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Prodigiosin alkaloids: recent advancements in total synthesis and their biological potential

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Despite recent developments in combinatorial chemistry and related techniques for facilitating drug discovery and development, natural products continue to play a prominent and evolving role for the development of new therapeutic agents. Pyrrole containing natural products constitute an integral part of this strategy. The structure and reactivity of pyrrole along with its propensity to polymerize renders it a relative speciality and certainly not something for the faint of heart. Besides, the well known tetrapyrrolic "Pigments of life," other fascinating natural products incorporating multiple copies of the pyrrole ring system are attracting the attention of organic medicinal chemists and must be acknowledged.

1. Introduction

Prodigiosin (PG) alkaloids represent a family of naturally occurring red pigments produced by *Streptomyces* and *Serratia*[1–3] with a common pyrrolylpyrromethene skeleton. From early times, extensive records have indicated the appearance of red colour on bread and wafers which was mis-interpreted in certain religious or symbolic contexts as the miraculous appearance of blood.[2] The secretion of "blood" like material by *S. marcescens* caused this considerable confusion and was responsible for many seemingly miraculous (prodigious) events. With an eventual transition from superstition to science, prodigiosins attracted considerable attention from both chemists and biologists because of their synthetically arduous and unique molecular architectures and range of potentially useful biological activities. Prodigiosin-like pigments have been isolated from several bacteria including *S. plymuthica*, *S. rubidaea*, *S. coelicolor*, *P. magnesiorubra*, *V. psychroerythrus* and γ-*Proteobacteria etc.* and have an unusual structure comprising of three pyrrole rings. Two of the pyrrole rings are directly linked to each other, while the third one is attached through a methane bridge 2,3. "Prodigiosin" has a series of close relatives bearing the same

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Mr Kewal Kumar has obtained his B.Sc. degree from SPN College, Mukerian with distinction in Chemistry in 2007. He joined the Department of Applied Chemistry, Guru Nanak Dev University, Amritsar for his master's degree and achieved Gold medal of academic excellence in 2009. Afterwards, he joined Ranbaxy Research Laboratories as Research trainee, where he was awarded for "making a difference and driving excellence" in work in 2010. In the same year, he joined Dr Vipan's research group as INSPIRE Fellow for pursuing his doctoral degree. During his doctoral work, he worked extensively on the synthesis and bio-evaluation of ferrocene/uracil based molecular conjugates. He has published fifteen research papers in journals of international repute and has one US patent.

pyrrolylpyrromethene ("prodiginine") core with different alkyl substituents which are often tied back to form medium-sized rings or macrocycles, as shown in Fig. 1.

Past decade has witnessed the emergence of a number of reports on the impressive biological properties such as immunosuppressive,[4] antimalarial,[5,6] antimicrobial,[7] antitumor,[7a,b,8] anticancer,[9] cell pH regulation by H^+/Cl^- symport/antiport activity,[10] phosphatase inhibition[11] and DNA-interchelation activities[12] exhibited by natural and synthetic prodigiosins. Most interesting are their immunosuppressive activities at doses that are not cytotoxic. *In vivo* studies further suggested that the prodigiosins act synergistically with cyclosporine A or FK506,[4c,13,14] which are presently the dominant drugs in clinical immunosuppressive regimens. Its derivative Obatoclax (GX15-070), commercially developed by the pharmaceutical company Gemin X Pharmaceuticals (recently acquired by Cephalon), is also involved in phase I/II clinical trials on leukemia, lymphoma, and solid tumor malignancies with promising anticancer potential.

Given the immense medicinal potential of prodigiosins and the complexities of their structural assignments, various synthetic chemists have developed novel synthetic approaches for their total synthesis in order to unambiguously confirm their assigned structures. The present review article is an attempt to focus on the developments, the past decade has witnessed, in the total synthesis of prodigiosin alkaloids along with their medicinal potential. The aim will be to provide an inspiration to the marvels and pit falls of constructing the polypyrrole heterocycles with in the complex systems.

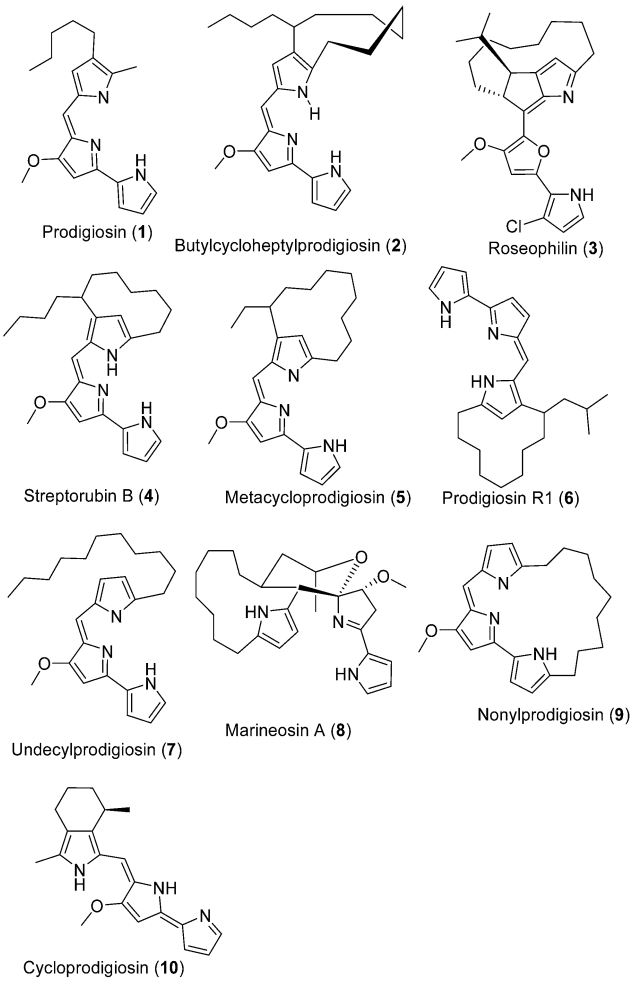


Fig. 1 Representative members of the prodigiosin family.

2. Biological potential of prodigiosins and their analogues

The emergence of drug-resistant pathogens and the subsequent urgent need for novel effective molecules has resulted in the re-engineering and re-positioning of the known bio-active molecules. Bacterial prodigiosins are considered as remarkable molecules in terms of their effectiveness as anti-tumor, immunosuppressants and antimalarials at non-toxic levels.

Vipan kumar Ph.D, has been working as an Assistant Professor in the Department of Chemistry, Guru Nanak Dev University, Amritsar since 2009. He obtained his Ph.D with Prof. MP Mahajan, in the Department of Applied Chemistry, GNDU. In 2007, he moved to the University of Cape Town (UCT), South Africa to pursue his postdoctoral studies with Prof. Kelly Chibale and extensively worked on molecular hybridization protocols for the preparation of molecular conjugates intended for HIV–malaria co-infections. His research interests include the development of diverse synthetic protocols for synthesis of novel molecular frameworks targeting tropical infections. He has also been engaged in the utilization of β-lactam synthon protocols for the synthesis of functionally decorated and biologically relevant heterocycles with medicinal potential.

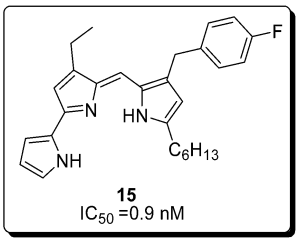
2.1. Antimalarial properties of prodigiosins

Although the antimalarial activity of natural prodigiosins was reported several years ago,[15] the parasiticidal activity of prodigiosin analogues was reported only recently, with encouraging results. Many prodigiosins *viz.* metacycloprodigiosin (**5**), undecylprodigiosin (**7**), streptorubin B (**4**) were shown to exhibit potent *in vitro* activity against *P. falciparum*. Papireddy[6] and co-workers studied the *in vitro* antimalarial activity of natural and synthetic prodigiosins against *P. falciparum* pansensitive D6 with chloroquine (CQ) as a reference drug. Assessment results revealed that the prodigiosin (**1**), undecylprodigiosin (**7**), metacycloprodigiosin (**5**), and streptorubin B (**4**) displayed potent antimalarial activity with very low IC_{50} values *viz.* 8, 7.7, 1.7 and 7.8 nM respectively.

Patil *et al.*[16] evaluated the larvicidal potential of microbial pigment prodigiosin produced by *Serratia marcescens* NMCC46 against *Aedes aegypti* and *Anopheles stephensi*. These results

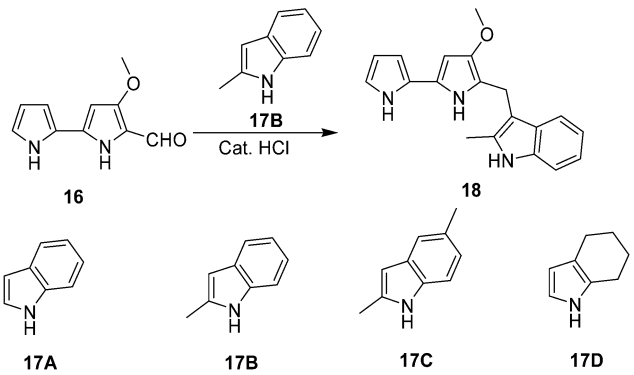
confirmed that these species would be more useful against vectors responsible for diseases of public health importance. Thompson and co-workers[17] synthesized and evaluated prodigiosin complexes with tin, cobalt, boron and zinc (**11–14**) (Fig. 2). The antimalarial activities of these prodigiosins were evaluated *in vitro* against the 3D7 strain of *P. falciparum*. The presence of a nitrogen atom in the A-ring is needed for antimalarial activity while the presence of an alkyl group at the β-position of the C-ring seems detrimental. Dibutyl tin complexes exhibited IC_{50} values in the nanomolar range with equal or improved activity compared to the free-base prodigiosin ligand, despite the fact that the general toxicity of tin complex is lower than that of the free bases.

Mahajan *et al.*[18] synthesized 53 prodigiosins and assayed their *in vitro* anti-malarial activity against *P. falciparum* pan-sensitive D6, with chloroquine (CQ) as a reference drug. These synthetic prodigiosins having various substituents like –F, –Cl, alkyl, $–NH_2$, *etc.* at different positions were also explored in the CoMSIA (Comparative Molecular Similarity Indices Analysis) model in order to explore the role of structural features on the antimalarial activity. The analyses revealed that the lipophilicity, hydrogen donor/acceptor and steric factors of the synthesized prodiginines play crucial role in the design of new analogues. The most active compound of the series **15** displayed an IC_{50} value of 0.9 nM against D6 strain of *P. falciparum* (Fig. 3).



15
IC_{50} =0.9 nM

Fig. 3 Most active antimalarial synthetic prodigiosin **15**.



Scheme 1 Synthesis of prodigiosin analogue **18**.

2.2. Anticancer properties of prodigiosins

Baldino *et al.*[19] reported the synthesis of novel prodigiosin analogs, formed by the condensation of C-10 methoxybipyrrole aldehyde precursor **16** with indole derivatives (Scheme 1) and evaluated their cytotoxicity against a panel of cancer cell lines *viz.* A549, DLD-1, HT29, MDA-MB-231 and NCI-H460. The activity data revealed that the metacycloprodigiosin (**5**) having IC_{50} 0.3–1.7 μM is approximately 10-fold less potent than the prodigiosin (**1**) with an IC_{50} = 0.03–0.17 μM. The compound **19** exhibited greatest inhibition of cellular proliferation similar to metacycloprodigiosin (**5**), having IC_{50} in the range between 0.2 and 0.8 μM (Fig. 4). The aliphatically substituted C-ring pyrrole compounds exhibited greatest activity, while the incorporation of the additional pyrrole ring and methoxy substituent appeared to reduce cell proliferation of the chemotype by 100-fold, similar to the indoloprodigiosin analogs.

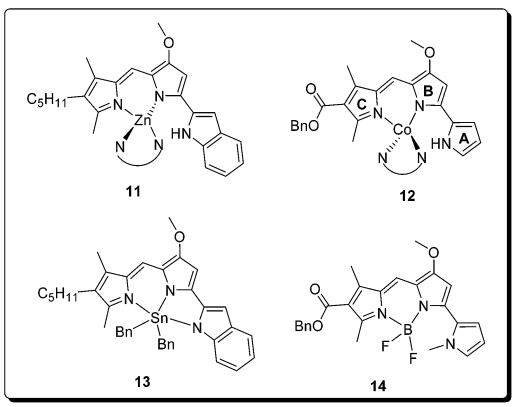


Fig. 2 Complexes of prodigiosin with zinc (**11**), cobalt (**12**), tin (**13**) and boron (**14**).

Sainis and co-workers[20] in a recent communication investigated the mechanism of cell death induced by the *N*-alkylated prodigiosin analogue *viz.* 2,2′-[3-methoxy-1′-amyl-5′-methyl-4-(1″-pyrryl)]dipyrryl-methene (MAMPDM) 20 (Fig. 5) in S-180 and EL-4 tumour cell lines. Investigations into the mechanism of cell death by MAMPDM in S-180 cells showed the absence of characteristics of apoptotic cell death such as activation of caspase 3, DNA fragmentation and presence of cells with sub-diploid DNA content. However, rapid loss of membrane integrity was observed as assessed by the uptake of propidium iodide, which is a characteristic of necrosis. In contrast to the induction of necrosis in S-180 cells, MAMPDM has also shown to induce apoptotic cell death in EL-4 cells as evident by activation of caspase 3, fragmentation of DNA and sub-diploid DNA containing cells.

Antiproliferative activities of prodigiosins derived from *Serratia marcescens* against HT-29 and T47D cancer cell lines was reported by Samadi *et al.*[21] using MTT assay. The evaluation studies clearly elucidated the potential of PG as potent apoptotic agents in human colon adenocarcinoma exhibiting an IC_{50} value of 400 nM; better than doxirubicin.

Thomson[22] and co-workers synthesized prodigiosin analogues **21** bearing an additional methyl and a carbonyl group at the C-ring. *In vitro* anticancer activity (NCI) and the study of modes of action (copper-mediated cleavage of double-stranded DNA and transmembrane transport of chloride anions) showed that the presence of the methyl group is not

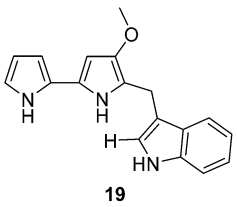


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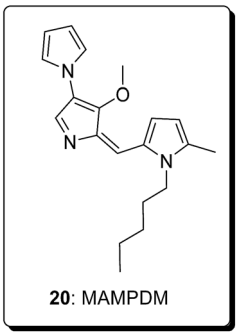
Fig. 4 Most potent compound **19** with greatest inhibition of cellular proliferation.

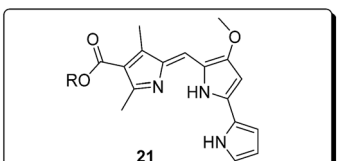


20: MAMPDM

Fig. 5 *N*-Alkylated prodigiosin analogue, 2,2′-[3-methoxy-1′-amyl-5′-methyl-4-(1″-pyrryl)]dipyrryl-methene (MAMPDM).

detrimental to their activity (Fig. 6). Although the presence of an ester conjugated to the prodigiosin C-ring have shown to decrease both pK_a and chloride transport efficacy compared to the natural product, these analogues still exhibited a high rate of chloride ion transport. All synthesized analogues exhibited good *in vitro* anticancer activity and reduced toxicity as compared to the natural product with an acute systemic toxicity of 100 mg kg^{-1} in mice *vs.* 4 mg kg^{-1} for prodigiosin suggesting a larger therapeutic window of synthetic analogues than for the natural product.

Thompson *et al.*[9] further synthesized a novel series of prodigiosin analogues **22** incorporating pendent functional esters and β-carbonyl substituents on the C-ring and evaluated for their anticancer activities (Fig. 7). The synthesized prodigiosin analogues retained the activity of prodigiosin in 60 human cancer cell lines with no reduction in efficacy being observed by the introduction of conjugated β-carbonyl group or the pendent ester.



21

21a: R = *O*-methyl
21b: R = *O*-benzyl
21c: R = *O*-i-proyl
21d: R = *O*-butyl
21e: R = *O*-octyl
21f: R = *O*-phenyl
21g: R = *O*-pentyl
21h: R = *O*-$C_{13}H_{27}$
21i: R = *O*-$C_{16}H_{33}$
21j: R = *N*H-i-propyl

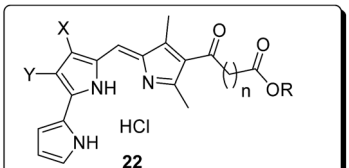
Fig. 6 Prodigiosin analogues with anticancer activity.

2.3. Immunosuppresant properties of prodigiosins

Immunosuppression plays a potential role in the therapy of autoimmune diseases and is required to reduce detrimental immune reactions. Main indications of immunosuppressive therapy are prevention and treatment of acute and chronic allogeneic organ transplant rejection and graft-*versus*-host disease (GVHD). Although the use of cyclosporin A (CyA) has been considered as a major advancement in organ transplantation,[23,24] current immunosuppressive therapies[25] still have strong limitations because of its low efficacy and relevant side effects on transplant recipients. One of the most attractive properties of prodigiosins are their immunosuppressive activities at doses that are not cytotoxic. *In vivo* studies suggested that the prodigiosins act synergistically with cyclosporine A or FK506 (Tacrolimus), which are presently the dominant drugs in clinical immunosuppressive regimens.

Sainis[26] and co-workers have also reported immunosuppressive activity of *N*-alkylated prodigiosin analogue, 2,2′-[3-methoxy-1′-amyl-5′-methyl-4-(1″-pyrryl)]dipyrryl-methene (MAMPDM) **20** in mitogen stimulated spleen cells (Fig. 5). An increase in the accumulation of interlukin-2 (IL-2) and induction of apoptotic cell death was observed in these studies. Since IL-2 regulates both cellular proliferation and activation induced cell death (AICD), the effect of MAMPDM on the expression of IL-2 regulated genes involved in these two opposite processes was further investigated. The mitogen stimulated mouse spleen cells did not undergo a single division in presence of proliferation inhibitory concentrations of MAMPDM. An increase in the percentage of apoptotic cells was observed in the undivided cell population. The cells were arrested in G1 phase independent of the p53 expression. Expression of IL-2 regulated genes such as CD71, proliferating cell nuclear antigen (PCNA) and cyclin D was suppressed while the expression of Fas remain unchanged. MAMPDM therefore selectively inhibited the pro-mitogenic signaling without affecting proapoptotic signaling by IL-2. The induction of apoptosis in presence of MAMPDM was the effect rather than cause for the antiproliferative activity.

Kim *et al.*[27] compared the inhibitory potency and mode of action of Prodigiosin with cyclosporine A (CsA) in a mouse model. PG efficiently inhibited T cell proliferation with an IC_{50} of 3.37 ng mL^{-1}, while CsA exhibited an IC_{50} of 2.71 ng mL^{-1}. PG has shown to inhibit only IL-2Ra expression and not IL-2



22

22a: n = 2, X = OMe, Y = H, R = Me
22b: n = 4, X = OMe, Y = H, R = Me
22c: n = 4. X = OMe, Y = H, R = Et
22d: n = 4, X = Me, Y = Et, R = Me
22e: n = 8, X = OMe, Y = H, R = Me

Fig. 7 Anticancer Prodigiosin analogues with pendent functional esters and β-carbonyl substituents on the C-ring.

expression, whereas CsA inhibited both. Exogenously added IL-2 reversed the suppressive activity of CsA, but not that of PG. Further although both PG and CsA markedly reduced mortality rates in lethal acute graft-*versus*-host disease (GVHD), the combined treatment was shown to be more effective than either drug alone. These results clearly demonstrated that PG and CsA have similar inhibitory potencies, but different modes of action suggesting the potential use of PG as a supplementary immunosuppressant in combination with CsA for the treatment of GVHD.

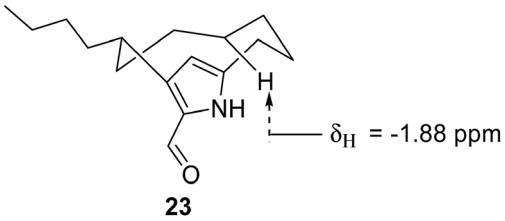


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Fig. 8 High-field shift of an aliphatic proton as a characteristic signature of the ^{1}H NMR spectrum of compound with a rigid *meta*-pyrrolophane structure.

3. Total synthesis of prodigiosins

From a structural point of view, streptorubin B (**4**) and metacycloprodigiosin (**5**) possess highly strained pyrrolophane cores formed by oxidative ring closure of undecylprodigiosin (**7**). Prodigiosin R1 (**6**) has a structural similarity to metacycloprodigiosin (**5**) and is considered as an interesting link between these scaffolds and roseophilin (**3**).

3.1. Total synthesis of butylcycloheptylprodigiosin

Butylcycloheptylprodigiosin **2** is a secondary metabolite originally isolated from *Streptomyces* sp. Y-42, *Streptomyces abikoensis* and a culture broth of *Streptomyces coelicolor* mutants.[28,29] Historically, there has been considerable doubt about the existence of butylcycloheptylprodigiosin (**2**) as a natural product. Gerber and co-workers in 1975,[28] first proposed the structure **2** for a pink pigment isolated from *Streptomyces* sp. Y-42 and *S. rubrireticuli*. The structure, however was reassigned to that of streptorubin B (**4**) in 1978. Likewise, Floss in 1985, isolated a pink pigment from *S. coelicolor* which was structurally assigned as **2**.[29] However, Weyland and co-workers isolated another pink pigment from *actinomycete* and showed that their sample was the *meta*-bridged isomer streptorubin B **10** rather than the *ortho*-annulated compound **2**.[30] However, Weyland's conclusions looked premature on the basis of ^{1}H NMR spectra where *meta*-pyrrolophanes exhibited a characteristic fingerprint. The rigidity of the ten-membered ring in **4** forces one of the protons of the ansa-chain to reside within the anisotropy cone of the pyrrole ring resulting in a substantial upfield-shift to $\delta = -1.55$ in **4** and -1.88 ppm in core-segment **23**, shown in Fig. 8.[31] Since no such signal was identified in case of butylcycloheptylprodigiosin **2**, it was suspected that **2** exists as a natural product distinct from **4**.

3.1.1. Furstner's total synthesis of butylcycloheptylprodigiosin. In order to unequivocally establish the structure of butylcycloheptylprodigiosin, Furstner and co-workers have successfully attempted its total synthesis in a 16-step sequence with an approximate yield of 1.5%.[32]

Retrosynthetically, the assembly of the pyrrolopyrromethane **2** was envisaged from the corresponding building blocks **24–26** by successive condensation and cross-coupling reactions as shown in Fig. 9.[33,34] Because of ease of availability of **25** and **26**, the success of this synthesis entirely hinged upon the synthesis of aldehyde **24**.

For the preparation of aldehyde **24**, cyclononadienylacetone **27** was considered as the optimal substrate because of (1) the presence of two double bonds increasing the number of reactive encounters during Narasaka–Heck cyclization; (2) the remaining double bond that should provide a handle for the introduction of the butyl side chain; and (3) the symmetrical structure, facilitating its large scale preparation.

The total synthesis of desired butylcycloheptylprodigiosin **2** started with an initial reduction of (*Z*,*Z*)-cyclononadienone[5a,28] **27** using diisobutyl-aluminium hydride (DIBAL-H) with subsequent acetylation to result in the corresponding acetate **28** in quantitative yields (Scheme 2). The treatment of **28** with methyl acetoacetate in the presence of NaH and catalytic amount of $[Pd(PPh_3)_4]$ interestingly led to the isolation of *Z*-configured **29**, advocating the notion that the two allylic sites in **28** were uncoupled during Tsuji–Trost reaction.[35] Krapcho decarboxylation[36] of **29** yielded the cyclononadienylacetone **30** which was converted to pentafluorobenzoyl oxime ester **31** under standard conditions. The synthesized oxime ester **31** underwent Narasaka–Heck cyclization[37] in the presence of a catalyst prepared *in situ* from $Pd(OAc)_2$ and $[P(o\text{-tolyl})_3]$ in DMF at 110 °C, to yield the unsaturated bicyclic imine **32** in good yields. In order to aromatize the product **32**, potassium 3-aminopropylamide[38] (KAPA) in 1,3-diaminopropane was used. This, through a series of thermodynamic deprotonation/reprotonation resulted in the selective shift of the 9,10 double bond to deliver the highly sensitive pyrrole **33**, which was immediately *N*-Boc protected to yield **34**.[39]

The functionalization of alkene in **34** by using $BH_3\cdot THF$ followed by stepwise oxidation with H_2O_2 and Dess–Martin periodinane yielded ketone **35** as anti-Markovnikov isomer (Scheme 3).[40,41] Wittig olefination of **35** delivered the product **36**

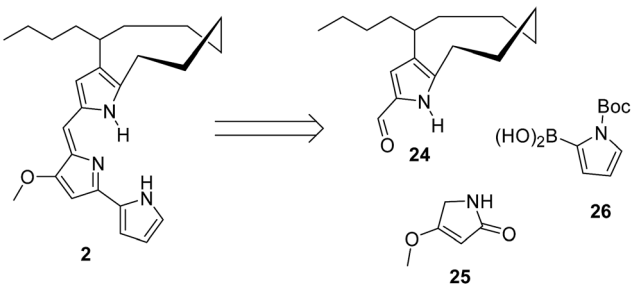
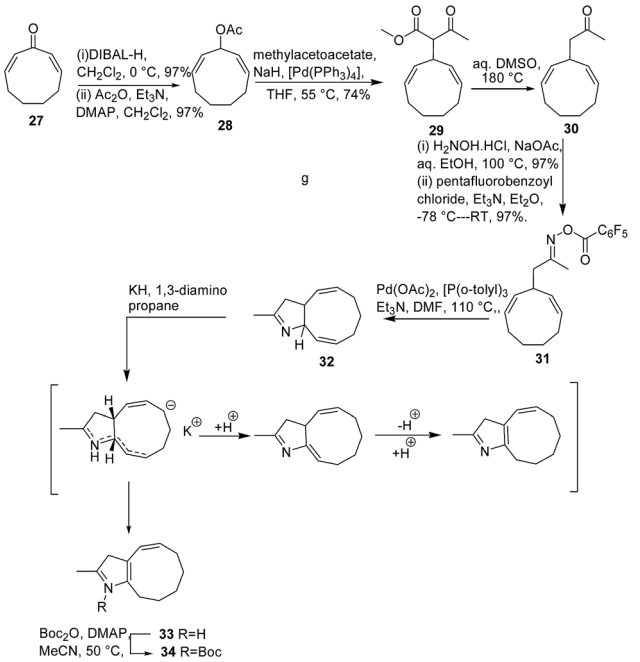


Fig. 9 Retrosynthetic analysis of butylcycloheptylprodigiosin **2**.



Scheme 2 Synthesis of the *ortho*-pyrrolophane core structure.

which was subsequently selectively reduced with $[Ir(pyridine)(cod)(PCy_3)]PF_6$ (ref. 42) to yield **37**. Subsequent oxidation of methyl substituent in **37** was optimized by the use of cerium ammonium nitrate (CAN) in $CHCl_3/H_2O$ mixture using a small amount of 1,2-dimethoxy ethane (DME) as a phase transfer catalyst to yield the product **38**.

Base promoted condensation of aldehyde **38** with commercially available lactam **25** with subsequent cleavage of the *N*-Boc protecting group led to the formation of **39**. The reaction of **39** with Tf_2O (Tf = trifluoromethanesulfonyl) induced a re-organization of the π-system yielding the corresponding triflate **40** as the substrate for Suzuki coupling. The treatment of boronic acid **26** with **40** in the presence catalytic amounts of $[Pd(PPh_3)_4]$ and LiCl afforded butycycloheptylprodigiosin **2** in 70% yield as a deeply red–pink colored solid.

3.1.2. Concise total synthesis of butylcycloheptylprodigiosin using Narasaka–Heck reaction. In another report, Furstner and co-workers[31a] described the total synthesis of this complex alkaloid *via* catalysis based approach featuring the first application of a Narasaka–Heck reaction in natural product chemistry.[43–45] Retro-synthetically, the pyrrolopyrromethane portion of **2** could be assembled *via* successive condensation/cross coupling steps with aldehyde **24** as the key building block (Fig. 10).[33a,34] The preparation of **24** is non-trivial because of the disfavoured thermodynamic and kinetic grounds.[46] Thus, the preferred strategy comprised of the annulation of the pyrrole nucleus to the pre-existing cyclononane *via* palladium promoted intramolecular aza-Heck reaction of **42** having two synthetically equivalent double bonds.[43–45,47]

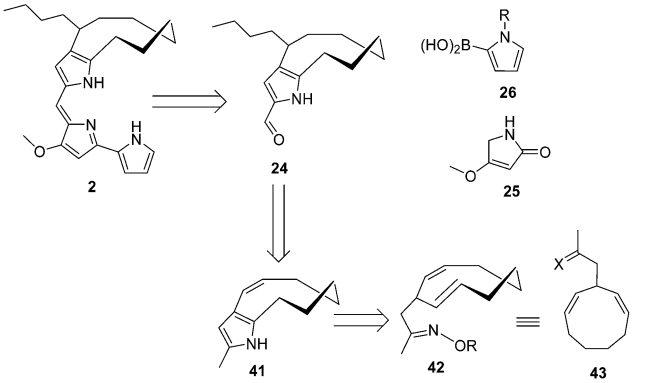
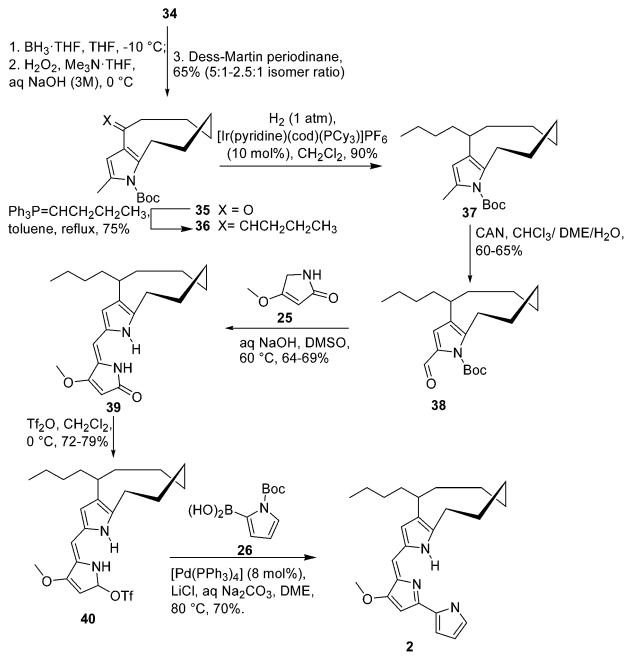
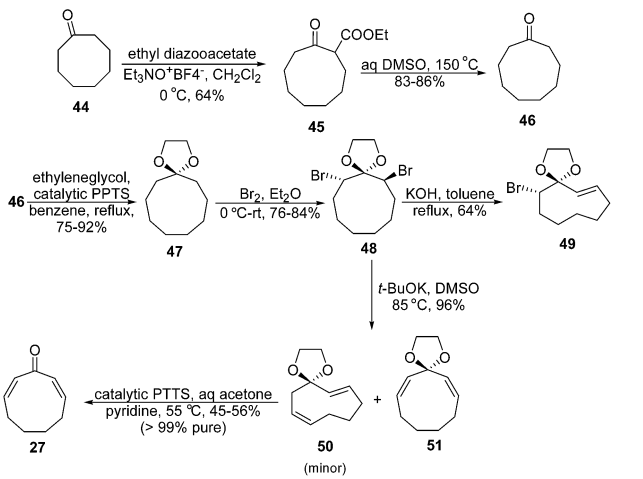


Fig. 10 Retrosynthetic analysis of butylcycloheptylprodigiosin **2**.



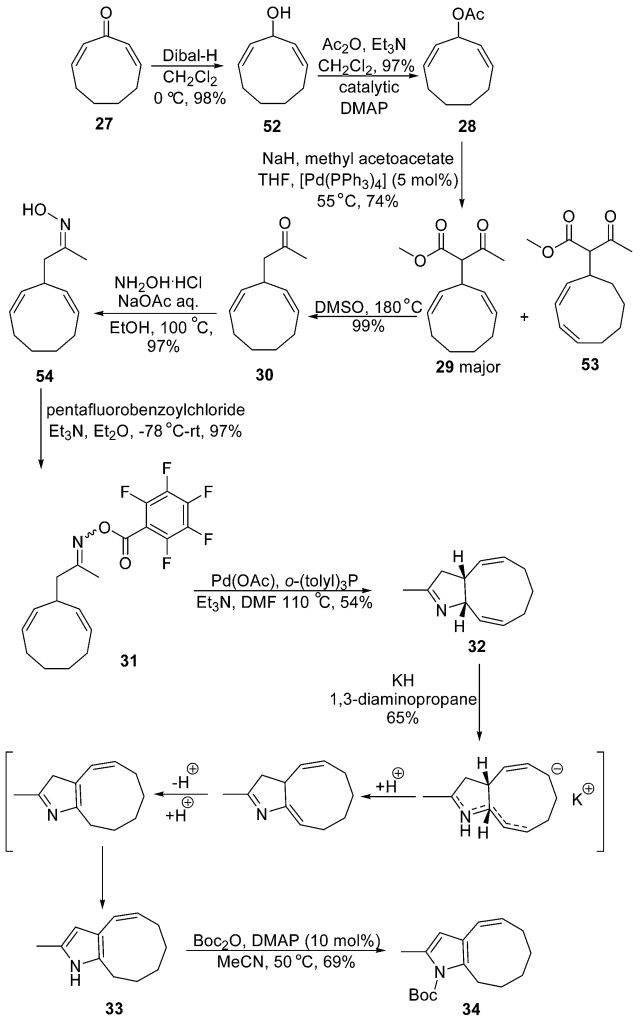
Scheme 3 Total synthesis of butylcycloheptylprodigiosin.



Scheme 4 Large-scale adaptable synthesis of cyclononadienone **27**.

The synthetic methodology involved an initial ring expansion of cyclooctanone **44** using ethyl diazoacetate in the presence of Meerwein salt ($Et_3O^+BF_4^-$)[48] resulting in the isolation of ketoester 45 (Scheme 4). Krapcho decarboxylation[36] of ketoester **45** ensured the synthesis of cyclononanone **46.** Cyclononanone **46** was converted to acetal **47** which when reacted with Br_2 led to the isolation of corresponding dibromide **48** as the major product. Potassium *tert*-butoxide promoted dehydrobromination of **48** transformed it into (*Z*,*Z*)-configured di-unsaturated ketal **51** along with the isomeric diene **50** as a minor product. *trans*-Deacetalization of this reaction mixture with acetone in the presence of catalytic amount of pyridinium *p*-toluene sulfonate afforded the desired (*Z*,*Z*)-cyclononadiene **27**.

Treatment of **27** with diisobutylaluminium hydride (Dibal-H) afforded the corresponding doubly allylic alcohol **52** which was subsequently acetylated to yield **28** (Scheme 5). Reaction of **28** with methylacetoacetate in the presence of NaH and catalytic amount of $[Pd(PPh_3)_4]$ afforded **29** as the major isomer along with small amount of conjugated diene isomer **53.** Krapcho decarboxylation[36] of **29** with subsequent conversion of the resulting cyclononadienylacetone **30** into the pentafluorobenzoyl oxime ester **31** *via* the corresponding oxime **54** set the stage for Narasaka–Heck cyclization (Scheme 5).[37] $Pd(OAc)_2$ and $P(o\text{-tolyl})_3$ promoted transformation of **31** delivered the unsaturated bicyclic imine **32.** Reluctancy of **32** to undergo spontaneous aromatization promoted the workers to deprotonate the compound at the bridge head position α to nitrogen which will form a stable aza-pentadienylanion. Thus, the treatment of **32** with KAPA (potassium 3-aminopropylamide)[38] led to the formation of labile **33** *via* a series of thermodynamic deprotonation/re-protonation events. The highly labile **33** was immediately *N*-Boc protected to yield the compound **34.**



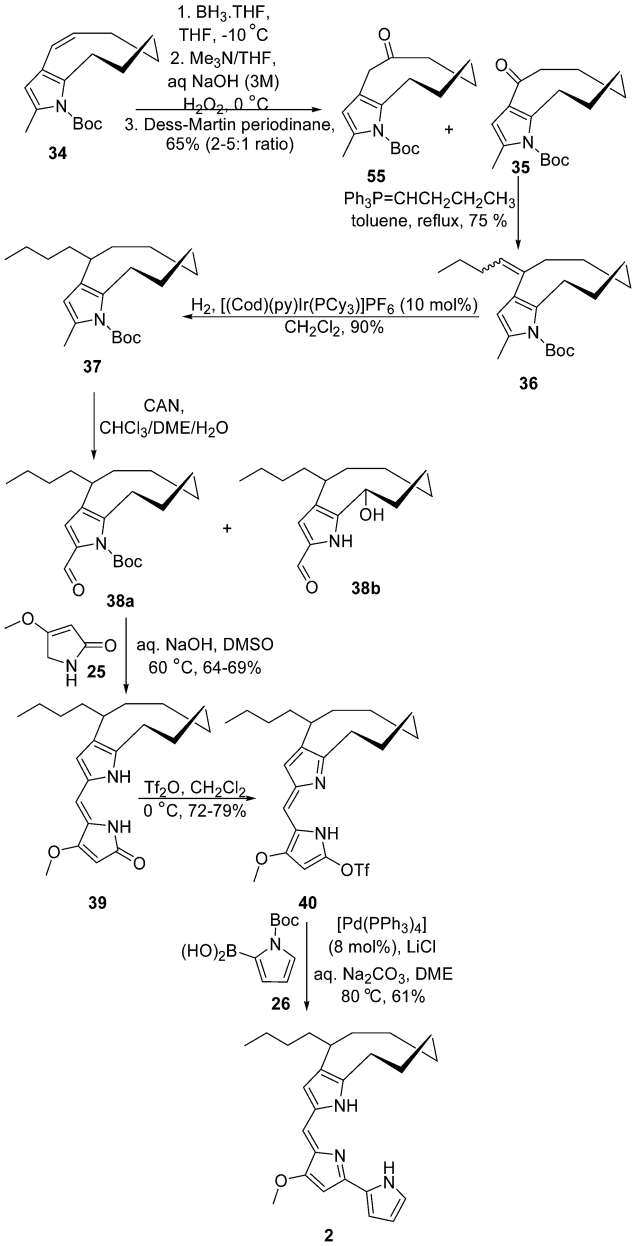
Scheme 5 Synthesis of the *ortho*-pyrrolophane core structure **34**.

Hydrogenation of **34** with $BH_3\cdot THF$ followed by stepwise oxidation with H_2O_2 and subsequent treatment with Dess–Martin periodinane[41] furnished ketone **35** and the unconjugated regio-isomer **55** (Scheme 6). Wittig olefination of **35** in boiling toluene delivered the corresponding olefin **36** as a mixture of both stereoisomers. The synthesized tri-substituted alkene was hydrogenated using $[(cod)(pyridine)Ir(Pcy_3)]PF_6$ (ref. 42) to give the desired *ortho*-pyrrolophane **37** without reducing the pyrrole ring.

The oxidation of **37** with CAN[49] in the presence of dimethoxyethane (DME) afforded the desired aldehyde **38a** in good yields along with minor quantities of alcohol **38b**. Base promoted condensation of **38a** with commercially available lactam **25** with subsequent deprotection resulted in the synthesis of **39**. Treatment of **39** with Tf_2O induced reorganization of the π-system resulted in the corresponding triflate **40** as the substrate for the final Suzuki coupling.[50] Treatment of **40** with boronic acid **26** in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ and LiCl afforded prodigiosin **2** in 61% yield. A comparison of the spectrum of the synthesized prodigiosin **2** and authentic sample showed an excellent match confirming the fact that butylcyclohepytylprodigiosin **2** is a natural product distinct from streptorubin B **4.**

3.1.3. Reeves' concise synthesis of butylcycloheptylprodigiosin. Reeves and co-workers in 2007 have reported a concise total synthesis of butylcycloheptylprodigiosin **2** in 5 steps from cyclononenone.[51a] The retrosynthetic analysis of **2** as depicted in Fig. 11, included an *O*-triflation/Suzuki cross-coupling simplification of **2** to lactam **56** with subsequent condensation to result in the key formylpyrrole **24.**[31–33]

Total synthesis of **2** was initiated by the oxidation of commercially available cyclononanone with IBX (*o*-iodoxybenzoate) to yield cyclononenone **58** as reported by Nicolaou and co-workers.[51b] CuI-catalyzed addition of *n*-BuMgCl to **58** proceeded efficiently in THF at −40 °C (Scheme 7).[52] The resulting enolate was trapped with **59**, obtained by partial reduction of commercially available ethyl-4-oxazole carboxylate, to give **57** as a single diastereomer. The treatment of **57** with $MsCl/Et_3N$ in THF resulted in the synthesis of desired formyl pyrrole **24** in good yields. The elaboration of **24** into **2** was done in three steps *viz.* the condensation of **24** with commercially available pyrrolinone **25** to yield **56,** the treatment of **56** with Tf_2O to yield the corresponding triflate **40,** Suzuki cross coupling of **40** with boronic acid **26** with subsequent hydrolysis to yield (±)butylcycloheptyl prodigiosin **2** in good yields (5 steps, 23% overall yield).[31a,32,34]



Scheme 6 Total synthesis of butylcycloheptylprodigiosin.

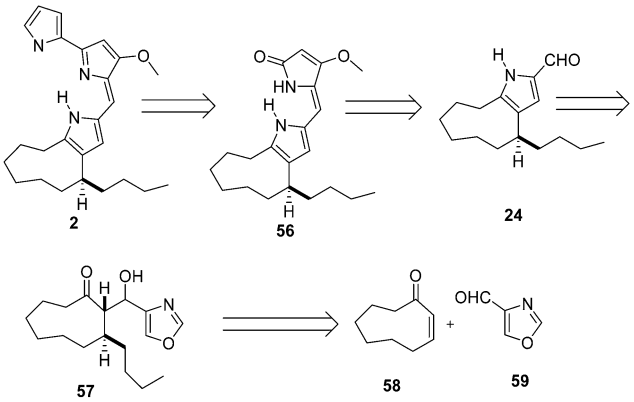
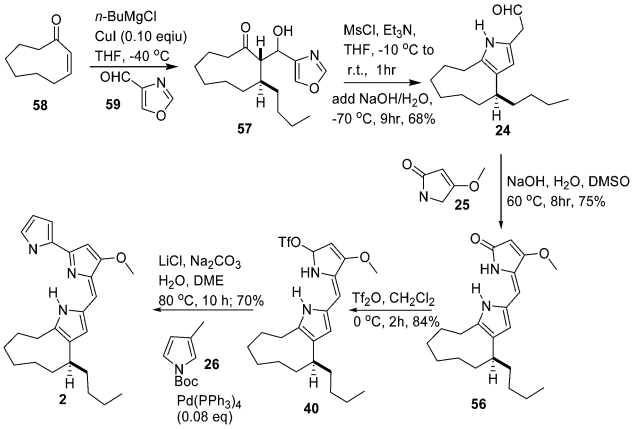


Fig. 11 Reeves' retrosynthetic analysis of 2.



Scheme 7 Total synthesis of butylcycloheptylprodigiosin from cyclononenone 58.

Following these synthetic studies, Challis and co-workers[53] isolated a cyclic prodigiosin from *S. coelicolor* M511 and assigned it as streptorubin B (**4**). The findings by Challis and co-workers did not match with the report by Floss and the structural confirmation by both Furstner and Reeves, thus creating a doubt whether BCHP (**2**) is a natural product or not. Thomson and co-workers,[54] in a recent communication reported the detailed studies regarding the electron impact (EI) mass spectra of synthetic BCHP (**2**) and streptorubin B (**4**). These studies motivated by a proposed evolutionary hypothesis have concluded that BCHP (**2**) was not the compound isolated from *S. coelicolor* A3 by Floss and infact was streptorubin B, as indicated by identical EI-MS fragmentation patterns with report of Challis and co-workers. The combination of mass spectral comparisons with genetic and biochemical data provided evidence that BCHP (**2**) is not a natural product produced by *S. coelicolor*.

3.2. Total synthesis of roseophilin

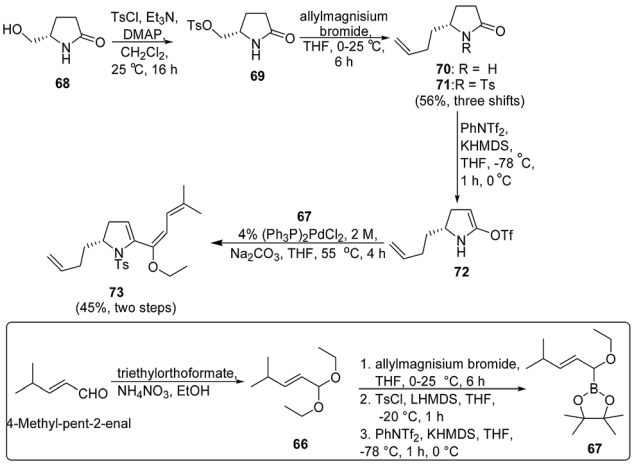
Roseophilin, isolated from the culture broth of *Streptomyces griseoviridis*, is a macrocyclic pigment that exhibit potent cytotoxicity against human cancer cell lines.[55] The presence of unique ansa-bridged cyclopenta[*b*]pyrrole structural core of roseophilin has attracted the attention of synthetic organic chemists towards its partial or total synthesis.[56] The first total synthesis of racemic roseophilin was reported by Furstner[56*o*] while the asymmetric synthesis of *ent*(−)roseophilin and the natural enantiomer was reported by Boger and Tius.[56*m*,*n*] A number of protocols have been developed on the formal synthesis of roseophilin, focused largely on the construction of macrotricyclic core **3**.

3.2.1. Remote stereo-controlled Nazarov cyclization protocol. Occhiato *et al.* has reported the synthesis of **3** *via* highly stereocontrolled Nazarov reaction of divinyl ketones in which one of the double bonds have been embedded in properly substituted N-heterocyclic structure.[57] Retrosynthetic approach

for the synthesis of macrotricyclic core **3** is depicted in Fig. 12 involving the synthesis of ketopyrrole **63** in an enantiopure form by electrocyclization of pyrroline **65**. The presence of correctly oriented buten-3-yl chain on the heterocycle would control the absolute stereochemistry in the Nazarov product **64**.

Thus the treatment of enantiopure **69** with allyl magnesium bromide,[58] under refluxing in the THF[59] led to the synthesis of **70** which was subsequently *N*-tosylated to yield **71**. The lactam **71** was converted to vinyl triflate **72** which was subjected to Pd-catalyzed coupling with α-ethoxydienyl boronate **67** to yield ethoxytriene **73** in good yields (Scheme 8).[60] The hydrolysis of **73** to furnish desired **63** did not proceed under mild acidic conditions while the harsh conditions (80 °C with 20% H_2SO_4) were not compatible with the delicate moieties involved, thus abandoning the developed approach.[61]

Another approach developed by the same workers included a linear sequence starting from enantiopure (*R*)-pyrrolidine **74** which after *O*-TBDMS-protection was transformed into the corresponding vinyl triflate and carbonylated (10% $Pd(OAc)_2$, Ph_3P, Et_3N, CO)[62] in the presence of methanol to yield **76** and 77 (Scheme 9). The synthesized esters *viz.* **76** and 77 were transformed into corresponding Horner–Emmons–Wadsworth reagents **79** and **80** as per the protocol developed by Chiu for related carbacyclic systems olefination[63] yielding the corresponding dienone **82** and **83** which were directly used for electrocyclization in cold TFA. The reaction on completion furnished cyclopentafused **84** and **85** albeit in 40% and 27% yields respectively with subsequent oxidation with DDQ[64] to form **63**. The key intermediate **63** in the synthesis of roseophilin was obtained in eight steps from compound **69** in 3% overall yield.



Scheme 8 Synthesis of ethoxytriene **73**.

3.2.2. Dudley's ring expansion approach. Dudley and co-workers have reported palladium catalyzed annulation/oxidative cleavage sequence for the synthesis of cyclopentanone fused pyrrolophane which serves as a model for the tricyclic core of roseophilin.[65] Retrosynthetic approach for the synthesis of roseophilin is depicted in (Fig. 13) and features oxidative cleavage of a bridged bicyclic system as a synthetic strategy to reveal an appropriately functionalized precursor to the ansa-bridged ketopyrrole.

The methodology initiated with the synthesis of requisite bicycle *via* Buono's enamine bis-allylation protocol.[66] Addition

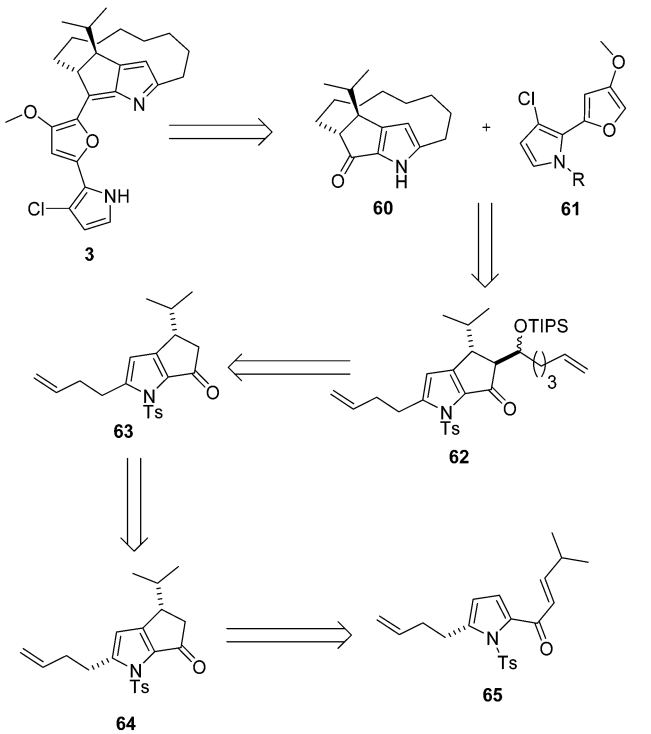
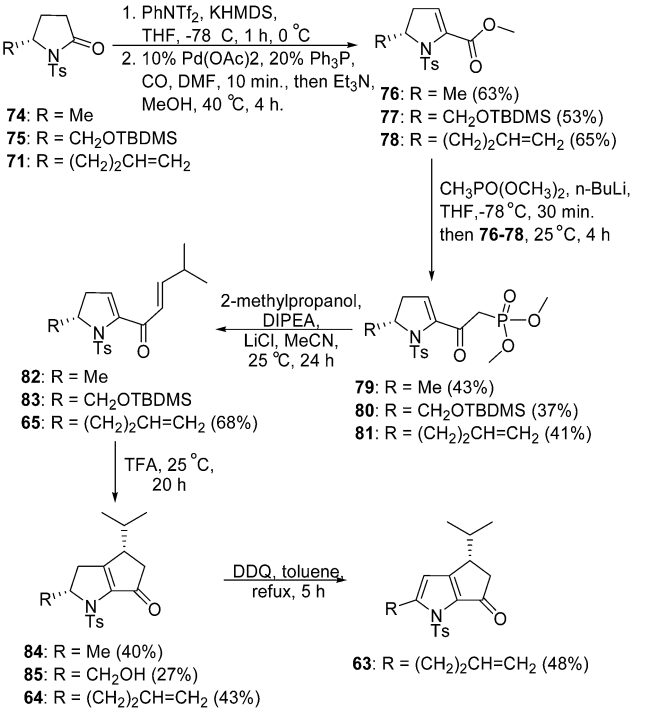


Fig. 12 Retrosynthetic analysis of roseophilin **3**.



Scheme 9 Synthesis of enantiopure bicyclic ketopyrrole **63** *via* electrocyclization of pyrroline **65**.

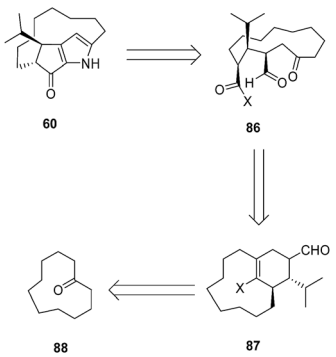


Fig. 13 Retrosynthetic analysis of tricyclic core of roseophilin.

of LDA resulted in an efficient conversion of **91** to **92.** Rubottom oxidation[67] of **92** provided an easy access to **93** which was subjected to subsequent epoxidation using *m*-CPBA to yield **94** in good yields.

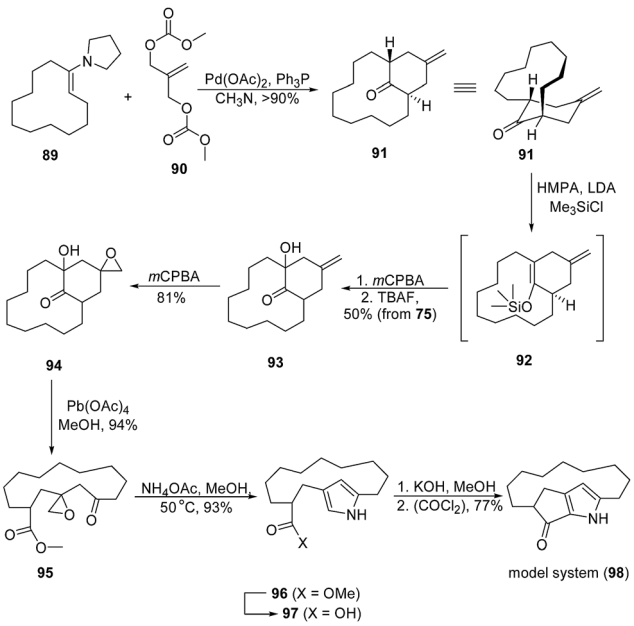
The oxidative cleavage of **94** using lead tetraacetate in methanol afforded the corresponding ketoester **95** which served as an aldehyde equivalent for pyrrole condensation (Scheme 10). Treatment of **95** with ammonium acetate under Paal–Knorr conditions with subsequent saponification of the methyl ester afforded the desired model system **98** *via* an intramolecular Friedel–Crafts acylation reaction.

3.2.3. Frontier's formal synthesis of (±)roseophilin. A formal synthesis of (±)-roseophilin was reported by Frontier.[68] The retro-synthesis was elucidated in Fig. 14 and involved the preparation of macrocyclization precursor **99**, obtained *via* Nazarov cyclization[69] of pyrrolyl-vinyl ketone **100** which in turn could be assembled *via* [3 + 2]cycloaddition/chelotropic extension of the alkynyl ester **101**.[70]

The synthesis involved an initial desymmetrization of cyclohexene **102** with subsequent Jones oxidation of the intermediate aldehyde to provide carboxylic acid **103** (Scheme 11).[71] The refluxing of **103** with trifluoroacetic anhydride and *N*-tosylpyrrole resulted in the selective acylation to form ketopyrrole.[72] Reductive deoxygenation of ketopyrrole using zinc iodide and sodium cyanoborohydride provided the corresponding ester **104.**[73] The treatment of **104** with DIBAL-H with subsequent Swern oxidation provided the corresponding aldehyde **105** which was converted to α,β-unsaturated ester **106** *via* reaction with methyldiethyl phosphonoacetate using Horner–Wadsworth–Emmons[74] conditions.

The synthesized **106** upon Vilsmeier–Haack formylation[75] led to the formation of pyrrolyl carboxaldehyde **107** which upon Corey–Fuchs transformation[76] afforded gem-dibromoalkene **108** (Scheme 12).

Reduction of **108** with DIBAL-H and subsequent silylation of alcohol **109** yielded gem-dibromoalkene **110** which was converted to corresponding alkyne **111.** Corey–Fuchs sequence selective deprotonation of **111** with lithium hexamethyldisilazide and subsequent addition of methylchloroformate yielded alkynyl ester **112.** [1,3]-Dipolar cycloaddition reaction of **112** with nitrone **113** provided the corresponding isoxazole **114.**



Scheme 10 Synthesis of roseophilin's ketopyrrole unit **98**.

The synthesis of Nazarov cyclization precursor was affected by treatment of **114** with a slight excess of *m*-chloroperbenzoic acid (*m*-CPBA) at 0 °C affording the β-ketoester **115** (Scheme 13). The silyl protecting group in the Nazarov substrate **115** was exchanged with an acetyl protecting group to yield **116** which was subsequently heated with the catalytic amount of scandium(III)triflate and 1 eq. of perchlorate providing the Nazarov product **117.**[77]

The addition of sodium enolate of **117** to a refluxing solution of tetrakis(triphenylphosphine)palladium provided a 4 : 1 mixture of macrocycle **118** to a product resulting from β-hydride elimination **A** as shown in Scheme 14.

Recrystallization led to the isolation of **118** which upon hydrogenation and subsequent deprotection of the pyrrole nitrogen furnished the macrocyclic β-ketoester **119** (Scheme 15). Krapcho dealkoxy carbonylation of **119** in the final step delivered **60** in good yields.

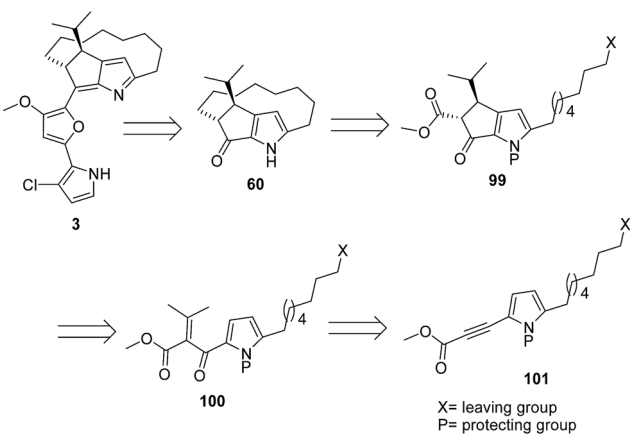
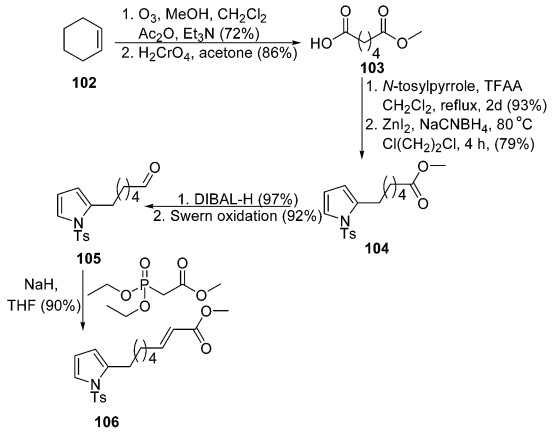
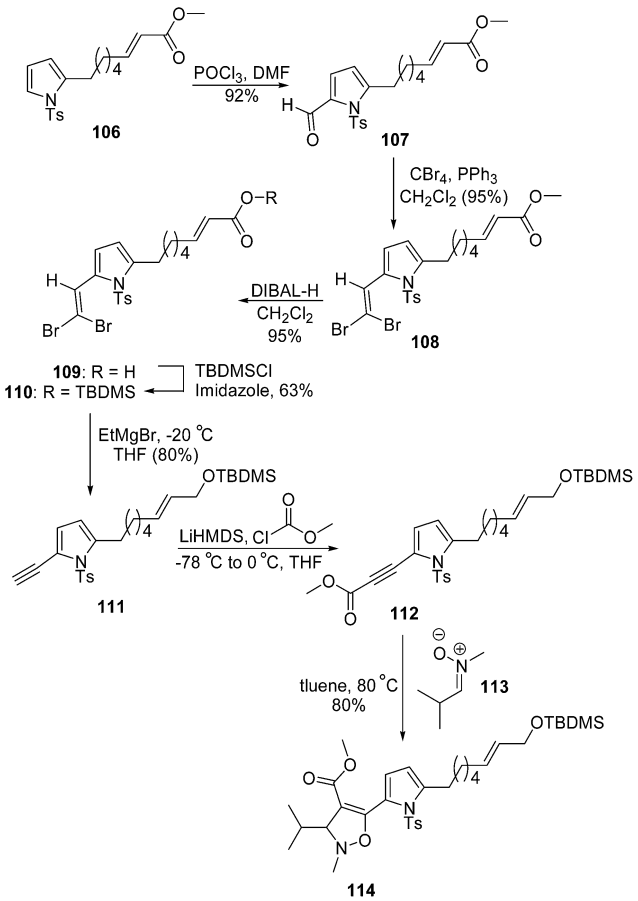


Fig. 14 Retrosynthetic analysis of **3**.

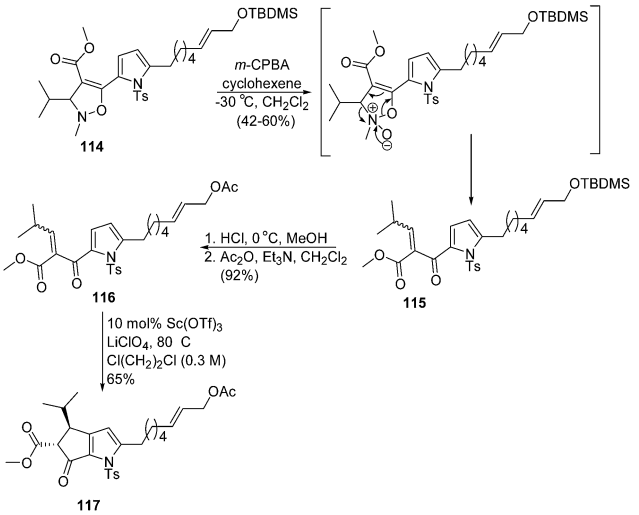


Scheme 11 Synthesis of α,β-unsaturated ester **106**.



Scheme 12 Synthesis of isoxazoline-4-methyl ester **114**.

3.2.4. Chang's convergent formal synthesis of (±)macrotricyclic core of roseophilin. A facile convergent synthesis of tricyclic core of roseophilin was reported by Chang and coworkers[78] involving tandem pyrrole acylation–Nazarov cyclization reaction as the key step for the for the formation of cyclopenta[*b*]pyrrole moiety (*i.e.* **122** + **123** → **121**) as shown in the retrosynthetic analysis.[69b] A late stage intramolecular



Scheme 13 Synthesis of Nazarov cyclized product **117**.

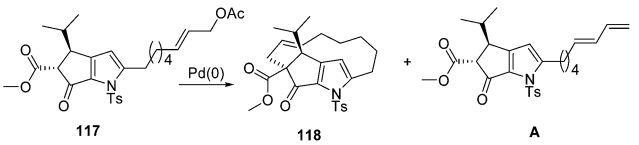
Tsuji–Trost reaction in case of **120** eventually will close the 13-membered ring affording **60** as shown in Fig. 15.

The methodology involved a regioselective acylation of *N*-tosylpyrrole **126** with 6-heptenoic acid[79] in the presence of TFAA to yield acylpyrrole **127**.[72] Reduction of carbonyl in **127** using borane-*tert*-butylamine complex in the presence of aluminium trichloride[80] led to the synthesis of 2-(6′-hetenyl)-pyrrole **123**.

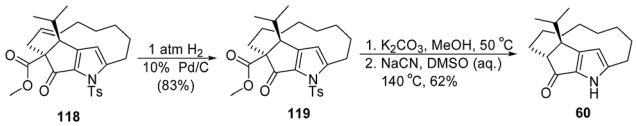
Another precursor 2-methoxy carbonyl-4-methyl pentenoic acid **122** was obtained *via* Knoevenagel condensation[81] between *tert*-butyl methyl malonate and isobutyraldehyde with subsequent removal of protecting group with TFA (Scheme 16). Tandem pyrrole acylation–Nazarov cyclization between **122** and **123** using TFAA resulted in the formation of variety of products. A variety of Lewis acids were employed to improve the yield of desired cyclopenta[*b*]pyrrole derivative **121**. $FeCl_3$ proved to be the most useful in the formation of **121** in 75% isolated yield. Cross olefin metathesis reaction of **121** with allylacetate gave **120** whose palladium catalyzed intramolecular Tsuji–Trost reaction[56e,h] resulted in **128** in moderate yields.

3.2.5. Total synthesis of (±)roseophilin *via* its 2-azafulvene prototropisomer. Harran *et al.* reported the total synthesis of (±)-roseophilin *via* 2-azafulvene prototropisomer.[82] Retrosynthetically, the approach involved two generic components *viz.* **130** and **131** linked in such a manner that C_9 in **129** would be at the oxidation state of a ketone. The α-olefin in **131** would incorporate the third component *viz.* **132** *via* alkene metathesis (Fig. 16).

The synthetic approach initiated with lithiation of methoxyfuran **133** with its subsequent $ZnBr_2$–Pd catalyzed carboxylation



Scheme 14 Palladium(0)-promoted macrocyclization of **117**.



Scheme 15 Synthesis of macrotricyclic core **60** of roseophilin.

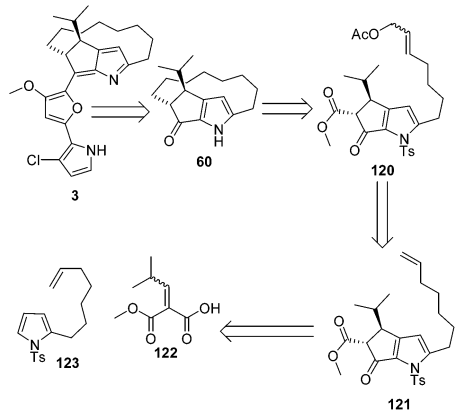
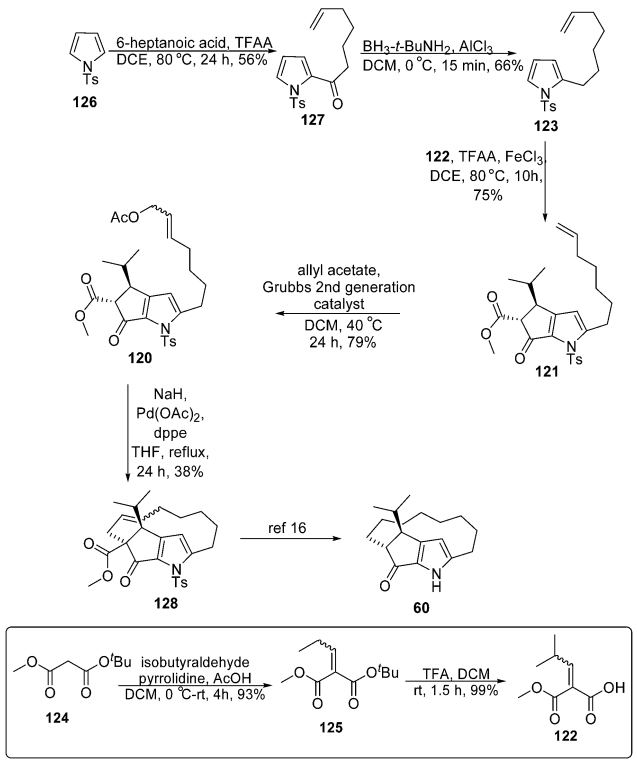


Fig. 15 Retrosynthetic analysis of roseophilin.



Scheme 16 Synthesis of roseophilin's macrotricyclic core **60**.

to yield the corresponding carboxylic acid **134** (Scheme 17).[83] Condensation of **134** with 1-(methanesulfonyl)-1*H*-benzotriazole afforded the corresponding amide which was acylated with 2-(8-nonenyl)pyrroleby using $TiCl_4$ (ref. 84) to yield the corresponding bis-heteroaryl ketone **135** in high yields. Treatment of **135** with KH and diethylchlorophosphite gave the *N*-phosphinyl derivative which was oxidized to corresponding phosphoramide **136.**[85] Metathesis of **136** with isopropyl ketone **137** (ref. 86) with subsequent *in situ* Pd-catalyzed hydrosilylation[87] gave the ketone **138** as an amber oil. The treatment of **138** with crown ether/KHMDS combination at 55 °C resulted in the gradual formation of pyrrolophane **141**, probably *via* a kinetic enolate **139** in equilibrium with hindered aldol salt **140.** The elimination of potassium diethyl phosphate from **141** afforded **142.** Hydrogenation of **142** in the presence of catalyst generated from $Rh(cod)_2OTf$ and a Josiphos ligand led to the isolation of *cis*-β-pyrrolyl ketone **144** with high diastereoselectivity (>25 : 1). Cyclo-dehydration of **144** using $[ReBr(CO)_3(thf)]_2$ smoothly afforded the unstable 2-azafulvene **145.** The unstable 2-azafulvene **145** was not isolated and treated *in situ* with dry HCl and substiochiometric amounts of *t*-BuOH to yield roseophilin hydrochloride **3** in 32% over all yields.

3.3. Total synthesis of streptorubin B

3.3.1. Chang's synthesis of streptorubin B core. Chang and co-workers have reported the synthesis of streptorubin B core starting from *trans*-4-hydroxyproline using intramolecular ring closing metathesis as the key step.[88] Retrosynthesis of streptorubin B core is as depicted in Fig. 17 and envisioned to involve a series of functional group transformations of *trans*-4-hydroxyproline **151** (ref. 89) to yield 2-substituted pyrrolidin-4-one **150.** Grignard addition to **150** with subsequent intramolecular ring closing metathesis would result in the formation of **147.** A sequence of hydrogenation dehydration reactions led to the synthesis of bicyclic pyrrole segment **147**, reported previously by Furstner and co-workers,[39] whose acid catalysed condensation with a known bipyrrole aldehyde **146** may result in the streptorubin B.

Synthetic protocol initiated with the synthesis of prolinol **152** from *trans*-4-hydroxyproline **151** *via* a sequence of four step reaction including esterification, tosylation, silylation and reduction. Prolinol **152**, thus obtained was transformed into α,β-unsaturated ethyl ester **153** *via* Swern oxidation and subsequent Wittig olefination (Scheme 18). Hydrogenation of **153** using hydrogen and catalytic amount of 10% palladium on carbon followed by reduction using lithium aluminium hydride resulted in the isolation of alcohol **154.** Pyridinium chlorochromate promoted oxidation of **154** with subsequent olefination with methyltriphenylphosphonium iodide gave the corresponding olefin **155.** The olefin **155** was desilylated with tetra-*n*-butylammonium fluoride and oxidized with pyridinium

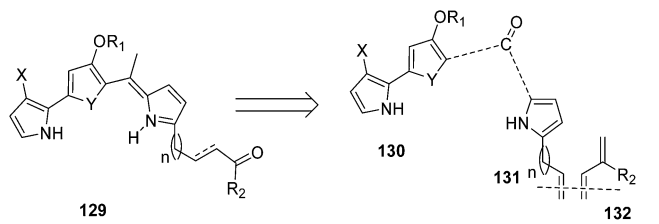
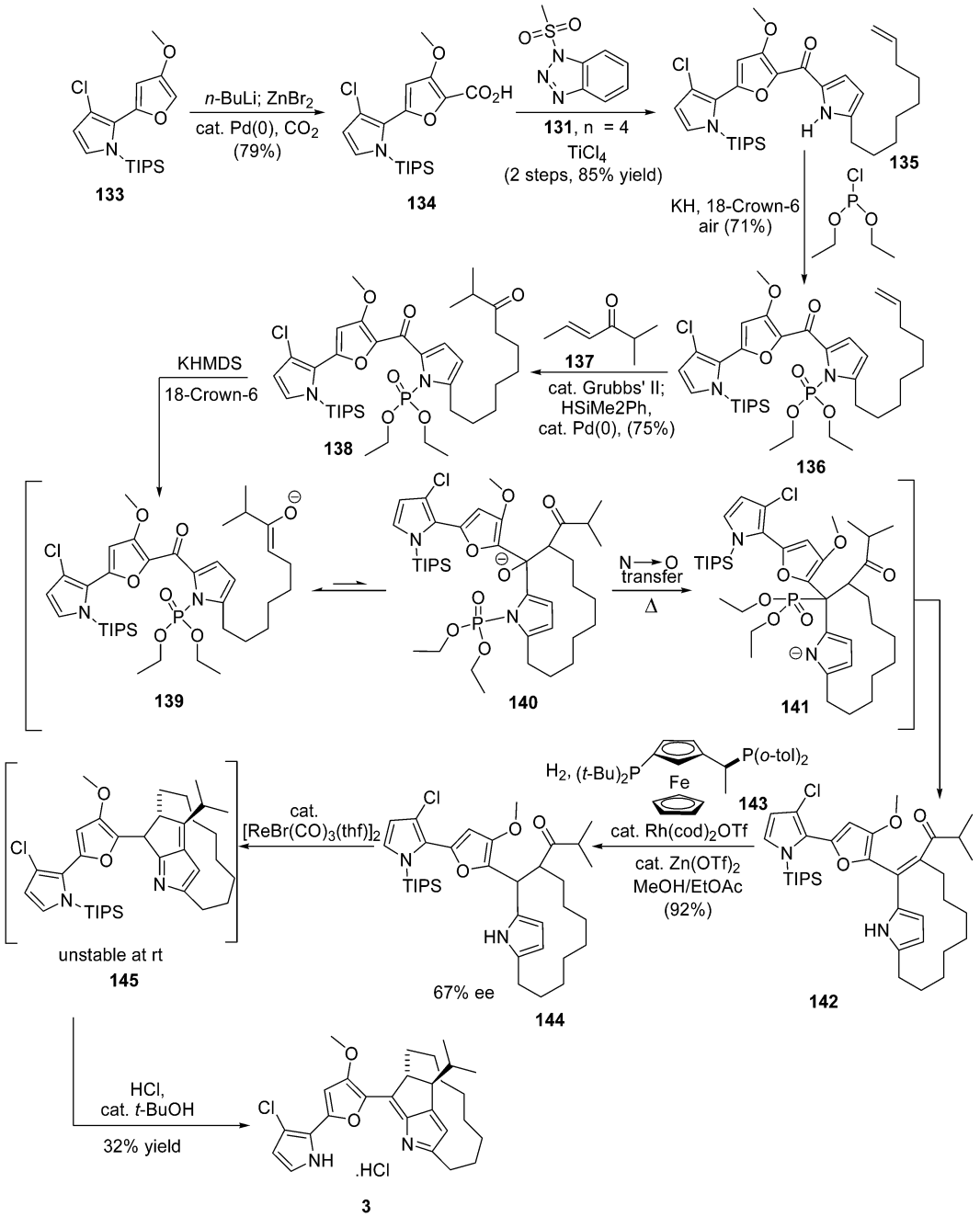


Fig. 16 Design and assembly of seco precursors.



Scheme 17 Total Synthesis of (+)-roseophilin **3**.

chlorochromate to result in the synthesis of ketone **150**. Grignard addition of 1-nonenyl-5-magnesium bromide **156** to the ketone **150** with subsequent ring closing metathesis using second generation Grubbs catalyst resulted in **157** in 58% yield. The product **157** was then transformed to known Furstner's intermediate **148** *via* hydrogenation with 10% Pd on carbon with subsequent dehydration by using boron triflouride etherate.

3.3.2. Thomson's enantioselective synthesis. Although, the structure and identity of streptorubin is beyond any doubt, Weyland and co-workers[30] noted an element of planar stereochemistry which may lead to the presence of two potential atropdiastereomers depending upon the relative stereochemistry of the butyl side chain and the bis pyrrole side arm (Fig. 18).

To solve this problem, Thomson and co-workers[90] has recently described the enatioselective total synthesis of streptorubin B involving a one pot enatioselective aldol cyclization/Wittig reaction and an anionic oxy-cope rearrangement as the key steps. The retrosynthesis devised for the preparation of streptorubin involved an initial disconnection of the bis-pyrrole side arm to generate the pyrrolophane core **158** (Fig. 19). Paal–

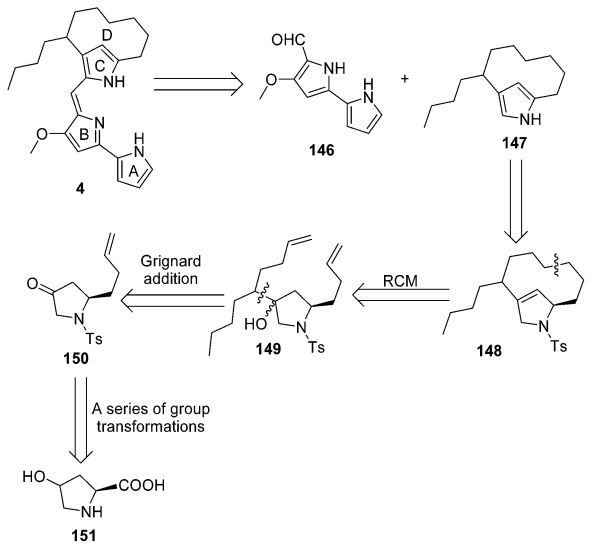
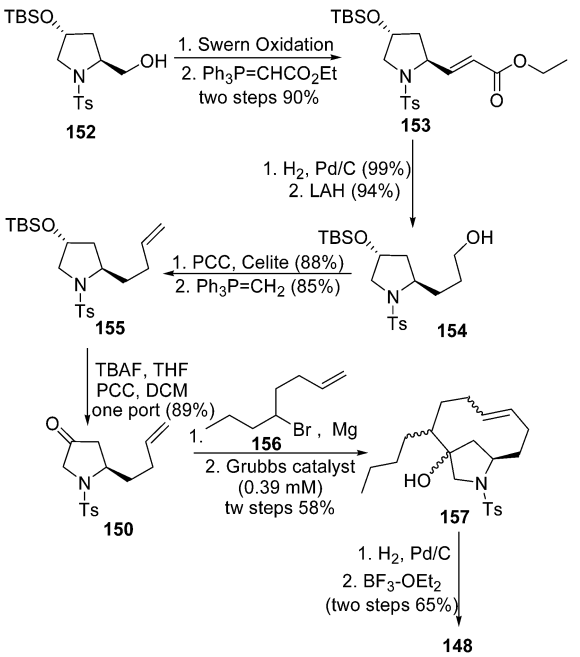


Fig. 17 Retrosynthetic analysis of streptorubin B.



Scheme 18 Synthesis of streptorubin B core structure (Furstner's intermediate **148**).

Knorr simplification of **158** with subsequent functional group interconversions led to the cyclodecanone **159,** containing the full retron for the anionic oxy-cope rearrangement.[91] The functionalized cyclohexanol precursor **160** could be assessed *via* a proline-catalysed enantioselective desymmetrizing intramolecular aldol reaction of dialdehyde **162** (ref. 92) with subsequent *in situ* Wittig reaction to form **161.**

Thus the treatment of **164**, obtained in a single step[93] from commercially available cycloheptene **163,** with 10 mol% (*s*)-proline with subsequent addition of ylide **166** resulted in the isolation of homoallylic alcohol **161** as a major diastereomer

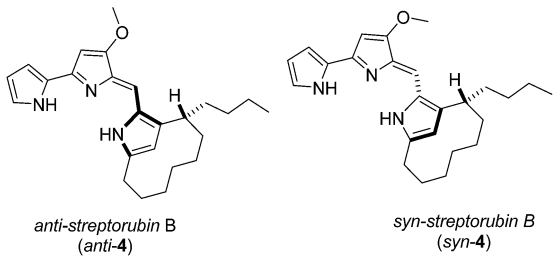


Fig. 18 Atropisomerism within streptorubin B.

(98 : 2 mixture of enantiomers). **161** upon oxidation followed by addition of the vinyl anion **167** (ref. 94) gave the precursor **160** required for anionics oxy-Cope rearrangement with an 97 : 3 ee. Treatment of alcohol **160** with KHDMS and 18-crown-6 yielded the desired 10-membered ring **159** with an enantiopurity of 97 : 3. The alkene reduction in **159** with concomitant benzyl ether cleavage, oxidation of the liberated alcohol to the aldehyde and the Paal–Knorr pyrrole synthesis afforded the pyrrole core **158.** Acid promoted condensation between pyrrole **158** and aldehyde **169,**[95] with subsequent removal of the Boc group *via* methanolysis yielded **4** in an enantioselective manner (Scheme 19). The streptorubin B **4** was prepared in nine steps from **163** in 20% overall yield. The comparison between CD spectra of synthesized and natural sample of streptorubin B coupled with X-ray crystallography confirmed the absolute stereochemistry of this prodigiosin.

3.4. Total synthesis of metacycloprodigiosin

3.4.1. Enantioselective synthesis of metacycloprodigiosin *via* merged conjugate addition/oxidative coupling approach. The first enantioselective synthesis of the biologically active metacycloprodigiosin **5** was devised by Thomson and coworkers.[96] The success of this protocol was hinged upon the controlled oxidative coupling of unsymmetrical silyl bis-enol intermediates[97] followed by 1,4-addition of Grignard reagent.

The synthesis of metacycloprodigiosin was initiated with the treatment of ethyl magnesium bromide to enone **170** using 6 mol% (*R*,*S*)-Josi Phos leading to an intermediate which was trapped with chlorosilane **171** yielding silyl bis-enol ether **172** (Scheme 20). **172** was directly subjected to the oxidative bond formation using ceric ammonium nitrate and di-*tert*-bu-

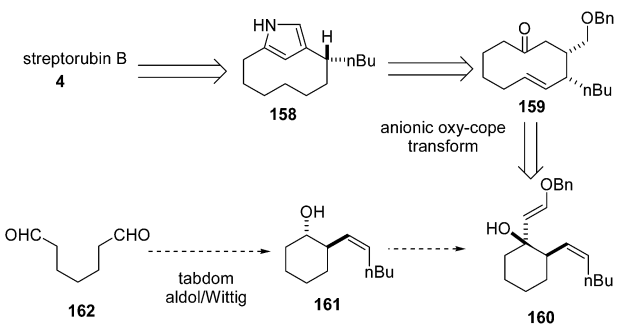
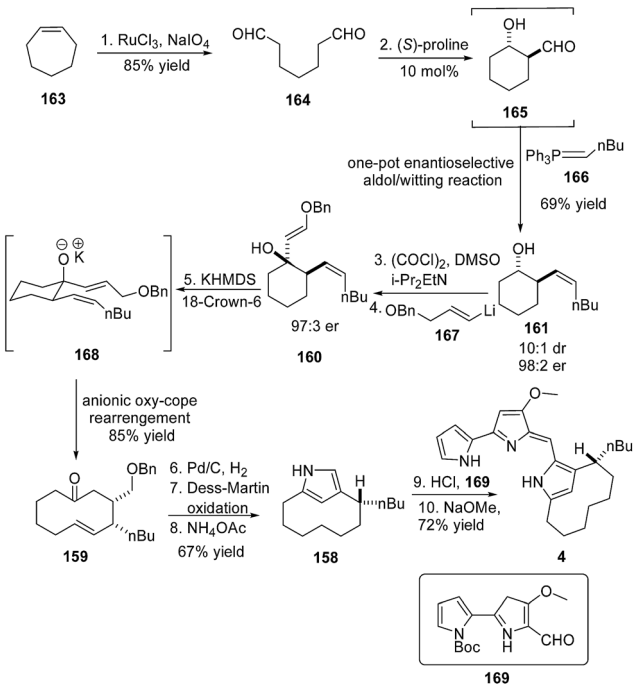
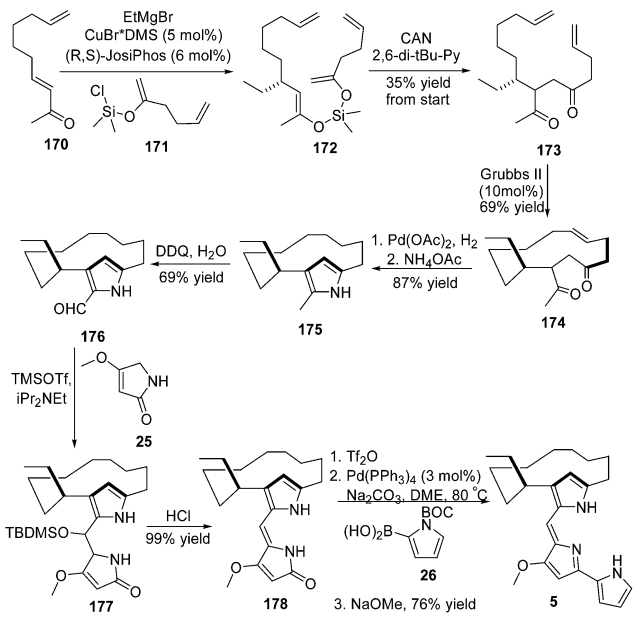


Fig. 19 Synthetic plan for the preparation of streptorubin B.



Scheme 19 Enantioselective total synthesis of streptorubin B.

pyridine affording dione **173** as a mixture of diastereomers. The treatment of dione **173** with 10 mol% of Grubbs second generation catalyst[98] led to the synthesis of 12-membred ring **174.** Subsequent hydrogenation with $H_2/Pd(OH)_2$ gave the fully saturated system which was converted to pyrrole **175** upon treatment with ammonium acetate. Trimethyl silyltriflate-mediated aldol coupling of **176** with **25** (ref. 99) gave ether **177** which upon treatment with HCl in THF afforded the requisite lactam **178.** Triflation of **178** with subsequent Suzuki cross-coupling with pyrrole **26** afforded metacycloprodigiosin **5** in 76% yields.



Scheme 20 Enantioselective Synthesis of Metacycloprodigiosin **5**.

3.5. Total synthesis of marineosins

Marineosin is a macrocyclic spiroaminal alkaloid isolated from marine-derived *Streptomyces* related actinomycete and exist as marineosin A and marineosin B.[100] Marineosin A displays potent inhibition against colon carcinoma cell growth, with an IC_{50} of 0.5 μM in HCT-166 cells.[100]

3.5.1. Lindsley's attempted total synthesis marineosins. The biosynthesis of marineosin A and B, as proposed by Fenical,[100] include an inverse electron demand hetero-Diels–Alder reaction to form the pyran ring and spiroaminal in a single step. In order to test the proposed biosynthesis, Lindsley and co-workers[101] have reported the total synthesis of acyclic biosynthetic intermediate and attempted the biomimetic synthesis of marineosin. Retrosynthetically, the approach would involve the condensation between the bis-pyrrole **146** and the enone containing pyrrole **179** to deliver the Diels–Alder substrate **180.** Intramolecular inverse-electron-demand hetero-Diels–Alder reaction of **180** would afford the desired spiroaminal core **181** with subsequent reduction as depicted in Fig. 20.

The synthetic methodology involved an initial Vilsmeier–Haack haloformylation of 4-methoxy-3-pyrrolin-2-one **25** to yield the bromoenamine **183.** Suzuki coupling of **183** with Boc-1*H*-pyrrol-2yl-boronic acid **26** afforded the Boc-protected analogue **169** in 48% yields (Scheme 21).

Another intermediate **179,** was prepared by a sequence of synthetic steps as shown in Scheme 22 involving the addition of Grignard **185** to pyrrole–aldehyde **184** to yield the corresponding secondary alcohol **186.** Ley oxidation of **186** yielded the ketone **187** which upon Muchowski's one-pot cascade synthesis led to the isolation of **188.**[102] Cross-metathesis of **188** with **189** in the presence of Grubbs II catalyst[103] resulted in the isolation of desired **179** along with the conjugate addition products **190** and **191.** Interestingly, increasing catalyst loading and lowering the temperature from 0.5 to 30 mol% improved the yield of cross-metathesis product **179** (40% yield).

Acid promoted condensation of biosynthetic fragments **179** and **169** delivered the C1–C25 acyclic precursor **180,** required

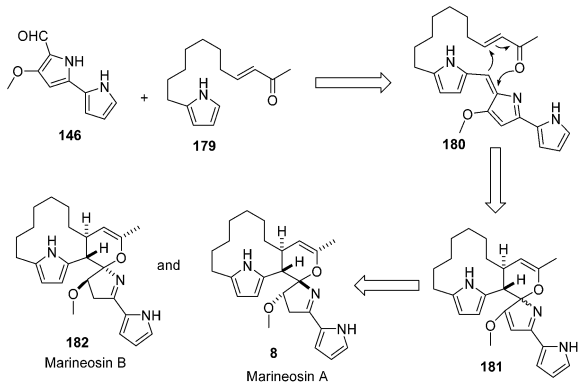
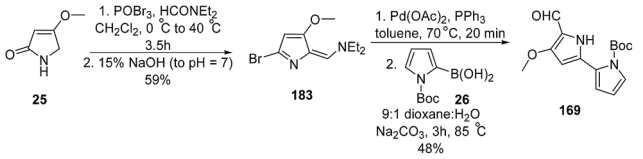
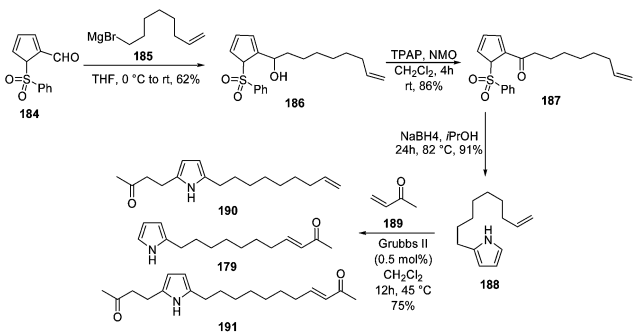


Fig. 20 Retrosynthetic approach for the synthesis of marineosin A and B.



Scheme 21 Synthesis of C1–C9 protected bis-pyrrole **169**.

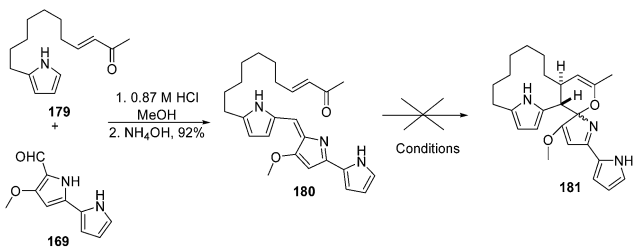


Scheme 22 Synthesis of C1–C25 Diels–Alder substrate **179**.

for the proposed inverse-electron-demand hetero-Diels–Alder reaction. However, the use of varied reaction conditions (heat, microwave, photochemical, Lewis acid catalysis, mineral acid, solvent and additives) to carry out the inverse-electron-demand hetero-Diels–Alder reaction failed to deliver **181** from **180**, which was further supported by modelling studies (Scheme 23).

3.5.2. Lindsley's enantioselective total synthesis of macrotricyclic pyran core of marineosin A. Lindsley and co-workers,[104] in a recent communication reported the enantioselective construction of the 12-membered macrocyclic pyrrole core of marineosin A from (*s*)-propylene oxide. Retrosynthesis of marineosin **8** relied upon the synthesis of spiroaminal **192** *via* acid mediated cyclization of intermediate **193** (Fig. 21).

A Paal–Knorr pyrrole synthesis with subsequent ring closing metathesis (RCM) would facilitate the formation of macrocycle **194** from 1,4-diketone **195. 195** in turn, would be obtained *via* key setter reaction from **196** which is a critical intermediate derived from Evan's auxillary phosphonate **197**, vinyl magnesium bromide and (*s*)-propylene oxide as depicted in Scheme 24. The synthetic protocol involved a copper catalyzed Grignard addition to (*s*)-propylene oxide **198** with subsequent *in situ* silylation of the resulting alcohol to yield olefin **200**. Ozonolysis of **200** resulted in the corresponding aldehyde **201** which upon



Scheme 23 Synthesis of C1–C25 Diels–Alder substrate **180**.

Horner–Wadsworth–Emmons olefination with Evan's auxillary phosphonate, prepared in two steps from (*R*)-oxazolidinone **204**, yielded acyloxazolidinone **205**. Cu-promoted conjugate addition of allyl magnesium bromide to **205** delivered **206** with >20 : 1 dr.

Another intermediate **207** was prepared *via* an initial mono-PMB protection of *cis*-butene-1,4-diol to yield alcohol **208** with subsequent oxidation using MnO_2 to yield **209.** $TiCl_4$-mediated aldol reaction of **206** with **209** under Crimmin's conditions delivered Evan's *syn* product **210** with 10 : 1 dr as shown in Scheme 25.[105,106] Hydrolysis of the auxillary with $LiBH_4$ generated corresponding alcohol which was immediately protected as TIPS silyl ether **211** (Scheme 25). $VO(acac)_2$-promoted epoxidation of **211** yielded the oxirane **212** as a single stereoisomer.[107] The secondary alcohol functionality in **212** was protected as the benzyl ether while subsequent removal of PMB group using DDQ led to the formation of primary alcohol **213.** The ring opening of epoxide using Red-Al yielded 1,3-diol **214** with >20 : 1 ratio over the 1,2-diol congener.[108] The primary hydroxyl group in **214** was subsequently protected as a pivalate while secondary alcohol was converted to methyl ester affording **197** as a key intermediate.

Deprotection of TIPS in **197** using $BF_3 \cdot OEt_2$ resulted in the formation of primary alcohol **215** which upon oxidation by using Parikh–Doering condition led to the aldehyde **216** (Scheme 26).[109,110] A two step sequence *viz.* addition of vinyl Grignard reagent with subsequent Dess–Martin periodinane oxidation resulted in the corresponding α,β-unsaturated ketone **217**. Reaction of **217** with 6-heptenal under Stetter conditions yielded **218** which upon ring closing metathesis using Grubbs I catalyst (30%) afforded the desired RCM product **219**. Microwave promoted reaction of **219** using ammonium acetate in methanol delivered the desired macrocyclic pyrrole moiety **194** of marineosin **8** in 5.1% overall yield.

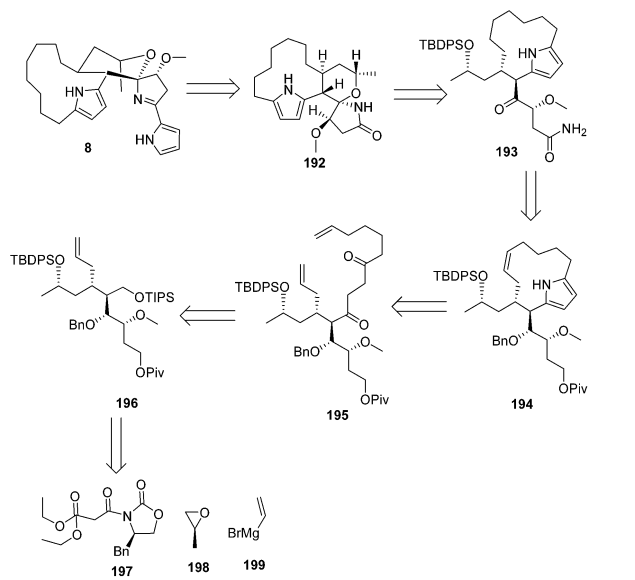
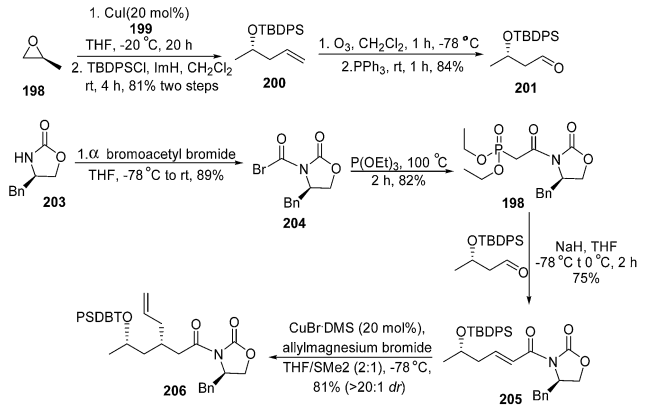
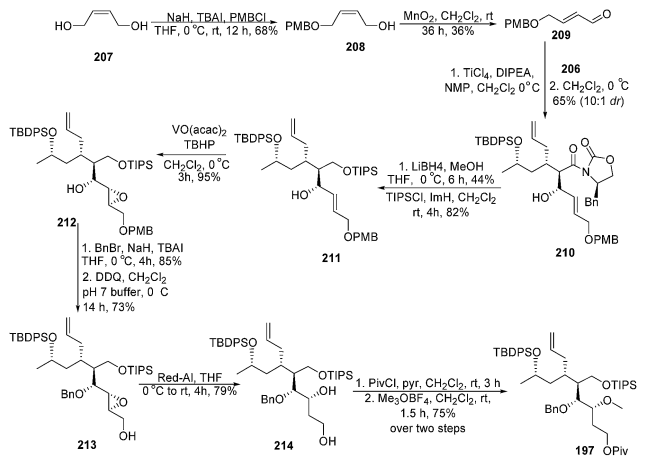


Fig. 21 Retrosynthesis of marineosin A **8**.



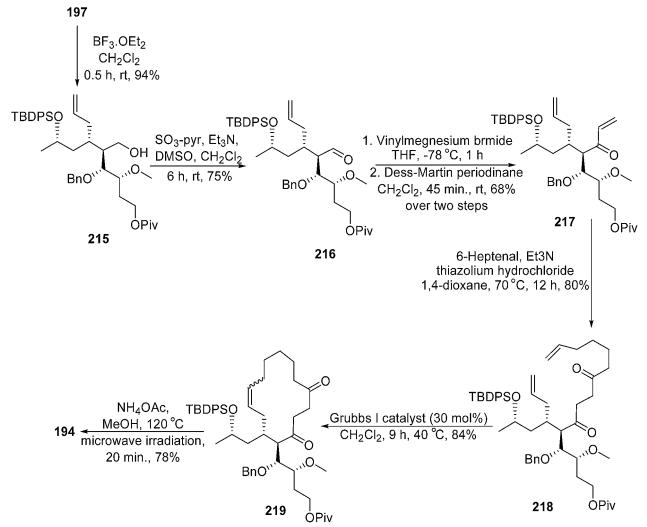
Scheme 24 Synthesis of advanced intermediate **206**.



Scheme 25 Synthesis of key intermediate **197**.

3.5.3. Synthesis of spiroiminal moiety of marineosin A and B by Snider. Snider *et al.*[111] reported the total synthesis of spiroiminal moiety of marineosins A and B starting from methyl valerolactone. The retrosynthetic route is as depicted in Fig. 22 and involved the spiroiminal formation from **220** which in turn was obtained from ketoisoxazoline **221** *via* hydrogenolysis of the N–O bond over RANEY® nickel with spontaneous formation of the hemi-iminal and subsequent *O*-methylation. Isoxazoline **221** would be obtained *via* nitrile N-oxide cycloaddition of vinylmagnesium bromide to lactone **222.**

The synthetic protocol was initiated by the addition of vinyl magnesium bromide to the readily available lactone **223** to yield the hydroxyketone **224.**[112] The hydroxyketone **224** was subsequently protected as its triethyl silyl ether to afford the corresponding enone **225** as shown in Scheme 27. Reaction of **225** with benzaldehyde oxide, *N*-chlorosuccinimide and triethylamine provided the corresponding isoxazoline **226a** which upon hydrogenolysis over RANEY® nickel led to the formation of hemi-iminal **227a** as a mixture of isomers. Sodium hydride promoted methylation of **227a** gave the methyl ether iminal **228a** with subsequent hydrolysis of triethyl silyl ether to result in the desired spiroiminals **230a**, **231a** and **233a**. The major



Scheme 26 Synthesis of marineosin A's macrocyclic pyrrole **194**.

isomer **230a** showed equilibration in 2 weeks to give 19 : 1 mixture of **230a** and **232a**, establishing the identical stereochemistry at C-4 and C-7 (Scheme 28). The methodology developed for the synthesis of phenyl-substituted spiroiminals was further extended towards the synthesis of spiroaminals with a pyrrole substituent. Thus, the treatment of **225** with the oxime of *N*-SEM-pyrrole-2-carboxaldehyde[113] NCS and Et_3N at −78 °C in THF afforded isoxazoline **226c** in <30% yield. However, the reaction of *N*-SEM-pyrrole-2-carboxaldehyde oxime with 5% aqueous NaOCl[114] generated the nitrile N-oxide which gave **226c** in 73% yield. Hydrolysis of triethyl silyl ether functionality in **228c** with 2 M aqueous hydrochloric acid gave the protected spiroaminals **230c** in an inseparable equilibrium mixture with **231c** and **233c**. Deprotection of **230c** with TBAF and molecular sieves in THF at 60 °C afforded spiroaminal **230b** in 54% yields.

3.6. Total synthesis of cycloprodigiosin

Cycloprodigiosin is a red pigment obtained from the bacterial strains *Pseudoalteromonas (Alteromonas) rubra*, *Pseudoalteromonas denitrificans*, and *Vibrio gazogenes*.[115] Although this natural product was known for a long time, its true structure was only secured in 1983.[116] Cycloprodigiosin has been reported as a

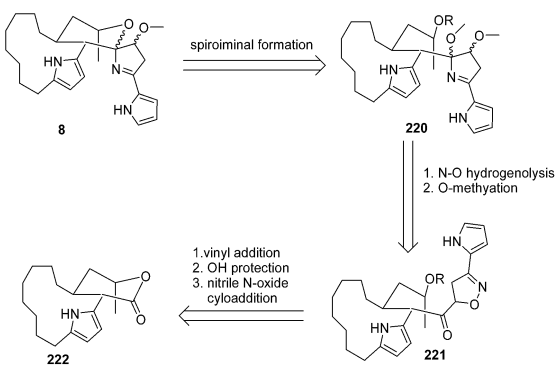
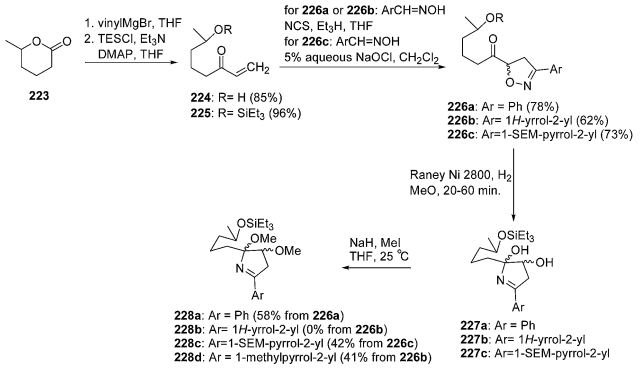
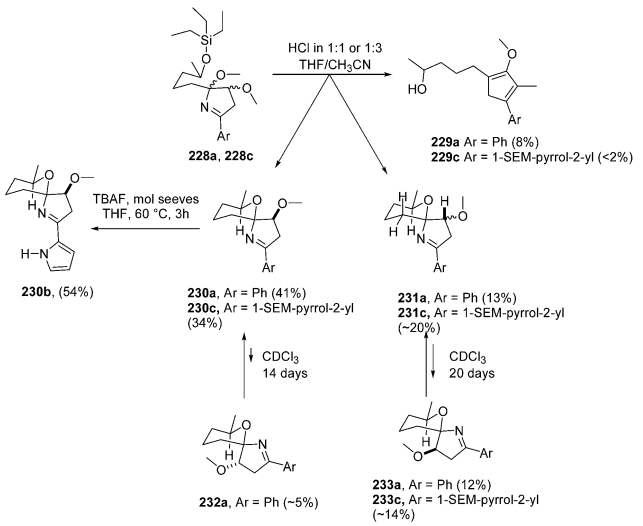


Fig. 22 Retrosynthesis of the marineosin.



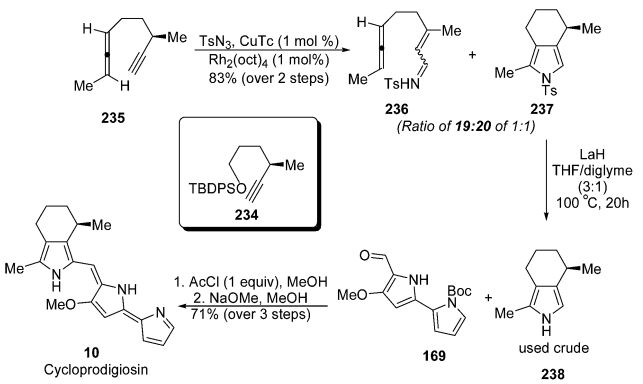
Scheme 27 Preparation of iminal **228**.



Scheme 28 Preparation of spiroiminlas **230a,c**, **231a,c** and **232a,c**.

potent proapoptotic anticancer compound[117] and immunosuppressant.[118] The first synthesis of cycloprodigiosin, was reported by Wasserman in 1984.[119]

3.6.1. Sarpong's total synthesis of cycloprodigiosin. Sarpong and co-workers[120] in a recent communication disclosed the total synthesis of cycloprodigiosin *via* Rh-trimethylenemethane



Scheme 29 Synthesis of cycloprodigiosin **10**.

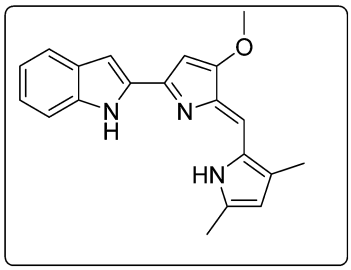


Fig. 23 Prodigiosin derivative Obatoclax (GX15-070).

variants generated from the interaction of a Rh-carbenoid with an allene. The synthetic methodology initiated with an enantioenriched allenylalkyne **235**, prepared in six steps from alkyne **234** as a mixture of diastereomers.[121] The treatment of **235** with TsN_3 in the presence of copper(I) thiophene-2-carboxylate (CuTc) and $Rh_2(oct)_4$ resulted in the isolation of a mixture of α,β-unsaturated imine **236** and the desired pyrrole **237** (Scheme 29). Lithium aluminium hydride (LAH) promoted removal of tosyl group led to the formation of pyrrole **238**.[122] Condensation of **238** and **169** under Lindsley's[101] condition afforded cycloprodigiosin **10** in 71% overall yield.

4. Conclusion

Prodigiosins (PGs) constitute a family of natural red pigments isolated mostly from Gram-negative bacteria, with promising therapeutic potential and characterized by a common pyrryldipyrrylmethene core with varying side chains. These scaffolds display a broad spectrum of activities such as anti-microbial, anti-malarial, anti-cancer and immunosuppressive. *In vitro*, prodigiosins essentially target the cancer cells irrespective of the p53 status with little or no effect on the normal cells. In addition, prodigiosins are considered useful in cancer cells associated with multidrug resistance phenotype and defects in apoptotic pathways, substantiating their role as attractive candidates for further development. Mechanistically, prodigiosins have been found to target different signaling pathways probably through induction of DNA double strand breaks and/or neutralization of pH gradients leading to changes in cell cycle proteins and apoptosis. PGs are also attracting increasing attention as immunosuppressive agents for preventing allograft rejection and autoimmunity. Unlike the well-known immunosuppressant cyclosporin A, PGs do not inhibit the secretion of IL-2 but inhibit the mitogenic signaling from IL-2, suggestive of a different mechanism of action. Therefore, PrGs appear to be potential candidates for pharmaceutical development as immunosuppressants and also as anti-cancer agents. Prodigiosin is currently under preclinical trials for pancreatic cancer treatment while its derivative Obatoclax (GX15-070) Fig. 23, commercially developed by the pharmaceutical company Gemin X Pharmaceuticals, is in phase I/II clinical trials on leukemia, lymphoma, and solid tumor malignancies.

The synthetically strenuous prodigiosins with enthralling biological potential will always be an attraction for synthetic

organic chemists. The examples cited in the review, summarizes both the achievements and contribution of organic synthesis in total synthesis of bacterial prodigiosins. Note-worthy are the explicit assignment of structures to prodigiosins and the remarkable control of stereoselectivity demonstrated in some synthesis.

One of the crucial factors impeding the clinical development of prodigiosins is their high synthetic cost and therefore the development of simple and concise routes for the enantioselective synthesis of prodigiosins and their analogues with biological relevance is indeed desirable.

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