SYNTHESIS OF LATRUNCULINS

A DISSERTATION REPORT

SUBMITTED IN PARTIAL FULFILMENT OF THE DEGREE

OF

M.SC. IN ORGANIC CHEMISTRY

BY

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DECLARATION

I hereby declare that the literature review entitled “Synthesis of Latrunculins” is based on the results of investigation carried out by me at the School of Chemical Sciences, Goa University, Goa, under the supervision of Dr. Rupesh Kunkalkar and the same has not been submitted elsewhere for the award of a degree or diploma.

Siddhi Madkaikar

20P0490048

CERTIFICATE

This is to certify that the literature review entitled “Synthesis of Latrunculins” is a bonafide work carried out by Miss Siddhi Madkaikar during the academic year 2021-22 under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

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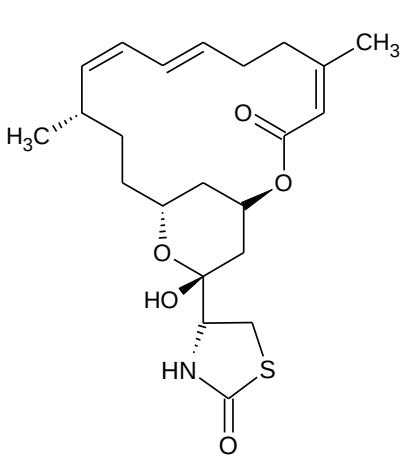
INTRODUCTION:

The two novel toxins - Latrunculin A **1** & B **2** were first isolated & characterised by Kashman et al. in 1981 from the Red Sea Sponge, *Latrunculia magnifca* (Keller).[1] More recently, it has been found in the Pacific nudibranch family Chromodorididae, including: *Chromodoris lochi, C. hamiltoni, C. quadricolor* & *Chromodoris elisabethina*, *Hyattela sp*. and in a species *Spongia mycofijiensis* present in Fijian waters. [2,3] Though this sponge grows in the Gulf of Eilat, completely exposed to a hostile sea environment, it was observed that it exudes a reddish fluid with very powerful icthyotoxic properties causing the fish to flee as a part of its defence mechanism. As such, colonies of this sponge were never observed to be damaged or eaten by the fish. This proved to be an event of special significance to the community of natural products & biologists.[2] It was observed that when *Latrunculia magnifca* is squeezed into an aquarium it causes poisoning and death of the fish within a mere span of 4-6 minutes. [4] Research has proved that latrunculins dramatically influence both mammalian as well as non-mammalian cells. Sub-micromolar quantities of **1** and **2** have shown to induce characteristic, reversible changes in cell morphology, disrupt the organization of microfilaments, and suppress microfilament-mediated processes during the process of fertilization & early development. [5] Other than its primary effect to protect the sponge against predators, experiments have proven that **1** exerts a strong reversible effect on microfilament organization in cultured mouse neuroblastoma cells and **2** displays potent cytotoxicity against the KB cell line. But owing to the nature of the original samples; **1** is physically a foam & **2** a viscous oil; their structures has only be partially determined. The relative configuration of latrunculin A has been extrapolated from that of its methyl acetal derivative, the structure of which was secured by X-ray crystallographic analysis, whereas latrunculin B has been fully characterised by assigning the ^{1}H and ^{13}C-NMR signals.[4] The latrunculins are significant to the world of chemists as they exhibit a new class of 14 and 16 membered macrolides to which the rare 2-thiazolidinone moiety is attached.[6] Following the discovery of **1** and **2**, several additional members of the latrunculin family have been isolated, including 6,7-epoxy- latrunculin & in every case the latrunculins have been found to contain a L-cystein-derived thiazolidinone moiety. [2]

Latrunculin A is also the most widely used reagent to depolymerize actin filaments in experiments on live cells. It binds actin monomers and sequesters them from polymerization. Low concentrations of **1** result in rapid (tens of seconds) disassembly of actin filaments in animal and yeast cells.[7] Actin is the most abundant protein in most eukaryotic cells. It is highly

conserved and participates in more protein-protein interactions than any known protein. Being one of the two major components of the cytoskeleton & due to its ability to transition between monomeric (G-actin) and filamentous (F-actin) states [8], it determines the shape and mechanical properties of eukaryotic cells and is also responsible for cell motility processes as fundamental as cytokinesis or exocytosis and endocytosis.[7] Cellular stiffness and the development of contractile force require actin filaments. Therefore measurements of stiffness and force can directly indicate the physical state of the actin cytoskeleton.[9] Owing to its significant role in the cell, the actin cytoskeleton is also disrupted or taken over by numerous pathogens.[8]



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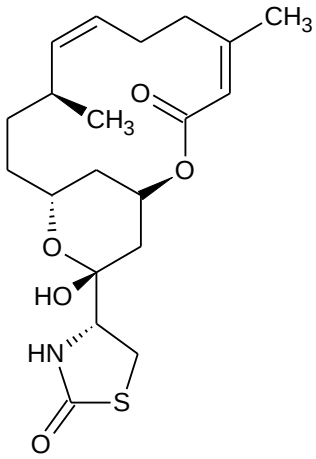


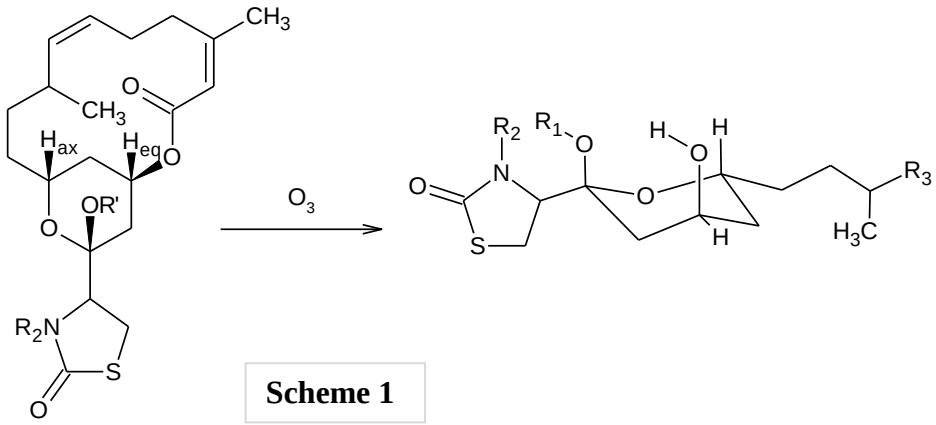
2

1 & 2 have been shown to display potent anti-migratory activity against highly metastatic human prostate cancer PC-3M-CT+ cells and murine brain-metastatic melanoma B16B15b cells, respectively. Hence, latrunculins, represent a prototype case of a "forward chemical genetics" approach to the field of molecular biology.[7]

SYNTHESIS:

I. 1986: An overview of the work done by Kashman et al.

The first synthetic studies related to latrunculines were published by Kashman et al. n 1986. Their route involved synthesis of several tetrahydropyranyl (THP)-thiazolidin-2-one systems/derivatives by degradation of latrunculin B or synthetically from L-cysteine. This route was only a prototype study of latrunculin B with no actual synthesis reported by them.[10]



Scheme 1

1a $R_1=R_2=H$

1b $R_1=Me$ $R_2=H$

1c $R_1=Me$ $R_2=Bn$

2 $R_1=R_2=H$ $R=CH_2OH$

3a $R_1=Me$ $R=H$ $R= CH_2OH$

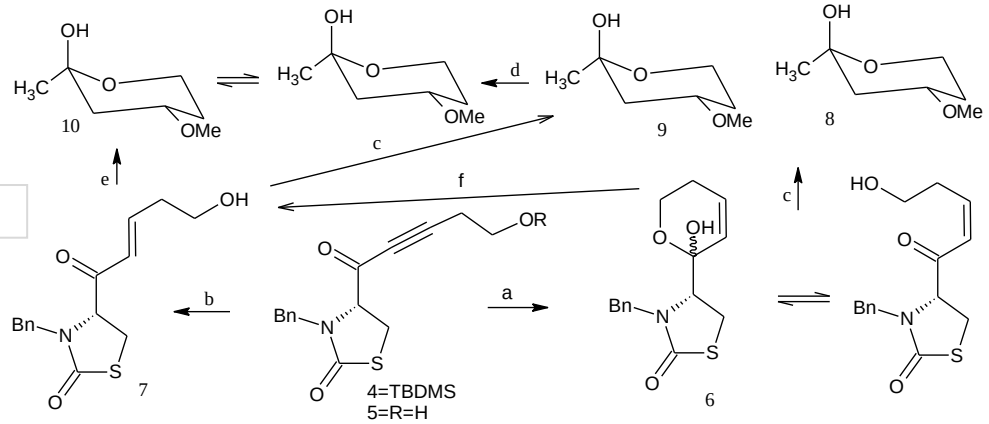
3b $R_1=Me$ $R=H$ $R=CHO$

3c $R_1=Me$ $R=Bn$ $R= CH_2OH$

Kashman et all chose an approach of reductive ozonolysis of the macrolide of **1b** to obtain the compound **3a** which upon acidic deketalization gave compound **2 (Scheme 1)**. In the process, compound **3b** was also furnished due to ozonolysis, possessing the 6-carboxaldehyde side chain. This was an important result as this compound **3b** was earlier suggested as a possible synthon for the latrunculins.

It was observed that in latrunculin B itself, the THP ring in **2** & **3** maintains the conformation in which both the 2-thiazolidinone and the 6-side chain are equatorial and the 2-OR and 4-OH groups are axial. Explanation for the same could be predominantly due to: 1. the larger THP substituents prefer the equatorial positions b. due to anomeric effect of the 2-OR group and c. the hydrogen bond between the axial 2-OH and 4-OR groups.[10]

The model bicyclic heterocycles were synthesised using 4 & 5 (Scheme 2) as follows:



Scheme 2

a. H_2 Lindlar catalyst b. H_2 Pd/BaS04, pyridine c. 1. MeOH, K_2CO_3 anhy. 2. BF_3-etherate d. SiO_2, H^+ e. MeOH, K_2CO_3 f. MeOH, pyridine

Compound **4** was obtained from the Pd(0) catalysed coupling of TBDMS-oxybutynyl tributylstannane with the acyl chloride of N-benzyl-2-oxo-thiazolidine-4-carboxylic acid. Hydrogenation of **5** over Lindlar catalyst led to the cis-α, β-enone **6** accompanied by an open enone. On the other hand, hydrogenation of **5** over Pd/BaS04 in pyridine formed the trans- α, β-enone **7.** Michael addition of MeOH, in the presence of K_2C0_3, to **6** or **7** followed by ketalization of the lactol by addition of BF_3-etherate to the MeOH solution, gave a mixture of two 2,4-dimethoxy derivatives, compounds **8** & **9** These were separated by HPLC. Upon acidic treatment each one of compounds **8** & **9** resulted in the formation of the corresponding lactol. In case of compound **9**, the acidic deketalization-product existed as a 40:60 mixture of the two possible 2,4-isomers **10**. Methanol addition to compound **7**, without ketalization, led to a mixture of the 2-OH, 4-OMe derivatives in which one of the two isomers possessing the 2ax-OH and 4ax-OMe groups predominates. Hence, this demonstrated the synthesis of 2,4,6 trisubstituted THP-rings as well as various 2,4-disubstituted ones.[10]

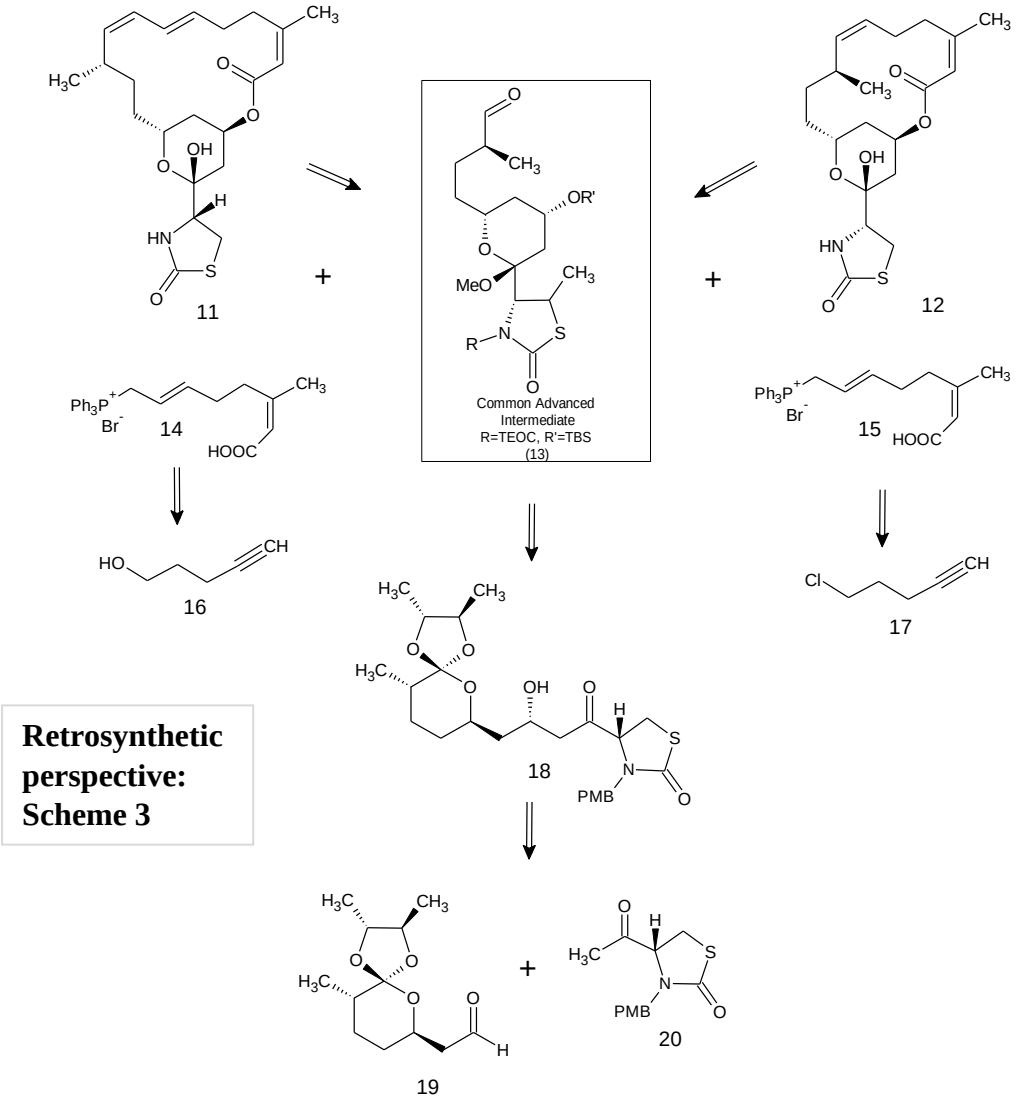
II. 1986: The first actual total synthesis of (+)-latrunculin A latrinculin B was reported by Smith et al.[2]

The total synthesis of (+)-latrunculin A & B **11 & 12** was achieved by a highly convergent and stereocontrolled route by Smith et al. in 1986l. From the retrosynthetic perspective, cleavage of the macrolide linkage in **11 & 12** and disconnection of the cis olefin lead to Wittig reagent 1**4** & **15** respectively and the common advanced intermediate, aldehyde 1**3 (Scheme 3)**. Analysis of 1**3** in turn generated p-hydroxy ketone 1**8**, the aldol product of aldehyde 1**9** with ketone **20**.[11] Here, the aldol addition of (-)-**20** to (-)-**19** was significantly improved by employing boron enolate technology. Specifically, treatment of (-)-**20** (2.5 equiv) with n-Bu_2BOTf (3.2 equiv) and i-Pr_2NEt (3.0 equiv) in CH_2C1_2 at -78°C, followed by reaction with aldehyde (-)-**19** at -78°C for 4 h, afforded (-)-**18** as the major component.

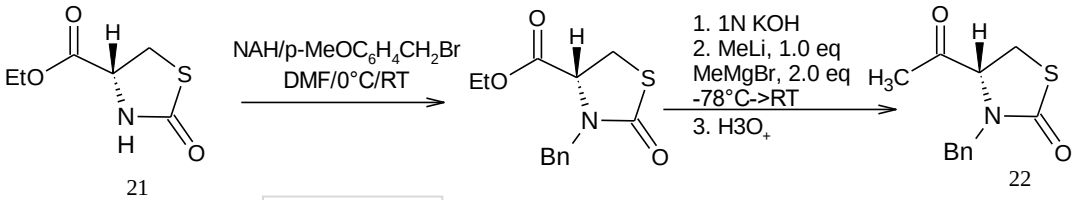
Now the two resulting starting materials 19 and 20 were synthesised as notified below:

Synthesis of **20**: It was initiated with ethyl 2-oxo-4-thiazolidinecarbxylate **21**. The amide nitrogen was protected with 4-methoxybenzyl bromide, the ester hydrolyzed, and the acid converted to methyl ketone **20** via the method of Rapoport. The overall yield from **21** was 30% **(Scheme 4).**

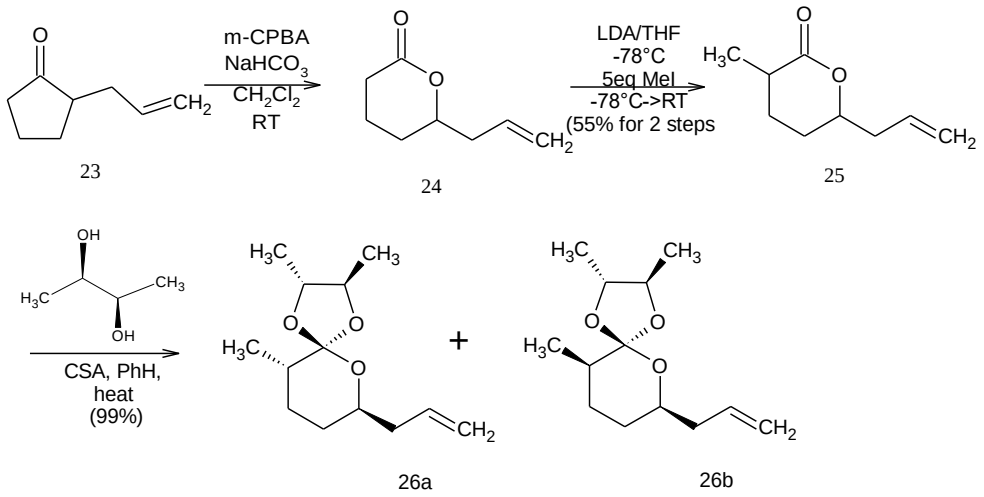
Synthesis of **19**: The aldehyde **19** was prepared in four steps beginning with the Baeyer-Villager oxidation of 2-allylcyclopentanone 23.14 Alkylation provided 25 as a 1:l mixture of lactones, which in turn was protected as the ortho ester, employing (+)-(R,R)- 2,3-butanediol.



Retrosynthetic perspective: Scheme 3



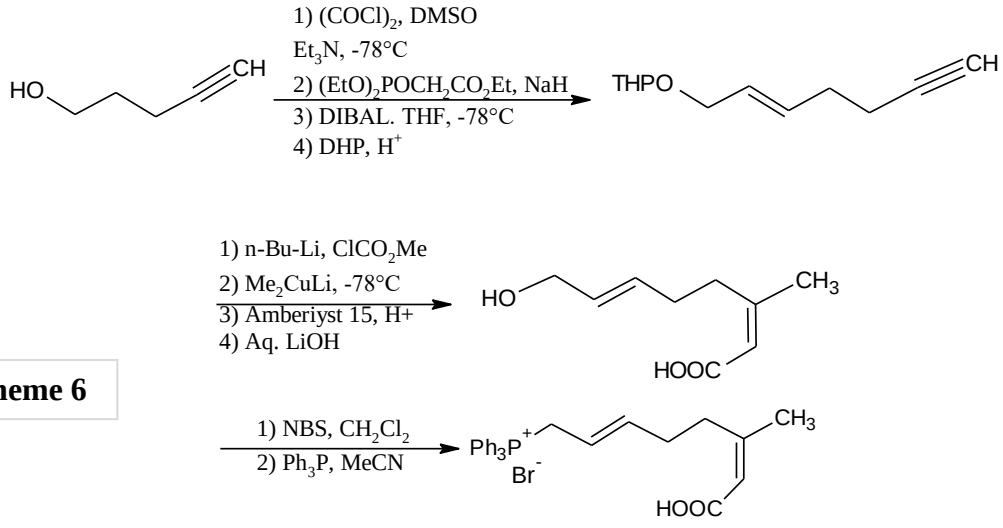
Scheme 4



Scheme 5

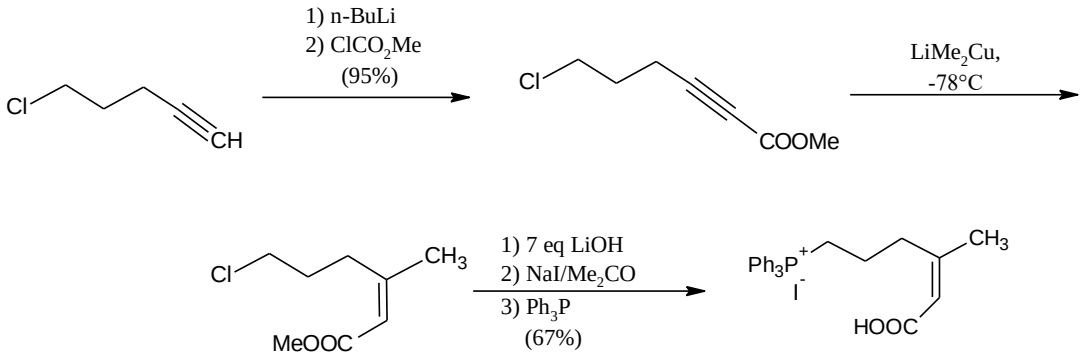
The requisite southern perimeter, Aldehyde **3**, was best obtained 10 via a reduction-oxidation sequence.

The northern perimeter for the synthesis of latrunculin A, Wittig reagent 1**4,** was prepared in 10 steps (30% overall yield) as outlined in **Scheme 6**. Wittig coupling proceeded via generation of the dianion **14** [2.0 equiv, with 3.8 equiv of NaN(TM& THF- HMPA (5:1)], followed by addition of aldehyde (-)-**13**, to furnish the desired cis-trans diene. Upon removal of the TBS group [pyridine.$(HF)_x$,THF] Mitsunobu macrocyclization formed the required lactone, which in turn was converted to (+)-**latrunculin A** by removal of the TEOC group (n-Bu_4NF, 83%) and ketal hydrolysis [3 N HCl, (THF (3:1)] (49% yield, 72% based upon recovered starting material).[5]



Scheme 6

The northern perimeter for the synthesis of latrunculin B, Wittig reagent 1**5**, on the other hand, was prepared in a stereocontrolled manner in five steps (54% overall) from commercial 5-chloro-1-pentyne as outlined in **Scheme 7**. With ample quantities of both the northern and southern hemispheres available, execution of the Wittig coupling [2.9 equiv of dianion of **5** (generated with 5.8 equiv of KN(SiMe,),/THF, 0 OC and careful exclusion of oxygen)] followed by removal of the TBS group [pyridine-$(HF)_x$, THF, 98%] in anticipation of macrolactonization. Later, Mitsunobu lactonization (4 equiv of DEAD/Ph_3P in benzene) followed by removal of the 4-methoxybenzyl group (with 2.0 equiv of $Ce(NH_4)_2(NO_3)_6$ at a concentration of 0.25 M [CH_3CN/H_2O (3:l); 68%], & hydrolysis of the mixed methyl ketal (mild acid [HOAc/THF/H_2O (3:1:1), 60 "C] yielded latrunculin B.[1]

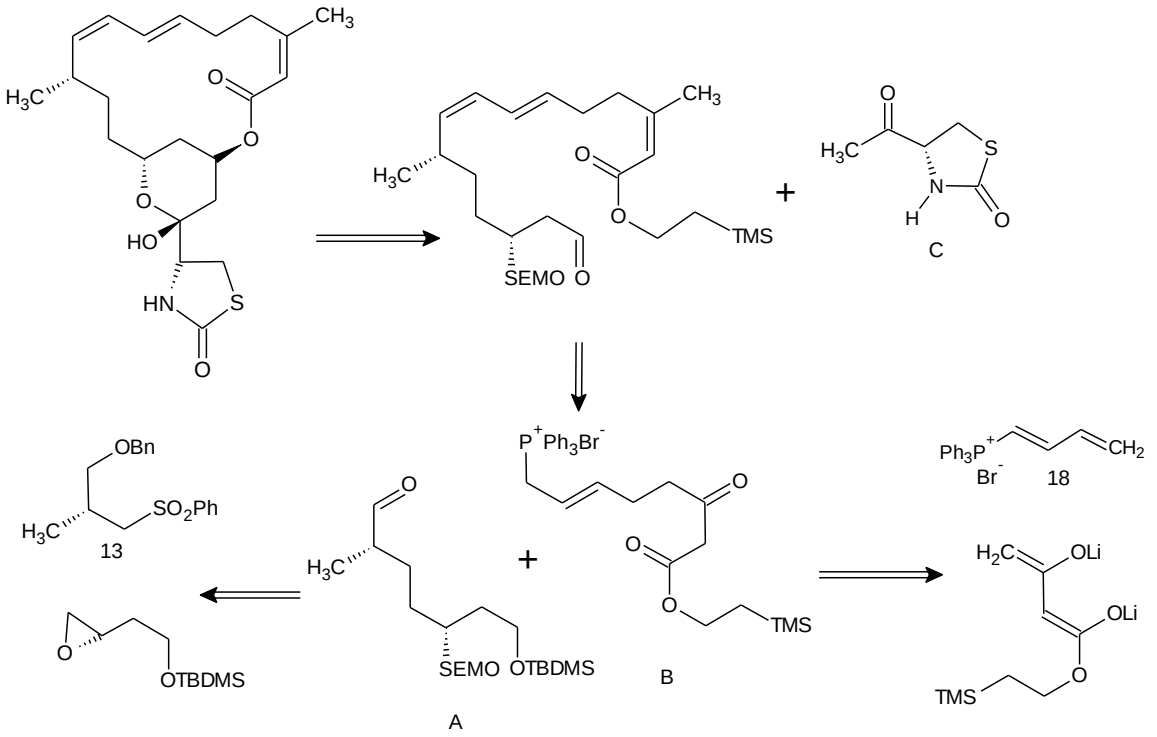


Scheme 7

III. 1992: Total Synthesis of (+)-Latrunculin A by James D. White and Motoji Kawasaki.[2]

The synthesis developed by White and Kawasaki also makes use of a Wittig reaction to establish the Z-configured olefin in the molecule followed by macrolactonization. Furthermore, White used an aldol reaction between aldehyde **11** and ketone 12 as a key step. The main difference between the approaches developed by Smith and White, respectively, lays in the order of events. White and Kawasaki made a Wittig reaction with the ylide derived from **16** with aldehyde **15** first and then employed an aldol reaction between fragment **11** and the unprotected ketone **12**, whereas Smith first performed an aldol reaction followed by a Wittig reaction.

The route to synthesise the target was designed synthesising three major subunits A, B, and C

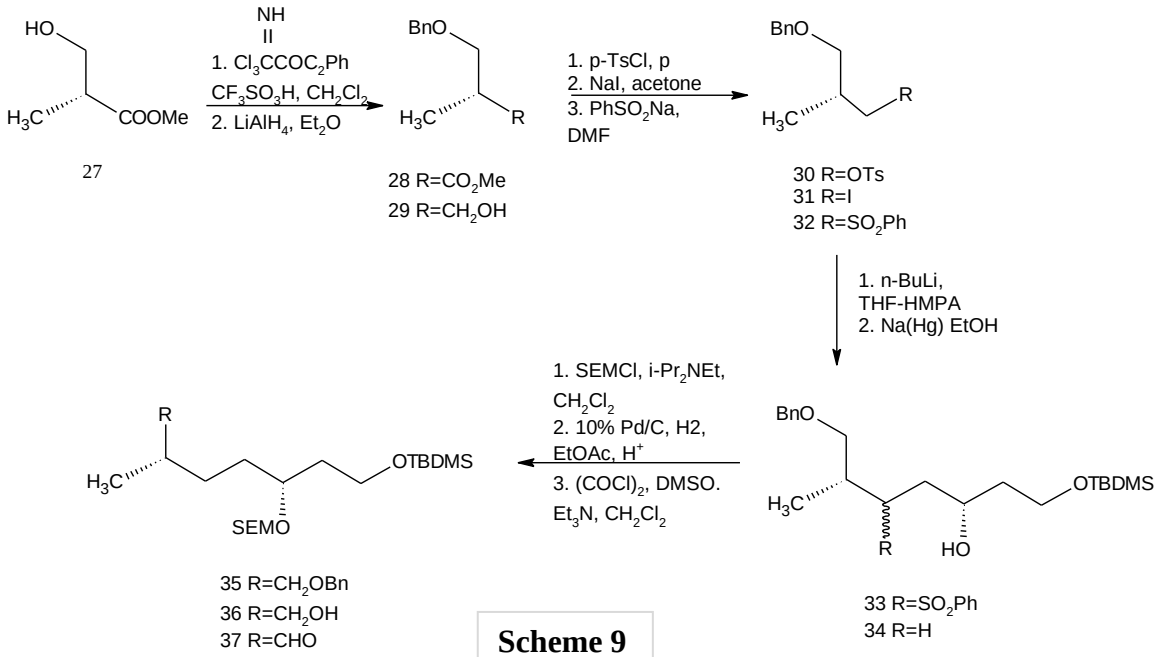


Retrosynthetic perspective: Scheme 8

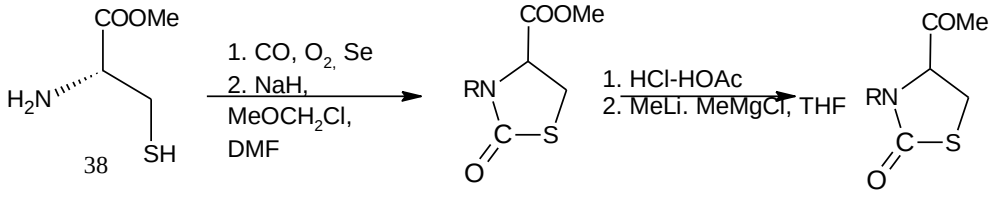
Synthesis of **aldehyde A:** Methyl (R)-3-hydroxy-2-methylpropionate **27** acquired the desired sulfone by the sequence shown in **Scheme 9**. Conversion of **27** into its ether **28** with benzyl trichloroacetimidate was followed by reduction of the ester to yield alcohol 29. The derived tosylate **30** was transformed efficiently to **32** by displacement of iodide **31** with sodium benzenesulfiiate in DMF. Coupling of the lithium anion of **32** produced **33**, from which the sulfone was excised reductively to give optically pure **34**. Protection of this alcohol as its SEM ether **35** was followed by hydrogenolysis. A Swern oxidation of **36** finally gave aldehyde **37** (A).

Synthesis of **thiazolidinone subunit B:** The second segment B needed for assembling the skeleton of the target was prepared from methyl (R)-cysteinate **38** as shown in **Scheme 10**. The latter was converted with CO and O_2 in the presence of selenium to thiazolidinone **42** from which the ester was cleaved by hydrolysis.

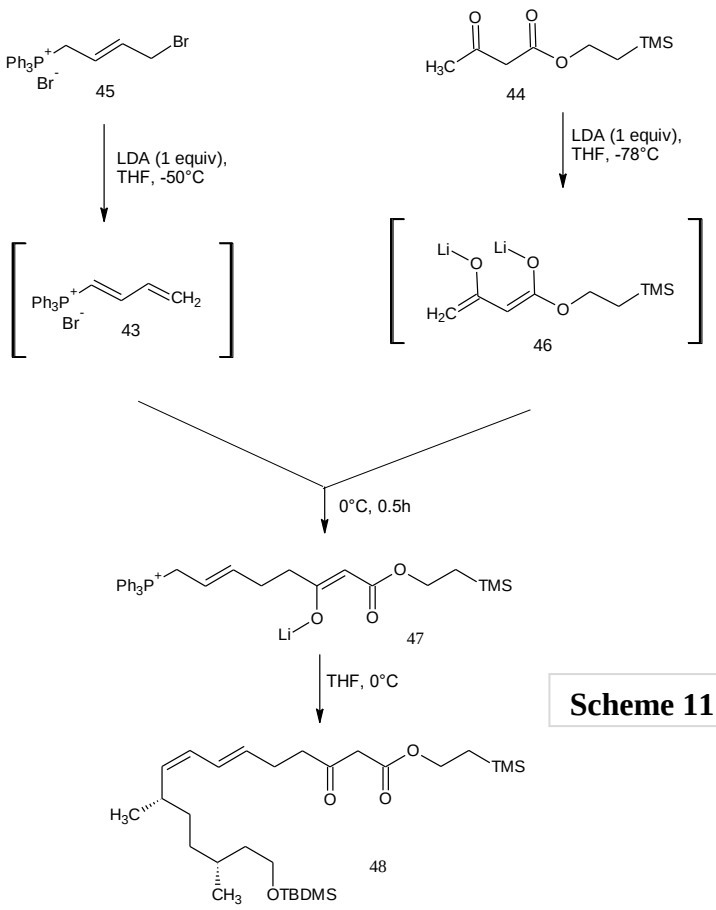
Synthesis of **C:** A three-component coupling of butadienyltriphenylphoaphonium bromide 41 with a nucleophile and then with aldehyde **37 (Scheme 11).** The (trimethylsily1)ethyl ester grouping in **44** was chosen as that would facilitate release of the carboxyl function under non-hydrolytic conditions at a late state of the synthesis. Diene **43** generated from phosphonium bromide **45** with one equivalent of base, was found to be a reasonably stable species. Its reaction with dilithio dianion **46** was characterized by formation of a yellow-orange color characteristic of allylic phosphorane **47** which disappeared after addition of **37**, and diene **48** was isolated in 60% yield along with a trace of the E,E-diene.



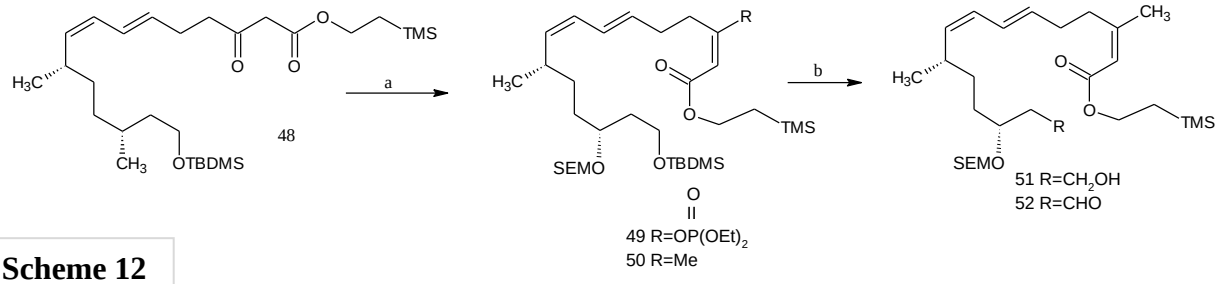
Scheme 9



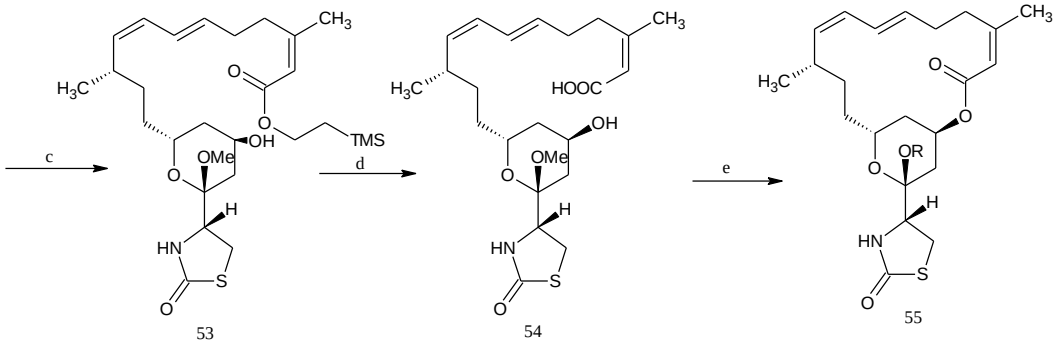
Scheme 10



Scheme 11



Scheme 12



a.1. $(EtO)_2POCl$, i-Pr_2NEt, DMAP, HMPA 2. MeCu, MeMgCl **b.** 1. MeOH, H^+ 2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 **c.** 1. HF, MeCN 2. MeOH, H^+ **d**. n-Bu_4NF, DMSO **e**. $_{Ph3P}$, DEAD, C_4H_4 2. H_2O-HOAc, 60°C

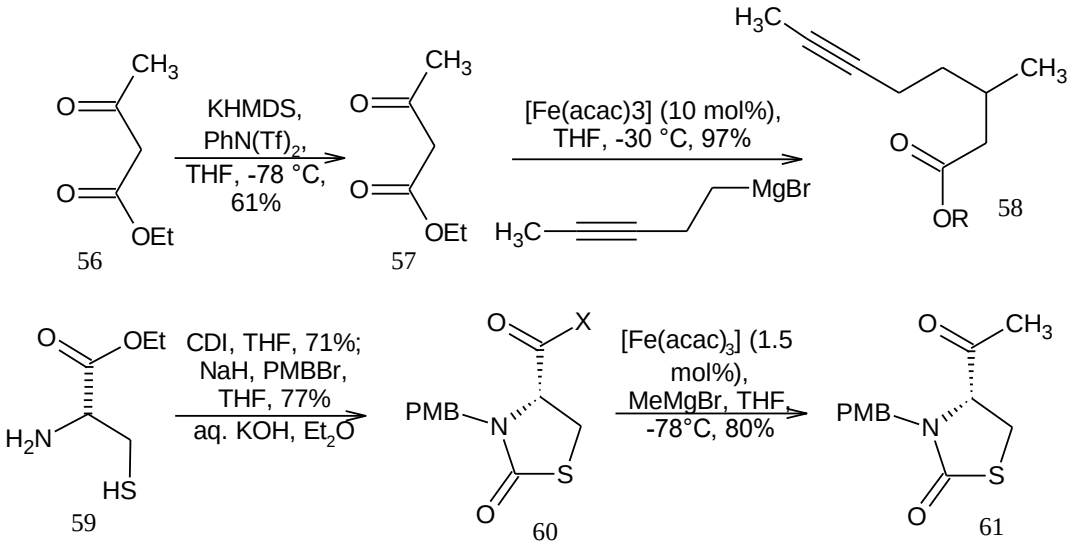
Combining A, B & C: The dianion of **39** was found to be quite compatible with **52** and led to a crossed aldol product in good yield. Thus, by employing its mixed lithio-cerio dianion the route from **41** to **55** was considerably simplified. Further, **53** seco acid **54** was accompanied by a small quantity of an anhydro product containing a dihydropyran which resulted from elimination of methanol. Lactonization using the Mitsunobu approach furnished in good yield the methyl ketal of latrunculin A. Final hydrolysis gave a synthetic latrunculin A.

IV. 2003: Catalysis-based total synthesis of latrunculin B by Fürstner, Alois

De Souza, Dominic, Parra-Rapado, et al.

Desired products cysteine derived ketone **61** and aldehyde **66** were prepared as notified in **Scheme VI**.

Fürstner et al. used catalysis based synthesis which began with transformation of ethyl acetoacetate **56** to its corresponding triflate **57**. Further, treatment using Gringnard reagent derived from 1-bromo-3-pentyne in the presence of [Fe(acac)$_3$] as a precatalyst afforded the desired product **58**. Other fragment cysteine derived ketone **61** was prepared from (R)-ethyl 2-amino-3-mercaptopropanoate **59** which was first converted to acid chloride **60** using standard method and using iron catalysis yielded **61 (Scheme 13)**.[12]

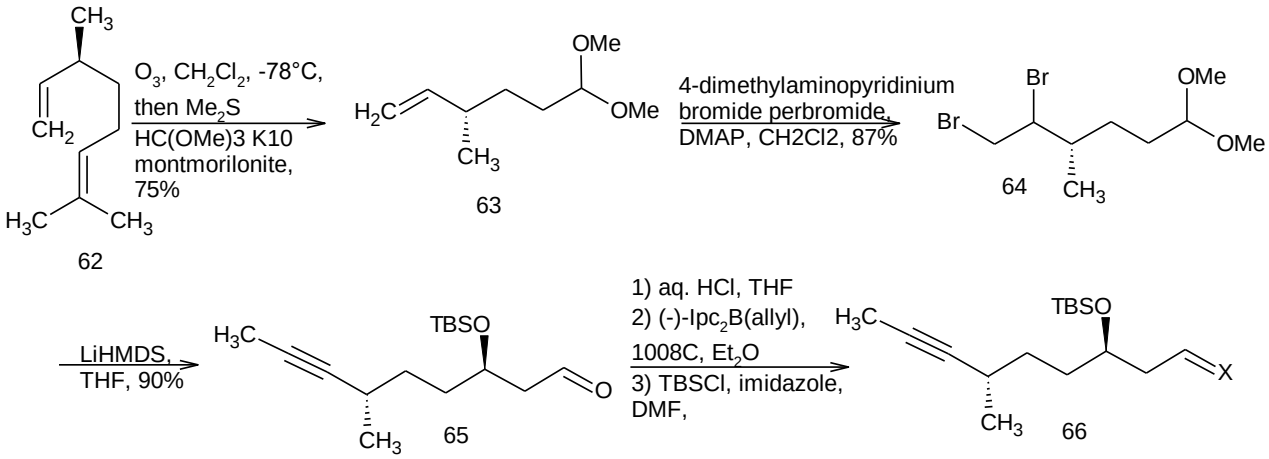


Preparation of desired product cysteine derived ketone

Scheme 13

The third building block was synthesized from (+)-citronelene (**62,** 91% ee) by selective ozonolysis and acetalization to get **63**. Further, bromination of **63** provided **64** which on treatment with LiHMDS gave **65**. Deprotection of acetal group in **65** and allylation of the resulting aldehyde with (-)-Ipc_2B(allyl) protection with a TBS group furnished & final, selective ozonolysis of its alkene entity afforded the required product **66 (Scheme 14).**

[13]

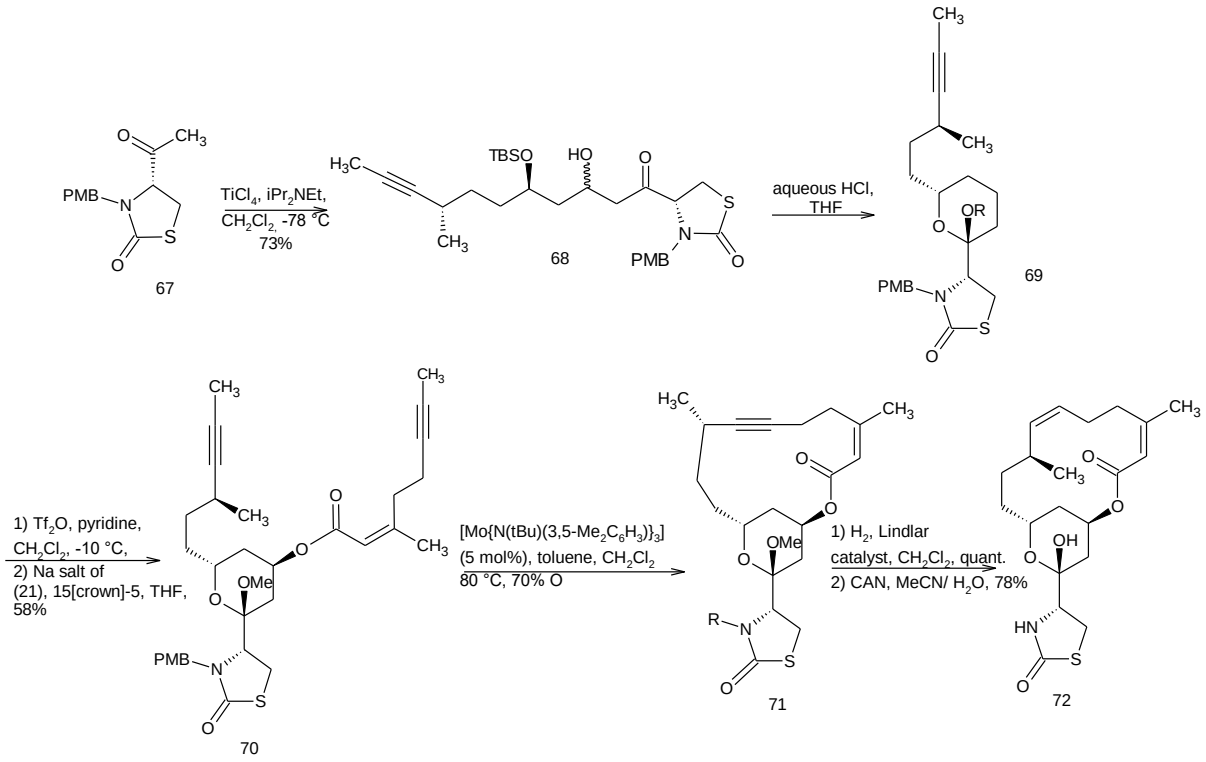


Preparation of desired aldehyde

Scheme 14

Reaction of aldehyde **66** with the titanium enolate derived from ketone **67** gave aldol **68** as a mixture (2:1) of diastereomers. Glycosylation with MeOH, conversion of product **69** into the corresponding triflate, and reaction with the sodium salt of acid **21** furnished diyne **70**, the substrate for the envisaged macrocyclization by RCAM. The reaction proceeded well in the presence of precatalyst $[Mo\{N(t\text{-}Bu)(3,5\text{-}Me_2C_6H_3)\}_3]$ and activated in CH_2Cl_2 to get cycloalkyne **71**. This was further subjected to Lindlar reduction to ensure the stereoselective formation of Z-alknene entity, followed by cleavage of the N-PMB group and the methyl glycoside with CAN (ceric ammonium nitrate) to provide latrunculin B **72 (Scheme 15).**

This was the first case of using iron catalysed cross coupling reaction of an enol triflate. As such, it adds to the now rapidly growing number of examples in which cheap and benign iron salts serve as substitutes for established palladium or nickel catalysts in a variety of cross-coupling processes in general. [13]

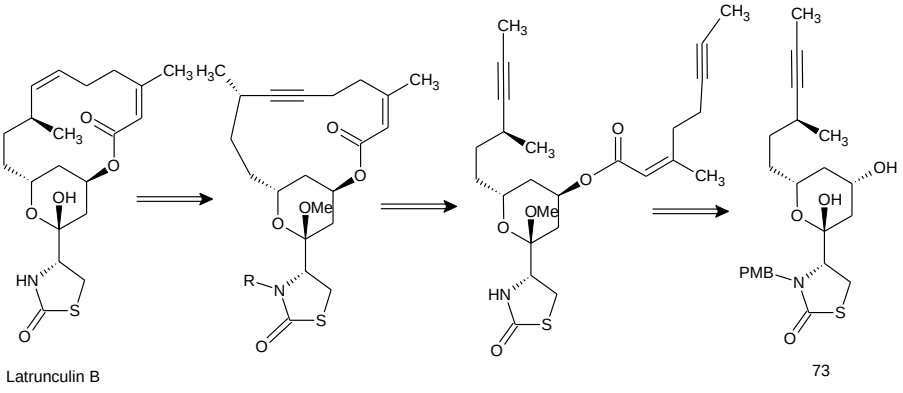


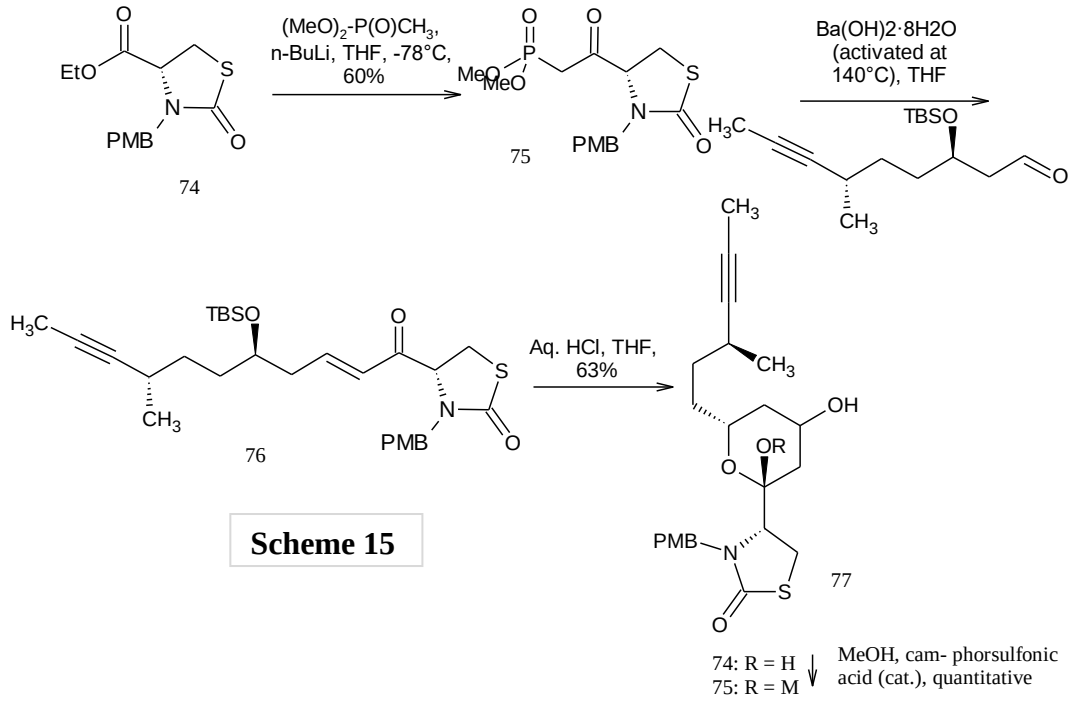
Scheme 15: Total synthesis of latrunculin B

V. 2005: Ring-Closing Enyne–Yne Metathesis-based synthesis of latrunculin A by Alois Fürstner and Laurent Turet.

Fürstner et al. developed an efficicient approach for the total synthesis of latrunculin A based upon the use of ring-closing alkyne metathesis (RCAM). It incorporates a metathetic event between an alkyne and a conjugated enyne, as opposed to that of synthesis of Lat-B (IV) which relies on a regular RCAM reaction of a properly protected diyne to cycloalkyne followed by Lindlar reduction.[14]

Retrosynthetic analysis of latrunculin A gives the building block **73** as follows:



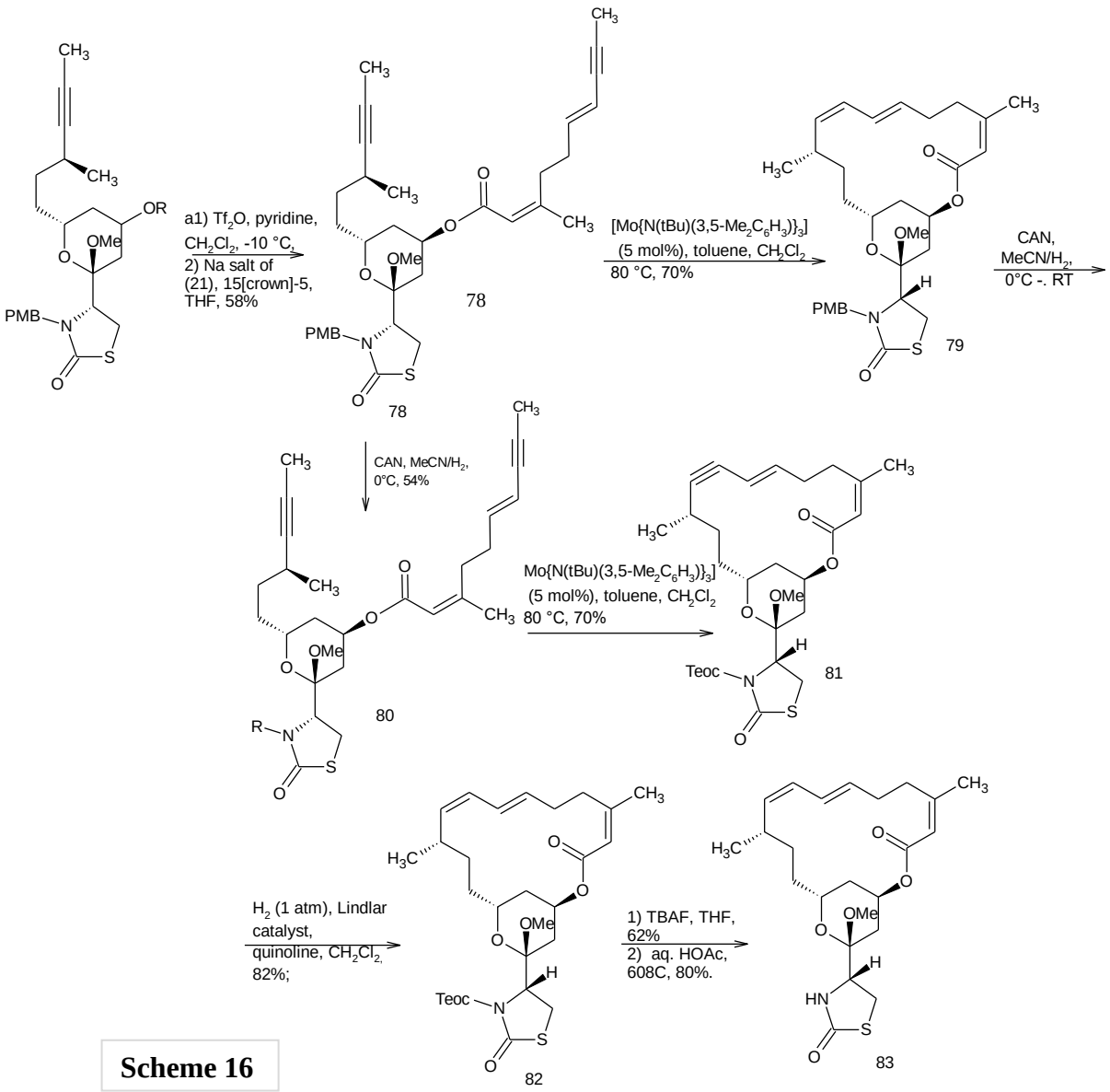


Scheme 15

Since compound **73** is the key building block en route this synthesis, its preparation relies on an aldol reaction which is not fully satisfactory. As such, an improved synthesis **(Scheme 15)** was designed involving reaction of ester **74** (derived from cysteine in two high-yielding steps) with deprotonated $(MeO)_2$-$P(O)CH_3$ afforded ketophosphonate **75** to be condensed with the aldehyde. Studies proved that this Horner–Wadsworth–Emmons reaction proceeded best when activated $Ba(OH)_2$ was used as the base.

Further, cleavage of the N-PMB group followed by the resulting product **78** underwent productive enyne–yne metathesis to give the desired product **79** in the presence of catalytic amounts of $[Mo\{N(tBu)(Ar)\}_3]$ **(Scheme 16)** into the Teoc derivative **80** allowed the ring-closing enyne–yne metathesis proceeds with rigorous chemoselectivity at the triple bonds to form the highly strained 16-membered cyclic product **81** in 70% yield. This is the smallest ring size ever to be formed by ring-closing enyne–yne metathesis.

Z-Selective semihydrogenation of the triple bond in **81** with Lindlar's catalyst in the presence of a large excess of quinoline to suppress overreduction followed by consecutive cleavage of the Teoc group and the methyl glycoside in **82** under standard conditions furnished latrunculin A **(83)**.[14]

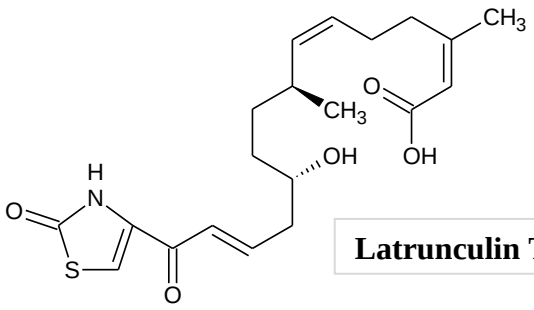


Scheme 16

RECENT STUDIES:

Recently, several grams of latrunculin B, together with a new latrunculin named latrunculin T have been isolated from a recent collection of *N. magnifica*. Semisynthetic modifications of **Lat-B**, including acetylation, acetalization, and *N*-hydroxymethylation, afforded four new & two known semisynthetic analogues. Specifically, 15-*O*-methyllatrunculin B showed a promising antiangiogenic activity in a chick chorioallantoic membrane assay and antimigratory activity in Boyden's chamber assay. [15]

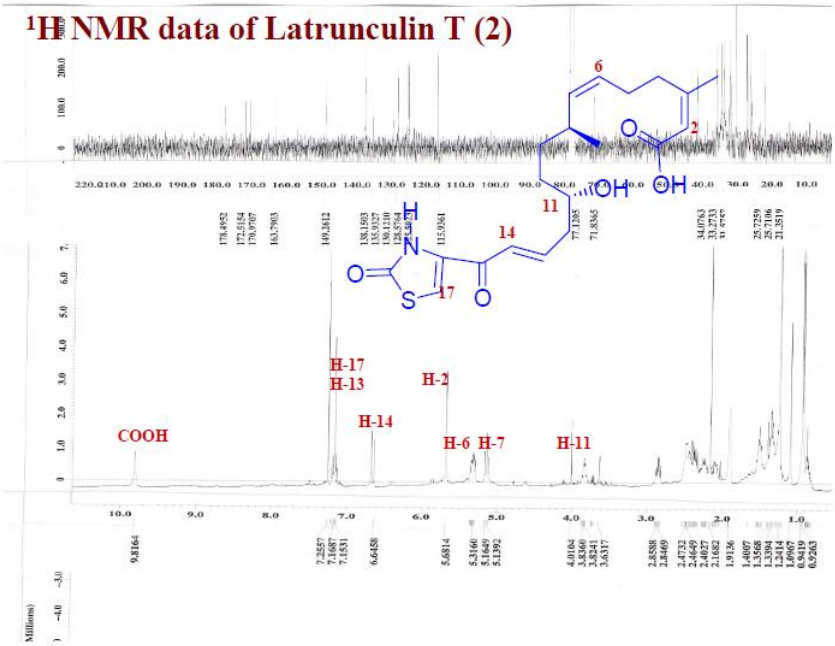
Structure & characterization of the novel Latrunculin T:



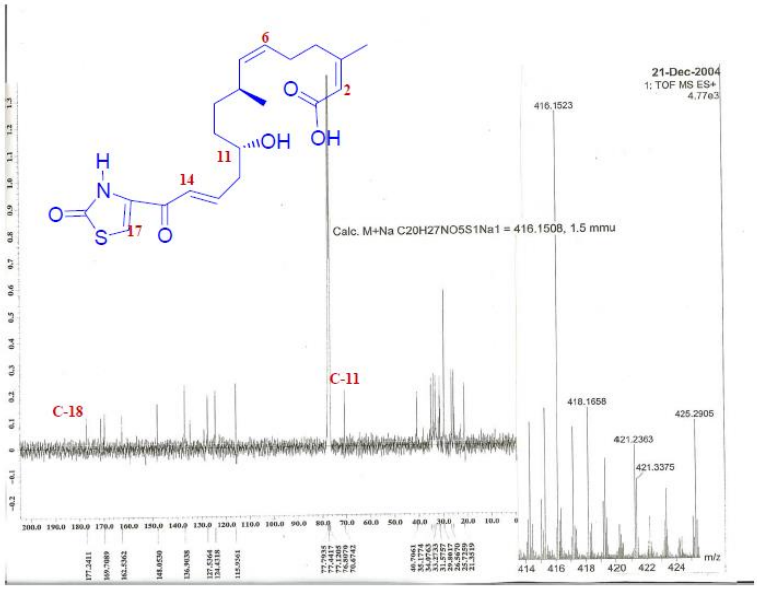
Latrunculin T

(^{1}H, ^{13}C, MS, COSY, and HMBC NMR spectra of the above compound has been reported) [15]

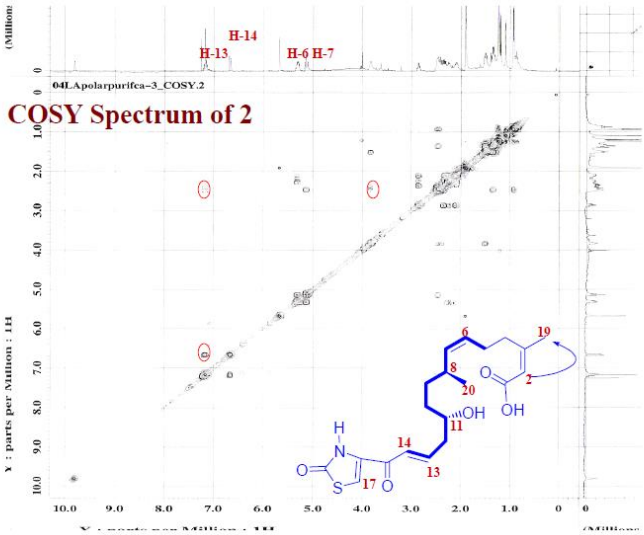
1. ^{1}HNMR Spectrum



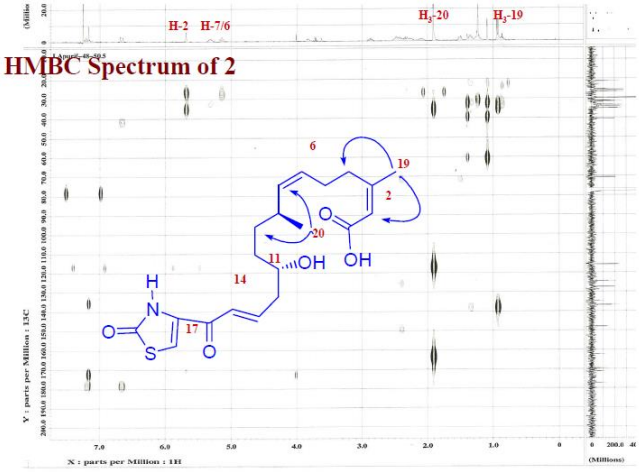
2. ^{13}CNMR Spectrum



3. COSY Spectrum



4. HMBC Spectrum



CONCLUSION:

Over the past few years macrolides of marine origin have continued to be of interest on account of their diverse biological properties, particularly, Latrunculin A & B. The two were first isolated from the red sea sponge *Latrunculia magnifica*. Latrunculin A is an actin binding macrolide & is known to disrupt actin polymerization, prevent mitotic spindle formation and thus cell replication. Thus, the latrunculins hold considerable promise as specific probes of actin-microfilament structure and function. Various approaches to synthesise latrunculins have been devised right from 1986 during its discovery by Kashman et al. Total synthetic methods by Smith et al & White & Kawasaki which are based on Wittig ylide formation are well known. Newer catalysis-based & RCAM-based synthetic approaches also have been reported by Fürstner et al.

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