A project report entitled

SYNTHESIS OF NATURAL PRODUCTS USING WITTIG REACTION

Dissertation submitted to Goa University in partial fulfilment of the requirement

for the degree of

MASTER OF SCIENCE

IN

CHEMISTRY

By

VALANKA CARVALHO

Organic chemistry

Under the guidance of

DR. SANDESH BUGHDE

Assistant professor

School of Chemical Sciences

Goa University

School of Chemical Sciences

Goa University

Taleigao Plateau

Goa

May 2022

STATEMENT

I hereby declare that the matter presented in this dissertation certified "**Synthesis of Natural Products Using Wittig Reaction**" is the result of investigation carried out by me, under the supervision of Assistant Professor Dr. Sandesh Bugde and for the award of a degree.

Ms. Valanka Carvalho

CH-20-07

CERTIFICATE

This is to certify that the dissertation entitled "**Synthesis of Natural Products Using Wittig Reaction**" is bonified work carried out by Ms. Valanka Carvalho under my supervision in partial fulfilment of the requirements for the award of the degree of Master of Science in Chemistry at the school of sciences, Goa University.

Dr. Sandesh Bugde
Assistant Professor
School of Science
Goa University

14/05/2022

Prof. Dr. Vidyadatta Verenkar
Dean of School of Chemical Sciences
Goa University

ACKNOWLEDGEMENT

It gives me an immense pleasure to present my dissertation topic
"**Synthesis of Natural Products Using Wittig Reaction**."

I extend my whole hearted thanks to my project guide Dr. Sandesh Bugde, Assistant Professor, School of Chemical sciences, Goa University, for his valuable guidance, encouragement and immense knowledge without which project would not have been successfully executed.

My sincere thanks to Prof. Dr. Vidyadatta Verenkar, dean of School of science, Goa University for providing all necessary facilities during the project work

Last but the least, I wish to thank my parents for their moral support and financial assistance without whom I would have not been able to pursue my studies.

CONTENT

INTRODUCTION

Undoubtedly, the Wittig reaction is known as one the most important and useful name reactions in the art of organic chemistry.[1] More than sixty years ago Georg Wittig and co-workers published the first example of a carbonyl olefination, the conversion of cyclohexanone into methylenecyclohexane.[2,3] The discovery of this reaction and the awareness of its importance, guided Wittig and co-workers to conduct several experiments, from which the methodology arises as a general and very important synthetic tool to produce an alkene functional group that links two molecules or moieties. The Wittig reaction is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide to give an alkene and triphenylphosphine oxide[Fig. 1,2].[4,5] Literature survey shows a huge number of papers and reviews on the applications of Wittig reaction in organic synthesis. They cover different issues and aspects of this reaction reflecting its significance, describing it from the synthetic and mechanistic points of view.[6,7]

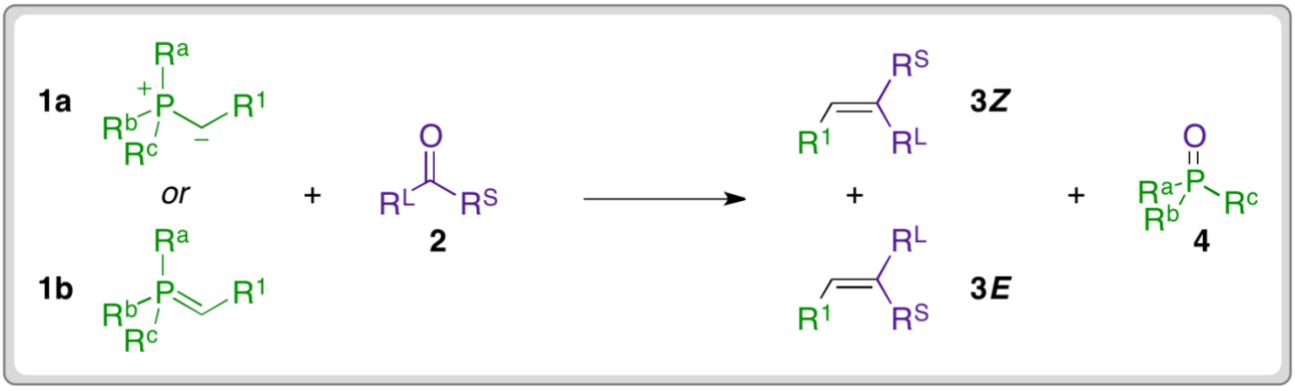


Figure 1: General Reaction[8]

Nowadays, Wittig reaction is well-documented as a powerful tool in synthetic organic chemistry as well as the total synthesis of naturally occurring compounds, which has created advancement in the area of total synthesis of natural products, thus attracted much attention of synthetic organic chemists worldwide.[9] Natural products obtained from oceans are the gorgeous source of biologically active compounds,[10] for example, alkaloids,[11] cyclic peptides,[12] and cyclic depsipeptides.[13] Natural products are an ironic source of latent medications and painkillers.[14] Several of them showed therapeutic benefit and had been used as folk medicines form ancient time and for centuries for treatment of different diseases. However, nowadays, pharmaceutical companies pay less attention to natural sources for different reasons. They are a) unreliable access and supply, b) intellectual property concerns, c) seasonal or local of erraticism composition, d) loss of sources due to environmental destruction, e) green-house effect, f) deficiency in raining rates and g)

drought.[15] To circumvent to some of these restrictions for the source plants for extraction of their biologically potent natural products, they can also be prepared by total synthesis.

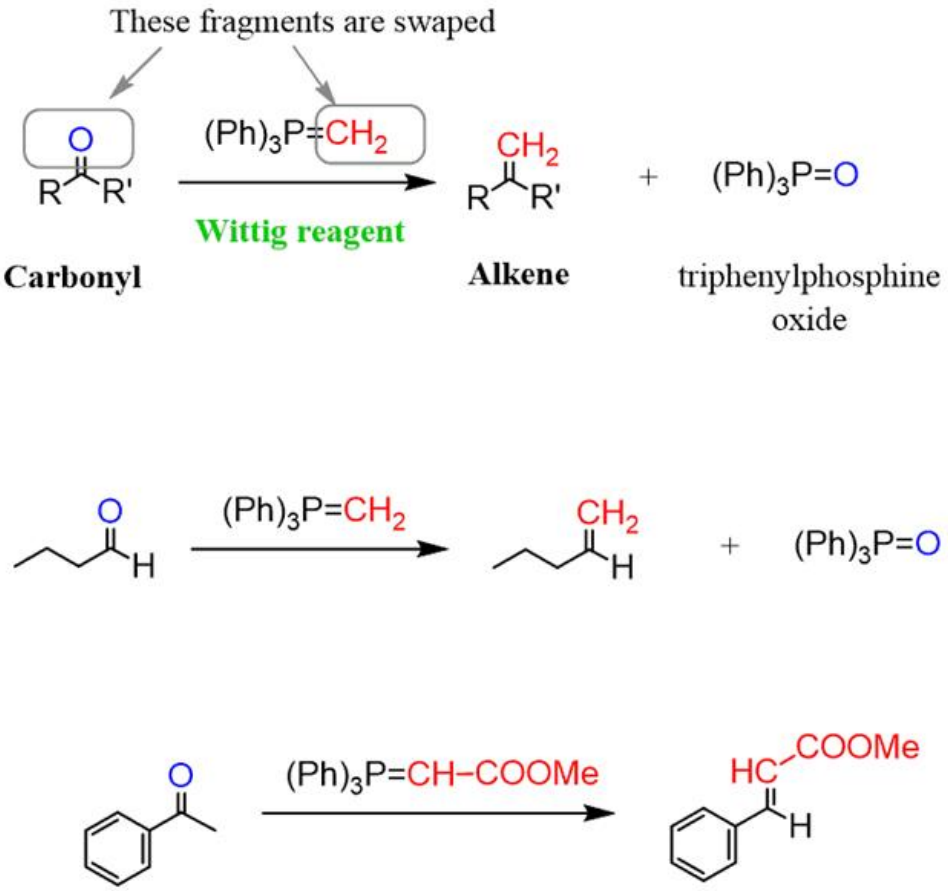


Figure 2: Examples[16]

In continuation of our interest in the applications of name reactions in the total synthesis of natural products and due to the importance of Wittig reaction in total synthesis of natural products leading to publication of large number of related papers, herein, we try to underscore the applications of the Wittig reaction in the total synthesis of natural products showing diverse biological properties focusing on their structures.[17,18]

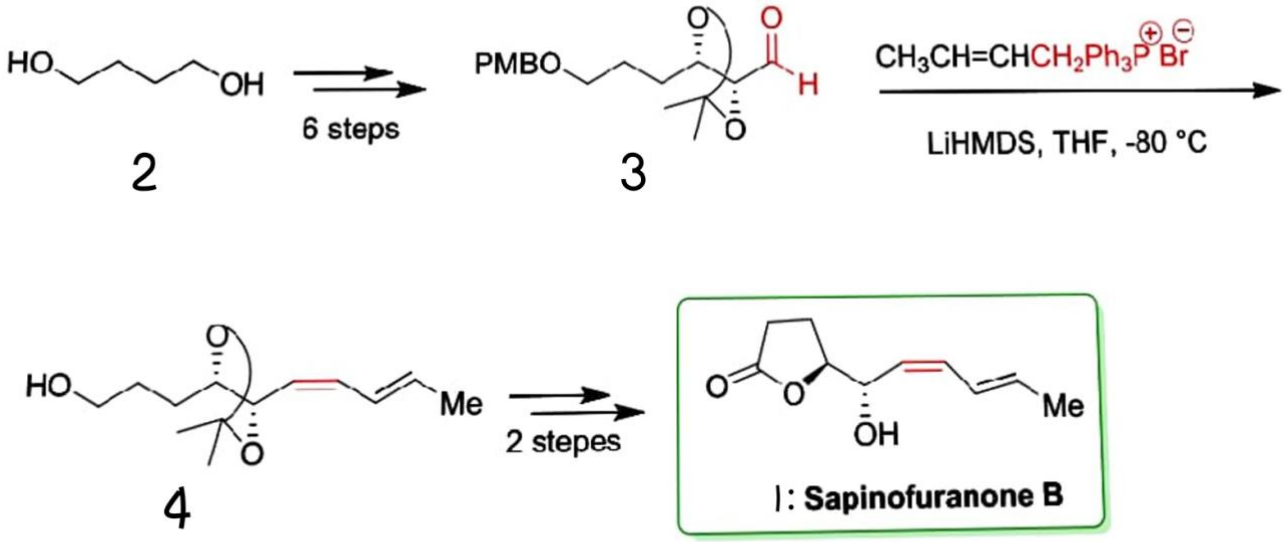
LITERATURE REVIEW

Synthesis of Natural Products Using Wittig Reaction

1) Efficient Total Synthesis of Sapinofuranone B

Sapinofuranone B **1**, was extracted from liquid cultures of *Sphaeropsis sapinea*.[19] Kumar and co-workers in 2004 reported synthesis of sapinfuranone **1** from commercially available 1,4-butanediol **2** via Sharpless asymmetric dihydroxylation, Sonogashira coupling, and Wittig olefination reaction. **2** were converted to an aldehyde **3** via 6 step reaction. The aldehyde **3** was subjected to Wittig olefination to give a mixture of cis and trans Wittig products (Z:E = 80:20). The Z-isomer **4** was separated by silica gel column chromatography. The Z-isomer **4** on several steps gave the natural product **1** with an overall yield of 67%.[20]

Scheme 1

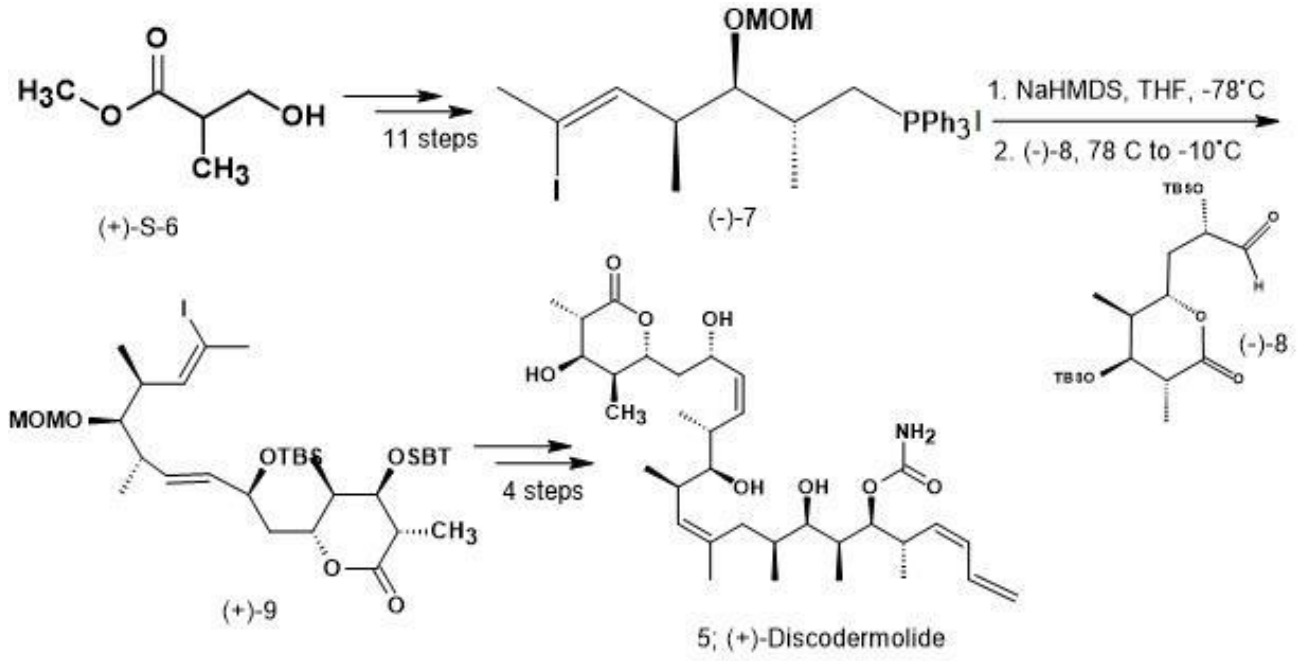


2)Total Synthesis of (+)-Discodermolide: A Highly Convergent Fourth-Generation Approach

(+)-Discodermolide **5** has been isolated from the deep sea marine sponge *Discodermia dissolute*.[21] (+)-Discodermolide **5** displays significant tumor cell growth inhibitory activity against a wide range of known cancer cell lines. Paterson and co-workers had disclosed the synthesis of **5** with linear sequence of 21 steps. In 2005, Smith and co-workers devised a

fourth generation synthesis of (+)-Discodermolide **5** with a longest linear sequence of 17 steps starting with (+)-S-Roche's ester **6**. With several steps Wittig salt **(-)-7** was obtained from (+)-S-Rosche's ester **6**. They found that vinyl iodide can be converted into the Wittig salt **(-)-7** in three steps without concomitant cyclopentane formation. The availability of Wittig salt **(-)-7** made the process highly convergent and bidirectional. In the event, slow addition of NaHMDS to THF solution of the Wittig salt at -78°C improved the construction of the desired phosphonium ylide by reductive β-removal of the vinyl iodide. Subsequently, tetrahydrofuran solution of aldehyde **(-)-8** was added to the obtained ylide, warmed at -10°C followed by an aqueous quench and workup to give vinyl iodide**(+)-9**. Then vinyl iodide**(+)-9** upon several steps was converted to **5** with an overall yield of 9%.[22]

Scheme 2

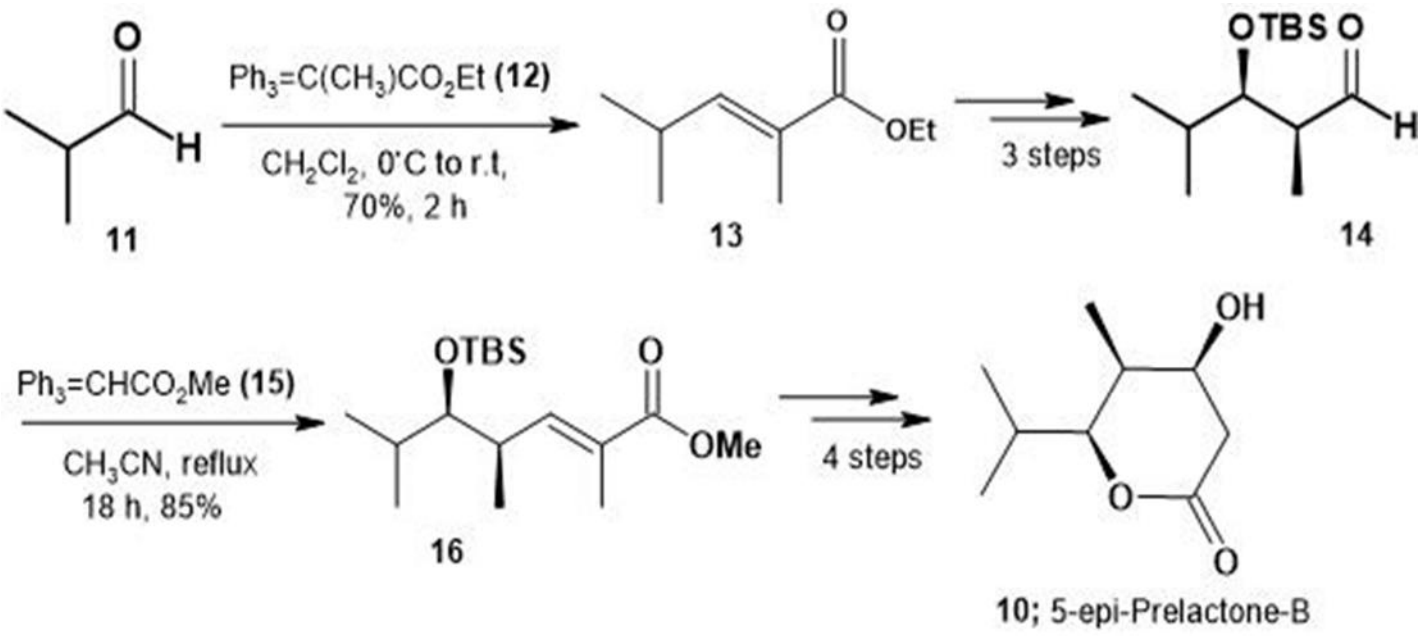


3) First Concise Total Synthesis of 5-Epi-prelactone B

Prelactone B **10** was isolated from *Streptomyces griseus*.[23] It has been used as a standard for investigations concerning the mechanism of polyketide synthase (PKS).Synthesis of 5-epi-prelactone **10** was reported by Srihari and co-workers in 2008 with the commercially available isobutraldehyde **11**. The key steps involved in the synthesis of **10** were Sharpless asymmetric epoxidation and intramolecular hydride transfer reaction for formation of the aldol product by nonaldol chemistry. Wittig reaction of **11** was carried out with [1(ethoxycarbonyl)ethyl]tri- phenylphosphoniumbromide **12** to give only the trans-ester **13**. The trans-ester **13** on several step gave aldehyde **14** which was reacted with (methoxycarbonylmethyl)triphenylphosphonium bromide **15** to provide the trans-

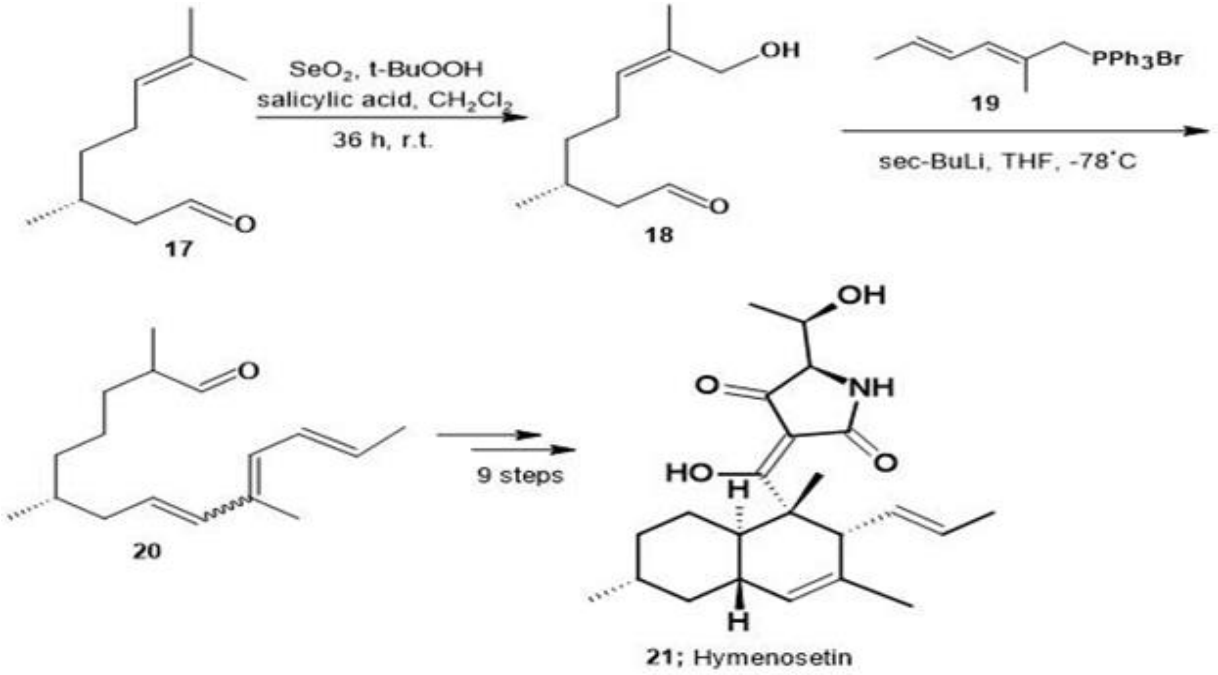
homologated product **16**. Finally, the compound **16** was converted into 5-epi-prelactone **10** with an overall yield of 21%.[24]

Scheme 3



4)Total Synthesis of (–)-Hymenosetin

Scheme 4



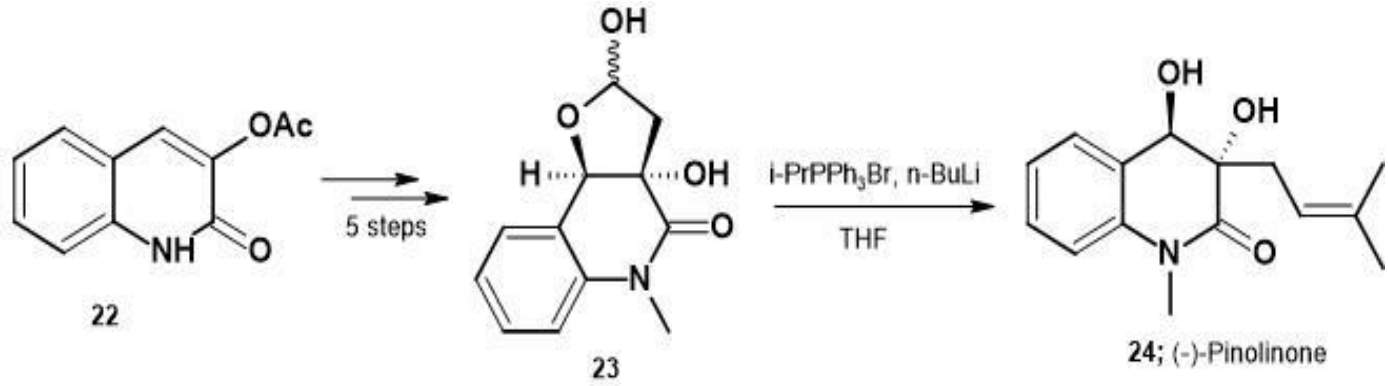
(-)-Hymenosetin **21** was extracted from *Hymenoscyphus pseudoalbidus*.[25,26] It shows antifungal and moderate cytotoxic effects against the mouse fibroblast cell line L929 along with biological activities against Gram-positive bacteria. Kauhl and co-workers reported the synthesis of **21** using an intramolecular Diels-Alder reaction as the key step with an overall yield of 70%. Wittig reaction between allylic alcohol **18** obtained from (+)-citronellal **17** and

phosphonium bromide **19** was done to give the desired triene alcohol **20** and satisfactory stereoselectivity (3:2 E/Z). The triene alcohol **20** was converted to **21** after several steps.[27]

5) Enantioselective, intermolecular [2+2] photocycloaddition reactions of 3-acetoxyquinolone: total synthesis of (-)-pinolinone

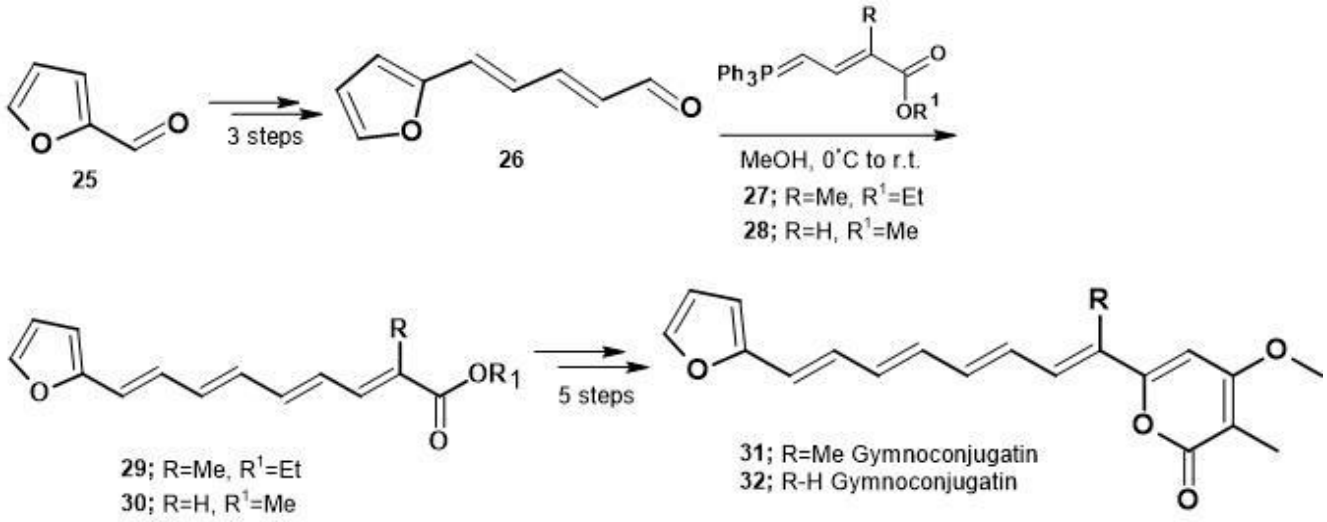
(-)-Pinolinone **24** was isolated from dried roots of *Boronia pinnata* Sm. (Rutaceae).[28] In six steps with an overall yield of 55% total synthesis of pinolinone **24** starting with 3-acetoxyquinolone **22** was demonstrated by Mayr and co-workers. Upon several steps **22** was converted to lactol **23** which should be in equilibrium with the γ-hydroxyaldehyde and hence expected being involved in Wittig reaction. The Wittig reaction was performed at 0°C by adding lactol to an excess of the ylide in THF as the solvent to provide pinolinone **24**.[29]

Scheme 5



6)Facile total synthesis of gymnoconjugatin A and B

Scheme

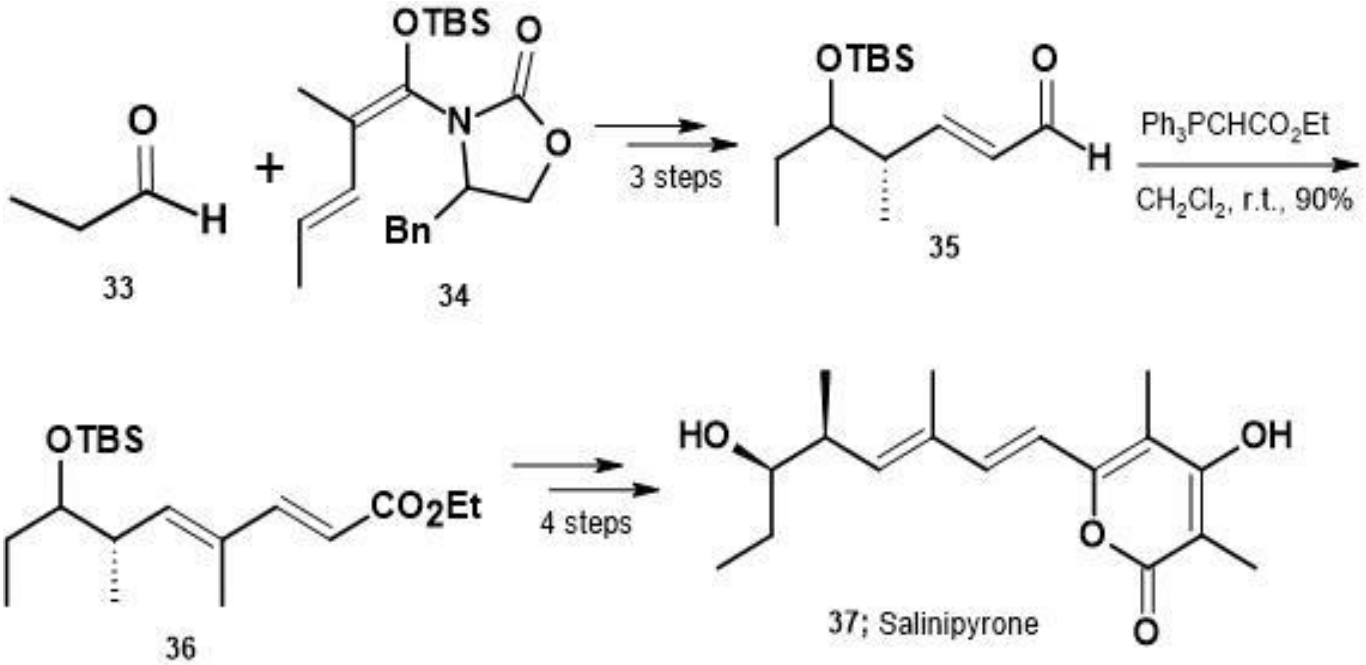


Gymnoconjugatin A and B were isolated from the soil microbe of *Gymnoascus reessii*.[30] Samala and co-workers devised the total synthesis of gymnoconjugatin A and B starting with furfural **25** to provide aldehyde **26** after three steps. The phosphorus ylide **27** & **28** was formed by allylic bromination followed by Wittig reaction of ethyl tiglate and methyl crotonate respectively. The trans tetraene ester **29** & **30** was obtained by reacting aldehyde with phosphorus ylide **27** & **28** respectively. After several steps **29** & **30** was converted to gymnoconjugatin A and B.[31]

7) First total synthesis of salinipyrone A using highly stereoselective vinylogous Mukaiyama aldol reaction

salinipyrones A **37** was isolated from cultures of the obligate marine actinomycete *Salinispora pacifca* CNS-237.[32] Ramesh and co-worker reported the first asymmetric total synthesis of salinipyrone A **37** starting with vinylketene silyl N,O-acetal **34**. Vinylketene silyl N,O-acetal **34** and propionaldehyde **33** was reacted in the presence of $TiCl_4$ (vinylogous aldol reaction) to produce anti-adduct which on several steps gave compound **35**. Next, **35** was homologated to (E)-α,β-unsaturated ester **36** through Wittig olefnation reaction with Ph3P=CHCO2Et in dichloromethane. After several steps, **36** was converted into salinipyrone A **37** with an overall yield of 14%.[33]

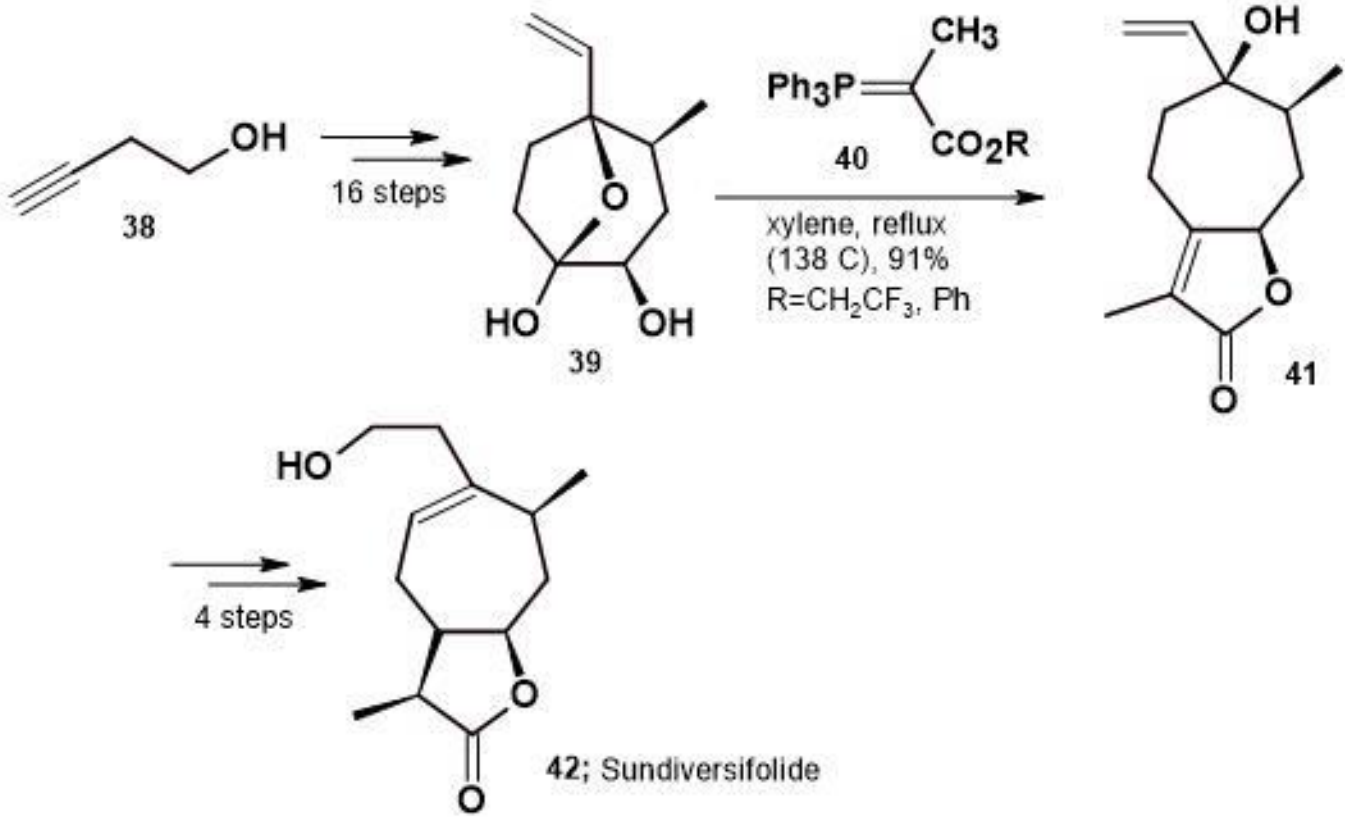
Scheme 7



8) Total Synthesis of (+)- and(−)-Sundiversifolide via IntramolecularAcylation and Determination of the Absolute Configuration

Sundiversifolide **42** was extracted from the exudate of germinating sunflowers (*Helianthus annuus* L.).[34] Ohtsuki and co-workers demonstrated the synthesis of **42** commenced from 3-butyn-1-ol **38**. Upon several step, afforded the hydroxyl hemiacetal **39** which was treated with trifluoroethyl ester **40** under reflux in xylene produced the butenolide **41**. Next, butenolide **41** was converted into the desired natural product **42** after several steps with an overall yield of 85%.[35]

Scheme 8

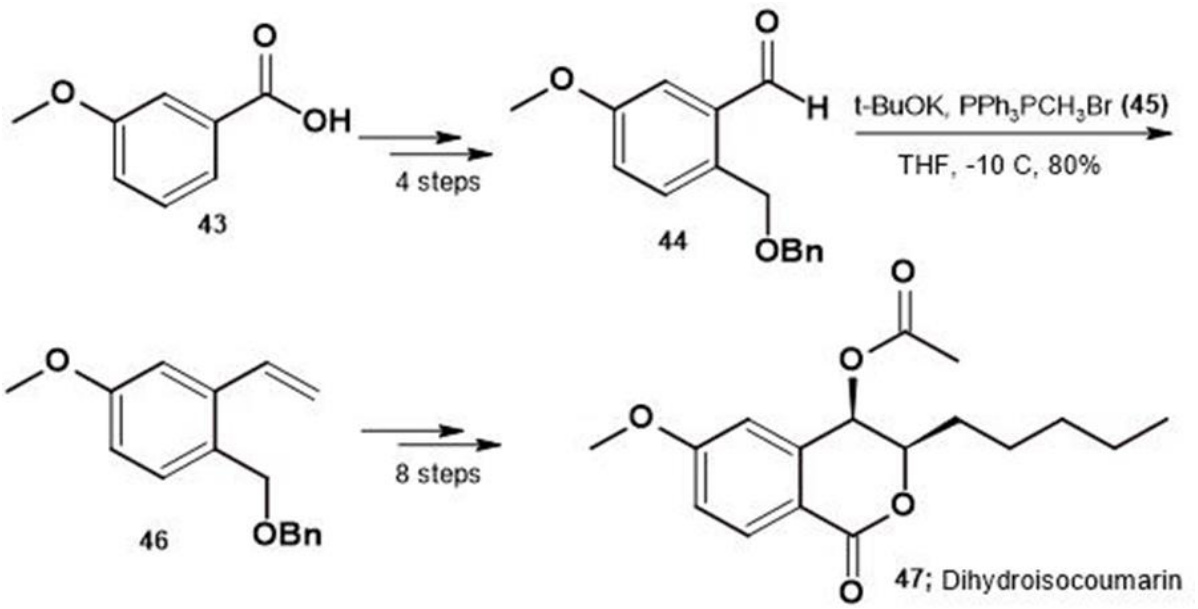


9)Total Synthesis of the aromatase inhibitor dihydroisocoumarin via protective opening of lactones

Dihydroisocoumarin **47** was found from aerial parts of *Xyris pterygoblephara*.[36] Venkateswarlu and co-workers reported the total synthesis of dihydroisocoumarin **47** with Wittig reaction, Grubbs cross metathesis, and Sharpless dihydroxylation reactions as the main steps. Starting with meta-methoxybenzoic acid **43** that upon 4 steps afforded aldehyde **44**. Using Wittig reaction with methyltriphenylphosphonium bromide salt **45** in

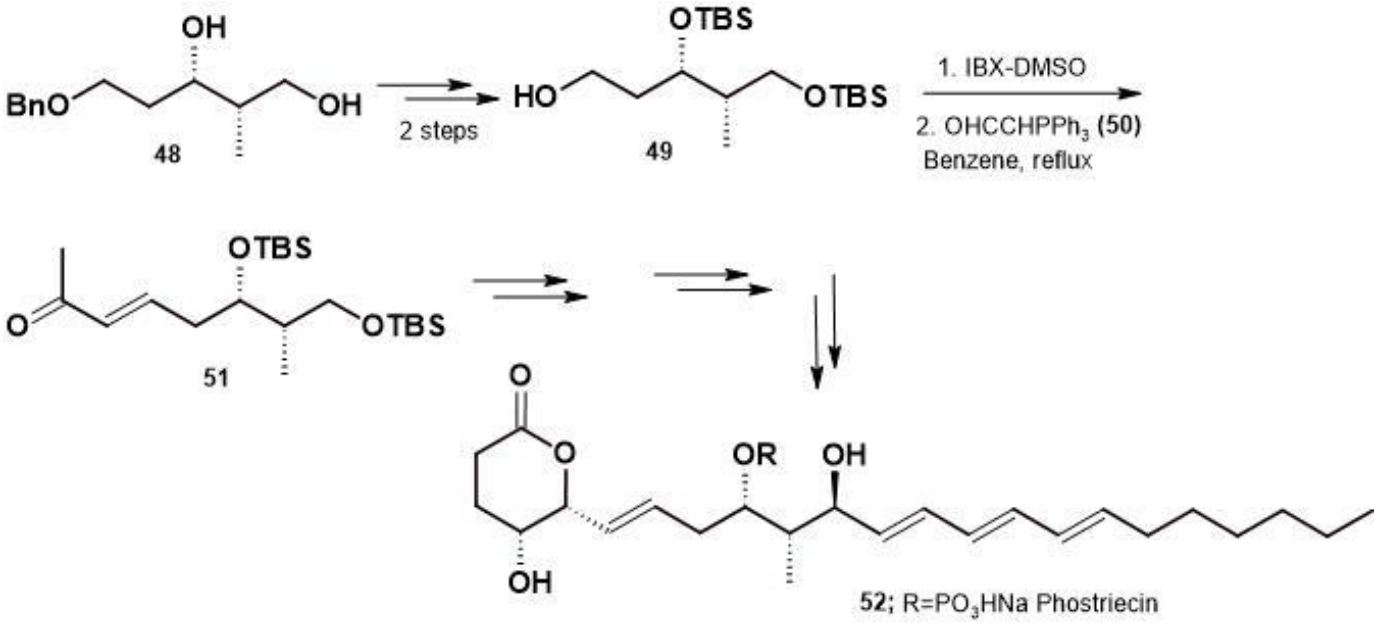
the presence of potassium tert-butoxide the aldehyde was converted into compound **46** which on several steps produced dihydroisocoumarin **47** with an overall yield of 16%.[37]

Scheme 9



10) Studies towards the total synthesis of Phostriecin

Scheme 10

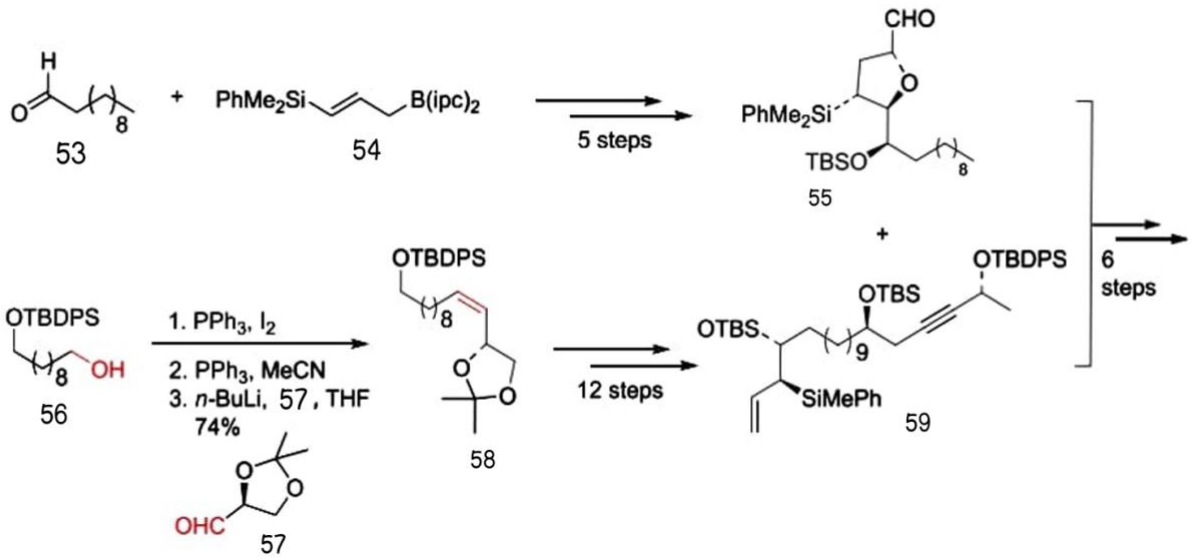


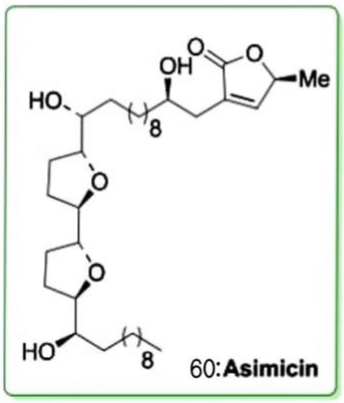
Phostriecin **52** is a structurally unique phosphate ester produced by *Streptomyces roseiscleroticus* No.L827-7 which was isolated from a soil sample of Gujarat state in India.[38] Yadav and co-workers described the synthesis C1–C13 and C14–C22 segments of

the antitumor natural product phostriecin **52**. Total synthesis of phostriecin **52** commenced from diol **48** to get primary alcohol **49**. This **49** was oxidised to give aldehyde which was subjected to two carbon Wittig reaction by treatment with (triphenylphosphoranylidene)acetaldehyde **50** in benzene under reflux conditions to afford α,β-unsaturated aldehyde **51**. After several steps, 51 gave phostriecin **52**.[39]

11) Total Synthesis of Asimicin via Highly Stereoselective [3 + 2] Annulation

Scheme 11



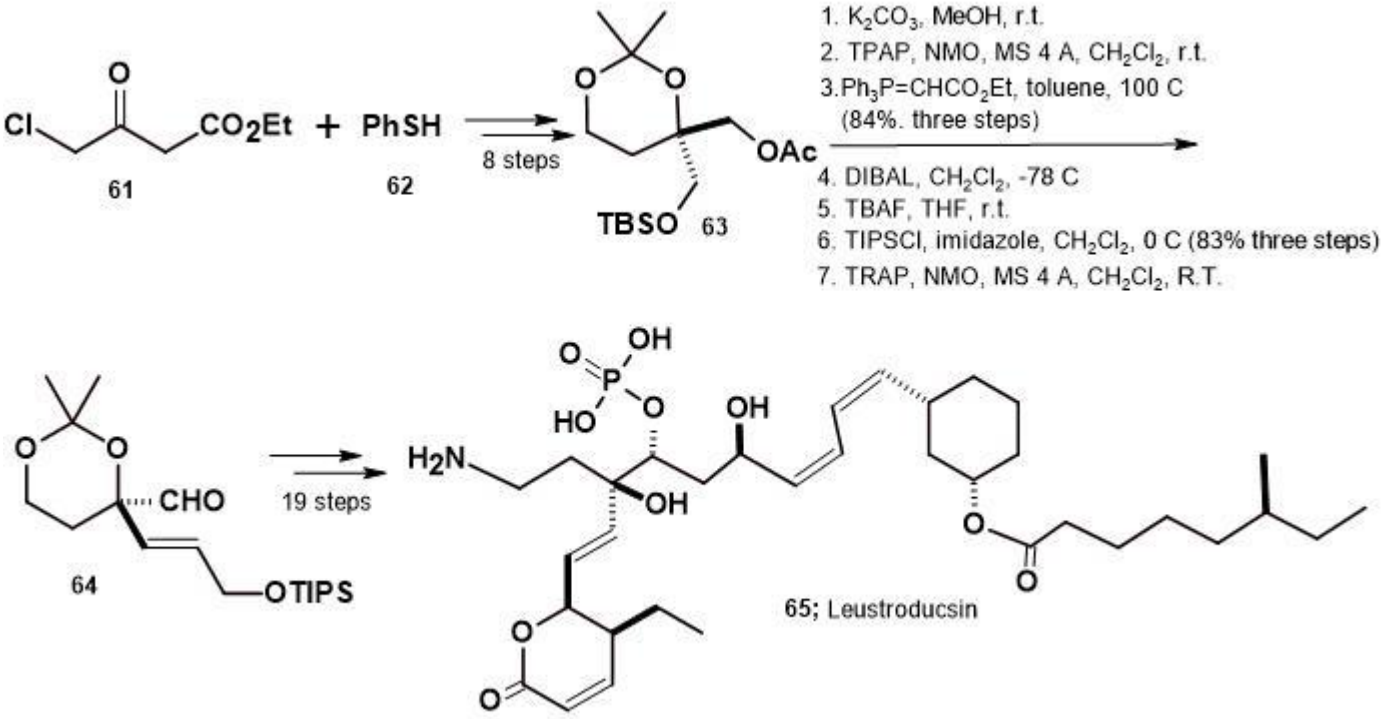


The annonaceous acetogenins, a structurally varied group of naturally occurring compounds, have been extracted from the Annonaceae group.[40] Rousch and co-workers devised an extremely enantioselective synthesis of asimicin **60**. They predicted that the bis-tetrahydrofuran part of asimicin might be provided from two sequential chelate controlled [3+2] annulation of allylsilanes and suitably functionalized aldehydes. The synthesis started by treating market purchasable undecanal **53** with the (E)-γ-silylallylborane **54**, derived

from (-)-Ipc2BOMe to produce β-hydroxyallysilane which on several steps afforded aldehyde **55**. The formation of the highly substituted allylsilane **59** was initiated by conversion of **56** (prepared by monosilylation of 1,10-decanediol) to the primary iodide. Treatment of the iodide with triphenylphosphine and subsequent Wittig reaction with (S)-glyceraldehyde acetonide **57** provided **58** which on several steps gave allylsilane **59**. Finally the reaction between allylsilane **59** and aldehyde **55** after several steps gave asimicin **60**.[41]

12) Total Synthesis of Leustroducsin B

Scheme 12

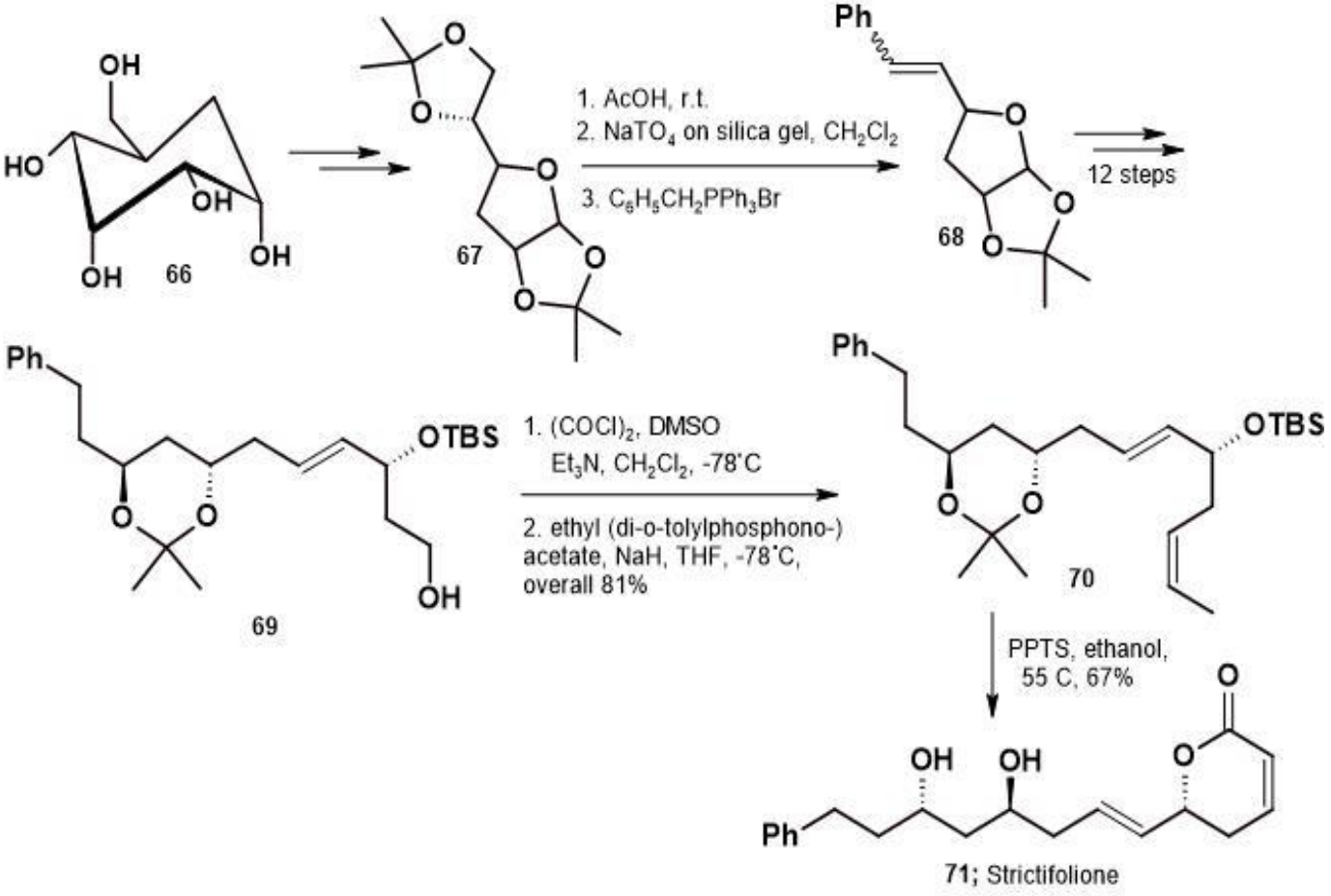


Leustroducsin B **65** is a potent colony-stimulating factor inducer isolated from the culture broth of *Streptomyces platensis* SANK 60191 by Sankyo's groups.[42–44] Total synthesis of Leustroducsin B **65** was demonstrated by Shimada and co-workers with an overall yield of 51% in 16 steps using TBS ether as starting materials via Wittig reaction as the key step. Total synthesis commenced with the reaction of ethyl 4-chloroacetoacetate **61** and Thiophenol **62** that after several steps gave TBS ether **63**. Next, elimination of the acetyl substituent of TBS **63**, oxidation reaction of the alcohol to the expected aldehyde, and Wittig reaction using Ph3P=CHCO2Et completed the corresponding α,β-unsaturated ester **64**. Then reduction of the ethyl ester and deprotection of the TBS substituent generated a diol in which less hindered allyl alcohol has been selectively protected as the TIPS ether and remaining was converted into an aldehyde **64**. Lastly, upon several steps aldehyde **64** produced leustroducsin **65**.[45]

13) A carbohydrate-based approach for the total synthesis of Strictifolione

Strictifolione **71** was extracted by Aimi and co-workers from the stem bark of *Cryptocarya strictifolia* that grows in the Indonesian tropical rainforests.[46] Total synthesis of strictifolione **71** was commenced starting from d-glucose **66** by Ramana and co-workers. D-Glucose upon several steps afforded 3-deoxy-1,2;5,6-di-O-isopropylidene-α-d-glucofuranose **67**. Next, selective deprotection of the 5,6-O-isopropylidene group, sodium periodate-catalyzed oxidative removal and Wittig olefnation reaction with benzyltriphenylphosphorane provided an impure mixture of styrene derivative **68**. Upon several steps, compound **68** was converted to **69**. Next, the free hydroxyl group of **69** was subjected to Swern oxidation and HWE reaction using ethyl (di-o-tolylphosphono)acetate and sodium hydride in tetrahydrofuran to provide only the Z-unsaturated ester **70**. Lastly unsaturated ester **70** was converted to the natural product **71** with an overall yield of 67%.[47]

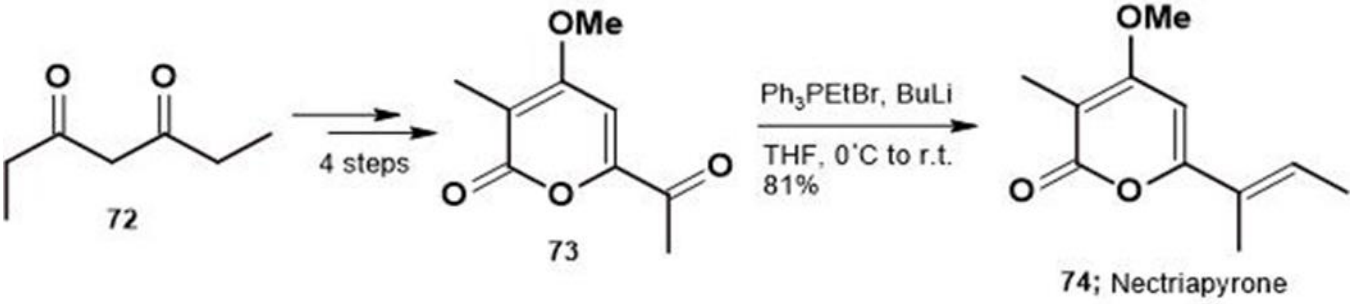
Scheme 13



14) Total synthesis of nectriapyrone

Infectopyrone, a 2-pyrone was first isolated from *Alternaria infectoria* and furthermore produced by *Stemphyllium* and *Ulocladium sp*. Podlech and co-workers in 2012 demostrated the total synthesis of the 2-pyrone naturally occurring compounds nectriapyrone **74**, aplysiopsenes A–C, ent-aplysiopsene D, phomapyrones A and D, and of 8,9-dehydroxylarone using Wittig olefnation initiating from vermopyrone **73**.

Scheme14

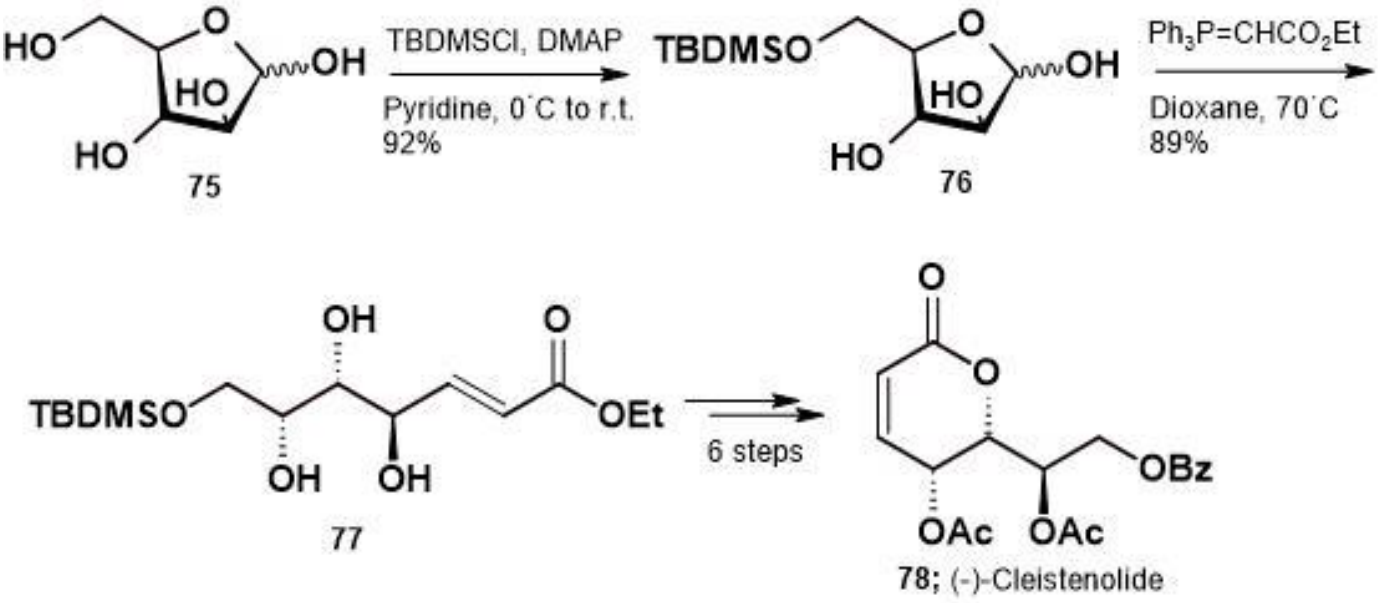


Coleman and co-workers synthesised vermopyrone **73** from 3,5-heptanedione **72** in four steps.[30] Vermopyrone **73** was reacted with an ylide prepared from the respective ethylphosphonium salt to provide nectriapyrone **74** with an E/Z selectivity of 7:3, where the natural E isomer was obtained by a simple chromatography.[48]

15) Stereoselective Total Synthesis of (-)-Cleistenolide

Total synthesis of Cleistenolide **78** a natural product, extracted from the *Cleistochlamys kirkii* Oliver,[49] was commenced from natural chiral template d-arabinose **75**.

Scheme 15

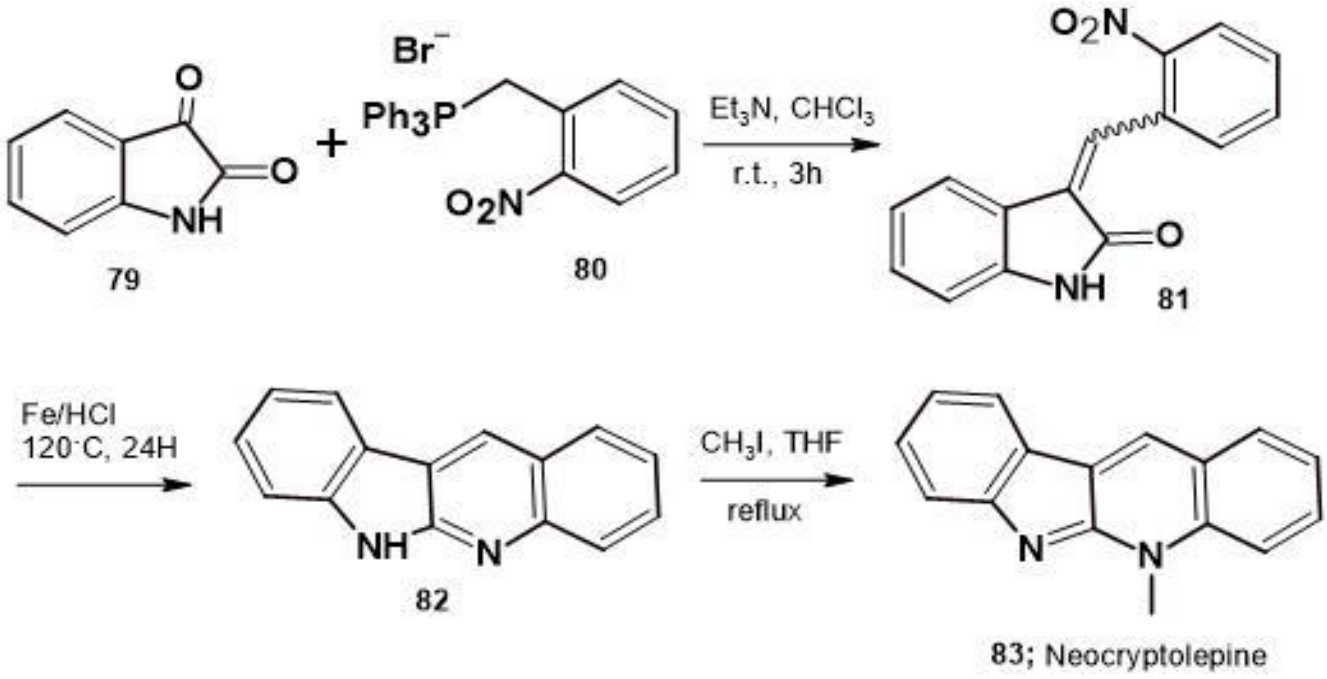


Reaction of D-arabinose **75** with TBDMSCl in pyridine at 0°C regioselectively gave 5-O-silyl aldehyde **76**. Wittig olefination of aldehyde **76** with ethyl (triphenylphosphoranylidene)acetate in dioxane at 70°C produced α,β-unsaturated ester **77**. After several steps, the α,β-unsaturated ester **77** was transformed into (−)-cleistenolide **78** in 91% yield.[50]

16) Highly efficient one-pot synthesis of D-ring chloro-substituted neocryptolepines via a condensation--Pd-catalyzed intramolecular direct arylation strategy

Neocryptolepine **83** was isolated from *Cryptolepis sanguinolenta*.[51] A total synthesis of neocryptolepine **83** was performed in 3 steps with 68% overall yield starting from isatin **79**. Condensation of isatin **79** and (2-nitrobenzyl)triphenylphosphonium bromide **80** in the presence of triethyl amine provided the Wittig product **81**. Finally, the reduction of **81** with Fe in the presence of HCl afforded 6H-indolo[2,3-b]quinolone **82**, which was regioselectively methylated to obtain neocryptolepine **83**.[52]

Scheme 16

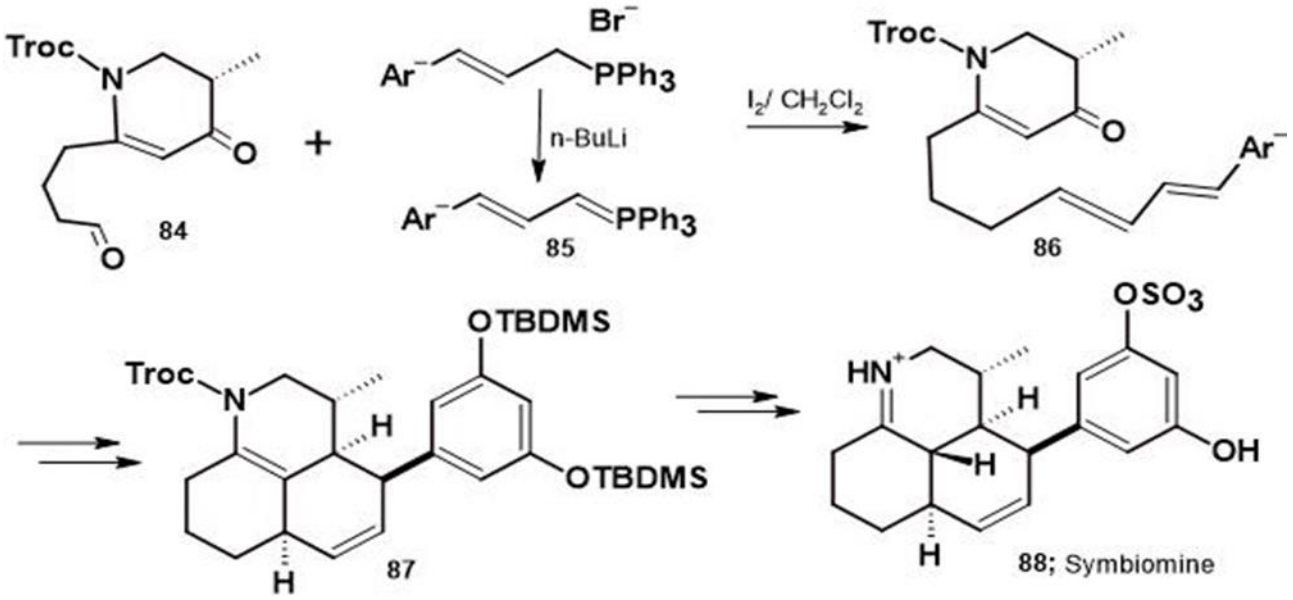


17) Total Synthesis of (±)-Symbioimine

Uemura and co-workers recently reported the isolation of tricyclic iminium sulfate symbioimine **88** from a cultured marine *dinoflagellate Symbiodinium sp*.[53,54] Zou and co-workers demonstrated synthesis of symbioimine **88** with an overall yield of 58%.

Compound **84** is readily available in six steps from ethyl acetoacetate and then used in the synthesis of (±)-Symbioimine **88**.]

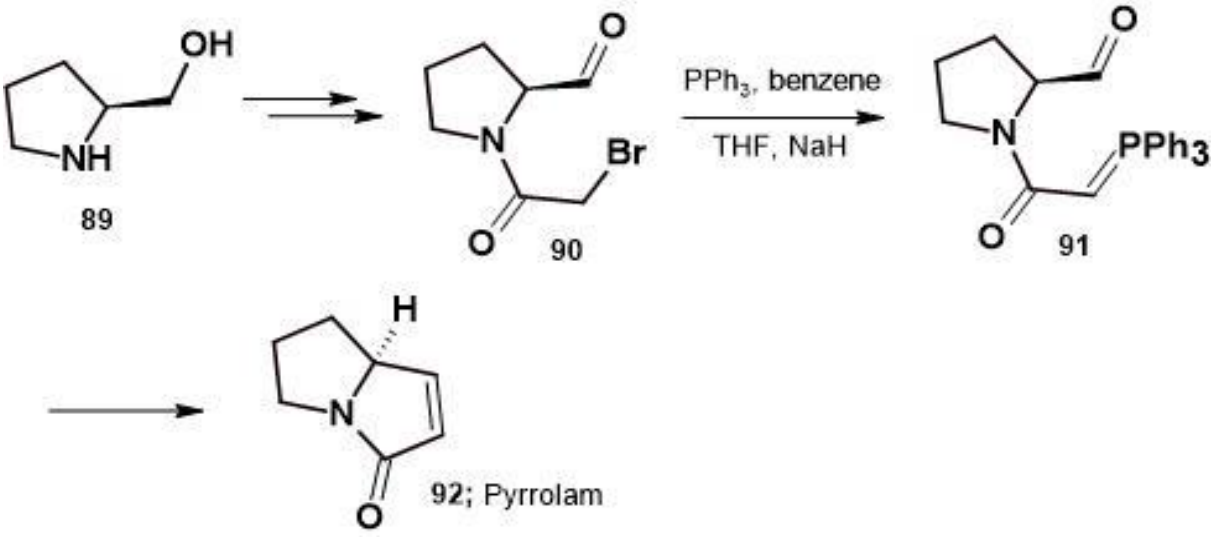
Scheme 17



Phosphorane **85** is produced in situ through a treatment of the phosphonium salt with n-BuLi and reacts with compound **84**. Equilibration with I_2 in CH_2Cl_2 afforded dienyl ketone **86**. The reaction proceeds through the reduction and intramolecular Diels-Alder reaction of compound **86** to obtain product **87**. The cleavage of Troc and TBDMS groups followed by the reaction with SO3/DMF and anhydrous sodium sulphate in pyridine afforded the desired (±)-symbioimine **88**.[55]

18) Intramolecular Wittig Reaction: A New Synthesis of (S)-Pyrrolam A

Scheme 18

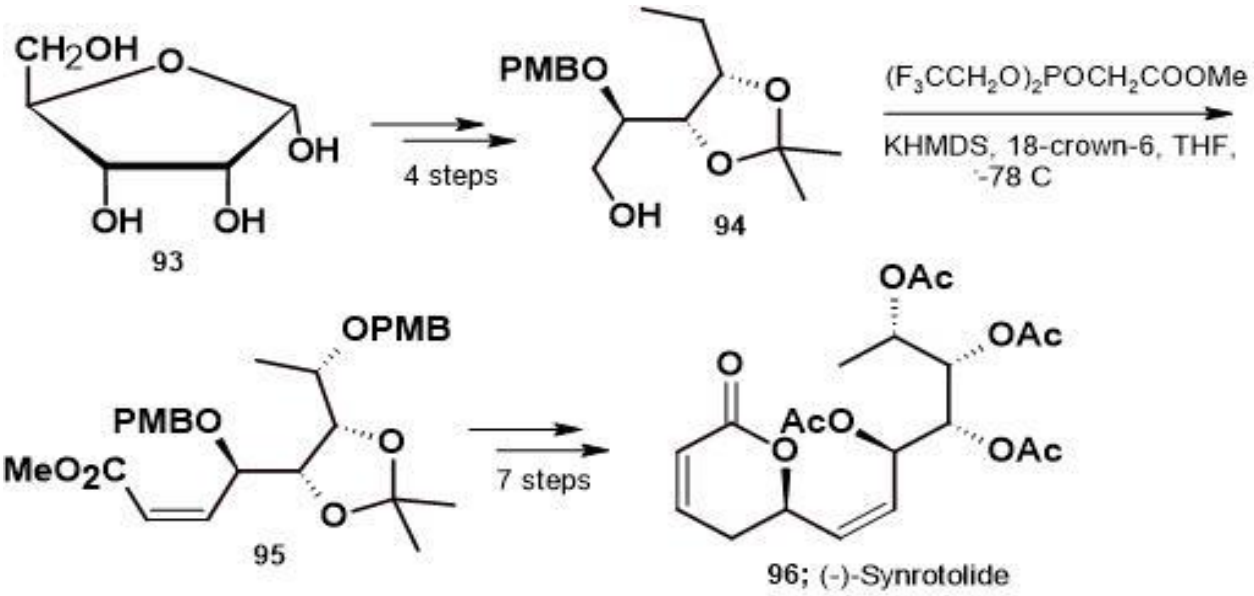


(S)-Pyrrolam **92** was isolated from the bacterial strain *Streptomyces olivaceus*.[56] Total synthesis of (S)-pyrrolam **92** was accomplished starting from L-proline **89**. L-proline **89**, upon several steps aforded (S)-1-(2-bromoacetyl)pyrrolidine-2-carbaldehyde **90**. **90** on reacting with PPh_3 formed the corresponding phosphonium salt **91** which on deprotonation with NaH led to **92**.[57]

19) Stereoselective total synthesis of (L)-synrotolide diacetate from D-ribose

(L)-Synrotolide **96** an α-pyrone-containing natural product was isolated from *Syncolostemon rotundifolius*.[58] Krishna and co-workers in 2007 reported the synthesis of (L)-Synrotolide **96** starting with D-ribose **93**. Upon several steps, D-ribose **93** aforded compound **94** that has been oxidized to an aldehyde via Swern reaction and exposed to a Wittig olefnation reaction to give the corresponding α,β-unsaturated ester **95** mostly as the (Z)-isomer. After several steps, α,β-unsaturated ester **95** aforded synrotolide **96**.[59]

Scheme 19

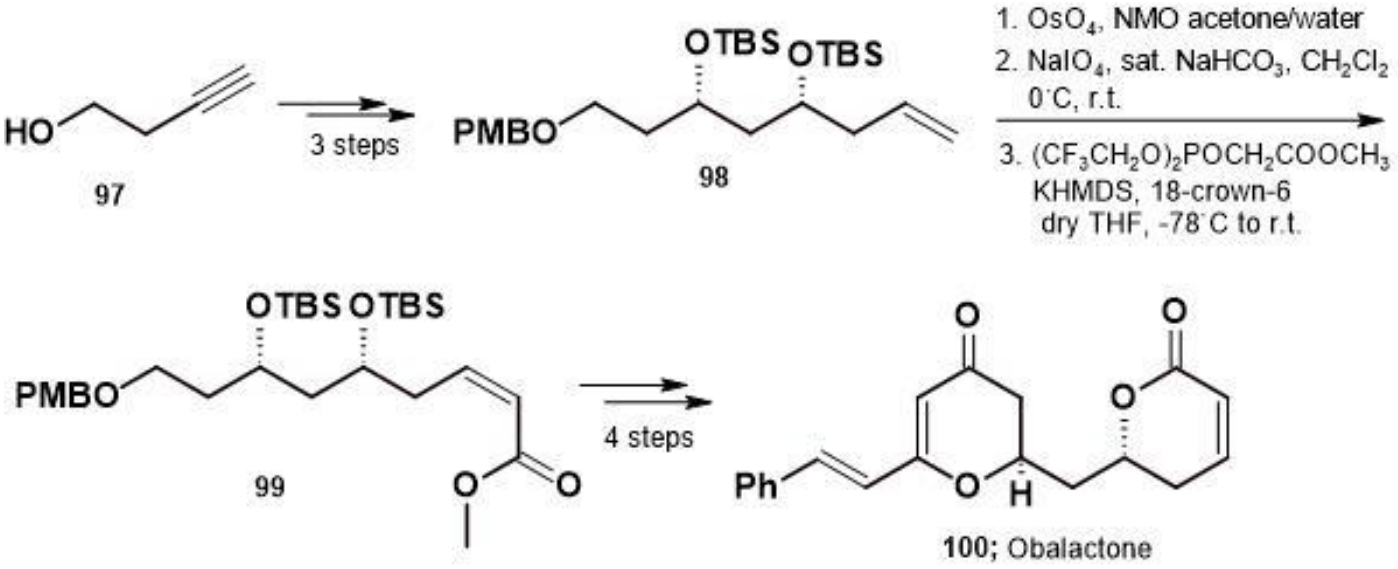


20) PTSA-catalyzed tandem cyclization protocol for the stereoselective total synthesis of obolactone

Obolactone **100** was extracted by Guéritte and co-workers from *Cryptocarya obovata*.[60] Krishna and co-workers in 2010 reported the total synthesis from commercially available homopropargyl alcohol **97**, which after two steps transformed into compound **98**. Since the terminal olefin present in **98** has been considered as the protected carbonyl group,

its dihydroxylation and oxidative elimination afforded the desired aldehyde using Wittig olefnation reaction to give the α,β-unsaturated ester **99** mostly as the (Z)-isomer. Lastly, upon several steps, compound **99** aforded the desired naturally occurring compound **100** (75%) via a multiple reaction set, specifcally silyl deprotection-tandem ring-closing reaction.[61]

Scheme 20



CONCLUSION

In this review we try to underscore and emphasize the significance and importance of Wittig reaction as a unique reaction under new perspective, its applications in the total synthesis of natural products. It is also used in the synthesis of natural analogues aiming to obtain compounds with a large spectrum of biological properties. The useful of the Wittig reaction in organic synthesis is enormous, it allow the formation of new carbon-carbon double bonds with one specific stereochemistry depending on the reaction conditions. Wittig reaction can be used to shorten the linear sequence of the total synthesis of some natural products.

References

1. Wittig, G. & Geissler, G. Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate. *Justus Liebigs Ann. Chem.* **580**, 44–57 (1953).
2. Wittig, G. & Schöllkopf, U. Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien (I. Mitteil. *Chem. Ber.* **87**, 1318–1330 (1954).
3. Edition, R. H.-A. C. I. & 2001, undefined. Wittig and his accomplishments: still relevant beyond his 100th birthday. *Wiley Online Libr.*
4. Maryanoff, B. E. & Reitz, A. B. The Wittig Olefination Reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects. *Chem. Rev.* **89**, 863–927 (1989).
5. A. Johnson, Ylides and Imines of Phosphorus, Wiley,... - Google Scholar. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=A.+Johnson%2C+Ylides+and+Imines+of+Phosphorus%2C+Wiley%2C+New+York%2C+chapters+8%2C+1993%2C+221&btnG=.
6. Cadogan JIG (1979) Organophosphorus reagents in organic... - Google Scholar. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Cadogan+JIG+%281979%29+Organophosphorus+reagents+in+organic+syn%02thesis.+Academic+Press%2C+Londo&btnG=.
7. Rocha, D. H. A., Pinto, D. C. G. A. & Silva, A. M. S. Applications of the Wittig Reaction on the Synthesis of Natural and Natural-Analogue Heterocyclic Compounds. *European Journal of Organic Chemistry* vol. 2018 2443–2457 (2018).
8. Byrne, P. A. mechanism. (2013) doi:10.1039/c3cs60105f.
9. O. Tour, S. R. Adams, R. A. Kerr, R. M. Meijer, T.... - Google Scholar. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=O.+Tour%2C+S.+R.+Adams%2C+R.+A.+Kerr%2C+R.+M.+Meijer%2C+T.+J.+Sejnowski%2C+R.+W.+Tsien%2C+R.+Y.+Tsien%2C+Nat.+Chem.+Biol.+2007%2C+3%2C+423&btnG=.
10. Blunt, J., Copp, B., Keyzers, R., … M. M.-N. P. & 2016, undefined. Marine natural products. *pubs.rsc.org*.
11. Zhang, P. *et al.* Prenylated indole alkaloids from the marine-derived fungus Paecilomyces variotii. *Elsevier*.
12. Zhan, K.-X. *et al.* Reniochalistatins A–E, Cyclic Peptides from the Marine Sponge Reniochalina stalagmitis. *ACS Publ.* **77**, 2678–2684 (2014).
13. Kitagaki, J., Shi, G., Miyauchi, S., … S. M.-A. & 2015, undefined. Cyclic depsipeptides as potential cancer therapeutics. *journals.lww.com*.
14. products, M. B.-J. of natural & 2004, undefined. The role of natural product chemistry in drug discovery. *ACS Publ.* **67**, 2141–2153 (2004).
15. Li, J., Science, J. V.- & 2009, undefined. Drug discovery and natural products: end of an era or an endless frontier? *science.org* **325**, 161–165 (2009).
16. wittig reaction - Bing images. https://www.bing.com/images/search?view=detailV2&ccid=dwE%2F%2BJ%2B%2F&id=3E772788A59888794814ADB715C3E84E45D5CD14&thid=OIP.dwE_-J-_jAwRWIv8J-LviAHaHD&mediaurl=https%3A%2F%2Fwww.chemistrysteps.com%2Fwp-content%2Fuploads%2F2020%2F01%2FWittig-reaction-examples.png&exph=733&expw=770&q=wittig+reaction&simid=608054437556020250&FORM=IRPRST&ck=AEE40B655429F4E82FFB31836D5E446B&selectedIndex=6&ajaxhist=0&ajaxserp=0.
17. Heravi, M. M., Hashemi, E. & Nazari, N. Negishi coupling: An easy progress for C-C bond construction in total synthesis. *Mol. Divers.* **18**, 441–472 (2014).
18. Heravi, M., Lashaki, T., Asymmetry, N. P.-T. & 2015, undefined. Applications of Sharpless asymmetric epoxidation in total synthesis. *Elsevier*.
19. Evidente, A., Sparapano, L., Fierro, O., Bruno, G. & Motta, A. Sapinofuranones A and B, two

new 2(3H)-dihydrofuranones produced by Sphaeropsis sapinea, a common pathogen of conifers. *J. Nat. Prod.* **62**, 253–256 (1999).
20. Kumar, P., Naidu, S. V. & Gupta, P. Efficient total synthesis of sapinofuranone B. *J. Org. Chem.* **70**, 2843–2846 (2005).
21. Gunasekera, S. P., Gunasekera, M., Longley, R. E. & Schulte, G. K. Discodermolide: A New Bioactive Polyhydroxylated Lactone from The Marine Sponge Discodermia Dissoluta. *J. Org. Chem.* **55**, 4912–4915 (1990).
22. Smith, A. B., Freeze, B. S., Xian, M. & Hirose, T. Total synthesis of (+)-discodermolide: A highly convergent fourth-generation approach. *Org. Lett.* **7**, 1825–1828 (2005).
23. Bindseil, K. U. & Zeeck, A. Metabolic Products of Microorganisms. Part 265. Prelactones C and B, oligoketides from Streptomyces producing concanamycins and bafilomycins. *Helv. Chim. Acta* **76**, 150–157 (1993).
24. Srihari, P., Ravindar, K., Somaiah, R. & Yadav, J. S. First concise total synthesis of 5-epi-prelactone B. *Synth. Commun.* **38**, 1389–1397 (2008).
25. Hymenosetin, a 3-decalinoyltetramic acid antibiotic from cultures of the ash dieback pathogen, Hymenoscyphus pseudoalbidus. *Elsevier*.
26. Baral, H. O., Queloz, V. & Hosoya, T. Hymenoscyphus fraxineus, the correct scientific name for the fungus causing ash dieback in Europe. *IMA Fungus* **5**, 79–80 (2014).
27. Kauhl, U. *et al.* Total Synthesis of (-)-Hymenosetin. *J. Org. Chem.* **81**, 215–228 (2016).
28. Ito, C. *et al.* Constituents of Boronia pinnata. *J. Nat. Prod.* **63**, 1344–1348 (2000).
29. Mayr, F., Wiegand, C. & Bach, T. Enantioselective, intermolecular [2+2] photocycloaddition reactions of 3-acetoxyquinolone: total synthesis of (−)-pinolinone. *Chem. Commun.* **50**, 3353–3355 (2014).
30. Coleman, R. S. & Walczak, M. C. Total synthesis of gymnoconjugatins A and B. *J. Org. Chem.* **71**, 9841–9844 (2006).
31. Samala, R., Patro, B., Basu, M. K., Kameswara Rao, N. S. & Mukkanti, K. Facile total synthesis of gymnoconjugatin A and B. *Tetrahedron Lett.* **54**, 3624–3626 (2013).
32. Oh, D. C., Gontang, E. A., Kauffman, C. A., Jensen, P. R. & Fenical, W. Salinipyrones and pacificanones, mixed-precursor polyketides from the marine actinomycete Salinispora pacifica. *J. Nat. Prod.* **71**, 570–575 (2008).
33. Ramesh, P. & Meshram, H. M. First total synthesis of salinipyrone A using highly stereoselective vinylogous Mukaiyama aldol reaction. *Tetrahedron* **68**, 9289–9292 (2012).
34. A species-selective allelopathic substance from germinating sunflower (Helianthus annuus L.) seeds. *Elsevier*.
35. Ohtsuki, K. *et al.* Total synthesis of (+)- and (-)-sundiversifolide via intramolecular acylation and determination of the absolute configuration. *Org. Lett.* **10**, 1247–1250 (2008).
36. Li, X., Qian, Z., He, Y., Letters, Z. G.-T. & 2021, undefined. Visible-light-mediated radical addition/cyclization tandem reaction for the synthesis of 3-bromomethyl-3, 4-dihydroisocoumarins. *Elsevier*.
37. Chanti, D., Rao, C. B., Ramesh, D., Swamy, S. R. & Venkateswarlu, Y. Total synthesis of the aromatase inhibitor dihydroisocoumarin via protective opening of lactones. *Elsevier* (2012) doi:10.1016/j.tetlet.2012.05.012.
38. Ohkuma, H. *et al.* Sultriecin a new Antifungal and Antitumor Antibiotic from Streptomyces roseiscleroticus Production, Isolation, Structure and Biological Activity. *jstage.jst.go.jp* **45**, 1239.
39. Kumar, G. C., Muralikrishna, K., Satyanarayana, V., Kumar, C. S. & Yadav, J. S. Studies towards the total synthesis of Phostriecin. *Tetrahedron Lett.* **59**, 454–456 (2018).
40. Alali, F., Liu, X., products, J. M.-J. of N. & 1999, undefined. Annonaceous acetogenins: recent progress. *ACS Publ.* **62**, 504–540 (1999).
41. Tinsley, J. M. & Roush, W. R. Total synthesis of asimicin via highly stereoselective [3 + 2] annulation reactions of substituted allylsilanes. *J. Am. Chem. Soc.* **127**, 10818–10819 (2005).
42. FUSHIMI, S., FURIHATA, K., Antibiotics, H. S.-T. J. of & 1989, undefined. STUDIES ON

NEW PHOSPHATE ESTER ANTIFUNGAL ANTIBIOTICS PHOSLACTOMYCINS II. STRUCTURE ELUCIDATION OF PHOSLACTOMYCINS A TO F. *jstage.jst.go.jp*.
43. Kohama, T. *et al.* NOVEL MICROBIAL METABOLITES OF THE PHOSLACTOMYCINS FAMILY INDUCE PRODUCTION OF COLONY-STIMULATING FACTORS BY BONE MARROW. *jstage.jst.go.jp* **46**,.
44. Shibata, T., Kurihara, S., Yoda, K., Tetrahedron, H. H.- & 1995, undefined. Absolute configuration of leustroducsins. *Elsevier*.
45. Shimada, K., Kaburagi, Y. & Fukuyama, T. Total synthesis of leustroducsin B. *J. Am. Chem. Soc.* **125**, 4048–4049 (2003).
46. Juliawaty, L., Kitajima, M., Takayama, H., Phytochemistry, S. A.- & 2000, undefined. A 6-substituted-5, 6-dihydro-2-pyrone from Cryptocarya strictifolia. *Elsevier*.
47. Ramana, C. V., Raghupathi, N., Gurjar, M. K. & Chorghade, M. S. A carbohydrate-based approach for the total synthesis of strictifolione. *Tetrahedron Lett.* **46**, 4073–4075 (2005).
48. Geiseler, O. & Podlech, J. Total synthesis of infectopyrone, aplysiopsenes A-C, ent-aplysiopsene D, phomapyrones A and D, 8,9-dehydroxylarone, and nectriapyrone. *Tetrahedron* **68**, 7280–7287 (2012).
49. Samwel, S. *et al.* Cleistenolide and cleistodienol: Novel bioactive constituents of Cleistochlamys kirkii. *Nat. Prod. Commun.* **2**, 737–741 (2007).
50. Cai, C., Liu, J., Du, Y. & Linhardt, R. J. Stereoselective total synthesis of (-)-cleistenolide. *J. Org. Chem.* **75**, 5754–5756 (2010).
51. Cimanga, K., Bruyne, T. De, Pieters, L., letters, M. C.-T. & 1996, undefined. New alkaloids from Cryptolepis sanguinolenta. *Elsevier*.
52. Parvatkar, P. T. & Tilve, S. G. An efficient synthesis of indoloquinoline alkaloid - Neocryptolepine (cryptotackieine). *Tetrahedron Lett.* **52**, 6594–6596 (2011).
53. Kita, M. & Uemura, D. Iminium alkaloids from marine invertebrates: Structure, biological activity, and biogenesis. *Chem. Lett.* **34**, 454–459 (2005).
54. Kita, M. *et al.* Symbioimine Exhibiting Inhibitory Effect of Osteoclast Differentiation, from the Symbiotic Marine Dinoflagellate Symbiodinium sp. *J. Am. Chem. Soc.* **126**, 4794–4795 (2004).
55. Zou, Y., Che, Q. & Snider, B. B. Total synthesis of (±)-symbioimine. *Org. Lett.* **8**, 5605–5608 (2006).
56. R. Grote, A. Zeeck, J. Stümpfel, H. Zähner, L. No Title. *Ann. Chem.* 525–530 (1990).
57. Majik, M. S., Parameswaran, P. S. & Tilve, S. G. *Intramolecular Wittig Reaction: A New Synthesis of (S)-Pyrrolam A*.
58. Application of molecular mechanics in the total stereochemical elucidation of spicigerolide, a cytotoxic 6-tetraacetyloxyheptenyl-5, 6-dihydro-α-pyrone from Hyptis. *Elsevier*.
59. Krishna, P. R. & Reddy, P. S. Stereoselective total synthesis of (-)-synrotolide diacetate from d-ribose. *Tetrahedron* **63**, 3995–3999 (2007).
60. Total synthesis of (+)-synargentolide A. *Elsevier*.
61. Radha Krishna, P. & Srinivas, P. PTSA-catalyzed tandem cyclization protocol for the stereoselective total synthesis of obolactone. *Tetrahedron Lett.* **51**, 2295–2296 (2010).