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Synthesis of Bioactive Macrocycles Involving Ring-Closing Metathesis Strategy

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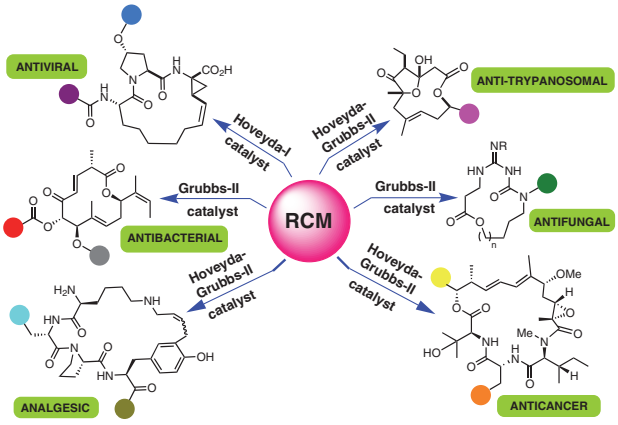

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Crowd-Reviewed

Abstract This review reports the synthesis of various bioactive macrocycles, involving ring-closing metathesis as a key step, developed since ca. 2000. These macrocycles exhibited biological activities such as antiviral, antifungal, antibacterial, and anticancer activities, and more. Thus, their syntheses and utilization are essential for both synthetic organic and medicinal chemists.

Key words macrocycles, ring-closing metathesis, antiviral, antifungal, anticancer, antibiotic

1 Introduction

Over a prolonged period of time, macrocyclic compounds constituting ester/keto/amide moiety have remained as the backbone of various natural products and clinical drugs. The naturally occurring compounds possessing macrocyclic skeletons have exhibited remarkable biological activities including antibiotic, anticancer, immunosuppressant, Hsp90 inhibitor, cytotoxic, etc.[1] Nonactin and valinomycin, a class of oxygen-bearing macrocycles, are examples of naturally occurring antibiotics obtained from *Streptomyces* species.[2] The actinoallolides, a family of complex polyketides, show potent activity against *Trypanosoma* protozoan parasites causing Chagas disease and African trypanosomiasis.[3] Solomonamides, a class of macrocycles with an amide moiety, isolated from the marine sponge *Theonella swinhoei*, display anti-inflammatory activity while preliminary biological evaluations of solomonamide precursors exhibited antitumor activity against various tumor cells.[4] In addition, several other macrocycles reported in the literature are the building blocks of distinguished natural products with significant pharmacological properties like antibiotic,[5] antiviral,[6] immunosuppressing,[7] and more.[8–15] Owing to the broad spectrum of biological activities, several routes have been developed for the synthesis of various macrocycles on a large scale. Quite a few of them include the Dieckmann condensation,[16] Stille coupling,[17] radical reactions,[18] semipinacol rearrangement,[19] homologation of cyclic ketones with diazo compounds,[20] and ring-closing metathesis (RCM) reactions.[21–23] Among them, the RCM strategy has been recognized as an effective tool for furnishing simple ring systems,[24] heterocycles,[25] macrocycles,[26] polymers,[27] and natural products[28] as it seemed to be the most straightforward and reliable method to afford olefinic double bonds in cyclic as well acyclic systems. Incorporating the ideology of synthesizing macrocycles, exhibiting biological activities in the field of medicine, by using RCM protocol as a key step has initiated a whole new level of research. After garnering information about such research articles, we have realized in our limited knowledge that a recent review on the topic synthesis of bioactive macrocyclic compounds involving RCM strategy has still not been targeted upon. As we are currently engaging in the synthesis of macrocyclic compounds and subsequently we have published an article,[1] we decided to write a review article mentioning the synthetic routes developed since 2000, to graft bioactive macrocycles using RCM methodology. We are hopeful that this review will benefit researchers who are working in the field of medicinal chemistry to facilitate the development of novel macrocyclic compounds required for drug discovery.

2 Antiviral

Hepatitis C virus (HCV) is a worldwide epidemic and affects millions of individuals every year. It is the primary cause of liver disease and spreads through contaminated blood. Symptoms for the disease might take a prolonged period of time to appear until this 'silent infection' has already damaged the liver enough. Another common viral infection occurring globally is herpes simplex virus (HSV) which is both orally and sexually transmitted. It causes mild to severe painful blisters and the symptoms are recurring. In order to eradicate the diseases, the scientific community is always concerned about creating new drugs to ensure the treatment of affected people.

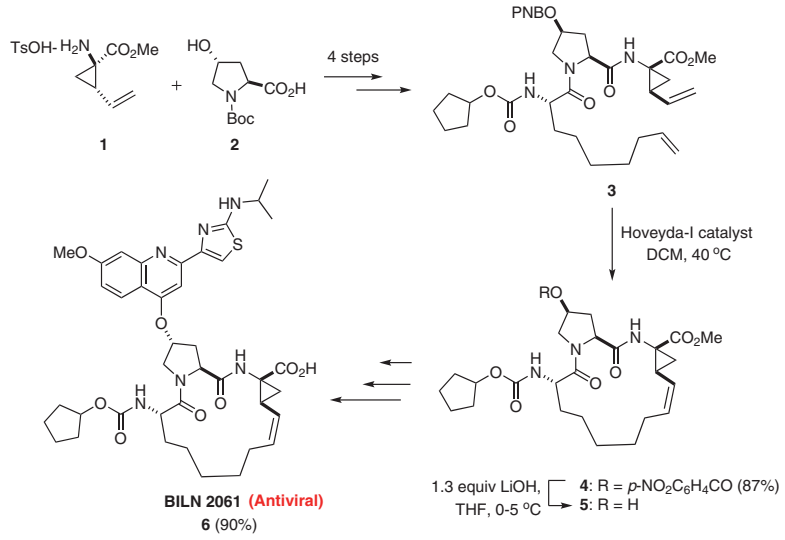
The 15-membered ring macrocyclic tripeptide BILN 2061 (**6**) is a potent inhibitor of HCV NS3-4A protease. In 2006, Yee *et al.* established an efficient large-scale synthesis of the tripeptide **6** by utilizing ring-closing metathesis as a crucial step (Scheme 1).[29] The synthetic route commenced by using compounds **1** and **2** as the starting materials. A series of consecutive reactions led to the formation of RCM precursor **3** which was subjected to macrocyclization conditions using Hoveyda-I catalyst in DCM at 40 °C. The reaction afforded the macrocycle **4** in an excellent yield of 87%. Further reactions were carried out upon compound **4** and the target molecule BILN 2061 was obtained in 90% yield in the final step.

In order to combat the growing HCV infection, various clinical studies undertaken over the years exhibited that NS3, a dual function enzyme, could act as a target for treating HCV using peptide inhibitors. In 2007, a group led by Velázquez and Venkataraman designed a synthetic method to prepare macrocyclic inhibitors **17** and **23** of the HCV NS3 protease (Scheme 2).[30] The investigation started with the synthesis of ω-unsaturated *N*-Boc-protected amino acid **10a** and amine hydrochloride salt **11b**. The monoester **7** was at first converted into α,β-unsaturated esters **8a** and **8b** through Knoevenagel condensation by using pent-4-enal and hex-5-enal, respectively. After two successive reactions the *N*-Boc-protected amino acids **9a** and **9b** were obtained which were later individually converted into **10a** and **11b**, respectively. HATU coupling of **10a** with dimethylcyclopropyl proline **12** resulted in the formation of dipeptide **13** which upon further hydrolysis provided the acid **14**. The amino acid **11b** was next introduced in the reaction to develop the RCM precursor **15**. The ultimate RCM reaction was conducted using Grubbs' first-generation (Grubbs-I) catalyst in toluene at 60 °C to afford the corresponding mac-

Biographical Sketches

Nasrin Jahan was born in 1993 in Durgapur, West Bengal, India. She graduated in Chemistry (2015) from the University of Burdwan, West Bengal, India and obtained her M.Sc. degree (2017) from Kazi Nazrul University, West Bengal, India. Currently, she is pursuing her Ph.D. degree at the University of Burdwan.

Dr. I. Ansary was born in 1983 in Raghunathpur, Purulia, West Bengal, India. He received his B.Sc. in Chemistry (2004) from The University of Burdwan, Burdwan, India and obtained his M.Sc. degree (2006) from the University of Calcutta, Kolkata, India. He received his Ph.D. in Chemistry (July 2013) under the supervision of Dr. B. Roy from the University of Kalyani. He joined as an Assistant Professor in Chemistry in November 2012 at The University of Burdwan, West Bengal and teaches Organic Chemistry in the postgraduate level. His research interests are in the areas of development of new synthetic routes and methodologies to construct nitrogen and oxygen heterocycles of different ring sizes and their application on the basis of molecular modeling and docking studies. Recently, he has been working in the field of pesticide residue analysis. He has published 30 research articles and 2 book chapters. He also reviewed several research articles of some internationally reputed journals. Under his supervision 2 students have been awarded Ph.D. degrees and currently 3 students are still working in his group. Moreover, he also supervised more than 50 M.Sc. students to successfully submit their project-based term papers.

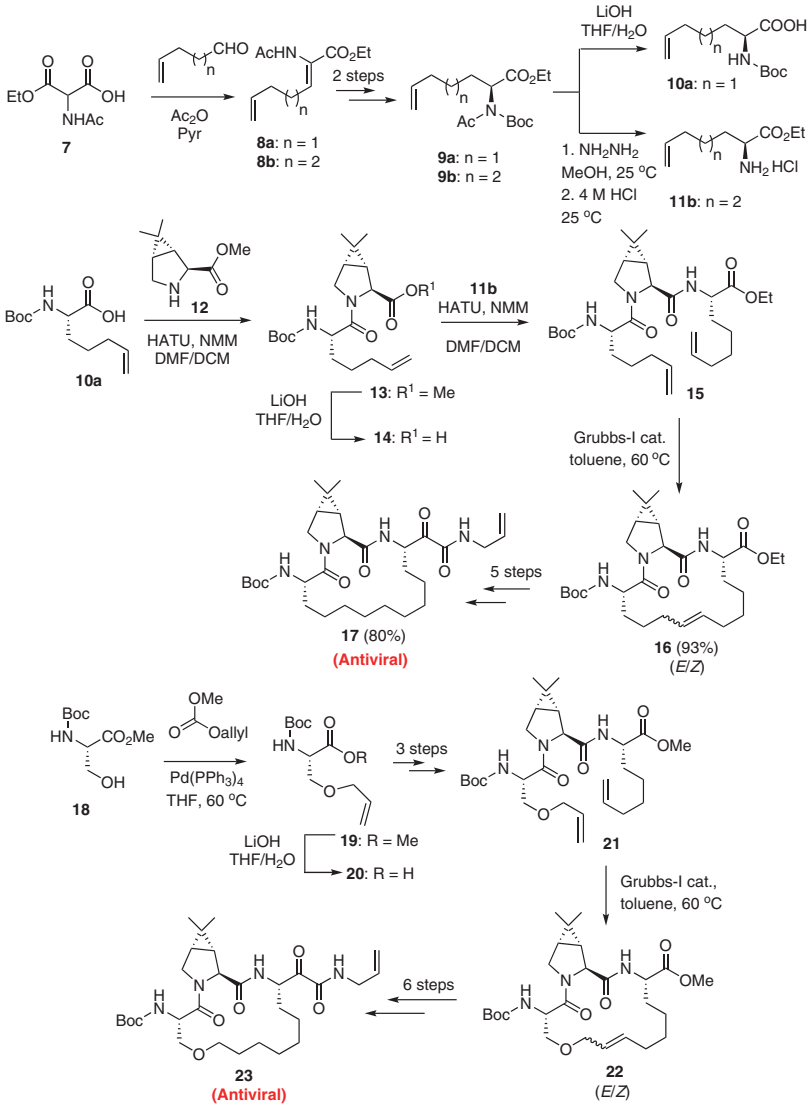


Scheme 1 Synthesis of HCV protease inhibitor BILN 2061

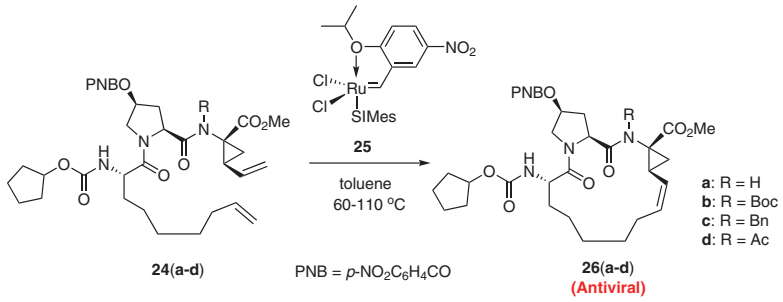
rocycle **16** in 93% yield as a mixture of *E*/*Z* isomers. The keto-amide moiety, which served as a serine trap in the class of inhibitors, was of interest for the researchers' group and hence, it was incorporated within the 16-membered macrocycle **17** through a series of consecutive reactions. Further investigation was carried out by the group to introduce heteroatoms within the macrocyclic core. Construction of macrocycle **22** commenced when Boc-L-serine **18** was treated with methyl allyl carbonate and tetrakis(triphenylphosphine)palladium to produce **19**. Several steps were carried out to afford the RCM precursor **21** which underwent macrocyclization with Grubbs-I catalyst in toluene at 60 °C to afford the metathesis product **22** as an *E*/*Z* mixture. A further six consecutive reactions were conducted to furnish the desired oxygen-containing macrocycle **23**.

Shu *et al.*, in 2008, reported an improved method for the key RCM step while synthesizing the HCV protease inhibitor BILN 2061 (Scheme 3).[31] The macrocyclization of substrates **24a–d** was conducted using second-generation Ru catalyst **25** in toluene at various temperatures (60 °C or 110 °C) to afford the desired compounds **26a–d** in good yields. In 2008, the Randolph group synthesized a P3 aza-peptide analogue of macrocyclic tripeptide inhibitor **32** which was closely related to BILN 2061 (Scheme 4) *via* ring-closing metathesis reaction.[32] The synthesis advanced as esterification of heptenoic acid **27** took place followed by reduction to afford the aldehyde **28**. Through various consecutive reactions, the RCM precursor tripeptide **29** was produced and finally subjected to macrocyclization. The initial studies were conducted using Hoveyda's catalyst at 40 °C in DCM which furnished the macrocycle only in 50% yield after 3 days, in a 1:4 ratio of *E*/*Z* olefin products. On raising the temperature to 50 °C in toluene, the product was obtained in a 62% yield as a 2:3 ratio of *E*/*Z* olefin isomers leaving behind only a trace amount of precursor after 3 days of reaction. After separating the isomers and subjecting the macrocyclic tripeptide **31** to saponification, the target inhibitor **32** was achieved. The effect of the P3 aza-peptide modification on *in vitro* potency was next tested and found that it resulted in a loss in activity in both the enzyme inhibition and replicon assays.

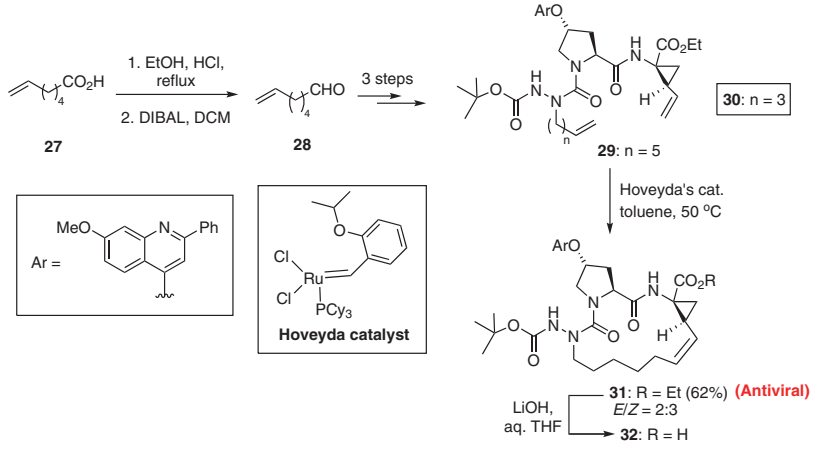
In 2013, Wei *et al.* reported an efficient synthesis to produce the macrocyclic HCV protease inhibitor BI 201302 (**40**) (Scheme 5).[33] The synthesis progressed with the coupling of (*S*)-2-((cyclopentyloxycarbonyl)amino)non-8-enoic acid (**33**) and *trans*-hydroxy-proline ester **34** in the presence of cyanuric chloride and hydrolyzed to produce the dipeptide **35**. Two successive reactions developed an intermediate which helped in a streamline one-pot preparation of the RCM precursor **36** which was subjected to macrocyclization in refluxing toluene by adding a solution of Grela's catalyst in portions. Completion of the reaction led to the formation of RCM product **37** in 93% assay yield which was further deprotected from the Boc, acetyl, and ester groups to produce the acid intermediate **38** in 75% yield. It was next subjected to S_NAr reaction conditions with **39** by using *t*-BuOK. The *tert*-butyl carbamate analogue of BI201302 was the only significant impurity (1–2%) present within the medium which was removed by using potassium 3,7-dimethyl-3-octanoxide (KDMO) during the reaction. After crystallization, the target macrocycle BI201302 (**40**) was obtained as its meglumine (MU) salt in 74% yield.



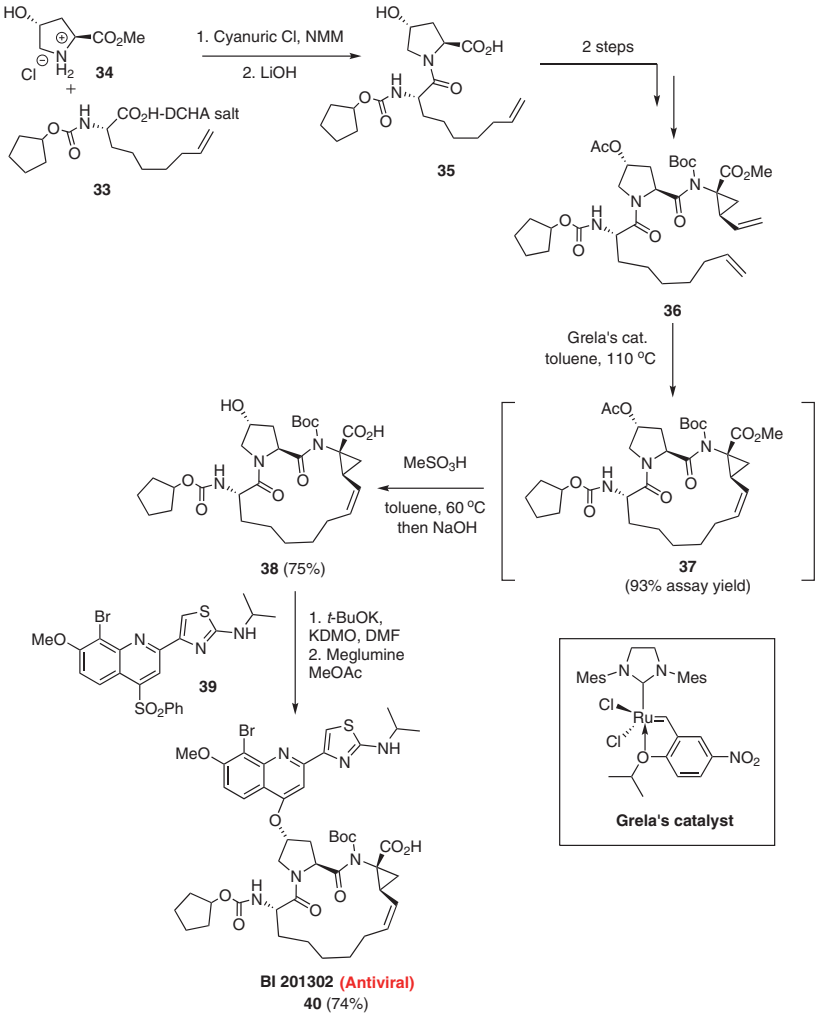
Scheme 2 Synthesis of macrocyclic inhibitors of HCV NS3 protease



Scheme 3 Synthesis of HCV protease inhibitor BILN 2061



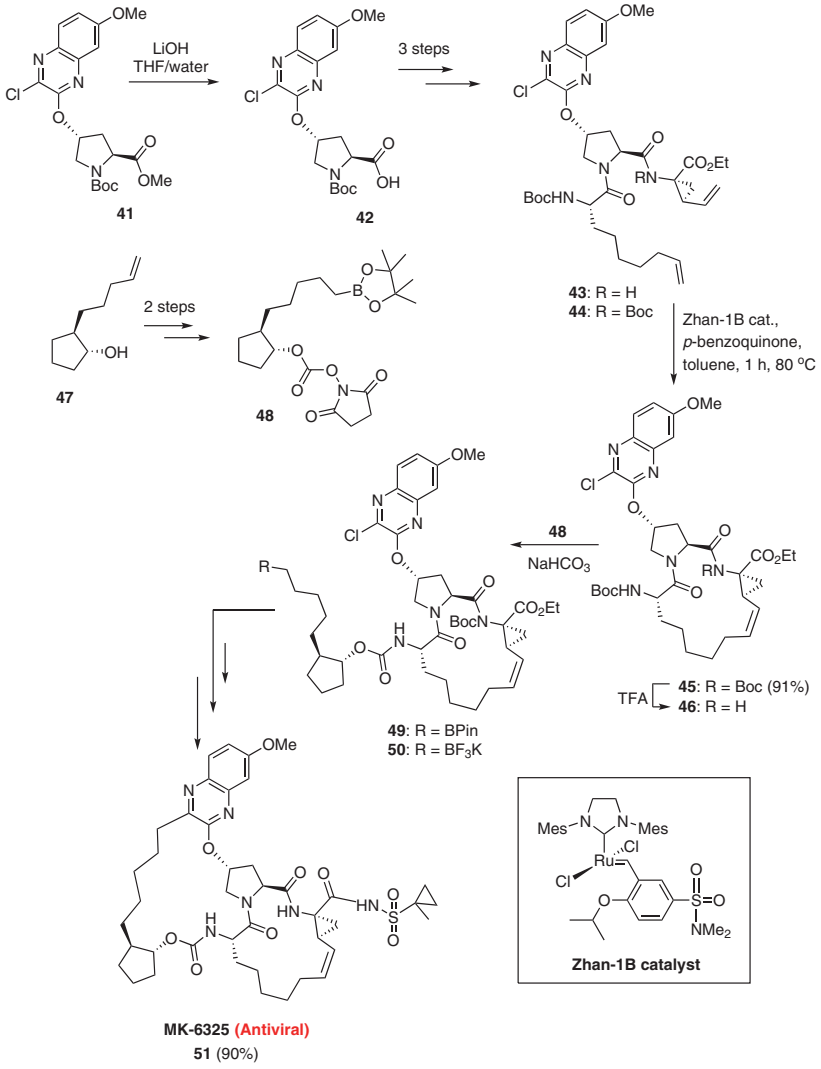
Scheme 4 Synthesis of P3-aza peptide analog of a potent macrocyclic tripeptide HCV protease inhibitor



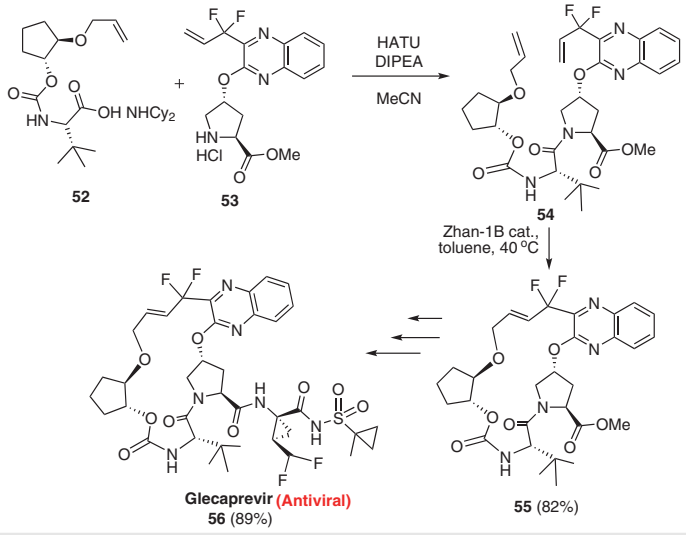
Scheme 5 Synthesis of HCV protease inhibitor BI201302

MK-6325 (**51**), on being found to be a potent HCV NS3/4A protease inhibitor, was required to be clinically evaluated. Hence, in 2015 Li *et al.* developed a practical asymmetric synthesis of this bis-macrocyclic compound (Scheme 6).[12] MK-6325 was curated using a 15-membered macrocycle **45** and the cyclopentyl building block **48**. Synthesis of **45** involved the crucial ring-closing metathesis step and the entire route commenced from the quinoxaline derivative **41**. On treating **41** with lithium hydroxide in THF and water, the acid **42** was obtained. Three consecutive reactions upon **42** produced the RCM precursor **44** which was subjected to metathesis conditions involving Zhan-1B catalyst and *p*-benzoquinone (BQ) in toluene at 80 °C for 1 h to afford the 15-membered macrocycle **45** as a solid crystal in 91% yield. Further deprotection of **45** using TFA produced the amine **46**. Sequentially, the intermediate **48** was prepared from cyclopentanol **47** in two steps. Combination of **46** with **48** synthesized the BPin Suzuki–Miyaura substrate **49** and subsequent reactions afforded the desired compound MK-6325 (**51**) in 90% yield.

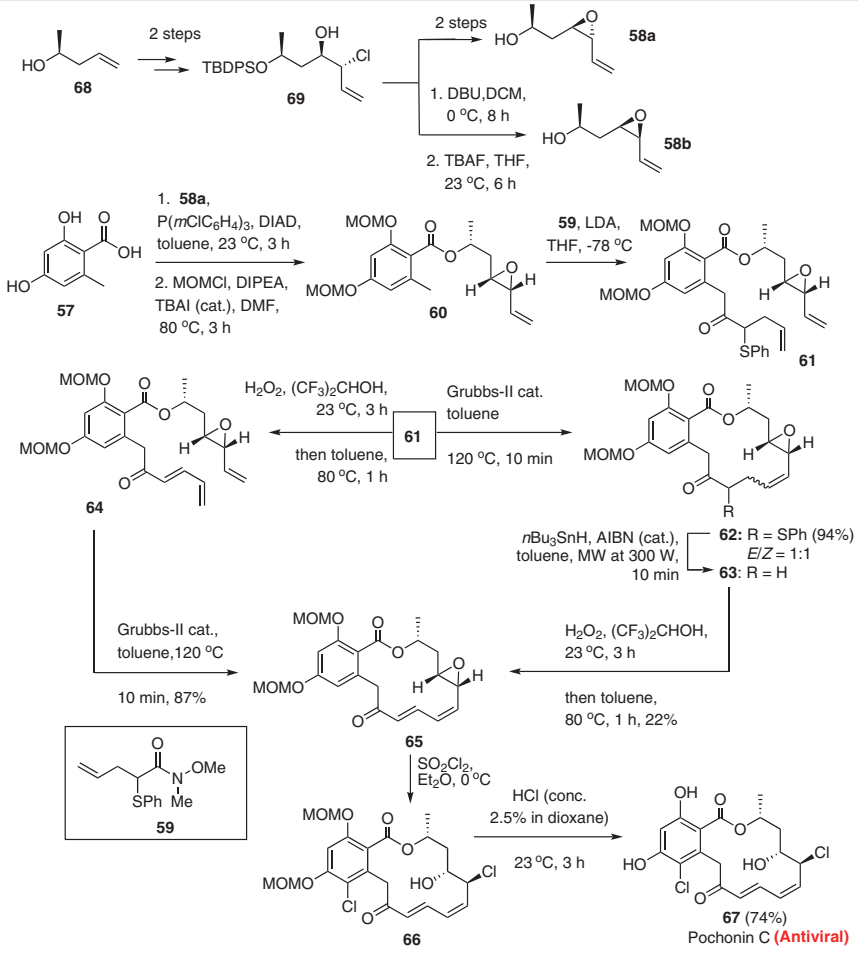
On being identified as a potent HCV NS3/4A protease inhibitor, glecaprevir (**56**) was successfully synthesized by the Cink group in 2020 (Scheme 7).[6] The synthetic pathway advanced with the coupling of the two fragments **52** and **53**, using HATU as the coupling reagent, to afford the RCM precursor **54**. The final macrocyclization step took place by subjecting **54** to metathesis conditions involving Zhan-1B catalyst in toluene at 40 °C to produce the *trans*-macrocycle **55** in 82% yield. Use of Grubbs-II catalyst instead of Zhan-1B also afforded the product **55** in 79% yield. Continuation of a series of reactions upon the macrocycle, furnished the target compound glecaprevir (**56**) in 89% yield.



Scheme 6 Synthesis of HCV protease inhibitor MK-6325



Scheme 7 Synthesis of glecaprevir



Scheme 8 Synthesis of pochonin C

Pochonin C (**67**) was discovered to be a novel antiviral agent against herpes simplex virus (HSV). Belonging to a family of six related macrolides (pochonins A–F), pochonin C has the highest selectivity index (Tox50/IC50) against HSV. Barluenga *et al.*, in 2004, developed a synthetic procedure in which the target macrocycle **67** could be disconnected into three main building blocks **57**, **58**, and **59** (Scheme 8).[34] The *trans*-epoxides **58a** and **58b** were achieved from alcohol **68**. Several consecutive reactions, ozonolysis, Brown allylation, epoxidation, and deprotection, led to the synthesis of **58b**. Further reactions upon intermediate **69** yielded the oxirane **58a**. In order to achieve **67**, acid **57** was chosen as the starting material and subjected to protection of the two phenol groups with MOMCl to afford the toluic ester **60**. Next, deprotonation of the benzylic position was carried out with LDA and quenched with the Weinreb amide **59** to yield the RCM precursor **61**. On being treated with Grubbs' second generation (Grubbs-II) catalyst in toluene at 120 °C, **61** underwent cyclization to afford the macrocycle **62** in 94% yield as an inseparable mixture of *E*/*Z* (1:1) products. To obtain the dihydroradicicol macrocycle **63**, the thioether group could be removed under free radical conditions. Oxidation with H_2O_2 was also conducted upon **61** in a separate pathway to obtain the diene **64** which upon further exposure to macrocyclization conditions with Grubbs-II catalyst in toluene at 120 °C produced the compound **65** in 87% yield. Subsequently, **63** was also converted into **65** *via* oxidation with H_2O_2. Finally, chlorination of the aryl ring in **65** and stereoselective opening of the epoxide were carried out using excess SO_2Cl_2 followed by deprotection of the MOM groups to afford the target compound pochonin C (**67**) in 74% yield.

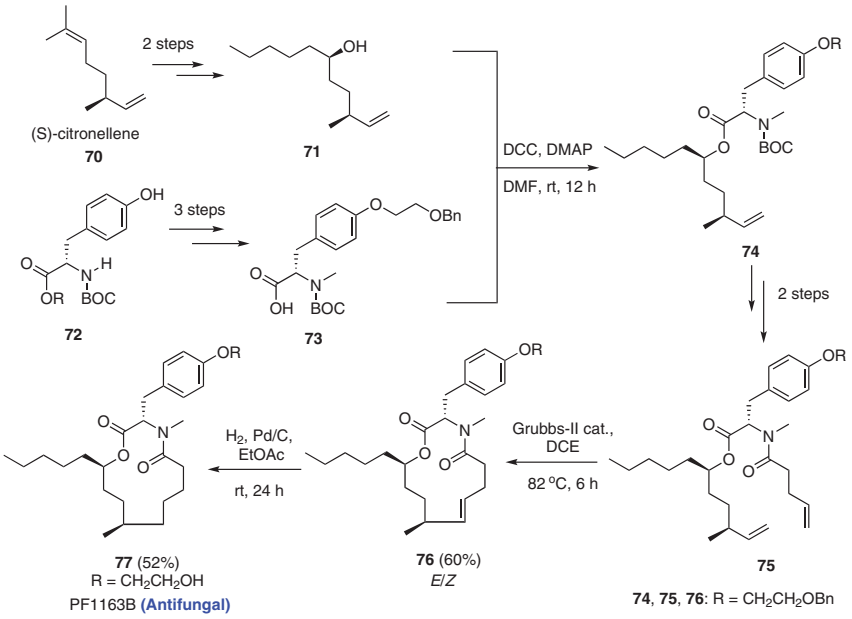
3 Antifungal

Fungal infections are the most common health issues in today's world as inhaling or coming in direct contact with fungal spores leads to skin infection. The effect of SARS-CoV-2 has worsened the scenario globally as the affected people who are dealing with intubation, ventilation, and long-term hospitalization are highly susceptible to develop fungal infections. Systemic fungal infections can affect organs, such as lungs, eyes, liver, and brain, particularly for immunocompromised patients while invasive fungal infections (IFIs) cause severe illness and high mortality among them.

The most predominant pathogenic species, *Candida*, is responsible for almost half the IFIs. In order to treat *Candida* infections, a limited number of chemotherapeutic agents were relied upon. Owing to their low toxicity and high degree of bioavailability, azoles helped in treating a wide range of candidiasis. However, the spread of drug resistant fungal species halted the use of classical antifungal drugs like fluconazole and posed a challenge amongst the scientific community to redevelop therapy and diagnosis to ensure eradication of fungal infections. Studies upon the antimycotics have advanced over the recent decades compelling various researchers to provide significant attention towards marine-derived fungi. Melearoride A and PF1163B are two novel 13-membered macrolides isolated from marine-derived fungi with inherent azole resistant antifungal property.

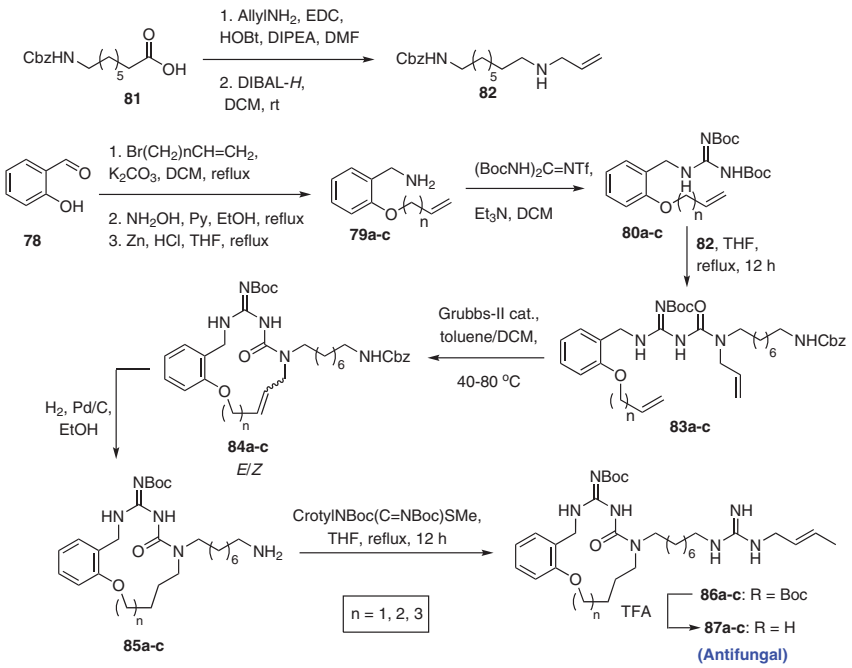
Bouazza *et al.*, in 2003,[35] reported the synthesis of the macrocyclic antifungal agent (–)-PF1163B (**77**) (Scheme 9). Preparation of the first building block **71** commenced from (*S*)-citronellene (**70**) whereas, the second building block **73** was synthesized from *N*-Boc-L-tyrosine **72** in a few sequential steps. Next, these two fragments were made to undergo an esterification process with DCC in DMF in the presence of DMAP to afford compound **74**. After two subsequent steps, the RCM precursor **75** was achieved and subjected to metathesis conditions in refluxing dichloroethane with Grubbs-II catalyst for 6 hours. The macrocycle **76** was afforded in 60% yield as a mixture of *E*/*Z* isomers. Finally, the newly formed double bond was reduced followed by hydrogenolysis of the benzyl group and it resulted in the formation of the target compound PF1163B (**77**) as a colorless oil in 52% yield.

In 2013, Sanguinetti *et al.* synthesized macrocyclic amidinourea derivatives **87a–c** and **94a**,**b** to investigate the effects of ring-size development and incorporation of polar/apolar moieties while evaluating their antifungal activity (Schemes 10 and 11).[9] The development of **87a–c** (Scheme 10) started off by using aldehyde **78** which was *O*-alkylated with alkenyl bromides and condensed with NH_2OH to produce oximes. Further reduction of the substrate in the presence of Zn resulted in the synthesis of amines **79a–c** which underwent guanylation to create the guanidine-based fragments **80a–c**. The building block **82** was synthesized in two steps as Cbz-aminooctanoic acid **81** was exposed to consequent amidation-reduction reactions. The two blocks **80a–c** and **82** coupled to produce the RCM precursors **83a–c**. On being treated with Grubbs-II catalyst at 40–80 °C in toluene/DCM solvent, **83a–c** afforded the macrocycles **84a–c** as a mixture of *E*/*Z* isomers in high yields. Reduction of the double bond present in the macrocyclic core and Cbz cleavage produced the primary amines **85a–c** which upon further guanylation with *N*,*N*′-diBoc-*N*-crotyl-*S*-Me-isothiourea and treatment with trifluoroacetic acid furnished the desired derivatives **87a–c**. In order to synthesize the second set of derivatives, β-alanine (**88**) was used as the precursor (Scheme 11). Consequent reactions like guanylation and esterification of **88** led to the production of guanidines **89a**,**b**. Further conversion of **89a**,**b** into dienes **90a**,**b** took place in refluxing toluene by using allylamine **82**. The dienes served as the RCM precursors and underwent macrocyclization in the presence of Grubbs-II catalyst in DCM at 40 °C to afford the macrocycles **91a**,**b**. On completion of this key step, **91a**,**b** were hydrogenated, gua-

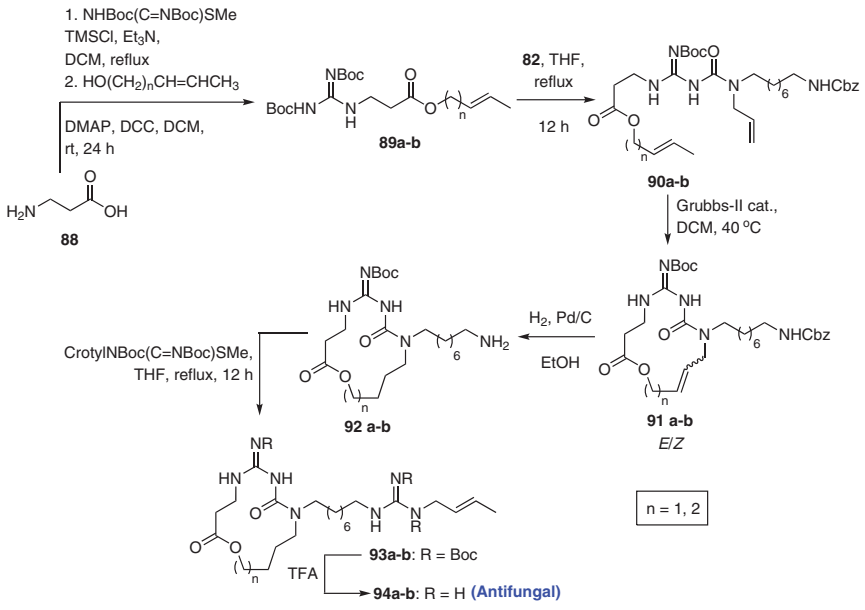


Scheme 9 Synthesis of antifungal agent PF1163B

nylated, and Boc deprotected to afford the desired derivatives **94a**,**b**. The compounds **87a–c** and **94a**,**b** were assayed against clinical isolates of seven different wild-type *Candida* species and were found to exhibit antifungal activity. The presence of an aromatic substitution on macrocycles as seen in **87a–c** caused those derivatives to show a stronger activity than the compounds **94a**,**b** which bore ester moieties. The increasing ring size of macrocycles **87a–c** from 13- to 15-membered also proved to effectively increase the antifungal activity towards all *Candida* species. A similar trend was noted in case of compounds **94a**,**b** where the macrocycle with a larger ring size was evaluated to exhibit a stronger activity as compared to the one with smaller ring size.

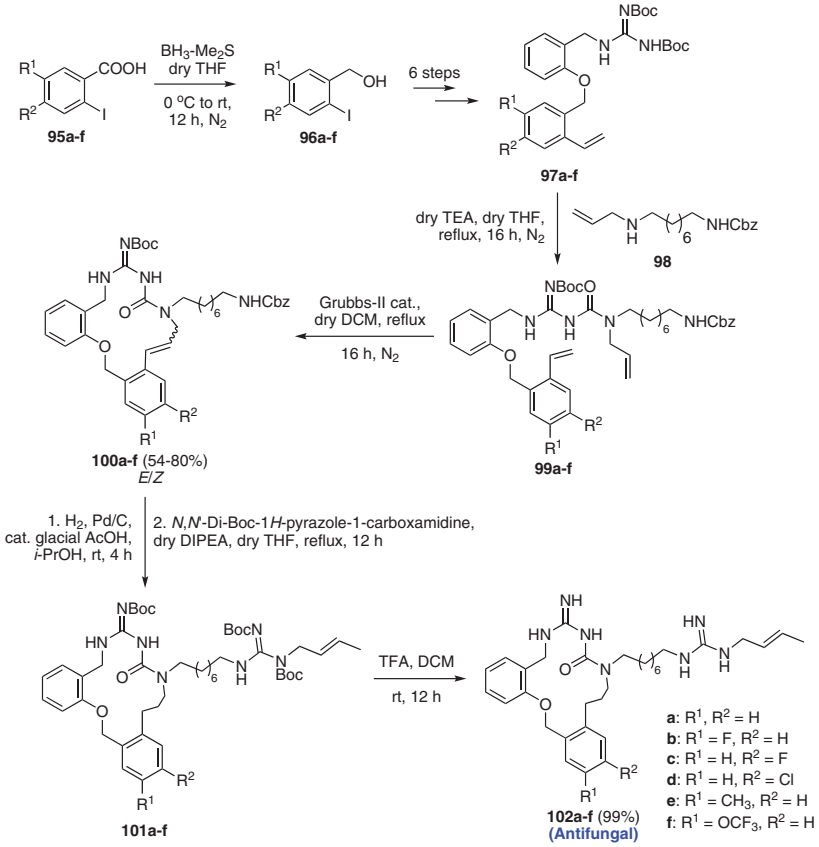


Scheme 10 Synthesis of macrocyclic amidinoureas: series 1



Scheme 11 Synthesis of macrocyclic amidinoureas: series 2

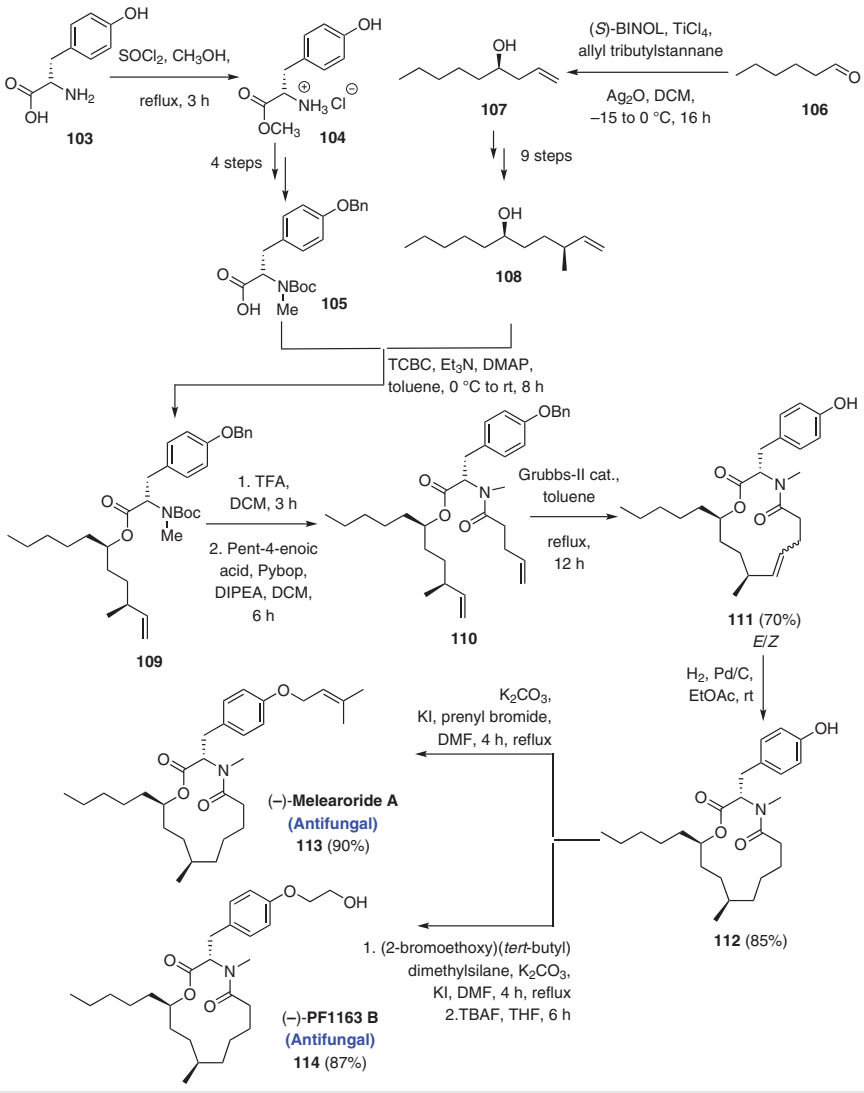
Balestri *et al.*, in 2022,[36] synthesized derivatives of macrocyclic amidinoureas **102a–f** which were confirmed to be active on a large panel of *Candida* spp. and *C. neoformans* through biological evaluation (Scheme 12). Their synthetic protocol began with the reduction of substituted 2-iodobenzoic acids **95a–f** into benzyl alcohols **96a–f.** Six consec-



Scheme 12 Synthesis of macrocyclic amidinoureas derivatives

utive steps led to the formation of diBoc-guanidino moiety **97a–f** which was made to react with **98** to afford Boc-protected amidinoureas **99a–f**. These substrates served as the RCM precursors and were exposed to macrocyclization in the presence of Grubbs-II catalyst in refluxing DCM for 16 h to obtain the macrocycles **100a–f** in good yields (54–80%). Subsequently, the benzyloxycarbonyl (Cbz) protecting group was removed and the olefin was reduced simultaneously followed by guanylation with *N*-crotyl-guanylating agent to furnish derivatives **101a–f**. Finally, the desired compounds **102a–f** were achieved through Boc cleavage and were found to exhibit antifungal activity overall stronger than hit compounds BM1 and fluconazole.

Yasam and Pabbaraja were intrigued by the structural and stereochemical features of melearoride A (**113**) and PF1163B (**114**) differing only in alkyl chain appendage. In 2022, they developed an efficient, stereoselective approach to the synthesis of these two macrolides (Scheme 13).[37] Interestingly, this was done through the development of a common macrocyclic skeleton **112** which was achieved from two building blocks **105** and **108**. The fragment **105** was obtained from commercially available L-tyrosine (**103**). On being refluxed in methanol with $SOCl_2$, **103** afforded the methyl ester **104**. Subjecting **104** to four subsequent reactions resulted in the production of amino acid **105**. The second fragment **108** was produced from commercially available *n*-hexanal (**106**) by subjecting it to Keck asymmetric allylation to afford homallylic alcohol **107**. Nine subsequent reactions upon **107** helped to furnish the alcohol **108**. Esterification of acid **105** with alcohol **108** under Yamaguchi conditions afforded the ester **109** which upon Boc deprotection with TFA followed by acylation with pent-4-enoic



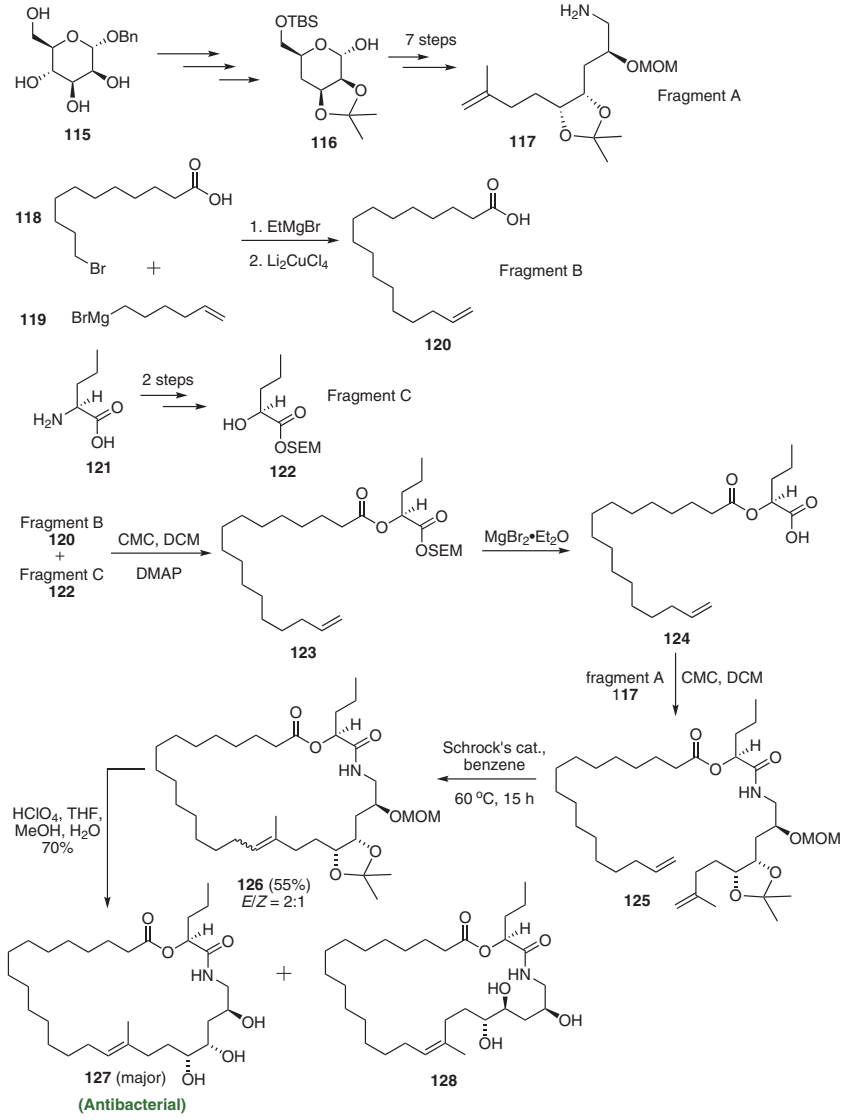
Scheme 13 Synthesis of (–)-melearoride A and (–)-PF1163B

acid using DIPEA/Pybop afforded the RCM precursor **110**. Subsequently, it was exposed to metathesis conditions in refluxing toluene with Grubbs-II catalyst for 12 h to produce macrocycle **111** in 70% yield as a mixture of (*E*)- and (*Z*)-diastereomers. Reduction and debenzylation *via* hydrogenation gave the desired macrocyclic core **112** in 85% yield. Ultimately, the target molecule melearoride A (**113**) was achieved in 90% yield through *O*-alkylation of phenol **112** by using prenyl bromide. The other target macrolide PF1163B (**114**) was obtained in 87% yield *via O*-alkylation of **112** with (2-bromoethoxy)(*tert*-butyl)dimethylsilane and subsequent TBS deprotection.

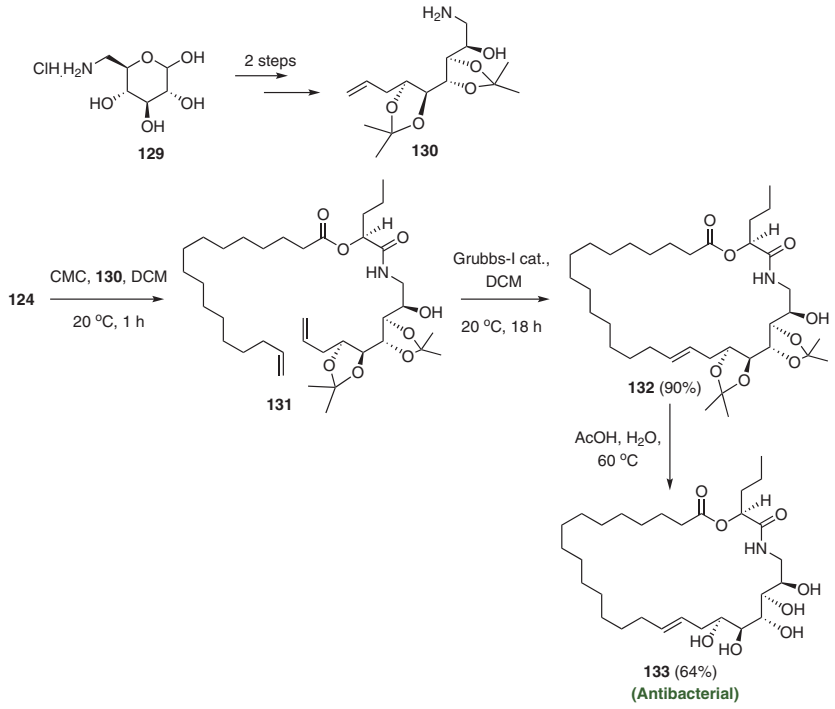
4 Antibacterial

Antibiotic resistance has been one of the biggest threats known to mankind as it affects global health, food security, and development in the world. With a growing list of infections in our everyday life, scientists are always looking out to cope with these ever-emerging problems by investing in new research which ensures the development of new antibacterial agents.

Myxovirescin A_1, an antibiotic produced by gliding bacteria of the *Myxococcus* species, had been very important amongst researchers due to its unique mode of action. Content, Dutton, and Roberts developed an efficient protocol in 2003 to synthesize the analogues of myxovirescin A_1 **127** and **133** (Schemes 14 and 15).[38] The target macrocyclic core



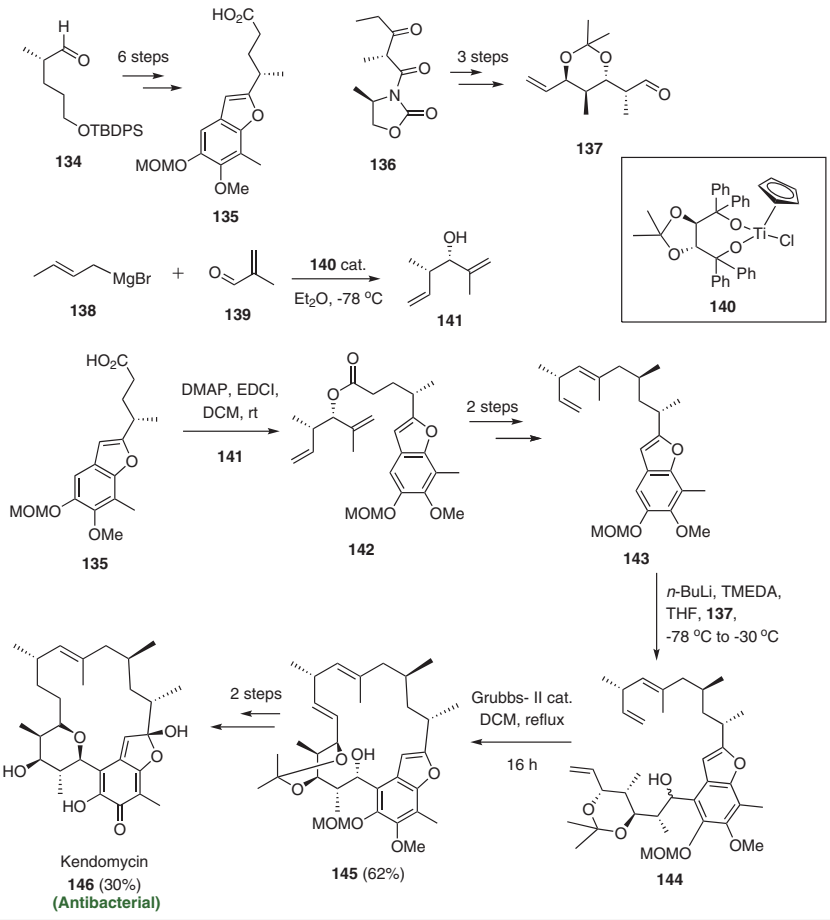
Scheme 14 Synthesis of myxoviresin A_1 analogues



Scheme 15 Synthesis of myxoviresin A_1 analogues

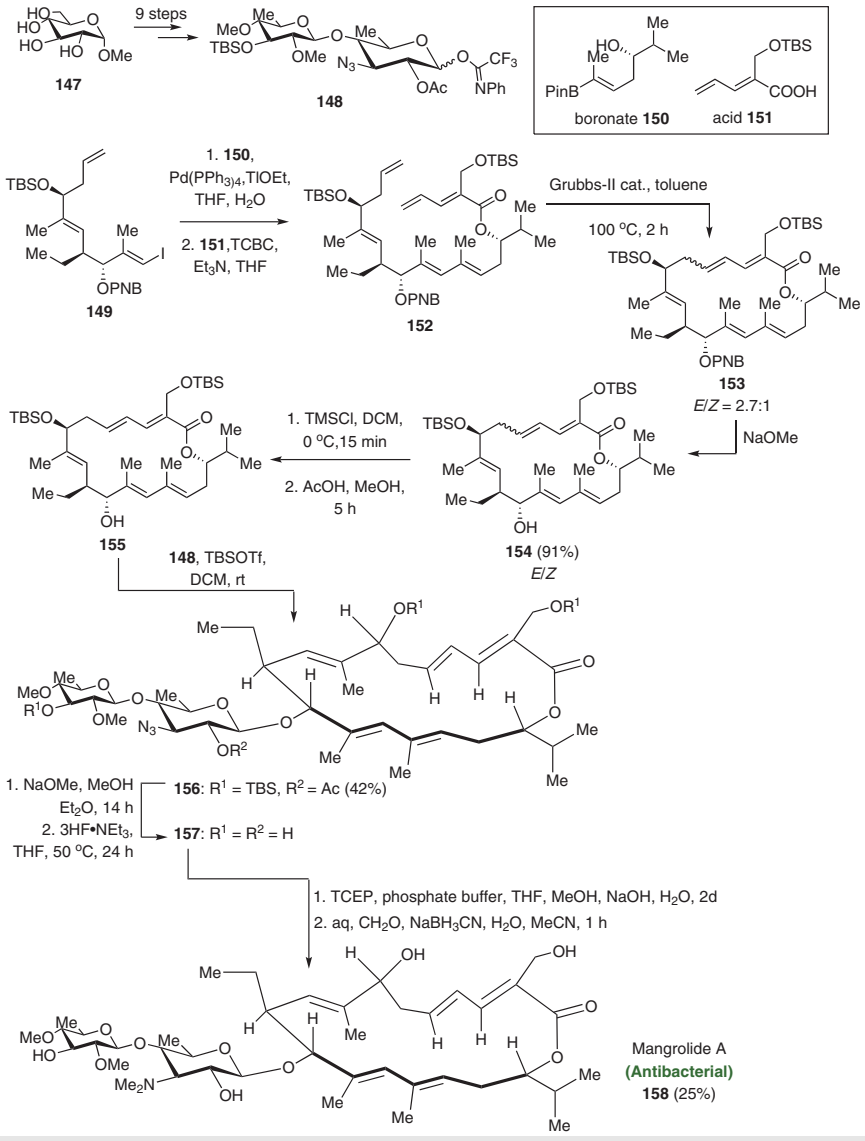
could be fragmented into three main parts *viz*. A, B, and C (Scheme 14). Preparation of fragment A **117** commenced by using the commercially available α-D-mannopyranoside **115** which was transformed into the hemiacetal **116**. Seven consecutive steps led to the formation of **117**. 11-bromoundecanoic acid (**118**) and the Grignard-derived from bromohexene **119** underwent a copper-catalyzed coupling reaction to afford the fragment B **120** (heptadec-16-enoic acid) whereas, L-norvaline (**121**) went through a double inversion of an intermediate nitronium species to produce 2-(*S*)-hydroxyvaleric acid and then it was converted into its SEM ester **122** (fragment C). The two fragments B and C were coupled together using the coupling agent 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide (CMC) to afford **123**. The SEM group was subsequently removed to form intermediate **124** which was coupled with fragment A using CMC to furnish the metathesis precursor **125**. Exposure of **125** to macrocyclization conditions by treatment with Mo-based Schrock's catalyst in benzene at 60 °C for 15 h afforded the macrocycle **126** as a 2:1 mixture of inseparable isomers in 55% yield. Finally, the acetal groups were deprotected to afford the target molecule (triol) **127**. After separating the two isomers, the desired *E* isomer was obtained in the majority. Another analogue of myxovirescin A_1 was produced by varying the triol unit of the molecule (Scheme 15). The protocol advanced with the use of commercially available amino-sugar **129** which afforded the bis-acetonide **130** in just two steps. This fragment was coupled with the previously prepared intermediate **124** by using CMC to synthesize the metathesis precursor **131**. After being subjected to Grubbs-I catalyzed macrocyclization conditions in DCM, the macrocycle **132** was obtained in 90% yield. Finally, deprotection with aqueous acetic acid gave the desired myxovirescin analogue **133** in 64% yield. Both the analogues **127** and **133** showed prominent antibacterial activity when assessed biologically.

Kendomycin [(−)-TAN 2162], isolated as an antagonist for endothelin receptor, was reported to exhibit antibacterial activities against drug-resistant *Staphylococcus aureus* strains. Back in 2009, Magauer *et al.* reported a synthetic protocol to produce kendomycin (**146**) with RCM being its key step (Scheme 16).[39] The RCM precursor **144** was constructed using the building blocks **135**, **137**, and **141**. The carboxylic acid fragment **135** was synthesized in six steps from the aldehyde **134** whereas the ketoimide **136** underwent a three-step reaction to yield the aldehyde **137**. The reaction of but-2-enyl-MgBr **138** with titanate **140** and methacrolein (**139**) afforded the alcohol **141**. Esterification of the acid **135** with alcohol **141** produced the ester **142** which underwent two subsequent reactions to furnish the intermediate **143**. Upon further treatment with *n*-BuLi, TMEDA, and **137**, the RCM precursor **144** was formed as a diastereomeric mixture. On exposing **144** to macrocyclization conditions using Grubbs-II catalyst in refluxing DCM, the *E*-olefin **145** was achieved in 62% yield. Finally, the desired antibiotic kendomycin (**146**) was furnished in 30% yield after conducting a few more reactions upon **145**.



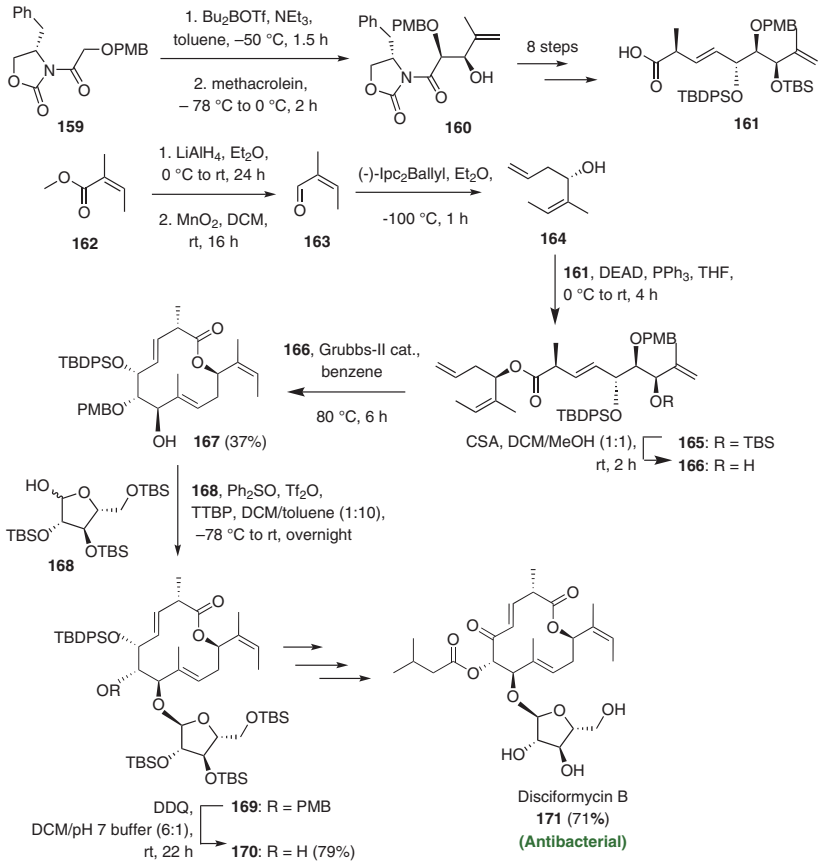
Scheme 16 Synthesis of kendomycin

Mangrolide A, isolated from the SNA18 strain of *Actinoalloteichus sp*, is a natural product described to be active against Gram-negative bacteria, including *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In 2018, Hattori *et al.* reported first total synthesis of mangrolide A (**158**) and conducted its biological evaluation against bacterial pathogens (Scheme 17).[40] The synthesis advanced with the preparation of azidodisaccharide donor **148** from methyl D-glucoside (**147**) in nine consecutive steps. Suzuki coupling between the synthesized iodide **149** and boronate **150** afforded an intermediate which was further transformed into the RCM precursor **152** *via* Yamaguchi esterification. Subsequently, **152** was subjected to macrocyclization with Grubbs-II catalyst in toluene at 100 °C for 2 h to afford the macrocycle **153**. Subsequent hydrolysis led to the production of **154** as a mixture of *E*,*E* and *E*,*Z* isomers. Sequential TMS protection, separation of isomers, and silyl removal yielded the *E*,*E* isomer **155**. The key fragment **148** was made to react with **155** to furnish the desired β-isomer **156** in 42% yield. The acetyl and TBS groups were removed to form **157** while reduction of the azide group with consecutive reductive amination afforded the target compound **158** in 25% yield. The synthetically produced mangrolide A (**158**) and its derivative **157** were tested against bacterial pathogens but, only minimal activity was observed.



Scheme 17 Synthesis of mangrolide A

Waser and Altmann developed an efficient strategy, in 2020,[5] to synthesize a potent antibiotic disciformycin B (**171**) (Scheme 18). Disciformycin B showed a significant antibacterial activity against the Gram-positive bacteria, methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA/VRSA) strains. Synthesis commenced as *N*-acyloxazolidinone **159** was transformed into the *syn*-aldol product **160** in two steps with eight subsequent reactions to produce the carboxylic acid **161**. Methyl angelate (**162**) yielded the aldehyde **163** by $LiAlH_4$ reduction and oxidation with activated MnO_2 which upon further treatment with (–)-Ipc_2Ballyl afforded **164**. The tetraene **166** was gradually produced *via* Mitsunobu esterification of acid **161** and alcohol **164** with **165** serving as an intermediate. Finally the crucial RCM gave the desired macrocycle **167** in 37% yield using Grubbs-II catalyst in benzene at 80 °C for 6 h. The macrolactone **167** was further subjected to dehydrative glycosylation with TBS-protected D-arabinofuranose **168**, followed by DDQ-mediated cleavage of PMB ether to produce the secondary alcohol **170**. Through several subsequent reactions, the synthesis of desired antibiotic disciformycin B (**171**) was achieved in 71% yield.

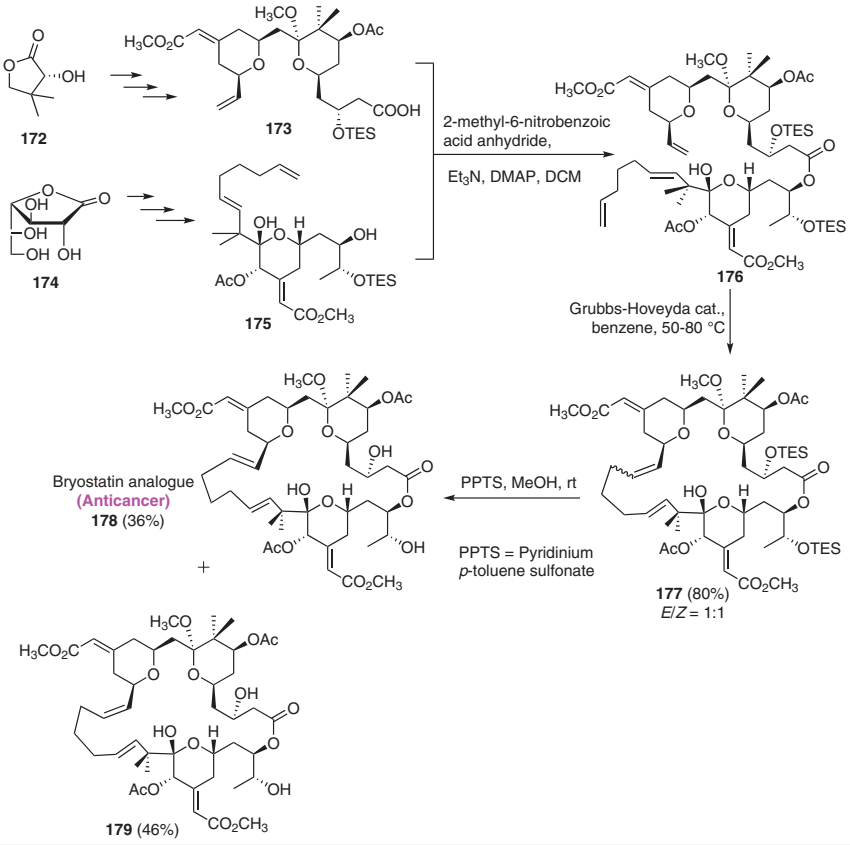


Scheme 18 Synthesis of disciformycin B

5 Anticancer

Cancer, one of the leading causes for global death, occurs when abnormal cells grow uncontrollably in almost any organ or tissue of the body. Lung, prostate, stomach, liver, thyroid, breast cancer etc. are most common among people. It has been realized that cancer mortality can be reduced through early detection and treatment; so, the scientific community is engaging in new ways to find appropriate and effective methods to prevent and cure this disease.

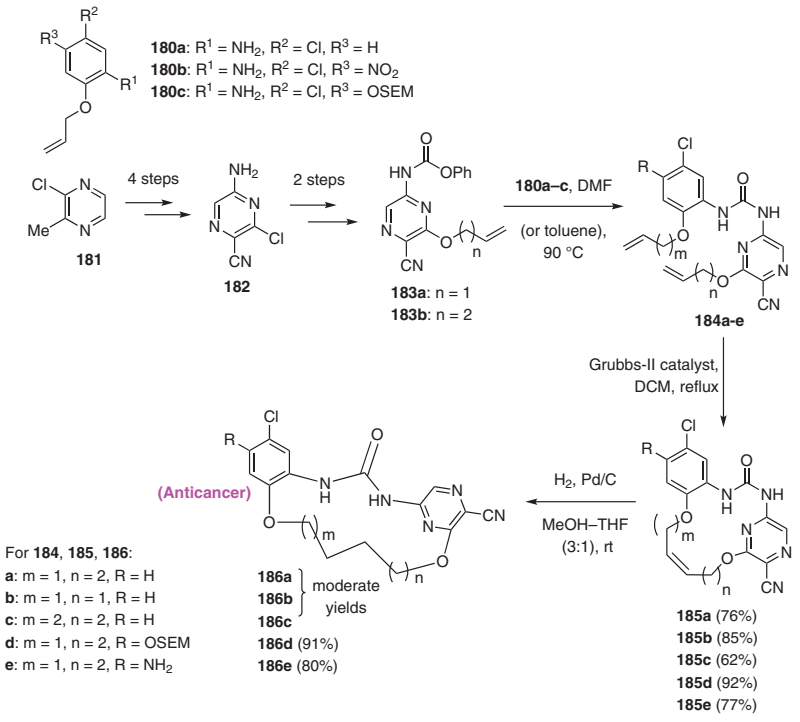
The natural product bryostatin displays a wide range of biological activities, notably anticancer activity *in vivo*. In 2007, Trost *et al.* reported the synthesis of a bryostatin analogue **178** (Scheme 19).[41] The total synthesis commenced by developing the synthons **173** and **175** separately. The fragment **173** was prepared from (*R*)-pantolactone (**172**) in several steps. Similarly, the other fragment **175** was obtained from D-glactonic acid 1,4-lactone **174** in many steps. The two synthons were then coupled in the presence of 2-methyl-6-nitrobenzoic acid anhydride to afford the metathesis precursor **176**. The crucial macrocyclization step was conducted next using Grubbs–Hoveyda catalyst in benzene at 50–80 °C to furnish the 31-membered lactone **177** as a 1:1 *E*/*Z* mixture in an excellent yield of 80%. Finally, deprotection of the macrocycle led to the formation of the target compound **178** (36%) and compound **179** (46%) which were separated and tested against several cancer cell lines. It was observed that the bryostatin analogue **178** inhibits the growth of NCI-ADRsa breast cancer cell line.



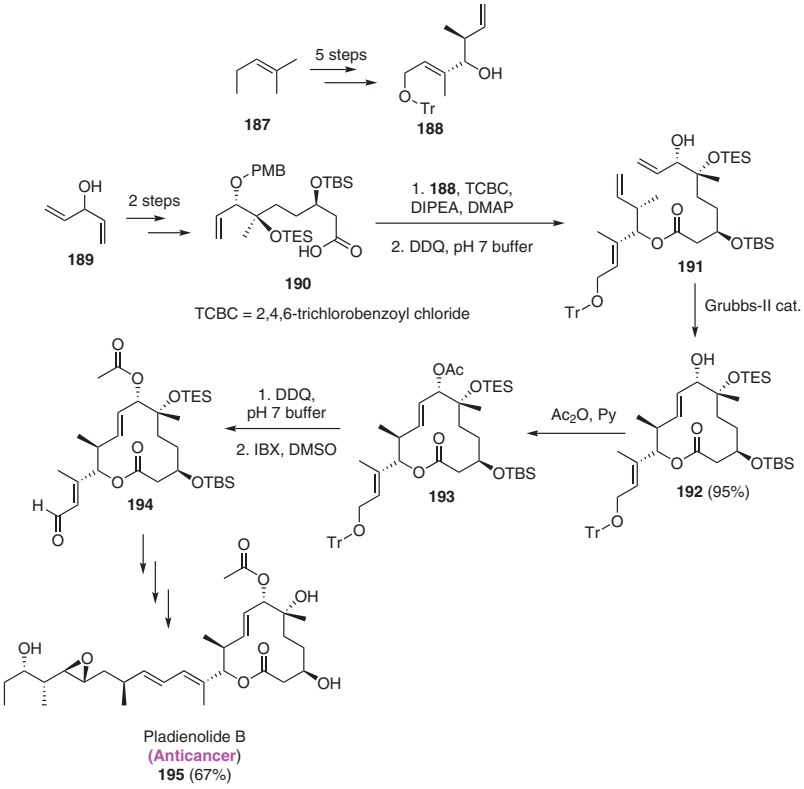
Scheme 19 Synthesis of bryostatin analogue

Small-molecule kinase inhibitors were found to exhibit great potential as novel therapeutics in the treatment of cancer. In 2007, Tao *et al.* noted that the unique binding mode and kinase inhibition profile caused the urea-based protein kinase inhibitors to serve as a major focus of medicinal chemists.[42] They showed interest in a class of diaryl ureas as checkpoint kinase 1 (Chk1) inhibitors which significantly potentiated the cytotoxicity of DNA-damaging agents in cancer cells and hence, designed macrocyclic ureas **186a–e** as a new class of kinase inhibitors (Scheme 20). In order to synthesize them, various intermediates **180a–c** were prepared. The synthesis of the advanced intermediate cyanopyrazine **182** commenced when methylpyrazine **181** was reacted upon in four consecutive steps following a patent literature procedure. **182** was gradually converted into **183a**,**b** in two steps. Subsequently, the metathesis precursors **184a–e** were achieved when **183a**,**b** were coupled with aniline intermediates **180a–c** in DMF or toluene at 90 °C. Finally, the urea products **184a–e** cyclized *via* olefin metathesis in the presence of Grubbs-II catalyst in refluxing DCM and afforded the desired macrocycles **185a–e** in moderate to excellent yield. The unsaturated macrocycles were next hydrogenated in the presence of palladium catalyst to produce the macrocycles **186a–e**.

Pladienolides A–G, a class of 12-membered macrocyclic compounds, isolated from a culture of an engineered strain of *Streptomyces platensis*, were found capable of inhibiting the proliferation of human cancer cells and binding to the SF3b subunit of the spliceosome while inhibiting the splicing of pre-mRNA to translatable mRNA. In 2012, Ghosh and Anderson showed their interest in developing a synthetic pathway for most active pladienolide B (**195**) (Scheme 21).[43] The plan commenced when the synthesis of alcohol **188** was carried out in five steps from prenyl alcohol **187**. Subsequently, commercially available divinyl carbinol (**189**) was made to undergo a series of consecutive reactions to produce the acid **190**. With access to two main intermediates for the construction of the macrocyclic core, esterification of acid **190** with alcohol **188** was carried out followed by DDQ oxidative removal of the PMB ether to provide the RCM precursor **191**. The crucial metathesis reaction of **191** with Grubbs-II catalyst afforded the cyclized compound **192** in 95% yield. After treating the product with Ac_2O in pyridine, lactone **193** was obtained which on being further exposed to DDQ for 24 h, removed the trityl ether. Oxidation of the resulting alcohol with IBX furnished the macrocycle **194** in 75% yield. Finally, the 12-membered macrocycle pla-



Scheme 20 Synthesis of macrocyclic urea kinase inhibitors

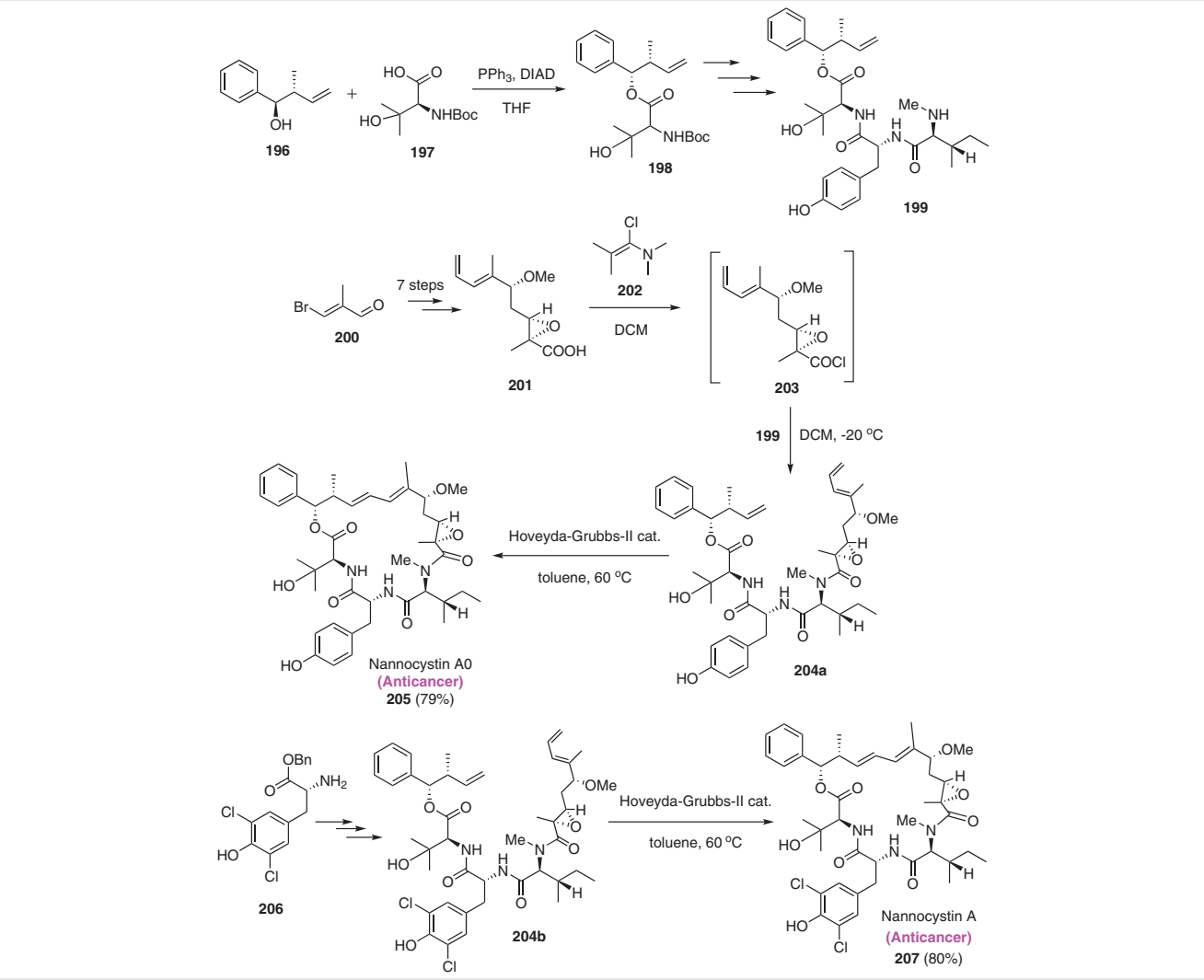


Scheme 21 Synthesis of pladienolide B

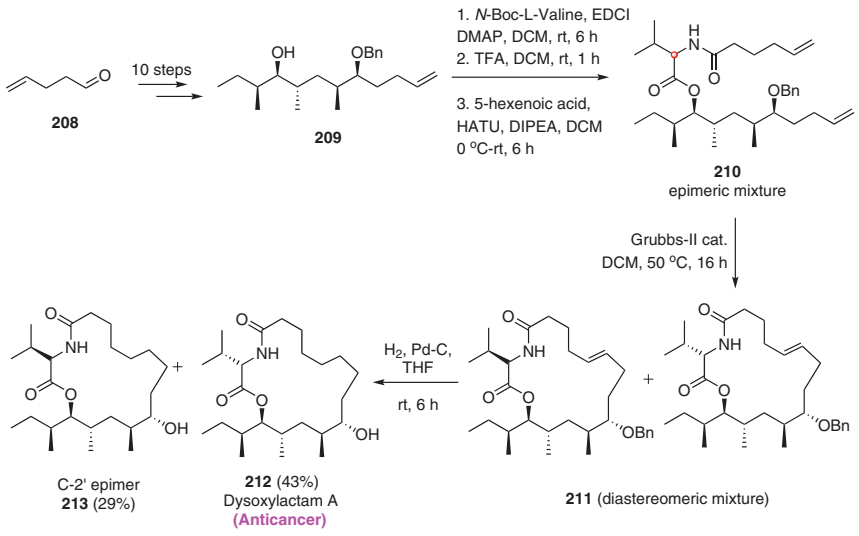
dienolide B (**195**) was assembled in 67% yield when several consecutive reactions were conducted upon the macrocycle **194**.

Huang and Wang, in 2016,[44] reported the first asymmetric total syntheses of natural products nannocystin A0 (**205**) and nannocystin A (**207**) bearing anticancer activity (Scheme 22). The synthetic route for production of nannocystin A0 proceeded by synthesizing the fragment **199**. Compounds **196** and **197** were made to undergo Mitsunobu reaction to afford **198** upon which several reactions were conducted to prepare **199**. Simultaneously, the acid **201** was prepared from (*E*)-3-bromomethacrolein (**200**) in seven consecutive steps followed by the preparation of acyl chloride **203** by the action of Ghosez reagent **202** upon the fragment **201**. Subsequently, a solution of **203** dissolved in DCM was added dropwise to a solution of fragment **199** in DCM at –20 °C to afford the desired RCM precursor **204a**. Finally, the target natural product **205** was achieved in 79% yield by exposing **204a** to ring-closing metathesis conditions using Hoveyda–Grubbs-II catalyst in toluene at 60 °C. A similar synthetic sequence was applied for the synthesis nannocystin A (**207**) using 3,5-dichloro-D-tyrosine benzyl ester (**206**). The RCM precursor **204b** in this case furnished the target **207** in 80% yield.

A macrolactam named dysoxylactam A, isolated from the bark of *Dysoxylum hongkongense*, was found to hold the ability to reverse multidrug resistance in cancer cells and inhibit the function of P-glycoprotein, a key mediator in multidrug resistance.[45] In 2020, Reddy and Yu established a total synthesis of dysoxylactam A (**212**) using RCM as its key step (Scheme 23).[45] The process advanced with the preparation of the polypropionate fragment **209** being achieved in a stereocontrolled manner through 10 sequential reactions from commercially available pent-4-enal



Scheme 22 Synthesis of nannocystin A0 and A

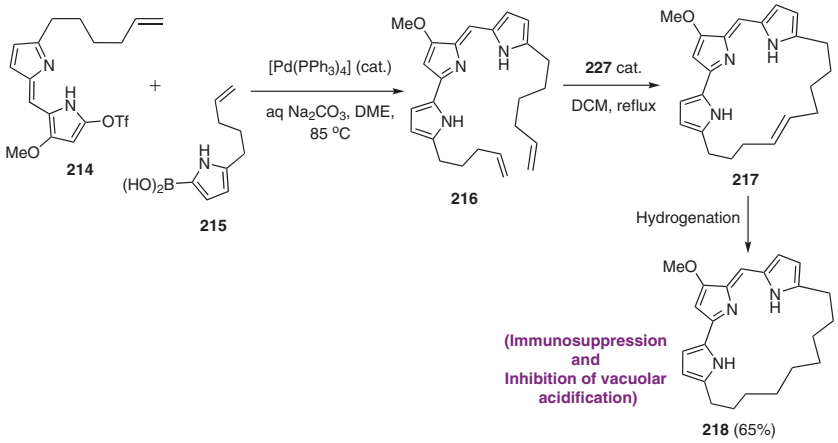


Scheme 23 Synthesis of dysoxylactam A

(**208**). This was followed by the esterification of **209** with *N*-Boc-L-valine in the presence of EDCI and an excess amount of DMAP in DCM to afford an inseparable epimeric mixture of the esters formed at the valine residue. Subsequently, the Boc-protected esters were converted into free amines as their TFA salts and made to react with hex-5-enoic acid to give the RCM precursor **210** (epimeric mixture). Ring-closing metathesis with Grubbs-II catalyst in refluxing DCM was conducted next to afford macrocycles **211** as an inseparable diastereomeric mixture. Finally, **211** were hydrogenated with Pd/C under 1 atm H_2 to furnish the desired macrocycle dysoxylactam A (**212**) in 43% yield and its C-2′ epimer **213** in 29% yield.

6 Miscellaneous

We would also like to throw light upon certain areas of synthetic organic chemistry which helped develop bioactive macrocycles for treatment of various other diseases and medical issues. The drugs required for the treatment of inflammation, sleeping sickness, obesity, leukemia, and many more have always been a topic of concern for medicinal chemists. In 2001, the Fürstner group reported the total synthesis of naturally occurring macrocyclic nonylprodigiosin (**218**) involving RCM methodology (Scheme 24).[46] The RCM precursor **216** was prepared by Suzuki reaction between heteroaryl triflate **214** and boronic acid **215**. The subsequent metathesis reaction in refluxing DCM with catalyst **227** (see Figure 1) afforded **217** which furnished the target compound **218** *via* hydrogenation in 65% yield. By re-



Scheme 24 Synthesis of macrocyclic nonylprodigiosin

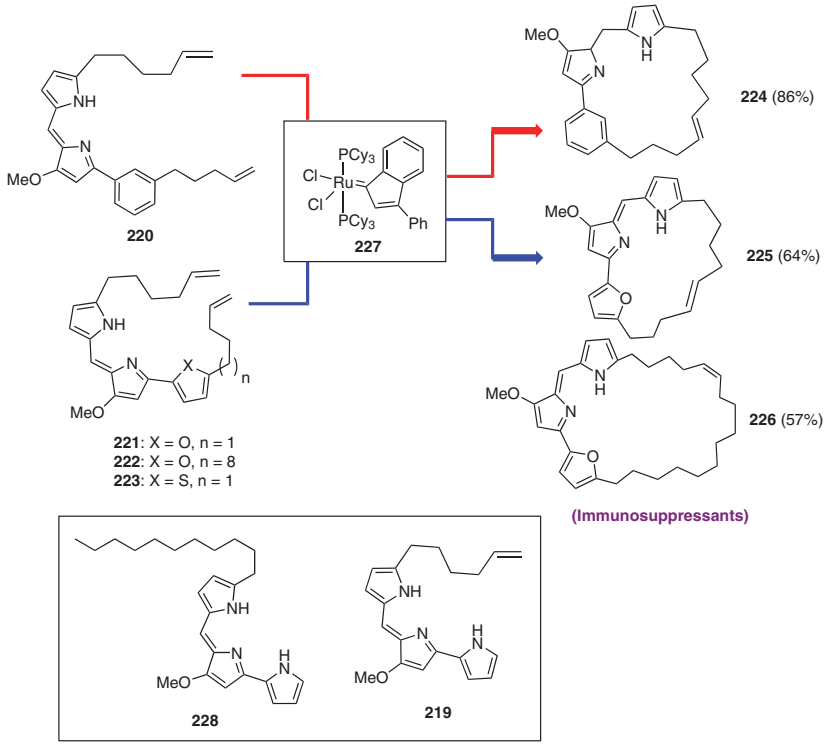
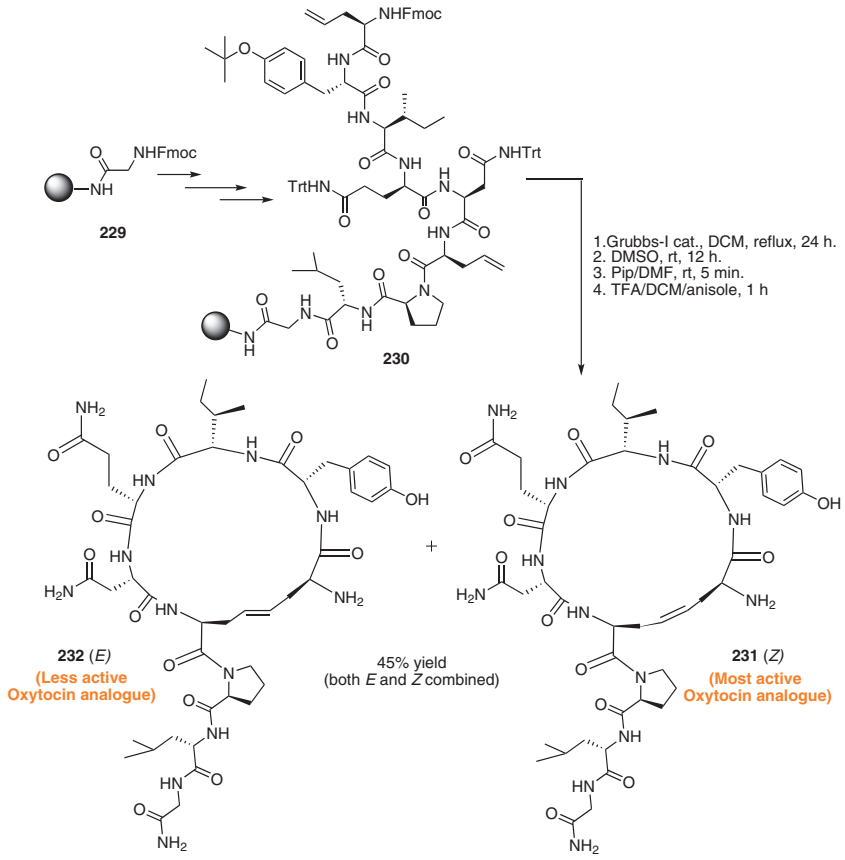


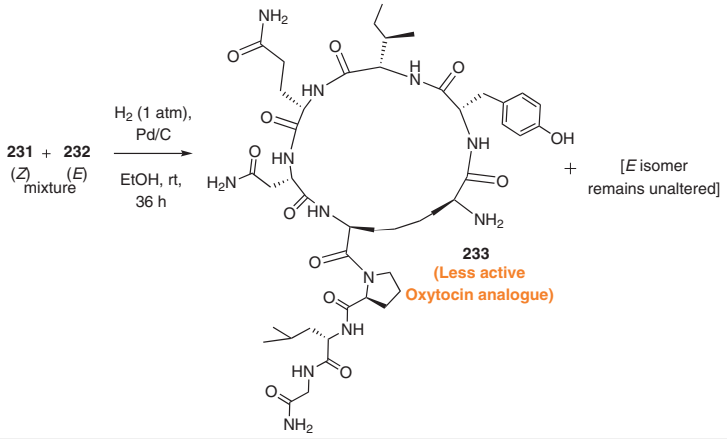
Figure 1 Some macrocycles and their precursors

placing the synthon **215** with different functionalized boronic acid derivatives, several other RCM precursors **219**–**223** were prepared (Figure 1). The hydrochloride salts of precursors **220**–**222** were subjected to RCM to obtain the corresponding nonylprodigiosin analogues **224**–**226** in excellent yields (Figure 1). The thiophene derivative **223** resisted ring closure while **219** afforded a dimer under RCM conditions. Comparison of the newly synthesized prodigiosin derivatives **218** and its analogues with undecylprodigiosin **228** was done in two different experiments: (i) proliferation of murine spleen cells induced by lipopolysaccharides (LPS) and concanavalin A (Con A), and (ii) vacuolar acidification of baby hamster kidney (BHK) cells. These macrocycles were found to suppress the Con A induced T-cell proliferation in a manner stronger than the LPS-induced B-cell proliferation although derivative **218** exhibited lower activity than its parent compound **228**. Macrocycle **218** prevented vacuolar acidification but **224**–**226** either exhibited trace effects or had no effect at all. It was concluded that three pyrrole units were required for the exhibition of inhibitory activity of prodigiosins on vacuolar acidification.

Oxytocin, a mammalian nonapeptide hormone, was modified by the Vederas group[47] in 2003 to create its fully saturated dicarba analogue **233**. They synthesized **231** (*Z*) and **232** (*E*) olefinic analogues of oxytocin through RCM (Schemes 25 and 26). The linear peptide **230** was first synthesized by replacing cysteine with allylglycine on Rink amide NovaGel resin (Scheme 25). The resin-bound linear peptide **230** was next subjected to macrocyclization conditions involving Grubbs-I catalyst in refluxing DCM for 24 h to afford a mixture of olefinic products. DMSO was consecutively added to the resin-bound peptide, the Fmoc group was removed, and side chain deprotection synthesized a 4:1 mixture of **231** (*Z*) and **232** (*E*) isomers in 45% yield. Hydrogenation of the mixture led to the reduction of the olefinic double bond in **231** without altering the nature of **232** and ultimately, the saturated derivative **233** was obtained (Scheme 26). All three analogues (**231**–**233**) were biologically tested on rat uterus strips and it was concluded that the *Z* isomer **231** was the most active analogue with an EC50 value 14-fold less than that of oxytocin. The *E* isomer **232** and the saturated analogue **233** were found to be less active than the *Z* isomer.

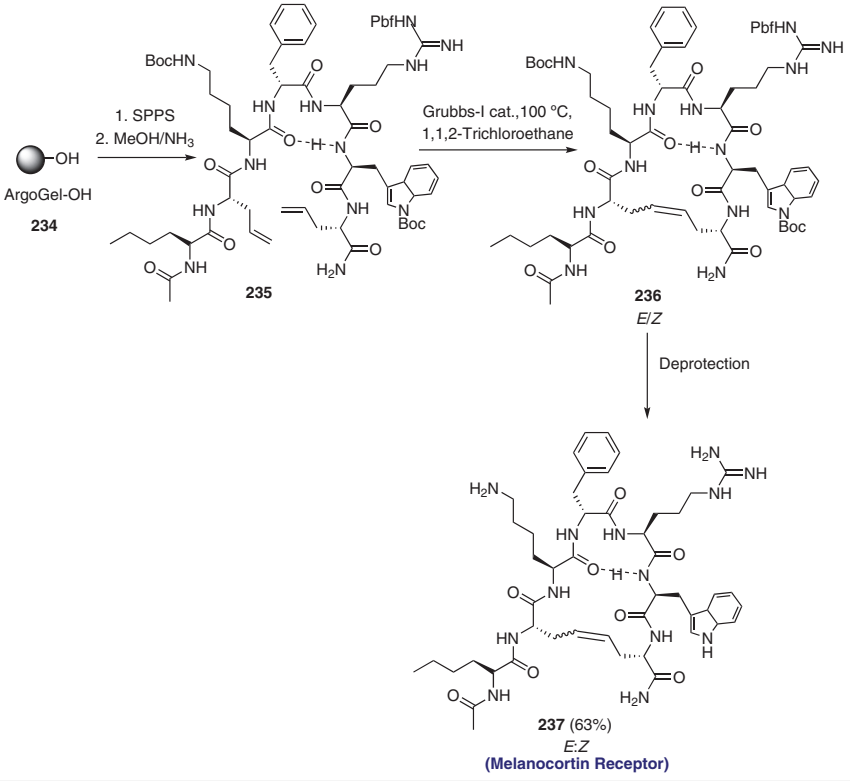


Scheme 25 Synthesis of oxytocin analogues



Scheme 26 Synthesis of a saturated oxytocin analogue

The melanocortin receptor (MC4-R) regulates the body weight in mammals and has been found to be associated with obesity. On finding it as a target for drug design, in 2005 the Liskamp group synthesized a novel potent cyclic peptide MC4-ligand **237** *via* metathesis (Scheme 27).[48] By using an automated peptide synthesizer, peptide **235** was synthesized on ArgoGelTM-OH resin **234**. Next, it was cleaved through aminolysis of the ester linkage using a saturated solution of ammonia in methanol. The linear peptide **235** was afforded in a high yield and subjected to macrocyclization conditions using Grubbs-I catalyst at 100 °C in 1,1,2-trichloroethane. After an hour, the second portion of catalyst was added on cooling the reaction mixture 40 °C. Finally, through deprotection and purification, the production of cyclized peptide **237** resulted in 63% yield as a mixture of *E* and *Z* isomers.

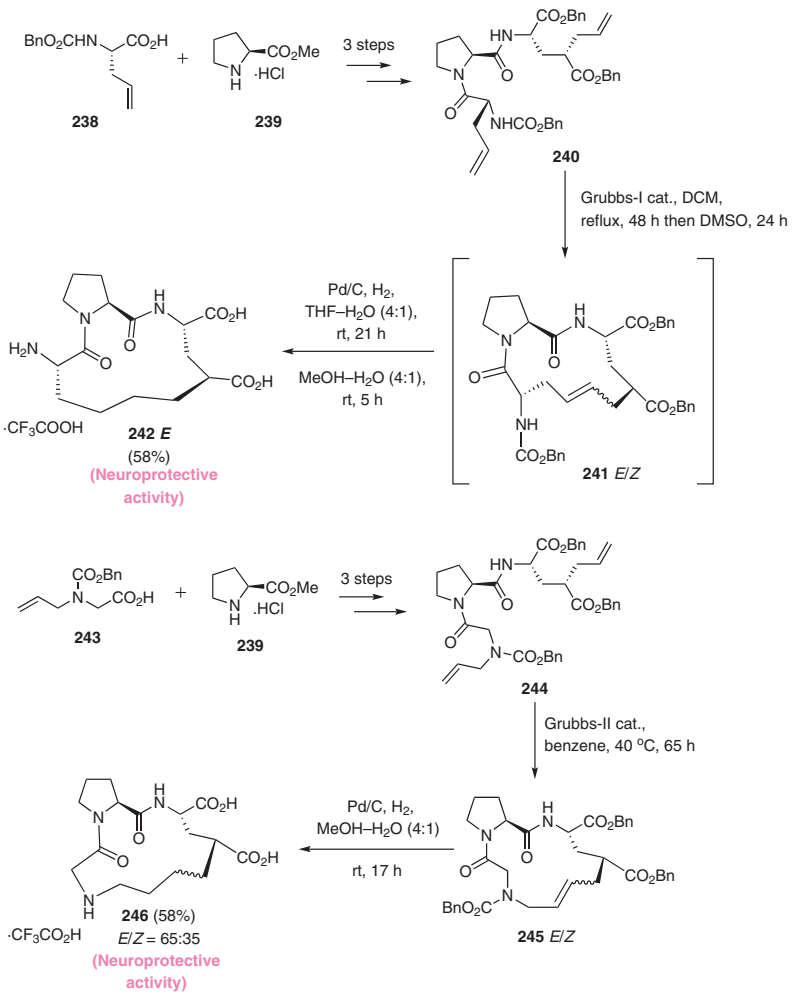


Scheme 27 Synthesis of melanocortin (MC-4) ligand

Analogues of the neuroprotective agent glycyl-L-prolyl-L-glutamic acid (GPE) were synthesized by Harris and Brimble in 2006 (Scheme 28).[49] In order to synthesize the macrocycle **242**, proline methyl ester **238** and Cbz-(*S*)-allylglycine **239** were chosen as the starting materials. Subsequent reactions produced the RCM precursor **240** which underwent macrocyclization using Grubbs-I catalyst in refluxing DCM to afford an isomeric mixture of **241**. Reduction of **241** followed by deprotection of the benzyloxycarbamate and the benzyl esters furnished the desired macrocycle **242** in 58% yield (*E*). Similarly, the macrocycle **246** was produced using ester **243** and **239** as the starting materials. Through consequent reactions in three steps, the precursor **244** was produced and made to undergo metathesis using Grubbs-II catalyst in benzene at 40 °C to obtain the olefinic macrocycle **245** (*E*/Z mixture). Hydrogenation and deprotection of **245** followed next to produce the target compound **246** in 58% yield as a 65:35 mixture of *E*/*Z* isomers.

In 2010, Sliwa *et al.*[50] synthesized 1,3-bridged azetidin-2-ones by RCM reaction from 1,3-bis-ω-alkenoyl-3(*S*)-aminoazetidin-2-one precursors (Scheme 29). Through computational study the target molecules were found to be potent inhibitors of R39 D,D-carboxypeptidase, a bacterial model enzyme for penicillin binding proteins (PBPs). The synthetic route advanced with the production of compound **249** from Boc-L-serine **247** and **250** from Boc-Me-L-serine **248**. The RCM precursor *N*-Boc bis-acylated monocyclic azetidinones **251a–c** were next furnished in one step by treating **249** with alkenoyl chlorides in the presence of lithium hexamethyldisilazanide. Another set of precursors **252a–c** and **253a–c** were prepared by subsequent reactions of **249** and **250**.

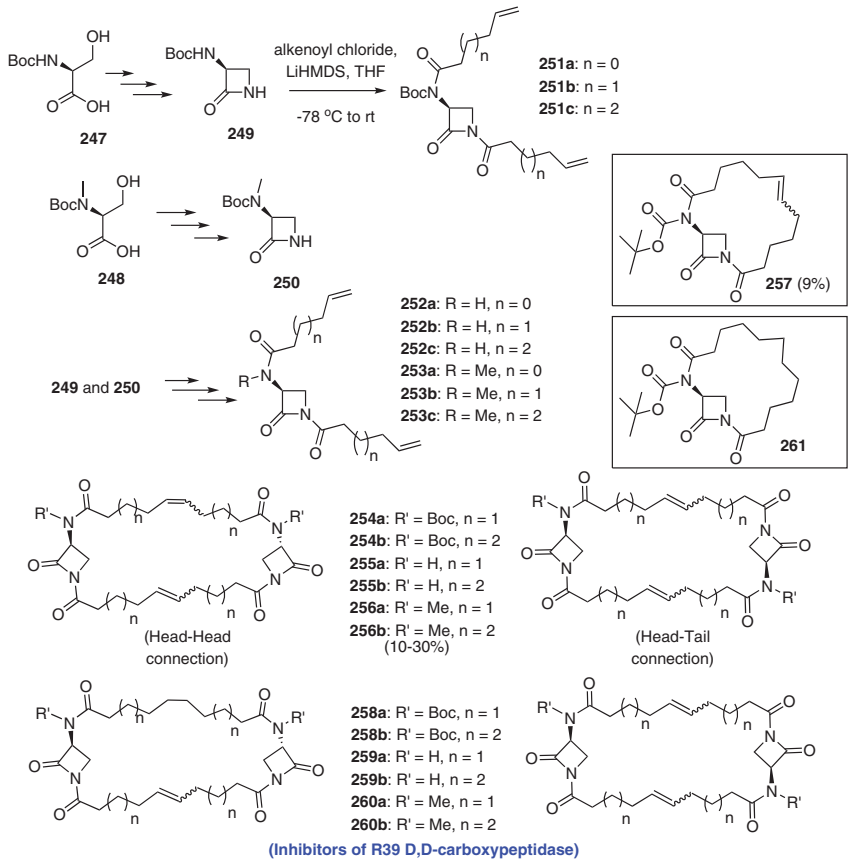
When the precursors with n = 1(**251b**, **252b**, and **253b**) were exposed to macrocyclization conditions with Grubbs-II catalyst in DCM at 40 °C, the products **254a**, **255a**, and **256a**, respectively, were obtained. Similarly, precursors with n = 2 (**251c**, **252c**, and **253c**) afforded the macrocycles **254b**, **255b**, and **256b**, respectively, in (10–30%) yields. It was noted that all the isolated compounds formed cyclic dimers. The RCM precursors with n = 0 did not undergo cyclization and only one monomer **257** was obtained in a very poor yield (9%). The monomer **257** and dimers **254**–**256a**,**b** were subjected to catalytic hydrogenation and the olefins were reduced to produce the saturated macrocycle **261** and **258**–**260a**,**b**, respectively. The tests done for biological activity showed promising results using the R39 serine-enzyme. The bicyclic β-lactams **257** and **261** were confirmed to be good inhibitors of D,D-peptidase. The macrocycles **254c**, **255b**,**c**, and **259b**,**c** also exhibited remarkable inhibitory effect.



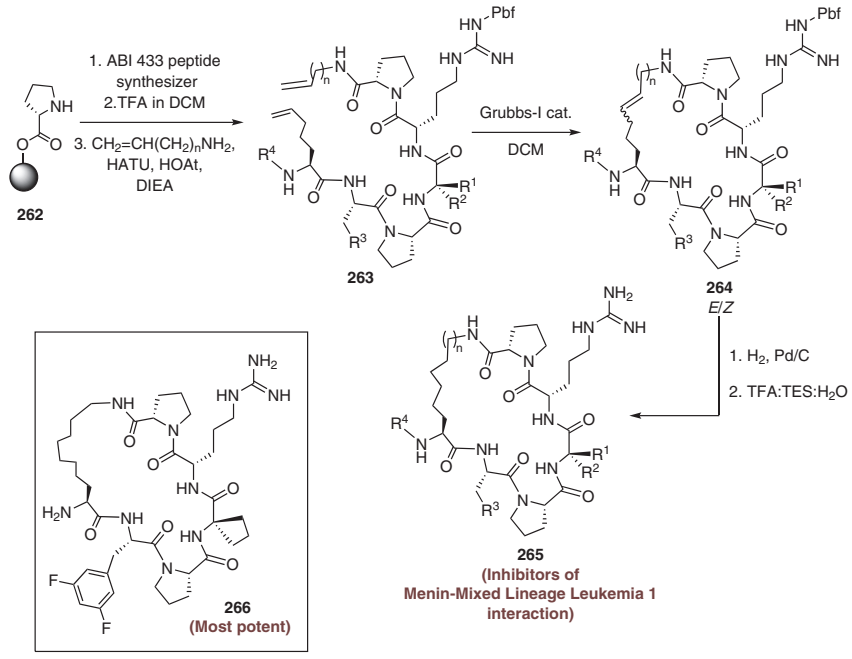
Scheme 28 Synthesis of neuroprotective agent GPE analogues

In 2013, Zhou *et al.* targeted the menin–mixed lineage leukemia 1 (MLL1) protein–protein interaction as it blocked MLL1-mediated leukemogenesis.[15] They designed a class of macrocyclic peptidomimetic inhibitors of the menin–MLL1 interaction by using ABI 433 peptide synthesizer with proline preloaded 2-chlorotrityl chloride resin (Scheme 30). Cleavage of the peptides by treatment with TFA in DCM followed by coupling with corresponding amines (CH_2=CH-$(CH_2)_nNH_2$) led to the formation of RCM precursors **263**. Macrocyclization was conducted next by using Grubbs-I catalyst in DCM solvent to afford **264**. The newly formed double bond was gradually reduced through catalytic hydrogenation and subsequent deprotection afforded the desired macrocyclic compounds **265**. Within this generated class of macrocycles, compound **266** was found to be most potent macrocyclic peptidomimetic.

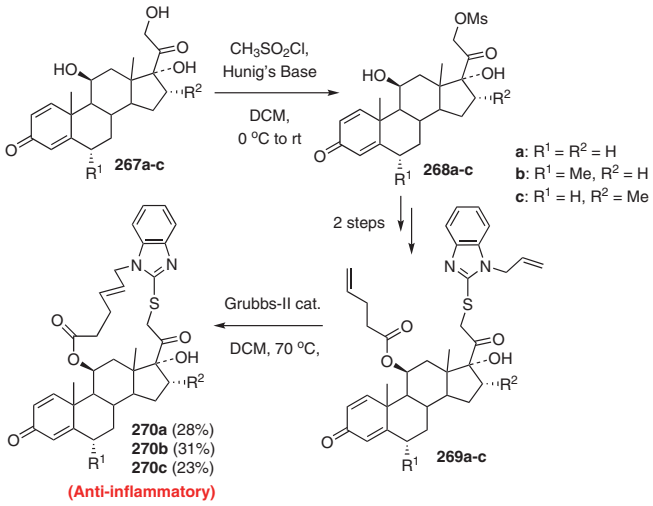
In 2015, Biju *et al.* initiated the synthesis of novel corticosteroids from widely used anti-inflammatory steroid prednisolone (**267a**) (Schemes 31 and 32).[51] Following up the structural design of a reported compound, two macrocycles 16-membered **270a** and 13-membered **275** were furnished from commercially available prednisolone (**267a**). Another set of macrocycles **270b**,**c** were prepared from 6-methylprednisolone (**267b**), and 16-methylprednisolone (**267c**). The synthetic route proceeded by conversion of prednisolones into their corresponding mesylates **268a–c** (Scheme 31). Two subsequent steps resulted in the production of RCM precursors **269a–c** which were gradually subjected to metathesis reaction in the presence of Grubbs-II catalyst in refluxing DCM to afford the macrocycles **270a–c** as *E* isomers in 28%, 31%, and 23% yields, respectively. Mesylation of prednisolone **271** followed by displacement with *N*-allyl-2-mercapto-benzimidazole produced **272** which upon treatment with pent-4-enoyl chloride and DMAP in DCM developed a metathesis precursor **273** (Scheme 32). On subjecting **273** to RCM conditions, the corresponding macrocycle **274** was formed in 66% yield as the *E* isomer. Further deprotection led to the formation of the



Scheme 29 Synthesis of 1,3-bridged azetidin-2-ones

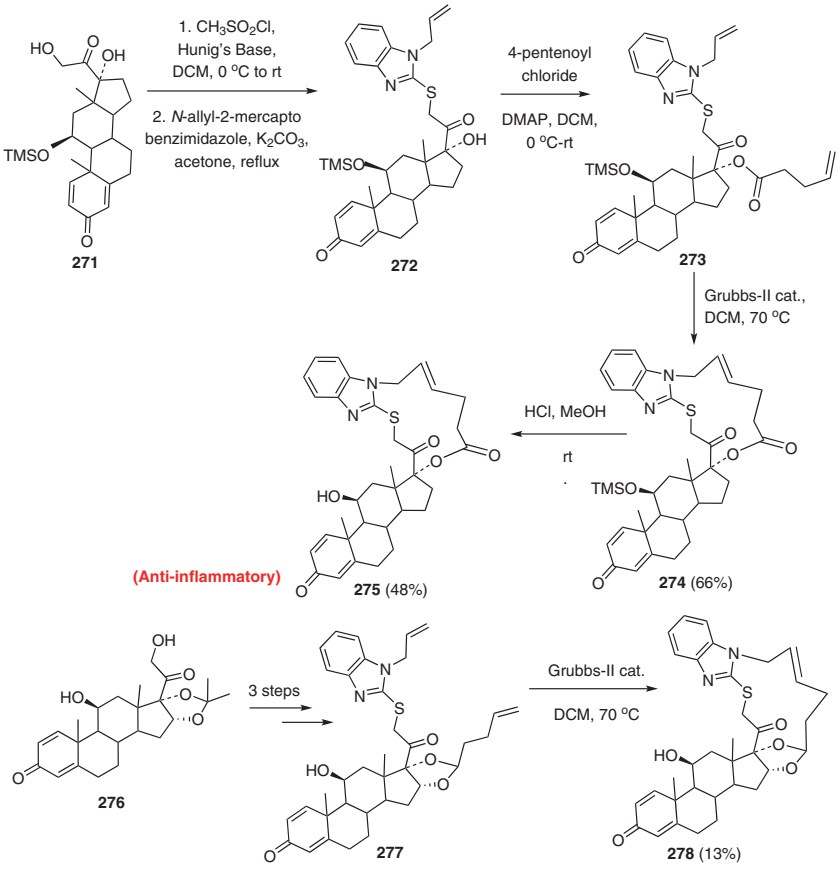


Scheme 30 Synthesis of inhibitors of the menin-mixed lineage leukemia 1 interaction



Scheme 31 Synthesis of glucocorticoids

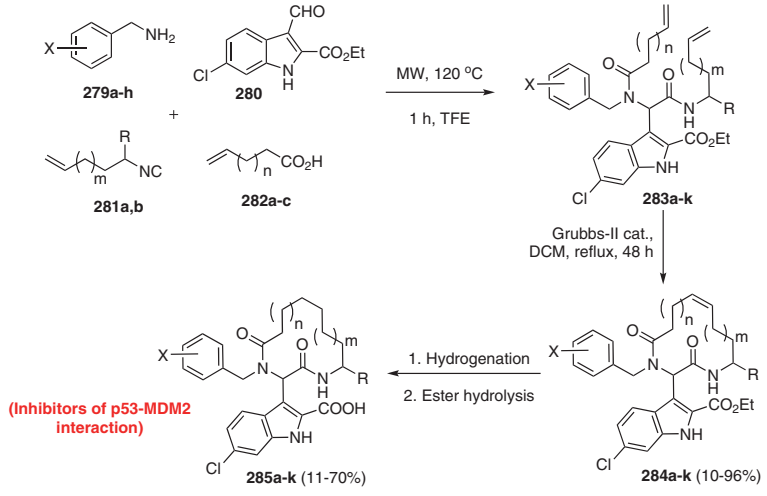
desired 13-membered macrocyclic compound **275** in 48% yield. Commercially available **276** was converted into the olefinic precursor **277** and upon macrocyclization through RCM, **278** was achieved as a 3:1 mixture of isomers in 13% yield.



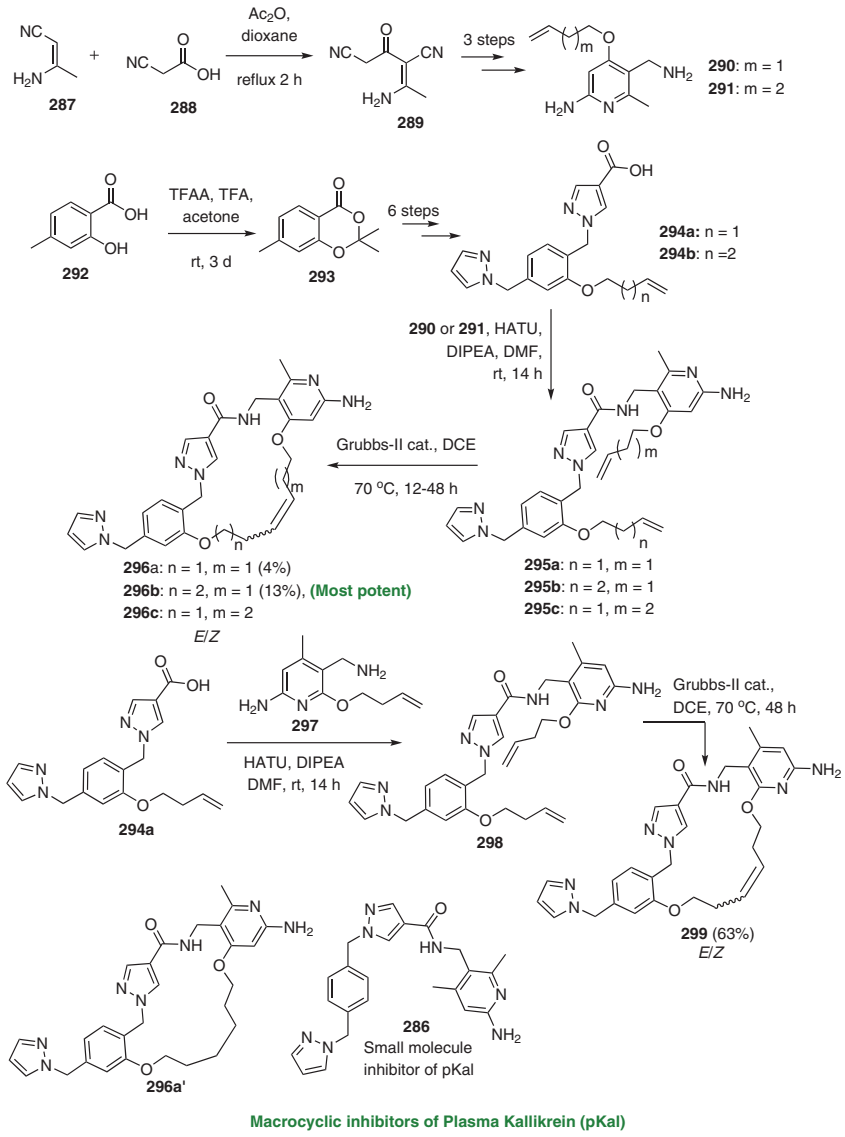
Scheme 32 Synthesis of glucocorticoids

In 2017, Estrada-Ortiz *et al.* synthesized a library of novel macrocycles **285a–k** of various ring sizes (12, 13, 18, 19, and 24) using RCM and classical Ugi four-component (U-4CR) reactions as key steps (Scheme 33).[14] These macrocycles were found to target the hydrophobic region around Tyr67, Gln72, His73, Val93, and Lys94 and inhibit the p53–MDM2 interaction. The Ugi-adduct was synthesized through four building blocks benzylamines **279a–h**, 6-chloro-indole-3-carbaldehyde **280**, aliphatic carboxylic acids **282a–c** and the isocyanides **281a**,**b**. The benzylamines **279a–h** were either commercially available or synthesized through Williamson ether synthesis. Vilsmeier–Haack formylation reaction afforded the aldehyde **280** using a 6-chloro-indole derivative. The isocyanides **281a**,**b** were synthesized from their corresponding formamides while the carboxylic acids **282a–c** were obtained commercially. On irradiation at 120 °C for 1 h in a microwave oven, the equimolar mixture of the four components furnished the RCM precursors **283a–k**. Finally, the metathesis reaction was conducted in refluxing DCM using Grubbs-II catalyst to afford compounds **284a–k** in 10–96% yield as a mixture of *E*/*Z* isomers. The cyclized products were next hydrogenated on Pd/C to isolate the compounds and finally ester hydrolysis was conducted to obtain compounds **285a–k** in 11–70% yield. The inhibitory affinities (K_i) of the macrocycles against MDM2 were determined and most of them were found to be active towards MDM2. The affinity was noticed to improve as the ring size increased from 12 to 18 whereas one large 24-membered macrocycle showed decreased activity.

In 2017, Li *et al.* designed a series of macrocyclic analogues following up the cocrystal structure of small molecule plasma kallikrein (pKal) inhibitor **286** (Scheme 34).[13] The synthesis advanced with the initial condensation of 3-aminocrotononitrile (**287**) and 2-cyanoacetic acid (**288**) with acetic anhydride to afford bis-nitrile **289** which underwent three consecutive reactions to produce the intermediates 4-alkenyloxy-2-aminopyridines **290** and **291**. Next, 2-hydroxy-4-methylbenzoic acid (**292**) was made to react with acetone under acidic conditions to furnish the acetonide **293**. Subsequently, the acids **294a**,**b** were formed in two steps and coupled with either amine **290** or **291** to give the RCM precursors **295a–c**. On subjecting them to RCM reaction with Grubbs-II catalyst in DCE at 70 °C, the macrocycles **296a–c** were synthesized as *E*/*Z* isomers. The isomers of **296a** were found to exhibit weak inhibition of pKal when compared to the small molecule **286**. Hydrogenation of **296a** produced its corresponding saturated macrocycle **296a'** which was found to be even less potent than **296a** *E* and *Z*. The macrocycle **296b**, with a 9-atom linker, was



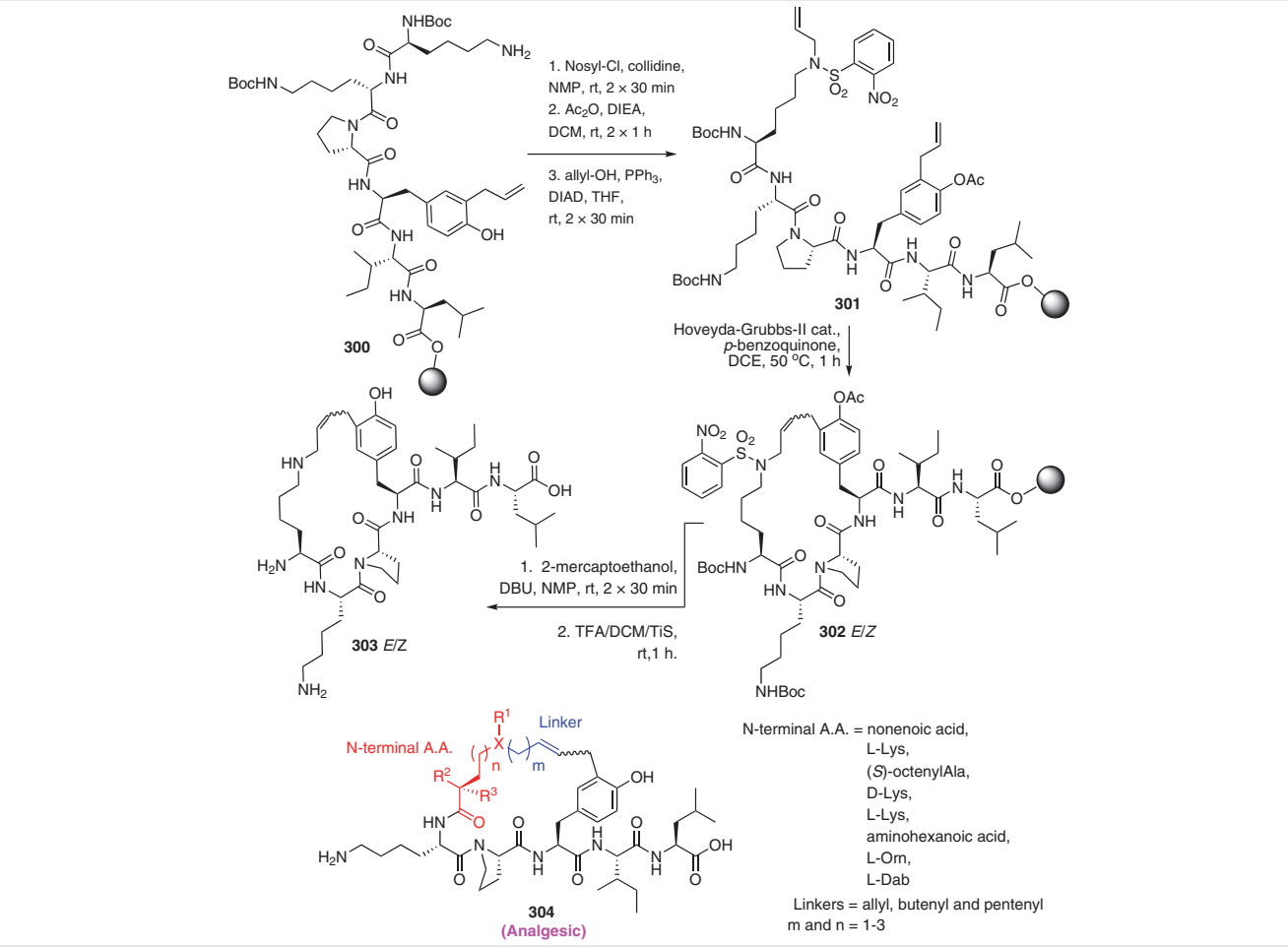
Scheme 33 Synthesis of macrocyclic inhibitors of the p53-MDM2 interaction



Scheme 34 Synthesis of macrocyclic inhibitors of plasma kallikrein

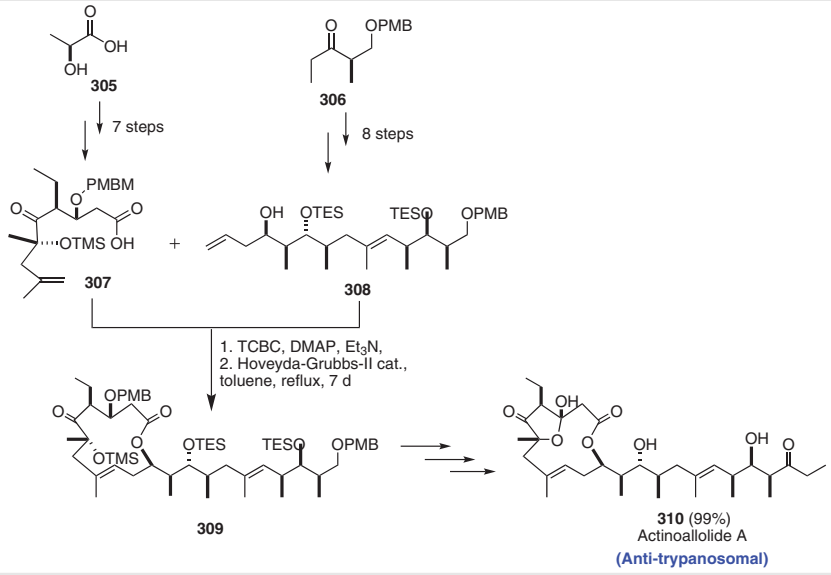
found to be 250-fold more potent than **296a** *E* and *Z* whereas the macrocycle **299** formed *via* RCM by using **297** was found to be 40-fold less potent than **296a** *E* and *Z* isomers.

Neurotensin (NT) is a tridecapeptide known to induce a strong analgesic action when administered to rodents. In 2018, Sousbie *et al.* reported macrocyclic peptide analogues of NT **304** by employing RCM methodology (Scheme 35).[10] The precursor **300** was produced by using Fmoc solid-phase peptide synthesis (SPPS). Fmoc-Tyr(3-allyl)-OH helped in the insertion of the first allyl group required for metathesis. Consecutively, Fmoc was deprotected, the nosyl group was introduced on resin, and acetylation of the tyrosine phenol was conducted. The second allyl group was inserted through optimized Fukuyama–Mitsunobu conditions to afford the RCM precursor **301**. The crucial macrocyclization step was carried out next using Hoveyda–Grubbs-II catalyst in *p*-benzoquinone in DCE at 50 °C to afford macrocycle **302** which underwent deprotection of the nosyl and acetyl groups to produce the desired compound **303**. Following this similar strategy, several analogues **304** of various ring sizes (21–25) were prepared by changing their N-terminal amino acid and linkers.

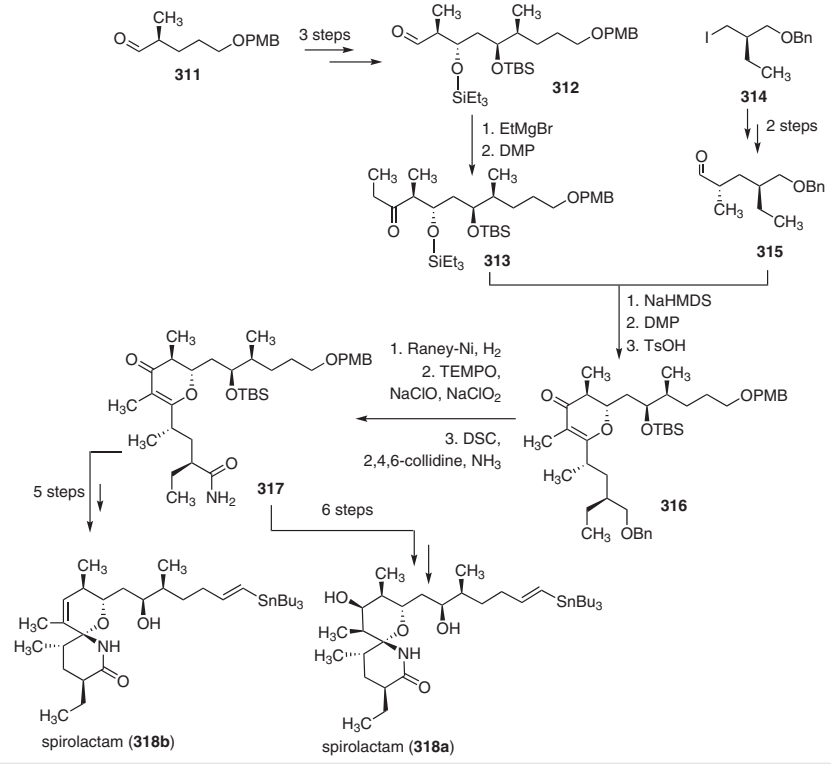


Scheme 35 Synthesis of macrocyclic peptide analogues of neurotensin (NT)

Neglected tropical diseases like Chagas disease and sleeping sickness caused by protozoan parasites of the genus *Trypanosoma* have caused adverse effects on the health of people.[3] Taking this factor into consideration, in 2020, the Paterson group developed an efficient total synthesis of the potent anti-trypanosomal macrolide (+)-actinoallolide A (**310**) (Scheme 36).[3] Construction of the target macrocycle progressed with the preparation of the acid **307** and the alcohol **308**. (*S*)-Lactic acid (**305**) was subjected to several reactions in seven consecutive steps to prepare **307** whereas the chain fragment **308** was synthesized by exposing an ethyl ketone derivative **306** to subsequent reactions in eight steps. Yamaguchi esterification between fragments **307** and **308** developed the macrocyclic precursor which finally, produced the 12-membered macrolactone **309** when treated with Hoveyda–Grubbs-II catalyst in refluxing toluene. Several steps followed the key step of RCM to afford their target compound actinoallolide A (**310**) in an excellent yield of 99%.

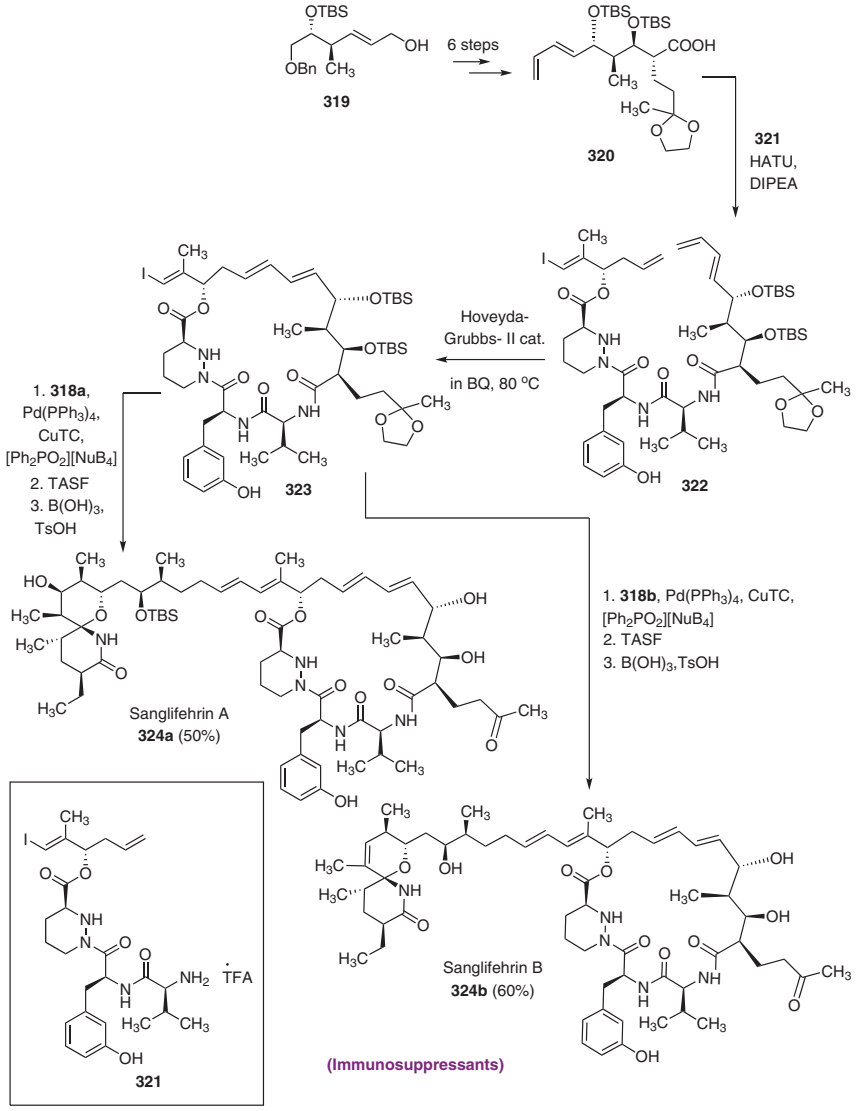


Scheme 36 Synthesis of actinoallolide A



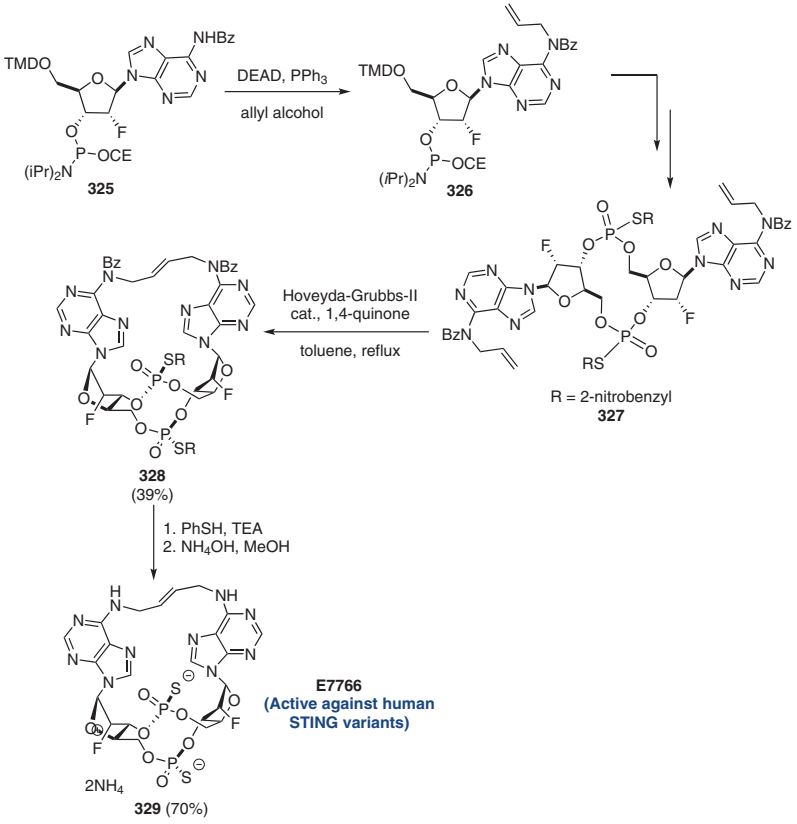
Scheme 37 Synthesis of sanglifehrin spirolactams

In 2021, Chang *et al.* reported the total synthesis and biological evaluation of immunosuppressants sanglifehrin A (**324a**) and sanglifehrin B (**324b**) (Schemes 37 and 38).[7] Sanglifehrin, a class of macrolides, derived from the isolates of *Streptomyces sp.* A92-308110 in 1999, were screened to identify novel immunosuppressants which target cyclophilin A (CypA).[7] Construction of the 22-membered macrocycles commenced with the production of building blocks **313** and **315**. In order to prepare the ketone **313**, a readily available aldehyde **311** was chosen as the starting material (Scheme 37). Upon adding an ethyl group to **312** following Grignard addition, the substrate could ultimately be oxidized using Dess–Martin periodinane to furnish **313**. The synthesis of the aldehyde **315** was carried out in two steps



Scheme 38 Synthesis of sanglifehrin A and B

from the iodide **314**. With these building blocks in hand, pyran-4-one **316** was synthesized through cross-aldol coupling of **313** and **315** followed by oxidation and acid-catalyzed cyclization. Several reactions like regioselective debenzylation, TEMPO-mediated oxidation, and one-pot amide transformations were consecutively followed to produce **317**. The primary amide **317** underwent a series of reactions to afford the sanglifehrin B spirolactam moiety **318b** in five steps while sanglifehrin A spirolactam moiety **318a** was synthesized in six steps. Subsequently, the fragment **320** was obtained in sequential reactions starting from the allyl alcohol **319** (Scheme 38). Amide coupling between the acid **320** and tripeptide **321**·TFA synthesized the RCM precursor **322** which on treatment with Hoveyda–Grubbs-II catalyst in BQ at 80 °C afforded the macrocycle **323** in 12% yield. It was improved to 24% upon using modified Hoveyda–Grubbs-II catalyst and up to 48% upon using catalytic amount of 2,6-bis(trifluoromethyl)phenylboronic acid. Stille–Migita cross coupling of macrocycle **323** with **318a** and further deprotection of silyl and ketal groups afforded the desired compound sanglifehrin A (**324a**) in 50% yield. A similar methodology was followed to afford sanglifehrin B (**324b**) in 60% yield. Evaluation of biological activities of both sanglifehrin A and B clarified that they exhibited moderate antiproliferative effects in Jurkat cells but sanglifehrin B proved to be more potent. Structural modification about the spirolactam, specifically at the C40 position, enhanced the activity of sanglifehrin analogues against Jurkat cells.



Scheme 39 Synthesis of macrocyclic-bridged STING agonist E776

Also, it was found that sanglifehrin A preferentially forms higher-order protein complexes between CypA and IMPDH2.

The stimulator of interferon genes (STING) pathway has an increased viability as a drug target for treatment of various diseases including infections, cancers etc. In 2021, Kim *et al.* developed a synthetic route to create E7766 using RCM as a crucial step (Scheme 39).[52] Commercially available **325** was made to react with allyl alcohol to produce alkene **326**. After several consecutive reactions, the RCM precursor **327** was synthesized which upon exposure to metathesis conditions with Hoveyda–Grubbs-II catalyst in refluxing toluene, the desired macrocycle-bridged construct **328** was obtained in 39% yield as the *E* isomer. The two 2-nitrobenzyl groups were removed with PhSH/TEA consecutively as well as the two benzoyl groups with ammonium hydroxide and ultimately E7766 (**329**) was furnished in 70% yield. Through various tests it was found that E7766 showed superior and pan-genotypic activity against four major human STING variants than 2′,3′-cyclic guanosine monophosphate–adenosine monophosphate (cGAMP).

7 Conclusion

In conclusion, we have reported several synthetic methods for the development of various biologically active macrocycles involving ring-closing metathesis (RCM) as a key step. It served as a crucial step of macrocyclization in each synthetic route presented in this review. These macrocycles exhibited inherent properties like antiviral, antifungal, antibacterial, anticancer, and more. Hence, their development and utilization has been very crucial in the medicinal and synthetic organic chemistry field.

Conflict of Interest

The authors declare no conflict of interest.

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