2006

# STUDIES TOWARD SYNTHESIS OF POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS

Roxana Ciochina
*University of Kentucky*, rcioc2@uky.edu

ABSTRACT OF DISSERTATION

Roxana Ciochina

The Graduate School
University of Kentucky
2006

# STUDIES TOWARD SYNTHESIS OF POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS

---

ABSTRACT OF DISSERTATION

---

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the College of Arts and Sciences
at the University of Kentucky

By

Roxana Ciochina

Lexington, KY

Director: Dr. R. B. Grossman, Professor of Chemistry

Lexington, KY

2006

ABSTRACT OF DISSERTATION

STUDIES TOWARD SYNTHESIS OF POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a class of compounds that reveal intriguing biological activities and interesting and challenging chemical structures. These products are claimed to possess antioxidant, antiviral, and antimitotic properties. Increasing interest is related to their function in the CNS as modulators of neurotransmitters associated to neuronal damaging and depression. All these features make PPAPs targets for synthesis. We decided to focus our own initial efforts in this area on the type A PPAP, nemorosone because we thought that its fairly simple structure relative to other PPAPs would present fewer hurdles as we developed our methodology.

In the past decade many approaches to the synthesis of the bicyclo[3.3.1]nonane-2,4,9-trione structure of type A PPAPs have been reported, but only two total syntheses of any PPAP, garsubellin A by Shibasaki and Danishefsky, have been published recently, near the end of 2005. All approaches have relied on the α,α′-annulation of a three-carbon bridge onto a cyclohexanone, although the methods used to execute this annulation differ dramatically. The methods most often used to form the two new C–C bonds have involved classical carbonyl chemistry.

We have developed a short and efficient synthetic approach to the bicyclo[3.3.1]nonane skeleton of the PPAPs that involves a novel three-carbon α,α′-annulation of a sterically hindered cyclic β-keto ester with 3,3-diethoxypropyne. The alkynylation reaction permits the construction of the two contiguous quaternary centers of the PPAPs in reasonable yield and without complications from side reactions. We have also successfully applied a recently developed syn hydrosilylation to the very hindered product of this alkynylation reaction. Our methodology received positive feedback already, and we see this total synthesis of nemorone as an ideal platform for the implementation of new synthetic methodologies.

# STUDIES TOWARD SYNTHESIS OF POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS

By

Roxana Ciochina

Robert B Grossman, Ph.D
*Director of Dissertation*

Mark S. Meier, Ph.D
*Director of Graduate Studies*

May 3, 2006
*Date*

RULES FOR THE USE OF DISSERTATIONS

Unpublished theses submitted for the Doctor's degree and deposited in the University of Kentucky Library are as a rule open for inspection, but are to be used only with due regards to the rights of authors. Bibliographical references may be noted, but quotations or summaries of parts may be published only with the permission of the author, and with the usual scholarly acknowledgments.

Extensive copying or publication of the dissertation in whole or in part also requires the consent of the Dean of the Graduate School of the University of Kentucky.

DISSERTATION

Roxana Ciochina

The Graduate School

University of Kentucky

2006

# STUDIES TOWARD SYNTHESIS OF POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS

---

DISSERTATION

---

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Arts and Sciences at the University of Kentucky

By

Roxana Ciochina

Lexington, KY

Director: Dr. R. B. Grossman, Professor of Chemistry

Lexington, Kentucky

2006

For my dear parents

## ACKNOWLEDGEMENTS

This dissertation is a culmination of an amazing journey that would have not been possible without numerous contributions. First and foremost, I would like to thank my mentor, Dr. Robert B. Grossman, for his continuous guidance and support. Dr. Grossman has contributed immensely to my growth as a scientist through his knowledge, his expertise, and most importantly his dedication and his passion for science. Dr. Grossman has meticulously supervised this research and has provided input critical to both the achievement and interpretation of this work. I would also like to thank the members of dissertation committee: Dr. Cammers, Dr. Atwood, and Dr. Boatright. I would also like to thank Dr. Stoltz for serving as my outside examiner.

I wish to express my profound gratitude to my parents Catalina and Ioan Ciochina and my sister Raluca for their unconditional support and encouragement throughout my life. Dan, my dear husband, helped me tremendously with his love, understanding and patience, joining me in joy during the good days and teaching me how to go on during not-so-good days of graduate school. Lastly, I would like to thank my friends Aska, Darina, Mirela, Gilbert, Ani, Dana, and Ashley for their moral support.

## TABLE OF CONTENTS

## LIST OF FIGURES

## LIST OF SCHEMES

## LIST OF TABLES

# Chapter 1. Introduction to PPAPs

## 1.1. Introduction

In earlier times, all drugs and medicinal agents were derived from natural substances. New drug discovery involved a trial-and-error approach on naturally derived materials and substances until the end of the nineteenth century. The first half of the twentieth century witnessed systematic pharmacological evaluations of both natural and synthetic compounds. However, most new drugs until the 1970s were discovered by serendipity. For example, penicillin, the first antibiotic to be discovered, was found by chance in 1928 when Alexander Fleming accidentally contaminated a petri dish containing bacteria (*Staphylococcus aureus*) with the mold that produces this antibiotic (*Penicillium*).

Plants have long been a very important source of drugs, and many plant species have been screened to see if they contain substances with therapeutic activity. For example, digoxin from foxgloves (an old discovery) was used to treat heart failure, and paclitaxel (discovered in yew bark) is a more recent anticancer agent.

For many diseases, the current drug repertoire is limited or inadequate, and the problem is being further exacerbated by the emergence of drug resistance. New drugs are desperately needed and will continue to be needed for the foreseeable future.

Depression is a serious disorder that affects roughly 25% of women and 10% of men at some point of their lives. Studies showed that, just in the USA, more than 19 million adults suffer from depression. There are three main types of depressive disorders: major depressive disorder, dysthymic disorder, and bipolar disorder (manic-depressive illness). The cause of this illness is still unknown, but it is thought to be partly hereditary and partly caused by everyday stress. Throughout the years, depression has affected many accomplished people, including Abraham Lincoln, Ernest Hemingway, Peter Tchaikovsky, Charles Dickens, Virginia Woolf, and Mary Shelley. The good news is that this mental disorder is treatable in more than 90% cases with the right medication and under doctor supervision.

In recent years, the antidepressant activity of *Hypericum perforatum*, commonly known as St. John's wort, has attracted much attention from both scientists and the wider public.[1,2] Investigations of the constituents of St. John's wort and other plants from the family Guttiferae and related families have revealed a class of compounds, polycyclic polyprenylated acylphloroglucinols (PPAPs), with fascinating chemical structures and intriguing biological activities. The PPAPs feature a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-1,3,5-trione core, to which are attached $C_5H_9$ or $C_{10}H_{17}$

(prenyl, geranyl, etc.) side chains (the latter in several isomeric forms). The PPAPs can be divided into three classes: type A PPAPs have a C(1) acyl group and an adjacent C(8) quaternary center, type B PPAPs have a C(3) acyl group, and type C PPAPs have a C(1) acyl group and a distant C(8) quaternary center (Figure 1.1).[3] (Only a handful of type C PPAPs are known.) Secondary cyclizations involving the β-diketone and pendant olefinic groups may occur to afford adamantanes, homoadamantanes or pyrano-fused structures.

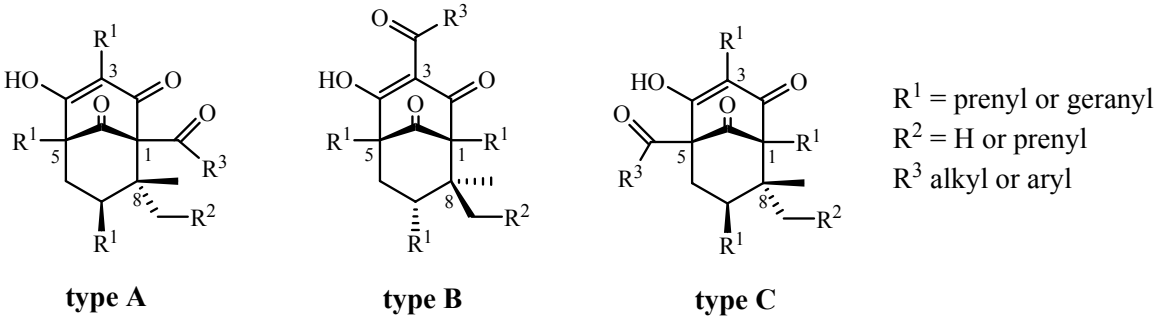
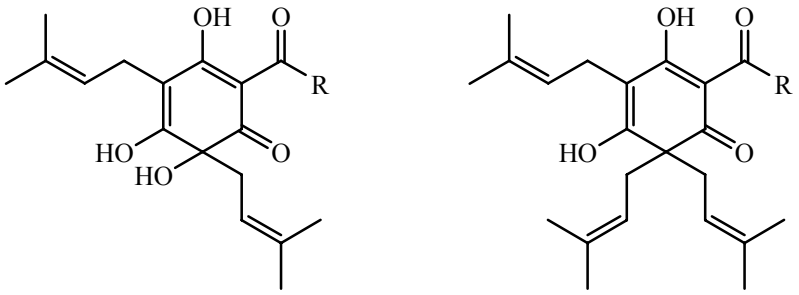



**Figure 1.1: Type A, B, and C PPAPs**

PPAPs are biosynthetically derived from the less complex monocyclic polyprenylated acylphloroglucinols (MPAPs), which are found in many plants from the Myrtaceae and Cannabinaceae families, often as dimers. MPAPs are reported to show antimicrobial, antifungal and antifeedant activity.[4,5] For example, *Humulus lupulus* (Cannabinaceae), commonly known as hops, is used in folk medicine as an antibacterial (in the form of wound powders and salves), a tranquilizer (sleep inducer), a diuretic, and to ameliorate the symptoms of menopause. Perhaps more importantly, the female inflorescences (hop cones) of hops are also used in beer production. Two classes of MPAPs are found in hops (Figure 1.2). The α-acids are converted during the brewing process into iso-α-acids, the compounds that are responsible for the flavor and the bitter taste of beer.[6] The β-acids do not add any taste because of decomposition. Although β-acids are not important to the brewing industry, they show radical scavenging activity, inhibition of lipid peroxidation, and antimicrobial activity.[7]




**α-acids** **β-acids**

| R | α-acids | β-acids |
|---|---|---|
| *i*-Pr | cohumulone | colupulone |
| *i*-Bu | humulone | lupulone |
| *s*-Bu | adhumulone | adlupulone |

**Figure 1.2: Hops-derived α- and β-acids**

Little is known about the synthesis of these hop acids, most of the studies being made in early 1970s.[8-10] All the attempts resulted in formation of β-acids and their derivatives in very low to moderate yield and no α-acids were obtained.

### 1.2. Survey of PPAPs

A list with type A, B, and C PPAPs reported and isolated so far is presented in Tables 1–3, respectively. The majority of these compounds are type A and B. Only three natural products, garcinelliptones K–M (**117**–**119**), are reported to have type C structures.[11] Nemorosone (**5**), was classified first as a type C structure,[12,13] but its structure has since been corrected to a type A structure.[3] One may wonder if the three structures of garcinelliptones K–M have been correctly determined, because if the two bridgehead groups of garcinielliptone K, L, and M are switched, the structures become identical to those of hyperibone B,[14] garsubellin C, and garsubellin D (**29**, **32**, and **27**),[15,16] respectively, and the garsubellins and garcinielliptones are both isolated from *Garcinia subelliptica*.[11,15,16] At a closer look, though, the two type C structures of garcinielliptones K and M seem to be correctly assigned due to the observation of an NOE interaction between the acyl group and one of the H atoms of the ring $CH_2$ group in these two compounds.[11] Moreover, by examining the NMR spectra of garcinielliptone K and hyperibone B, one can observe that they do not match, so it is unlikely that the structure of garcinielliptone K has been misassigned and that the two compounds are both **29**.[11,14] Unfortunately, we cannot do the same examination of the NMR spectra of the garcinielliptones L and M and garsubellins C and D, respectively to determine whether they are identical, because the NMR spectra of the garsubellins were measured in $C_6D_6$,[15,16] and those of the garcinielliptones were measured in $CDCl_3$.[11]

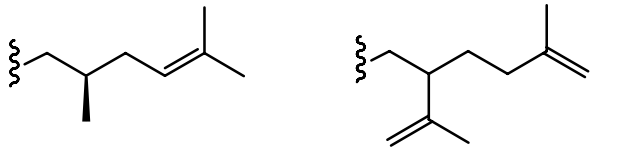
The stereochemistry of plukenetiones F and G (**39** and **41**), was assigned by Grossman and Jacobs, who have shown that the orientation of the C(7) substituent in PPAPs (endo or exo) can be easily determined by examining the $^1H$ and $^{13}C$ NMR spectra of the PPAPs.[17] When the C(7) substituent is exo, the difference in chemical shifts of the two H(6) atoms is ~0.5 ppm, and the chemical shift of C(7) is 45–48 ppm; but when the C(7) substituent is endo, the difference in chemical shifts of the two H(6) atoms is ~0.1 ppm, and the chemical shift of C(7) is 41–44 ppm. Using the same technique when examining the stereochemistry of other PPAPs, we noticed that hypersampsone F and hyperibones C, E, F, H, and I (**42**, **35**, **20**, **21**, **101**, and **102**) have endo C(7) substituents, not exo as first proposed.[14,18,19] We also noticed, using NMR and optical rotation data, that garcinielliptone I is enantiomeric to that of hyperibone A (**33**), not identical to that of hyperibone B (**29**), as originally proposed.[14,20]

Herath[21] reports a compound which he calls guttiferone I as having a C(7) endo substituent but at a closer look at its NMR data (δ value of C(7) is 41.2 ppm, Δδ value for H(8) is 0.72 ppm, and H(7)–$H(8)_{ax}$ coupling constant is 13.0 Hz) suggest that it is an exo compound. Also, he reports that guttiferone I has an NMR spectrum similar to that of

guttiferone G, **97** and concludes that they are different because of their different optical rotation values (+8.7° for **98** vs. - 25° for **97**). We think that guttiferone I is identical to guttiferone G, and one or the other optical rotation reported for this compound is inaccurate. The correct structure of guttiferone I has been reported by Nilar.[22]

To our knowledge, the only PPAPs whose absolute configurations have been determined experimentally are hyperforin,[23] xanthochymol,[24] and isoxanthochymol[24] (**1**, **88**, and **99**). Some PPAPs (hyperibone G **13** and propolone D **14**,[14,25] hyperibone A **33** and garcinielliptone I **34**,[14,20,25] guttiferone E **84** and garcinol **85**,[26-31] isoxanthochymol **99** and isogarcinol **100**[18,28-33]) have been isolated in both enantiomeric forms. Although we chose to draw the C(9) ketone pointing toward the reader, one cannot infer the information about absolute configuration of a compound.

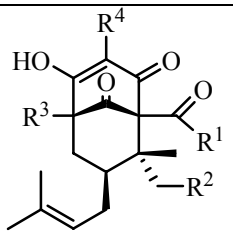
In the Tables, the isogeranyl and ω-isogeranyl groups are defined as in Figure 1.3.



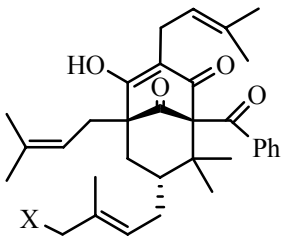
(*R*)-isogeranyl ω-isogeranyl

**Figure 1.3: Isogeranyl and ω-isogeranyl groups**

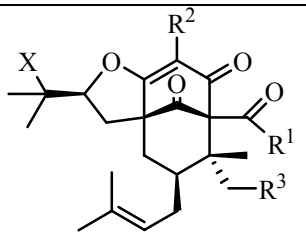
**Table 1.1: Type A PPAPs**

| No. | Structure | Name | Source[a] | $[\alpha]_D$[b] |
|---|---|---|---|---|
| |  | | | |
| **1** | $R^1$ = *i*-Pr; $R^2$, $R^3$, $R^4$ = prenyl | Hyperforin[c] | *H. perforatum*[34-36] | +41 (e, 5) |
| **2** | $R^1$ =*s*-Bu; $R^2$, $R^3$, $R^4$ = prenyl | Adhyperforin[d] | *H. perforatum*[37] | NR |
| **3** | $R^1$ = *i*-Pr; $R^2$, $R^3$= prenyl; $R^4$ = H | Hyperevolutin A | *H. revolutum* Vahl[38] | +84.4 (m, 0.5) |
| **4** | $R^1$ = *s*-Bu; $R^2$, $R^3$ = prenyl; $R^4$ = H | Hyperevolutin B[d] | *H. revolutum* Vahl[38] | NR |
| **5** | $R^1$ = Ph; $R^2$ = H; $R^3$, $R^4$ = prenyl | Nemorosone | Cuban propolis, *C. rosea, C. grandiflora, C. insignis, C. nemorososa*[3,12,13,39] | +113 (0.1); OMe: +150 (m, 0.8) and +49 (1.4) |

| | | | | |
|---|---|---|---|---|
| **6** | $R^1$ = 3-hydroxyphenyl;<br>$R^2$ = H;<br>$R^3$, $R^4$ = prenyl | Hydroxynemorosone *e* | *C. nemorososa*[13] | OMe: +143 (m, 0.7) |
| **7** | $R^1$ = Ph; $R^2$ = H;<br>$R^3$ = isogeranyl;<br>$R^4$ = prenyl | Chamone I[d] | *C. grandiflora*[39] | NR |
| **8** | $R^1$ = isopropyl; $R^2$ = H;<br>$R^3$ = $CH_2CH_2CMe_2OH$;<br>$R^4$ = prenyl | Garcinielliptone A | *G. subelliptica*[40] | –33 (0.6) |
| **9** | $R^1$ = *s*-Bu; $R^2$ = H;<br>$R^3$ = prenyl;<br>$R^4$ = $CH_2CH_2CMe_2OH$ | Garcinielliptone D | *G. subelliptica*[40] | –22 (0.1) |
| **10** | $R^1$ = *sec*-butyl; $R^2$ = H;<br>$R^3$ = prenyl;<br>$R^4$ = (*E*)-CH=$CHCMe_2OH$ | Garcinielliptone F | *G. subelliptica*[20] | –23 (0.09) |

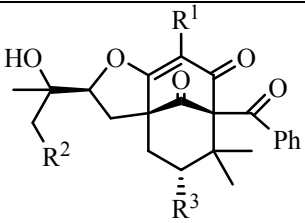
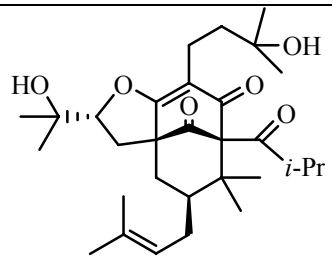
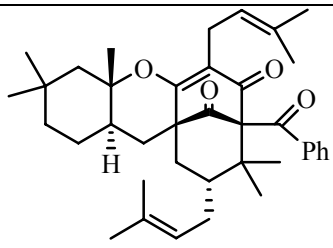


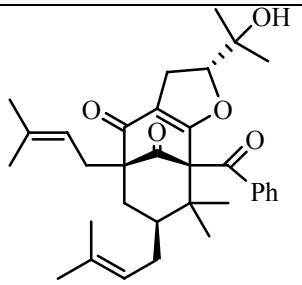
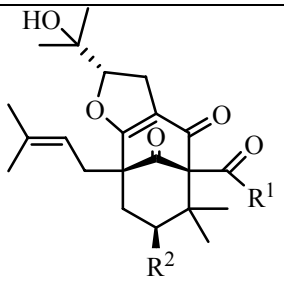
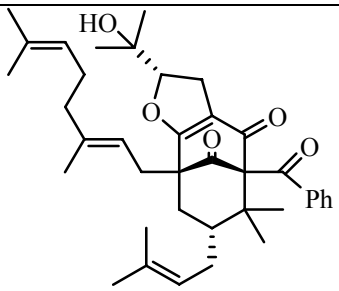
| | | | | |
|---|---|---|---|---|
| **11** | X = H | Plukenetione D/E | *C. nemorosa, C. plukenetii*[41,42] | OAc: +34.5 (0.03), –37.6 (0.1); OMe: +10.7 (3.1) |
| **12** | X = OAc | Insignone | *C. insignis*[43] | OMe: +92.7 (1.6) |

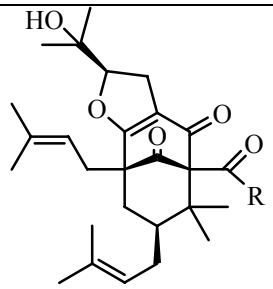
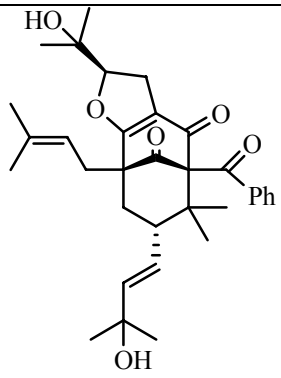
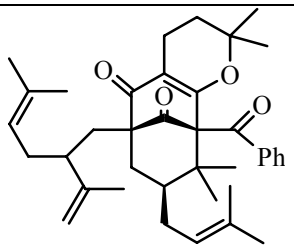


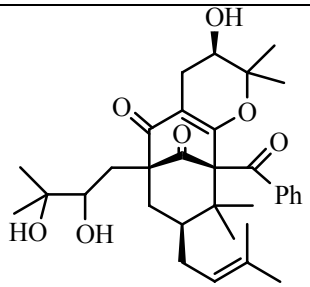
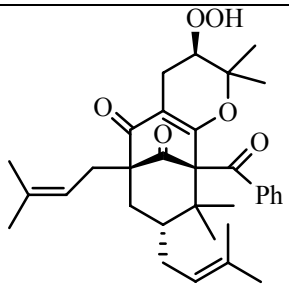
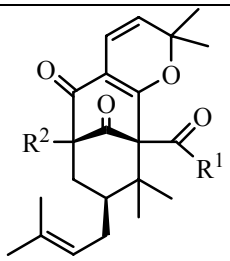
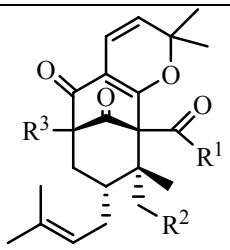

| | | | | |
|---|---|---|---|---|
| **13** | $R^1$ = Ph; $R^2$ = prenyl; $R^3$ = H; X = OH | Hyperibone G | *H. scabrum*[14] | –29.3 (0.9) |
| **14** | $R^1$ = Ph; $R^2$ = prenyl; $R^3$ = H; X = OH (enantiomer) | Propolone D | Cuban propolis[25] | +48.5 (0.7) |

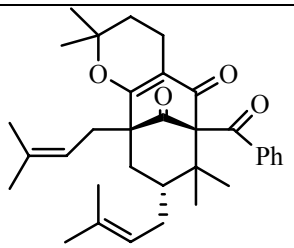
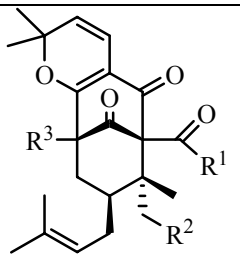
| | | | | |
|---|---|---|---|---|
| **15** | $R^1$ = Ph; $R^2$ = $CH_2CH(OH)CMe=CH_2$; $R^3$ = H; X = OH | Hyperibone D[d] | *H. scabrum*[14] | –61.9 (0.7) |
| **16** | $R^1$ = *i*-Pr; $R^2$ = prenyl; $R^3$ = H; X = OH | Garsubellin A | *G. subelliptica*[15,16] | –21 (e, 1.1) |
| **17** | $R^1$ = *s*-Bu; $R^2$ = prenyl; $R^3$ = H; X = OH | Garsubellin B[d] | *G. subelliptica*[16] | –36 (e, 0.6) |
| **18** | $R^1$ = *i*-Pr; $R^2$, $R^3$ = prenyl; X = OH | Furohyperforin | *H. perforatum*[44,45] | +62.4 (0.9), +81.9 (0.9, m), +68 (0.2) |
| **19** | $R^1$ = *i*-Pr; $R^2$, $R^3$ = prenyl; X = OOH | 33-Deoxy-33-hydroperoxy-furohyperforin | *H. perforatum*[46] | +75 (1.2) |

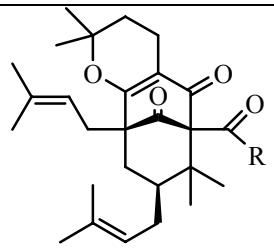
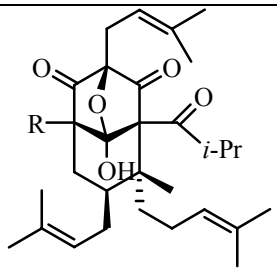
| | | | | |
|---|---|---|---|---|
| |  | | | |
| **20** | $R^1$ = $CH_2CH(OH)CMe{=}CH_2$; $R^2$ = H; $R^3$ = (*E*)-CH=CHCMe$_2$OH | Hyperibone E[d,f] | *H. scabrum*[14] | –56.0 (0.2) |
| **21** | $R^1$ = prenyl; $R^2$ = H; $R^3$ = (*E*)-CH=CHCMe$_2$OH | Hyperibone F[f] | *H. scabrum*[14] | –31.0 (0.2) |
| **22** | $R^1$, $R^2$, $R^3$= prenyl | Sampsonione K[e] | *H. sampsonii*[47] | –5.6 (1.1) |
| **23** | $R^1$, $R^3$= prenyl; $R^2$ = H | Sampsonione L | *H. sampsonii*[47] | +55 (0.06) |
| **24** |  | Garcinielliptone C | *G. subelliptica*[40] | –40 (0.2) |
| **25** |  | No name | *C. obdeltifolia*[48] | +30.9 (0.3) |

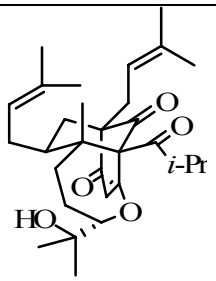
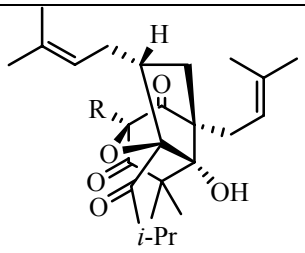
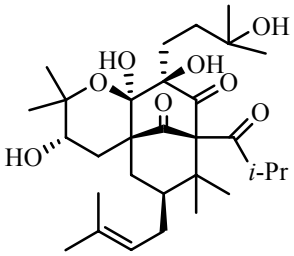
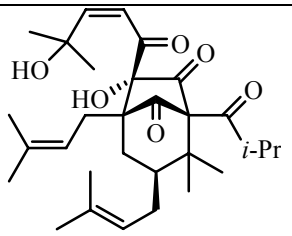
| | | | | |
|---|---|---|---|---|
| **26** |  | Propolone C | Cuban propolis[25] | +35.7 (0.2) |
| |  | | | |
| **27** | $R^1$ = isopropyl; $R^2$ = prenyl | Garsubellin D | *G. subelliptica*[16] | –12 (e, 0.4) |
| **28** | $R^1$ = *sec*-butyl; $R^2$ = prenyl | Garsubellin E | *G. subelliptica*[16] | –7 (e, 0.4) |
| **29** | $R^1$ = Ph; $R^2$ = prenyl | Hyperibone B | *H. scabrum*[14,25] | –20.8 (0.5); –42.2 (0.1) |
| **30** | $R^1$ = 3,4-dihydroxyphenyl; $R^2$ = (*R*)-isogeranyl | Garcinielliptone FB | *G. subelliptica*[49] | –66 (0.2) |
| **31** |  | Sampsonione M | *H. sampsonii*[47] | +55 (0.04) |

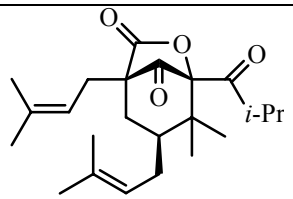
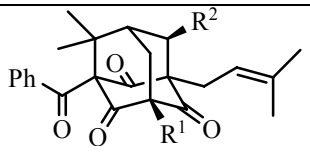
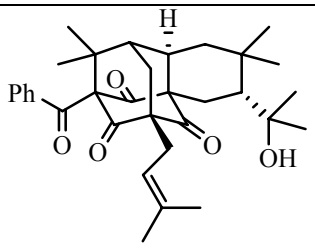
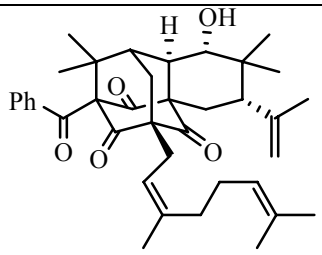
| | | | | |
|---|---|---|---|---|
| |  | | | |
| **32** | R = isopropyl | Garsubellin C | *G. subelliptica*[15,16] | +39 (e, 0.4) |
| **33** | R = Ph | Hyperibone A | *H. scabrum*[14,25] | +57 (0.2); +63.7 (0.4) |
| **34** | R = Ph (enantiomer) | Garcinielliptone I[g] | *G. subelliptica*[20] | –37.7 (1.1) |
| **35** |  | Hyperibone C | *H. scabrum*[14] | –27.3 (0.3) |
| **36** |  | Chamone II[d] | *C. grandiflora*[39] | NR |

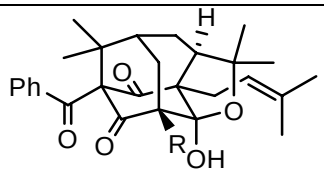
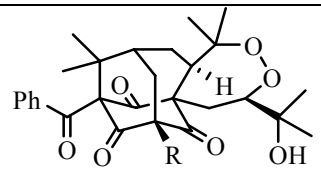
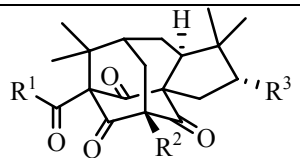
| | | | | |
|---|---|---|---|---|
| **37** |  | Propolone B[d] | Cuban propolis[25] | +38.2 (0.6) |
| **38** |  | 15,16-dihydro-16-hydroperoxy-plukenetione F | *C. havetiodes* var. *stenocarpa*[50] | +24.7 (0.3) |
| |  | | | |
| **39** | $R^1$ = *i*-Pr; $R^2$ = Me | Papuaforin B | *H. papuanum*[51] | NR |
| **40** | $R^1$ = Ph; $R^2$ = prenyl | Scrobiculatone B | *C. scrobiculata*[43] | +44.7 (0.2) |
| |  | | | |
| **41** | $R^1$ = Ph; $R^2$ = H; $R^3$ = prenyl | Plukenetione F[h] | *C. plukenetii*[41] | –53.6 (0.03) |
| **42** | $R^1$ = Ph; $R^2$,$R^3$ = prenyl | Hypersampsone F[f] | *H. sampsonii*[52] | +30 (0.2) |

| | | | | |
|---|---|---|---|---|
| **43** |  | Plukenetione G[h] | *C. plukenetii*[41] | NR |
| |  | | | |
| **44** | $R^1$ = *i*-Pr;<br>$R^2$, $R^3$ = prenyl | Pyrano[7,28-*b*]-hyperforin | *H. perforatum*[53] | +83.5 (0.3) |
| **45** | $R^1$ = Ph;<br>$R^2$ = H; $R^3$ = prenyl | Scrobiculatone A | *C. scrobiculata*[43,51] | +44.7 (0.2) |

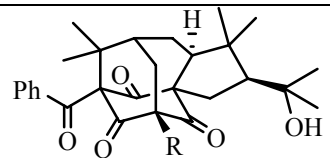
| | | | | |
|---|---|---|---|---|
| **46** | $R^1$ = *i*-Pr; $R^2$ = H; $R^3$ = $CH_3$ | Papuaforin A | *H. papuanum*[51] | +13 (0.1, m) |
| **47** | $R^1$ = *s*-Bu; $R^2$ = H; $R^3$ = $CH_3$ | Papuaforin C[d] | *H. papuanum*[51] | +23 (0.1, m) |
| **48** | $R^1$ = *s*-Bu; $R^2$ = prenyl; $R^3$ = $CH_3$ | Papuaforin D[d] | *H. papuanum*[51] | +64 (0.1, m) |
| **49** | $R^1$ = *i*-Pr; $R^2$ = prenyl; $R^3$ = $CH_3$ | Papuaforin E | *H. papuanum*[51] | +41 (0.1, m) |
| |  | | | |
| **50** | R = Ph | Propolone A | Cuban propolis[26] | +40 (0.1) |
| **51** | R = *i*-Pr | Garcinielliptone B | *G. subelliptica*[40] | –23 (0.1) |
| |  | | | |
| **52** | R = prenyl | 8-Hydroxyhyperforin-8,1-hemiacetal | *H. perforatum*[46] | +34 (1.0) |

| | | | | |
|---|---|---|---|---|
| **53** | R = $CH_3$ | Hyperibone J | *H. scabrum*[54] | +16.9 (0.3) |
| **54** |  | Oxepahyperforin | *H. perforatum*[46] | –73.7 (0.8) |
| |  | | | |
| **55** | R = prenyl | Garcinielliptin oxide | *G. subelliptica*[55] | +1 (0.3) |
| **56** | R = $CH_2CH_2CMe_2OH$ | Garcinielliptone E | *G. subelliptica*[40] | –51 (0.2) |
| **57** |  | Garcinielliptone H | *G. subelliptica*[20] | –14.3 (0.1) |
| **58** |  | Garcinielliptone G | *G. subelliptica*[20] | –53 (0.1) |

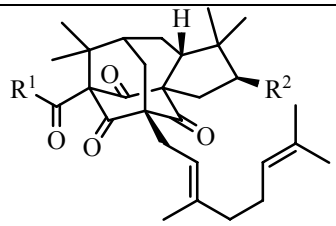
| | | | | |
|---|---|---|---|---|
| **59** |  | Garcinielliptone J | *G. subelliptica*[20] | –166 (0.2) |
| |  | | | |
| **60** | $R^1$ = prenyl; $R^2$ = $CH{=}CMe_2$ | Plukenetione A | *C. plukenetii*[56] | +1 (0.8) |
| **61** | $R^1$ = prenyl; $R^2$ = (*S*)-2,2-dimethyloxiranyl | 28,29-Epoxyplukenetione A | *C. havetiodes* var. *stenocarpa*[50] | –4.4 (1.0) |
| **62** | $R^1$ = geranyl; $R^2$ = (*S*)-2,2-dimethyloxiranyl | Sampsonione J | *H. sampsonii*[47] | +1.48 (0.2) |
| **63** |  | No name | *C. obdeltifolia*[48] | +10.0 (0.4) |
| **64** |  | Sampsonione I | *H. sampsonii*[47] | +16.88 (0.1) |

| | | | | |
|---|---|---|---|---|
| |  | | | |
| **65** | R = geranyl | Sampsonione A | *H. sampsonii*[57] | –49 (0.4) |
| **66** | R = prenyl | Sampsonione B | *H. sampsonii*[57] | NR |
| |  | | | |
| **67** | R = prenyl | Plukenetione C | *C. plukenetii*[41,50] | +65.9 (0.1) |
| **68** | R = (*E*)-CH=CHCMe$_2$OOH | 33-hydroperoxy-isoplukenetione C | *C. havetiodes* var. *stenocarpa*[50] | –3.9 (0.2) |
| |  | | | |
| **69** | R$^1$ = Ph; R$^2$ = prenyl; R$^3$ = CMe$_2$OH | Plukenetione B | *C. plukenetii*[41] | +17.2 (0.03) |
| **70** | R$^1$ = Ph; R$^2$ = geranyl; R$^3$ = *i*-Pr | Hypersampsone D | *H. sampsonii*[52] | –35 (0.2) |
| **71** | R$^1$ = *i*-Pr; R$^2$ = geranyl; R$^3$ = CMe=CH$_2$ | Hypersampsone A | *H. sampsonii*[52] | +21 (0.3) |

| | | | | |
|---|---|---|---|---|
| **72** | $R^1$ = Ph; $R^2$ = geranyl; $R^3$ = $CMe_2OH$ | Sampsonione C | *H. sampsonii*[58] | +13 (0.2) |
| **73** | $R^1$ = Ph; $R^2$ = geranyl; $R^3$ = isopropenyl | Sampsonione D | *H. sampsonii*[58] | +12 (0.2) |
| **74** | $R^1$ = Ph; $R^2$ = geranyl; $R^3$ = O (ketone) | Sampsonione E | *H. sampsonii*[58] | +57.7 (0.03) |
| **75** | $R^1$ = Ph; $R^2$ = geranyl; $R^3$ = H | Sampsonione H | *H. sampsonii*[58] | +5.2 (0.07) |




| | | | | |
|---|---|---|---|---|
| **76** | R = geranyl | Sampsonione F | *H. sampsonii*[58] | +14.5 (1.1) |
| **77** | R = prenyl | Sampsonione G | *H. sampsonii*[58] | +10.0 (0.01) |




| | | | | |
|---|---|---|---|---|
| **78** | $R^1$, $R^2$ = *i*-Pr | Hypersampsone B | *H. sampsonii*[52] | +12 (0.3) |
| **79** | $R^1$ = *i*-Pr; $R^2$ = H | Hypersampsone C | *H. sampsonii*[52] | +14.3 (0.2) |

| | | | | |
|---|---|---|---|---|
| **80** | $R^1$ = Ph; $R^2$ = *i*-Pr | Hypersampsone E | *H. sampsonii*[52] | +39 (0.2) |

[a]*C. = Clusia*, *G. = Garcinia, H. = Hypericum*.

[b]OMe or OAc indicates the specific rotation was measured for that derivative. The values in parentheses are the concentration and the solvent (e = EtOH, m = MeOH, no indication = $CHCl_3$). NR = not reported.

[c]The absolute configuration is known to be as shown.

[d]The positions of the two bridgehead groups have been swapped from where they were placed in the original literature reports;[12,13]

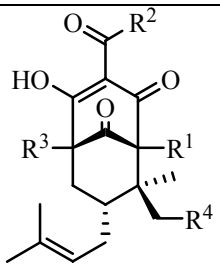
[e]Not all the stereocenters' configurations have been assigned.

[f]The stereochemistry of the C(7) substituent has been reassigned on the basis of the NMR spectra;[17] see the text.

[g]The originally assigned relative configuration[20] has been corrected.

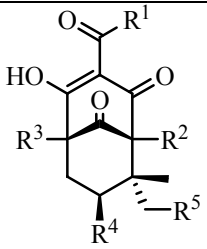
[h]The stereochemistry was assigned by the method of Grossman and Jacobs.[17]

**Table 1.2: Type B PPAPs**

| No. | Structure | Name | Source[a] | $[\alpha]_D$[b] |
|---|---|---|---|---|
| |  | | | |
| **81** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$, $R^3$, $R^4$ = prenyl | Guttiferone A | *S. globulifera, G. livingstonei, G. humilis*[28,59] | +34 (1.7) |
| **82** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$, $R^4$ = prenyl; $R^3$ = □-isogeranyl | Guttiferone C[c] | *S. globulifera* | as mix with **83**: +92 (0.9) |
| **83** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$, $R^4$ = prenyl; $R^3$ = isogeranyl | Guttiferone D[c] | *S. globulifera* | as mix with **82**: +92 (0.9) |
| **84** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$ = prenyl; $R^3$ = (*S*)-isogeranyl; $R^4$ = H | Guttiferone E | Cuban propolis, *C. rosea, G. ovafolia*[26-28] | +101 (0.5) |

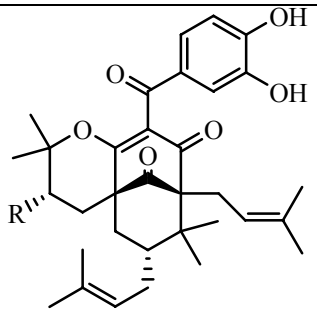
| | | | | |
|---|---|---|---|---|
| **85** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$ = prenyl; $R^3$ = (*S*)-isogeranyl; $R^4$ = H (enantiomer) | Garcinol (camboginol) | *G. cambogia, G. indica*[29-31] | –138 (0.1) |
| **86** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$ = prenyl; $R^3$ = (*R*)-isogeranyl; $R^4$ = H | Guttiferone F | *Allanblackia stuhlmannii*[60] | –293 (0.4) |
| **87** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$ = prenyl; $R^3$ = geranyl; $R^4$ = H | Guttiferone I[e] | *G. griffithii*[22] | –68 (1.2) |
| **88** | $R^1$ = 3,4-$(HO)_2C_6H_3$; $R^2$ = prenyl; $R^3$ = (*S*)-□-isogeranyl; $R^4$ = H | Xanthochymol[f] | Cuban propolis, *G. xanthochymus, G. mannii, G. staudtii, G. subelliptica, Rheedia madrunno*[18,24,26,27,33,61-63] | +138 (0.1) |
| **89** | $R^1$ = $CH_3$; $R^2$ = Ph; $R^3$ = prenyl; $R^4$ = H | Hyperibone L | *H. scabrum*[54] | +69.5 (0.2) |
| **90** | $R^1$ = $CH_3$; $R^2$ = *i*-Pr; $R^3$ = prenyl; $R^4$ = H | Hyperpapuanone | *H. papuanum*[51] | +15 (0.1, m) |

| | | | | |
|---|---|---|---|---|
| **91** | $R^1$, $R^3$ = prenyl;<br>$R^2$ = Ph; $R^4$ = H | 7-*epi*-Clusianone | *C. sandinensis, C. torresii*[64-67] | +62.3 (1.1) |
| **92** | $R^1$ = $CHPhCH_2CO_2H$;<br>$R^2$ = *i*-Bu;<br>$R^3$ = prenyl; $R^4$ = H | Laxifloranone[c] | *Marila laxiflora*[68] | +23.6 (m, 0.8) |

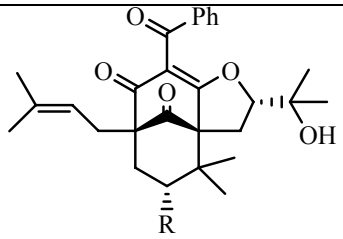
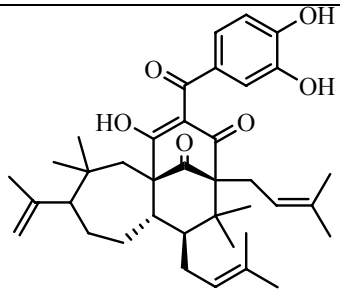
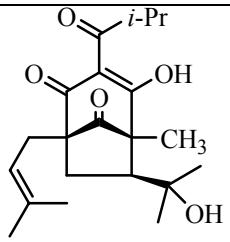
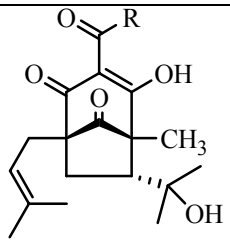



| | | | | |
|---|---|---|---|---|
| **93** | $R^1$ = 3,4-dihydroxyphenyl;<br>$R^2$, $R^3$, $R^4$ = prenyl;<br>$R^5$ = H | Aristophenone[d] | *G. xanthochymus*[18,19] | +58 (0.1); OAc: +53 (0.1), +54 (0.1) |
| **94** | $R^1$ = Ph;<br>$R^2$, $R^3$, $R^4$ = prenyl;<br>$R^5$ = H | Clusianone[g] | *C. congestiflora, C. spiritu-santesis, C. torresii*[13,66,69] | +58.3 (0.7) OMe: +61 (1.4) |
| **95** | $R^1$ = Ph;<br>$R^2$, $R^4$ = prenyl;<br>$R^3$ = isogeranyl;<br>$R^5$ = H | Spiritone[c] | *C. spiritu-sanctensis*[69] | NR |

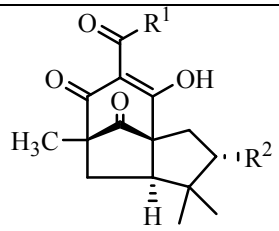
| | | | | |
|---|---|---|---|---|
| **96** | $R^1$ = 3,4-dihydroxyphenyl; $R^2$ = prenyl; $R^3$, $R^4$ = geranyl; $R^5$ = H | Guttiferone B | *S. globulifera*[28] | –44 (0.5) |
| **97** | $R^1$ = 3,4-dihydroxyphenyl; $R^2$, $R^3$, $R^5$ = prenyl; $R^4$ = geranyl | Guttiferone G | *G. humilis, G. macrophylla*[21,59] | –25 (0.04) |



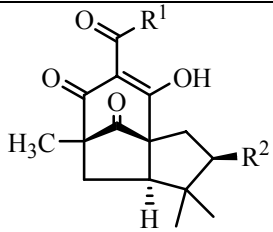

| | | | | |
|---|---|---|---|---|
| **98** | R = prenyl | Isogarcinol (cambogin)[g] | *G. indica, G. cambogia, G. pedunculata*[29-31,61,63] | –224 (m, 0.1) |
| **99** | R = prenyl (enantiomer) | Isoxanthochymol[f] | *G. pyrifera, G. subelliptica, G. xanthochymus, G. ovafolia*[18,28,32,33] | +181 (e, 0.6) |
| **100** | R = $CH_2CH_2CMe{=}CH_2$ | Cycloxanthochymol | *G. pyrifera, G. subelliptica*[32,33] | as 2:3 mix with **72**: +158 (m, 0.1) |

| | | | | |
|---|---|---|---|---|
| |  | | | |
| **101** | R = (*E*)-CH=CHCMe$_2$OH | Hyperibone H[d] | *H. scabrum*[14] | +12.4 (0.4) |
| **102** | R = prenyl | Hyperibone I[d] | *H. scabrum*[14] | +13.3 (0.3) |
| **103** |  | Guttiferone H[c,h] | *G. xanthochymus*[18] | +94 (0.006) |
| **104** |  | Enaimeone A | *H. papuanum*[70] | +27.8 (0.1, m) |
| |  | | | |
| **105** | R = *i*-Pr | Enaimeone B | *H. papuanum*[70] | +29.4 (0.1, m) |

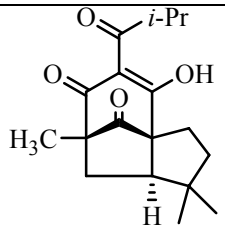
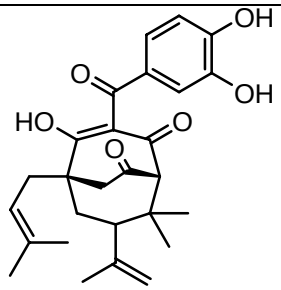
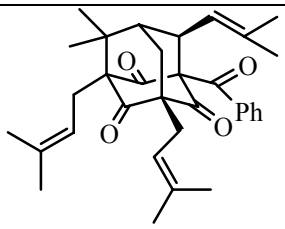
| | | | | |
|---|---|---|---|---|
| **106** | R = *s*-Bu | Enaimeone C[c] | *H. papuanum*[70] | +32.9 (0.1, m) |



| | | | | |
|---|---|---|---|---|
| **107** | $R^1$ = *i*-Pr; $R^2$ = $CMe{=}CH_2$ | Ialibinone A | *H. papuanum*[71] | –22 (0.1) |
| **108** | $R^1$ = *s*-Bu; $R^2$ = $CMe{=}CH_2$ | Ialibinone C[c] | *H. papuanum*[71] | –26 (0.1) |
| **109** | $R^1$ = *i*-Pr; $R^2$ = $CMe_2OH$ | 1′-Hydroxyialibinone A | *H. papuanum*[70] | +3.7 (0.1, m) |



| | | | | |
|---|---|---|---|---|
| **110** | $R^1$ = *i*-Pr; $R^2$ = $CMe{=}CH_2$ | Ialibinone B | *H. papuanum*[71] | –91 (0.1) |
| **111** | $R^1$ = *s*-Bu; $R^2$ = $CMe{=}CH_2$ | Ialibinone D[c] | *H. papuanum*[71] | –72 (0.1) |
| **112** | $R^1$ = *i*-Pr; $R^2$ = $CMe_2OH$ | 1′-Hydroxyialibinone B | *H. papuanum*[70] | –35.7 (0.1, m) |

| | | | | |
|---|---|---|---|---|
| **113** | $R^1$ = *s*-Bu;<br>$R^2$ = $CMe_2OH$ | 1′-Hydroxyialibinone D[c] | *H. papuanum*[70] | –30.3 (0.1, m) |
| **114** |  | Ialibinone E | *H. papuanum*[71] | –33 (0.1) |
| **115** |  | Gambogenone[c] | *G. xanthochymus*[18] | –5 (0.003, m) |
| **116** |  | Hyperibone K | *H. scabrum*[54] | +22.3 (0.3) |

[a]*C. = Clusia*, *G. = Garcinia, H. = Hypericum, S. = Symphonia.*

[b]OMe or OAc indicates the specific rotation was measured for that derivative. The values in parentheses are the concentration and the solvent (e = EtOH, m = MeOH, no indication = $CHCl_3$).

[c]Not all the stereocenters' configurations have been assigned.

[d]The stereochemistry of the C(7) substituent has been reassigned on the basis of the NMR spectra; see the text.[17]

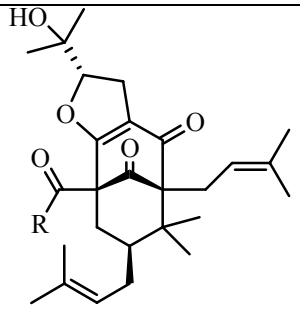
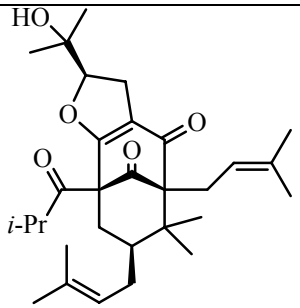
[e]Two different compounds reported almost simultaneously have both been named guttiferone I.[21,22]

[f]The absolute configuration is known and is opposite to what is shown.

[g]The absolute configuration is known to be as shown.

[h]The stereochemistry of the C(9) bridge relative to the C(6) and C(7) substituents has been assigned on the basis of the H(6)–H(7) coupling constant; see the text.[17]

**Table 1.3: Type C PPAPs**

| No. | Structure | Name | Source[a] | $[\alpha]_D$[b] |
|---|---|---|---|---|
| |  | | | |
| **117** | R = Ph | Garcinielliptone K | *G. subelliptica*[11] | +27 (0.3) |
| **118** | R = isopropyl | Garcinielliptone M | *G. subelliptica*[11] | +73 (0.2) |
| **119** |  | Garcinielliptone L | *G. subelliptica*[11] | –41 (0.3) |

[a]*G. = Garcinia.*

[b]The values in parentheses are the concentrations (solvent is $CHCl_3$).

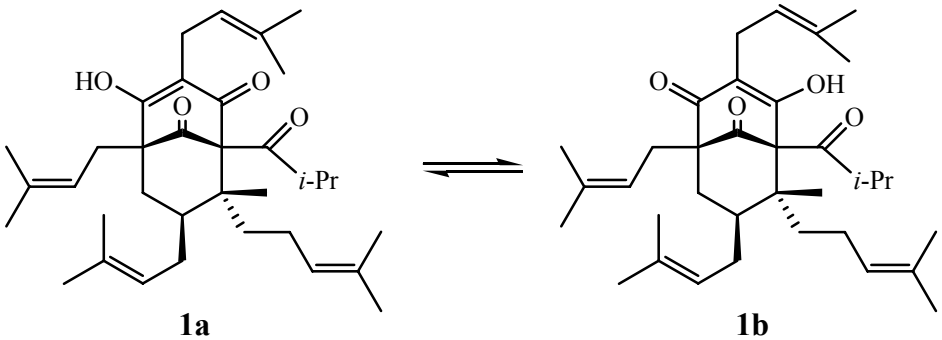
## 1.3. Biological activity of PPAPs

In this section, the PPAPs that have been shown to have some biological activity are discussed. Many PPAPs have been found to possess moderate antioxidant, antiviral, or antimitotic properties. Increasing interest is related to their function in the CNS as modulators of neurotransmitters associated to neuronal damaging and depression.

### 1.3.1. Type A PPAPs

#### 1.3.1.1. Hyperforin

Hyperforin (**1a/1b**, Figure 1.4), a type A PPAP, is thought to be responsible for much of the antidepressant activity of *Hypericum perforatum* (St. Johns' wort).[72] *In vitro* studies showed that hyperforin (at concentrations of 0.1–1.0 μM) inhibited the synaptosomal uptake of many neurotransmitters (see below), but it is still unclear if this mechanism is active *in vivo*.[73-75] The ancient Greeks used St. John's wort for its antidepressive properties as well as for treatment of skin injuries, burns, and neuralgia. In modern times, it has become very famous as a treatment for mild depression, anxiety, and schizophrenia. Clinical studies have shown St. John's wort to be as effective as a conventional synthetic antidepressant for treatment of mild to moderate depression.[76] Its mechanism of action has been attributed to its ability to inhibit synaptosomal uptake of several neurotransmitters, including serotonin, dopamine, norepinephrine, γ-aminobutyric acid (GABA), and L-glutamate, when concentrations become low ($IC_{50}$ = 1.1 μg/mL).[77] Serotonin, dopamine, and norepinephrine balance mood and emotion, and GABA decreases anxiety and increases relaxation. By inhibiting the reuptake of these neurotransmitters, hyperforin increases their levels in the neural synapses, reinstates emotional balance, and improves mood. *Hypericum perforatum* reveals not only antidepressant activity but also some side effects like nausea, rash, fatigue, restlessness, photosensitivity, and acute neuropathy.[78]




**1a** **1b**

**Figure 1.4: Hyperforin**

Hyperforin has also long been known to have antibacterial activity.[36,75,79,80] A recent report on inhibition of penicillin-resistant and methicillin-resistant *S. aureus* has increased the interest in hyperforin as an antibacterial agent.[81]

Beside all these positive effects of hyperforin, this natural product can repress some other drugs' effectiveness.[82] A recent study has shown that, when patients took St. John's wort together with the asthma drug theophylline, the anticlotting drug warfarin, birth control pills, or the immunosuppressant cyclosporine, the blood concentration levels of the latter drug decreased drastically. Hyperforin is a ligand for the pregnane X receptor, which regulates the expression of cytochrome $P_{450}$, an enzyme involved in the oxidative metabolism of the above mentioned drugs.[82,83] One should be alert to the side effects of herbal medicines and always make sure that the efficacy of prescribed drugs is not diminished by use of folk medicines.

Pure, isolated hyperforin is susceptible to oxidation. The instability of hyperforin can be attributed to its β-hydroxy enone functionality, which is susceptible to air oxidation. The oxidation products differ depending on the nature of the oxidant, the solvent, and the type of hyperforin used (ammonium salt or free acid form).[84] If hyperforin is treated with peroxidic reagents, the main organic product is the hemiacetal **52**, formed possibly through a C(3)-hydroxylated intermediate (Figure 1.5). When nonperoxidic reagents are used, a mixture of products is formed, the main ones being furan and pyran derivatives, **120** and **44**, respectively.

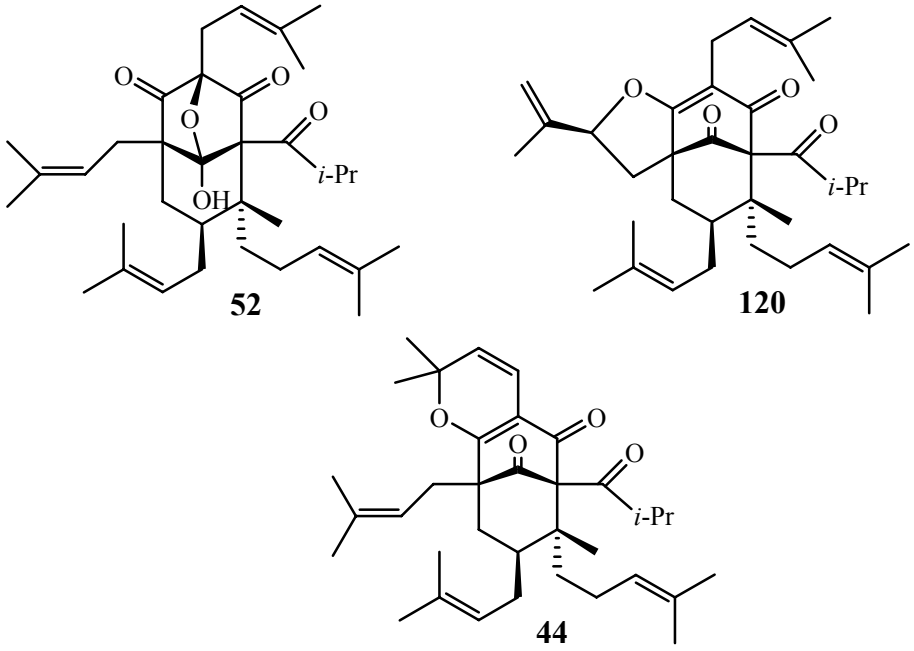



**Figure 1.5: Products of oxidation of hyperforin**

As is true of many β-hydroxy enones, hyperforin may be *O*- or *C*-alkylated when treated with an alkylating agent (Figure 1.6).[84,85] *O*-Methylation occurred when hyperforin was treated with methanol under Mitsunobu conditions or with diazomethane, whereas *C*-methylation occurred when hyperforin was treated with MeI.

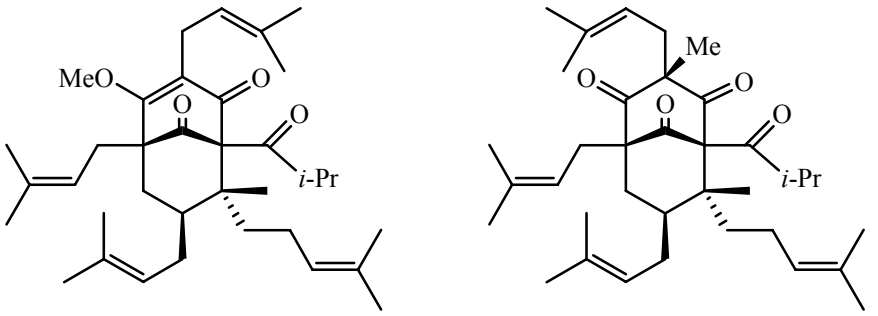



**Figure 1.6: *O*- and *C*-methylhyperforin**

A variety of acylated, alkylated, and oxidized derivatives of hyperforin were the subject of structure–activity studies.[84] All derivatives studied were less potent than hyperforin in their inhibition of neurotransmitter uptake, with $IC_{50}$ values >10 μg/mL. These results are in accordance with the findings of other authors that suggest that removing the β-hydroxy enone group of hyperforin dramatically reduces its biological activity.[45,46,53] The mechanism of action of hyperforin and its derivatives is not fully understood, and more studies are required to determine structure–activity relationships in this class of compounds.

Hyperforin has also recently been found to induce apoptosis in ten human and seven rat cancer cell lines, with $IC_{50}$ values of 3–15 μM,[81] and in K562 and U937 leukemia cells, LN229 brain glioblastoma cells, and normal human astrocytes, with $GI_{50}$ values of 14.9–19.9 μM.[86] Hyperforin together with hypericin, a natural product also isolated from *H. perforatum*, synergistically exert a growth inhibitory effect on K562 and U937 leukemia cells that is much larger than either compound exerts individually (2.0 μM **1**, 6.0% and 2.1%; 10.0 μM hypericin, 22.3% and 0.6%; combined, 43.6% and 20.2%).[86]

A mixture of hyperevolutin A and a small amount of hyperevolutin B (**3** and **4**) has been found to inhibit the growth of Co-115 colon tumor cells with an $ED_{50}$ value of 2 μM.[38]

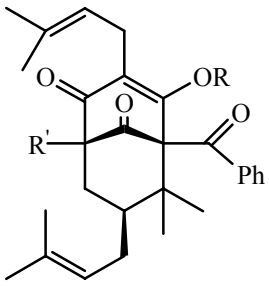
#### 1.3.1.2. Nemorosone

Nemorosone (**5**), another type A PPAP, is found in the resins and latex of plants of *Clusia* (Clusiaceae) species.[39] Bees use these resins and latex to build their hives, at least partly because they make a good construction material for sealing openings in the hive and hardening the cell walls.[39] Propolis, an extract of beehives, has been known since ancient times as an antiseptic; in fact, Aristotle himself urged people to use it as a means to treat abscesses and wounds.[87] Studies on bee behavior have revealed that after bees kill heavy intruders, they cover them with propolis! Not being able to throw the corpses off the hives, the bees make sure that their nest will not develop a bacterial infection.

A large portion of the constituents of propolis are derived from plants. There are over 200 chemical substances in propolis,[88,89] their ratio depending on the region from which the propolis is collected. In Europe, the major biological active constituents are flavonoids and cinnamic acid derivatives, whereas in tropical regions, the home of many *Clusia* plants, the major compounds are polyprenylated benzophenones such as PPAPs.[27] Despite the differences in their chemical composition, propolis samples from various geographical regions have always been found to be biologically active.[27]

Nemorosone is the major constituent of *Clusia* species resin that is responsible for its antimicrobial activity, constituting about 50% of the resin by mass.[12,13] When a crude extract of *Clusia* species resin is methylated, *O*-methylnemorosone, 16-hydroxymethylnemorosone, and 7-*epi*-methylnemorosone (*O*-methylplukenetione D/E) are obtained.[12,13] Cuesta–Rubio has corrected the type C PPAP structure initially proposed for nemorosone[12,13] to **5** (Figure 1.7) and its tautomer by switching the

originally assigned positions of the groups at the bridgeheads.[3] Cuesta–Rubio has also shown that the structure of *O*-methylnemorosone is **121**.




| compound | R | R' |
|---|---|---|
| **5** | H | prenyl |
| **121** | Me | prenyl |
| **36** | H | isogeranyl |

**Figure 1.7: Nemorosone, *O*-methylnemorosone, and chamone II**

The bactericidal activities of both **5** and **121** were studied, but the latter was not active.[27,39] The conclusion was that the enol form was necessary for nemorosone to be biologically active. Even the prenylation pattern proved to be essential for the antimicrobial effect of this type of natural products, as chamone II (**36)** was less effective than **5** as a bactericide against *Paenibacillus* honeybee pathogens.

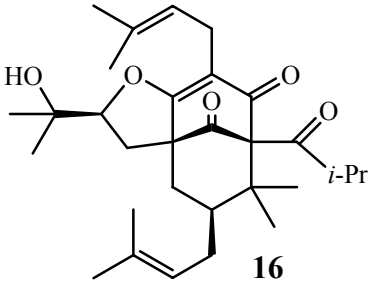
Besides antimicrobial activity, nemorosone showed cytotoxicity and antioxidant activity.[27] The $IC_{50}$ values of nemorosone against four cancer cell lines (3.3–7.2 μM) were comparable to those of doxorubicin. Nemorosone also targets DNA topoisomerases and telomerase, but to a much lower extent, the required concentration being 10 to 38 times higher than that necessary for a 50% inhibition of cellular growth. Compound **121** showed much lower cytotoxic and antioxidant activities, the $IC_{50}$ values being 10–30 times and 10 times higher, respectively, with respect to that of the reference.

Nemorosone showed an $EC_{50}$ of 0.8 μM against HIV infection of C8166 human T lymphoblastoid cells.[66]

#### 1.3.1.3. Garsubellin A

Garsubellin A (**16**, Figure 1.8) has been isolated from *Garcinia subelliptica*, a tree that grows in Okinawa.[16] Studies have shown garsubellin A to be an inducer of choline acetyltransferase (ChAT) in P10 rat septal neuron cultures, increasing it by 154% at a 10 μM concentration.[15] Acetylcholine is a neurotransmitter, and a low concentration of this compound is associated with neurodegenerative diseases like Alzheimer's disease. Garsubellin A also inhibits the release of β-glucuronidase and histamine, the 50% inhibition concentration ($IC_{50}$ = 15.6 μM) being even lower than that of the reference mepacrine ($IC_{50}$ = 20.6 μM).[40] This property is associated with antiinflamatory activity. Other phloroglucinol derivatives isolated from the same plant (garcinielliptones A–D, F,

H, I, K–M) show little or no such activity.[11,20] The idea that garsubellin A might have potential for the treatment of Alzheimer's disease has led to an increased interest over the past decade in studying the biological activity of and possible synthetic approaches[90,91] to this class of compounds.

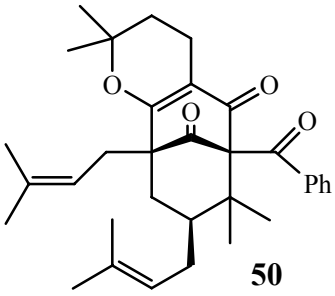



**16**

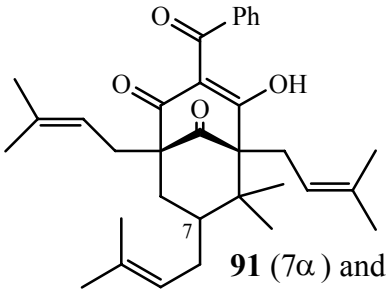
**Figure 1.8: Garsubellin A**

#### 1.3.1.4. Other type A PPAPs

Propolone A (**50**), 7-*epi*-clusianone (**91**), and clusianone (**94**) (Figure 1.9) were tested for their activity against HIV infection of C8166 human T lymphoblastoid cells.[66] Propolone A showed the best results, with an $EC_{50}$ of 0.32 μM, followed by 7-*epi*-clusianone, with $EC_{50}$ of 2.0 μM. Clusianone was very active ($EC_{50}$ = 0.02 μM), but it also showed increased cytotoxicity. The absence of a free enol in propolone A showed that this group was not essential to antiviral activity. Also, the different $EC_{50}$ values of the two epimers, 7-*epi*-clusianone and clusianone, showed that the C(7) configuration was important to the PPAP's potency.




**50**




**91** (7α) and **94** (7β)

**Figure 1.9: Propolone A, 7-*epi*-clusianone, and clusianone**

Propolone A also showed antibacterial activity against two Gram-positive bacteria (*Streptomyces chartrensis* and *Streptomyces violochromogenes*), but it was not active toward Gram-negative bacteria and yeasts.[26]

In a different study, 7-*epi*-clusianone exhibited high *in vitro* activity against *Trypanosoma cruzi*, the microbe responsible for Chagas' disease, with an $LC_{50}$ = 260 μM, 29 times higher than that of the drug used to treat this disease.[64] Unfortunately, it was inactive in *in vivo* studies in the mouse model. More studies with related natural or

synthetic compounds are needed to find more active derivatives that could be used as chemoprophylactic agents.

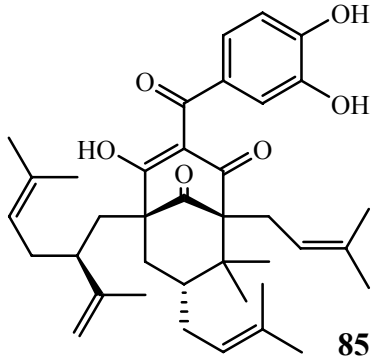
Hyperibone J (**52**), a hyperforin analog very close in structure to hemiacetal **51**, showed moderate cytotoxicity against breast and lung tumor cells ($IC_{50}$ = 17.8 μg/mL and >20 μg/mL, respectively).[54]

Papuaforins A (**46**), B (**39**), and C–E (**47**–**49**), which are extracted from *Hypericum papuanum* (Papua New Guinea), show moderate cytotoxic activity against the KB cell line ($IC_{50}$ = 4.9–13.0 μg/mL) and weak antibacterial activity toward three bacteria (*Micrococcus luteus*, *Staphylococcus epidermis*, and *Bacillus cereus*).

### 1.3.2. Type B PPAPs

#### 1.3.2.1. Garcinol and its derivatives

Garcinol (**85**, Figure 1.10),[31] also known as camboginol, is extracted from *Garcinia indica* and several other plants as a yellow pigment.[29,32,92] The dried fruit rind is used in folk medicine and as a garnish for curry in India. Garcinol shows antibiotic activity,[32] scavenging activity for 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical (three times more effective than DL-α-tocopherol), hydroxyl radical (more effective than DL-α-tocopherol), methyl radical, and superoxide anion.[93,94] These results suggest that garcinol can play an important role in treatment of gastric ulcer caused by the hydroxyl radical[95,96] or by a chronic infection with *Helicobacter pylori*, a global pathogen, which, together with cells from gastric mucous membrane, produces hydroxyl radicals and superoxide anions.[97] Nowadays, antibiotics like clarithromycin are used to treat *H. pylori* infection, but there are some side effects when using antibiotics, such as the development of resistance. Garcinol may be a viable alternative to conventional antibiotics.




**85**

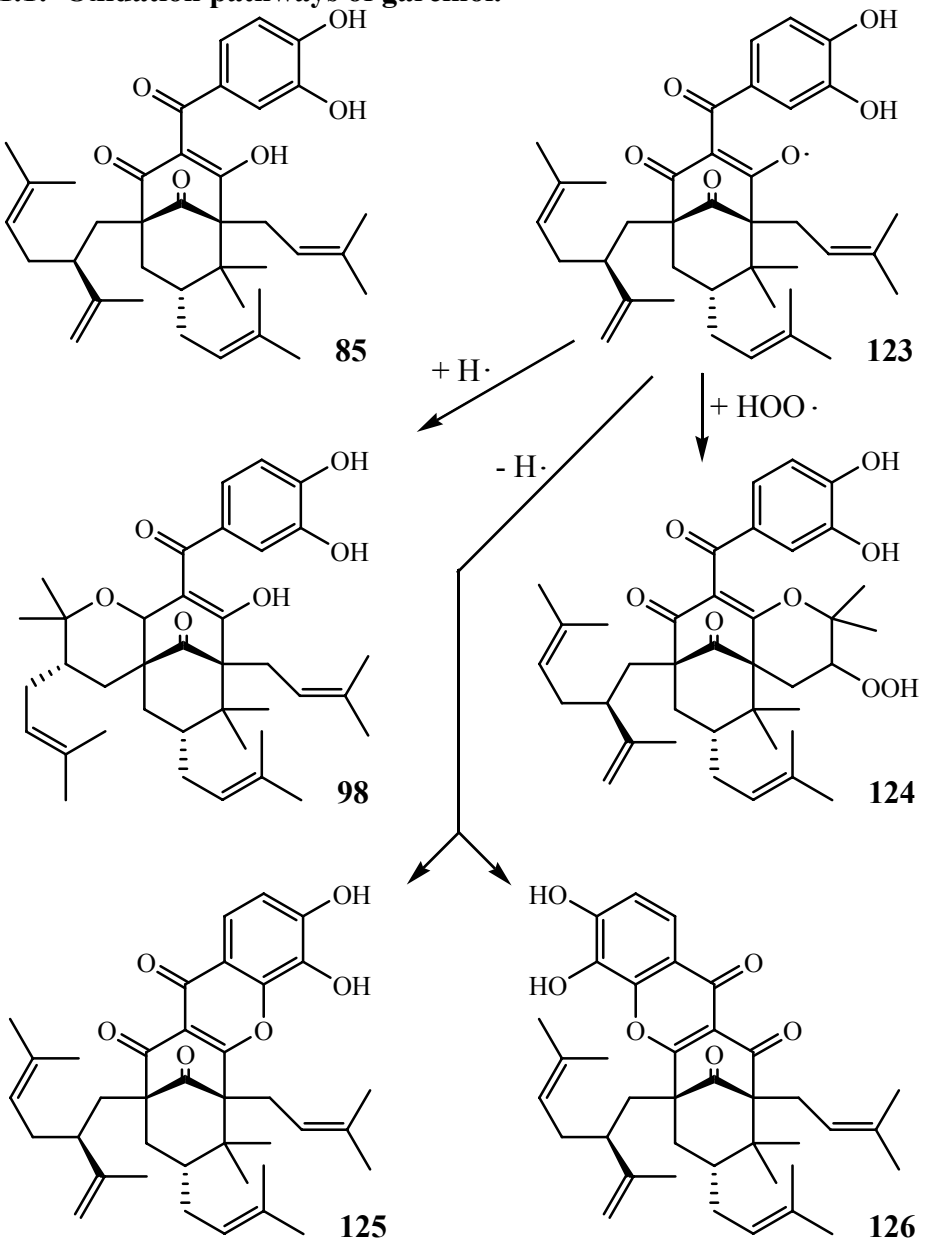
**Figure 1.10: Garcinol (camboginol)**

Sang *et al.* has recently reported the structure of some oxidation products of garcinol and has proposed mechanisms for the formation of these products (Scheme

1.1).[98,99] The reaction of garcinol with AIBN or the stable free DPPH radical generates the conjugated radical **123**. Cyclization then occurs, involving the catechol ring or a pendant alkenyl group to give both compounds known to occur naturally (isogarcinol, **98**) and those that have not (yet) been isolated from natural sources (**124**–**126**). Isogarcinol shows biological activities similar to garcinol; it has been claimed to be an antiinflammatory and antitumor compound, a lipase inhibitor, an antiobesity agent, and an antiulcer agent.[98] It also inhibits the growth of methicillin-resistant *S. aureus*.

Garcinol, together with compounds **125** and **126**, proved to have good antitumor activity, being more effective than curcumin, a well-known antioxidant used as a reference in these studies. The possible chemotherapeutic property of garcinol was also tested on other cell lines (human leukemia HL-60 cells, human promyelocytic HL-60 cells, murine macrophage RAW 264.7 cells, and cyclin D1-positive cells), and the same positive effect was obtained.[100-102] It inhibits histone acetyltransferases (HATs, $IC_{50} \approx 7$ μM) and p300/CPB-associated factor (PCAF, $IC_{50} \approx 5$ μM), both of which modulate gene expression. If HAT and/or HDAC (histone deacetylase) activities are altered, diseases like cancer or neurodegenerative disease can develop.[103]

**Scheme 1.1: Oxidation pathways of garcinol.**




### 1.3.2.2. Guttiferones A–E, xanthochymol, and their analogs

Xanthochymol (**88**) and guttiferone E (**84**) (Figure 1.11) are extracted as a mixture from *Garcinia* and *Clusia* species[33,60,62] and are said to be inseparable.[28] This mixture has a strong inhibitory activity against tubulin depolymerization in vitro ($IC_{50}$ = 20 μM), comparable to that of paclitaxel ($IC_{50}$ = 0.5 μM), making it a possible inhibitor of cell replication. However, if the β-hydroxy enone or both phenolic OH groups are methylated, or if the double bonds are hydrogenated, a complete loss of activity is observed.[33] Some activity is retained if only one phenolic OH group is methylated.

Unfortunately, the mixture shows no effect on whole cells, suggesting that it cannot cross the cell membrane or is deactivated by cellular processes. Xanthochymol also shows antibiotic activity against methicillin resistant *Staphylococus aureus*[32] and inhibit topoisomerases I and II.[104]

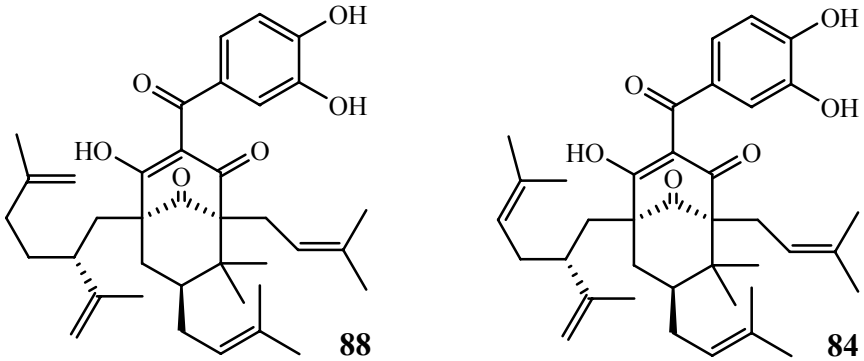



**Figure 1.11: Xanthochymol and guttiferone E**

Guttiferones A, B, E, C, and D (**81**, **96**, **84**, **82**, and **83**) (Figure 1.12), the latter two isolated as an inseparable mixture, were tested for anti-HIV biological activity.[28] All showed inhibitory effects on *in vitro* infection in human lymphoblastoid CEM-SS cells, with $EC_{50}$ values of 1–10 μg/mL, but there was no indication of a decrease in indices of viral replication. In a different study, guttiferone F (**86**) showed both cytoprotection against HIV-1 in vitro ($EC_{50}$ = 23 μg/mL) and cytotoxicity to the host cells ($IC_{50}$ = 82 μg/mL).[60]

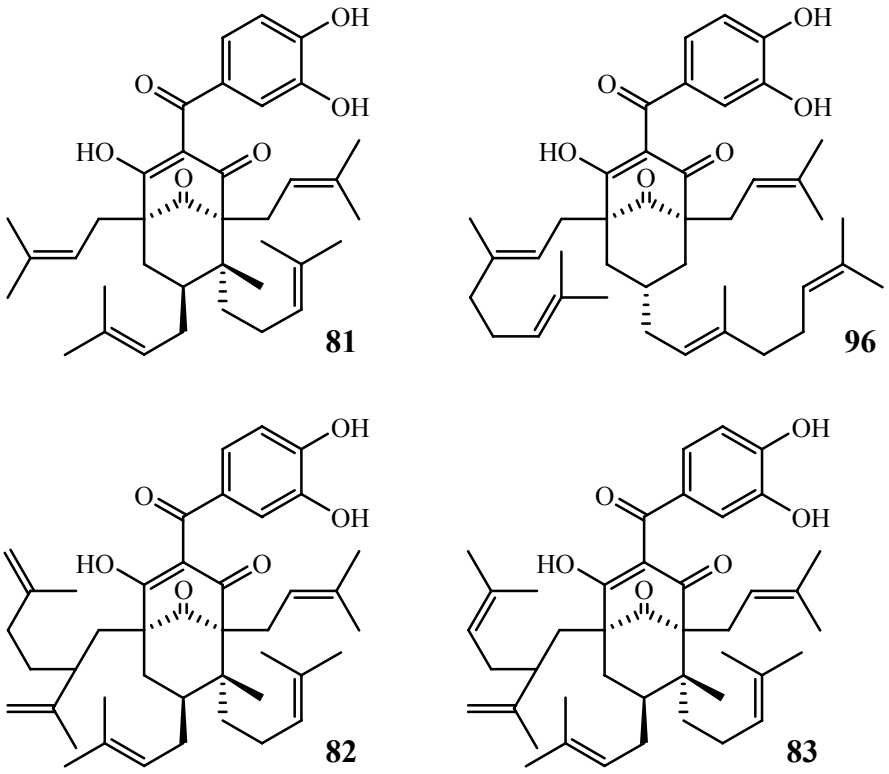



**Figure 1.12: Guttiferones A, B, C, and D**

Guttiferone E, xanthochymol, aristophenone (**93**), isoxanthochymol (**99**) and cycloxanthochymol (**100**) (Figure 1.13) exhibit cytotoxic activity against SW-480 colon cancer cells ($IC_{50}$ = 7.5–33.3 μM) and antioxidant activity in the DPPH free radical assay ($IC_{50}$ = 53–125 μM).[18]

Guttiferone I (**87**) (Figure 1.13) inhibits the binding activity of $\alpha$-liver X receptor (LXR$\alpha$) but is less effective against $\beta$-receptor (LXR$\beta$), with $IC_{50}$ = 3.4 μM and >15 μM, respectively.[21] LXR agonists are therapeutical agents for the control of plasma cholesterol levels, increasing reverse cholesterol transport.

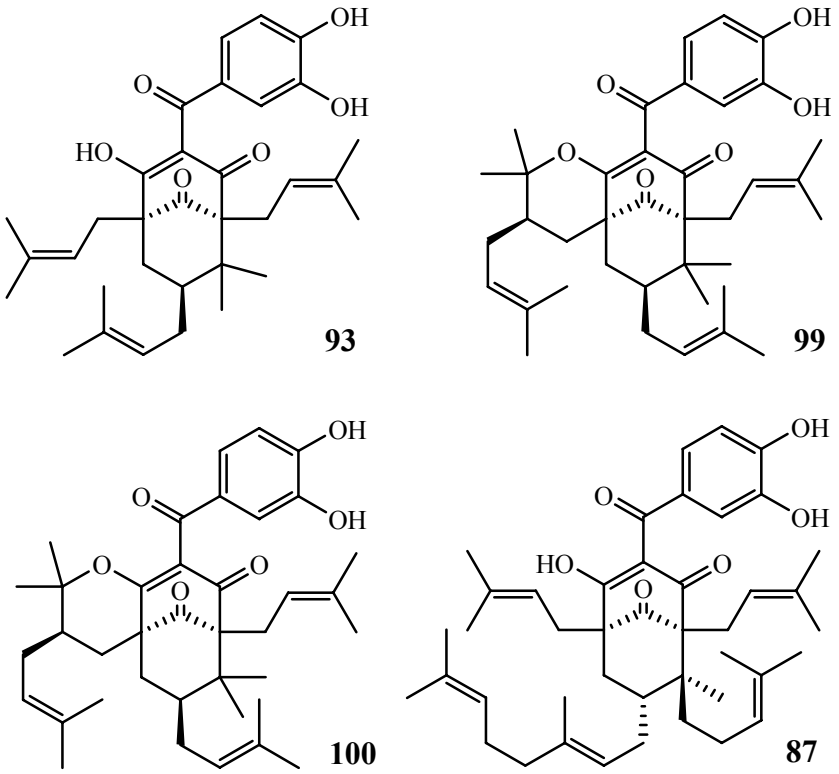



**Figure 1.13: Aristophenone, isoxanthochymol, cycloxanthochymol, and guttiferone I**

### 1.3.2.3. Ialibinones A–E and analogs

Ialibinones A–E (**107**, **110**, **108**, **111**, and **114**) (Figure 1.14) were isolated from *Hypericum papuanum*.[71] When tested for antibacterial activity, ialibinones C and D showed stronger activity than ialibinones A and B against *Bacillus cereus* and *Staphylococcus epidermis* but almost identical effectiveness against *Micrococcus luteus*. Ialibinone E was ineffective regardless of the bacteria used in the experiment.

The dried aerial parts of *Hypericum papuanum* are traditionally used as a remedy for sores and wounds due to their antibacterial activity. The active components of this plant are hyperpapuanone, 1′-hydroxyialibinones A, B, and D, and enaimeones A–C (**90**, **109**, **112**, **113**, and **104**–**106**) (Figure 1.15).[51,70] 1′-Hydroxyialibinones A, B, and D show identical or slightly reduced antibacterial acivity compared with the ialibinones A, B, and D, whereas hyperpapuanone has moderately potent antibacterial activity against *Micrococcus luteus*, *Staphylococcus epidermis*, and *Bacillus cereus*. The cytotoxicities of the 1′-hydroxyialibinones are three to five times weaker than that of the corresponding ialibinones. Enaimeones A–C have antibacterial activity similar to ialibinones A–C, but show a rather weak cytotoxicity against KB cells.

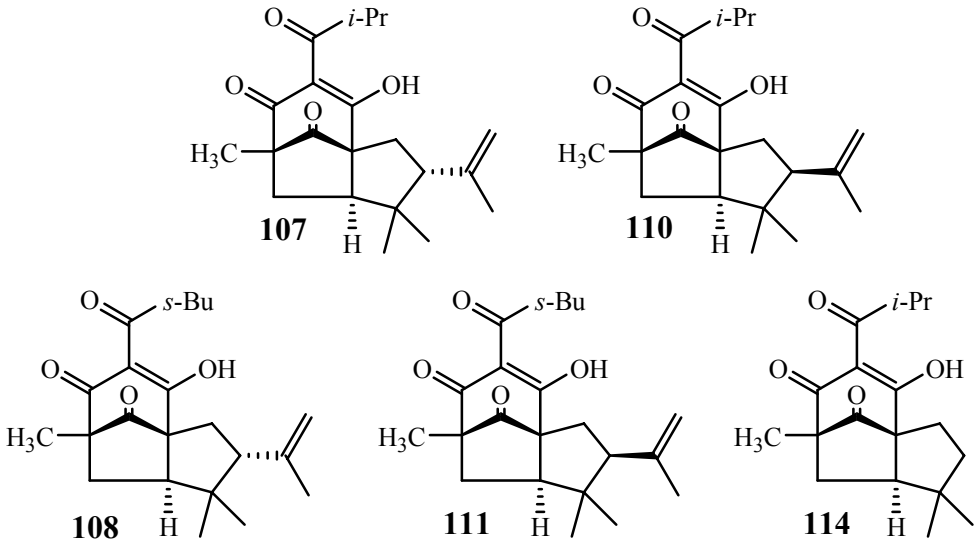



**Figure 1.14: Ialibinones A–E**

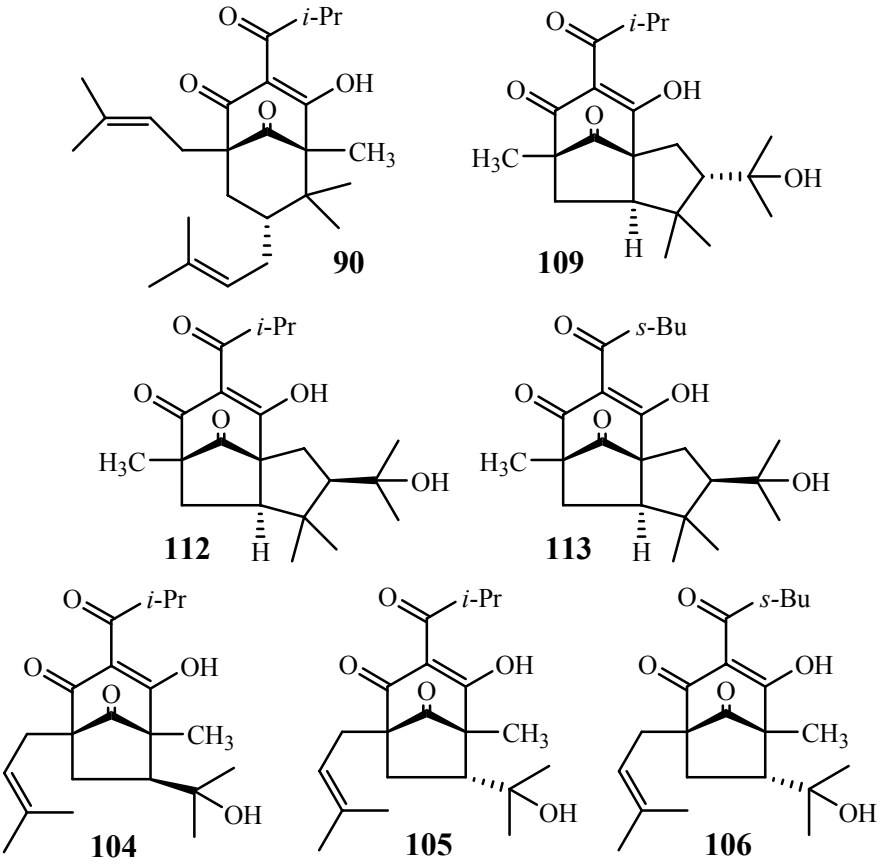



**Figure 1.15: Hyperpapuanone, 1′-hydroxyialibinones A, B, and D, and enaimeones A–C**

### 1.3.2.4. Other type B PPAPs

Laxifloranone (**92**) (Figure 1.16) exhibits moderate inhibition of the cytopathic effects of HIV-1 in a human T-lymphoblastoid cell line (CEM-SS, $EC_{50}$ = 0.62 μg/mL and $IC_{50}$ = 6.6 μg/mL).[68] Hyperibones K and L (**116** and **89**) moderately inhibit breast ($IC_{50}$ = 10.0 μM and 15.0 μM, respectively) and lung ($IC_{50}$ = 13.7 μM and 9.2 μM, respectively) tumor cell replication, but they show no anti-HIV activity.[54]

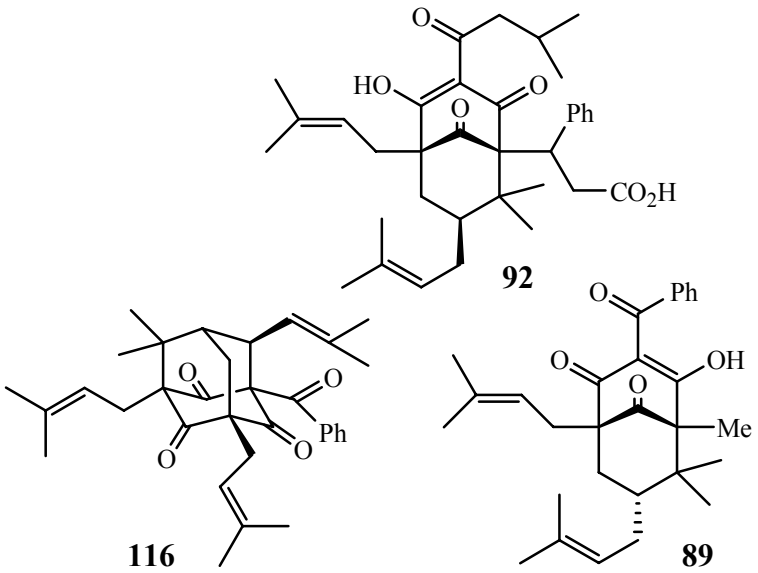



**Figure 1.16: Laxifloranone and hyperibones K and L**

### 1.3.3. Type C PPAPs

Garcinielliptones L (**119**) and M (**119**) (Figure 1.17), isolated from *Garcinia subelliptica*, inhibit the release of *β*-glucuronidase and histamine (**119**: $IC_{50}$ = 22.9 and >30 μg/mL; **118**: $IC_{50}$ = 13.6 and 19.0 μg/mL), activity which makes them potential antiinflammatory agents.[11] Mepacrine, a positive control, has corresponding $IC_{50}$ values of 13.6 and 23.3 μg/mL. The two garcinelliptones also have inhibitory effects on the accumulation of $NO_2^-$ in the culture of RAW 264.7 and N9 cells and slight inhibitory effects on tumor necrosis factor α production in cultured RAW 264.7 cells. Garcinielliptone FB, isolated from the same plant, shows moderate cytotoxic activity against liver, breast and colon cancer cell lines ($IC_{50}$ = 6.8, 6.3, and 11.2 μg/mL, respectively).[49]

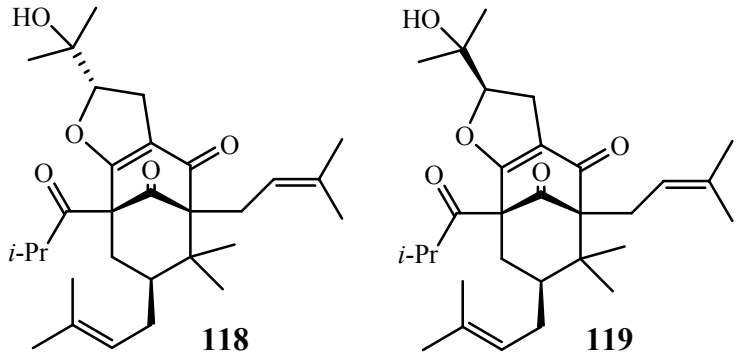
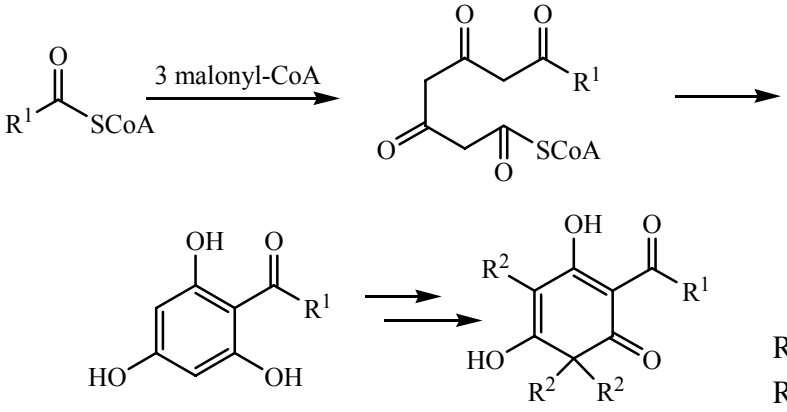



**Figure 1.17: Garcinielliptones L and M**

## 1.4. Biosynthesis of PPAPs

Early labeling experiments provided evidence for a polyketide-type biosynthesis for bitter acids which involves one acyl-CoA and three malonyl-CoA units (Scheme 1.2).[76,105-107] Similarly, numerous enzymological studies showed that the biosynthesis of acylphloroglucinols involves condensation of three molecules of malonyl-CoA and one molecule of acyl-CoA. The product, a tetraketide, is subsequently cyclized by Dieckmann condensation into an acylphloroglucinol.[108,109] The prenylation or geranylation of this compound occurs through an enzyme-catalyzed addition of prenyl or geranyl pyrophosphate to the phloroglucinol moiety.[6,110-114]

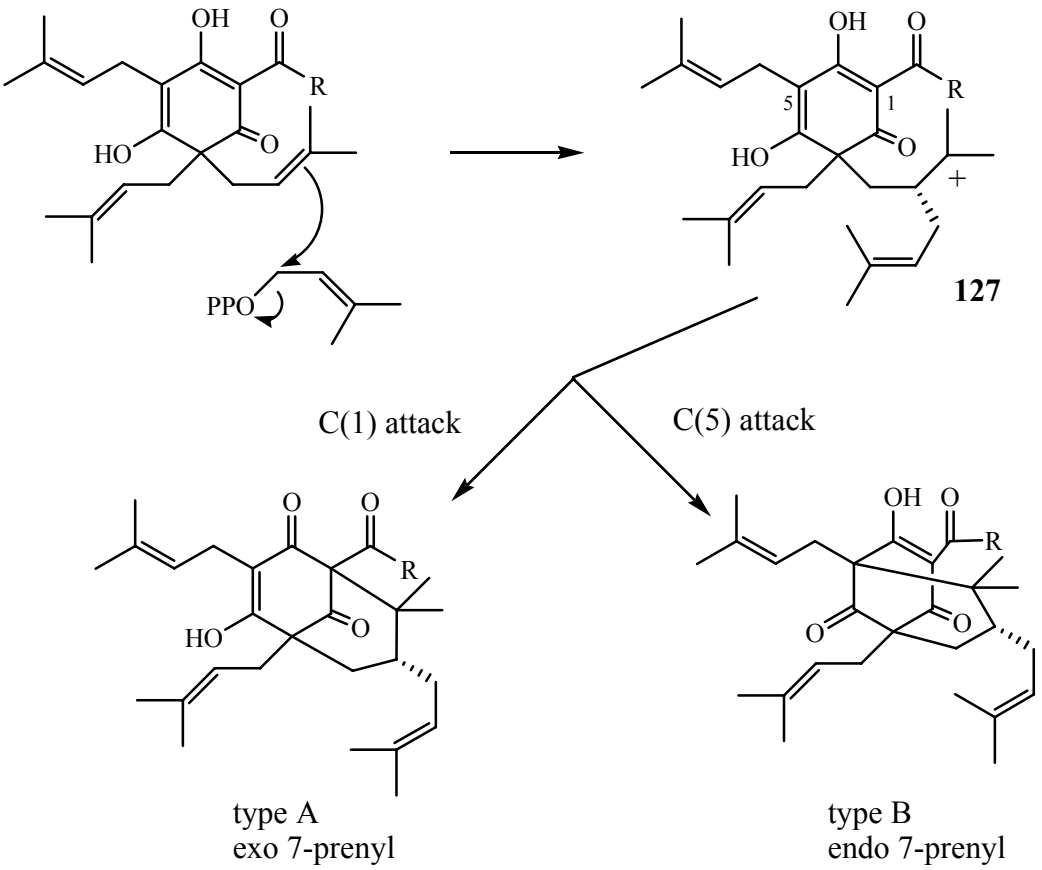
**Scheme 1.2: Biosynthesis of MPAPs.**



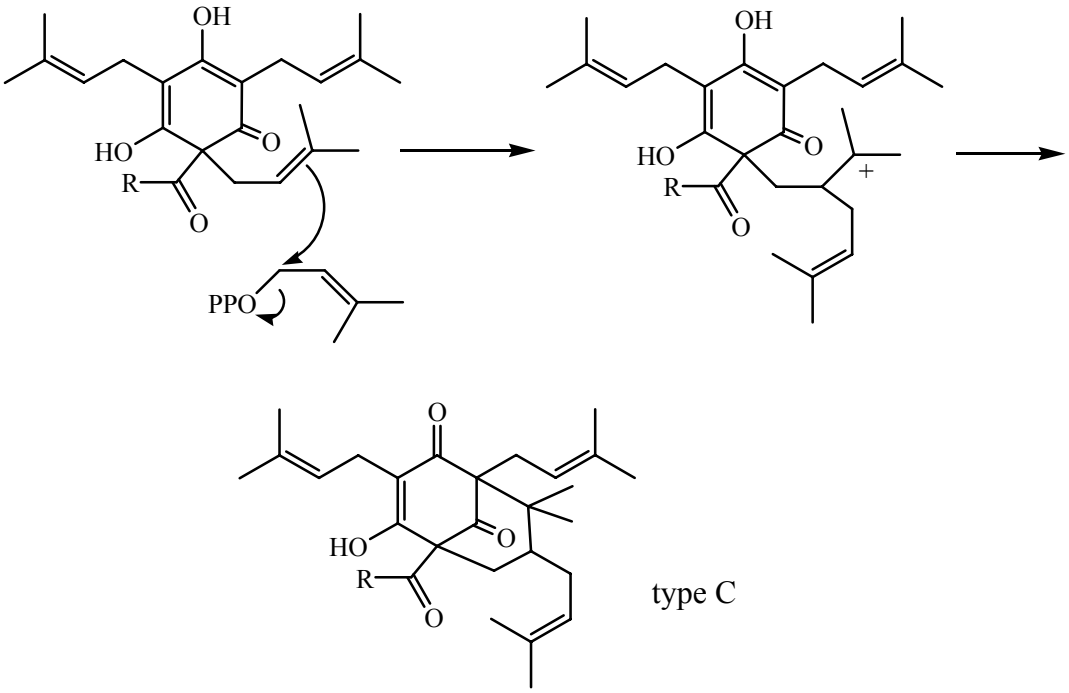

$R^1$=Ph, *i*-Pr, etc.;
$R^2$=prenyl or geranyl

Cuesta–Rubio proposed that MPAPs are cyclized to both type A and type B PPAPs via a common precursor (Scheme 1.3).[3] Attack of one of the geminal prenyl groups of an MPAP on prenyl pyrophosphate gives the tertiary carbocation **127**. Attack of C(1) of **127** on the pendant carbocation (or the corresponding pyrophosphate) would provide a type A PPAP, whereas attack of C(5) would provide a type B PPAP. Moreover, a single diastereomer of **127** can lead to either a type A PPAP with an exo 7-prenyl group or a type B PPAP with an endo 7-prenyl group. A majority of type A PPAPs have exo 7-prenyl groups, and most type B PPAPs have endo 7-prenyl groups. A similar mechanism is proposed for hyperforin biosynthesis.[76] The most likely scheme for the biosynthesis of the type C PPAPs, by contrast, would require that the initial MPAP have its quaternary center bear the acyl group (Scheme 1.4).

**Scheme 1.3: Cyclization of MPAPs to give type A or B PPAPs.**



**Scheme 1.4: Possible biosynthesis of type C PPAPs.**



## Chapter 2. Synthetic efforts toward PPAPs

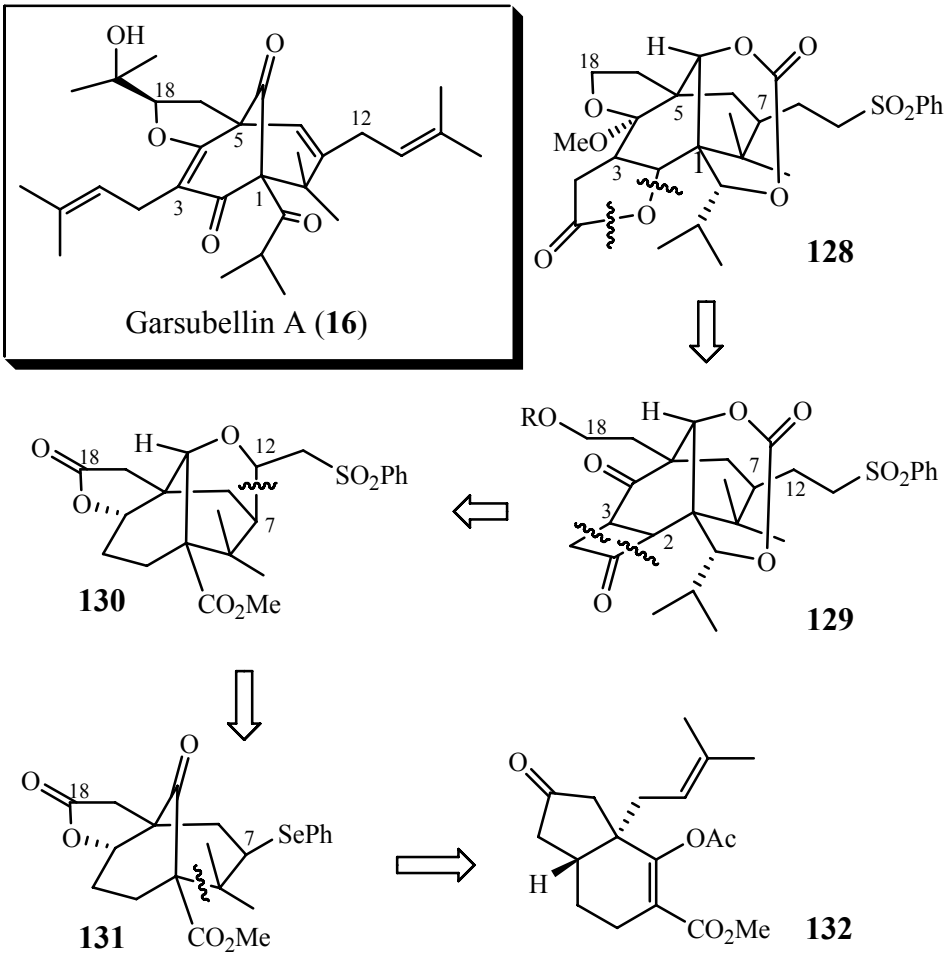
In the past decade many papers on the approaches to the synthesis of the acylbicyclo[3.3.1]nonane-2,4,9-trione structure of type A PPAPs have been published, but only two total syntheses of any PPAP, garsubellin A, have so far been reported by Shibasaki and Danishefsky[90,91] at the end of 2005. All approaches, with no exception, were linear. Linear synthesises have the drawback not only of an overall low yield but also of devoting a large amount of time to the process of converting starting material into the final product through numerous steps. Although a convergent synthetic protocol would always be desirable, it was hard to apply such methods in the case of these topological complex molecules. From a synthetic point of view, one can notice that all approaches have relied on the α,α′-annulation of a three-carbon bridge onto a cyclohexanone. The methods most often used to form the two new C–C bonds have involved classical carbonyl chemistry. Shibasaki's first approach used an addition–elimination with a β-chloroacrylate derivative followed later by an aldol reaction,[115,116] Stoltz used a Claisen–Dieckmann reaction with malonyl chloride,[117] Kraus used two addition–elimination reactions with a diacetoxyvinyl sulfone,[118] and Nicolaou used a Michael–aldol reaction with methacrolein.[119] Shibasaki's second and successfully completed approach to garsubellin A used an aldol reaction and an *O*-allylation to install vinyl and allyl groups at the α- and α′-positions of a cyclohexanone, then used a ring-closing metathesis to form the three-carbon bridge.[90] Danishefsky and Nicolaou used biomimetic approaches, namely electrophile-mediated cyclizations of a pendant prenyl group,[91,120,121] Young used an intramolecular [3 + 2] cycloaddition between an allene and a pendant nitrile oxide,[122] and Kraus and Mehta both used an intramolecular metal-catalyzed addition of a ketone to a pendant alkene.[123-125] Our group have also used an α,α′-annulation, with key steps of a lead-mediated alkynylation followed later by an aldol reaction (Chapter 3).[126] Nicolaou's first approach was unique because it annulated the three-carbon bridge containing the quaternary center (*gem*-dimethyl group) onto the cyclohexanone,[120,121] whereas all others annulated the three-carbon bridge containing the β-dicarbonyl moiety.

### 2.1. Nicolaou's Se-mediated electrophilic cyclization approach

The first efforts toward synthesis of a PPAP were done by Nicolaou. [120,121] The model compound **128** chosen by Nicolaou's group contained the key structural features of garsubellin A (**26**), including the extra ring fused to the bicyclic core (Scheme 2.1) but it was a rather long approach with no less than 23 steps. The lactone ring of **128** was

formed by a Baeyer–Villiger reaction of cyclobutanone **129**, which was derived from **130** via a [2 + 2] cycloaddition. The C(7)–C(12) bond of **130** was derived from C(7) selenide **131** via radical addition to an alkenyl sulfone, and the C(1)–C(6) bond of **131** was constructed by electrophilic cyclization of the prenylated β-keto ester **132**.

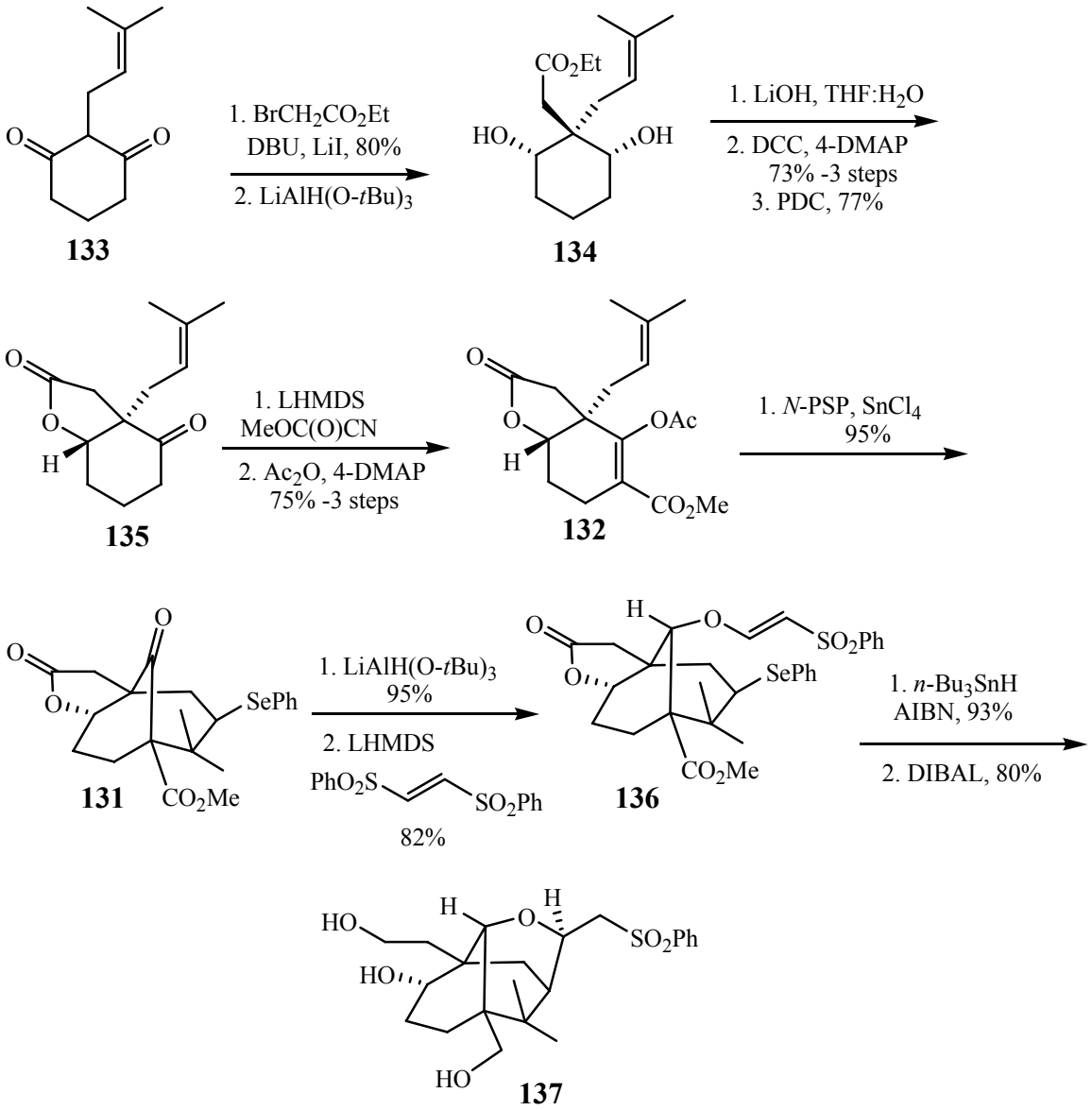
**Scheme 2.1: Nicolaou's retrosynthesis of garsubellin A.**




The synthesis of **128** began with *C*-alkylation of 1,3-diketone **133** and stereoselective reduction to give diol **134** (Scheme 2.2). Hydrolysis of the ester of **134**, lactonization with DCC and 4-DMAP, and oxidation of the remaining alcohol provided keto lactone **135**. Deprotonation of **135**, treatment with methyl cyanoformate, and acetylation gave enol acetate **132**. The key step of the synthesis, the selenium-mediated cyclization, occurred upon addition of $SnCl_4$ to a mixture of **132** and *N*-(phenylseleno)phthalimide at –23 °C to give bicyclo[3.3.1nonane **131** in 95% yield. The PhSe group in **131** was placed exclusively in the thermodynamically favored exo

orientation. Stereoselective reduction of the ketone of **131** provided a secondary alcohol, which was further converted to vinylogous sulfonate **136** upon addition of *trans*-1,2-bis(phenylsulfonyl)ethylene. Treatment of **136** with *n*-$Bu_3SnH$ and AIBN formed the C(7)–C(12) bond, and global reduction gave triol **137**.

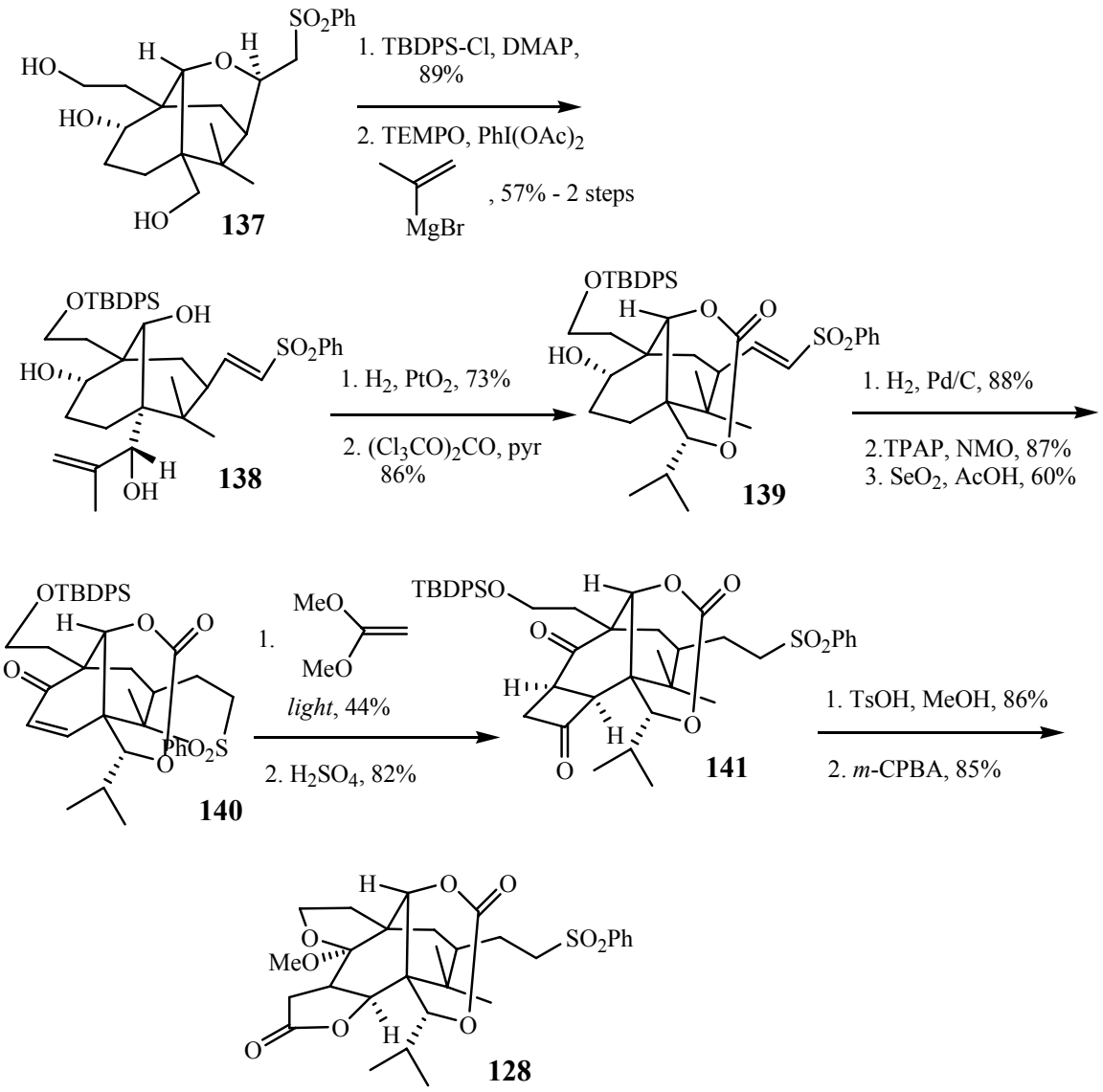
**Scheme 2.2: Nicolaou's approach to garsubellin A, part 1.**




The least hindered hydroxyl group of **137** was protected, and the remaining primary alcohol was oxidized to the aldehyde (Scheme 2.3). Addition of *i*-PrMgBr resulted only in reduction of the aldehyde, but isopropenylmagnesium bromide not only added stereoselectively to the aldehyde, but it also promoted β-elimination of the β-alkoxy sulfone side chain to give triol **138**. Conditions to reduce both C=C π bonds of

**138** could not be identified, so the isopropenyl group was reduced with $H_2$ and $PtO_2$, and addition of triphosgene and pyridine gave the cyclic carbonate **139**. Hydrogenation of **139** was then followed by oxidation of the remaining hydroxyl group to the ketone. Conversion of the ketone to the enone **140** proved to be challenging, and it could be accomplished only by addition of $SeO_2$ in AcOH at 110 °C. The light-promoted cycloaddition of dimethoxyethylene to **140** occurred regio- and stereoselectively from the *exo*-face of the enone. The dimethoxyketal thus formed was converted to cyclobutanone **141** upon hydrolysis with $H_2SO_4$. The TBDPS group of **141** was removed, and the C(4) ketone was protected as the cyclic methyl acetal. Treatment with excess *m*-CPBA then promoted a regioselective Baeyer–Villiger reaction of the cyclobutanone to give the desired model lactone **128** in good yield.

**Scheme 2.3: Nicolaou's approach to garsubellin A, part 2.**

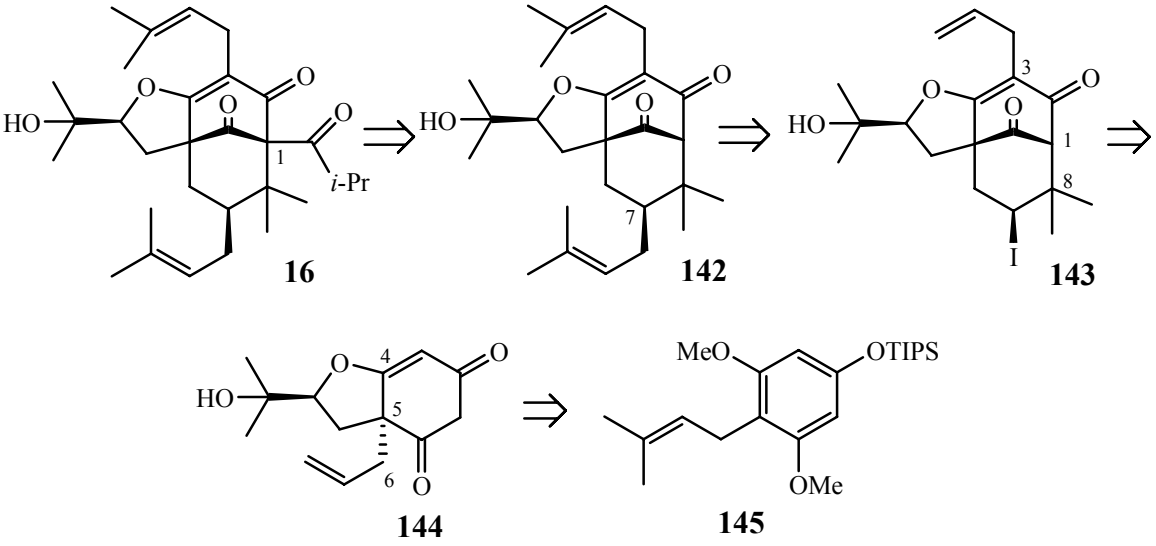



## 2.2. Danishefsky's I-mediated electrophilic cyclization approach

Very recently, Danishefsky has described a total synthesis of garsubellin A that uses an electrophilic attack of a cyclohexanone on a prenyl group, reminiscent of that described by Nicolaou.[91] The beauty of this synthesis is not only that is relatively short but also that in the key steps it uses some very interesting and creative iodine-based reactions. The main drawback of Danishefsky's synthesis is that the introduction of the C(1) acyl group proceeds in fairly poor and variable yield and that it is a racemic synthesis. Future work is needed to extend this methodology to the synthesis of other PPAPs such as hyperforin.

In Danishefsky's retrosynthetic analysis (Scheme 2.4), the C(1) acyl group of **16** would be introduced by deprotonation of **142** and addition of isobutyraldehyde. The C(7) prenyl group of **142** would be introduced by free-radical allylation of the iodide **143**. Removal of the C(3) allyl group of **143** and disconnection of the C(1)–C(8) bond by an iodocyclization reaction then led back to bicyclic **144**, which would be produced by dihydroxylation and alkylative dearomaticization of the phloroglucinol derivative **145**.

**Scheme 2.4: Danishefsky's retrosynthesis of garsubellin A.**

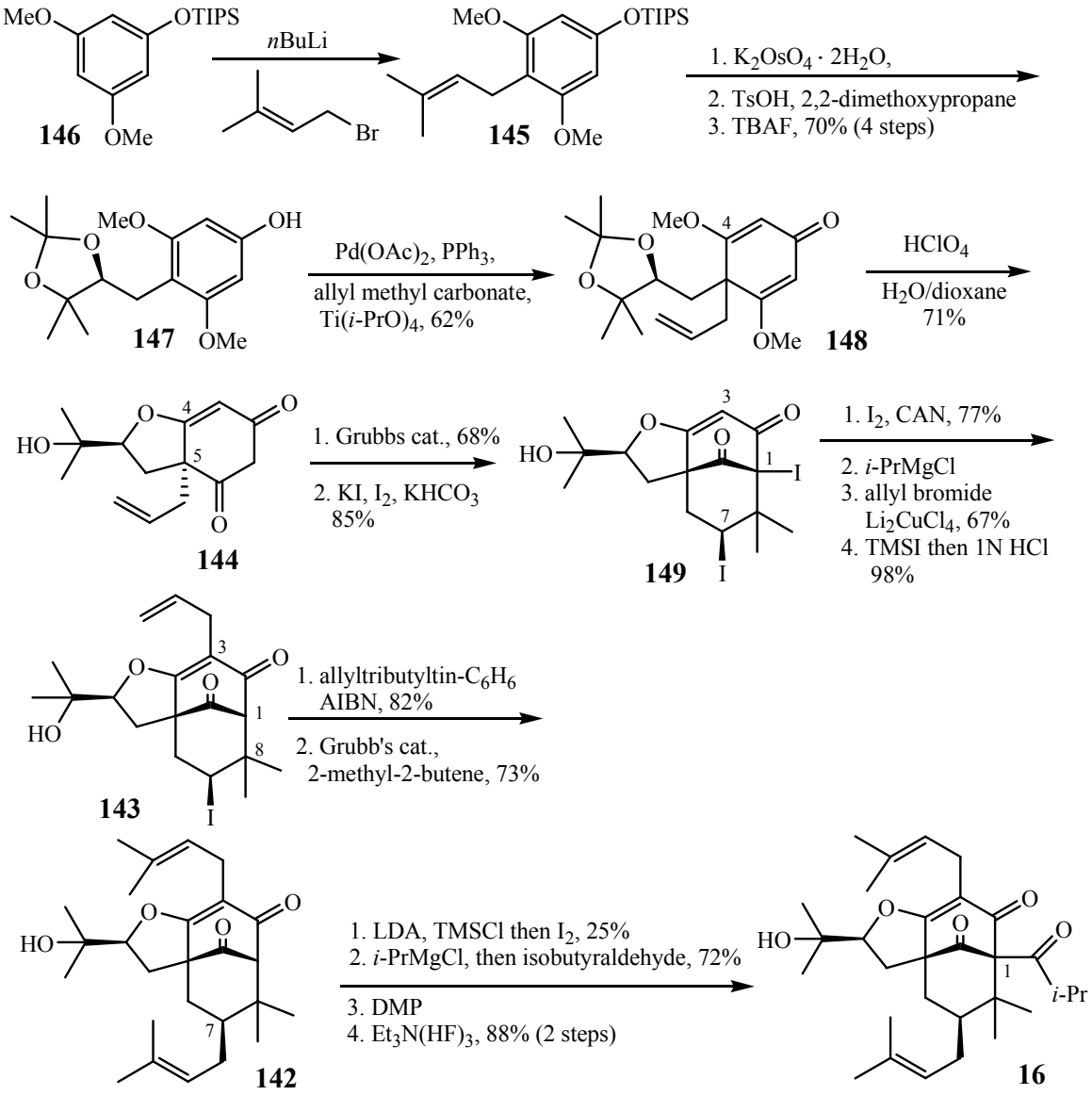



The Danishefsky synthesis of **12** began by deprotonation of **146** and addition of prenyl bromide to give **145** (Scheme 2.5). Nonasymmetric Sharpless dihydroxylation of **145** was followed by acetonide formation and removal of the TIPS group to give **147**. Compound **147** was treated with allyl methyl carbonate in the presence of $Pd(OAc)_2$, $Ph_3P$, and $Ti(O\text{-}i\text{-}Pr)_4$, providing key dearomatized intermediate **148**, either by direct *C*-allylation or by *O*-allylation followed by a Pd-catalyzed Claisen rearrangement. Acidic hydrolysis of **148** removed the acetonide group and promoted conjugate addition of the nascent secondary alcohol to the ring to give a bicyclic acetal, forming the key O-C(4) bond; it followed the elimination of MeOH from the acetal and the hydrolysis of the other methyl enol ether eventually provided **144** as a single diastereomer.

The allyl group of **144** was subject to to convert it into a prenyl group, and, in a step reminiscent of Nicolaou's original approach, iodocyclization then provided the tricyclic diiodide **149**. Compound **149** was iodinated once again, at C(3), and halogen–metal exchange followed by treatment with allyl bromide not only introduced the allyl

group at C(3), but also promoted Wurtz-like coupling of C(1) and C(7). Fortunately, this cyclopropanation step was easily reversed by addition of TMSI, affording **143**.

**Scheme 2.5: Danishefsky's synthesis of garsubellin A.**

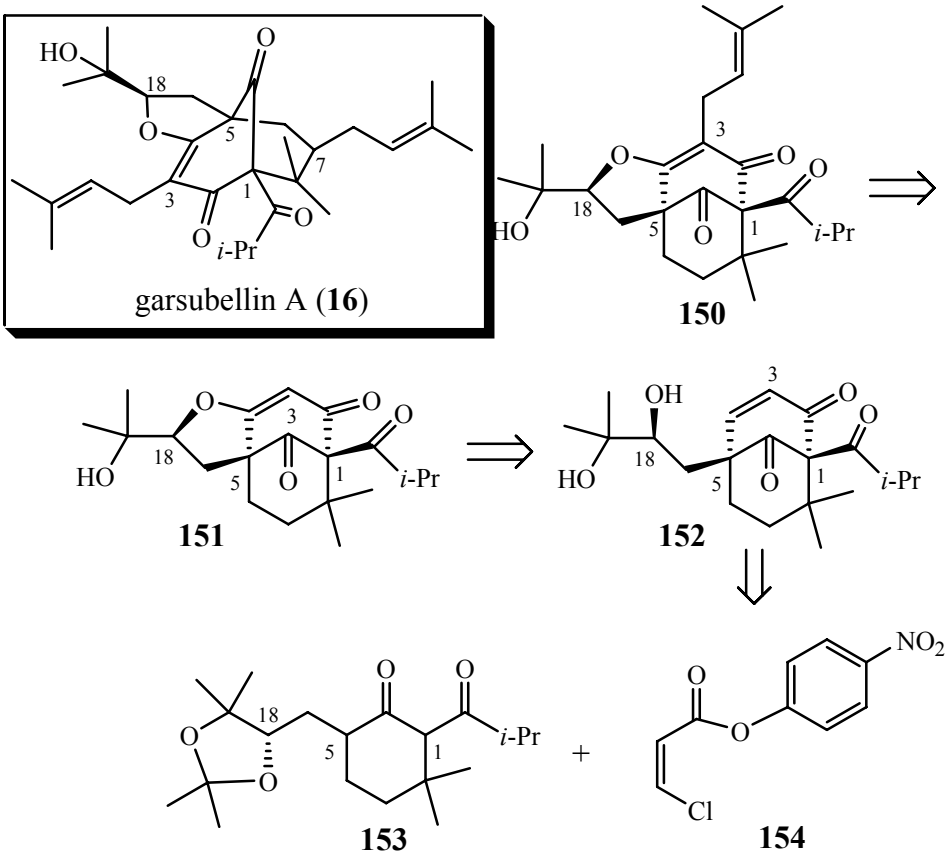



Iodide **143** was subject to free-radical allylation with allyltributyltin, installing the allyl group selectively in the sterically less hindered exo position, and another Grubbs cross-metathesis with 2-methyl-2-butene provided the diprenylated compound **142**. Finally, formation of the bridgehead silyl enol ether of **142**, iodination to give the bridgehead iodide, halogen–metal exchange and addition of isobutyraldehyde, and oxidation of the alcohol gave **16**.

## 2.3. Shibasaki's addition–elimination–aldol approach

Shibasaki's group chose as their model compound 7-deprenylgarsubellin A, **150** (Scheme 2.6), which has all the features of garsubellin A (**16**) except the prenyl group attached to C(7).[116] Their plan was to introduce the C(3) prenyl group in the last step via a Stille coupling reaction between tributylprenyltin and the iodide prepared from β-alkoxy lactone **151**. The C(4)–O bond of **151** would be constructed via an intramolecular Wacker-type reaction of enone **152**. The bicyclo[3.3.1]nonane core of enone **152** was to be constructed by a stereospecific addition–elimination reaction between 1,3-diketone **153** and α,β-unsaturated ester **154** followed by a Dieckmann reaction. This key step failed to work as planned, and considerable synthetic effort would be required to arrive at **152**.

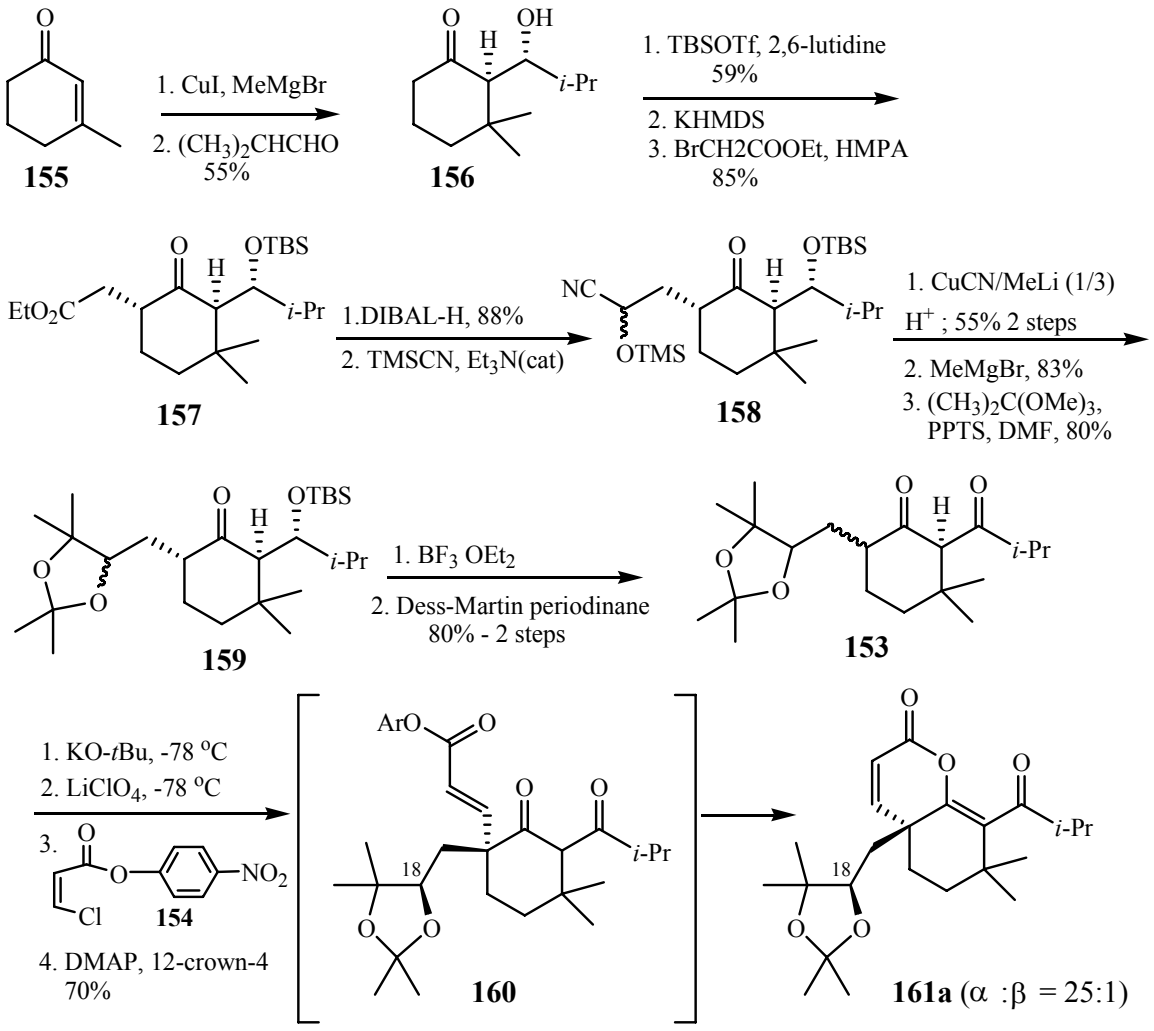
**Scheme 2.6: Shibasaki's retrosynthesis of garsubellin A.**




The synthesis began with conjugate addition of MeMgBr to α,β-unsaturated ketone **155** followed by trapping of the enolate with isobutyraldehyde to give **156** as a single stereoisomer (Scheme 2.7).[116] The OH group of **156** was protected, and the

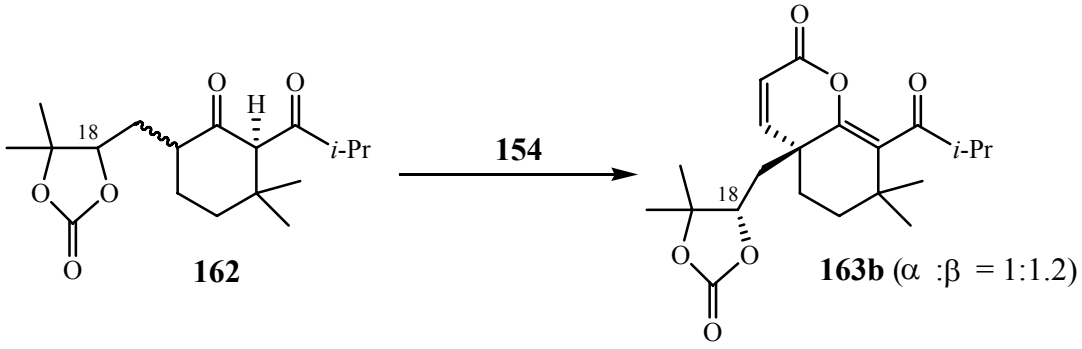
product was alkylated with ethyl bromoacetate to give **157** as a single trans isomer. Partial reduction of **157** with DIBAL and cyanosilylation of the aldehyde afforded **158** as an inconsequential 1.3:1 mixture of diastereomers. Addition of a higher order methylcuprate reagent to **158** gave a methyl ketone, which was further subjected to methylation and protection to give the acetonide **159**. Removal of the TBS group with $BF_3 \cdot Et_2O$ and oxidation of the resulting secondary alcohol with Dess-Martin periodinane gave key intermediate **153** as an inconsequential 1.3:1 mixture of diastereomers. Unfortunately, the addition–elimination reaction between 1,3-diketone **153** and *cis*-β-chloroacrylate **154** failed to proceed as desired. The authors expected that addition–elimination would occur with retention of configuration about the electrophilic π bond, and a Dieckmann condensation would then give **152** (protected as the acetonide). Instead, the major product was the trans acrylate **160**. The authors found that **160** could be converted into **161** in the presence of *p*-nitrophenol and base. Extensive optimization finally uncovered conditions under which **153** could be directly converted to **161** in good yield. Unfortunately again, the major diastereomer produced under these conditions was the undesired **161a**.

**Scheme 2.7: Shibasaki's approach to garsubellin A, part 1.**




Later, the Shibasaki group found that the carbonate **162** gave a much less diastereoselective addition–elimination reaction than the acetonide **153** did, affording larger quantities of the desired epimer **163b** (Scheme 2.8).[115]

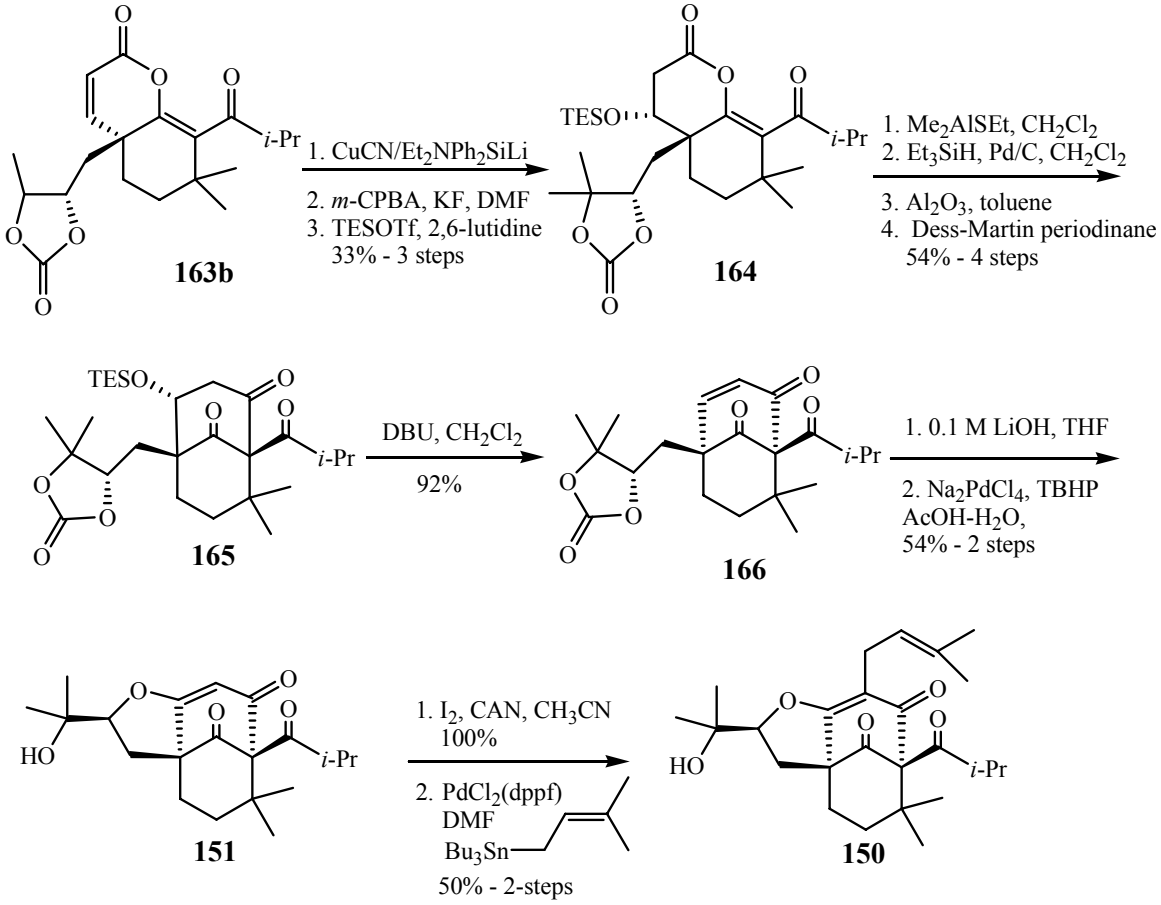
**Scheme 2.8: Shibasaki's approach to garsubellin A, part 2.**




Conjugate addition of an aminosilylcuprate to α,β-unsaturated lactone **163b** and immediate Tamao–Fleming oxidation with mCPBA afforded a β-hydroxy lactone, which was protected with a TES group to give **164** in modest yield over the three steps (Scheme 2.9).[115] Preparing the substrate for an aldol condensation, the lactone ring of **164** was opened with $Me_2AlSEt$ to give the corresponding thioester**,** Fukuyama reduction of the thioester gave an aldehyde, and the aldehyde underwent an aldol reaction upon treatment with $Al_2O_3$, with Dess-Martin periodinane treatment affording triketone **165**. From this point, the sequence of reactions went as planned in the retrosynthetic analysis. Thus, **165** was converted to enone **166** by DBU-promoted β-elimination of TESOH. Deprotection of the carbonate of **166** with LiOH was followed by Wacker oxidation to afford the β-alkoxy enone **151**. Treatment of **151** with $I_2$ and CAN afforded the vinyl iodide, and Stille coupling with tributylprenyltin catalyzed by $PdCl_2$(dppf) introduced the prenyl group on C(3) and completed the synthesis of **150**. The acetonide **161a** with the unnatural C(18) configuration was also carried on to the C(18) epimer of **150** via a similar sequence of reactions.[116]

Shibasaki later found that the aldol reaction leading from **164** to **165** failed when there was a prenyl group at C(7)[90] and the group abandoned this approach to garsubellin A. They later reported the total synthesis of garsubellin A in which a very different approach was used.

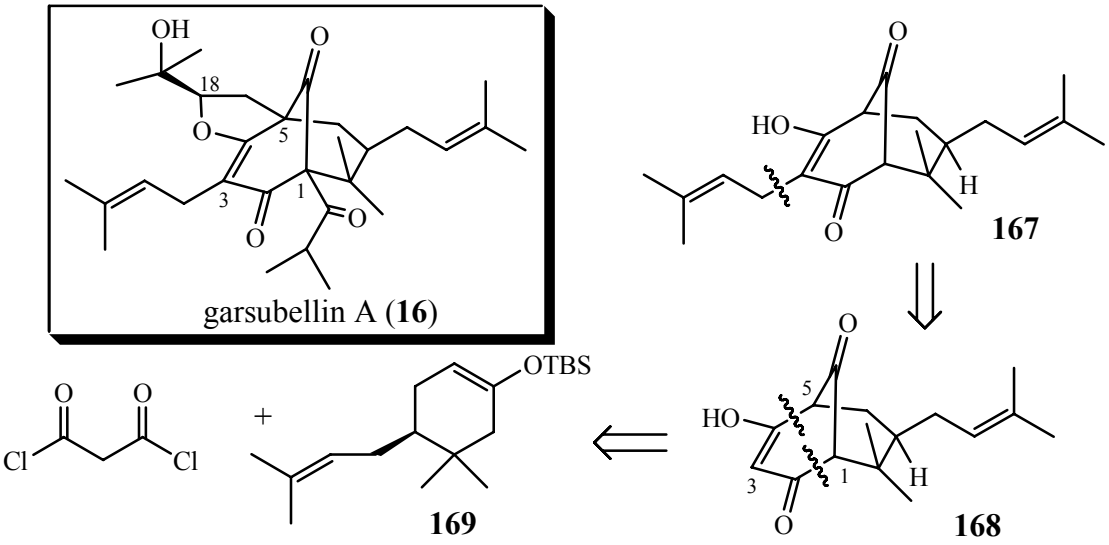
**Scheme 2.9: Shibasaki's approach to garsubellin A, part 3.**




## 2.4. Stoltz's Claisen–Dieckmann approach

Stoltz's approach to the PPAPs (Scheme 2.10) had the advantage of producing a diprenylated bicyclic core in just 10 steps,[117] but it also had the disadvantage of not being suitable for substrates with substituents at the α-position. The retrosynthesis of model compound **167** began with disconnection of the C(3) prenyl group to give **168**. The bicyclic core would then be introduced by a condensation reaction between silyl enol ether **169** and malonyl dichloride, similar to the reaction reported by Effenberg in 1984,[127] in which 1-methoxy-1-cyclohexene reacted with malonyl dichloride to give a bicyclo[3.3.1]nonane-2,4,9-trione.

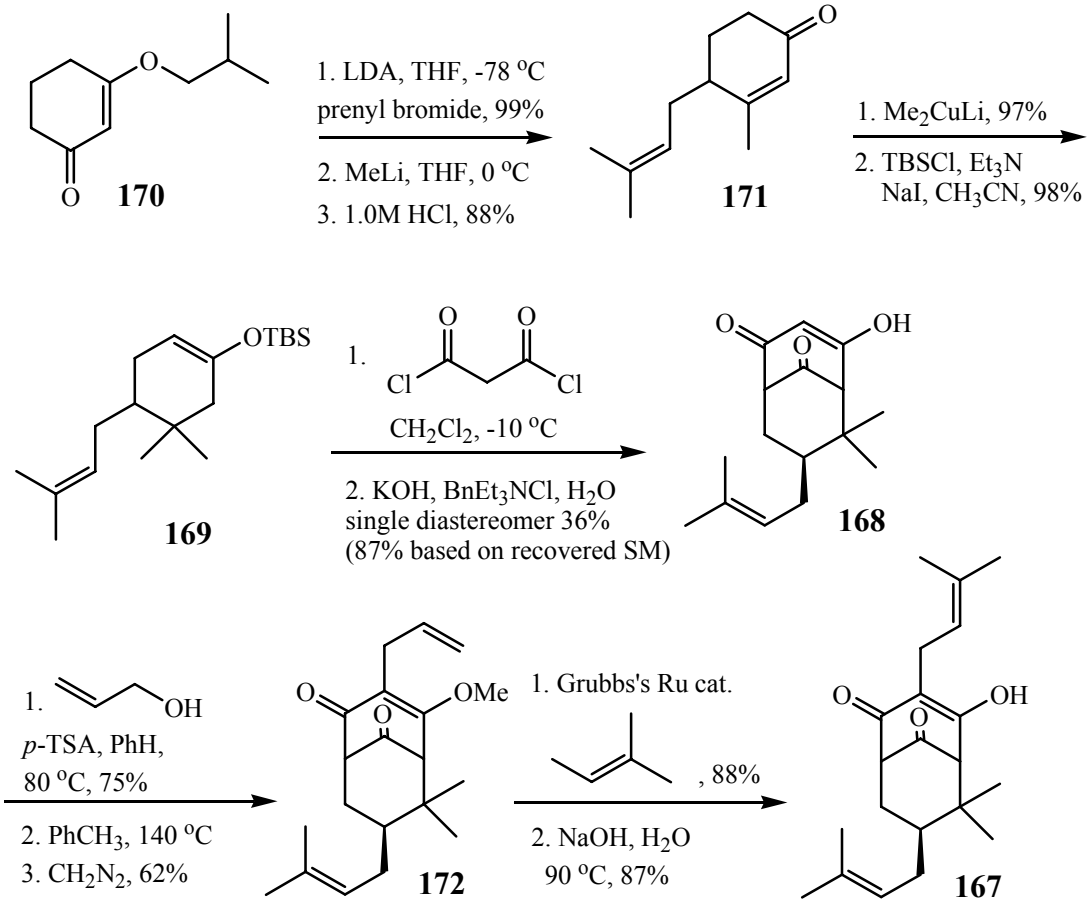
**Scheme 2.10: Stoltz's retrosynthesis of PPAPs.**




The synthesis of **167** began with α-prenylation of β-alkoxy enone **170** (Scheme 2.11). Addition of MeLi and acidic workup then gave α,β-unsaturated ketone **171**. Conjugate addition of dimethyl cuprate to **171** and subsequent addition of TBSCl provided the silyl enol ether **169**. Under optimal conditions, compound **169** underwent α,α′-annulation with malonyl dichloride to give the bicyclo[3.3.1]nonane-2,4,9-trione **168** as a single diastereomer in 36% yield. Unreacted enol ether was recovered in 59% yield as the keto form of **169**, which could be used again in the reaction sequence. Although the cyclization step proceeded only in modest yield, the previous steps were relatively easy to pursue and proceeded in excellent yields.

The introduction of the C(3) prenyl group into **168** began by treatment with allyl alcohol under acidic conditions under a Dean–Stark trap. Thermal Claisen rearrangement followed by methylation with $CH_2N_2$ afforded the *C*-allylated β-alkoxy enone **172**. Finally, olefin cross-metathesis with 2-methyl-2-butene catalyzed by Grubbs' second-generation catalyst and subsequent saponification of the methyl ether with aqueous NaOH gave the final target model compound **167**.

**Scheme 2.11: Stoltz's approach to garsubellin A.**



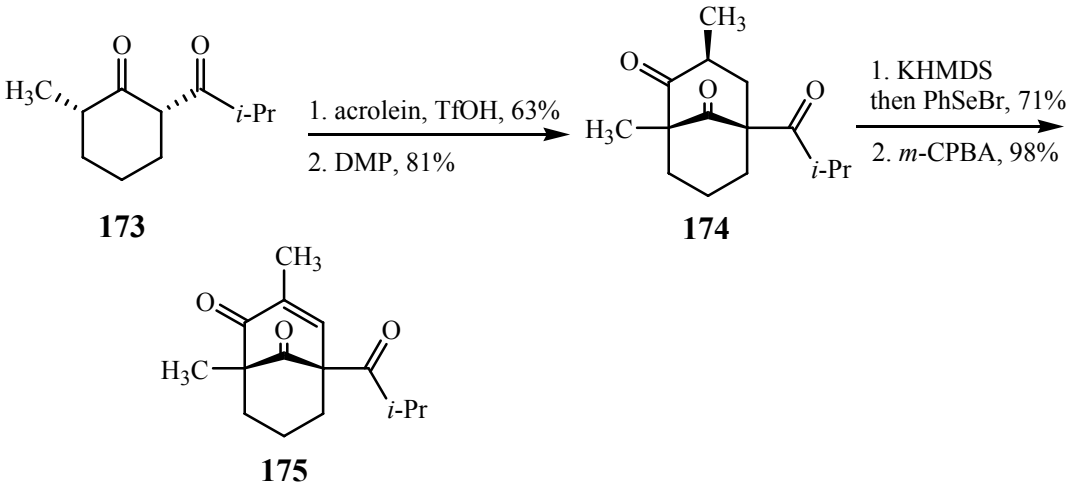

Stoltz tried to extend this methodology to analogs of **167** which would contain quaternary bridgehead C atoms, but most attempts failed, suggesting that the presence of substituents at the α-positions of the masked ketone affected the reactivity of the system. After prolonged experimentation, the group eventually found a way in which the methyl enol ether of 2,6-dimethylcyclohexanone would react with malonyl dichloride to give a bicyclo[3.3.1]nonane-2,4,9-trione but the product was obtained only in 25% yield, proving indeed that substituted enol ethers are not good substrates for the Claisen–Dieckmann approach.

## 2.5. Nicolaou's Michael–aldol approach

In a recent publication very different from his previous approach, Nicolaou showed that 2-acylcyclohexanone **173** (and 2-acylcycloalkanones of other ring sizes) underwent a TfOH-catalyzed tandem Michael–aldol reaction with methacrolein (Scheme 2.12).[119] Oxidation of the aldol product with Dess–Martin periodinane then afforded bicyclic triketone **174**, and desaturation of **174** to give **175** was easily

accomplished by selenation and oxidation. This strategy had the advantage of forming the two quaternary centers in just one step in relatively good yield from a simple cyclic ketone and aldehyde. The authors did not report whether the Michael reaction would proceed as readily when there was a quaternary center at C(3) of **173**. Conversion of the enone functionality of **175** to a β-diketone remained to be accomplished.

**Scheme 2.12: Nicolaou's Michael–aldol approach to PPAPs.**

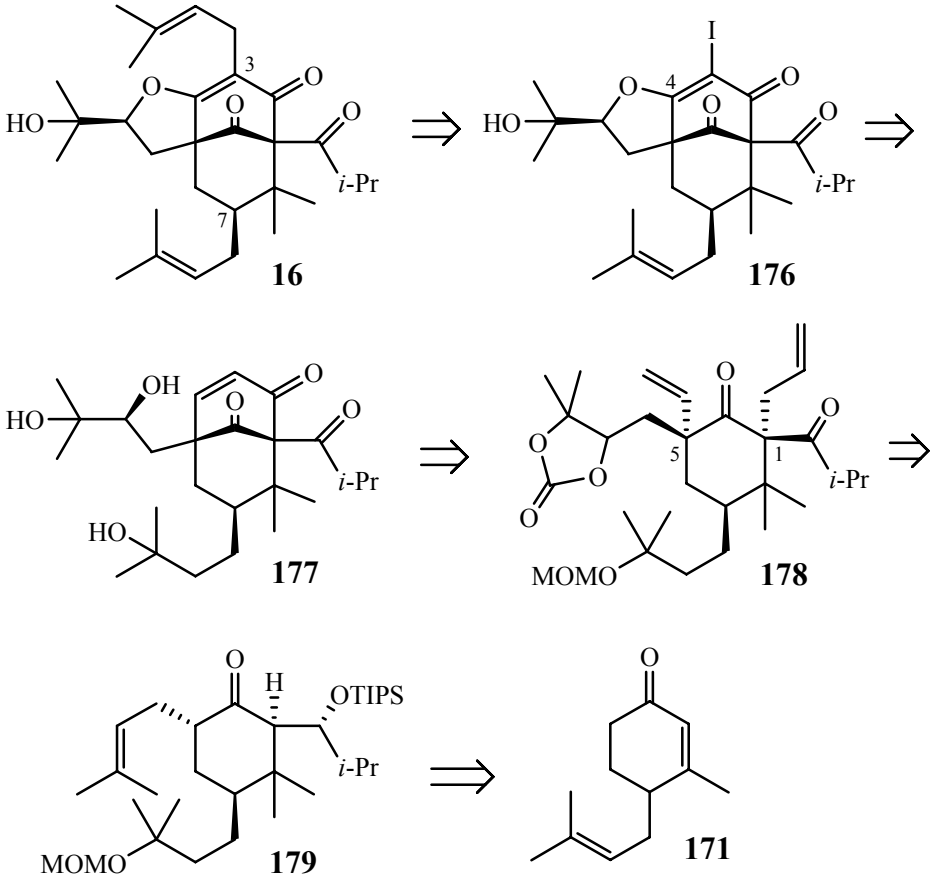



**173** **174** **175**

## 2.6. Shibasaki's ring-closing metathesis approach

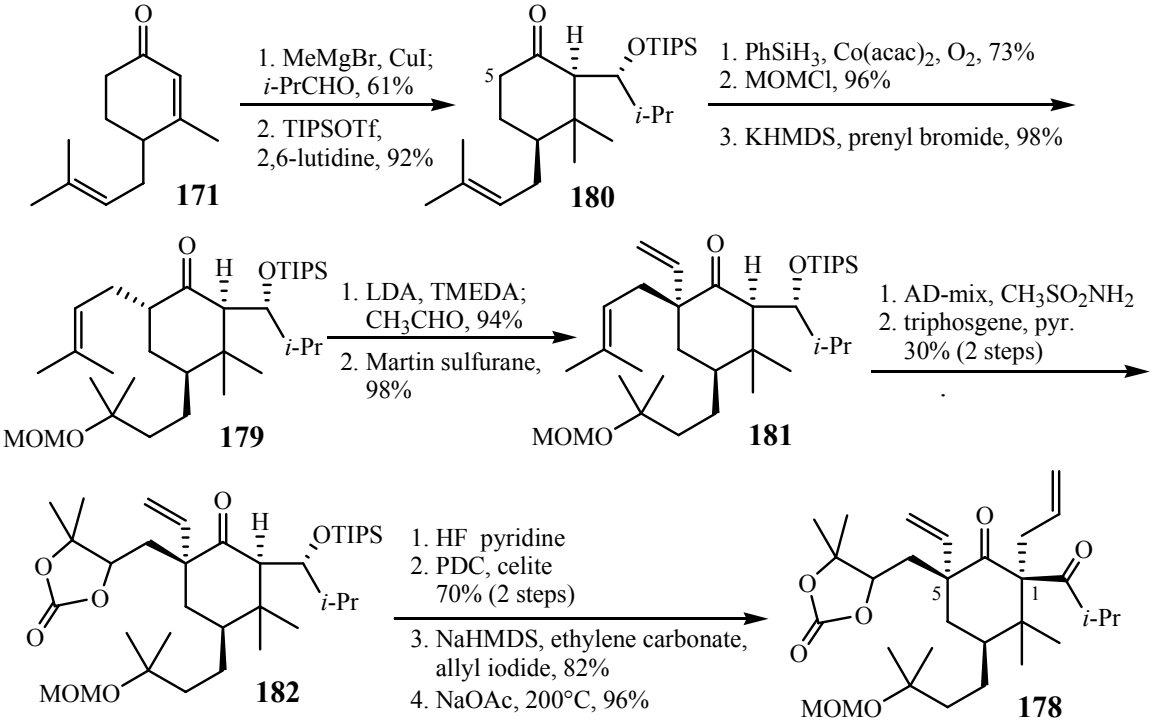
Shibasaki's group has very recently published a total synthesis of racemic garsubellin A.[90] Disconnection of the C(3) prenyl group of **16** gave **176**, whose O–C(4) bond was expected to be formed by an intramolecular Wacker oxidation, as precedented in the group's earlier studies,[115] leading back to enone **177** (Scheme 2.13). Because their previous intramolecular aldol route failed when a C(7) prenyl group was present, the authors decided to introduce the enone bridge of **177** by ring-closing metathesis of the very congested α-vinyl α′-allyl cyclohexanone **178**. The key C(1) and C(5) quaternary centers of **178** were introduced into simpler ketone **179** by an aldol reaction and dehydration (vinyl group) and by an *O*-allylation and Claisen rearrangement (allyl group). The ketone **179** was elaborated from simple enone **171**, an intermediate found also in Stoltz's studies (Scheme 15).[117]

**Scheme 2.13. Shibasaki's ring-closing metathesis approach to garsubellin A.**



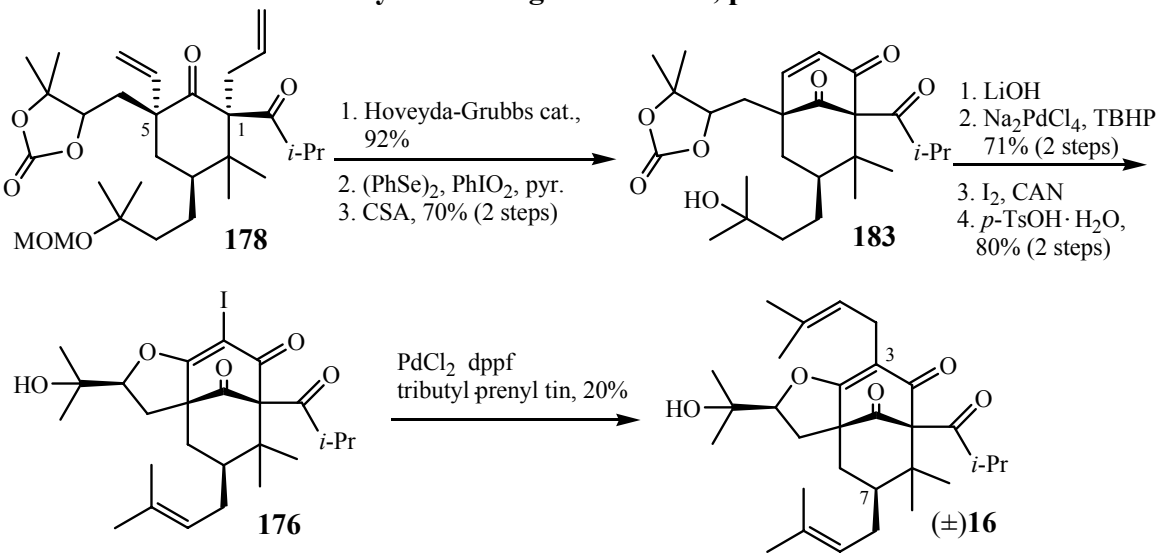

Copper-catalyzed conjugate addition of MeMgBr to **171**, trapping of the enolate with isobutyraldehyde, and protection of the resulting OH group with a TIPS group provided ketone **180** (Scheme 2.14). The prenyl group of **180** was hydrated and protected with a MOM group, and the ketone was then alkylated at the less hindered α-position, C(5), with prenyl bromide to give ketone **179**. Another deprotonation of **179**, again at C(5), was followed by another aldol reaction, this time with acetaldehyde; this reaction proceeded in surprisingly good yield, despite the tendency of sterically crowded aldols to fragment by a retro-aldol reaction. Dehydration of the aldol with Martin sulfurane then gave the α-vinyl ketone **181**. The prenyl group was then subject to Sharpless dihydroxylation with AD-mix-α, which provided the diol with zero diastereoselectivity. Formation of the carbonate and separation of the diastereomers gave **182**. The TIPS group of **182** was removed, the aldol was oxidized to the β-diketone, the ring O atom was allylated with allyl iodide, and a Claisen rearrangement on the face opposite the C(7) prenyl group provided fully quaternized diketone **178** with very high diastereoselectivity.

**Scheme 2.14: Shibasaki's synthesis of garsubellin A, part 1.**




Ring-closing metathesis of **178** proceeded smoothly with the Hoveyda–Grubbs catalyst, and the resulting alkene was oxidized in the allylic position with $(PhSe)_2$ and $PhIO_2$ (scheme 2.15). MOM protecting group was then removed to give **183**. After deprotection of the diol, the alcohol and enone moieties were condensed oxidatively in the intramolecular Wacker oxidation that worked so well in Shibasaki's earlier work, and C(3) iodination and acid-catalyzed dehydration of the tertiary alcohol gave **176**. Finally, Stille coupling of **176** with tributylprenyl tin afforded the target, **16**, in a total of 21 steps from **171**.

**Scheme 2.15: Shibasaki's synthesis of garsubellin A, part 2.**




Shibasaki also showed that alkylation of the Li enolate of 2-cyclohexenone with prenyl bromide in the presence of catalytic amounts of chiral tetraamine **184** (Figure 2.1), whose synthesis has not been published yet, gave 6-prenyl-2-cyclohexenone with 95% ee in 65% yield. This compound could then be converted to **171** by addition of MeLi and PCC oxidation.

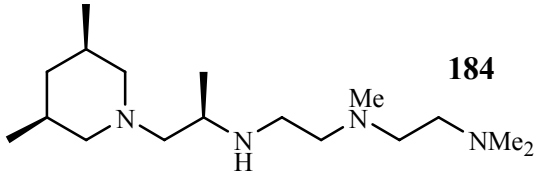


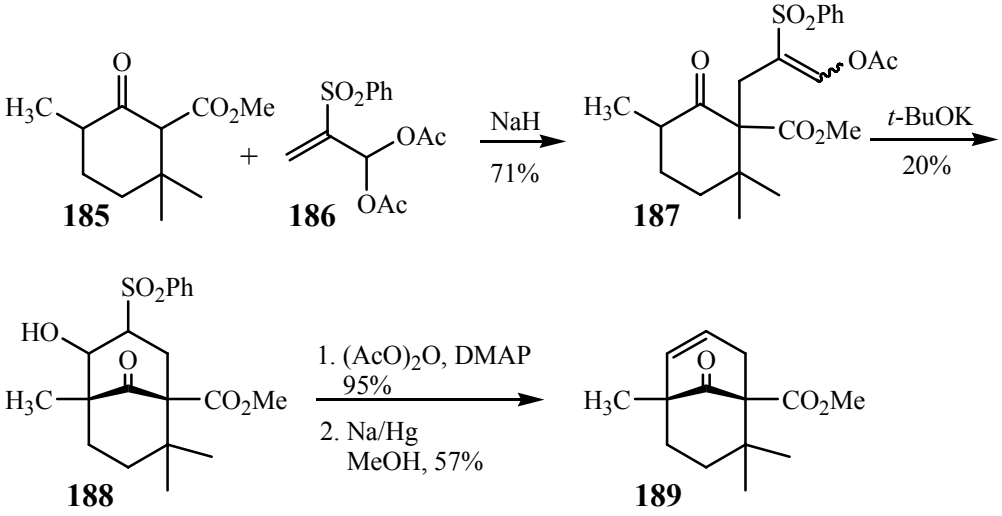

**Figure 2.1: Chiral amine catalyst for asymmetric prenylation of 2-cyclohexenone.**

Shibasaki's synthesis of garsubellin A is an important contribution to the synthesis of PPAPs, but it has some deficiencies. The dihydroxylation of **181** proceeded with no diastereoselectivity. Also, the oxidation of the C(2–4) enone of **183** to the β-alkoxy enone of **176** in the intramolecular Wacker oxidation relied on an internal OH group that attacked the enone–Pd complex in intramolecular fashion. Although this method is perfectly suitable for PPAPs with a tetrahydrofuran ring fused to the C(4,5) bond, such as garsubellin A, it is much less so for PPAPs (such as hyperforin, **1**) that lack this feature.

## 2.7. Kraus's addition–elimination–addition approach

Kraus found that β-keto ester **185** and diacetoxy vinyl sulfone **186** underwent a base-promoted addition–elimination reaction to give **187** (Scheme 2.16).[118] Transesterification of the acetate of **187** to the pivalate was followed by another base-promoted addition reaction to give bicyclic keto ester **188**, and acetylation of **188** followed by treatment with sodium amalgam gave alkene **189**. This method had the virtue of producing quaternary centers at both bridgehead C atoms of **189**, but no reports have been made so far regarding the functionalization of the alkene.

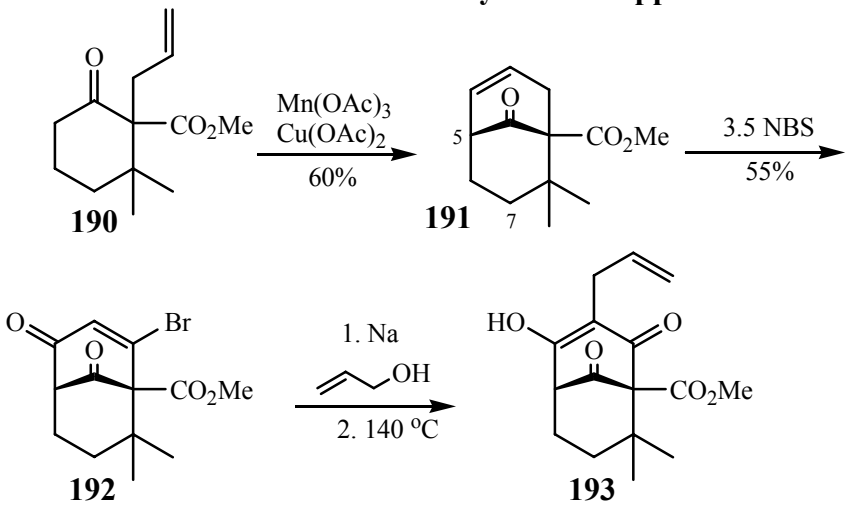
**Scheme 2.16: Kraus's addition–elimination–addition approach to PPAPs.**



## 2.8. Kraus's Mn-mediated oxidative free-radical cyclization approach

In an earlier approach to the synthesis of PPAPs, Kraus utilized a Mn(III)-based oxidative free-radical cyclization of unsaturated β-keto ester **190** to give bicyclic keto ester **191** (Scheme 2.17).[123,124] Treatment of **191** with 3.5 equivalents of NBS followed by hydrolysis afforded β-bromo enone **192** as a single regioisomer. Substitution of the bromide with an allyloxy group followed by a Claisen rearrangement then gave **193**. The main drawback of this approach was the lack of a substituent on C(5) and it was not clear whether the Mn(III)-based oxidative free-radical cyclization would work on the more complex substrates necessary to build the PPAPs' core.

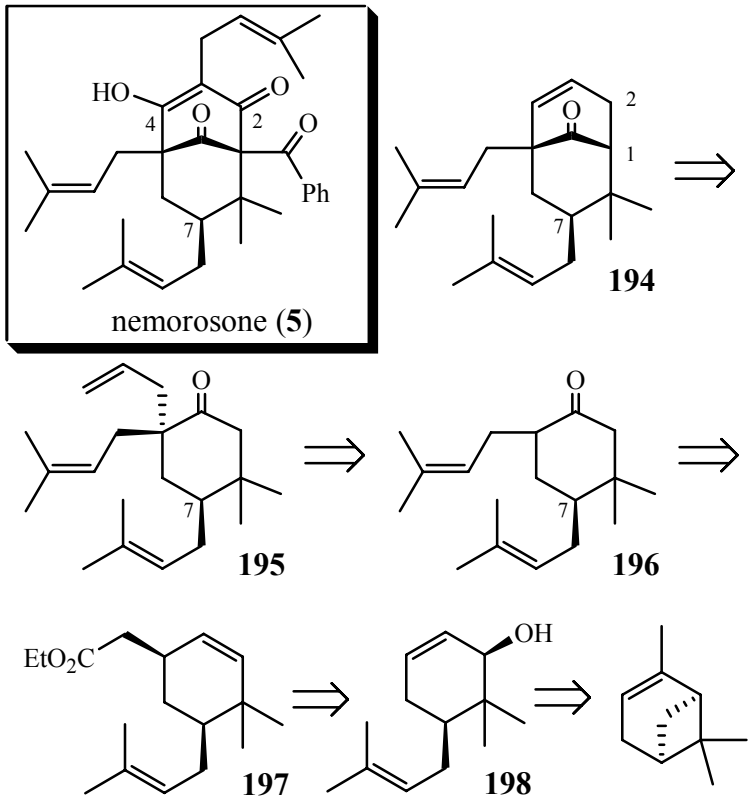
**Scheme 2.17: Kraus's oxidative free-radical cyclization approach to PPAPs.**




## 2.9. Mehta's Pd-mediated oxidative cyclization approach

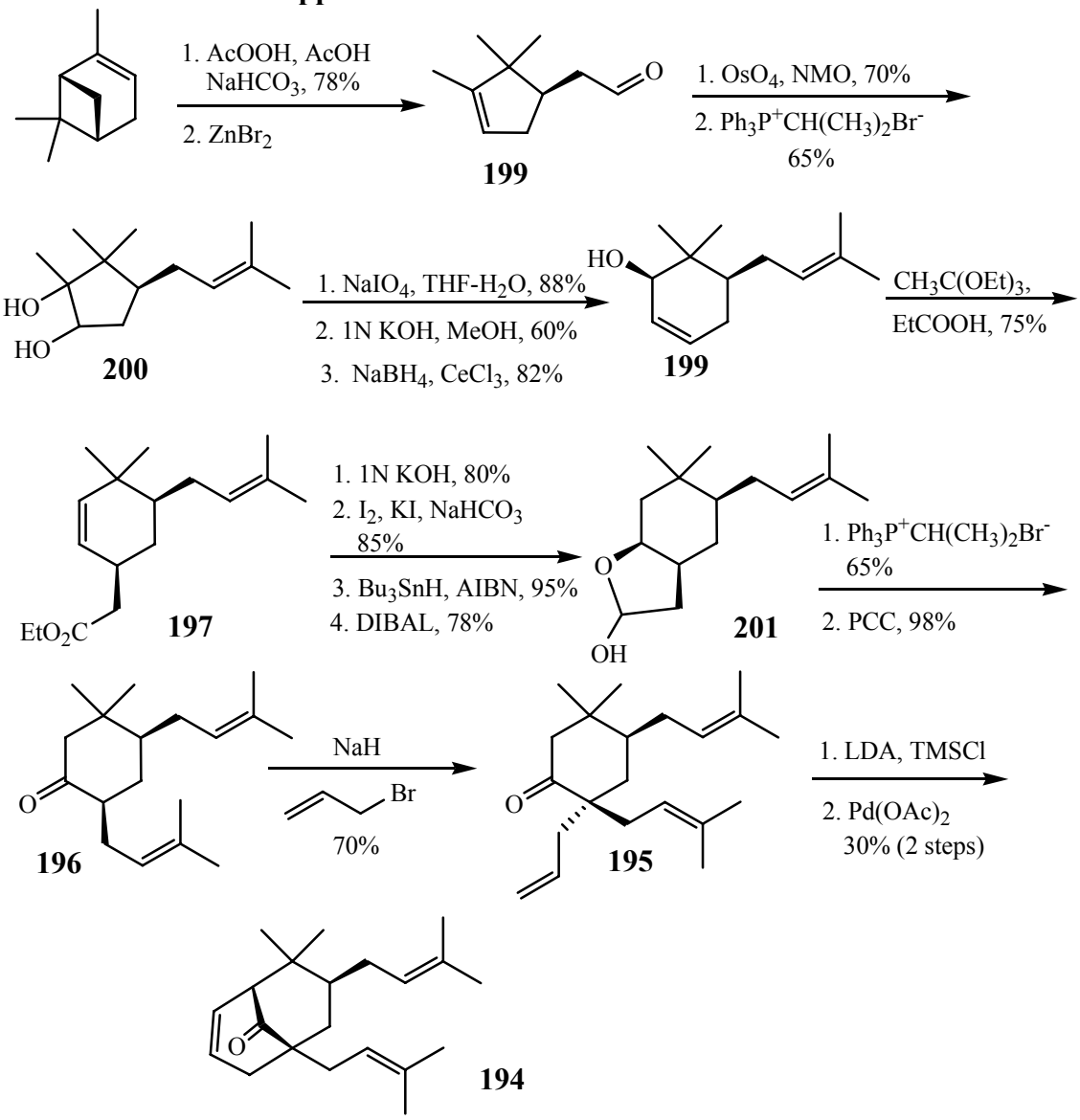
The first enantioselective approach to a PPAP was achieved by Mehta, who used (–)-α-pinene as the starting material in this rather lengthy approach.[125] Compound **194** (Scheme 2.18) was chosen as a model for nemorosone (**5**). As one can see, the model compound **194** lacked a lot of functionality, and no work has been reported so far to prove that the methodology can be applied to a more functionalized system.

**Scheme 2.18: Mehta's retrosynthesis of PPAPs.**




In a strategy similar to that of Kraus, alkene **194** was disconnected at the C(1)–C(2) bond to give the monocyclic, diprenylated 2-acylcyclohexanone **195**. Removal of the α-allyl and -acyl groups from **195** gave the diprenyl cyclohexanone **196**, which would be prepared by elaboration of ester **197**. Ester **197** would be prepared from cyclohexenol **198**, which, in turn, would be prepared from (–)-α-pinene.

**Scheme 2.19 Mehta's approach to PPAPs.**




α-Pinene was stereoselectively epoxidized, and the product fragmented upon addition of $ZnBr_2$ to give campholenic aldehyde **199** (Scheme 2.19).[128,129] $OsO_4$-catalyzed dihydroxylation of **199** and Wittig reaction of the aldehyde group with $Ph_3P{=}CMe_2$ gave the prenylated diol **200**. Oxidative cleavage of **200** with sodium periodate gave a keto aldehyde, which underwent intramolecular aldol cyclization to give an enone. A Luche reduction of the ketone occurred from the face opposite the prenyl group, producing allylic alcohol **198** with high selectivity. Compound **198** then underwent a stereospecific orthoester Claisen rearrangement to provide ester **197**. Hydrolysis of **197**, iodolactonization, and reductive deiodination with $Bu_3SnH$ gave lactone **201**. Reduction of the lactone to the lactol and a second Wittig reaction

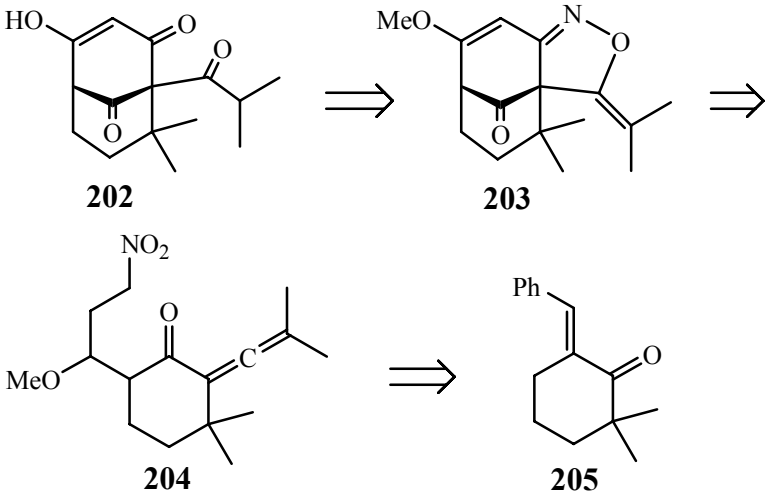
introduced the second prenyl group in moderate yield, and oxidation of the alcohol provided cyclohexanone **196**. The thermodynamic enolate of ketone **196** was formed with NaH, and alkylation with allyl bromide occurred exclusively from the kinetically favored axial direction to give triene **195** stereoselectively. In the key step, ketone **195** was converted to its silyl enol ether, and oxidative cyclization promoted by $Pd(OAc)_2$ gave the bicyclic compound **194** in modest yield.

### 2.10. Young's intramolecular allene–nitrile oxide cycloaddition approach

Young described an ingenious approach to the PPAPs that was completely different from all others to date (Scheme 2.20).[122] His method had the advantage that it was quite short and did not rely on carbonyl condensation reactions to form the key bonds, but it had the drawback of lacking of a substituent at C(5) of the model compound, as in the case of Stoltz's and Mehta's approaches.

Young proposed that the nonenolizable β,β′-triketone group of model compound **202** be derived from alkylidene isoxazole **203**. The latter could in turn be prepared from **204** by an intramolecular nitrile oxide–allene cycloaddition. The allenic ketone **204** would be prepared from alkylidene cyclohexanone **205**.

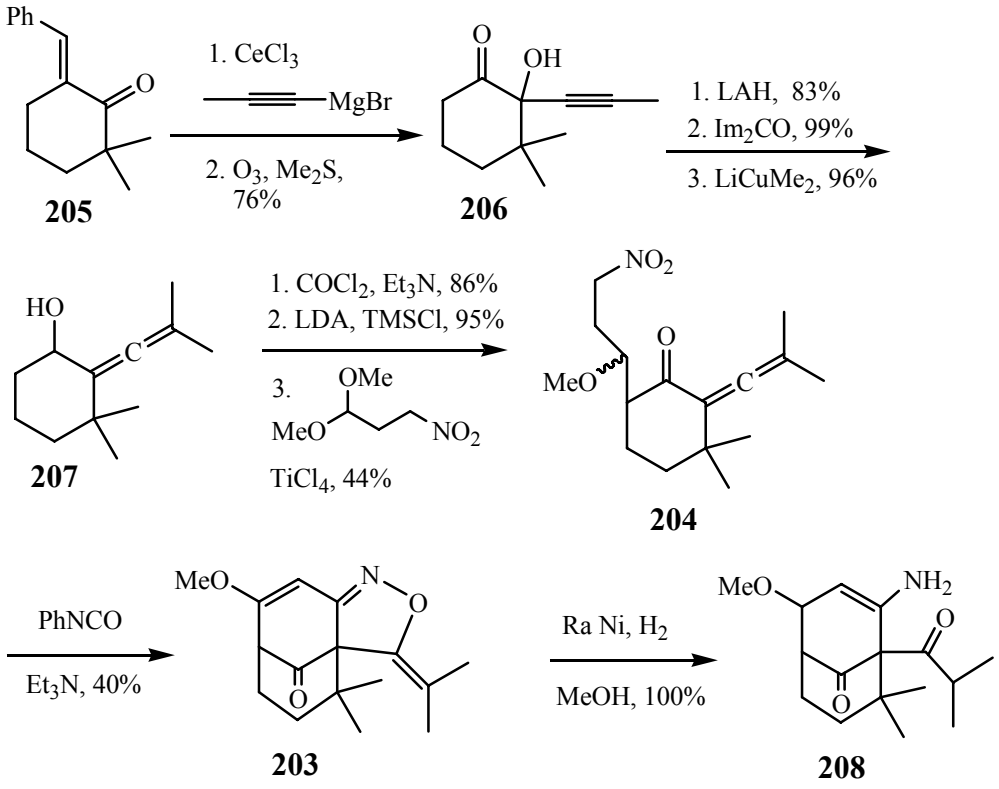
**Scheme 2.20: Young's retrosynthesis of PPAPs.**




Addition of propynylmagnesium bromide to **205** and ozonolysis of the double bond gave α-hydroxyketone **206** (Scheme 2.21). Reduction of **206** with $LiAlH_4$ gave a 1,2-diol (as a mixture of diastereomers), which was further converted to the carbonate after treatment with carbonyl diimidazole. Conjugate addition of dimethyl cuprate to this propargyl carbonate then provided allenic alcohol **207**. The alcohol **207** was oxidized to the ketone and converted to the silyl enol ether, and a $TiCl_4$-promoted aldol condensation

between this compound and the dimethyl acetal of 3-nitropropanal afforded nitro compound **204** as a mixture of diastereomers. The key step of the synthesis, the intramolecular nitrile oxide–allene cycloaddition, occurred after addition of phenyl isocyanate and $Et_3N$ to **204** to give bicyclic adduct **203** in 40% yield and as a single diastereomer. Reductive cleavage of the isoxazoline ring with methanolic Raney nickel afforded primary enamine **208**, which has most of the features of the PPAPs.

**Scheme 2.21: Young's approach to PPAPs.**




## 2.11. Grossman's alkynylation–aldol approach

Our synthetic approach to the bicycle[3.3.1]nonane skeleton involves a novel three-carbon α,α′-annulation of a sterically hindered cyclic *β*-keto ester with 3,3-diethoxypropyne. More details of this approach are presented in the next chapter.

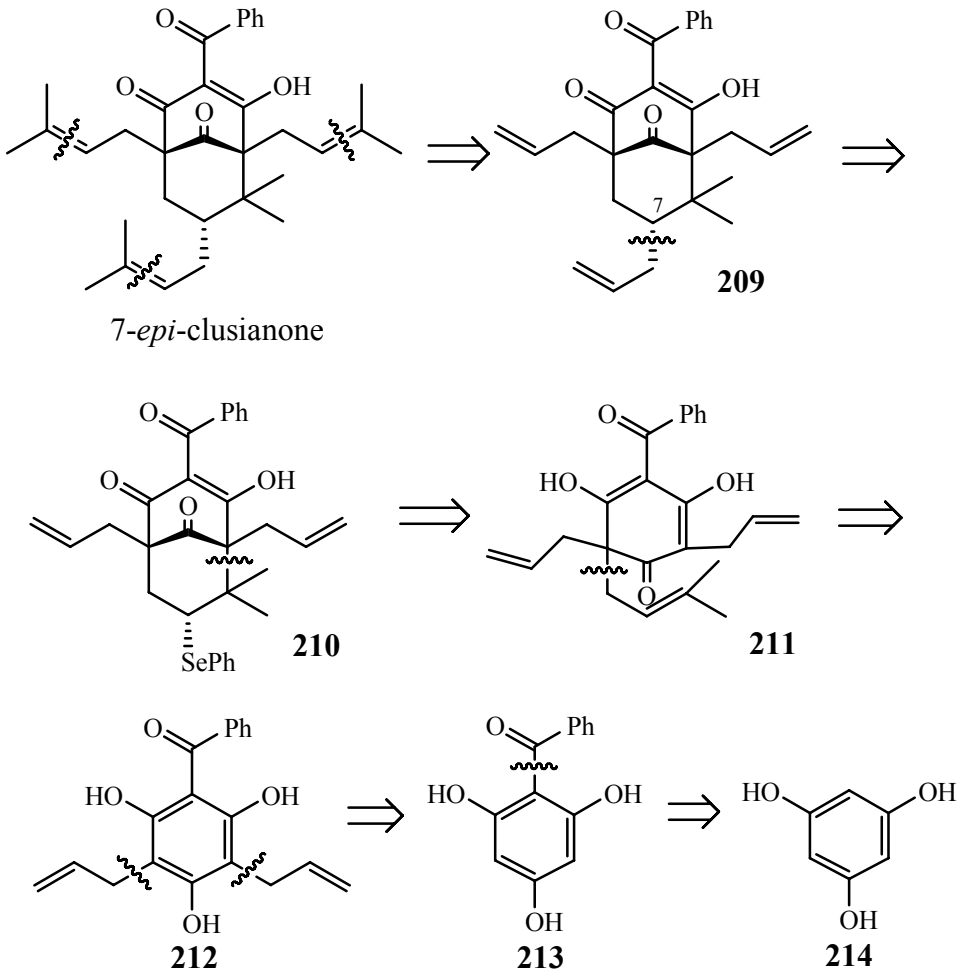
# Chapter 3. Our approach to PPAPs

## 3.1. Attempted biomimetic route to type B PPAPs

We started this project by exploring a biomimetic route to 7-*epi*-clusianone, a type B PPAP. The retrosynthesis is described in Scheme 3.1, and it starts with the masking of the prenyl groups with allyl groups; we plan to introduce the prenyl groups through a Ru-catalyzed cross-metathesis of **209** with 2-methyl-2-butene.[117,123,124]. The allyl group on C(7) is introduced by a free-radical allylation of selenium derivative **210** which, in turn, is formed through a Se-promoted cyclization of **211**.[120,121] The prenyl group of **211** is introduced by adding prenyl bromide in liquid ammonia to **212**. The precursor for **212** is benzoylphloroglucinol **213** which is readily available from phloroglucinol **214**.

Unfortunately, poor yields have thwarted this route. Moreover, while working on this approach, we have obtained good results with the non-biomimetic route, and we continued with pursuing the synthesis of type A PPAPs (see next section).

**Scheme 3.1: Retrosynthetic analysis for 7-*epi*-clusianone.**

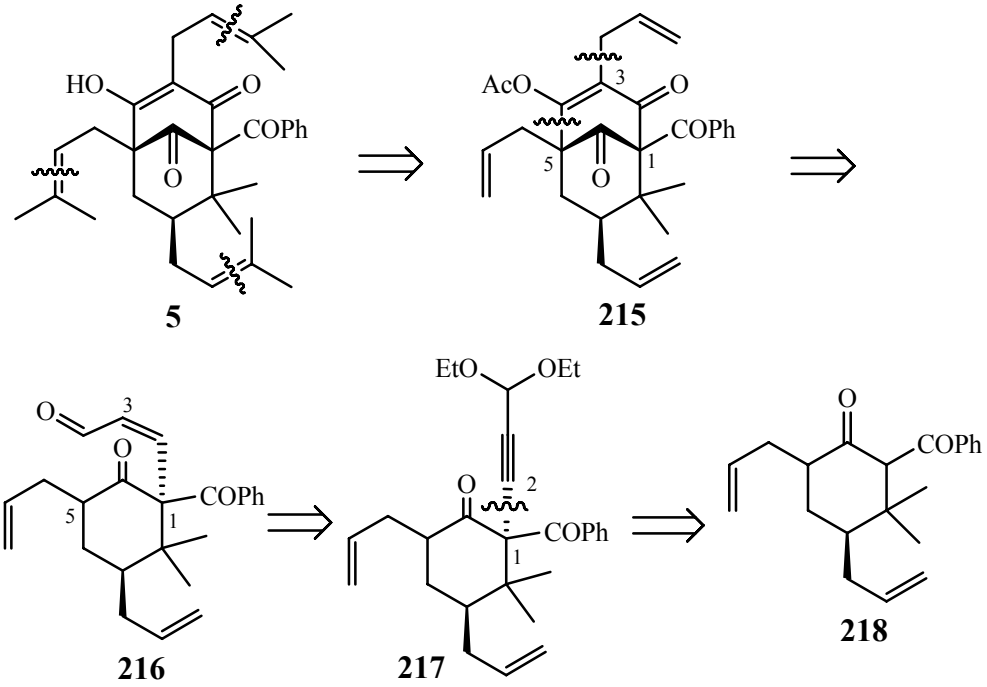



### 3.2. Retrosynthetic analysis for nemorosone

We focused our attention on nemorosone (**5**)[126] because it has a fairly simple structure relative to other A PPAPs and it also shows antibacterial, antioxidant and cytotoxic activity. The retrosynthetic analysis (Scheme 3.2) started with masking the sensitive prenyl groups as more robust allyl groups until the end of the synthesis, when they could be installed by Ru-catalyzed cross-metathesis of **215** with 2-methyl-2-butene.[117,123,124] The allyl group on C(3) would be installed by alkylation of the β-diketone group, whereas the C(4)−C(5) bond would be formed through an intramolecular aldol reaction of **216**. The key step of the retroanalysis was the construction of the C(1)−C(2) bond which would lead to formation of a product possessing two adjacent quaternary C atoms. Previous work in Dr. Grossman' lab regarding the synthesis of sterically congested compounds by the use of CN groups[130] led us to speculate that a 1-alkynyl group could be added to C(1) of **218** without much steric impedance from the

adjacent *gem*-dimethyl group. In fact, the Hashimoto and Moloney groups developed $Pb(OAc)_4$-mediated alkynylations of β-keto esters in the late 1980s[131,132] although they did not investigate substrates as hindered as **218**. Having known this, we decided that the next disconnection to be C(1)−C(2) in **217**, bond that would be constructed by alkynylation of **218** with commercially available 3,3-diethoxypropyne.

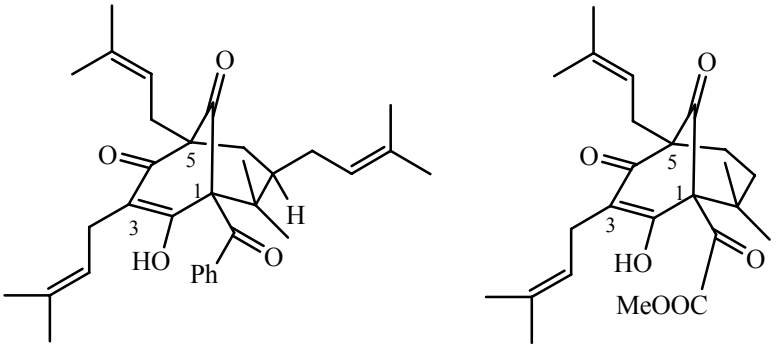
**Scheme 3.2: Retrosynthetic analysis for nemorosone.**




**5** **215** **216** **217** **218**

### 3.3. Building the substrate for alkynylation

Our investigation started with a model study. The model compound is depicted in Figure 3.1. As one can see, its structure is very similar with that of nemorosone; only the prenyl group on C(7) is missing.

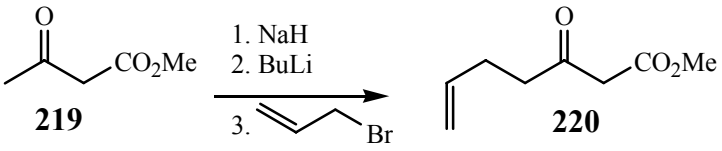



nemorosone model compound

**Figure 3.1: Nemorosone and model compound structures**

Our forward synthesis started with addition of allyl bromide to the commercially available methyl acetoacetate **219** (Scheme 3.3). Allylated ester **220** was easily made on a large scale in 81% yield, after the dianion of **220** was formed by adding NaH and BuLi in this order.

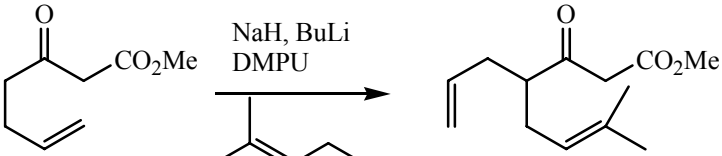
**Scheme 3.3: Addition of allyl bromide to 219.**




**219** **220**

Addition of prenyl bromide (Scheme 3.4) to the dianion of methyl 3-oxo-6-heptenoate **220** gave diene **221** in low yield (23-35%). However, when DMPU (*N*,*N*′-dimethylpropyleneurea) was added, a better yield was obtained (67%).

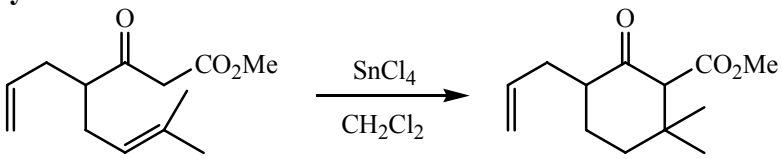
**Scheme 3.4: Addition of prenyl bromide to the dianion of 3-oxo-6-heptenoate 220.**




**220** **221**

Cyclization of **221** proceeded through an intramolecular cationic reaction. Addition of 1.5 equivalents of $SnCl_4$[133,134] to **221** in dichloromethane provided **222** in 84% yield (Scheme 3.5). Thus, the required *gem*-dimethyl group was introduced in the first ring of the bicyclo[3.3.1]nonane core.

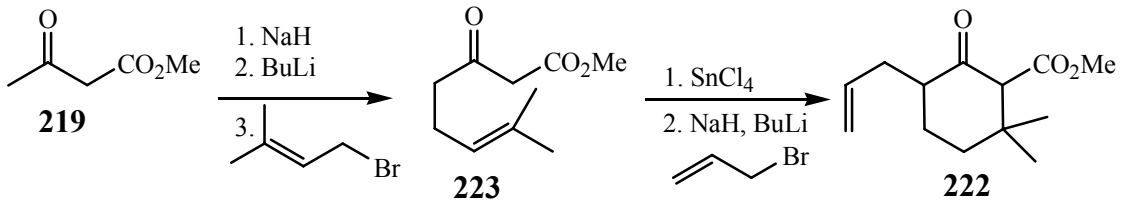
**Scheme 3.5: Cyclization of 221.**




**221** **222**

Another attempted route to compound **222** was the introduction of the prenyl group first, cyclization to compound **223**, and only at the last step addition of an allyl group to C(5) (Scheme 3.6). This route, though, did not provide a very good yield (31% over three steps).

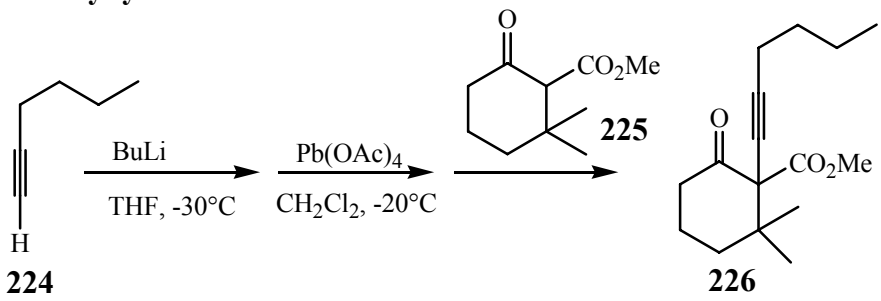
**Scheme 3.6: Another route to 222.**



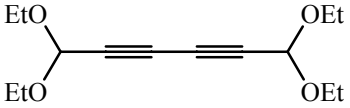

### 3.4. Alkynylation reaction

The next step was a very challenging one because we had to form a quaternary center adjacent to the *gem*-dimethyl group. We tried first Hashimoto's procedure[131] using 1-hexyne **224** and β-ketoester **225** (Scheme 3.7). Alkyne-ester derivative **226** was formed in 53% yield.

**Scheme 3.7: Alkynylation of 225.**




We were pleased with the result, and we next applied this procedure to 3,3-diethoxypropyne (**228**) and substrate **222**, but the desired alkynyl derivative of **222** was obtained in only 7% yield. The only significant products were the starting material (31%) and a 1,3-diyne compound (**227**, 13%) (Figure 3.2).

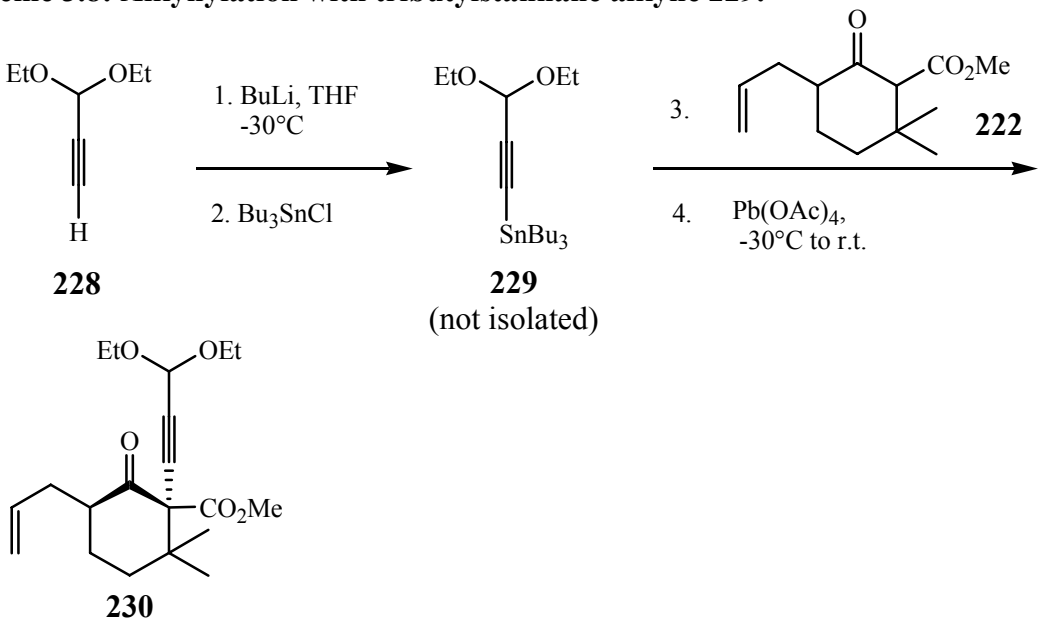



**227**

**Figure 3.2: The 1,3-diyne by-product**

However, when the tributylstannyl alkyne **229**[132] was used in the reaction, and the order of addition of **222** and lead tetracetate was reversed, the alkyne derivative **230** was obtained in 53% yield (Scheme 3.8). The stereochemistry of **230** is assigned as shown because H(5) is deshielded from H(5) in **222** due to the close proximity of the triple bond; the H(5) and alkynyl group are coaxial.

**Scheme 3.8: Alkynylation with tributylstannane alkyne 229.**



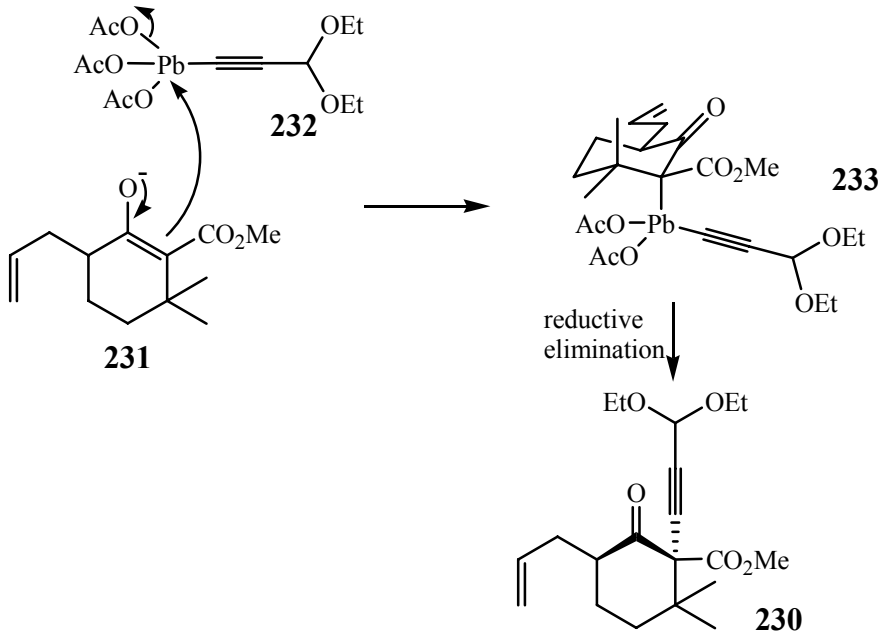

**228** **229** (not isolated) **222**




**230**

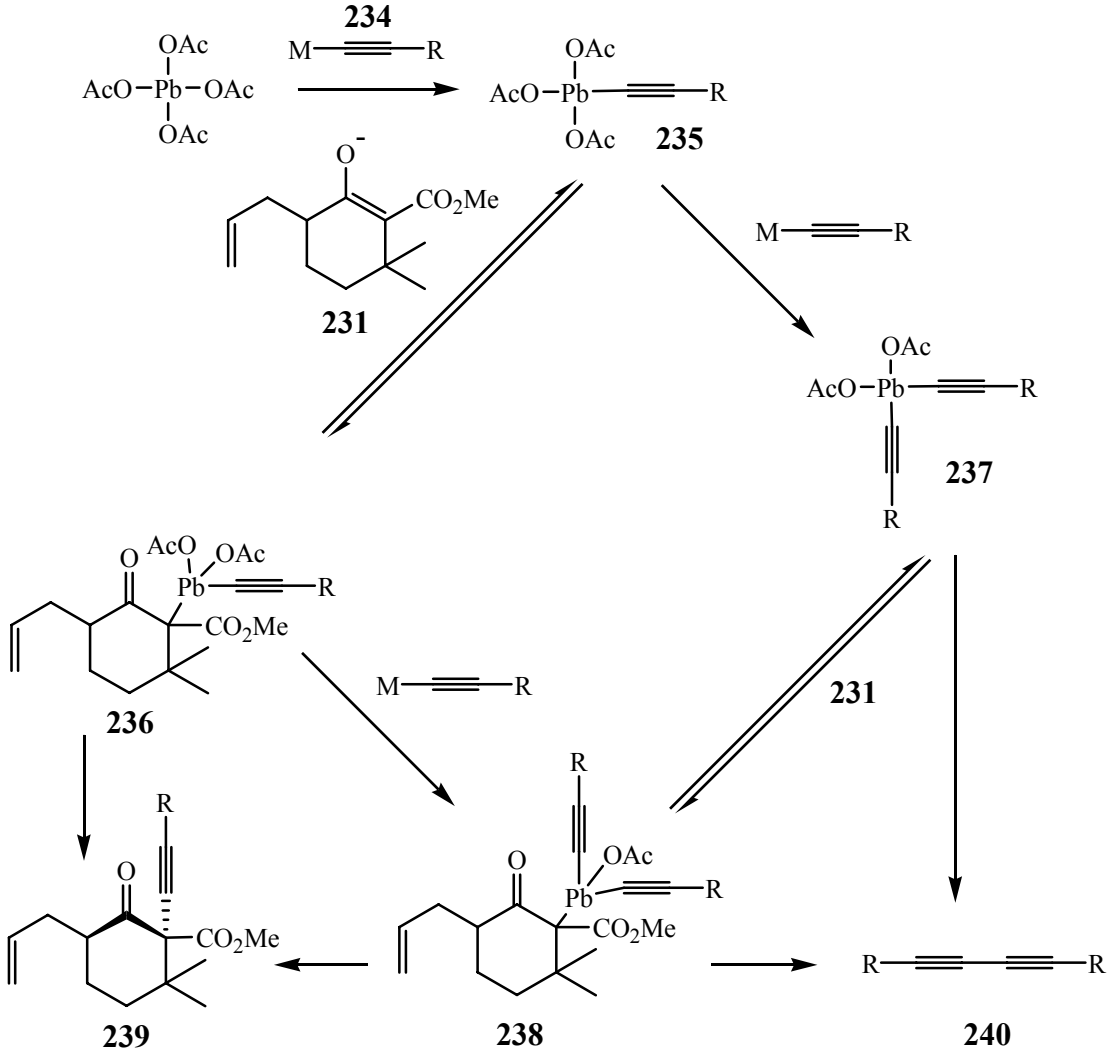
The proposed mechanism of this reaction is outlined in Scheme 3.9. The negative carbon of the enolate **231** attacks the alkynyllead intermediate **232**, formed from tributylstannyl alkyne **229** and $Pb(OAc)_4$, and a new lead derivative **233** is formed in which the lead is in the axial position. Compound **233** undergoes a reductive elimination with formation of the desired alkyne **230**. Konopelski[135] has shown that various substituted methyl 2-oxo-1-cyclohexanecarboxylates undergo the lead-mediated α-arylation reaction with formation of a 2-(alkynyllead)cyclohexanone as the intermediate, which further goes through a reductive elimination to the product with the aryl group in axial position.

**Scheme 3.9: The proposed mechanism for alkynylation reaction of enolate 231.**




We mentioned earlier that formation of the desired alkyne product *vs* the 1,3-diyne by-product depends on the nature of the alkynylmetal intermediate. We explain this behavior as follows: the alkynyllithium derivative (**234**, M = Li) is more reactive than its Sn homologue (**234**, M = Sn), so the formation of **238** and the conversions of **235** to **236**, **236** to **238**, and **237** to **240** proceed faster and the formation of **240** is favored (Scheme 3.10). When a tributylstannyl alkyne is present, all the above-mentioned steps are slower relative to the **236→239** transformation, so the desired alkyne product is formed.

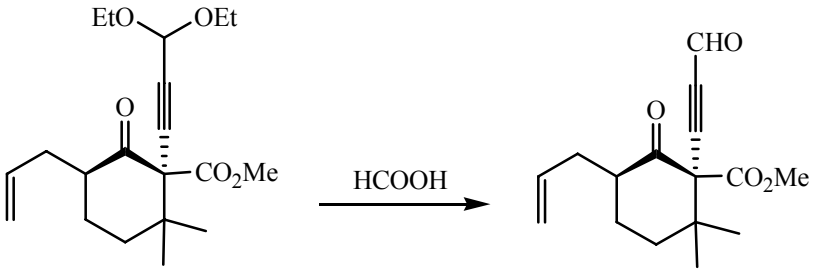
**Scheme 3.10: Formation of the alkyne product *vs* the 1,3-diyne by-product.**




### 3.5. Formation of the bicyclo[3.3.1]nonane skeleton

At this point, the syn reduction of the triple C≡C bond to a cis double bond would give the right stereochemistry necessary for the planned aldol reaction. Although hydrogenation of model compound **226** with Lindlar catalyst at 3 atm worked beautifully, the *cis*-adduct being formed in 87% yield, when we tried hydrogenation of **230**, the reduction of the allylic double bond occured faster than the alkyne triple bond. We believed that this behaviour was due to a combination of steric and electronic effects. The acetal group hindered the triple bond so the reagents could not reach it well. The acetal group is also an electron withdrawing group and makes the triple bond less reactive. Subsequently, we have converted acetal **230** to aldehyde **241** (Scheme 3.11) in neat $HCO_2H$ in 71% yield.

**Scheme 3.11: Conversion of acetal 230 to aldehyde 241.**




**230** **241**

Unfortunately, all attempts at the catalytic hydrogenation of **241** failed, even at very high pressures (ca. 1000 psi). We have tried numerous conditions for this reaction, changing the reagent, the solvent, and the pressure, but starting material alone, starting material together with hydrogenated C=C bond, trans product, or even hydrogenated carbonyl were obtained (Table 3.1).

**Table 3.1: Attempts for hydrogenation of 241**

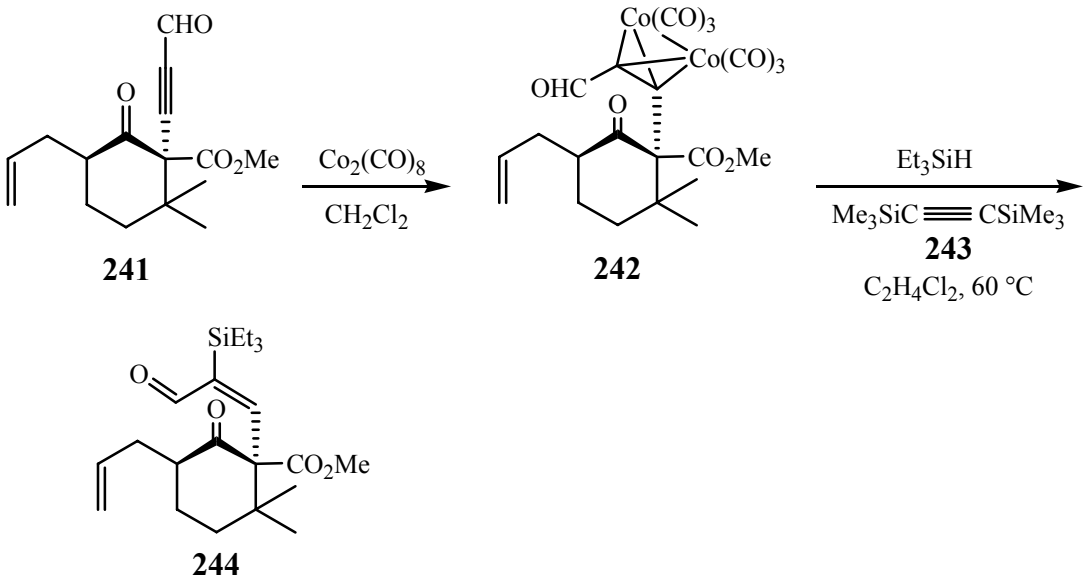
| No. | reagent | catalyst | solvent | product |
|---|---|---|---|---|
| 1 | $H_2$ | Lindlar | MeOH, r.t., 1 atm | **241** |
| 2 | $H_2$ | Lindlar | EtOAc, quinoline | **241** and/or *cis* C=C and saturated C≡C bond |
| 3 | $H_2$ | Lindlar | MeOH or THF | |
| 4 | HCOOH | Pd/C | $Et_3N$ | Hydrogenated carbonyl group (aldehyde) |
| 5 | $H_2$ | $Pd/CaCO_3$ | pyridine | *trans* product |

Alternatives to the syn hydrogenation of the C≡C triple bond were sought after many attempts to perform catalytic hydrogenation of **230** using various conditions. A literature survey revealed very few alternatives to Lindlar-type hydrogenation for the syn reduction of alkynes in the presence of unhindered alkene and carbonyl groups. Only one precedent stood out: an alkyne was syn hydrosilylated with $Et_3SiH$ via its $Co_2(CO)_6$ complex, and terminal alkenes in the substrate were unaffected.[136,137]

We obtained the $Co_2(CO)_6$ complex of **241** in 87% yield, despite the steric encumbrance around the C≡C bond in **241**. A $^1H$ NMR spectrum could not be recorded for the cobalt complex **242** probably because of the presence of some paramagnetic Co by-products. Treatment of the complex **242** with excess $Et_3SiH$ in the presence of

$Me_3SiC{\equiv}CSiMe_3$ gave the (*E*)-α-silyl enal **243** in 94% yield with complete regio- and stereoselectivity (Scheme 3.12). The triple bond from bis(trimethylsilyl)acetylene formed a red cobalt complex similar to that from **242;** in the absence of this coreagent, the reaction was very messy, and the desired product **244** could not be purified.

**Scheme 3.12: Syn reduction of alkyne 241.**




**241** **242** **243** **244**

Once the right stereochemistry of the silyl enone was set, we were able to proceed to the aldol reaction. Treatment of **244** with aqueous HCl gave two diastereomers, **245a** and **245b** (ca. 1:1 crude dr), in 72% combined yield (Scheme 3.13). The faster moving, crystalline diastereomer was initially proposed to be **245a** because its $^1$H NMR spectrum showed long-range allylic coupling between H(2) and H(4), whereas that of the slower, liquid diastereomer did not. A NOESY spectrum of the latter compound showed a cross-peak between a resonance attributed to H(4) and one attributed to H(6) or H(7), confirming it as **245b** (Figure 3.3). The C(4)−H(4) single bond was partially overlapping with the π system of the C(2)=C(3) double bond, hence the long-range allylic coupling between H(2) and H(4). The assignment of the former compound as **245a** was later confirmed by X-ray crystallographic analysis (Figure 3.4).

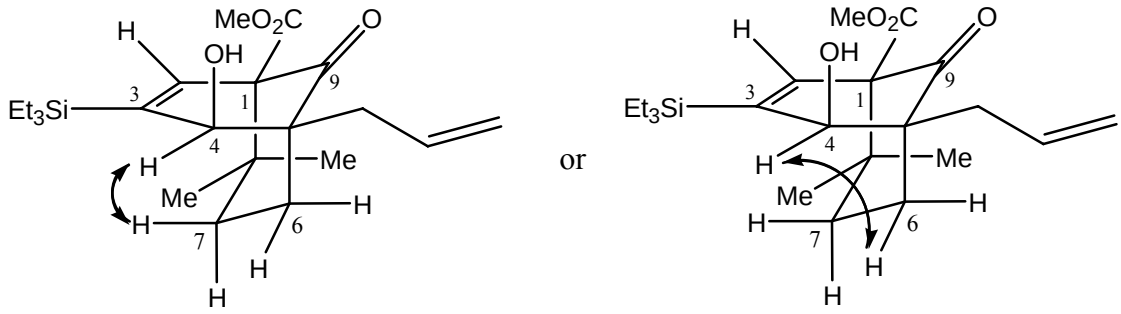
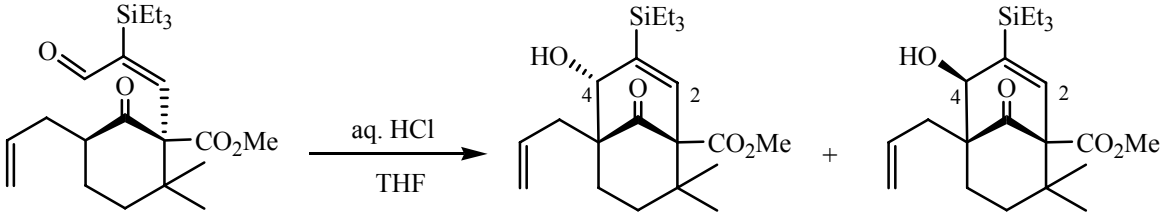



**Figure 3.3: NOE's of 4-exo-245 (245b)**

**Scheme 3.13: Formation of the endo and exo aldol adducts.**




**244** **245a** (endo OH) **245b** (exo OH)

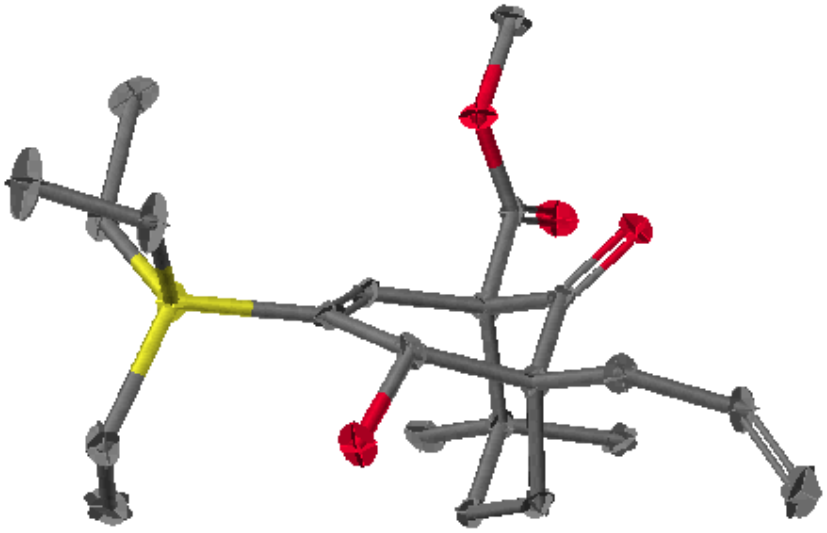
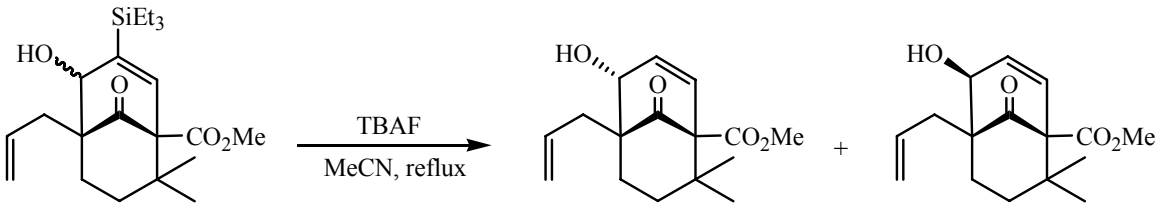


**Figure 3.4: X-ray crystal structure of 4-endo-245 (245a)**

Desilylation of **245**, in the presence of TBAF[138,139] led to formation of allylic alcohols **246a** and **246b** in 78% yield (Scheme 3.14). Although the reaction starts with a 1:1 dr of **245**, the outcome of the desilylation is a 4:1 dr (**246a**:**246b**) due to epimerization. It seems that fluoride anion acts both as a desilylating reagent and a base.

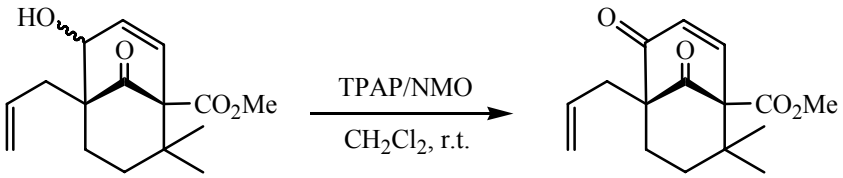
**Scheme 3.14: Desilylation of aldol adduct 245.**




**245** **246a** (endo OH) **246b** (exo OH)

Although the **246a,b** mixture is separable by flash chromatography, we used it as a mixture for the following reaction. The oxidation with TPAP/NMO[140] led to enone **247** in 85% yield (Scheme 3.15).

**Scheme 3.15: Oxidation of allylic alcohol 246 to enone 247.**



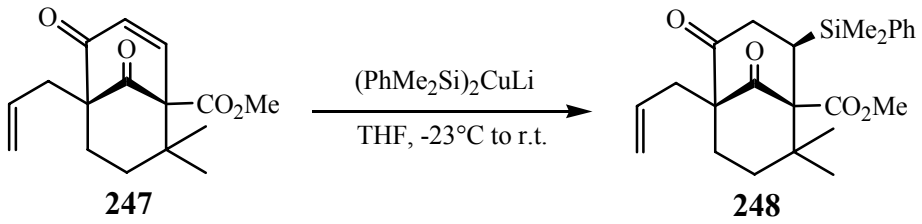

**246a,b** **247**

### 3.6. Attempts to form the 2,4,9-triketone system

The next step would be oxidizing C(2) of **247** to form the 2,4,9-triketone system present in PPAPs. We have tried a series of reactions but, unfortunately, all our approaches have so far been unfruitful.

Our original intention had been to introduce a silyl group through a conjugate addition reaction and to convert the C(2)-Si bond into a C(2)-O bond later. To this end, we treated **247** with $(PhMe_2Si)_2CuLi$ in THF (Scheme 3.16), and diketone **248** was obtained in 80% yield. $(PhMe_2Si)_2CuLi$ was formed *in situ* from $PhMe_2SiLi$ and CuI.[141] The assignment of C(2) stereochemistry in **248** was confirmed by X-ray crystallographic analysis (Figure 3.5).

**Scheme 3.16. Silylation of 247.**




**247** **248**

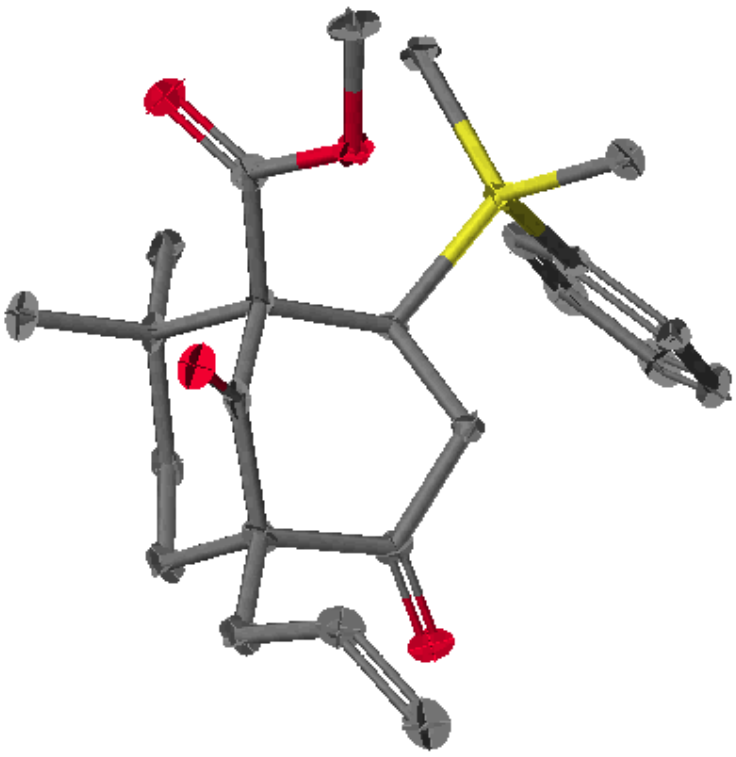
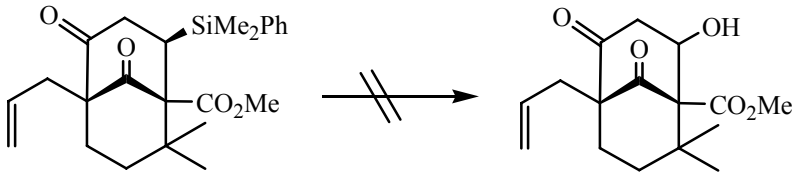


**Figure 3.5: X-ray crystal structure of 248**

**Scheme 3.17: Conversion of C(2)-Si bond into C(2)-O bond.**

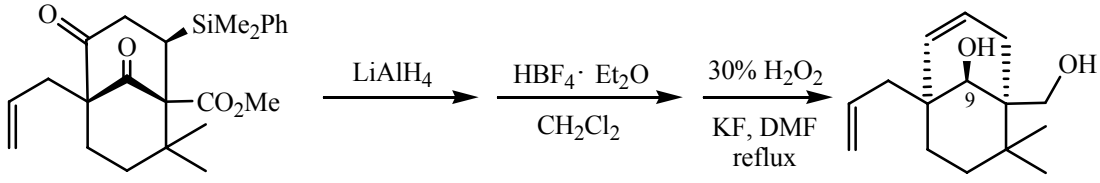



**248** **249**

Unfortunately, conversion of the C(2)−Si bond into a C(2)−O bond proved to be a formidable task. Although there are many precedents in the literature for this conversion, none worked for our substrate (Scheme 3.17). When we treated **248** with $HBF_4{\cdot}Et_2O$ in $CH_2Cl_2$ followed by *m*-CPBA and KF,[141] or KF, $H_2O_2$ in DMF,[142] or $BF_3{\cdot}2CH_3COOH$ in $CH_2Cl_2$ followed by *m*-CPBA and $NEt_3$,[143] only a very messy mixture was obtained. When **248** was treated with $CF_3COOH$ followed by KF, $KHCO_3$ and $H_2O_2$[144], the allyl and ester group were affected.

We think that the β-keto ester system affects the reactivity of the C(2)-Si bond. In order to prevent this adverse interference, we thought that by reducing the carbonyl groups of **248**, the reactivity of C(2)-Si bond will resemble more the ones that are in the literature. Thus, after reduction of **248** with $LiAlH_4$, we treated the triol thus formed with $HBF_4{\cdot}Et_2O$ in $CH_2Cl_2$ followed KF, $H_2O_2$ in DMF under reflux. Unfortunately, dehydrosilylation occurred, leading to formation of **250** (Scheme 3.18). The configuration at C(9) on **250** was assumed but not proven.

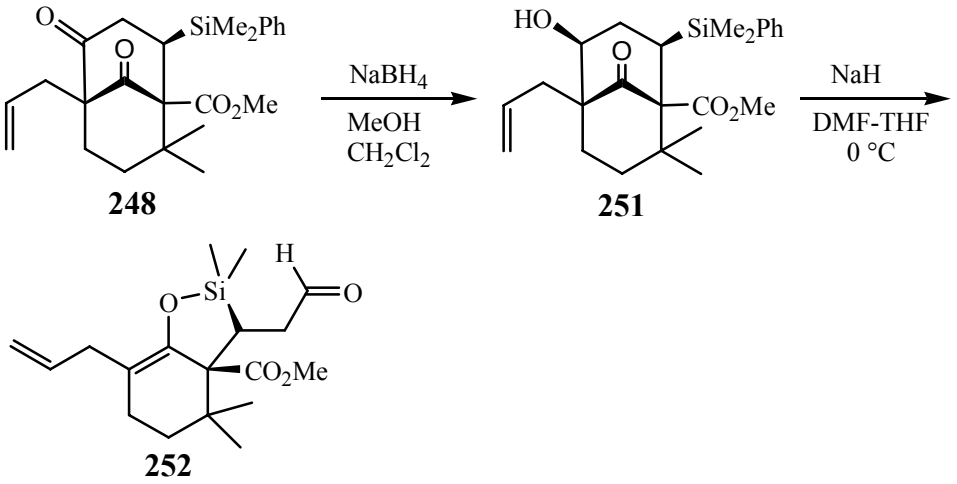
**Scheme 3.18: Dehydrosilylation of 248.**




**248** **250**

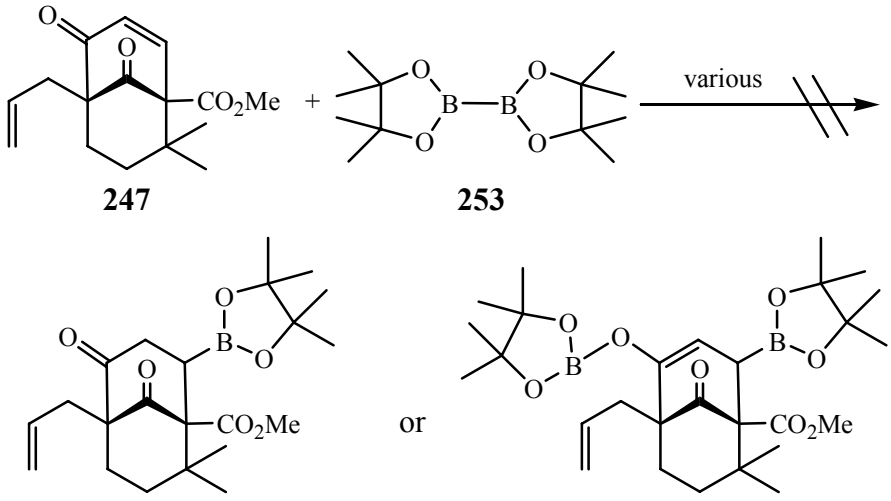
We also attempted reduction of C(4) with $NaBH_4$ in MeOH and $CH_2Cl_2$ to afford alcohol **251** followed by treatment with NaH in DMF and THF[145] but a retro-aldol reaction occurred instead (Scheme 3.19). $^1H$ and $^{13}C$ NMR spectra of **252** indicated the presence of the H from the aldehyde group as well as the absence of the phenyl group. We hoped that the nucleophilic $O^-$ atom, formed after deprotonation of OH group with NaH, would attack the Si, forming a five-membered ring which could be opened by a Tamao-Fleming oxidation reaction.

**Scheme 3.19: Retro-aldol reaction.**




We then, turned our attention to other groups that might be converted into a hydroxyl group. Our first choice was a S-based group. However, when PhSH[146] in the presence of $NEt_3$ was added to enone **247**, starting material was recovered. Even in the presence of the Lewis acid $InBr_3$,[147] the outcome of the reaction was the same. We have also tried boration of the α,β-enone with bis(pinacolato)diboron **253**. None of the conditions used (LiCl/CuCl[148] or $Bu_3P$/CuCl[149] in DMF at room temperature, $Pt(PPh_3)_4$ in toluene under reflux[150]) led us to the desired boron adduct (Scheme 3.20).

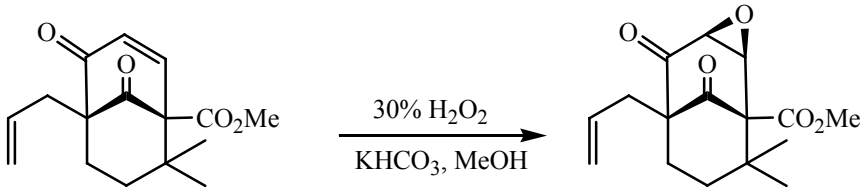
**Scheme 3.20: Attempted diboration.**




Another approach involved conversion of the double bond of the enone into an epoxide followed by epoxide opening. Treatment of enone **247** with 30% $H_2O_2$ in the presence of $KHCO_3$ in MeOH occurred to give the epoxide **254** in 64% yield (Scheme 3.21). This advanced intermediate clearly possessed all the oxygenated carbons found in

the phloroglucinol moiety of nemorosone. Therefore, our next task included two last steps: opening of the epoxide and oxidation of the hydroxyl group to the ketone.

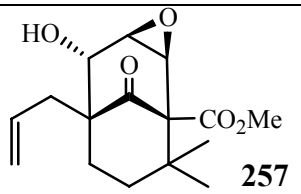
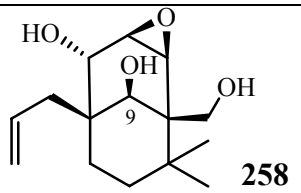
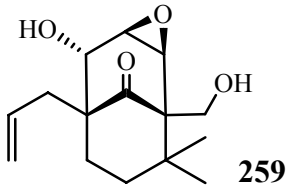
**Scheme 3.21: Epoxide formation.**



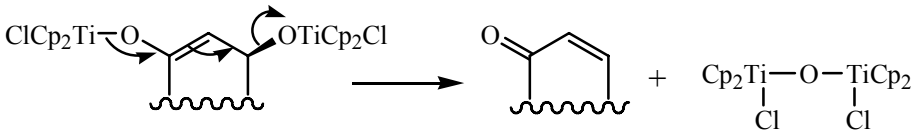

**247** **254**

Although there are many examples in the literature in which an epoxide ring is opene selectively to form a β-hydroxy ketone, unfortunately for us, nothing that we have tried has worked so far (table 3.2). Both the organoselenium-mediated[151,152] and the Zn-mediated[153] reductions converted the epoxide **254** back to enone **247**. Treatment of the epoxide with a titanocene (III) reagent,[154] $Cp_2TiCl_2$ and Zn in THF in MeOH, resulted in formation of enone and $Cp_2Ti(Cl)-O-Ti(Cl)Cp_2$; some starting material was also recovered. We believe that the enone is formed from intermediate **255** (Scheme 3.22), which, instead of reacting with MeOH to become the β-hydroxy ketone, ejects $^-OTiCp_2Cl$; this compound combines with $TiCp_2Cl$ to give the titanium-byproduct **256**. Enone **247** was also formed when we treated epoxide **254** with catalytic amounts of tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane. [155] The literature reports that a β-diketone is formed in moderate to very good yields under these conditions, but all substrates had the epoxyketone present as the only functional group; on the other hand, there are many other functional groups in our substrate which could affect its reactivity.

**Table 3.2: Attempts for epoxide ring opening**

| No | Reagent | Conditions | Reaction outcome |
|---|---|---|---|
| 1 | $NaBH_4$, $(PhSe)_2$ | EtOH, 0 ºC→r.t. | enone |
| 2 | Zn, AcOH | MeOH, reflux | enone |
| 3 | $Cp_2TiCl_2$, Zn | THF, MeOH | enone, SM, $Cp_2Ti(Cl)-O-Ti(Cl)Cp_2$ |
| 4 | $Pd(PPh_3)_4$, dpe | toluene, reflux | enone, SM |
| 5 | Al(Hg) | THF, $H_2O$, EtOH, $NaHCO_3$ | messy |
| 6 | $Me_2CuLi$ | THF or $Et_2O$ | messy |
| 7 | $SmI_2$ | THF, -78 ºC | SM |
| 8 | NaTeH | EtOH, 0 ºC |  **257** |
| 9 | $LiAlH_4$ | THF, reflux |  **258**  **259** |

**Scheme 3.22: Tetanocene-mediated reaction.**



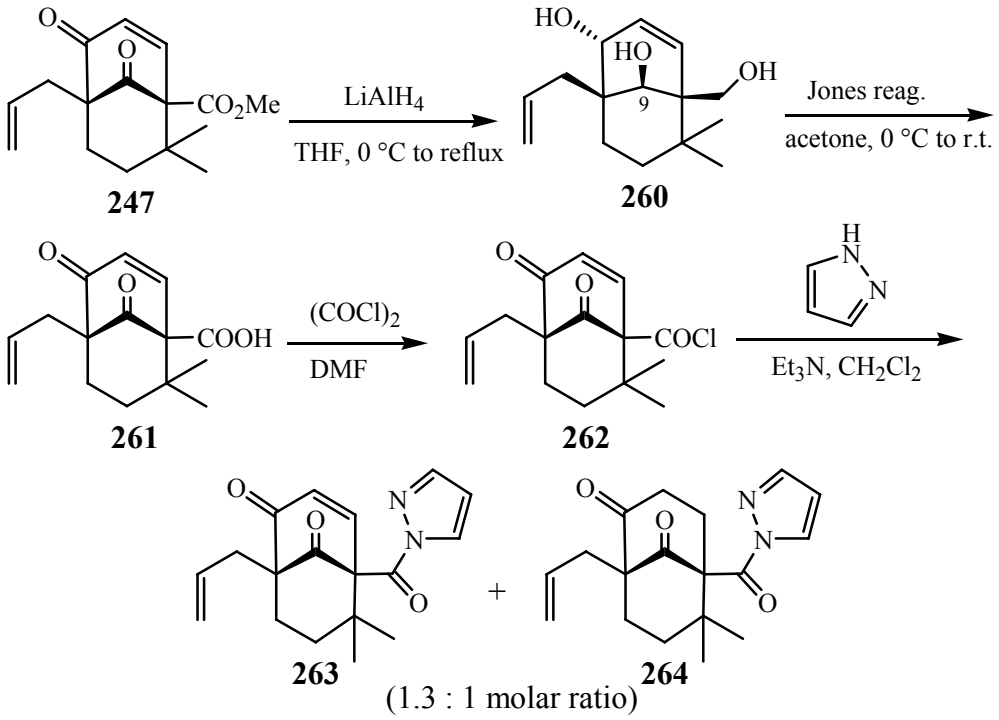

**255** **247**

The same epoxide **254** was found to be resistant toward opening with other reducing reagents. Reactions with both aluminum amalgam generated *in situ*[156-158] and $Me_2CuLi$[159] resulted in messy mixtures, and treatment with $SmI_2$[160] had no effect on the epoxide.

Hydrides are another class of reagents known for opening epoxides. However, our substrates proved to be resistant to them, and only ketone reduction occurred. For example, NaTeH[161] reduced the ketoepoxide to the hydroxyepoxide **257**, and $LiAlH_4$ in THF under reflux reduced the β-keto ester system with formation of the triol **258** (37% yield) and diol **259** (51% yield). The configuration at C(9) on **258** was assumed but not proven.

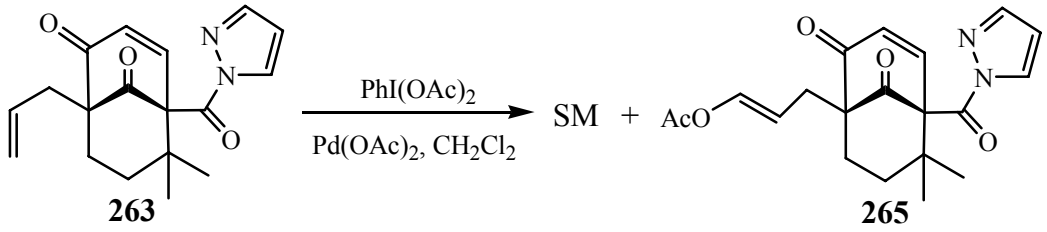
As discussed so far, all the attempts to form C(2)−O bond (without a C(3) bond) failed no matter what approach we tried. The studies on the development of palladium-catalyzed methods for the oxidative functionalization of $sp^2$-hybridized carbon[162-164] captured our attention. We planned to introduce the oxygen atom intramolecularly by activation of the C(2)-H bond of the enone. In order to do this, we first treated the ester **247** with $LiAlH_4$ to give triol **260** (Scheme 3.23). The configuration at C(9) on **260** was assumed but not proven. The crude mixture of triol **260** was further oxidized to acid **261** using Jones' reagent. Acid **261** was converted in the next step to acyl chloride **262** which upon treatment with pyrazole resulted in the desired acyl pyrazole derivative **263** together with some saturated diketone **264** (1.3:1 molar ratio in 50% yield after four steps. Compound **264** was obtained probably because part of enone **247** underwent conjugate reduction when it was treated with $LiAlH_4$.

**Scheme 3.23: Formation of the acyl pyrazole derivative 263.**



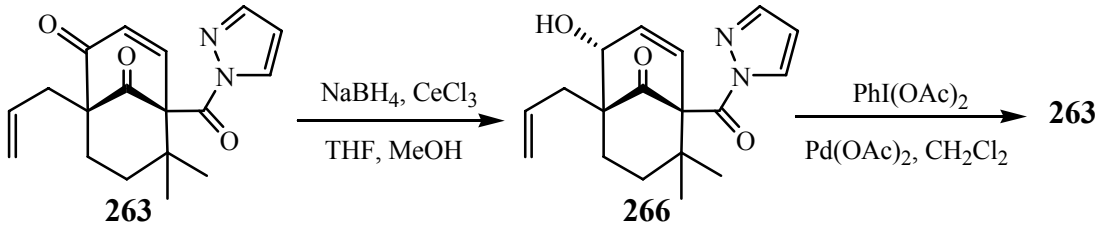

With compound **263** in hand, we proceeded further to regioselective C(2)−H bond oxidation. To our surprise, an intermolecular oxidative functionalization of the allyl group occurred (Scheme 3.24); upon treatment with iodobenzene diacetate and a catalytic amount of $Pd(OAc)_2$, we obtained compound **265** in about 35% yield (some phenyl containing by-product was also collected) together with some starting material.

**Scheme 3.24: Attempted oxidation of 263.**



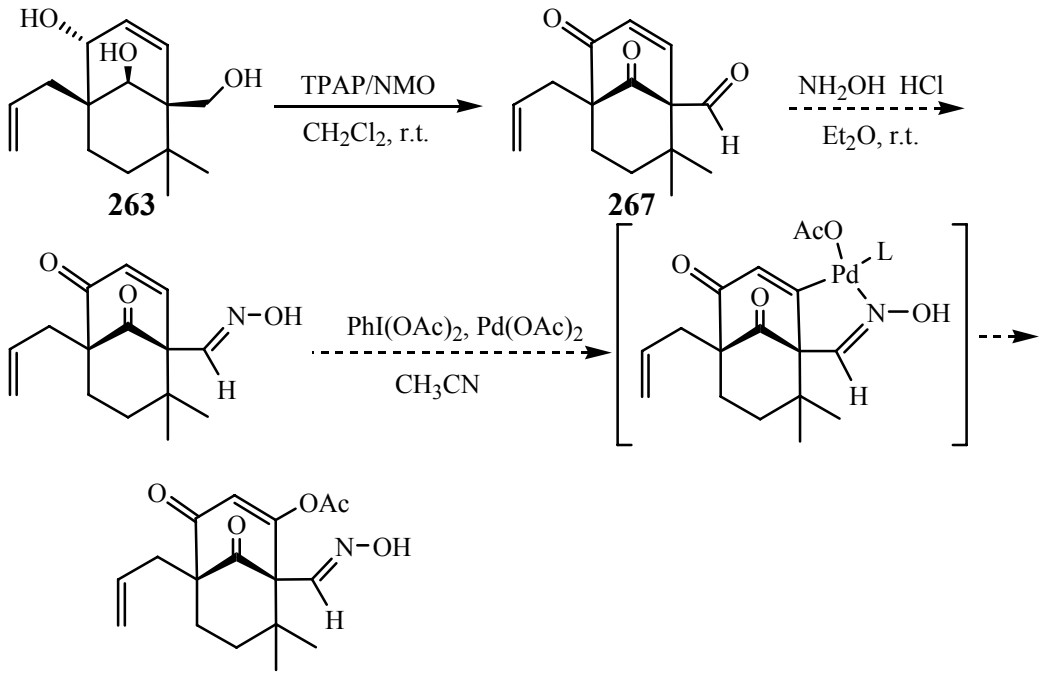

We decided first to reduce the enone to an allylic alcohol and then to perform the oxidation of C(2) in the hope that a less electron-deficient double bond might be more prone to undergo the C(2)−H activation reaction. Enone **263** proved to be resistant to the Luche reagent ($NaBH_4$ and $CeCl_3$), and the desired alcohol **266** was obtained in only 30% yield, the rest being recovered starting material (Scheme 3.25). We proceeded further to the planned oxidation but, unfortunately the allylic alcohol was oxidized back to the enone.

**Scheme 3.25: Luche reduction.**




There are other functional groups that might deliver the oxygen atom to C(2). We have oxidized alcohol **260** to diketo aldehyde **267**, which in turn will be converted to an oxime (Scheme 3.26). We hope that by heating the oxime with catalytic $Pd(OAc)_2$ and $PhI(OAc)_2$, we will activate the C−H bond and form the C(2) acetate derivative. The palladacycle intermediate would be a five-membered ring, whose formation we think would be kinetically more favorable compared to a six-membered ring, as in the case of **263** and **266**.

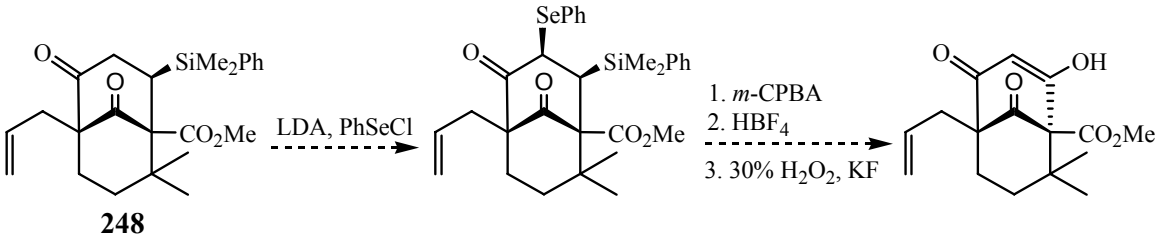
**Scheme 3.26: Alternative to oxidation of C(2).**




Another route that was not fully explored is the conversion of the C(2)−Si bond into a C(2)−O bond. Although in all our attempts the Ph−Si bond was resistant to cleavage under acidic conditions, there are other routes to explore. We could replace the phenyl group with *p*-anisyl, $Me_3Si$, or $Et_2N$[115,116]. Alternatively, we might treat **248** with PhSeCl (Scheme 3.27) to form an α-selenyl-β-silyl derivative, which in turn, upon

oxidation would turn into a β-silyl enone. Tamao-Fleming oxidation[165] would afford the desired 2,4,9-triketone derivative.

**Scheme 3.27: Se-mediated oxidation of 248.**

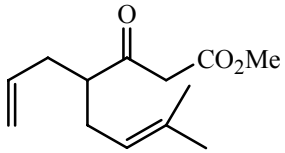



**248**

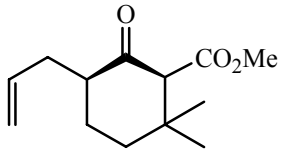
So far we have the bicyclo[3.3.1]nonane-4,9-dione core of nemorosone, leaving only the oxidation of C(2) for the completion of the skeleton. The completion of this synthetic project will allow us to make a valuable contribution to PPAPs chemistry.

### 3.7. Experimental Section

For all the compounds reported, the melting points were taken on an Electrothermal 910 and the IR data were collected on a Nicolet Magna-IR 560 spectrometer. The 400 MHz $^{1}H$ NMR and 100 MHz $^{13}C$ NMR data were collected on a Varian VXR-400S. The 50 MHz $^{13}C$ NMR data were collected on a Varian Gemini 200.

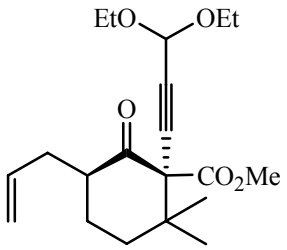



**Methyl 4-allyl-7-methyl-3-oxo-6-octenoate** (**221**). A suspension of NaH (1.99 g, 49.36 mmol) in dry THF (125 mL) at 0 °C was treated at 10 min intervals with methyl 3-oxo-6-heptenoate **220** (6.99 g, 44.87 mmol), BuLi (2.32 M, 20.3 mL, 47.11 mmol), DMPU (6.0 mL, 49.36 mmol), and prenyl bromide (5.8 mL, 49.36 mmol). The solution was allowed to warm to room temperature. The reaction was quenched with 1 M HCl, and the mixture was extracted with ether. The organic portion was dried over $MgSO_4$ and evaporated. Flash chromatography (15% EtOAc in petroleum ether) gave pure **221** (6.71 g, 29.95 mmol, 67% yield). $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 5.72 (m, 1H), 5.05 (m, 3H), 3.74 (s, 3H), 3.46 (s, 2H), 2.71 (tt, 6.2 Hz, 7.7 Hz, 1H), 2.15–2.42 (m, 4H), 1.70 (s, 3H), 1.60 (s, 3H). Selected peaks of the enol tautomer: δ 12.0 (s, 1H), 4.89 (s, 1H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 205.8, 167.9, 135.6, 134.8, 121.0, 117.6, 59.2, 52.4, 49.6, 34.4, 30.0, 26.2, 18.2. IR (neat): 3080, 2975, 2913, 1752, 1716, 1643, 1623 $cm^{-1}$. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.43; H, 8.90.

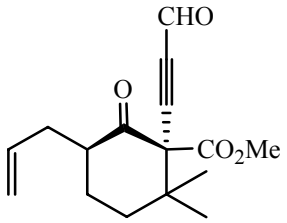



**Methyl (1*R**,3*R*)-3-allyl-6,6-dimethyl-2-cyclohexanonecarboxylate** (**222**). $SnCl_4$ (3.9 mL, 33 mmol) was added to a solution of **221** (6.71 g, 30.0 mmol) in $CH_2Cl_2$ (120 mL) at 0 °C, and the solution was allowed to stir at room temperature overnight. Ether (50 mL) was added, and the mixture was washed with 6 N HCl and water. The organic portion was dried over $MgSO_4$ and evaporated. Flash chromatography (5% EtOAc in petroleum ether) gave pure **222** (5.5 g, 24.55 mmol, 82% yield). $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 5.78 (dddd, 6.4 Hz, 7.7 Hz, 10.1 Hz, 16.9 Hz, 1H), 5.0–5.08 (m, 2H), 3.72 (s, 3H), 3.34 (s, 1H), 2.53 (m, 1H), 2.34 (m, 1H), 1.98–2.1 (m, 2H), 1.74 (m, 1H), 1.6 (m, 2H), 1.11 (s,

3H), 1.10 (s, 3H). $^{13}$C NMR (200 MHz, $CDCl_3$): δ 207.0, 169.6, 136.6, 117.4, 67.4, 52.2, 49.9, 41.1, 40.6, 34.2, 30.3, 29.4, 21.8. IR (neat): 3076, 2951, 2866, 1751, 1709, 1639 $cm^{-1}$.

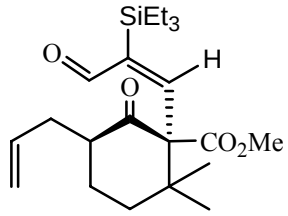



**Methyl (1*R**,3*R*)-1-(3,3-diethoxy-1-propynyl)-3-allyl-6,6-dimethyl-2-cyclohexanonecarboxylate** (**230**). A solution of 3,3-diethoxypropyne **228** (4.77 mL, 33.14 mmol) in THF (100 mL) at -30 °C was treated at 15 min intervals with BuLi (2.32 M, 14.3 mL, 33.14 mmol), $Bu_3SnCl$ (9.0 mL, 33.14 mmol), and a solution of **222** (5.50 g, 24.55 mmol) in THF (10 mL). $Pb(OAc)_4$ (16.31 g, 36.82 mmol ) was added, and the mixture was allowed to warm to room temperature. When the reaction was judged to be complete (TLC), water was added, and the mixture was extracted with ether. The aqueous layer was neutralized with 1 M HCl (a white salt formed), and it was extracted with ether again. The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (5% EtOAc in petroleum ether) gave **230** (4.12 g, 11.77 mmol, 53% yield) as a colorless liquid contaminated with a small amount of $Bu_3SnX$. $^1$H NMR (400 MHz, $CDCl_3$): δ 5.77 (m, 1H), 5.35 (s, 3H), 5.01–5.08 (m, 2H), 3.76 (s + m, 5H), 3.63 (q, 7.15 Hz, 2H), 3.22 (ddt, $J_d$ = 5.3 Hz, $J_d$ = 12.5 Hz, $J_t$ = 7.1 Hz 1H), 2.48 (m, 1H), 2.34 (dt, $J_d$ = 4.2 Hz, $J_t$ = 13.6 Hz, 1H), 2.02 (m, 2H), 1.65 (m, 1H), 1.53 (m, 1H), 1.25 (t, 7.15 Hz), 6H), 1.23 (s, 3H), 1.16 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 205.2, 167.8, 136.3, 117.4, 92.1, 85.0, 82.5, 66.9, 61.7, 53.1, 44.8, 38.0, 34.3, 29.1, 27.0, 22.7, 15.8 (× 2). IR (neat): 3076, 2975, 2932, 2237, 1752, 1720, 1639 $cm^{-1}$.




**Methyl (1*R**,3*R*)-1-(3-oxo-1-propynyl)-3-allyl-6,6-dimethyl-2-cyclohexanone carboxylate** (**241**). $HCO_2H$ (94.16 mmol) was added to neat **230** (11.77 mmol). The reaction mixture was allowed to stir overnight in the dark under $N_2$. Water was added,

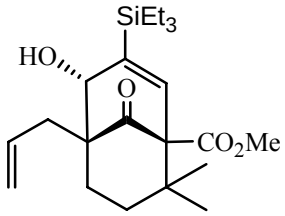
and the mixture was extracted with ether. Flash chromatography (10% EtOAc in petroleum ether) provided **241** (8.33 mmol, 71%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 5.77 (m, 1H), 5.03-5.11 (m, 2H), 3.8 (s, 3H), 3.11 (m, 1H), 2.5 (m, 1H), 2.28 (dt, $J_t$ = 13.7 Hz, $J_d$ = 4.3 Hz, 1H), 2.01-2.09 (m, 2H), 1.57 (m, 1H), 1.43 (ddd, $J_d$ = 14.3 Hz, $J_d$ = 4.4 Hz, $J_d$ = 2.56 Hz, 1H), 1.25 (s, 3H), 1.2 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 203.2, 176.9, 166.5, 135.8, 117.9, 93.2, 88.0, 67.6, 53.6, 45.5, 45.0, 37.9, 34.3, 29.0, 27.1, 22.8. IR (neat): 3076, 2952, 2878, 2206, 1755, 1724, 1670, 1456, 1437 cm$^{-1}$.



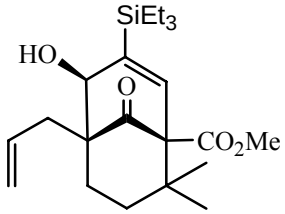

**Methyl (1*R**,3*R*,*E*)-1-(2-triethylsilyl-3-oxo-1-propenyl)-3-allyl-6,6-dimethyl-2-cyclo hexanonecarboxylate** (**244**). $Co_2(CO)_8$ (3.4 g, 10 mmol) was added to a solution of **241** (2.30 g, 8.33 mmol) in $CH_2Cl_2$ (32 mL) at 0 °C. After about 2 h, the solvent was evaporated. The residue was filtered through a short column of silica gel, eluting with hexane (the brown eluant was discarded) and then 30% EtOAc in petroleum ether. The solvent was evaporated to give the $Co_2(CO)_6$ complex of **241** (4.06 g, 7.21 mmol, 87% yield) as a dark red oil.

The complex (4.00 g, 7.09 mmol) was redissolved in dry $CH_2Cl_2$ (40 mL), and bis(trimethylsilyl)acetylene **243** (2.42 g, 14.2 mmol) and triethylsilane (6.4 mL, 40 mmol) were added. The mixture was allowed to stir at 65 °C for 3 h (monitored by TLC). The solvent was evaporated, and the residue was filtered through a short column of silica gel, eluting with hexane (the brown eluant was discarded) and then 30% EtOAc in petroleum ether. The solvent was evaporated to provide **244** (2.61 g, 6.66 mmol, 94% yield) as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 6.87 (s, 1H), 5.68 (m, 1H), 5.01 (m, 2H), 3.69 (s, 3H), 2.68 (dq, $J_d$ = 6.4 Hz, $J_q$ = 12.5 Hz, 1H), 2.48 (m, 1H), 1.98 (m, 3H), 1.62 (m, 1H), 1.49 (m, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 0.92 (t, 7.9 Hz, 9H), 0.73 (m, 6H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 207.8, 196.4, 169.2, 150.9, 146.7, 136.2, 117.7, 71.9, 52.7, 47.1, 43.2, 37.1, 34.4, 29.0, 26.1, 24.9, 7.9 (× 3), 3.7 (× 3). IR (neat): 2734, 2206, 1751, 1713, 1666, 1573, 1456 cm$^{-1}$. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.34; H, 8.82.

**Methyl (1*R**,4*S*,5*R*)- and (1*R**,4*R*,5*R*)-3-triethylsilyl-4-hydroxy-5-allyl-8,8-dimethyl bicyclo[3.3.1]non-2-en-9-one-1-carboxylate** (**245a and 245b**). Twenty drops of 6 M HCl were added to a solution of **244** (2.61 g, 6.66 mmol) in THF (25 mL). After 4.5 h (monitored by TLC), water was added. The aqueous layer was extracted with ether (2 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (8% EtOAc in petroleum ether) provided **245a** (endo OH) and **245b** (exo OH) (combined 4.77 mmol, 72% yield).

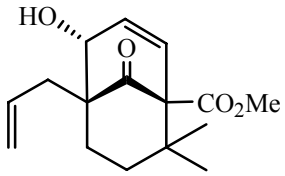



Compound **245a**. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 6.04 (m + d, 1.8 Hz, 2H), 5.15 (m, 2H), 4.42 (d, 4.6 Hz, 1H), 3.75 (s, 3H), 2.40 (dd, 8.8 Hz, 14.0 Hz, 1H), 2.32 (dddd, 14.0 Hz, 6.6 Hz, 1.5 Hz, 1.3 Hz, 1H), 2.24 (ddd, 14.1 Hz, 6.1 Hz, 2.0 Hz, 1H), 2.00 (dt, $J_d$ = 4.6 Hz, $J_t$ = 13.8 Hz, 1H), 1.91 (d, 6.0 Hz, 1H), 1.62 (ddt, $J_d$ = 0.9 Hz, $J_d$ = 5.3 Hz, $J_t$ = 14.1 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.15 (ddd, 2.0 Hz, 5.1 Hz, 13.7 Hz, 1H), 0.97 (t, 7.8 Hz, 9H), 0.72 (m, 6H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 212.5, 171.0, 142.4, 137.2, 136.6, 118.9, 80.7, 68.3, 56.3, 52.5, 43.6, 40.7, 36.4, 29.1, 25.8, 23.6, 8.1 (· 3), 4.1 (×3). IR (KBr): 3491, 1744, 1689, 1612 cm$^{-1}$. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.39; H, 8.81.

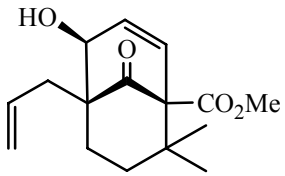



Compound **245b**. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 5.80 (dddd, 6.8 Hz, 8.1 Hz, 10.3 Hz, 16.8 Hz, 1H), 5.15 (m, 2H), 4.23 (s, 1H), 3.69 (s, 3H), 2.51 (dd, 8.2 Hz, 14.1 Hz, 1H), 2.32 (ddt, $J_d$ = 6.1 Hz, $J_d$ = 14.1 Hz, $J_t$ = 1.3 Hz, 1H), 1.84 (m, 2H), 1.67 (m, 1H), 1.30 (broad, 1H), 1.17 (s, 3H), 0.98 (s, 3H), 0.95 (m + t, 8.0 Hz, 10H), 0.68 (q, 8.0 Hz, 6H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 211.2, 170.8, 141.6, 140.8, 134.7, 119.3, 82.4, 69.0, 54.0, 52.7, 42.6, 37.9, 36.5, 32.2, 26.3, 23.4, 8.0 (× 3), 3.8 (× 3). IR (neat): 3522, 1752, 1713, 1608 cm$^{-1}$. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 66.98; H, 8.86.

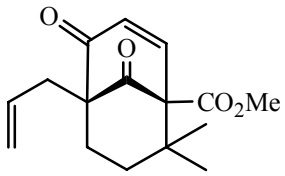
**Methyl (1*R**,4*S*,5*R*)- and (1*R**,4*R*,5*R*)-4-hydroxy-5-allyl-8,8-dimethyl bicyclo[3.3.1]non-2-en-9-one-1-carboxylate** (**246a and 246b**). To a solution of **245a**,**b** (0.46 g, 1.17 mmol) in 6 mL $CH_3CN$ it was added TBAF (1M THF) (3.51 mL, 3.51 mmol). The mixture was allowed to stir under reflux for six hours. The reaction mixture was poured into water and extracted with ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (18% EtOAc in petroleum ether) provided **246a** (endo OH) and **246b** (exo OH) (combined 0.29 g, 1.04 mmol, 89% yield).




Compound **246a**. mp: 87 ºC. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 5.98 (m + dd, 2.4 Hz, 10.1 Hz, 2H), 5.91 (dd, 1.6 Hz, 10.1 Hz, 1H), 5.10 (m, 2H), 4.39 (s, broad, 1H), 3.71 (s, 3H), 2.39 (dd, 8.6 Hz, 13.9 Hz, 1H), 2.30 (dd~t, 6.41 Hz, 13.9 Hz, 1H), 2.23 (ddd, 2.0 Hz, 4.9 Hz, 13.9 Hz, 1H), 2.01 (dt, $J_d$ = 4.8 Hz, $J_t$ = 13.9 Hz, 1H), 1.61 (dt, $J_d$ = 5.3 Hz, $J_t$ = 14.3 Hz, 1H), 1.25 (s, 3H), 1.14 (ddd, 2.0 Hz, 5.3 Hz, 14.1 Hz, 1H), 0.98 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 208.3, 171.0, 136.5, 132.8, 129.0, 119.4, 76.7, 67.3, 56.2, 53.0, 43.6, 43.6, 40.9, 36.5, 29.2, 26.0, 24.0. IR (neat): 3481, 3083, 1748, 1701cm$^{-1}$. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.48; H, 7.66.

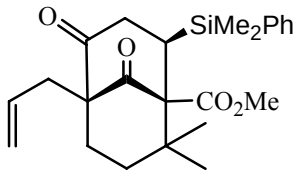



Compound **246b**. Selected $^{1}$H NMR data (400 MHz, $CDCl_3$): δ 6.20 (dd, 4.4 Hz, 9.7 Hz, 1H), 4.28 (d, 4.3 Hz, 1H), 3.75 (s, 3H), 2.63 (dd~t, 7.89 Hz, 14.1 Hz, 1H).

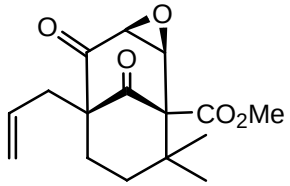



**Methyl (1*R**,5*R*)-5-allyl-8,8-dimethylbicyclo[3.3.1]non-2-en-4,9-dione-1-carboxylate** (**247**). To a solution of **246a**,**b** (1.04 mmol, 0.29 g) in 11 mL dry $CH_2Cl_2$ was added NMO (2.60 mmol, 0.30 g), crushed molecular sieves (4Å) and TPAP (0.056 mmol, 0.020 g), in this order. The mixture was allowed to stir at room temperature for one hour (monitored by TLC), and then it was filtered through a short column of silica gel and eluted with 18% EtOAc in petroleum ether. After the solvent was evaporated, pure **247** was obtained (0.091 mmol, 0.250 g, 87% yield). mp: 95 ºC. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J_d$ = 10.1 Hz , 1H), 6.47 (d, $J_d$ = 10.1 Hz , 1H), 5.79 (m, 1H), 5.09 (m, 2H), 3.79 (s, 3H), 2.57 (ddt, $J_t$ = 1.3 Hz, $J_d$ = 7.8 Hz, $J_d$ = 14.3 Hz, 1H), 2.49 (dd~t, 6.41 Hz, 13.9 Hz, 1H), 2.01 (dd, 4.4 Hz, 3.2 Hz), 1.97 (dt, $J_d$ = 4.4 Hz, $J_t$ = 13.2 Hz, 1H), 1.80 (dm, 14.5 Hz, 1H), 1.70 (m, 1H), 1.31 (s, 3H), 1.27 (m, 1H), 1.07 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 203.7, 199.1, 168.8, 147.2, 134.0, 131.8, 119.0, 68.5, 65.3, 52.8,

41.9, 35.3, 34.8, 34.1, 26.4, 23.0. IR (neat): 3072, 3007, 1752, 1720, 1679cm$^{-1}$. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.26; H, 7.30.

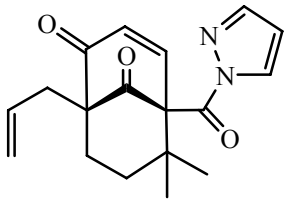



**Methyl (1*R**,2*R*,5*R*)-5-allyl-8,8-dimethyl-2-(dimethylphenylsilyl)bicyclo[3.3.1]non-4,9-dione-1-carboxylate** (**248**). $PhMe_2SiCl$ (4.10 mL, 24.2 mmol) was added to a solution of Li (0.41 g, 57.7 mmol) in 15 mL dry THF at 0 ºC. After about six hours, the mixture was added to a slurry of CuI (2.35 g, 12.1 mmol) in 10 mL dry THF under $N_2$, at -30 ºC. Enone **247** (0.477 g, 1.73 mmol) was added after four more hours, and the mixture was allowed to stir overnight at room temperature. The reaction mixture was quenched with 1 N HCl and extracted with ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (10% EtOAc in petroleum ether) provided **248** (0.57 g, 1.39 mmol, 80% yield). mp: 154 ºC. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.47 (m , 2H), 7.35 (m , 3H), 5.75 (m, 1H), 5.00 (m, 2H), 3.72 (s, 3H), 2.47 (dd, 13.5 Hz, 2.9 Hz, 1H), 2.41 (dd, 13.4 Hz, 6.2 Hz, 1H), 2.24 (dd, 13.4 Hz, 8.4 Hz, 1H), 2.15 (m, 1H), 2.05 (m, 1H, 1.70 (m, 3H), 1.51 (s, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 1.08 (m, 1H), 0.34 (s, 3H), 0.26 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 210.2, 209.4, 171.9, 139.3, 134.3, 133.3, 130.1, 128.8, 119.6, 67.2, 64.9, 52.1, 45.1, 44.2, 37.8, 36.3, 35.7, 26.1, 23.5, 23.4, -2.0, -4.6. IR (neat): 3068, 1748, 1728, 1699, 1426, 1388, 1107 cm$^{-1}$. Calcd for $C_{24}H_{32}O_4Si$: C, 69.86; H, 7.82. Found: C, 68.72; H, 7.60.

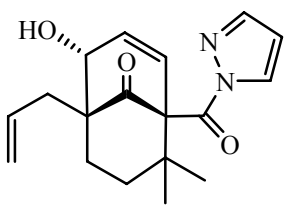



**Methyl (1*R**,2*R*,3*S*,5*R*)-5-allyl-8,8-dimethyl-2-oxa -bicyclo[3.3.1]non-4,9-dione-1-carboxylate** (**254**). Enone **247** (0.262 g, 1.00 mmol) was dissolved in 10 mL MeOH and a few drops of $CH_2Cl_2$. 30% $H_2O_2$ (0.67 mL) followed by $KHCO_3$ (0.024 g, 0.024 mmol) were added and the reaction mixture was allowed to stir overnight. After the evaporation of the solvent, a white solid was formed which was dissolved in 20% EtOAc in pet ether. Flash chromatography (20% EtOAc in petroleum ether) provided **254** (0.186 g, 0.640

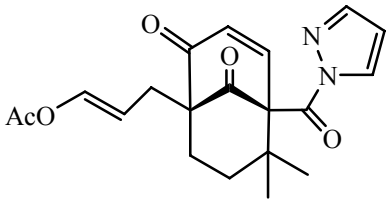
mmol, 64% yield). mp: 109 ºC. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 5.70 (m, 1H), 5.00-5.08 (m, 2H), 4.00 (d, 3.7 Hz, 1H), 3.87 (s, 3H), 3.71 (d, 3.5 Hz, 1H), 2.47 (m, 2H), 1.95 (m, 3H), 1.4 (m, 1H), 1.23 (s, 3H), 1.22 (s, 3H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 205.8, 200.0, 168.5, 133.5, 119.4, 67.1, 63.7, 57.5, 55.8, 53.2, 43.3, 38.7, 36.5, 36.0, 27.1, 25.7. IR (neat): 3081, 1753, 1720, 1704, 1234 $cm^{-1}$. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.43; H, 6.92.



**5-Allyl-8,8-dimethyl-1-(pyrazole-1-carbonlyl)-bicyclo[3.3.1]none-2-ene-4,9-dione** (**263**). To a solution of triol **260** (0.15 g, 0.59 mmol) in 6 mL acetone at 0 ºC it was added Jones reagent – $CrO_3$ (0.6 g, 6.0 mmol) and $H_2SO_4$ (0.5 mL) – and the reaction mixture was allowed to stir at room temperature for 7 hours (monitored by TLC). After addition of isopropanol, the mixture was extracted with $CH_2Cl_2$ three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The crude residue was dissolved in 1 mL $(COCl)_2$ and two drops of DMF. After approximatively 20 minutes, the remaining $(COCl)_2$ was evaporated and the crude residue was dissolved in 3 mL dry $CH_2Cl_2$. Pyrazole (0.041 g, 0.60 mmol) was added followed by $NEt_3$ (62.0 μL, 6.0 mmol). The reaction mixture was quenched with 1 N HCl and extracted with ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (10% EtOAc in petroleum ether) provided **263** (0.09 g, 0.30 mmol, 50% yield over three steps). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 2.9 Hz, 1H), 7.46 (d, 1.5 Hz, 1H), 6.98 (d, 10.0 Hz, 1H), 6.49 (d, 10.0 Hz, 1H), 6.37 (dd, 1.5 Hz, 2.9 Hz, 1H), 6.73 (m, 1H), 5.10 (m, 2H), 2.60 (m, 2H), 1.88 (m, 3H), 1.39 (s, 3H), 1.31 (s, 3H), 1.25 (m, 1H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 205.3, 199.5, 167.5, 146.8, 143.7, 134.4, 129.9, 129.5, 118.4, 110.0, 67.7, 66.3, 44.5, 37.6, 35.9, 34.7, 26.4, 22.2.



**(4*R*)-5-Allyl-4-hydroxy-8,8-dimethyl-1-(pyrazole-1-carbonyl)-bicyclo[3.3.1]non-2-en-9-one** (**266**). The enone **263** (0.09 g, 0.30 mmol) was dissolved in 1 mL MeOH and a few drops of dry THF. $CeCl_3 \cdot H_2O$ (0.11 g, 0.30 mmol) was added followed by$NaBH_4$ (0.011 g, 0.300 mmol). After about 1 hour (monitored by TLC), the reaction mixture was quenched with 1 N HCl and extracted with ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (30% EtOAc in petroleum ether) provided **266** (0.03 g, 0.1 mmol, 30% yield). Selected $^1$H NMR data (400 MHz, $CDCl_3$): δ 8.20 (dd, 1.7 Hz, 2.9 Hz, 1H), 7.45 (dd, 0.7 Hz, 1.5 Hz, 1H), 6.36 (dd, 1.5 Hz, 3.0 Hz, 1H), 6.03 (dd, 2.6 Hz, 10.1 Hz, 1H), 5.97 (m, 1H), 5.77 (dd, 2.2 Hz, 10.1 Hz, 1H), 5.15 (m, 2H), 4.7 (t, 2.0 Hz, 1H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 208.7, 169.2, 143.3, 136.4, 131.2, 129.6, 126.9, 118.6, 109.3, 74.1, 66.0, 56.2, 46.1, 39.7, 36.4, 31.6, 25.3, 22.3.




**Attempted oxidation of 263: 263** (0.08 g, 0.26 mmol), $PhI(OAc)_2$ (0.17 g, 0.52 mmol), and $Pd(OAc)_2$ (0.001 g, 0.010 mmol) were dissolved in 2 mL $CH_3CN$. The reaction mixture was allowed to stir for two days at 75 ºC. After cooling, the mixture was filtered though a short silica column. Selected $^1$H NMR data (400 MHz, $CDCl_3$): δ 8.24 (dd, 0.7 Hz, 2.9 Hz, 1H), 6.97 (d, 10.1 Hz, 1H), 6.50 (d, 10.1 Hz, 1H), 6.40 (d, 16.0 Hz, 1H), 6.33 (dd, 1.46, 2.9 Hz), 6.18 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H).

## Chapter 4. Conclusion

The aim of my research was to synthesize nemorosone, a natural product with antibacterial, antioxidant and anticancer activities, which is found in the resins and latex of plants of *Clusia* (Clusiaceae) species. Structurally, nemorosone is a polycyclic polyprenylated acylphloroglucinol (PPAP), a class of compounds that reveal intriguing biological activities and interesting and challenging chemical structures.

In the past decade many approaches to the synthesis of the bicyclo[3.3.1]nonane-2,4,9-trione structure of type A PPAPs have been reported, but only two total syntheses of any PPAP, garsubellin A by Shibasaki and Danishefsky, have been published recently, near the end of 2005. All approaches have relied on the α,α´-annulation of a three-carbon bridge onto a cyclohexanone, although the methods used to execute this annulation differ dramatically.

We have developed a short and efficient synthetic approach to the bicyclo[3.3.1]nonane skeleton of the PPAPs that involves a novel three-carbon α,α´-annulation of a sterically hindered cyclic β-keto ester with 3,3-diethoxypropyne. The alkynylation reaction permits the construction of the two contiguous quaternary centers of the PPAPs in reasonable yield and without complications from side reactions. We have also successfully applied a recently developed syn hydrosilylation to the very hindered product of this alkynylation reaction.

Once the total synthesis of nemorosone is completed and our methodology will prove to be successful, we can apply it to other compounds from this class, and in the long run, chemists will be able to evaluate and understand the relationships between the molecular structure and the biological activity.

The total synthesis of nemorosone is important not only because of the reasons above mentioned but also because of the opportunity to boost the limits of organic chemistry. Our methodology received positive feedback already, and we see this total synthesis of nemorone as an ideal platform for the implementation of new synthetic methodologies.

In conclusion, studies toward synthesis of this class of compounds have emerged in the past decade. We have competed successfully with renowned organic chemists from all around the world. We have achieved already, through a unique methodology, the backbone of our targeted natural product and our future plan is to complete its total synthesis.

## Appendix

**Table A.1:** Crystal data and structure refinement for **237a**. Refinement method for all structures is full-matrix least-square on $F^2$.

| | |
|---|---|
| Empirical formula | $C_{22}H_{36}O_4Si$ |
| Formula weight | 392.60 |
| Temperature | 90.0(2) K |
| Wavelength (Å) | 0.71073 |
| Crystal system | Monoclinic |
| Space group | ***C***2/c |
| Unit cell dimensions | |
| a (Å) | 19.1880(3) |
| α (°) | 90 |
| b (Å) | 9.48600(10) |
| β (°) | 90.6760(7) |
| c (Å) | 24.8430(4) |
| γ (°) | 90 |
| Volume ($Å^3$) | 4521.54(11) |
| Z | 8 |
| Calculated density ($Mg/m^3$) | 1.153 |
| Absorption coefficient ($mm^{-1}$) | 0.127 |
| F(000) | 1712 |
| Crystal size (mm) | 0.22 × 0.20 × 0.20 |
| Θ range for data collection (°) | 1.64 to 27.46 |
| Limiting indices | -24≤h≤24 |
| | -11≤k≤12 |
| | 32≤l≤32 |
| Reflections collected / unique | 9375 / 5163 |
| | [R(int) = 0.0411] |
| Completeness to Θ= 27.46 | 99.9 % |

| | |
|---|---|
| Absorption correction | None |
| Max. transmission | 0.9751 |
| Min. transmission | 0.9727 |
| Data / restraints / parameters | 5163 / 0 / 251 |
| Goodness-of-fit on $F^2$ | 1.472 |
| Final R indices [I>2σ(I)] | R1 = 0.0496 |
| | ωR2 = 0.1198 |
| R indices (all data) | R1 = 0.0869 |
| | ωR2 = 0.1353 |
| Largest diff. peak and hole ($e \cdot Å^{-3}$) | 0.539 and -0.248 |

**Table A.2:** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($A^2$ x 103) for **237a**. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Si(1) | 4212(1) | 4763(1) | 1175(1) | 21(1) |
| C(1) | 2153(1) | 3056(2) | 1100(1) | 14(1) |
| C(2) | 2913(1) | 3465(2) | 1021(1) | 15(1) |
| C(3) | 3289(1) | 4267(2) | 1354(1) | 16(1) |
| O(4) | 3192(1) | 6200(1) | 1952(1) | 24(1) |
| C(4) | 2998(1) | 4759(2) | 1887(1) | 16(1) |
| C(5) | 2194(1) | 4545(2) | 1955(1) | 15(1) |
| C(6) | 1768(1) | 5692(2) | 1653(1) | 17(1) |
| C(7) | 1819(1) | 5618(2) | 1041(1) | 18(1) |
| C(8) | 1656(1) | 4154(2) | 811(1) | 16(1) |
| O(9) | 1815(1) | 2113(1) | 1956(1) | 18(1) |
| C(9) | 2025(1) | 3132(2) | 1706(1) | 14(1) |
| C(10) | 1794(1) | 4165(2) | 205(1) | 22(1) |
| C(11) | 888(1) | 3784(2) | 905(1) | 21(1) |
| O(12) | 1582(1) | 1066(1) | 646(1) | 24(1) |
| C(12) | 2048(1) | 1532(2) | 918(1) | 16(1) |
| O(13) | 2572(1) | 728(1) | 1114(1) | 19(1) |
| C(13) | 2494(1) | -775(2) | 1030(1) | 23(1) |
| C(14) | 2027(1) | 4568(2) | 2561(1) | 18(1) |
| C(15) | 1268(1) | 4480(2) | 2697(1) | 23(1) |
| C(16) | 935(1) | 5417(2) | 2982(1) | 35(1) |
| C(17) | 4525(1) | 3620(2) | 610(1) | 23(1) |
| C(18) | 4640(1) | 2060(2) | 737(1) | 30(1) |
| C(19) | 4780(1) | 4504(3) | 1783(1) | 32(1) |
| C(20) | 5565(1) | 4602(3) | 1678(1) | 45(1) |
| C(21) | 4241(1) | 6623(2) | 926(1) | 40(1) |
| C(22) | 3829(1) | 6885(3) | 400(1) | 48(1) |

**Table A.3:** Bond lengths [Å] and angles [°] for **237a.**

| | |
|---|---|
| Si(1)-C(19) | 1.8679(19) |
| Si(1)-C(21) | 1.871(2) |
| Si(1)-C(17) | 1.8772(19) |
| Si(1)-C(3) | 1.8905(17) |
| C(1)-C(2) | 1.524(2) |
| C(1)-C(12) | 1.526(2) |
| C(1)-C(9) | 1.532(2) |
| C(1)-C(8) | 1.579(2) |
| C(2)-C(3) | 1.331(2) |
| C(2)-H(2) | 0.9500 |
| C(3)-C(4) | 1.516(2) |
| O(4)-C(4) | 1.425(2) |
| O(4)-H(4) | 0.8400 |
| C(4)-C(5) | 1.569(2) |
| C(4)-H(4A) | 1.0000 |
| C(5)-C(9) | 1.509(2) |
| C(5)-C(14) | 1.543(2) |
| C(5)-C(6) | 1.549(2) |
| C(6)-C(7) | 1.528(2) |
| C(6)-H(6A) | .9900 |
| C(6)-H(6B) | 0.9900 |
| C(7)-C(8) | 1.533(2) |
| C(7)-H(7A) | 0.9900 |
| C(7)-H(7B) | 0.9900 |
| C(8)-C(10) | 1.531(2) |
| C(8)-C(11) | 1.535(2) |
| O(9)-C(9)) | 1.220(2) |
| C(10)-H(10A) | 0.9800 |
| C(10)-H(10B) | 0.9800 |
| C(10)-H(10C) | 0.9800 |
| C(11)-H(11A) | 0.9800 |
| C(11)-H(11B) | 0.9800 |
| C(11)-H(11C) | 0.9800 |
| O(12)-C(12) | 1.1999(19) |
| C(12)-O(13) | 1.347(2) |
| O(13)-C(13) | 1.448(2) |
| C(13)-H(13A) | 0.9800 |
| C(13)-H(13B) | 0.9800 |
| C(13)-H(13C) | 0.9800 |
| C(14)-C(15) | 1.502(2) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(15)-C(16) | 1.309(3) |
| C(15)-H(15) | 0.9500 |
| C(16)-H(16A) | 0.9500 |
| C(16)-H(16B) | 0.9500 |

| | |
|---|---|
| C(17)-C(18) | 1.529(3) |
| C(17)-H(17A) | 0.9900 |
| C(17)-H(17B) | 0.9900 |
| C(18)-H(18A) | 0.9800 |
| C(18)-H(18B) | 0.9800 |
| C(18)-H(18C) | 0.9800 |
| C(19)-C(20) | 1.535(3) |
| C(19)-H(19A) | 0.9900 |
| C(19)-H(19B) | 0.9900 |
| C(20)-H(20A) | 0.9800 |
| C(20)-H(20B) | 0.9800 |
| C(20)-H(20C) | 0.9800 |
| C(21)-C(22) | 1.539(3) |
| C(21)-H(21A) | 0.9900 |
| C(21)-H(21B) | 0.9900 |
| C(22)-H(22A) | 0.9800 |
| C(22)-H(22B) | 0.9800 |
| C(22)-H(22C) | 0.9800 |
| C(19)-Si(1)-C(21) | 111.87(11) |
| C(19)-Si(1)-C(17) | 109.88(9) |
| C(21)-Si(1)-C(17) | 106.64(10) |
| C(19)-Si(1)-C(3) | 108.38(8) |
| C(21)-Si(1)-C(3) | 110.11(9) |
| C(17)-Si(1)-C(3) | 109.95(8) |
| C(2)-C(1)-C(12) | 109.06(14) |
| C(2)-C(1)-C(9) | 106.16(13) |
| C(12)-C(1)-C(9) | 108.24(14) |
| C(2)-C(1)-C(8) | 110.29(14) |
| C(12)-C(1)-C(8) | 114.48(13) |
| C(9)-C(1)-C(8) | 108.26(14) |
| C(3)-C(2)-C(1) | 125.37(16) |
| C(3)-C(2)-H(2) | 117.3 |
| C(1)-C(2)-H(2) | 117.3 |
| C(2)-C(3)-C(4) | 121.10(15) |
| C(2)-C(3)-Si(1) | 119.89(13) |
| C(4)-C(3)-Si(1) | 118.99(12) |
| C(4)-O(4)-H(4) | 109.5 |
| O(4)-C(4)-C(3) | 107.21(14) |
| O(4)-C(4)-C(5) | 111.60(14) |
| C(3)-C(4)-C(5) | 115.29(14) |
| O(4)-C(4)-H(4A) | 107.5 |
| C(3)-C(4)-H(4A) | 107.5 |
| C(5)-C(4)-H(4A) | 107.5 |
| C(9)-C(5)-C(14) | 111.50(15) |
| C(9)-C(5)-C(6) | 108.50(13) |
| C(14)-C(5)-C(6) | 110.40(14) |
| C(9)-C(5)-C(4) | 106.09(14) |

| | |
|---|---|
| C(14)-C(5)-C(4) | 108.57(13) |
| C(6)-C(5)-C(4) | 111.72(14) |
| C(7)-C(6)-C(5) | 114.23(15) |
| C(7)-C(6)-H(6A) | 108.7 |
| C(5)-C(6)-H(6A) | 108.7 |
| C(7)-C(6)-H(6B) | 108.7 |
| C(5)-C(6)-H(6B) | 108.7 |
| H(6A)-C(6)-H(6B) | 107.6 |
| C(6)-C(7)-C(8) | 113.44(15) |
| C(6)-C(7)-H(7A) | 108.9 |
| C(8)-C(7)-H(7A) | 108.9 |
| C(6)-C(7)-H(7B) | 108.9 |
| C(8)-C(7)-H(7B) | 108.9 |
| H(7A)-C(7)-H(7B) | 107.7 |
| C(10)-C(8)-C(7) | 108.87(14) |
| C(10)-C(8)-C(11) | 109.15(14) |
| C(7)-C(8)-C(11) | 110.04(14) |
| C(10)-C(8)-C(1) | 109.92(14) |
| C(7)-C(8)-C(1) | 108.01(13) |
| C(11)-C(8)-C(1) | 110.83(14) |
| O(9)-C(9)-C(5) | 124.44(15) |
| O(9)-C(9)-C(1) | 121.41(16) |
| C(5)-C(9)-C(1) | 114.15(14) |
| C(8)-C(10)-H(10A) | 109.5 |
| C(8)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| C(8)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| C(8)-C(11)-H(11A) | 109.5 |
| C(8)-C(11)-H(11B) | 109.5 |
| H(11A)-C(11)-H(11B) | 109.5 |
| C(8)-C(11)-H(11C) | 109.5 |
| H(11A)-C(11)-H(11C) | 109.5 |
| H(11B)-C(11)-H(11C) | 109.5 |
| O(12)-C(12)-O(13) | 122.87(17) |
| O(12)-C(12)-C(1) | 127.55(16) |
| O(13)-C(12)-C(1) | 109.57(14) |
| C(12)-O(13)-C(13) | 115.50(13) |
| O(13)-C(13)-H(13A) | 109.5 |
| O(13)-C(13)-H(13B) | 109.5 |
| H(13A)-C(13)-H(13B) | 109.5 |
| O(13)-C(13)-H(13C) | 109.5 |
| H(13A)-C(13)-H(13C) | 109.5 |
| H(13B)-C(13)-H(13C) | 109.5 |
| C(15)-C(14)-C(5) | 115.49(14) |
| C(15)-C(14)-H(14A) | 108.4 |

| | |
|---|---|
| C(5)-C(14)-H(14A) | 108.4 |
| C(15)-C(14)-H(14B) | 108.4 |
| C(5)-C(14)-H(14B) | 108.4 |
| H(14A)-C(14)-H(14B) | 107.5 |
| C(16)-C(15)-C(14) | 124.36(19) |
| C(16)-C(15)-H(15) | 117.8 |
| C(14)-C(15)-H(15) | 117.8 |
| C(15)-C(16)-H(16A) | 120.0 |
| C(15)-C(16)-H(16B) | 120.0 |
| H(16A)-C(16)-H(16B) | 120.0 |
| C(18)-C(17)-Si(1) | 116.84(13) |
| C(18)-C(17)-H(17A) | 108.1 |
| Si(1)-C(17)-H(17A) | 108.1 |
| C(18)-C(17)-H(17B) | 108.1 |
| Si(1)-C(17)-H(17B) | 108.1 |
| H(17A)-C(17)-H(17B) | 107.3 |
| C(17)-C(18)-H(18A) | 109.5 |
| C(17)-C(18)-H(18B) | 109.5 |
| H(18A)-C(18)-H(18B) | 109.5 |
| C(17)-C(18)-H(18C) | 109.5 |
| H(18A)-C(18)-H(18C) | 109.5 |
| H(18B)-C(18)-H(18C) | 109.5 |
| C(20)-C(19)-Si(1) | 114.73(14) |
| C(20)-C(19)-H(19A) | 108.6 |
| Si(1)-C(19)-H(19A) | 108.6 |
| C(20)-C(19)-H(19B) | 108.6 |
| Si(1)-C(19)-H(19B) | 108.6 |
| H(19A)-C(19)-H(19B) | 107.6 |
| C(19)-C(20)-H(20A) | 109.5 |
| C(19)-C(20)-H(20B) | 109.5 |
| H(20A)-C(20)-H(20B) | 109.5 |
| C(19)-C(20)-H(20C) | 109.5 |
| H(20A)-C(20)-H(20C) | 109.5 |
| H(20B)-C(20)-H(20C) | 109.5 |
| C(22)-C(21)-Si(1) | 114.64(16) |
| C(22)-C(21)-H(21A) | 108.6 |
| Si(1)-C(21)-H(21A) | 108.6 |
| C(22)-C(21)-H(21B) | 108.6 |
| Si(1)-C(21)-H(21B) | 108.6 |
| H(21A)-C(21)-H(21B) | 107.6 |
| C(21)-C(22)-H(22A) | 109.5 |
| C(21)-C(22)-H(22B) | 109.5 |
| H(22A)-C(22)-H(22B) | 109.5 |
| C(21)-C(22)-H(22C) | 109.5 |
| H(22A)-C(22)-H(22C) | 109.5 |
| H(22B)-C(22)-H(22C) | 109.5 |

**Table A.4:** Anisotropic displacement parameters ($Å^2$ x $10^3$) for **237a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| Si(1) | 16(1) | 24(1) | 22(1) | -2(1) | 4(1) | -4(1) |
| C(1) | 17(1) | 14(1) | 12(1) | 0(1) | 0(1) | -1(1) |
| C(2) | 16(1) | 15(1) | 15(1) | -1(1) | 3(1) | 2(1) |
| C(3) | 18(1) | 15(1) | 15(1) | -1(1) | 1(1) | 2(1) |
| O(4) | 28(1) | 21(1) | 22(1) | -8(1) | 5(1) | -8(1) |
| C(4) | 18(1) | 16(1) | 15(1) | -2(1) | 0(1) | -5(1) |
| C(5) | 18(1) | 16(1) | 12(1) | 0(1) | 1(1) | 0(1) |
| C(6) | 19(1) | 15(1) | 18(1) | -2(1) | 2(1) | 2(1) |
| C(7) | 21(1) | 15(1) | 17(1) | 2(1) | 1(1) | 2(1) |
| C(8) | 18(1) | 16(1) | 16(1) | 2(1) | 1(1) | 3(1) |
| O(9) | 21(1) | 17(1) | 16(1) | 4(1) | 2(1) | -2(1) |
| C(9) | 9(1) | 17(1) | 16(1) | 1(1) | -1(1) | 2(1) |
| C(10) | 30(1) | 21(1) | 15(1) | 2(1) | -3(1) | 0(1) |
| C(11) | 17(1) | 20(1) | 26(1) | 0(1) | -3(1) | 2(1) |
| O(12) | 26(1) | 19(1) | 26(1) | -3(1) | -7(1) | -3(1) |
| C(12) | 19(1) | 18(1) | 11(1) | 0(1) | 4(1) | 2(1) |
| O(13) | 22(1) | 13(1) | 21(1) | -1(1) | -1(1) | 2(1) |
| C(13) | 33(1) | 13(1) | 24(1) | 0(1) | 3(1) | 2(1) |
| C(14) | 22(1) | 20(1) | 12(1) | -4(1) | 2(1) | -1(1) |
| C(15) | 24(1) | 29(1) | 17(1) | -2(1) | 4(1) | 3(1) |
| C(16) | 31(1) | 40(2) | 36(1) | -9(1) | 10(1) | 0(1) |
| C(17) | 17(1) | 33(1) | 19(1) | 1(1) | 2(1) | 1(1) |
| C(18) | 30(1) | 35(1) | 25(1) | -5(1) | -3(1) | 12(1) |
| C(19) | 20(1) | 51(2) | 24(1) | -5(1) | -1(1) | -7(1) |
| C(20) | 21(1) | 78(2) | 37(1) | -1(1) | -3(1) | -10(1) |
| C(21) | 29(1) | 28(1) | 64(2) | -2(1) | 19(1) | -8(1) |
| C(22) | 62(2) | 33(1) | 51(2) | 21(1) | 28(1) | 17(1) |

**Table A.5:** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$ x $10^3$) for **237a**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | 3136 | 3121 | 708 | 18 |
| H(4) | 3204 | 6403 | 2281 | 35 |
| H(4A) | 3239 | 4211 | 2179 | 20 |
| H(6A) | 1273 | 5604 | 1754 | 21 |
| H(6B) | 1933 | 6631 | 1774 | 21 |
| H(7A) | 2296 | 5892 | 935 | 21 |
| H(7B) | 1491 | 6309 | 880 | 21 |
| H(10A) | 1486 | 4852 | 29 | 33 |
| H(10B) | 1703 | 3225 | 56 | 33 |
| H(10C) | 2281 | 4424 | 142 | 33 |
| H(11A) | 812 | 3650 | 1291 | 32 |
| H(11B) | 771 | 2914 | 712 | 32 |
| H(11C) | 592 | 4553 | 772 | 32 |
| H(13A) | 2058 | -1095 | 1190 | 35 |
| H(13B) | 2888 | -1271 | 1199 | 35 |
| H(13C) | 2484 | -975 | 642 | 35 |
| H(14A) | 2272 | 3769 | 2737 | 22 |
| H(14B) | 2219 | 5448 | 2718 | 22 |
| H(15) | 1012 | 3690 | 2566 | 28 |
| H(16A) | 1175 | 6219 | 3119 | 42 |
| H(16B) | 453 | 5296 | 3053 | 42 |
| H(17A) | 4183 | 3688 | 310 | 28 |
| H(17B) | 4971 | 4014 | 481 | 28 |
| H(18A) | 4972 | 1968 | 1038 | 45 |
| H(18B) | 4826 | 1583 | 420 | 45 |
| H(18C) | 4195 | 1627 | 835 | 45 |
| H(19A) | 4656 | 5222 | 2055 | 38 |
| H(19B) | 4678 | 3567 | 1939 | 38 |
| H(20A) | 5700 | 3860 | 1426 | 68 |
| H(20B) | 5823 | 4483 | 2018 | 68 |
| H(20C) | 5673 | 5526 | 1524 | 68 |
| H(21A) | 4054 | 7249 | 1209 | 48 |
| H(21B) | 4733 | 6889 | 869 | 48 |
| H(22A) | 3996 | 6245 | 120 | 72 |
| H(22B) | 3896 | 7863 | 284 | 72 |
| H(22C) | 3332 | 6715 | 461 | 72 |

**Table A.6:** Torsion angles [°] for **237a**.

| | |
|---|---|
| C(12)-C(1)-C(2)-C(3) | -141.57(18) |
| C(9)-C(1)-C(2)-C(3) | -25.2(2) |
| C(8)-C(1)-C(2)-C(3) | 91.9(2) |
| C(1)-C(2)-C(3)-C(4) | 5.4(3) |
| C(1)-C(2)-C(3)-Si(1) | -176.40(13) |
| C(19)-Si(1)-C(3)-C(2) | -134.65(16) |
| C(21)-Si(1)-C(3)-C(2)) | 102.68(17) |
| C(17)-Si(1)-C(3)-C(2) | -14.53(17) |
| C(19)-Si(1)-C(3)-C(4) | 43.61(17) |
| C(21)-Si(1)-C(3)-C(4) | -79.05(16) |
| C(17)-Si(1)-C(3)-C(4) | 163.74(13) |
| C(2)-C(3)-C(4)-O(4) | -137.59(17) |
| Si(1)-C(3)-C(4)-O(4) | 44.17(18) |
| C(2)-C(3)-C(4)-C(5) | -12.7(2) |
| Si(1)-C(3)-C(4)-C(5) | 169.10(12) |
| O(4)-C(4)-C(5)-C(9) | 162.12(13) |
| C(3)-C(4)-C(5)-C(9) | 39.5(2) |
| O(4)-C(4)-C(5)-C(14) | -77.92(17) |
| C(3)-C(4)-C(5)-C(14) | 159.46(15) |
| O(4)-C(4)-C(5)-C(6) | 44.06(18) |
| C(3)-C(4)-C(5)-C(6) | -78.56(19) |
| C(9)-C(5)-C(6)-C(7) | -49.37(19) |
| C(14)-C(5)-C(6)-C(7) | -171.83(14) |
| C(4)-C(5)-C(6)-C(7) | 67.24(19) |
| C(5)-C(6)-C(7)-C(8) | 51.9(2) |
| C(6)-C(7)-C(8)-C(10) | -174.37(14) |
| C(6)-C(7)-C(8)-C(11) | 66.05(18) |
| C(6)-C(7)-C(8)-C(1) | -55.05(18) |
| C(2)-C(1)-C(8)-C(10) | 61.38(18) |
| C(12)-C(1)-C(8)-C(10) | -62.05(18) |
| C(9)-C(1)-C(8)-C(10) | 177.13(14) |
| C(2)-C(1)-C(8)-C(7) | -57.27(17) |
| C(12)-C(1)-C(8)-C(7) | 179.30(14) |
| C(9)-C(1)-C(8)-C(7) | 58.48(17) |
| C(2)-C(1)-C(8)-C(11) | -177.88(14) |
| C(12)-C(1)-C(8)-C(11) | 58.69(18) |
| C(9)-C(1)-C(8)-C(11) | -62.13(18) |
| C(14)-C(5)-C(9)-O(9) | -3.2(2) |
| C(6)-C(5)-C(9)-O(9) | -124.98(17) |
| C(4)-C(5)-C(9)-O(9) | 114.84(17) |
| C(14)-C(5)-C(9)-C(1) | 177.81(13) |
| C(6)-C(5)-C(9)-C(1) | 56.02(18) |
| C(4)-C(5)-C(9)-C(1) | -64.16(17) |
| C(2)-C(1)-C(9)-O(9) | -122.89(16) |
| C(12)-C(1)-C(9)-O(9) | -5.9(2) |
| C(8)-C(1)-C(9)-O(9) | 118.70(17) |

| | |
|---|---|
| C(2)-C(1)-C(9)-C(5) | 56.15(18) |
| C(12)-C(1)-C(9)-C(5) | 173.12(13) |
| C(8)-C(1)-C(9)-C(5) | -62.26(17) |
| C(2)-C(1)-C(12)-O(12) | -135.15(18) |
| C(9)-C(1)-C(12)-O(12) | 109.76(19) |
| C(8)-C(1)-C(12)-O(12) | -11.1(2) |
| C(2)-C(1)-C(12)-O(13) | 45.04(17) |
| C(9)-C(1)-C(12)-O(13) | -70.04(16) |
| C(8)-C(1)-C(12)-O(13) | 169.12(13) |
| O(12)-C(12)-O(13)-C(13) | -7.2(2) |
| C(1)-C(12)-O(13)-C(13) | 172.63(13) |
| C(9)-C(5)-C(14)-C(15) | -67.7(2) |
| C(6)-C(5)-C(14)-C(15) | 53.0(2) |
| C(4)-C(5)-C(14)-C(15) | 175.80(16) |
| C(5)-C(14)-C(15)-C(16) | -122.8(2) |
| C(19)-Si(1)-C(17)-C(18) | 50.98(17) |
| C(21)-Si(1)-C(17)-C(18) | 172.42(14) |
| C(3)-Si(1)-C(17)-C(18) | -68.23(15) |
| C(21)-Si(1)-C(19)-C(20) | -69.0(2) |
| C(17)-Si(1)-C(19)-C(20) | 49.2(2) |
| C(3)-Si(1)-C(19)-C(20) | 169.39(17) |
| C(19)-Si(1)-C(21)-C(22) | 175.55(15) |
| C(17)-Si(1)-C(21)-C(22) | 55.39(17) |
| C(3)-Si(1)-C(21)-C(22) | -63.86(17) |

**Table A.7:** Bond lengths [Å] and angles [°] for **240.**

| | |
|---|---|
| Empirical formula | $C_{24}$ $H_{32}$ $O_4$ Si |
| Formula weight | 412.59 |
| Temperature (K) | 90.0(2) |
| Wavelength(Å) | 0.71073 |
| Crystal system | Orthorombic |
| Space group | Aba2 |
| Unit cell dimensions | |
| a (Å) | 13.78770(10) |
| α (°) | 90 |
| b (Å) | 27.9022(2) |
| β (°) | 90 |
| c (Å) | 11.44220(10) |
| γ (°) | 90 |
| Volume ($Å^3$) | 4401.90(6) |
| Z | 8 |
| Calculated density ($Mg/m^3$) | 1.245 |
| Absorption coefficient ($mm^{-1}$) | 0.134 |
| F(000) | 1776 |
| Crystal size (mm) | 0.42 x 0.20 x 0.12 mm |
| Θ range for data collection (°) | 1.46 to 27.48 |
| Limiting indices | -17≤h≤17 |
| | -36≤k≤35 |
| | -14≤l≤14 |
| Reflections collected / unique | 4899 / 4899 |
| | [R(int) = 0.0000] |
| Completeness to Θ= 27.46 | 100.00% |
| Absorption correction | Semi-empirical from equivalents |
| Max. transmission | 0.9841 |
| Min. transmission | 0.9460 |

| | |
|---|---|
| Data / restraints / parameters | 4899 / 1 / 267 |
| Goodness-of-fit on $F^2$ | 1.031 |
| Final R indices [I>2σ(I)] | R1 = 0.0317 |
| | ωR2 = 0.0730 |
| R indices (all data) | R1 = 0.0380 |
| | ωR2 = 0.0760 |
| Largest diff. peak and hole | .195 and -.167 |
| ($e \cdot Å^{-3}$) | |

**Table A.8:** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$) for **240**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Si(1) | 5921(1) | 1399(1) | 6992(1) | 14(1) |
| O(1) | 3290(1) | 190(1) | 7538(1) | 21(1) |
| O(2) | 4902(1) | 2203(1) | 9709(1) | 24(1) |
| O(3) | 5757(1) | 1521(1) | 9596(1) | 18(1) |
| O(4) | 3993(1) | 1166(1) | 10654(1) | 20(1) |
| C(1) | 4221(1) | 1496(1) | 8722(1) | 14(1) |
| C(2) | 4700(1) | 1220(1) | 7665(1) | 14(1) |
| C(3) | 4705(1) | 672(1) | 7874(1) | 15(1) |
| C(4) | 3689(1) | 500(1) | 8102(1) | 16(1) |
| C(5) | 3156(1) | 761(1) | 9096(1) | 16(1) |
| C(6) | 2271(1) | 1035(1) | 8577(1) | 21(1) |
| C(7) | 2562(1) | 1448(1) | 7776(1) | 18(1) |
| C(8) | 3300(1) | 1796(1) | 8320(1) | 17(1) |
| C(9) | 3824(1) | 1137(1) | 9616(1) | 15(1) |
| C(10) | 3581(1) | 2175(1) | 7406(2) | 22(1) |
| C(11) | 2812(1) | 2053(1) | 9361(2) | 24(1) |
| C(12) | 4972(1) | 1794(1) | 9386(1) | 17(1) |
| C(13) | 6502(1) | 1741(1) | 10312(2) | 23(1) |
| C(14) | 2797(1) | 394(1) | 10008(1) | 20(1) |
| C(15) | 3576(1) | 77(1) | 10499(2) | 21(1) |
| C(16) | 3598(1) | -391(1) | 10353(2) | 25(1) |
| C(17) | 6179(1) | 2056(1) | 7062(2) | 21(1) |
| C(18) | 6970(1) | 1051(1) | 7571(1) | 20(1) |
| C(19) | 5737(1) | 1237(1) | 5409(1) | 18(1) |
| C(20) | 5374(1) | 1577(1) | 4613(2) | 22(1) |
| C(21) | 5169(1) | 1451(1) | 3465(2) | 27(1) |
| C(22) | 5321(1) | 990(1) | 3082(2) | 31(1) |
| C(23) | 5688(1) | 649(1) | 3836(2) | 30(1) |
| C(24) | 5897(1) | 773(1) | 4993(2) | 22(1) |

**Table A.9:** Bond lengths [Å] and angles [°] for **240**.

| | |
|---|---|
| Si(1)-C(18) | 1.8640(16) |
| Si(1)-C(17) | 1.8681(15) |
| Si(1)-C(19) | 1.8849(16) |
| Si(1)-C(2) | 1.9174(15) |
| O(1)-C(4) | 1.2118(19) |
| O(2)-C(12) | 1.2027(19) |
| O(3)-C(12) | 1.3446(18) |
| O(3)-C(13) | 1.4500(18) |
| O(4)-C(9) | 1.2129(19) |
| C(1)-C(12) | 1.530(2) |
| C(1)-C(9) | 1.534(2) |
| C(1)-C(2) | 1.578(2) |
| C(1)-C(8) | 1.588(2) |
| C(2)-C(3) | 1.549(2) |
| C(2)-H(2) | 1.0000 |
| C(3)-C(4) | 1.503(2) |
| C(3)-H(3A) | 0.9900 |
| C(3)-H(3B) | 0.9900 |
| C(4)-C(5) | 1.538(2) |
| C(5)-C(9) | 1.517(2) |
| C(5)-C(14) | 1.543(2) |
| C(5)-C(6) | 1.557(2) |
| C(6)-C(7) | 1.526(2) |
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(7)-C(8) | 1.537(2) |
| C(7)-H(7A) | 0.9900 |
| C(7)-H(7B) | 0.9900 |
| C(8)-C(10) | 1.538(2) |
| C(8)-C(11) | 1.545(2) |
| C(10)-H(10A) | 0.9800 |
| C(10)-H(10B) | 0.9800 |
| C(10)-H(10C) | 0.9800 |
| C(11)-H(11A) | 0.9800 |
| C(11)-H(11B) | 0.9800 |
| C(11)-H(11C) | 0.9800 |
| C(13)-H(13A) | 0.9800 |
| C(13)-H(13B) | 0.9800 |
| C(13)-H(13C) | 0.9800 |
| C(14)-C(15) | 1.500(2) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(15)-C(16) | 1.318(2) |
| C(15)-H(15) | 0.9500 |
| C(16)-H(16A) | 0.9500 |
| C(16)-H(16B) | 0.9500 |
| C(17)-H(17A) | 0.9800 |
| C(17)-H(17B) | 0.9800 |
| C(17)-H(17C) | 0.9800 |
| C(18)-H(18A) | 0.9800 |
| C(18)-H(18B) | 0.9800 |

| | |
|---|---|
| C(18)-H(18C) | 0.9800 |
| C(19)-C(24) | 1.398(2) |
| C(19)-C(20) | 1.406(2) |
| C(20)-C(21) | 1.389(3) |
| C(20)-H(20) | 0.9500 |
| C(21)-C(22) | 1.375(3) |
| C(21)-H(21) | 0.9500 |
| C(22)-C(23) | 1.380(3) |
| C(22)-H(22) | 0.9500 |
| C(23)-C(24) | 1.398(2) |
| C(23)-H(23) | 0.9500 |
| C(24)-H(24) | 0.9500 |
| C(18)-Si(1)-C(17) | 110.39(7) |
| C(18)-Si(1)-C(19) | 108.73(7) |
| C(17)-Si(1)-C(19) | 107.59(8) |
| C(18)-Si(1)-C(2) | 113.76(7) |
| C(17)-Si(1)-C(2) | 113.92(7) |
| C(19)-Si(1)-C(2) | 101.82(7) |
| C(12)-O(3)-C(13) | 115.60(12) |
| C(12)-C(1)-C(9) | 105.31(12) |
| C(12)-C(1)-C(2) | 111.25(12) |
| C(9)-C(1)-C(2) | 110.01(11) |
| C(12)-C(1)-C(8) | 113.54(12) |
| C(9)-C(1)-C(8) | 104.59(11) |
| C(2)-C(1)-C(8) | 111.68(12) |
| C(3)-C(2)-C(1) | 111.41(12) |
| C(3)-C(2)-Si(1) | 108.35(10) |
| C(1)-C(2)-Si(1) | 123.24(10) |
| C(3)-C(2)-H(2) | 103.9 |
| C(1)-C(2)-H(2) | 103.9 |
| Si(1)-C(2)-H(2) | 103.9 |
| C(4)-C(3)-C(2) | 109.75(12) |
| C(4)-C(3)-H(3A) | 109.7 |
| C(2)-C(3)-H(3A) | 109.7 |
| C(4)-C(3)-H(3B) | 109.7 |
| C(2)-C(3)-H(3B) | 109.7 |
| H(3A)-C(3)-H(3B) | 108.2 |
| O(1)-C(4)-C(3) | 123.96(14) |
| O(1)-C(4)-C(5) | 121.00(14) |
| C(3)-C(4)-C(5) | 115.00(12) |
| C(9)-C(5)-C(4) | 109.09(12) |
| C(9)-C(5)-C(14) | 112.81(13) |
| C(4)-C(5)-C(14) | 109.79(12) |
| C(9)-C(5)-C(6) | 106.68(12) |
| C(4)-C(5)-C(6) | 108.97(12) |
| C(14)-C(5)-C(6) | 109.41(12) |
| C(7)-C(6)-C(5) | 113.18(12) |
| C(7)-C(6)-H(6A) | 108.9 |
| C(5)-C(6)-H(6A) | 108.9 |
| C(7)-C(6)-H(6B) | 108.9 |
| C(5)-C(6)-H(6B) | 108.9 |
| H(6A)-C(6)-H(6B) | 107.8 |
| C(6)-C(7)-C(8) | 114.02(13) |
| C(6)-C(7)-H(7A) | 108.7 |

| | |
|---|---|
| C(8)-C(7)-H(7A) | 108.7 |
| C(6)-C(7)-H(7B) | 108.7 |
| C(8)-C(7)-H(7B) | 108.7 |
| H(7A)-C(7)-H(7B) | 107.6 |
| C(7)-C(8)-C(10) | 109.02(13) |
| C(7)-C(8)-C(11) | 108.53(13) |
| C(10)-C(8)-C(11) | 108.29(13) |
| C(7)-C(8)-C(1) | 108.29(12) |
| C(10)-C(8)-C(1) | 110.93(12) |
| C(11)-C(8)-C(1) | 111.72(13) |
| O(4)-C(9)-C(5) | 123.22(14) |
| O(4)-C(9)-C(1) | 122.73(14) |
| C(5)-C(9)-C(1) | 113.95(12) |
| C(8)-C(10)-H(10A) | 109.5 |
| C(8)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| C(8)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| C(8)-C(11)-H(11A) | 109.5 |
| C(8)-C(11)-H(11B) | 109.5 |
| H(11A)-C(11)-H(11B) | 109.5 |
| C(8)-C(11)-H(11C) | 109.5 |
| H(11A)-C(11)-H(11C) | 109.5 |
| H(11B)-C(11)-H(11C) | 109.5 |
| O(2)-C(12)-O(3) | 123.06(14) |
| O(2)-C(12)-C(1) | 127.83(14) |
| O(3)-C(12)-C(1) | 109.09(12) |
| O(3)-C(13)-H(13A) | 109.5 |
| O(3)-C(13)-H(13B) | 109.5 |
| H(13A)-C(13)-H(13B) | 109.5 |
| O(3)-C(13)-H(13C) | 109.5 |
| H(13A)-C(13)-H(13C) | 109.5 |
| H(13B)-C(13)-H(13C) | 109.5 |
| C(15)-C(14)-C(5) | 114.54(13) |
| C(15)-C(14)-H(14A) | 108.6 |
| C(5)-C(14)-H(14A) | 108.6 |
| C(15)-C(14)-H(14B) | 108.6 |
| C(5)-C(14)-H(14B) | 108.6 |
| H(14A)-C(14)-H(14B) | 107.6 |
| C(16)-C(15)-C(14) | 123.67(16) |
| C(16)-C(15)-H(15) | 118.2 |
| C(14)-C(15)-H(15) | 118.2 |
| C(15)-C(16)-H(16A) | 120.0 |
| C(15)-C(16)-H(16B) | 120.0 |
| H(16A)-C(16)-H(16B) | 120.0 |
| Si(1)-C(17)-H(17A) | 109.5 |
| Si(1)-C(17)-H(17B) | 109.5 |
| H(17A)-C(17)-H(17B) | 109.5 |
| Si(1)-C(17)-H(17C) | 109.5 |
| H(17A)-C(17)-H(17C) | 109.5 |
| H(17B)-C(17)-H(17C) | 109.5 |
| Si(1)-C(18)-H(18A) | 109.5 |
| Si(1)-C(18)-H(18B) | 109.5 |

| | |
|---|---|
| H(18A)-C(18)-H(18B) | 109.5 |
| Si(1)-C(18)-H(18C) | 109.5 |
| H(18A)-C(18)-H(18C) | 109.5 |
| H(18B)-C(18)-H(18C) | 109.5 |
| C(24)-C(19)-C(20) | 117.43(15) |
| C(24)-C(19)-Si(1) | 121.89(12) |
| C(20)-C(19)-Si(1) | 120.58(13) |
| C(21)-C(20)-C(19) | 120.97(17) |
| C(21)-C(20)-H(20) | 119.5 |
| C(19)-C(20)-H(20) | 119.5 |
| C(22)-C(21)-C(20) | 120.45(17) |
| C(22)-C(21)-H(21) | 119.8 |
| C(20)-C(21)-H(21) | 119.8 |
| C(21)-C(22)-C(23) | 120.05(16) |
| C(21)-C(22)-H(22) | 120.0 |
| C(23)-C(22)-H(22) | 120.0 |
| C(22)-C(23)-C(24) | 119.90(17) |
| C(22)-C(23)-H(23) | 120.1 |
| C(24)-C(23)-H(23) | 120.1 |
| C(23)-C(24)-C(19) | 121.19(16) |
| C(23)-C(24)-H(24) | 119.4 |
| C(19)-C(24)-H(24) | 119.4 |

**Table A.10:** Anisotropic displacement parameters ($A^2$ x $10^3$) for **243**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [ $h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| Si(1) | 15(1) | 14(1) | 14(1) | 1(1) | 1(1) | -1(1) |
| O(1) | 24(1) | 19(1) | 21(1) | -2(1) | -3(1) | -4(1) |
| O(2) | 29(1) | 15(1) | 29(1) | -6(1) | -5(1) | 2(1) |
| O(3) | 17(1) | 16(1) | 20(1) | -3(1) | -6(1) | -1(1) |
| O(4) | 24(1) | 23(1) | 13(1) | -2(1) | -1(1) | 2(1) |
| C(1) | 14(1) | 13(1) | 14(1) | -1(1) | -1(1) | 3(1) |
| C(2) | 14(1) | 14(1) | 14(1) | 0(1) | -1(1) | 0(1) |
| C(3) | 17(1) | 14(1) | 15(1) | -1(1) | 2(1) | 0(1) |
| C(4) | 19(1) | 13(1) | 14(1) | 3(1) | -2(1) | 0(1) |
| C(5) | 14(1) | 16(1) | 16(1) | 2(1) | 0(1) | -1(1) |
| C(6) | 15(1) | 24(1) | 23(1) | 2(1) | -1(1) | 3(1) |
| C(7) | 14(1) | 22(1) | 18(1) | 2(1) | -3(1) | 4(1) |
| C(8) | 16(1) | 17(1) | 17(1) | 1(1) | -2(1) | 6(1) |
| C(9) | 14(1) | 16(1) | 16(1) | 0(1) | 1(1) | 5(1) |
| C(10) | 23(1) | 17(1) | 24(1) | 2(1) | -3(1) | 4(1) |
| C(11) | 24(1) | 23(1) | 25(1) | -2(1) | 1(1) | 9(1) |
| C(12) | 20(1) | 16(1) | 14(1) | 1(1) | -1(1) | 0(1) |
| C(13) | 24(1) | 23(1) | 23(1) | -1(1) | -9(1) | -5(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(14) | 20(1) | 21(1) | 19(1) | 4(1) | 4(1) | -2(1) |
| C(15) | 24(1) | 23(1) | 17(1) | 4(1) | 0(1) | -3(1) |
| C(16) | 28(1) | 28(1) | 20(1) | 3(1) | 2(1) | 1(1) |
| C(17) | 23(1) | 18(1) | 21(1) | 1(1) | 1(1) | -4(1) |
| C(18) | 17(1) | 23(1) | 20(1) | 2(1) | 1(1) | 0(1) |
| C(19) | 15(1) | 21(1) | 17(1) | 1(1) | 2(1) | -3(1) |
| C(20) | 19(1) | 26(1) | 20(1) | 3(1) | 2(1) | -1(1) |
| C(21) | 19(1) | 44(1) | 19(1) | 7(1) | 0(1) | 1(1) |
| C(22) | 19(1) | 58(1) | 16(1) | -9(1) | 1(1) | -4(1) |
| C(23) | 27(1) | 37(1) | 26(1) | -12(1) | 3(1) | -1(1) |
| C(24) | 19(1) | 25(1) | 21(1) | -2(1) | 2(1) | 0(1) |

**Table A.11:** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$ x $10^3$) for **240**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | 4227 | 1265 | 7011 | 17 |
| H(3A) | 4972 | 507 | 7179 | 18 |
| H(3B) | 5123 | 596 | 8552 | 18 |
| H(6A) | 1865 | 807 | 8130 | 25 |
| H(6B) | 1873 | 1163 | 9226 | 25 |
| H(7A) | 1973 | 1630 | 7559 | 22 |
| H(7B) | 2842 | 1314 | 7049 | 22 |
| H(10A) | 2998 | 2347 | 7149 | 32 |
| H(10B) | 3885 | 2018 | 6734 | 32 |
| H(10C) | 4039 | 2403 | 7753 | 32 |
| H(11A) | 3222 | 2320 | 9618 | 36 |
| H(11B) | 2726 | 1826 | 10007 | 36 |
| H(11C) | 2177 | 2176 | 9118 | 36 |
| H(13A) | 6655 | 2060 | 10004 | 35 |
| H(13B) | 7087 | 1542 | 10298 | 35 |
| H(13C) | 6268 | 1771 | 11118 | 35 |
| H(14A) | 2487 | 570 | 10659 | 24 |
| H(14B) | 2295 | 190 | 9641 | 24 |
| H(15) | 4081 | 222 | 10939 | 25 |
| H(16A) | 3102 | -546 | 9917 | 30 |
| H(16B) | 4109 | -574 | 10685 | 30 |
| H(17A) | 6305 | 2149 | 7874 | 31 |
| H(17B) | 5619 | 2234 | 6765 | 31 |
| H(17C) | 6750 | 2129 | 6583 | 31 |
| H(18A) | 7519 | 1080 | 7033 | 30 |

| | | | | |
|---|---|---|---|---|
| H(18B) | 6787 | 713 | 7648 | 30 |
| H(18C) | 7155 | 1177 | 8339 | 30 |
| H(20) | 5269 | 1897 | 4864 | 26 |
| H(21) | 4922 | 1685 | 2940 | 33 |
| H(22) | 5174 | 906 | 2297 | 37 |
| H(23) | 5799 | 331 | 3570 | 36 |
| H(24) | 6152 | 537 | 5506 | 26 |

**Table A.12:** Torsion angles [°] for **240**.

| | |
|---|---|
| C(12)-C(1)-C(2)-C(3) | 111.90(13) |
| C(9)-C(1)-C(2)-C(3) | -4.40(17) |
| C(8)-C(1)-C(2)-C(3) | -120.08(13) |
| C(12)-C(1)-C(2)-Si(1) | -19.50(17) |
| C(9)-C(1)-C(2)-Si(1) | -135.81(11) |
| C(8)-C(1)-C(2)-Si(1) | 108.51(13) |
| C(18)-Si(1)-C(2)-C(3) | -36.23(12) |
| C(17)-Si(1)-C(2)-C(3) | -163.94(10) |
| C(19)-Si(1)-C(2)-C(3) | 80.56(11) |
| C(18)-Si(1)-C(2)-C(1) | 96.40(13) |
| C(17)-Si(1)-C(2)-C(1) | -31.30(14) |
| C(19)-Si(1)-C(2)-C(1) | -146.81(12) |
| C(1)-C(2)-C(3)-C(4) | 55.96(16) |
| Si(1)-C(2)-C(3)-C(4) | -165.42(10) |
| C(2)-C(3)-C(4)-O(1) | 123.63(16) |
| C(2)-C(3)-C(4)-C(5) | -54.20(16) |
| O(1)-C(4)-C(5)-C(9) | -178.47(13) |
| C(3)-C(4)-C(5)-C(9) | -0.56(17) |
| O(1)-C(4)-C(5)-C(14) | 57.45(19) |
| C(3)-C(4)-C(5)-C(14) | -124.65(14) |
| O(1)-C(4)-C(5)-C(6) | -62.36(18) |
| C(3)-C(4)-C(5)-C(6) | 115.55(14) |
| C(9)-C(5)-C(6)-C(7) | 50.65(17) |
| C(4)-C(5)-C(6)-C(7) | -67.00(16) |
| C(14)-C(5)-C(6)-C(7) | 172.96(13) |
| C(5)-C(6)-C(7)-C(8) | -51.44(18) |
| C(6)-C(7)-C(8)-C(10) | 176.50(13) |
| C(6)-C(7)-C(8)-C(11) | -65.74(16) |
| C(6)-C(7)-C(8)-C(1) | 55.71(17) |
| C(12)-C(1)-C(8)-C(7) | -174.46(13) |
| C(9)-C(1)-C(8)-C(7) | -60.18(15) |
| C(2)-C(1)-C(8)-C(7) | 58.76(16) |
| C(12)-C(1)-C(8)-C(10) | 65.94(17) |
| C(9)-C(1)-C(8)-C(10) | -179.78(12) |
| C(2)-C(1)-C(8)-C(10) | -60.84(16) |
| C(12)-C(1)-C(8)-C(11) | -54.99(17) |

| | |
|---|---|
| C(9)-C(1)-C(8)-C(11) | 59.28(15) |
| C(2)-C(1)-C(8)-C(11) | 178.23(13) |
| C(4)-C(5)-C(9)-O(4) | -127.81(15) |
| C(14)-C(5)-C(9)-O(4) | -5.5(2) |
| C(6)-C(5)-C(9)-O(4) | 114.62(16) |
| C(4)-C(5)-C(9)-C(1) | 55.68(16) |
| C(14)-C(5)-C(9)-C(1) | 177.96(12) |
| C(6)-C(5)-C(9)-C(1) | -61.89(15) |
| C(12)-C(1)-C(9)-O(4) | 10.95(18) |
| C(2)-C(1)-C(9)-O(4) | 130.92(14) |
| C(8)-C(1)-C(9)-O(4) | -109.00(16) |
| C(12)-C(1)-C(9)-C(5) | -172.52(12) |
| C(2)-C(1)-C(9)-C(5) | -52.55(16) |
| C(8)-C(1)-C(9)-C(5) | 67.53(15) |
| C(13)-O(3)-C(12)-O(2) | 4.0(2) |
| C(13)-O(3)-C(12)-C(1) | -174.83(13) |
| C(9)-C(1)-C(12)-O(2) | -107.17(18) |
| C(2)-C(1)-C(12)-O(2) | 133.68(17) |
| C(8)-C(1)-C(12)-O(2) | 6.7(2) |
| C(9)-C(1)-C(12)-O(3) | 71.58(14) |
| C(2)-C(1)-C(12)-O(3) | -47.57(16) |
| C(8)-C(1)-C(12)-O(3) | -174.57(12) |
| C(9)-C(5)-C(14)-C(15) | -66.44(17) |
| C(4)-C(5)-C(14)-C(15) | 55.45(17) |
| C(6)-C(5)-C(14)-C(15) | 174.99(14) |
| C(5)-C(14)-C(15)-C(16) | -116.28(18) |
| C(18)-Si(1)-C(19)-C(24) | 35.50(15) |
| C(17)-Si(1)-C(19)-C(24) | 155.06(13) |
| C(2)-Si(1)-C(19)-C(24) | -84.88(14) |
| C(18)-Si(1)-C(19)-C(20) | -148.32(12) |
| C(17)-Si(1)-C(19)-C(20) | -28.76(14) |
| C(2)-Si(1)-C(19)-C(20) | 91.30(13) |
| C(24)-C(19)-C(20)-C(21) | 1.1(2) |
| Si(1)-C(19)-C(20)-C(21) | -175.24(12) |
| C(19)-C(20)-C(21)-C(22) | -0.3(3) |
| C(20)-C(21)-C(22)-C(23) | -0.6(3) |
| C(21)-C(22)-C(23)-C(24) | 0.6(3) |
| C(22)-C(23)-C(24)-C(19) | 0.3(3) |
| C(20)-C(19)-C(24)-C(23) | -1.1(2) |
| Si(1)-C(19)-C(24)-C(23) | 175.17(13) |

**Table A.13:** Hydrogen bonds for **243** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|

## References


(1) Golden, F. In *Time*, 2001; Vol. 157.
(2) Nagourney, E. In *The New York Times* New York, 2004.
(3) Cuesta–Rubio, O.; Velez–Castro, H.; Frontana–Uribe, B. A.; Cardenas, J. *Phytochemistry* **2001**, *57*, 279-283.
(4) Mizobuchi, S.; Sato, Y. *Ag. Biol. Chem.* **1985**, *49*, 399-403.
(5) Zhao, F.; Watanabe, Y.; Nozawa, H.; Daikonnya, A.; Kondo, K.; Kitanaka, S. *J. Nat. Prod.* **2005**, *68*, 43-49.
(6) Zuurbier, K. W. M.; Fung, S. Y.; Scheffer, J. J. C.; Verpoorte, R. *Phytochemistry* **1998**, *49*, 2315-2322.
(7) Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389-407.
(8) Collins, M.; Laws, D. R. J. *J. Chem. Soc., Perkin Trans.* **1973**, 2013-2015.
(9) Collins, M.; Laws, D. R. J.; McGuinness, J. D. *J. Chem. Soc. (C)* **1971**, 3814-3818.
(10) Drewett, K. J.; Laws, D. R. J. *J. Inst. Brewing* **1970**, *76*, 188-190.
(11) Weng, J. R.; Tsao, L. T.; Wang, J. P.; Wu, R. R.; Lin, C. N. *J. Nat. Prod.* **2004**, *67*, 1796-1799.
(12) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073-1079.
(13) de Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427-6430.
(14) Matsuhisa, M.; Shikishima, Y.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Shibata, H.; Higuti, T.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2002**, *65*, 290-4.
(15) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947-949.
(16) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853-857.
(17) Grossman, R. B.; Jacobs, H. *Tetrahedron Lett.* **2000**, *41*, 5165-5169.
(18) Baggett, S.; Protiva, P.; Mazzola, E. P.; Yang, H.; Ressler, E. T.; Basile, M. J.; Weinstein, I. B.; Kennelly, E. J. *J. Nat. Prod.* **2005**, *68*, 354-360.
(19) Cuesta–Rubio, O.; Padron, A.; Castro, H. V.; Pizza, C.; Rastrelli, L. *J. Nat. Prod.* **2001**, *64*, 973-975.
(20) Weng, J. R.; Lin, C. N.; Tsao, L. T.; Wang, A. P. *Chem. Eur. J.* **2003**, *9*, 5520-5527.
(21) Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Guan, Z. Q.; Borris, R. P.; Stijfhoorn, E.; Stevenson, D.; Wang, J. H.; Sharma, N.; MacNaul, K.; Menke, J. G.; Ali, A.; Schulman, M. J.; Singh, S. B. *J. Nat. Prod.* **2005**, *68*, 617-619.
(22) Nilar; Nguyen, L.-H. D.; Venkatraman, G.; Sim, K.-Y.; Harrison, L. J. *Phytochemistry* **2005**, *66*, 1718-1723.
(23) Brondz, I.; Greibrokk, T.; Groth, P. A.; Aasen, A. J. *Tetrahedron Lett.* **1982**, *23*, 1299-1300.
(24) Venkatswamy, G.; Yemul, S. S.; Rao, A. V. R.; Palmer, K. J. *Indian J. Chem.* **1975**, *13*, 1355.
(25) Hernandez, I. M.; Fernandez, M. C.; Cuesta–Rubio, O.; Piccinelli, A. L.; Rastrelli, L. *J. Nat. Prod.* **2005**, *68*, 931-4.
(26) Cuesta–Rubio, O.; A., C. C.; Rojas, N.; Velez Castro, H.; Rastreli, L.; Aquino, R. *J. Nat. Prod.* **1999**, *62*, 1013-1015.
(27) Cuesta–Rubio, O.; Frontana-Uribe, B. A.; Ramirez-Apan, T.; Cardenas, J. *Z. Naturforsch. C* **2002**, *57*, 372-378.
(28) Gustafson, K. R.; Blunt, J. W.; Munro, M. H. G.; Fuller, R. W.; Mckee, T. C.; Cardellina, J. H.; Mcmahon, J. B.; Cragg, G. M.; Boyd, M. R. *Tetrahedron* **1992**, *48*, 10093-10102.

(29) Krishnamurthy, N.; Lewis, Y. S.; Ravindranath, B. *Tetrahedron Lett.* **1981**, *22*, 793-6.
(30) Rama Rao, A. V.; Venkatswamy, G.; Pendse, A. D. *Tetrahedron Lett.* **1980**, *21*, 1975-8.
(31) Sahu, A.; Das, B.; Chatterjee, A. *Phytochemistry* **1989**, *28*, 1233-1235.
(32) Iinuma, M.; Tosa, H.; Tanaka, T.; Kanamaru, S.; Asai, F.; Kobayashi, Y.; Miyauchi, K.; Shimano, R. *Biol. Pharm. Bull.* **1996**, *19*, 311-314.
(33) Roux, D.; Hadi, H. A.; Thoret, S.; Guenard, D.; Thoison, O.; Pais, M.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 1070-1076.
(34) Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, 2791-4.
(35) Bystrov, N. S.; Gupta, S. R.; Dobrynin, V. N.; Kolosov, M. N.; Chernov, B. K. *Bioorg. Chem.* **1978**, *4*, 948-55.
(36) Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Riabova, I. D. *Antibiotiki* **1971**, *16*, 510-3.
(37) Maisenbacher, P.; Kovar, K. A. *Planta Med.* **1992**, *58*, 291-3.
(38) Decosterd, L. A.; Stoeckli-Evans, H.; Chapuis, J. C.; Msonthi, J. D.; Sordat, B.; Hostettmann, K. *Helv. Chim. Acta* **1989**, *72*, 464-71.
(39) Lokvam, J.; Braddock, J. F.; Reichardt, P. B.; Clausen, T. P. *Phytochemistry* **2000**, *55*, 29-34.
(40) Weng, J. R.; Lin, C. N.; Tsao, L. T.; Wang, J. P. *Chem. Eur. J.* **2003**, *9*, 1958-1963.
(41) Henry, G. E.; Jacobs, H.; Sean-Carrington, C. M.; McLean, S.; Reynolds, W. F. *Tetrahedron* **1999**, *55*, 1581-1596.
(42) Henry, G. E.; Jacobs, H.; Sean-Carrington, C. M.; McLean, S.; Reynolds, W. F. *Tetrahedron* **1999**, *55*, 1581.
(43) Porto, A. L. M.; Machado, S. M. F.; de Oliveira, C. M. A.; Bittrich, V.; Amaral, M. C. E.; Marsaioli, A. J. *Phytochemistry* **2000**, *55*, 755.
(44) Trifunovic, S.; Vajs, V.; Macura, S.; Juranic, N.; Djarmati, Z.; Jankov, R.; Milosavljevic, S. *Phytochemistry* **1998**, *49*, 1305-10.
(45) Verotta, L.; Appendino, G.; Belloro, E.; Jakupovic, J.; Bombardelli, E. *J. Nat. Prod.* **1999**, *62*, 770-772.
(46) Verotta, L.; Appendino, G.; Jakupovic, J.; Bombardelli, E. *J. Nat. Prod.* **2000**, *63*, 412-415.
(47) Hu, L. H.; Sim, K., Y *Org. Lett.* **1999**, *1*, 879-882.
(48) Teixeira, J. S. A. R.; Cruz, F. G. *Tetrahedron Lett.* **2005**, *46*, 2813-2816.
(49) Wu, C. C.; Weng, J. R.; Won, S. J.; Lin, C. N. *J. Nat. Prod.* **2005**, *68*, 1125-7.
(50) Christian, O. E.; Henry, G. E.; Jacobs, H.; McLean, S.; Reynolds, W. F. *J. Nat. Prod.* **2001**, *64*, 23-5.
(51) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701-706.
(52) Lin, Y.-L.; Wu, Y.-S. *Helv. Chim. Acta* **2003**, *86*, 2156.
(53) Shan, M. D.; Hu, L. H.; Chen, Z. L. *J. Nat. Prod.* **2001**, *64*, 127-130.
(54) Tanaka, N.; Takaishi, Y.; Shikishima, Y.; Nakanishi, Y.; Bastow, K.; Lee, K. H.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2004**, *67*, 1870-5.
(55) Lin, C.-N.; Kiang, C.-W.; Lu, C.-M.; Wu, R.-R.; Lee, K.-H. *Chem. Commun.* **1996**, 1315.
(56) Henry, G. E.; Jacobs, H.; Carrington, C. M. S.; McLean, S.; Reynolds, W. F. *Tetrahedron Lett.* **1996**, *37*, 8663-8666.
(57) Hu, L. H.; Sim, K., Y *Tetrahedron Lett.* **1998**, *39*, 7999-8002.
(58) Hu, L. H.; Sim, K., Y *Tetrahedron Lett.* **1999**, *40*, 759-762.
(59) Williams, R. B.; Hoch, J.; Glass, T. E.; Evans, R.; Miller, J. S.; Wisse, J. H.; Kingston, D. G. *Planta Med.* **2003**, *69*, 864-6.

(60) Fuller, R. W.; Blunt, J. W.; Boswell, J. L.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 130-132.
(61) Blount, J. F.; Williams, T. H. *Tetrahedron Lett.* **1976**, 2921-4.
(62) Dreyer, D. L. *Phytochemistry* **1974**, *13*, 2883-4.
(63) Karanjgoakar, C. G.; Rao, A. V. R.; Venkataraman, K.; Yemul, S. S.; Palmer, K. J. *Tetrahedron Lett.* **1973**, 4977-80.
(64) de Almeida Alves, T. M.; de Oliveira Alves, R.; Romanha, A. J.; Zani, C. L.; dos Santos, M. H.; Nagem, T. J. *J. Nat. Prod.* **1999**, *62*, 369-371.
(65) Delle Monache, F.; Delle Monache, G.; Gacs–Baitz, E. *Phytochemistry* **1991**, *30*, 2003-2005.
(66) Piccinelli, A. L.; Cuesta–Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206-8211.
(67) Santos, M. H.; Speziali, N. L.; Nagem, T. J.; Oliveira, T. T. *Acta Cryst. C* **1998**, *54*, 1990-1992.
(68) Bokesch, H. R.; Groweiss, A.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 1197-9.
(69) McCandlish, L. E.; Hanson, J. C.; Stout, G. H. *Acta Cryst.* **1976**, *B.32*, 1793-1801.
(70) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2001**, *84*, 3380.
(71) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2000**, *63*, 104-8.
(72) Mennini, T.; Gobbi, M. *Life Sci.* **2004**, *75*, 1021-1027.
(73) Chatterjee, S. S.; Bhattacharya, S. K.; Wonnemann, M.; Singer, A.; Muller, W. E. *Life Sci.* **1998**, *63*, 499-510.
(74) Chatterjee, S. S.; Noldner, M.; Koch, E.; Erdelmeier, C. *Pharmacopsychiatry* **1998**, *31*, 7-15.
(75) Muller, W. E.; Singer, A.; Wonnemann, M.; Hafner, U.; Rolli, M.; Schafer, C. *Pharmacopsychiatry* **1998**, *31 Suppl 1*, 16-21.
(76) Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786-4793.
(77) Moore, L. B.; Goodwin, B.; Jones, S. A.; Wisely, G. B.; Serabjit-Singh, C. J.; Willson, T. M.; Collins, J. L.; Kliewer, S. A. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7500-2.
(78) Rodriguez-Landa, J. F.; Contreras, C. M. *Phytomedicine* **2003**, *10*, 688-699.
(79) Kaehler, S. T.; Sinner, C.; Chatterjee, S. S.; Philippu, A. *Neurosci. Lett.* **1999**, *262*, 199-202.
(80) Muller, W. E.; Singer, A.; Wonnemann, M. *Pharmacopsychiatry* **2001**, *34 Suppl 1*, S98-102.
(81) Schempp, C. M.; Pelz, K.; Wittmer, A.; Schopf, E.; Simon, J. C. *Lancet* **1999**, *353*, 2129.
(82) Vogel, G. *Science* **2001**, *291*, 35-7.
(83) Chen, Y. P.; Ferguson, S. S.; Negishi, M.; Goldstein, J. A. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 495-501.
(84) Verotta, L.; Appendino, G.; Belloro, E.; Bianchi, F.; Sterner, O.; Lovati, M.; Bombardelli, E. *J. Nat. Prod.* **2002**, *65*, 433-438.
(85) Bystrov, N. S.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Chernov, B. K. *Bioorg. Chem.* **1978**, *4*, 791-7.
(86) Hostanska, K.; Reichling, J.; Bommer, S.; Weber, M.; Saller, R. *Eur. J. Pharm. Biopharm.* **2003**, *56*, 121.
(87) Salatino, A.; Teixeira, E. W.; Negri, G.; Message, D. *Evid. Based Complement. Alternat. Med.* **2005**, *2*, 33-38.
(88) Bankova, V. S.; de Castro, S. L.; Marcucci, M. C. *Apidologie* **2000**, *31*, 3-15.
(89) Marcucci, M. C. *Apidologie* **1995**, *26*, 83-99.

(90) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200-14201.
(91) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, ASAP.
(92) Krishnamurthy, N.; Ravindranath, B.; Row, T. N. G.; Venkatesan, K. *Tetrahedron Lett.* **1982**, *23*, 2233-6.
(93) Yamaguchi, F.; Ariga, T.; Yoshimura, Y.; Nakazawa, H. *J. Ag. Food Chem.* **2000**, *48*, 180-185.
(94) Yamaguchi, F.; Saito, M.; Ariga, T.; Yoshimura, Y.; Nakazawa, H. *J. Ag. Food Chem.* **2000**, *48*, 2320-2325.
(95) Das, D.; Bandyopadhyay, D.; Banerjee, R. K. *Free Rad. Biol. Med.* **1998**, *24*, 460-469.
(96) Das, D.; Bandyopadhyay, D.; Bhattacharjee, M.; Banerjee, R. K. *Free Rad. Biol. Med.* **1997**, *23*, 8-18.
(97) Chatterjee, A.; Yasmin, T.; Bagchi, D.; Stohs, S. J. *Mol. Cell Biochem.* **2003**, *243*, 29-35.
(98) Sang, S. M.; Liao, C. H.; Pan, M. H.; Rosen, R. T.; Lin-Shiau, S. Y.; Lin, J. K.; Ho, C. T. *Tetrahedron* **2002**, *58*, 10095-10102.
(99) Sang, S. M.; Pan, M. H.; Cheng, X. F.; Bai, N. S.; Stark, R. E.; Rosen, R. T.; Lin-Shiau, S. Y.; Lin, J. K.; Ho, C. T. *Tetrahedron* **2001**, *57*, 9931-9938.
(100) Pan, M. H.; Chang, W. L.; Lin-Shiau, S. Y.; Ho, C. T.; Lin, J. K. *J. Ag. Food Chem.* **2001**, *49*, 1464-1474.
(101) Tanaka, T.; Kohno, H.; Shimada, R.; Kagami, S.; Yamaguchi, F.; Kataoka, S.; Ariga, T.; Murakami, A.; Koshimizu, K.; Ohigashi, H. *Carcinogenesis* **2000**, *21*, 1183-1189.
(102) Yoshida, K.; Tanaka, T.; Hirose, Y.; Yamaguchi, F.; Kohno, H.; Toida, M.; Hara, A.; Sugie, S.; Shibata, T.; Mori, H. *Cancer Lett.* **2005**, *221*, 29-39.
(103) Balasubramanyam, K.; Altaf, M.; Varier, R. A.; Swaminathan, V.; Ravindran, A.; Sadhale, P. P.; Kundu, T. K. *J. Biol. Chem.* **2004**, *279*, 33716-33726.
(104) Tosa, H.; Iinuma, M.; Tanaka, T.; Nozaki, H.; Ikeda, S.; Tsutui, K.; Yamada, M.; Fujimori, S. *Chem. Phar. Bull.* **1997**, *45*, 418.
(105) Drawert, F.; Beier, J. *Phytochemistry* **1974**, *13*, 2149-2155.
(106) Drawert, F.; Beier, J. *Phytochemistry* **1976**, *15*, 1695-1696.
(107) Drawert, F.; Beier, J. *Phytochemistry* **1976**, *15*, 1693-1694.
(108) Liu, B.; Falkenstein-Paul, H.; Schmidt, W.; Beerhues, L. *Plant J.* **2003**, *34*, 847-55.
(109) Klingauf, P.; Beuerle, T.; Mellenthin, A.; El-Moghazy, S. A. M.; Boubakir, Z.; Beerhues, L. *Phytochemistry* **2005**, *66*, 139-145.
(110) Zuurbier, K. W. M.; Fung, S. Y.; Scheffer, J. J. C.; Verpoorte, R. *Phytochemistry* **1995**, *38*, 77-82.
(111) Hecht, S.; Wungsintaweekul, J.; Rohdich, F.; Kis, K.; Radykewicz, T.; Schuhr, C. A.; Eisenreich, W.; Richter, G.; Bacher, A. *J. Org. Chem.* **2001**, *66*, 7770-7775.
(112) Eisenreich, W.; Rohdich, F.; Bacher, A. *Trends Plant Sci.* **2001**, *6*, 78-84.
(113) Gabrielsen, M.; Rohdich, F.; Eisenreich, W.; Grawert, T.; Hecht, S.; Bacher, A.; Hunter, W. N. *Eur. J. Biochem.* **2004**, *271*, 3028-3035.
(114) Boubakir, Z.; Beuerle, T.; Liu, B.; Beerhues, L. *Phytochemistry* **2005**, *66*, 51-57.
(115) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621-3624.
(116) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859-862.
(117) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943-1946.
(118) Kraus, G. A.; Jeon, I. *Tetrahedron* **2005**, *61*, 2111-2116.
(119) Nicolaou, K. C.; Carenzi, G. E.; Jeso, V. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 3895-9.
(120) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G. Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807-810.

(121) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724-4725.
(122) Young, D. G. J.; Zeng, D. X. *J. Org. Chem.* **2002**, *67*, 3134-3137.
(123) Kraus, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975-8978.
(124) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659-661.
(125) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113-1116.
(126) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619-21.
(127) Schonwalder, K.-H.; Kollat, P.; Stezowski, J. J.; Effenberger, F. *Chem. Ber.* **1984**, *117*, 3280.
(128) Chapuis, C.; Brauchli, R. *Helv. Chim. Acta* **1992**, *75*, 1527-1546.
(129) Vialemaringe, M.; Bourgeois, M. J.; Campagnole, M.; Montaudon, E. *Helv. Chim. Acta* **2000**, *83*, 616-629.
(130) Grossman, R. B. *Synlett* **2001**, *1*, 13-21.
(131) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1100-1102.
(132) Moloney, M. G.; Pinhey, J. T.; Roche, E. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, *2*, 333-341.
(133) Skeean, R. W.; L., T. G.; White, J. D. *Tetrahedron Lett.* **1976**, *17*, 525.
(134) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Oog. Chem.* **1985**, *50*, 1939-1948.
(135) Elliott, G. I.; Konopelski, J. P.; Olmstead, M. M. *Org Lett* **1999**, *1*, 1867-1870.
(136) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **2002**, *39*, 2609-2612.
(137) Kira, K.; Tanda, H.; Hamajina, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485-6492.
(138) Fristad, W. E.; Bailey, T. R.; Paquette, L. A. *J Org Chem* **1980**, *45*, 3028 - 3037.
(139) Yamamoto, K.; Kimura, T.; Tomo, Y. *Tetrahedron Lett.* **1985**, *26*, 4505-4508
(140) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.
(141) Garside, D.; Kirk, D. N.; Waldron, N. M. *Steroids* **1994**, *59*, 702-711.
(142) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103-4110.
(143) Fleming, I.; Higgins, D.; Lawrence, N. J.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3331-3349.
(144) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J Am Chem Soc* **1993**, *115*, 6487 - 6498.
(145) Harada, T.; Imanaka, S.; Ohyama, Y.; Matsuda, Y.; Oku, A. *Tetrahedron Lett.* **1992**, *33*, 5807-5810
(146) Bakuzis, P.; Bakuzis, M. L. F. *J Org Chem* **1981**, *46*, 235 - 239.
(147) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J Org Chem* **2002**, *67*, 3700-4.
(148) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47-53.
(149) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821-6825.
(150) Abu Ali, H.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3862-3965.
(151) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469-12486
(152) Thominiaux, C.; Chiaroni, A.; Desmaële, D. *Tetrahedron Lett.* **2002**, *43*, 4107-4110
(153) Yamakawa, K.; Nishitani, K. *Chem. Pharm. Bull.* **1976**, 2810.
(154) Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J Org Chem* **2001**, *66*, 1046-8.
(155) Suzuki, M.; Watanabe, A.; Noyori, R. *J Am Chem Soc* **1980**, *102*, 2095-2096.
(156) Corey, E. J.; Ensley, H. E. *J Org Chem* **1973**, *38*, 3187 - 3189.
(157) Jung, M. E.; Piizzi, G. *Org Lett* **2003**, *5*, 137-40.
(158) Ley, S. V.; Somovilla, A. A.; Broughton, H. B.; Craig, D.; Slawin, A. M. Z.; Toogood, P. L.; Williams, D. J. *Tetrahedron* **1989**, *45*, 2143-2164

(159) Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, A. *J Org Chem* **1998**, *63*, 122-128.
(160) Molander, M. A.; Hahn, G. *J Org Chem* **1986**, *51*, 2596 - 2599.
(161) Osuka, A.; TAka-Oka, K. *Chem. Lett* **1984**, 271.
(162) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J Am Chem Soc* **2004**, *126*, 2300-1.
(163) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J Am Chem Soc* **2005**, *127*, 12790-1.
(164) Kalyani, D.; Sanford, M. S. *Org Lett* **2005**, *7*, 4149-52.
(165) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599-7662

## Vita

The author was born on February 24, 1974 in Iasi, Romania. She received a Bachelor of Science degree in Biochemical Engineering in 1997 and a Master of Science degree in Chemistry from "Gh. Asachi" Technical University, Department of Industrial Chemistry, Iasi, Romania. Roxana worked under the supervision of Dr. Valeria Marta Gorduza and her title M.S. thesis title was "Antioxidants in Red Wine". Roxana joined the Graduate Program at the Chemistry Department, University of Kentucky in the Fall of 2000, and joined the research group of Dr. Robert B. Grossman in the Spring of 2001. During his tenure at the University of Kentucky she was the recipient of the Commonwealth Research Award (2003) and the Distinguished Visiting Professor Dissertation committee member award (2006). Roxana is an author or co-author of four peer-reviewed manuscripts.

- "The Polyprenylated Polycyclic Acylphloroglucinols": **Roxana Ciochina** and Robert B. Grossman. *Chemical Reviews*. Manuscript submitted on January 2006.
- "EPOCH: An Organic Chemistry Homework Program that Offers Response-Specific Feedback.": Raghu Ram Chamala, **Roxana Ciochina**, Raphael A. Finkel, Robert B. Grossman, Saravana Kannan, and Prasanth Ramachandran. *J. Chem. Ed.* 2006, *83(1)*, 164-169.
- "A New Synthetic Approach to the Polyprenylated Polycyclic Acylphloroglucinols.": **Roxana Ciochina** and Robert B. Grossman. *Org. Lett.* 2003, *5(24)*, 4619-4622.
- "The Voltammetric and Spectral Characterization of *o*-, *m*-, and *p*-Phenylenediamines": Al. Duca, **Roxana Ciochina**, Doina Bejan and Maria Gaburici. *Analele St. Univ. "Al. Ioan Cuza", Iasi*, s. Chim. VIII, 1, (2000).