 5'-hydroxyl group led to the exclusive formation of the product, formed by 3'-carbon attack of the reducing agent.

Further exhaustive analysis of the concerted reductive ring-opening of the epoxide containing Vince lactam revealed an intriguing stereochemical reversal (85, Scheme 21), on

Scheme 21. Mechanism for Concerted Reductive Lactam and Epoxide Opening

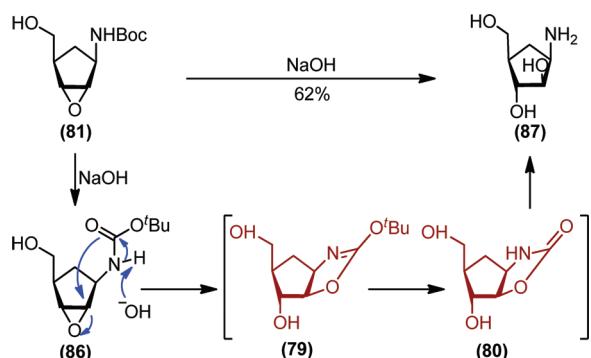


performing methanolysis of the Boc-protected Vince lactam (70, Scheme 21). The phenomenon necessitated elevated temperatures with NaBH_4 in methanol reagent. Interestingly, on heating the reaction mixture of 81 with NaOH as an oxygen nucleophile source, the product with a reversal of stereochemical orientation was obtained (87, Scheme 22). For methanolysis, activation of methoxide anion toward attack of 3'-carbon by an intermediate such as 84 was envisaged.

For base hydrolysis of the epoxide, participation of hydroxide anion as an oxygen nucleophile (86, Scheme 22) leading to intermediates congruent to those observed by Katagiri (79 and 80) were predicted as the most likely intermediary species (Scheme 22).

These studies paved the way for optimum utilization of Vince lactam as a precursor for the synthesis of carbocyclic nucleosides. The epoxide ring-opening furnishes a very

Scheme 22. Mechanism for Epoxide Ring-Opening with Nucleophilic Oxygen

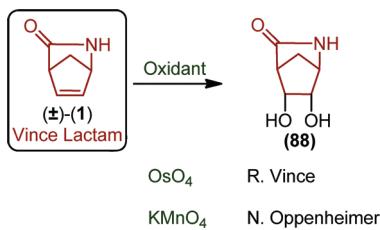


desirable regiochemical control over the outcome of the reaction and allows for various functionalities to be incorporated on 2'- and 3-carbons of the sugar moiety.

3.2.2. Hydroxylation of Vince Lactam. The double bond provides a convenient prospective site for functionality modulation on the molecule.²⁰¹ In our early work, we exploited it for the introduction of hydroxyl groups for the preparation of the sugar fragment.²⁰² The facial selectivity introduced at the stage of hydroxylation has considerable implications on the stereogenic properties of the later products. exo-cis-Hydroxylation leads to carbocyclic ribosides and its analogues while endo-cis-hydroxylation provides the carbocyclic lyxosides. Later studies included numerous other functional groups underscoring the inherent versatility of the lactam.

Our initial studies included the dihydroxylation of Vince lactam by the catalytic use of OsO₄²⁰² (88, Scheme 23).^{203,204}

Scheme 23. Dihydroxylation of Vince Lactam

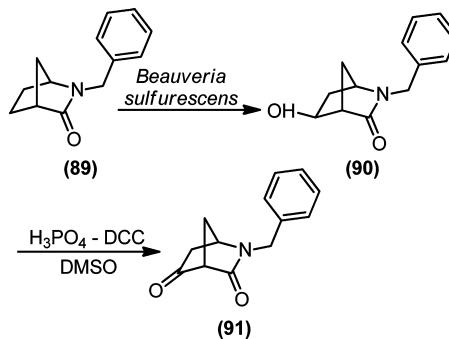


N-Methylmorpholine *N*-oxide was utilized for the regeneration of the catalyst.²⁰⁵ Kam and Oppenheimer also pursued the dihydroxylation²⁰⁶ route for the synthesis of carbocyclic ribofuranosylamine and lyxofuranosylamine compounds.²⁰³ The desired compound was obtained in a stereoselective manner by the use of KMnO₄ as the oxidizing agent, obviating the requirement of resolution of the stereoisomers.

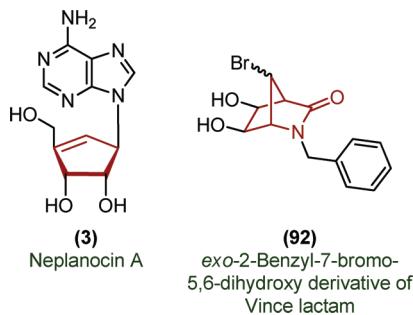
Alternative to chemical methods, Archelas and Morin developed a bioenzymatic hydroxylation protocol for *N*-benzyl protected saturated Vince lactam.²⁰⁷ The use of enzyme *Beauveria sulfurescens* led to the monohydroxylation of the saturated backbone of the lactam (90, Scheme 24), which was further derivatized to obtain the keto analogue (91, Scheme 24).

The Snider group identified Vince lactam as a potential starting point for the synthesis of neplanocin A²⁰⁸ (3, Scheme 25).²⁰⁹ The exo-dihydroxylated intermediate (92, Scheme 25) was synthesized as the key intermediate to perform the synthesis. The obstructive blockage of the exo face of the molecule by the sterically encumbering bromide on the

Scheme 24. Enzymatic Hydroxylation of C(5) of Vince Lactam



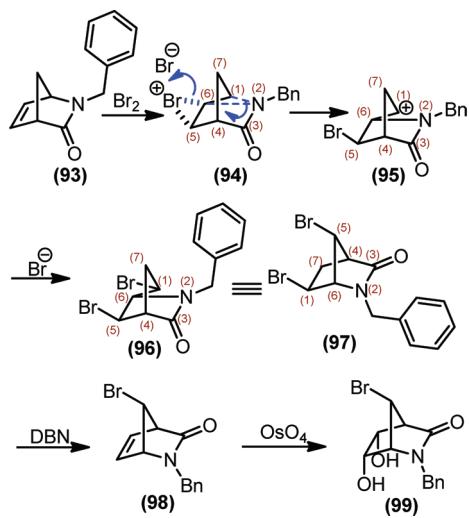
Scheme 25. Neplanocin A and the Vince Lactam Derived Key Intermediate for the Synthesis of Neplanocin A



bridging carbon of the lactam, was deemed detrimental to attaining the required stereochemistry in the product. However, the presence of several examples corroborating the propensity of Vince lactam for the formation of exo-cis-dihydroxylation product in the literature, prompted the authors to attempt the preparation of neplanocin A via this route.

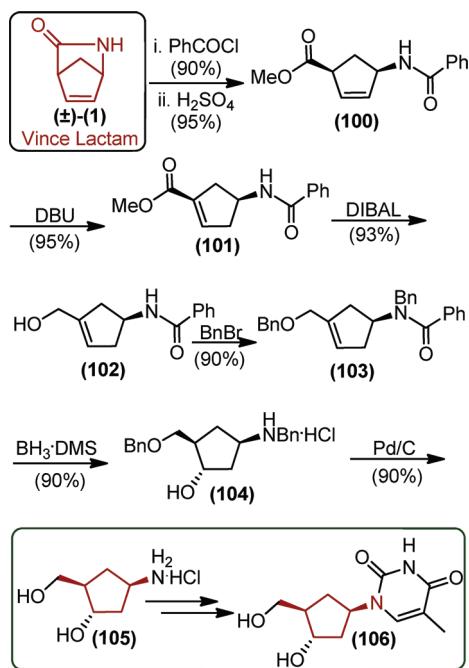
On performing the reactions it was observed that all attempts to induce dehydrohalogenation of 6,7-dibromo-2-azabicyclo[2.2.1]heptan-3-one, failed to provide the desirable product. To eradicate the participation of the charged amide functionality, and to formulate a better solubility profile of the synthetic protocol, the lactam was benzylated and brominated again. It was envisaged that the presence of benzyl group would also encourage the formation of exo-product. The reaction proceeds via a carbonium ion rearrangement leading to a 1,2 bond cleavage and migration of a nitrogen as detailed in scheme 26.²¹⁰ The dehydrohalogenation of the benzyl protected dibromo analogue (97, Scheme 26) proceeded very efficiently to furnish the desirable intermediate (98). The unsaturated intermediate (98) displays favorable reactivity toward *cis*-dihydroxylation with catalytic OsO₄. The reaction proceeded to furnish a single diol product. Although complete NMR analysis was performed, crystal structure analysis was performed for more comprehensive structural information. X-ray diffraction data unambiguously confirmed the initial reservations of the authors. An exclusive formation of the endo-product (99, Scheme 26) was confirmed. The synthetic plan was abandoned at this point. Synthesis of neplanocin A via different synthetic routes was developed and reported by various groups during the Snider group's attempts to achieve the laboratorial preparation of this molecule.^{208,211} Nevertheless, the authors were able to present their findings as an expansion of approaches for the synthesis of 7-substituted-2-azabicyclo lactams and their derivatives.²⁰⁹

Scheme 26. Bromination Followed by Dihydroxylation of Vince Lactam: endo-Hydroxylation



Bray, Dolan, and co-workers devised a novel synthetic strategy for the preparation of 4-amino-2-(hydroxymethyl)-cyclopentanol (**105**, Scheme 27) as prospective synthetic

Scheme 27. Bray and Dolan's Monohydroxylation Protocol and the Structure of a Related Carbocyclic Thymidine (**106**)

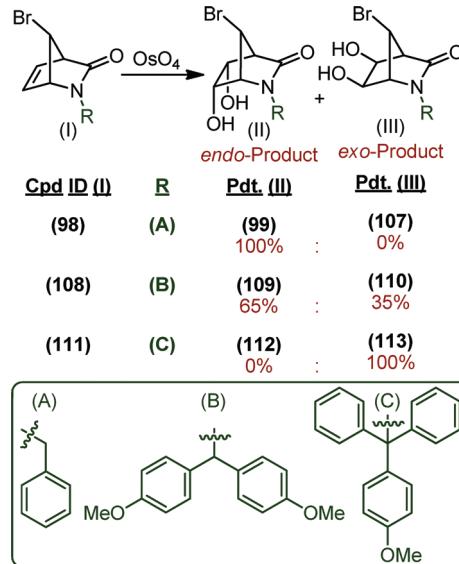


precursor for 2'-deoxycarbocyclic sugar bearing nucleoside analogues.²¹² Monohydroxylation of the *N*-benzoyl substrate was structured via double bond migration and subsequent selective hydroboration to obtain the desired monohydroxylated product. Otvos and co-workers reported the preparation of a related carbocyclic thymidine (**106**, Scheme 27).²¹³

As underscored throughout this section, the facial selectivity adopted by the molecule during hydroxylation results in the formation of stereospecific product. Slama et al. studied the effects of steric bulk at the nitrogen of the Vince lactam in the hydroxylation reaction. The goals of the study included

preparation of carbocyclic β -ribofuranosylamines.²¹⁴ Since presence of bulky groups on the nitrogen exerts a profound effect in formation of exo-hydroxylation products, the authors considered studying the stereochemical effect of the approach of hydroxylating agent from the least hindered side of *N*-protected Vince lactam. OsO_4 catalyzed cis-hydroxylation validated the hypothesis. *N*-Benzyl-protected lactam analogue (**98**, Scheme 28) demonstrated the formation of endo product

Scheme 28. endo-Dihydroxylation of Vince Lactam Revisited

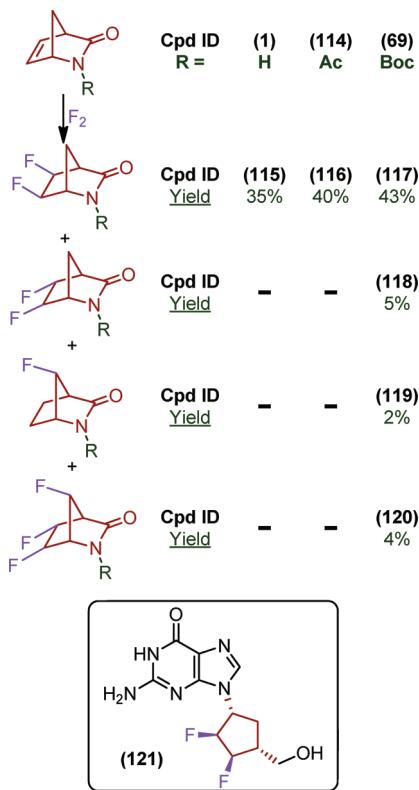


exclusively. On increasing the bulk on nitrogen by protecting it with dianisylmethyl group (**108**, Scheme 28), the molecule lost the exclusivity of approaching the double bond from endo side of the lactam. A mixture of exo and endo products was obtained. Further increase of bulkiness on nitrogen of the lactam by the introduction of a diphenylanisyl group (**111**, Scheme 28) hindered the approach of the catalyst from endo side of the substrate. The obstruction of catalyst from the exo side by the bromide on the bridging carbon becomes inconsequential in comparison, resulting in exclusive formation of the exo product (**113**).

3.2.3. Fluorination of Vince Lactam. Apart from the above-discussed more common transformations carried out on the double bond of the lactam, various groups have studied the analogues of Vince lactam with numerous other functional group substitutions.

In their efforts to prepare fluorine containing carbocyclic sugars, Toyota and co-workers wanted to carry out direct fluorination of 3-hydroxymethyl cyclopentenes.²¹⁵ However, the presence of different functionalities such as hydroxyl, olefin, allyl, tertiary protons, etc., on the cyclopentene molecule proved to be detrimental in clean formation of the fluoro products. The authors decided to utilize Vince lactam and the *N*-protected (acyl and Boc) analogues of Vince lactam, for their studies (Scheme 29). A stream of 5% fluorine in nitrogen was passed through the reaction mixture comprising of the substrate dissolved in a ternary solvent mixture of $\text{CFCl}_3/\text{CHCl}_3/\text{EtOH}$ in the ratio of 5:4:1.²¹⁶ Vince lactam and acyl protected analogue furnished the desirable exo-difluoro product exclusively. Boc-protecting group on the lactam, however, led to an unclean reaction with the formation of several side products (Scheme 29). Difluoro compound (**117**) was utilized to

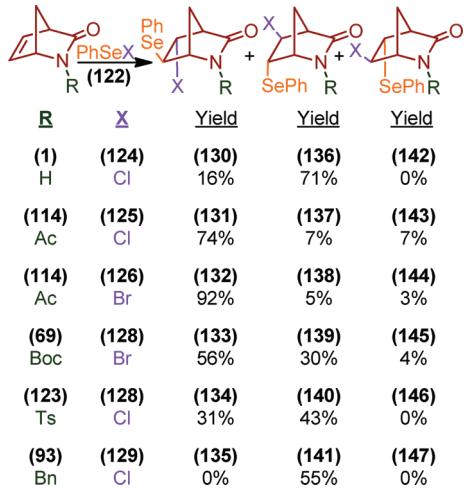
Scheme 29. Fluorinated Double Bond of Vince Lactam and a Nucleoside with Difluoro Carbocyclic Sugar



prepare a guanosine analogue with fluorine carbocyclic sugar moiety: 2-amino-9-((1*R*,2*S*,3*R*,4*R*)-2,3-difluoro-4-(hydroxymethyl)cyclopentyl)-1*H*-purin-6(9*H*)-one (**121**, Scheme 29). The methodology was further developed by preparing more examples of difluoro nucleoside compounds.²¹⁷

3.2.4. Phenylselenylation of Vince Lactam. Following the initial work done by Palmer and co-workers,²¹⁸ Toyota et al. explored the phenylselenylation of Vince lactam.²¹⁹ Various analogues were synthesized and their chemical properties studied. The study revealed formation of a mixture of compounds, as detailed in Chart 2.

Chart 2. Phenylselenylation of Vince lactam



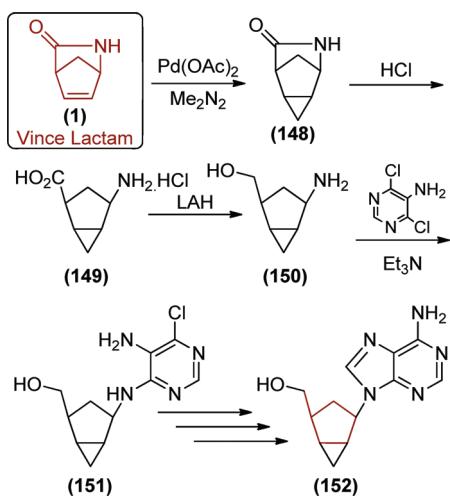
Interestingly, on increasing the electron density on the nitrogen of the lactam, an increase in endo selectivity in product formation was observed. Although the effect of sterics on the endo versus exo facial approach were universally accepted as the major reason for the observed stereoselectivity, exceptions to the rule did not go unnoticed. While studying phenylselenylation of norbornene and norbornadiene, Garrett and Kabo reported obtaining exo product with norbornene but endo product with norbornadiene as substrate.²²⁰ A similar discrepancy was observed on the comparison of reactivity between (**114**) and (**93**) in chart 2. Frontier Molecular Orbital (FMO) theory provided reasoning for apparent abnormal stereoselectivity observed with these compounds. The two degenerate orbitals of norbornadiene interact with each other leading to one becoming HOMO. Empty d-orbitals of selenium are inclined to interact favorably with HOMO of norbornadiene. Vince lactam (**1**) and its *N*-protected analogues (**69**, **93**, **114**, **123**) differ with each other in degree of possession of double bond character on the amide C–N bond. For Vince lactam (**1**) and its benzyl protected analogue (**93**), the spatial interaction between the olefin unsaturated function on the lactam and the C–N amide bond, allows the C–N bond to assume necessary double bond character. Hence, both Vince lactam (**1**), and its benzyl protected analogue (**93**), result in the formation of the endo product as in the case of norbornadiene. Presence of an electron withdrawing group on the lactam nitrogen lowers the corresponding energy level, restricting the possibility of a favorable overlap with empty d-orbitals of selenium from the endo face of the lactam and thus, leads to formation of the exo product as the predominant stereoisomer.²¹⁹

3.2.5. Cycloproylation on the Double Bond of Vince Lactam

Encouraged by the incorporation of cyclopropyl ring on the guanine sugar of the carbocyclic nucleoside reverse transcriptase inhibitor, abacavir,²²¹ as well as other non-carbocyclic nucleosides of therapeutic value,²²² Yamatoya et al. attempted the preparation of the carbocyclic analogue with a cyclopropyl functionality in place of the double bond.²²³ Their initial attempts to introduce cyclopropyl ring on Vince lactam via Simmons–Smith reaction proved futile.²²⁴ On exposure of the lactam and its protected forms to excess diazomethane, formation of side products was observed. Finally, the use of $PdCl_2(\text{PhCN})_2$ in dry reaction conditions proceeded to introduce cyclopropyl ring on the double bond of Boc-protected lactam. Meanwhile, perceptive to the fact that the structural advantage with the presence of carbon in a carbocyclic ring in place of the oxygen in furanose ring includes rigidity, we envisaged superior therapeutic activity and medicinal value of the nucleoside analogues, which undergo incorporation of cyclopropyl ring on the carbocyclic sugar ring. To that end, we focused our attention on the elegant work on palladium mediated chemistry by Denmark.²²⁵ Indeed, using Denmark's conditions with $Pd(OAc)_2$ as catalyst,²²⁶ we were able to achieve direct introduction of cyclopropyl ring on unprotected Vince lactam (**148**, Scheme 30).²²⁷ Further derivatization of the lactam analogue furnished the desired carbocyclic nucleoside (**152**, Scheme 30).²²⁸

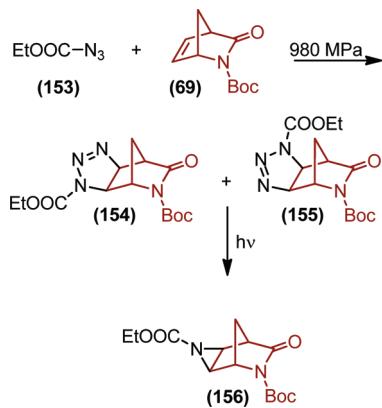
3.2.6. Aziridine Ring Formation on the Double Bond of Vince Lactam. Ishikura et al. exploited the accentuated reactivity of arylsulfonyl azides with electron rich olefins, or alkyl/aryl azides with electron poor olefins, to explore the aziridation of the double bond.²²⁹ The cycloaddition reaction necessitated high pressures. Cycloaddition of various electron-

Scheme 30. Synthesis of Conformationally Restricted 2',3'-*exo*-Methylene Carbocyclic Nucleosides from Vince Lactam



poor azides to the Boc-protected Vince lactam was performed leading to regioisomeric triazoline products.²³⁰ A representative example is presented in Scheme 31.

Scheme 31. Formation of Aziridine Ring on Vince Lactam



The sluggish reaction conditions (980 MPa, 70 h) were later modified by Ishikura to render the protocol more user-friendly by activating the reactants via the use of microwave radiation.²³¹ Similar reactions could be carried out within 30 min at temperatures ranging from 100 to 140 °C.

3.3. N-Modulation of the Amide Nitrogen on Vince Lactam

As noted above, the presence of a substituent on the –NH functionality of Vince lactam has significant effect on its reactivity profile. The ring-opening of a lactam is affected significantly by the chemical properties of the functionality on the nitrogen. section 3.1 consists of a detailed description of this phenomenon, within the context of its application to Vince lactam. Also presented are the examples demonstrating the exploitation of this phenomenon by various researchers, to achieve the synthesis of desired molecular structures. Apart from the protecting group chemistry with the usual amino-protecting groups, several additional instances of exciting developments related to the reactivity of the –NH functionality on Vince lactam have been reported. To avoid confusion in classification, and to acknowledge the main rationale behind the exploration of these transformations, these developments are

presented in the context of their specific applications. More detailed discussions pertaining to the modulation of the amide nitrogen of Vince lactam can be found in succeeding sections.

Section 4.2.2 details the utilization of Vince lactam without opening the bicyclic ring system. The advantageous properties imparted via modulation of the nitrogen on the lactam to the chemical synthesis of desirable biologically relevant molecules for the preparation of non-nucleoside therapeutics is presented. The applications of Vince lactam as a model substrate in the development of various transition metal mediated N-arylation methodologies has been underscored in section 4.3.1. Also presented is the reactivity of Vince lactam in palladium mediated tandem cyclization process. This non-therapeutic but fascinating reaction has been classified under miscellaneous transformations of Vince lactam in the presence of transition metals in section 4.3.3. The reactivity of Vince lactam in metathesis reactions has also been explored. Sections 4.4.2 and 4.4.3 present the details of metathesis reactions of N-protected Vince lactam.

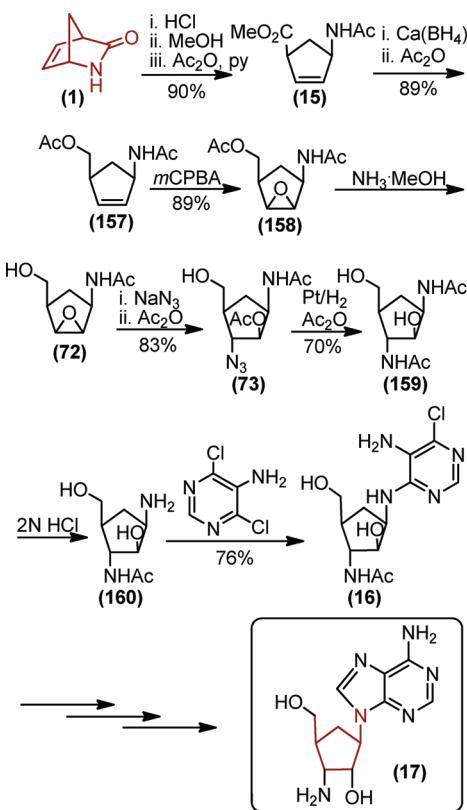
4. APPLICATIONS OF VINCE LACTAM

The vast literature available on various diverse applications and uses of Vince lactam is a testament to the significance of this lactam. These applications of Vince lactam include examples of it being used in diverse areas, including both therapeutic, as well as non-therapeutic fields.

4.1. Therapeutic Implications of the Use of Vince Lactam as a Synthetic Building Block for Various Carbocyclic Nucleoside Analogues

Vince lactam has been utilized most prominently by the pharmaceutical and drug sector. As mentioned earlier, Vince lactam has been utilized for preparing commercially available drugs²³² and has also found use in the preparation of numerous other potential therapeutic agents and candidates for medicinal use. Scheme 32 represents the initial protocol we used to synthesize nucleoside compounds with carbocyclic sugar moiety.⁵⁸ Briefly, acidic hydrolysis of Vince lactam with 2N HCl was followed by esterification of the carboxyl functionality in methanol via elevation of the reaction temperature to 65 °C. The amino group was then acylated by acetic anhydride–pyridine mixture to furnish the protected ring–opened lactam (15) in 90% yield. Next, the ester functionality was reduced by CaBH₄ and the olefinic back–bone was subjected to epoxidation by using *m*CPBA as the oxidizing agent. The presence of syn-directing allylic amide moiety favored the formation of cis-epoxide (158) in 89% yield. This represents a noteworthy example of the stereocontrol conferred by the use of Vince lactam, on the synthesis of desirable compounds. Ammonia facilitated removal of the acetate group and furnished the unprotected compound (72). Vulnerability of (72) to undergo nucleophilic attack from an azide was exploited to induce the opening of the epoxide ring and furnish compound (73) in 83% yield after acetylation. Platinum-catalyzed hydrogenation of (73) was performed in acetic anhydride to obtain the diacetamide (159). Treating the diacetamide with 2N HCl furnished the desired monoacetamide (160) representing the carbocyclic sugar ring structure with the desirable functionalities present at the appropriate carbons on the five membered ring. Further derivatization was performed by constructing the purine ring around the free amine on the carbocyclic sugar fragment of (16). The nucleoside precursor

Scheme 32. Representative Synthetic Route for the Preparation of Carbocyclic Aminonucleosides from Vince Lactam



was then subjected to various chemical transformations leading to the final carbocyclic nucleoside analogues.

Table 5 presents some examples of well-known nucleoside derivatives prepared from Vince lactam. Several representative examples of precursors of nucleosides reported by various research groups with Vince lactam as the starting material are also included. Synthetic routes and experimental details are not presented here. Reference for each compound is provided for further enquiry about the preparative techniques, chemical and physical properties of the individual compounds (Table 5).

In the preceding sections we mentioned puromycin and carbocyclic puromycin analogues (**161** and **162**, Table 5) and carbovir (**4**). Our early research efforts were directed equally toward the development of the antiviral nucleoside 9- β -D-arabinofuranosyladenosine (*araA*) and its analogues. Although initially synthesized as anti-cancer compounds by Baker et al.,^{233,234} strong antiviral activity of *araA* was considered intriguing.²³⁵ However, *araA* is inherently susceptible to the action of the enzyme, adenosine deaminase,²³⁶ and gives 9- β -D-arabinofuranosylhypoxanthine (*araH*) as an inactive metabolite.²³⁷ To address this challenge, we set out to synthesize carbocyclic analogue of *araA* (C-*araA*). The preparation and subsequent biological evaluation of C-*araA* (**163**), revealed superior biological activity. C-A demonstrated significant characteristics such as stability against both the action of adenosine deaminase, as well as glycosidic hydrolysis while maintaining significant antiviral activity.²³⁸

Apart from the carbocyclic nucleosides mentioned in Table 5 below, several groups have also reported preparation of functionalized cyclopentane derivatives. Prominent among them is the contribution of Fulop and co-workers.²³⁹ These

moieties have been identified as necessary synthetic fragments for corresponding distinct classes of nucleosides.

4.2. Applications of Vince Lactam in the Synthesis of Non-nucleoside Therapeutic Agents

Vince lactam has also found extensive implications in several non-therapeutic areas. It has been utilized in numerous fields for preparing a variety of different compounds. Selected examples of both therapeutic and non-therapeutic applications are presented in subsequent sections.

4.2.1. Use of Vince Lactam as a Cyclopentane Template for the Preparation of Non-nucleoside Compounds. The most prominent example of a non-nucleoside molecule prepared by the lactam was introduced earlier in section 1. Peramivir continues to make headway toward becoming a major option for the treatment of influenza by effectively inhibiting the neuraminidase enzymes. Other prominent examples include the compounds as presented in the following table (Table 6):

4.2.2. Unconventional Use of Vince Lactam as a Building Block for the Synthesis of Non-nucleoside Therapeutics.

4.2.2.1. Unusual Ring-Opening of Vince Lactam. Apart from the “usual” C–N bond ring-opening of the lactam to gain access to cyclopentane derivatives, some examples of intact use of the lactam have been reported. Such ‘unusual’ examples also include the reactions in which at least one ring of the bicyclic system is opened via cleavage of a bond other than the C–N bond. These include conformationally restricted 1,4-diazepane derivatives. The bridging C(7) of the lactam corresponds to the bridging atom in the final compounds lending the molecules a much desired steric constriction. The diazepane ring is constructed via ozonolysis of the olefinic moiety of Vince lactam and then subjecting the resultant di-aldehyde to reductive alkylation with benzylamine.²⁶¹ Merck Co. developed these compounds for targeting orexin receptors for the treatment of insomnia and related sleep disorders.²⁶² Other examples of similar *tangential* utilization of the features of Vince lactam include the synthesis of 2,4-pyrrolidine carboxylic acid compounds (**196** and **197**, Scheme 33) via opening of olefinic bond and retaining nitrogen as the heteroatomic constituent of pyrrolidine ring as described by Arakawa et al.²⁶³ The compounds were prepared as glutamic acid receptor modulators.

4.2.2.2. Use of the Intact Vince Lactam for the Preparation of Non-nucleoside Therapeutics. In a different approach, Cortex pharmaceuticals ventured a step beyond opening the ring of the lactam and prepared benzoxadiazolyl azabicyclic methanone derivatives as modulators of glutameric synaptic response (**198**, Scheme 34). Vince lactam is also known for its use as a bicyclic template congener for the development of *Muscador albus*²⁶⁴ as an environmentally benign biological insecticide to replace the customarily utilized chemical fumigants (**199**).²⁶⁵

AstraZeneca utilized the intact bicyclic structure to impart desirable characteristics to their clinical candidates (**200**, Scheme 34).²⁶⁶ The compounds were prepared as muscarinic antagonists targeting COPD. The compounds retain certain key structural elements from the muscarinic M₁/M₃ receptor antagonists (known drug Spiriva, **202** developed by Boehringer-Ingelheim, Scheme 35). Apart from the structural congruity (**201**) in terms of the presence of the aromatic ring, the heterocyclic ring and the hexacyclic cationic

Table 5. Various Carbocyclic Nucleosides Prepared from Vince Lactam^a

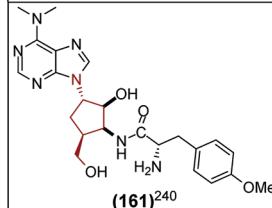
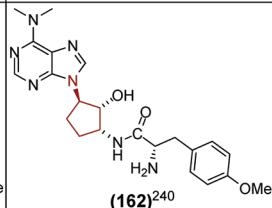
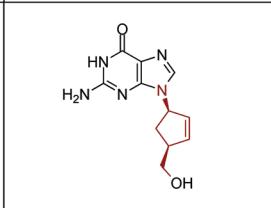
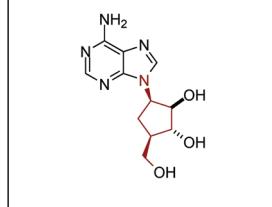
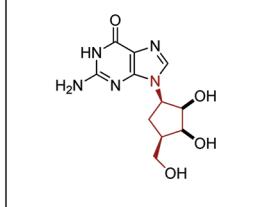
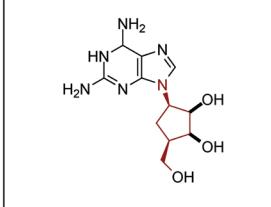
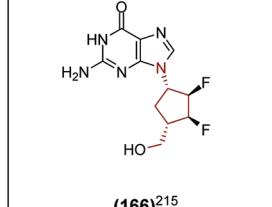
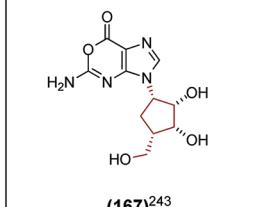
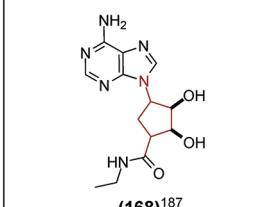
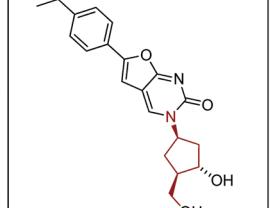
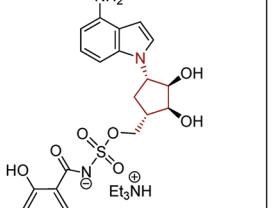
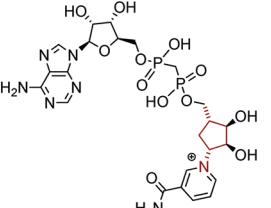
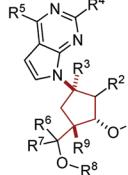
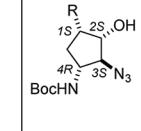
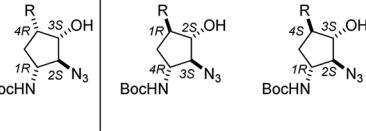
Structure	Structure	Structure
 (161) ²⁴⁰ Carbocyclic Puromycin Analogue: Antibiotic	 (162) ²⁴⁰ Carbocyclic Puromycin Analogue: Antibiotic	 (4) ²⁴¹ Carbovir: Antiviral
 (163) ^{58(b)} Carbocyclic araA: Antiviral	 (164) ¹³³ Guanine Derivative: HSV and HCMV ²⁴²	 (165) ¹³³ Diamino-derivative: HSV
 (166) ²¹⁵ 2',3'-Difluoro Guanosine derivative	 (167) ²⁴³ Carbocyclic Oxanosine: HIV	 (168) ¹⁸⁷ C-NECA: ²⁴⁴ Antiangular Agent
 (169) ²⁴⁵ C-BCNA ²⁴⁶ Furano Pyrimidine: Varicella-Zoster Virus	 (170) ^{247,248} Carbocyclic Indole Analogue: <i>Mycobacterium tuberculosis</i>	 (171) ²⁴⁹ Carbocyclic NAD+: ADP Ribosyl Cyclase Inhibitor

Table 5. continued

Structure	Structure	Structure
 <p>(172)²⁵⁰ E1 Activating Enzyme Inhib. Cell Proliferation Disorders (Millennium Pharma. Inc.)</p>	 <p>(173)^{184(a)} R = CO₂Et (174)^{184(a)} R = CH₂OH Precursors for Carbocyclic Azido-Nucleosides: Antiviral (Fulop et al.)</p>	 <p>(175)^{184(a)} R = CO₂Et (176)^{184(a)} R = CH₂OH Precursors for Carbocyclic Azido-Nucleosides: Antiviral (Fulop et al.)</p>

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tetralkylamine moiety, the presence of the bicyclic moiety (though spatially scrambled), is also noticeably present in the new compound (200).

Interestingly, the examples presented in scheme 34 (198, 199, and 200) also represent the instances of employing the dynamic reactivity profile of Vince via the modulation of the nitrogen of –NH functionality. These privileged and valuable molecular structures undergo the N-modulation to furnish the desirable biological properties.

4.3. Use of Vince Lactam as a Model Substrate for Methodology Development in the Presence of Transition Metals

The inclusion of metals in matters related to human health has long been considered undesirable. Overexposure to metals can generally cause noxious effects on biological systems. However, rapid and efficient advancements being made in metal mediated coupling reactions,²⁶⁷ such as Suzuki–Miyaura,^{268,269} Heck reaction,²⁷⁰ Sonogashira reaction,²⁷¹ α -arylation of ketones,²⁷² hydrosilylation of ketones,²⁷³ Buchwald–Hartwig amination,²⁷⁴ etc., have rendered it essential to encompass a broader point of view toward the possible contributions of metals to the betterment of human health. The discovery of antitumor properties of platinum provided an undeniable impetus to this perspective. Since Rosenberg's initial breakthrough,²⁷⁵ several efforts have been directed toward understanding such systems and to make *cis*-diaminedichloroplatinum(II) (cisplatin) analogues amenable to utilization as medicinal agents independent of toxic consequences.²⁷⁶ The versatility of Vince lactam is very well represented by the numerous transition metal catalyzed methodology development reactions which have used it as a model substrate of ample significance.

4.3.1. N-Modulation of Vince Lactam in the Presence of Transition Metals. The significance of substitution and modulation of the –NH functionality of Vince lactam has been underscored in sections 3.1 and 3.3. Apart from the conventional protecting group chemistry, effect of various different functionalities on the nitrogen of Vince lactam has also been studied. A relevant example includes the N-arylation of Vince lactam by the use of triaryl-bismuth reagents in a copper mediated system²⁷⁷ by Chan.²⁷⁸ Chan's work with bismuth

reagents was later applied to performing N-cyclopropylation of various cyclic amides and azoles with cyclopropyl bismuth reagent.^{279,280} Gagnon et al. utilized copper acetate for installing the cyclopropyl group on the nitrogen of Vince lactam (Scheme 36).²⁸¹ Meanwhile, Chan et al. had reported expansion of their work in replacing bismuth reagents with various arylboronic acids as reagents for performing N-arylation of Vince lactam.²⁸² The methodology employed stoichiometric equivalents of copper acetate and various tertiary amines as bases to promote formation of the desired products.

In 2008, Abe and co-workers further extended Chan's work with copper mediated N-arylation and made Vince lactam the model substrate of choice for exploring this transformation.²⁸³ The reactions were promoted by the presence of KOH and trimethylamine-N-oxide, and microwave radiation. The protocol achieved success in N-arylation of Vince lactam with catalytic amounts of copper acetate.

4.3.2. Transition Metal Mediated C-Arylation of Vince Lactam. Parallel to the copper mediated N-arylation with arylboronic acids, Abe and co-workers also explored rhodium catalyzed arylation of olefins with arylboronic acids.²⁸⁴ The protocol was developed as a substitute for Heck reaction.^{285,286} Interestingly, under similar reaction conditions underlined by microwave irradiation of the reaction mixture, the metal catalysts promoted formation of the arylated products in a chemoselective manner. While exclusive formation of N-arylated Vince lactam with copper catalyst was observed, the rhodium catalyst furnished only the products formed by the C-arylation on olefinic carbons of Vince lactam and its various N-protected congeners in excellent yields. Rh(COD)Cl-dimer was employed as the catalyst. Substrate scope was explored with various protecting groups as depicted in chart 3. The N-acyl-protected groups generally led to ring-opening via solvolysis of the amide bond.

Furthermore, reactivity of Vince lactam with arylboronic acid as the variable was also explored (Chart 4). Along with the anisyl, bromo, and naphthyl substrates, the reaction also proceeded favorably with various heterocyclic substrates, including pyridyl and thiophenyl rings. While introduction of difficult heterocyclic substrates led to moderate overall yields,

Table 6. Various Non-nucleoside Compounds Prepared from Vince Lactam^a

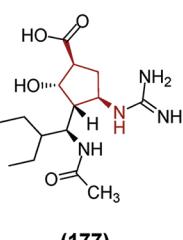
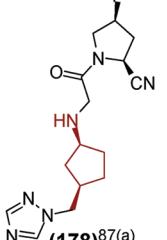
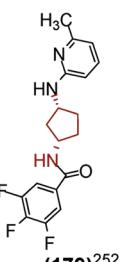
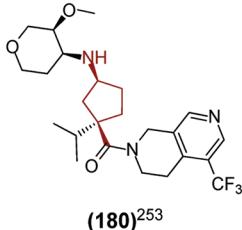
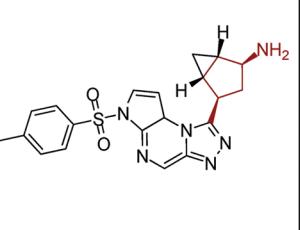
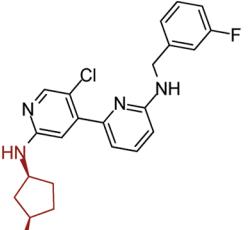
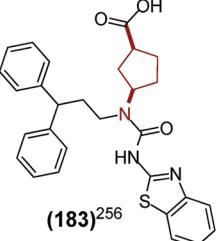
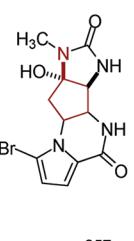
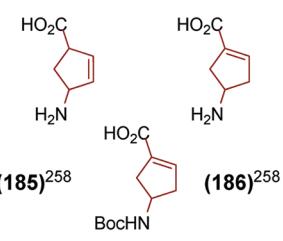
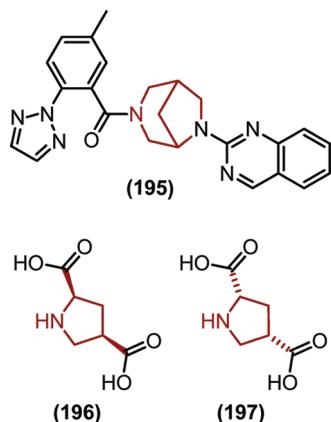
Structure	Structure	Structure
 (177) Peramivir - Neuraminidase Inhibitor: Influenza (BioCryst Pharmaceuticals)	 (178)^{87(a)} Meloglitin - DPP-IV Inhibitor: Diabetes (Glenmark Pharmaceuticals)	 (179)²⁵² MCH Receptor Antagonists: Obesity (Taisho Pharmaceuticals)
 (180)²⁵³ Chemokine Receptor Modulators: Inflammation, Rheumatoid Arthritis, etc. (Merck Sharp & Dohme Ltd.)	 (181)²⁵⁴ Antitumor and Immuno-modulatory Therapeutics (Abbott Laboratories)	 (182)^{255(a)} Protein Kinase Modulators; CDK9 Inhibitors: Antitumor (Novartis AG)
 (183)²⁵⁶ Calcium Sensing Receptor Modulator: Hypercalcemia/Hypocalcemia (Amgen Inc.)	 (184)²⁵⁷ (-)-Agelastatin A: Antitumor (J. Du Bois et al.)	 (185)²⁵⁸ (186)²⁵⁸ (187)²⁵⁸ Vigabatrin Analogue - GABA-AT Inhibitors: Epilepsy (R. B. Silverman et al.)

Table 6. continued

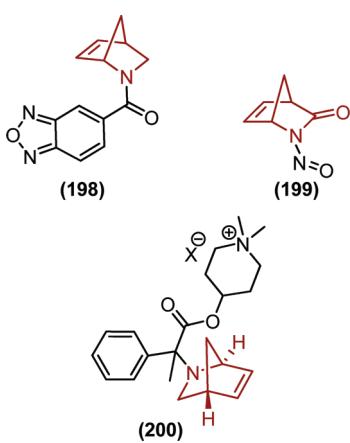
Structure	Structure	Structure
<p>(188)²⁵⁹ (189)²⁵⁹</p> <p>GABA-AT Inhibitors: Epilepsy (R. D. Allan et al.)</p>	<p>(190)²⁵⁹ (191)²⁵⁹</p> <p>GABA-AT Inhibitors: Epilepsy (R. D. Allan et al.)</p>	<p>(192)²⁶⁰ (193)²⁶⁰</p> <p>(194)²⁶⁰</p> <p>Scaffolds for Glycosidase Inhibitors: Diabetes, Influenza (M. Rommel et al.)</p>

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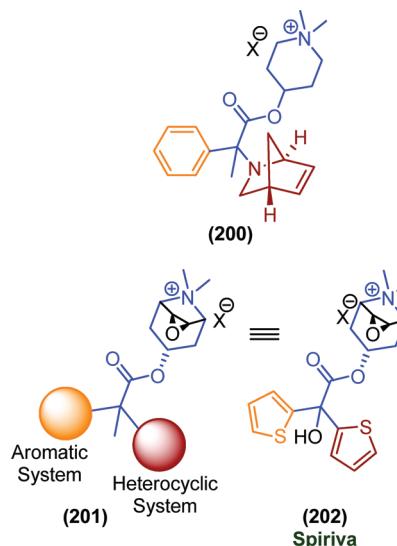
Scheme 33. Various Non-nucleoside Compounds Prepared via “Unusual” Opening of Vince Lactam



Scheme 34. Various Non-nucleoside Compounds Prepared from “Intact” Vince Lactam



Scheme 35. Structural Comparison of AstraZeneca’s Muscarinic Antagonist and Boehringer-Ingelheim’s Spiriva



the selectivity increased many folds, leading to exclusivity in the formation of product (Chart 4).²⁸⁴

The authors further expanded this work and reported a direct comparison between copper and rhodium systems for the arylation of Vince lactam.²⁸⁷ The stepwise mechanistic details of the two transformations are depicted in scheme 37. The reactions were noted to proceed efficiently with 10 mol % copper, and 3 mol % rhodium catalyst, respectively, for N-arylation and C-arylation of Vince lactam.²⁸⁷

Pietrowski et al. studied the hydroarylation of unsaturated heterocyclic compounds as a means of preparing insecticides.^{288,289} Increasing interest of the research community toward Vince lactam prompted the authors to explore the transformation with the lactam as focal point of their latest

Scheme 36. Copper-Catalyzed N-Modulation of Vince Lactam

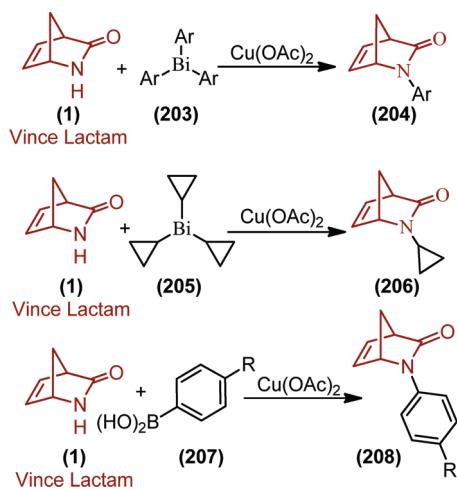


Chart 3. Rhodium-Catalyzed Arylation of Vince Lactam and Its Various N-Protected Analogues with Arylboronic Acids

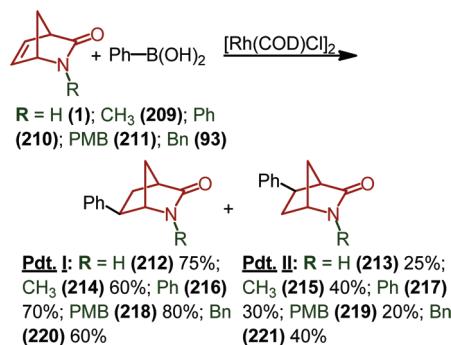
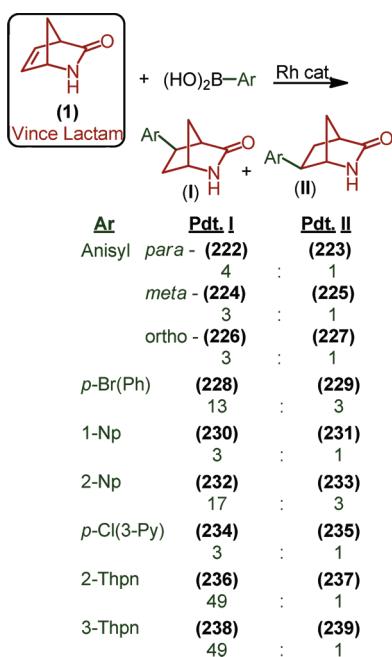


Chart 4. Substrate Scope in Rhodium Catalyzed Arylation of Vince Lactam with Various Functionally Divergent Arylboronic Acids



efforts. In a recent report Pietrowski and Polivkova have revealed achieving C–arylation of Vince lactam in palladium mediated reaction system.²⁹⁰ Effective couplings were achieved with 5 mol % palladium catalyst loadings. Substrate scope of the reaction was explored with electron-rich as well as electron-deficient aryl iodides. Performed at 65 °C, the reactions furnished the coupling product in excellent yields. A hetero-aryl substrate (entry 7, Table 7) provided the product in moderate yield of 59%.

4.3.3. Miscellaneous Transformations: Reactivity of Vince Lactam in the Presence of Metals. Grigg has done extensive work with palladium as catalyst for tandem cyclization–anion capture reactions.²⁹¹ Grigg, Fretwell and co-workers also reported palladium mediated tandem cyclization of Vince lactam, leading to the formation of molecular scaffolds of interest to synthetic chemists (Scheme 38).²⁹² Sodium hydride promoted the formation of chiral N-benzylated product (262, Scheme 38) on reacting Vince lactam with 1-(chloromethyl)-2-iodobenzene (261) in THF at 65 °C. (1S,4R)-2-(2-iodobenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (262), was then utilized as the substrate to perform 6-exo-trig cyclization, with iodo group leaving during the cyclization step. The reaction is promoted by 10 mol % palladium acetate along with 20 mol % triphenylphosphine. Various functional groups could be installed on the endo face of Vince lactam via the use of different tributyltin compounds. The resulting products were prepared in moderate to excellent yields (30–88%).

Following Brunner and Loskot's initial work,²⁹³ Becker and Bergman studied the preparation and reactivity of cobalt dinitroso-alkane complexes²⁹⁴ with various substrates containing olefinic functionality. Toste, Bergman, and co-workers further extended the work and chose Vince lactam among a few selected substrates with olefinic functionality to be utilized for the preparation of cobalt–dinitroso complexes.²⁹⁵ The cobalt–dinitroso complex with Vince lactam (269, Scheme 39) was prepared in 44% yield. Similar complexes prepared from various bicyclic olefins were utilized for studying the C–H functionalization of alkenes. The authors detailed a plausible mechanistic pathway for the observed reactivity of the prepared complexes. As depicted in Scheme 39, the increased acidity of the protons α to the nitroso group, renders them facile toward the abstraction of a proton by a base. Following a path through the resonance structures (270) and (271), a Michael acceptor can then be attacked by the nucleophilic complex furnishing the functionalized intermediate (273). In the final step, the excess of olefinic reagent (Vince lactam, Scheme 39) leads to retrocycloaddition²⁹⁶ providing the functionalized olefinic product (274) and regenerating the regenerating the dinitroso-cobalt complex (269) back in the catalytic cycle.

4.4. Use of Vince Lactam as a Versatile Substrate in Metathesis Reactions

Metathesis chemistry has been recognized for its value as a potent synthetic tool.²⁹⁷ The field received additional endorsement in 2005 when the Nobel Committee conferred the Nobel Prize for chemistry (2005) to three scientists considered pioneers of this field. Robert H. Grubbs (Scheme 40),^{299,300} Richard R. Schrock (Scheme 41),^{301,302} and Yves Chauvin (Scheme 42)^{303,304} were jointly honored for their groundbreaking contributions to metal catalyzed metathesis reactions.³⁰⁵

Olefin metathesis is a highly valuable tool in the hands of a synthetic chemist and has been a subject of numerous studies in

Scheme 37. Mechanistic Details of Copper-Mediated N-Arylation of Vince Lactam and Rhodium Mediated C-Arylation of Vince Lactam

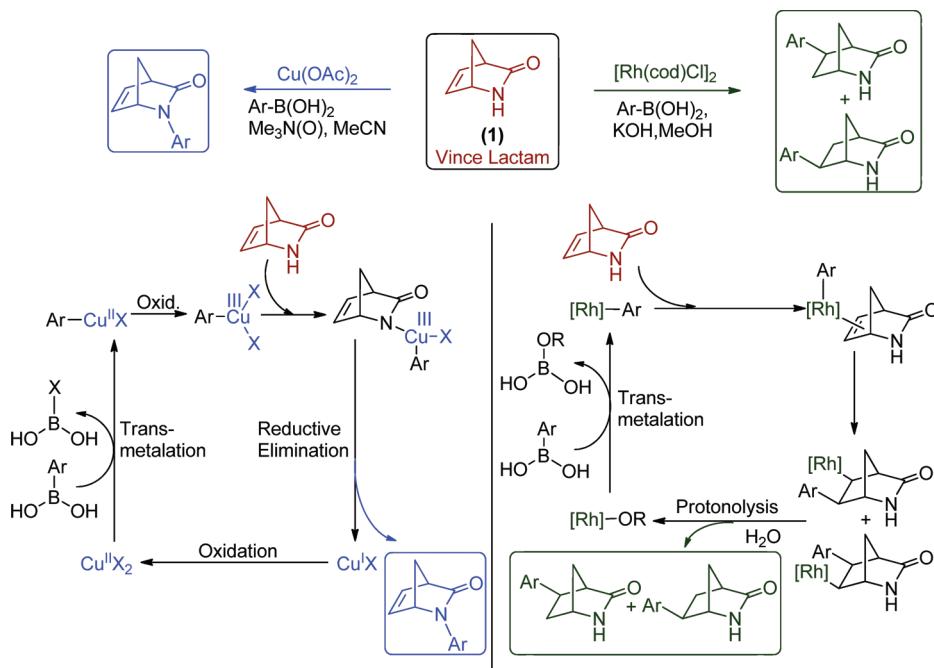


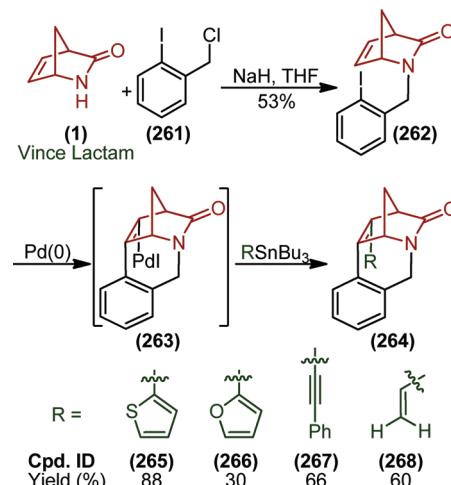
Table 7. Palladium-Catalyzed C-Arylation of Vince Lactam with Various Aryl Iodides^a

Entry	R	Pdt. I		Yield (%)
		(240)	(241)	
1	Ph	14	11	93
2	4-CH ₃	57	43	92
3	3-CF ₃	14	11	91
4	3-OCH ₃	53	47	98
5	4-OCH ₃	1	1	98
6	3,5-Cl	11	9	95
7	6-Cl-3-py	1	1	59

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very divergent fields of chemistry.³⁰⁶ Most common classes of metathesis reaction include ring-opening metathesis polymerization (ROMP),³⁰⁷ ring-closing metathesis (RCM),³⁰⁸ ring-opening metathesis (ROM),³⁰⁹ acyclic diene metathesis (ADMET),³¹⁰ and cross-metathesis (CM).³¹¹ Metathesis assumes additional significance when directed toward bicyclic systems as substrates because they offer opportunities for incorporating additional structural complexity in the desired product. Moreover, the bicyclic framework of the substrate

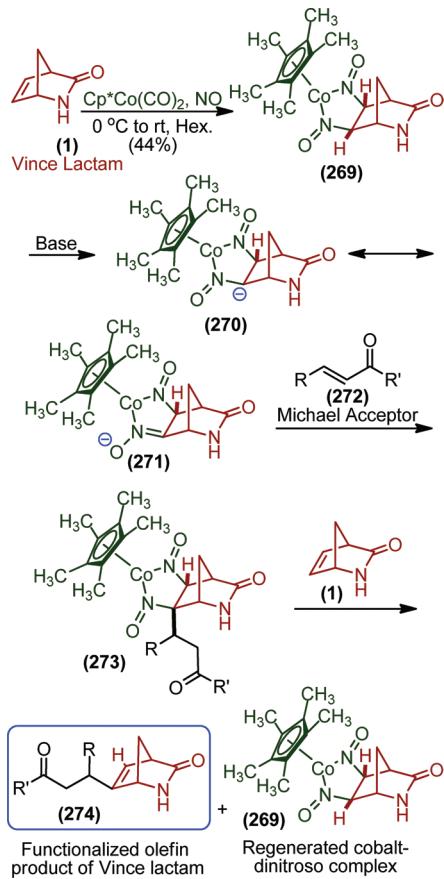
Scheme 38. Palladium-Catalyzed Tandem Cyclization of Vince Lactam



provides an added avenue to impart the required structural features to the product. Olefinic backbone of Vince lactam provides for an ideal substrate for metathesis. Vince lactam has been subjected to a lot of metathesis studies resulting in very appealing methodologies which are amenable to applications in industry.

4.4.1. Ring-Opening Metathesis Polymerization (ROMP) with Vince Lactam. Choi and Cho directed their research efforts toward performing group (VI) metals' catalyzed ROMP on Vince lactam.³¹² The transition metal catalysts used included tungsten (WCl_6 and $(\text{CO})_5\text{W}=\text{C}(\text{OEt})\text{Ph}$), molybdenum (MoCl_5) and rhenium (ReCl_5). Varying molar ratios of AlEt_3 , Et_2AlCl , $(^i\text{Bu})_3\text{Al}$, SnPh_4 , TiCl_4 , etc., were studied as co-catalysts. A limited optimization of reaction conditions with respect to solvent, temperature and monomer to catalyst molar ratio was performed. The best results achieved were

Scheme 39. Preparation of Cobalt–Dinitroso–Vince Lactam Complex and Plausible Mechanism for the Olefinic Functionalization Mediated by It

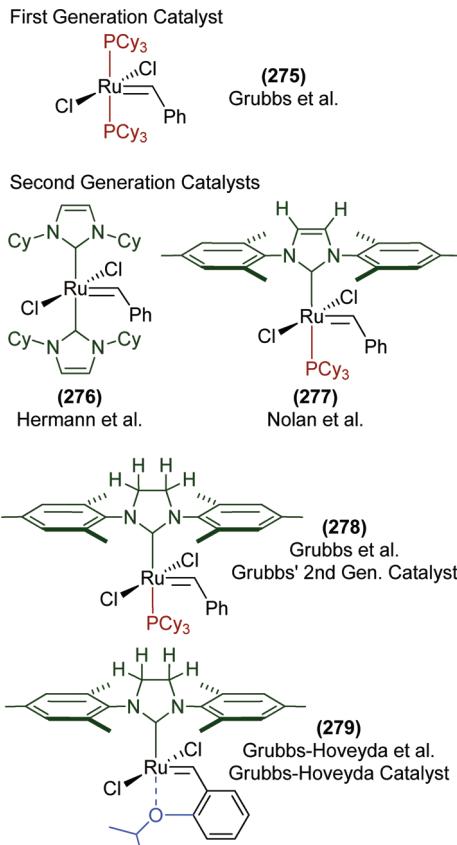


represented by a moderate 34% conversion with the inherent viscosity of 0.18 dL/g in the reaction mediated by $\text{WCl}_6\text{-Et}_3\text{Al}$ (1:4). Other factors for achieving optimum reaction conditions included heating the reactants at 60 °C in chlorobenzene and with the loading ratio of monomer: $\text{WCl}_6 = 200$.

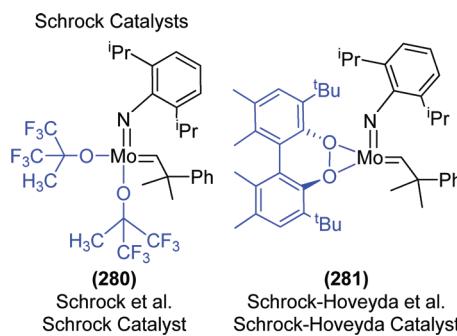
4.4.2. Enantioselective Synthesis of Various Heterocyclic Compounds via ROM–CM–RCM Domino Metathesis of Vince Lactam. Following Blechert's initial investigations on Boc-protected Vince lactam as a part of study of ring-opening metathesis of functionalized olefins,³¹³ an elegant study aimed at achieving enantioselective synthesis of various derivatives of heterocycles such as quinolizidines, pyrrolizidines, pyrrolidinoazepine, and pyrrolidinoazocines was reported by Arjona, Plumet and co-workers.³¹⁴ The authors capitalized on Vince lactam's steric (strain) and electronic (olefin) properties and evaluated the reaction system comprising of N-alkylation of Vince lactam, followed by a domino metathesis strategy. The protocol included ruthenium catalyzed ROM-CM step, followed by ruthenium and molybdenum mediated RCM step to successfully prepare the desirable compounds (Scheme 44).

The authors later expanded their protocol to include alkyne–alkene metathesis in the domino process of their reaction.³¹⁵ N-alkynylated Vince lactam derivatives were prepared from the reaction of (+)-(1) and respective halides of the desired compounds. Both, first and second generation Grubbs' catalysts were used for mediating the reactions. Furthermore, Arjona and Plumet independently revealed their studies focused on

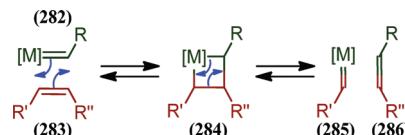
Scheme 40. Grubbs' Catalysts for Olefin Metathesis



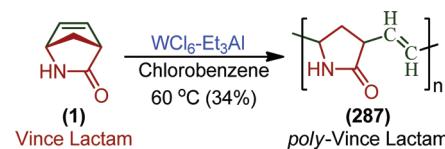
Scheme 41. Schrock Catalysts for Olefin Metathesis



Scheme 42. Chauvin Mechanism for Olefin Metathesis

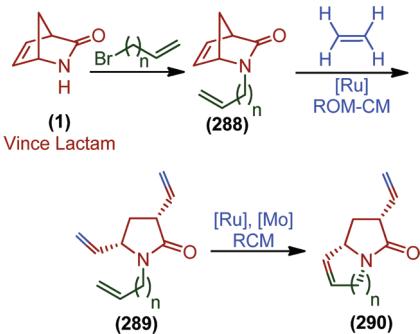


Scheme 43. Transition Metal-Catalyzed Ring-Opening Metathesis Polymerization (ROMP) of Vince Lactam



preparing 3,5-disubstituted pyrrolidines and prolines,³¹⁶ and the preparation of functionalized tetrahydro-6*H*-pyrrolizidin-3-

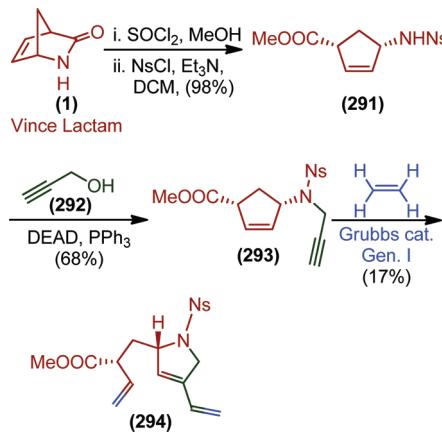
Scheme 44. Enantioselective Synthesis of Various Heterocyclic Compounds via Domino Metathesis Strategy with Ruthenium and Molybdenum Catalysts



ones,³¹⁷ respectively, from the domino metathesis of Vince lactam. Their efforts established the substrate scope of various olefins as prospective reactants.

4.4.3. Enantioselective Synthesis of Various Heterocyclic Compounds via ROM-RCM Domino Metathesis of Ring-Opened Vince Lactam Derivatives. Meanwhile, Mori et al. opened the ring of the lactam and introduced nosyl protecting group on the amine (291, Scheme 45).³¹⁸ The

Scheme 45. Domino Metathesis after Opening the Ring of Vince Lactam



cyclopentene fragment was then derivatized under Mitsunobu conditions³¹⁹ to obtain the metathesis precursor (293). The domino metathesis (ROM-RCM) was then performed with Grubbs' first generation catalyst in the presence of ethylene to obtain the final desired heterocyclic molecular scaffold (294) in 17% yield (Scheme 45). The authors further explored ROM-RCM domino metathesis of cyclopenten-ynes obtained from Vince lactam and in a detailed report revealed achieving a one-step synthesis of various bicyclic heterocycles.³²⁰

Since the change of functionality on the nitrogen of Vince lactam proceeds to provide different products, it is worthy of mention that Arjona and Plumet's domino metathesis methodology is yet another method to utilize the dynamic N-modulatory properties of Vince lactam.

4.5. Use of Vince Lactam as a Standard in Chemical Analysis of Compounds and Optical Activity of Stereoisomers

Interestingly, Vince lactam has also been used for nonsynthetic purposes. Armstrong and co-workers included Vince lactam in

a library of chiral building blocks of high synthetic value and analyzed the constitution of enantiomeric impurities for each chiral molecule.³²¹ A commercial sample of Vince lactam was analyzed via chiral HPLC. The results showed presence of the unwanted isomer at 0.01% level. Same authors have used Vince lactam as a standard to compare the separation prowess of their three newly constructed chiral columns.³²² The analysis was performed by comparison of their columns with a commercially known model. In a separate study by Garcia-Mera et al., Vince lactam was made the compound of choice to use as the standard for characterizing their synthesized compounds. The authors compared melting points and spectroscopic properties to characterize their optically active compounds between their compounds and Vince lactam to perform qualitative analysis of their compounds.³²³

5. CONCLUSIONS

In conclusion, we have provided a comprehensive view of the structural features, chemical reactivity and various avenues utilizing Vince lactam in distinct fields of chemistry. The bicyclic γ -lactam has been a moiety of interest for several research groups in both medicinal and non-medicinal related areas. It holds the unique distinction of being utilized as a building block for two universally available drugs which are presently being used as inexorable components of chemotherapeutic efforts directed toward fighting fatal diseases (AIDS–HIV and influenza). It is indeed notable that the commercially viable synthesis of structurally distinct drugs, abacavir and peramivir, as well as several clinical candidates, such as Merck's MK-0812, AstraZeneca's AZD-muscarinic antagonist, Glenmark Pharmaceutical's Meloglitin, etc., target a wide array of diseases but germinate from the same molecular scaffold of Vince lactam. Apart from these medicinally relevant applications, Vince lactam has found use in fields as varied as metathesis, metal-mediated methodology development, organic synthesis, etc. The significant impact of Vince lactam is a testament to its versatility. These diverse but significant applications of this lactam, make it imperative that a compilation detailing its chemical profile and utilization be provided for the general chemistry readership. We hope that this article will generate higher academic interest in the related chemistry and will help advance the development of sustainable and commercially viable methodologies.

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Notes

The authors declare no competing financial interest.

Biographies



After obtaining his M.S. (Hons. School) in chemistry from Panjab University (Chandigarh, India), Rohit Singh joined Prof. Steven P. Nolan's group at the University of New Orleans (New Orleans, LA) in Spring of 2002. His graduate work focused on the development of N-heterocyclic carbenes as efficient organic catalysts, and ligands for palladium mediated coupling chemistry. During the course of his doctoral studies, he earned his second Master's degree based on his work on organocatalytic transesterification of secondary alcohols (2003). He obtained his doctoral degree in organic chemistry in 2007 and joined Center for Drug Design (CDD) at the University of Minnesota, for post-doctoral work. He is currently a Research Associate at CDD. His research is focused on the design and discovery aimed at developing antitumor therapeutics, and reverse transcriptase/integrase (RT/IN) inhibitors for the treatment of HIV–AIDS.



Dr. Robert Vince obtained his doctoral degree in medicinal chemistry in 1966 from the College of Pharmacy at SUNY Buffalo. In 1967, he joined the Medicinal Chemistry Faculty at the University of Minnesota, where he continues to maintain his research program. His invention, the HIV drug, abacavir, was commercialized by GSK and has resulted in generation of revenue more than 600 million US dollars for the University of Minnesota. In 2002, he established the Center for Drug Design within the Academic Health Center of the University of Minnesota. He has been honored for his work by a career development award from NIH (1972–1976), the 1979 University of Minnesota Scholar of the year award, and Certificate of Commendation by the Governor of Minnesota (1989). In recognition of achievements as an inventor, he was honored by the Minnesota Medical Alley, and Award of the New York Cayuga Community College (2002). At University of Minnesota, he is recognized on 'Scholars Walk and Wall of Discovery' 2006 and was inducted into the Academy for Excellence in Health Research in 2009. He has also been

inducted into the Medicinal Chemistry Hall of Fame (2007) by the American Chemical Society. He was awarded an honorary Doctorate of Science degree by his alma mater, SUNY-Buffalo (2010). The International Society for Nucleosides, Nucleotides and Nucleic Acids awarded him the 2010 Imbach Townsend Award. He was inducted in Minnesota Inventors Hall of Fame along with Nobel laureate Dr. Norman Borlaug (posth.) by the Minnesota Inventor's Congress in 2010. Recently, he has been inducted into the Minnesota Science and Technology Hall of Fame (2011).

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ABBREVIATIONS

ABC	abacavir
Ac	acetyl
ADMET	acyclic diene metathesis
ADP	adenosine diphosphate
AG	aktien gesellschaft (German)
AIBN	azobisisobutyronitrile
AIDS	acquired immune deficiency syndrome
aq	aqueous
Ar	aryl
araA	9-β-D-arabinofuranosyladenosine
araH	9-β-D-arabinofuranosylhypoxanthine
AZT	azidothymidine
Å	angstroms
Bn	benzyl
Boc	tertiary-butoxy carbonyl
C-araA	carbocyclic 9-β-D-arabinofuranosyladenosine
cat	catalyst
C-BCNA	carbocyclic bicyclic nucleoside analogue
CBV	carbovir
CC	<i>candida cylindrica</i>
CCR2	chemokine (C–C) receptor 2
CDK-9	cyclin dependent kinase-9
cisplatin	<i>cis</i> -diamminedichloroplatinum(II)
CM	cross metathesis
C-NECA	carbocyclic 5'-N-ethyl carboxamido adenosine
COD	cyclooctadiene
COPD	chronic obstructive pulmonary disease
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cpd	compound
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
deg	degrees
DIBAL	diisobutylaluminium hydride
DMS	dimethyl sulfide
DNA	DNA
DPP-4	dipeptidyl peptidase-4
Et	ethyl
ETV	entecavir
GABA-AT	gamma aminobutyric acid–aminotransferase
Gen	generation

GSK	glaxosmithkline
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCMV	human cytomegalovirus
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
hrs	hours
HSV	herpes simplex virus
H1N1	type 1 hemagglutinin, type 1 neuraminidase
ⁱ Bu	iso-butyl
IN	integrase
Inhib	inhibitors
LUMO	lowest unoccupied molecular orbital
MCH	melanin concentrating hormone
mCPBA	meta-chloroperoxybenzoic acid
Me	methyl
min	minutes
MPa	megapascal
NAD ⁺	nicotinamide adenine dinucleotide
NHC	N-heterocyclic carbene
NMO	N-methylmorpholine-N-oxide
Np	naphthalene
Ns	nosyl
OTV	oseltamivir
oxid	oxidation
Ph	phenyl
PMB	para-methoxybenzyl ether
PPL	porcine pancreatic lipase
PRV	peramivir
psi	pounds per square inch
py	pyridine
RBV	ribavirin
RCM	ring closing metathesis
Red-Al	reducing aluminum: sodium bis(2-methoxyethoxy) aluminumhydride
ref	reference
RNA	ribonucleic acid
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
rt	room temperature
RT	reverse transcriptase
sp	species
TBDMS	tertiary-butyldimethylsilyl
Thpn	thiophene
TMSOTf	trimethylsilyl trifluoromethanesulfonate
ZDV	zidovudine
3TC	lamivudine
(ABC+3TC)	epzicom (U.S.A.); kivexa (Europe)
(ABC+AZT+3TC)	trizivir

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