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Research Article

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Strategic Application of Synthon Disconnection Approach in the Synthesis Planning of Antifungal Natural Product "Pyrrolnitrin"

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ABSTRACT

Natural products continue to play a pivotal role in modern drug discovery and development since they are superior new drug leads compared with purely synthetic compounds. The ability to procure useful quantities of natural products approved as pharmaceuticals by simple, scalable routes is emerging as an important goal in natural product synthesis. In this context, synthon disconnection approach pioneered by Prof. E. J. Corey of Harvard University is undoubtedly a useful and powerful tool in planning their synthesis for obtaining higher amounts of natural products. This paper highlights the strategic application of synthon disconnection approach in the synthesis planning of antifungal natural product 'Pyrrolnitrin' keeping a bird's eye view on the works published in journals and patent literatures.

Key words: antifungal, natural products, pyrrolnitrin, synthesis planning, synthon disconnection approach.

INTRODUCTION

Nature is an irrefutable source of inspiration for the discovery and development of potent biologically active compounds. About 30% of the worldwide sales of drugs are based on natural products. Chemical synthesis of these bioactive agents provides an alternative to nature as the source of useful compounds. But the synthesis of these naturally occurring compounds are one of the most fascinating and challenging areas of research in natural product chemistry owing to complexity in their structure. The complex structural features of natural products always need multi-step synthesis and require careful plans with respect to sequence of steps from starting materials to the final product for achieving their total syntheses. The design of synthetic methodologies for convergent and efficient synthesis is very fundamental to natural product synthesis. The details as to how the synthetic chemists formulate the sequence of steps are not always published. Among synthetic chemists, retrosynthetic analysis / synthon disconnection approach [1,2,3] developed by Noble Laureate Prof.E.J.Corey of Harvard University, has emerged as the most popular approach for designing chemical synthesis. This strategy systematically simplifies the target molecule by repeated bond disconnections in retrosynthetic direction, leading to progressively smaller precursors until recognized starting material emerges.

Natural products bearing halogen atoms are rare and have, historically, played an important role in the discovery and development of medicinal agents especially antifungal and antibacterial activities. Such biologically active organo halogens are synthesized by marine organisms, bacteria, terrestrial plants, and higher life forms including humans [4]. These products display distinct physiological and biochemical roles in the organisms that produce them. 'Pyrrolnitrin' (Fig-1), which contains two carbon-chlorine bonds, is a biocontrol agent produced by several strains of

Pseudomonas [5].This halogenated bacterial metabolite with antifungal and anti bacterial activities serves as a lead structure of synthetic fungicides. Several Pyrrolnitrin-producing bacteria are considered to be promising biopesticides [6, 7].

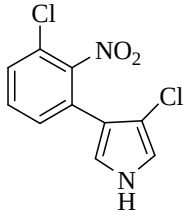


Fig-1

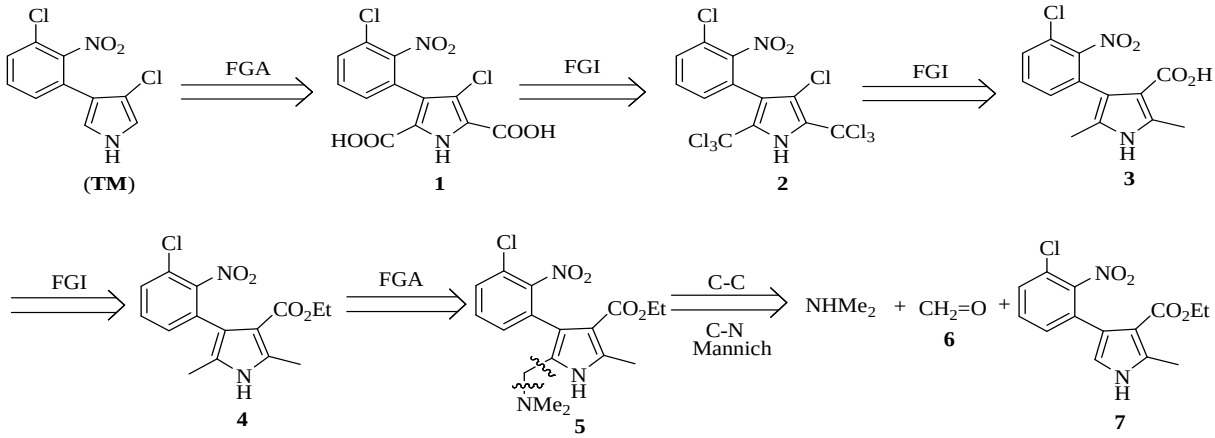
Few synthetic methodologies for 'Pyrrolnitrin' although well cited in the literature, some alternative synthetic routs and improvement in its existing processes are constantly required in pharmaceutical industries for market development. In continuation with our interests in the designing of synthesis of natural products, we, herein, propose a good number of synthesis schemes for 'Pyrrolnitrin' keeping a bird's eye view on the works published in journals [8-13]. Our synthesis approach is based on synthon disconnection approach/ retrosynthetic analysis and the utilization of recognized building block while designing synthetic routes for achieving its total synthesis. It is an innovative work that has not been reported earlier. The choice of this molecule for synthesis planning is obvious as natural organohalogen biopesticides are very rare and synthesis can be undoubtedly a useful and powerful tool for obtaining higher amounts of this natural products and/or structural modifications thereof.

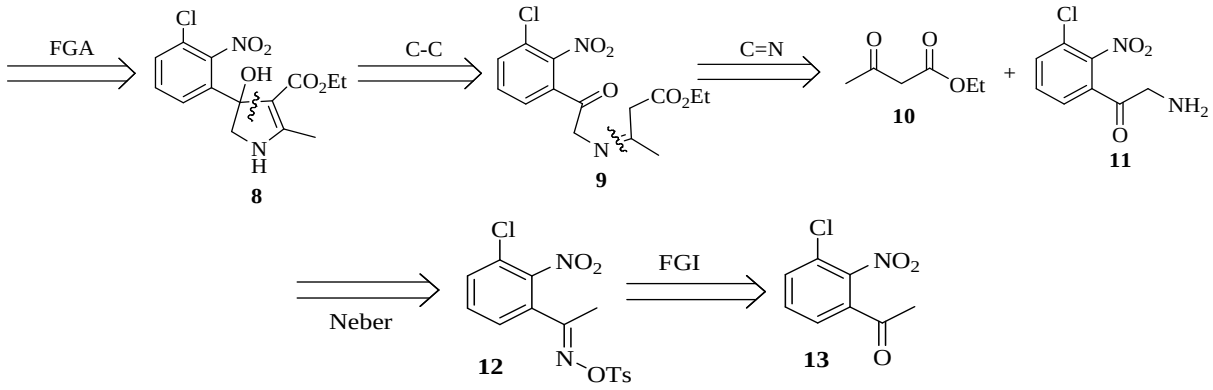
EXPERIMENTAL SECTION

The structure and information regarding 'Pyrrolnitrin' as a natural antifungal agent has been collected from different books [14-17]. The proposed synthesis planning are then exploited in a novel way from the result of retrosynthetic analysis of natural product structure using the basic principle outlined in the pioneering works of Prof. E.J. Corey. The terms, abbreviations and symbols used during synthesis planning are synonymous to that represented in books [18-24]. The analysis–synthesis schemes being theoretical propositions, obviously the synthesis have not been executed in the laboratory. Most of the retrosynthesis schemes have been derived taking in to account the synthesis earlier done for its preparation as found from different literatures. The actual laboratory execution requires the cross examination of a considerable number of factors such as reagents, reactions, order of events, economical viability, environmental benign, saftyness, short time and scalable synthesis.

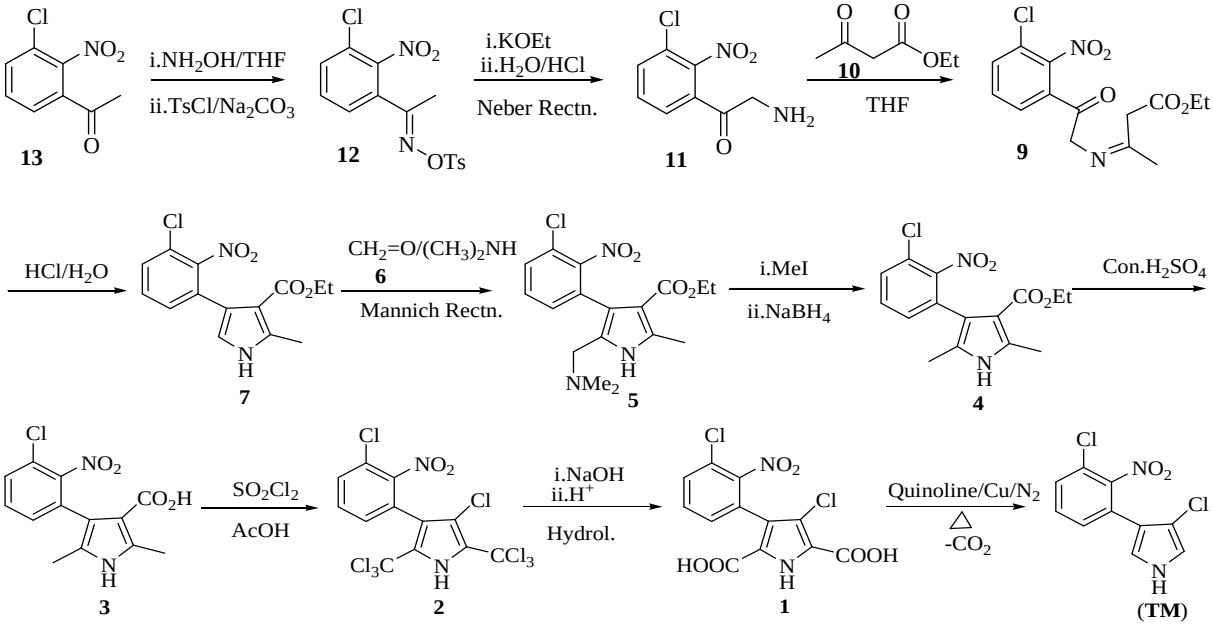
RESULTS AND DISCUSSION

Retrosynthetic Analysis-1





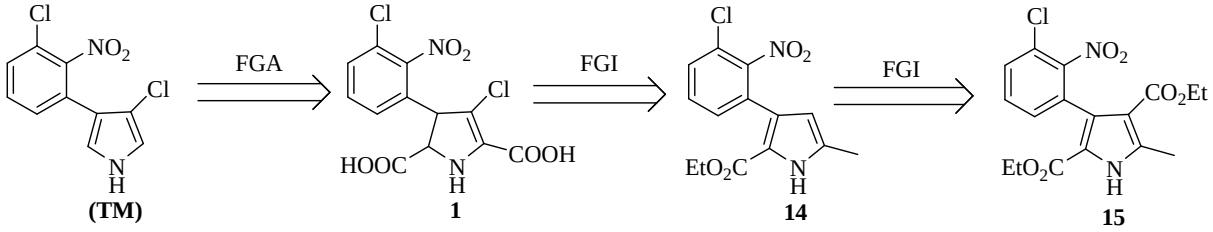
Synthesis-1

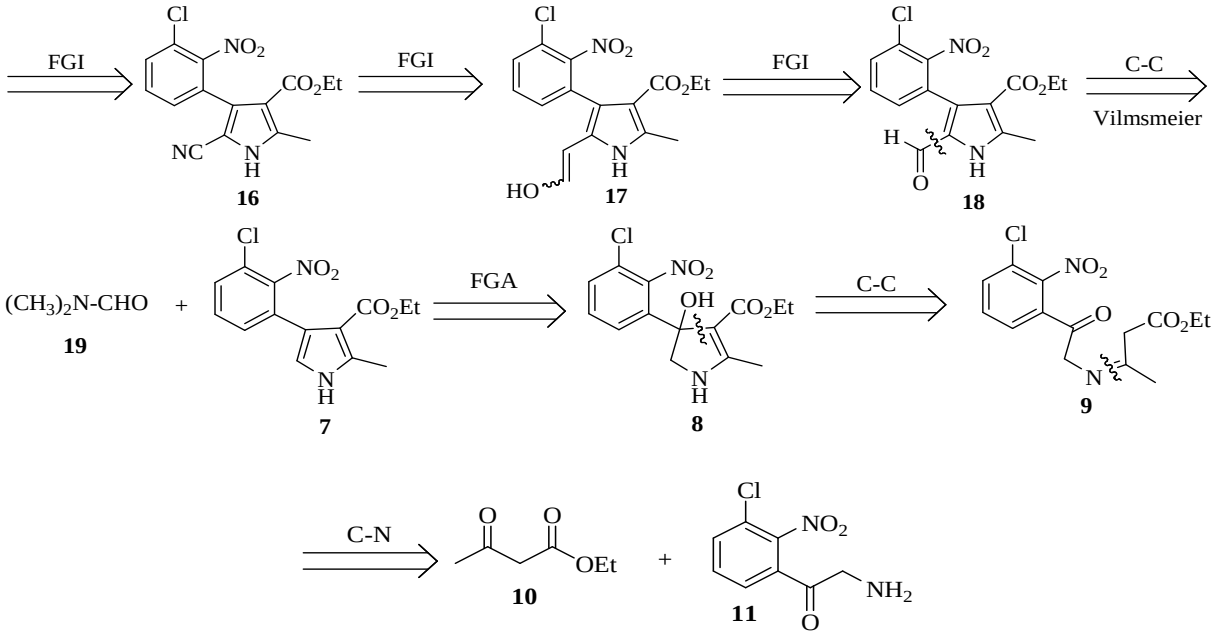


Scheme-1

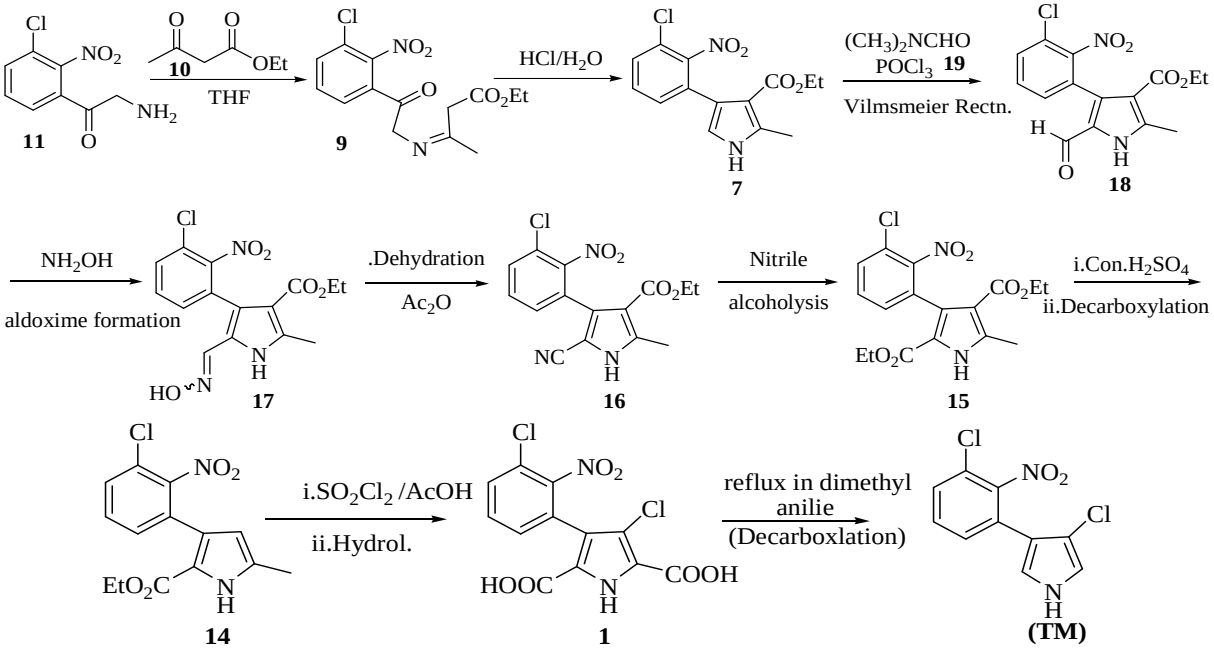
2-Nitro-3-Chloroacetophenone (**13**) forms the corresponding oxime and then oximetosylate (**12**) on treatment withNH_2OH followed by $TsCl/Na_2CO_3$. Neber rearrangement of (**12**) produces the amino ketone (**11**).Acid catalyzed condensation of the amino ketone with ethyl acetoacetate (**10**) forms the biaryl compound (**7**) with the appropriately substituted benzene ring via the intermediate (**9**). Mannich reaction of (**7**) with formaldehyde (**6**) and a 2^0 amine forms 5-*N*, *N*-dimethyl aminomethyl derivative (**5**).The methiodide derivative of (**5**) on subsequent reduction with $NaBH_4$ affords aryl substituted pyrrole 3-carboxylate (**4**). Hydrolysis of this ethyl ester with conc. H_2SO_4 gives corresponding carboxylic acid (**3**). Chlorination of (**3**) with sulfurylchloride and subsequent hydrolysis offers 3-chloro-4-(3'-chloro-2'-nitrophenyl)-pyrrole-2, 5-dicarboxylic acid (**1**). Decarbaxyletion of this dicarboxylic acid produces Pyrrolnitrin (**TM**). (Scheme-1)

Retrosynthetic Analysis-2





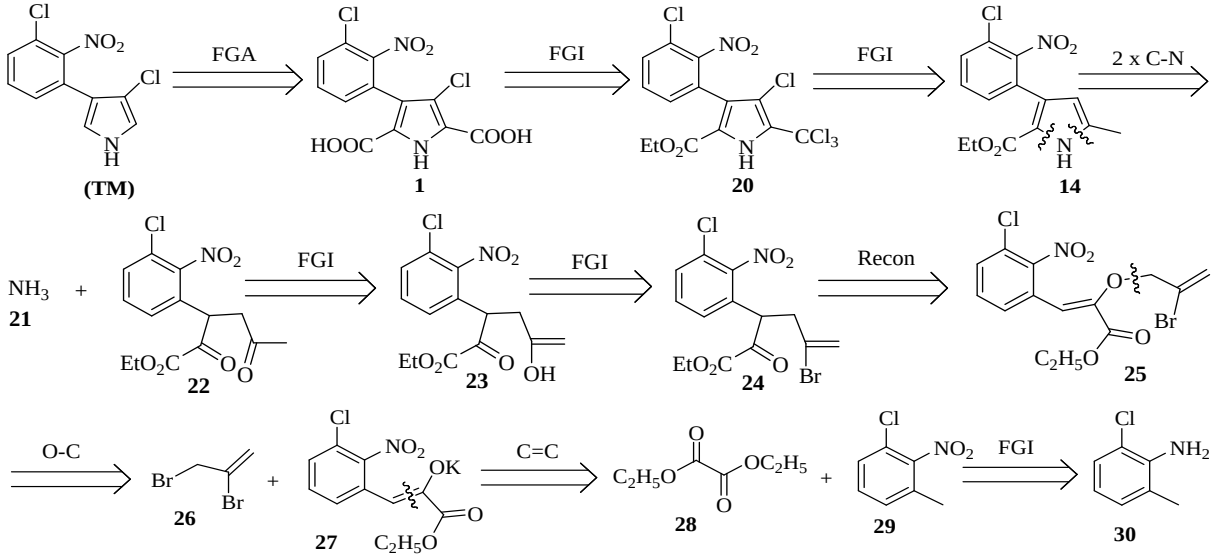
Synthesis-2



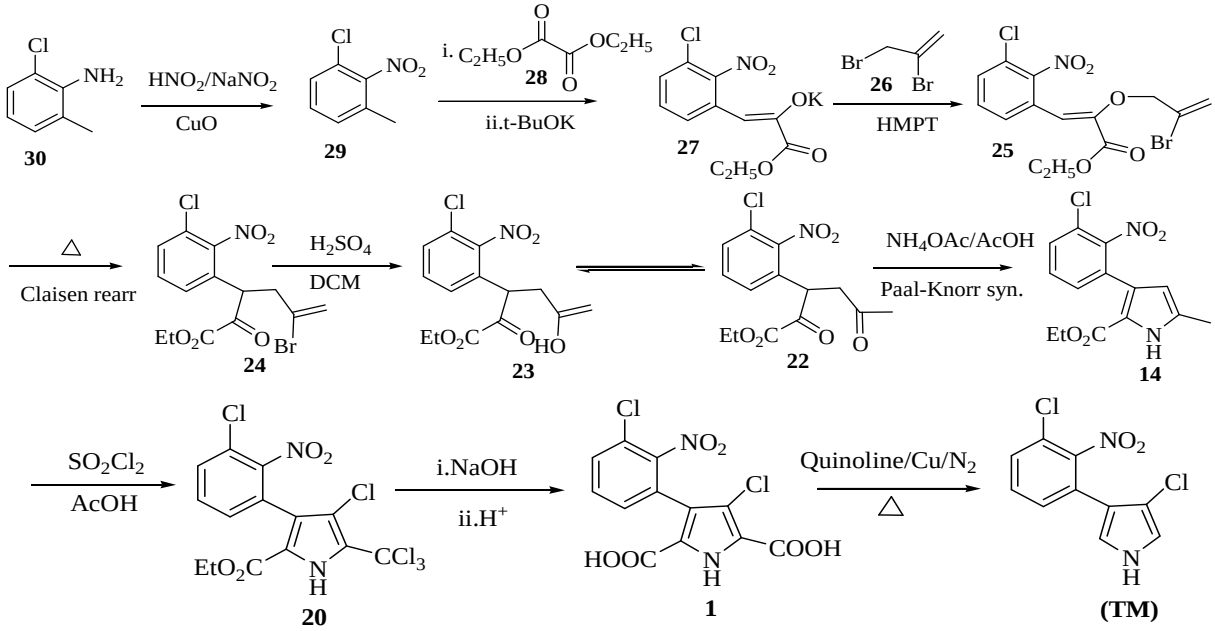
Scheme-2

The aminoketone (**11**) prepared as in (Scheme-1) undergoes acid catalyzed condensation with ethyl acetoacetate (**10**) and forms the biaryl compound (**7**) through the intermediate (**9**). Vilsmeier reaction of (**7**) with $(CH_3)_2N$-CHO/$POCl_3$ affords 5-formyl pyrrole(**18**) .Oximination of (**18**) followed by dehydration produces the corresponding nitrile (**16**).Alcoholysis converts this nitrile to 3,5-diester(**15**).Partial hydrolysis of the diester with con.H_2SO_4 followed by subsequent decarboxylation affords the half ester(**14**).Treatment of (**14**) with sulfuryl chloride in AcOH followed by hydrolysis and decarboxylation affords Pyrrolenitrin (**TM**).(Scheme-2)

Retrosynthetic Analysis-3



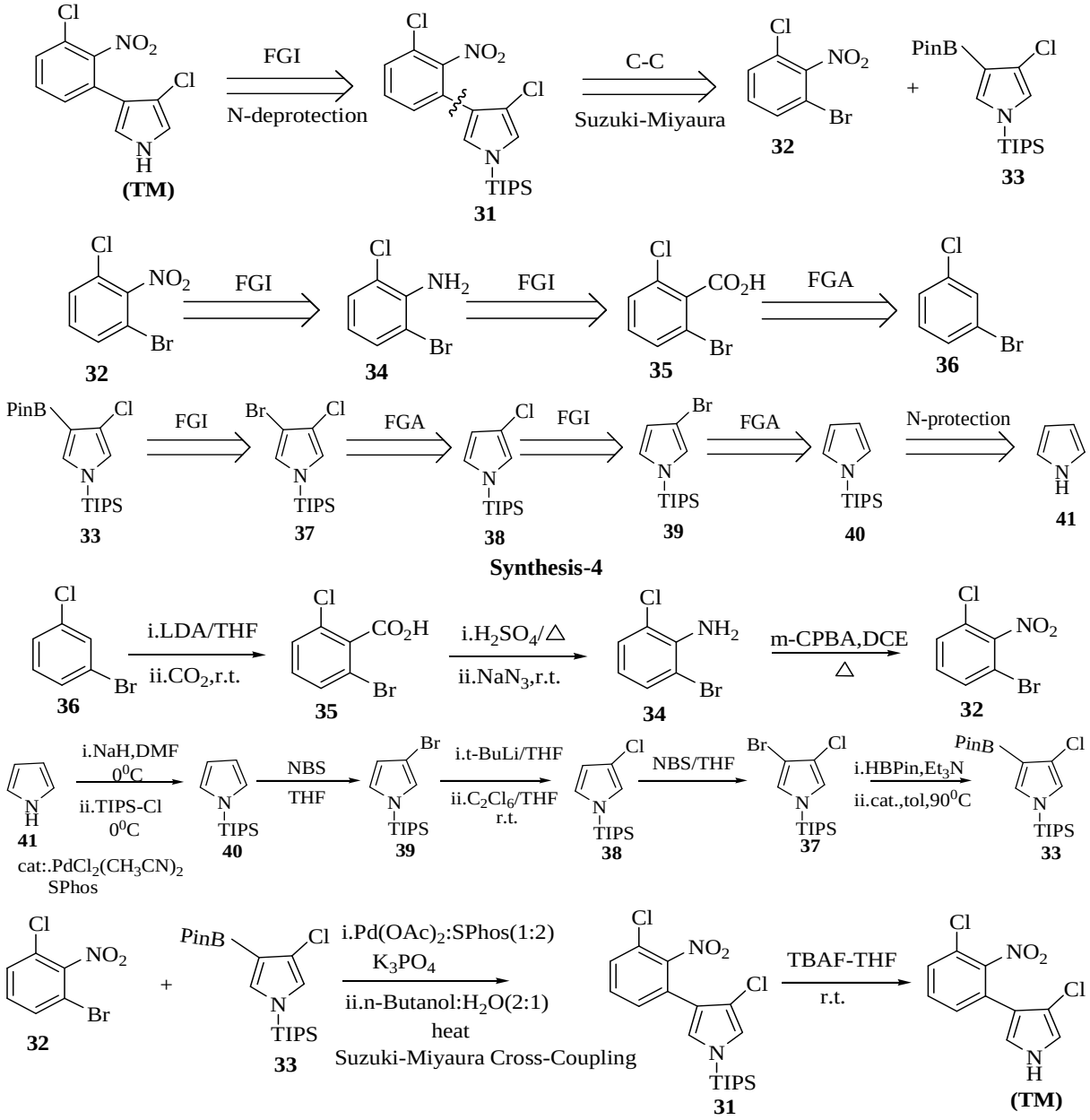
Synthesis-3



Scheme-3

2-Nitro-3-chloro toluene (**29**)prepared from 2-Amino-3-chloro toluene (**30**) undergoes oxalate ester(**28**) condensation and forms (**27**).Reaction of (**27**) with 2,3-dibromopropene (**26**) in presence of hexamethylphosphorous triamide (HMPT) gives an intermediate(**25**) which undergoes Claisen rearrangement and affords the enoate (**24**).The enoate on treatmet with H_2SO_4/DCM produces an intermediate(**23**) that rearranges to the dicarbonyl compound(**22**). Paal-Knorr synthesis of the dicarbonyl compound affords ethyl 3-(3'-chloro-2'-nitrophenyl)-5-methyl pyrrol-2-carboxylate (**14**). Treatment of (**14**) with sulfuryl chloride in AcOH followed by hydrolysis and decarboxylation affords Pyrrolenitrin (**TM**). (Scheme-3).

Retrosynthetic Analysis-4



Synthesis-4

Scheme-4

Llithiation-carboxylation of 1-bromo-3-chloro benzene (**36**) produces 2-chloro-6-bromo benzoic acid (**35**). Schmidt reaction of (**35**) affords the desired 2-bromo- 6-chloroaniline (**34**). Oxidation of this 2, 6- dihaloanilines with *m*-chloroperbenzoic acid in DCM produces 2-bromo-6-chloronitrobenzene **(32).**Regioselective installation of bromine using NBS on N-protected pyrrole (**40**) using Muchowski procedure [**26**], generates 3-bromo-1-TIPS-pyrrole (**39**). Subsequent lithium-halogen exchange followed by quenching of the organolithium with an electrophilic chlorine source (e.g., hexachloroethane) allows access to new halogenated pyrroles i.e; 3-bromo-4-chloropyrrole (**37**). (**37**) produces the pinacolboronate ester i.e; 1-(TIPS)-3-chloro-4-(BPin) pyrrole (**33**) using Billingsley and Buchwald procedure [**27**]. Suzuki-Miyaura Cross-Couplings of the Pyrrole Pinacolboronate ester (**33**) with (**32**) produces (**31**).Deprotection of (**31**) using TBAF/THF affords Pyrrolnitrin (**TM**). (Scheme-4)

(TIPS-Triisopropylsilyl, TBAF-Tetra-n-butylammonium fluoride, THF- Ttetrahydrofuran, BPin-Pinacol Boronate)

CONCLUSION

Synthon disconnection approach/ Retrosynthetic analysis is a technique for solving problems in the planning of organochemical synthesis. This approach is expected to provide new and innovative synthetic strategies in a logical manner for design, execution and development of new synthesis or improvement in existing process. It is a paper exercise; a full analysis of this type will provide many routes for synthesizing the target molecule. As a consequence of this approach, we have proposed a good number of analysis-synthesis schemes for natural antifungal agent 'Pyrrolnitrin. Scalable synthetic routes for extremely scare natural products, pharmaceuticals and useful compounds not available in adequate quantities from natural resources can be best provide by this approach. Through Synthon disconnection approach and with the application of new synthetic reactions and reagents developed within the academic community, it is now time to rethink the synthesis of bioactive natural products for the improvement of the existing process for their commercial success.

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