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Synthesis of Protoilludanes and Related Sesquiterpenes

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Natural products continue to hold the interest and attention of a wide chemical community. This is due to their biological properties and potential applicability in health care and plant protection, as well as their frequently complex molecular architectures and arrays of functionality, which make them a challenge for total synthesis and a testing ground for novel methodology. These criteria are met to an extraordinary degree by protoilludanes, which are sesquiterpenes with a characteristic tricyclic 5/6/4-framework. The fortieth anniversary of the first protoilludane synthesis has now been taken as an occasion to review the main aspects of this fascinating class of compounds. Biosynthesis, biological properties and the unusually rich variety of synthetic approaches developed over the past forty years are discussed. About 80 different substitution patterns and 15 completed or uncompleted synthetic routes are listed in this review with the goal of providing a multifacetted picture of the changes in and development of synthetic philosophy and methodology from past to present.

Introduction

Fungal and bacterial extracts are rich sources of highly interesting natural products, some of them most beneficial for human society. Prominent examples are penicillin, isolated by Fleming in 1929,[1] or streptomycin, the first antibiotic found to be active against tuberculosis.[2] Modern society depends heavily on these metabolites and today a number of natural products isolated from fungal or bacterial sources are prepared synthetically or derived by biotechnological methods.

Higher fungi are known to produce structurally diverse terpenoids from common precursors. Some of these ter-

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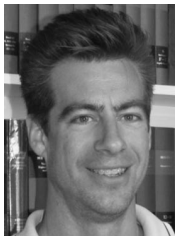
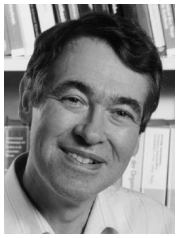


Peter Siengalewicz studied chemistry at the University of Innsbruck and worked with Prof. Schantl (Innsbruck) and Prof. Hudlicky (Gainesville, Fl) on the synthesis of Amaryllidaceae alkaloids. In 2003 he joined the research group of Prof. Mulzer to pursue graduate studies and received his PhD in 2008. After doing postdoctoral research in the pharmaceutical industry he returned to Prof. Mulzer's research group and works in the area of terpenoid chemistry.



Johann Mulzer received his PhD in 1974 at Ludwig Maximilians University in Munich under the supervision of Rolf Huisgen, after which he joined the group of E. J. Corey at Harvard as a postdoctoral fellow. Between 1982 and 1996 he held professorships at the University of Düsseldorf, the Freie Universität Berlin, and Frankfurt University. Currently he holds a position as full professor of Organic Chemistry at the University of Vienna. His main research interests lie in the field of total synthesis of structurally and physiologically interesting natural products.

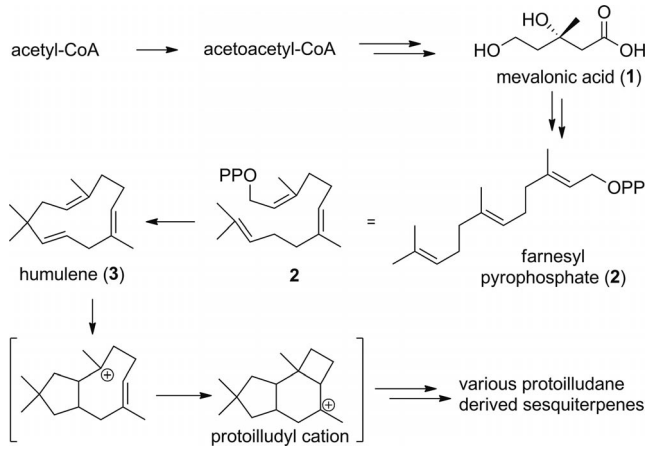
Uwe Rinner studied chemistry at the Technical University in Graz before moving to Gainesville, Florida to pursue graduate studies under the guidance of Prof. Hudlicky. In 2003, he received his Ph.D. and moved to Brock University, Ontario for postdoctoral studies. After returning to Austria, he joined the research group of Prof. Mulzer and started his own group in 2007. His current interests include the synthesis of diterpenes and the preparation of other biologically interesting natural products.

penes are biologically active and serve as chemical defence weapons to protect fruiting bodies against attacks from other species.[3] Because of their biological activities, but also because of their interesting structures, fungal metabolites continue to attract considerable scientific interest and much effort has been devoted to the isolation, characterization and synthesis of such medicinally relevant natural products.

The intended purpose of this review article is to give an overview of the important class of protoilludane sesquiterpenes as well as structurally related L-shaped natural products with an annulated 5/6/4-ring system characteristic of fungi of the *Basidiomycotina* subdivision.[4,5] The review starts with a short discussion of the biosynthesis of protoilludanes by the humulene pathway. A comprehensive overview of all protoilludanes and related sesquiterpenes isolated to date is provided in the Supporting Information, along with biological properties and activities. The main section is devoted to a detailed discussion of syntheses of prominent members of protoilludane sesquiterpenes in chronological order, with emphasis on comparison of different strategies employed in the elaboration of the characteristic tricyclic skeleton. This also gives a good impression of how pertinent synthetic methodology has developed over the years. Syntheses of related natural products with protoilludanes as synthetic intermediates and advanced unfinished approaches are also included in this overview.

Biosynthesis

The biosynthesis of sesquiterpenes in higher fungi is well investigated and follows the humulene cyclization pathway as outlined in Scheme 1.[5] Mevalonic acid (**1**) is converted into farnesyl pyrophosphate (**2**). This then undergoes an enzymatic cyclization to provide humulene (**3**), which serves as a key intermediate in the biosynthesis of various structurally different sesquiterpenes.[5,6] Interestingly, closely related derivatives of humulene are rare in fungi, because this intermediate is further elaborated mainly to bicyclic and tricyclic sesquiterpenes. Some plants, however, are known to contain humulene-derived sesquiterpenes and although these compounds do not exhibit biologically relevant properties, they often possess characteristic flavors and therefore serve as important fragrances; such compounds can be found in beer, for example.[7,8]



Scheme 1. Biosynthesis of protoilludanes and related sesquiterpenes.

Humulene can be converted into various structurally complex bicyclic and tricyclic sesquiterpenes. The most important pathway generates the protoilludane skeleton through a cationic cyclization sequence as shown in Scheme 1.[9] The protoilludane skeleton itself is highly susceptible to further transformations to minimize the ring strain of the cyclobutane moiety and various different classes of sesquiterpenes can be obtained through Wagner–Meerwein rearrangement reactions.[10,11] A selection of protoilludane-derived sesquiterpenes, demonstrating the broad spectrum of different structural features, is presented in Figure 1.

The biosynthetic pathway briefly outlined above is the most important transformation of humulene in members of the basidiomycete subdivision and clearly demonstrates the

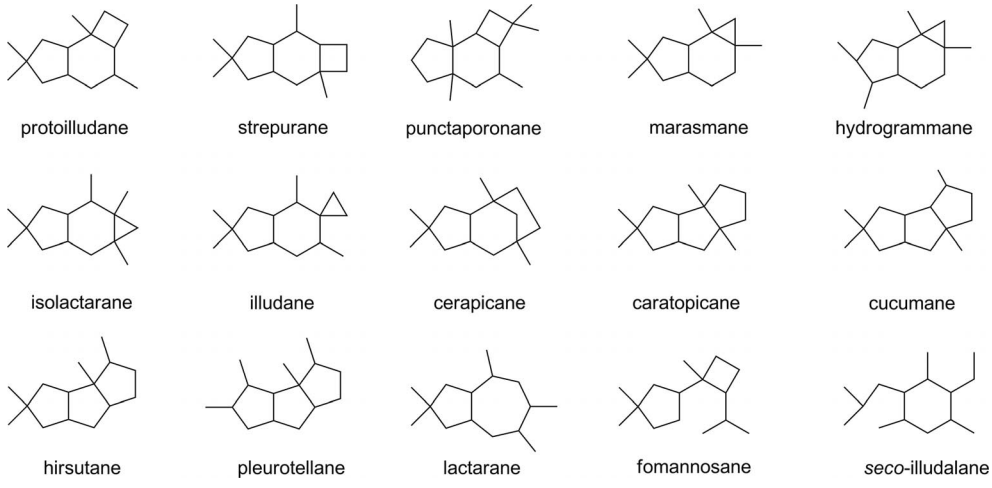


Figure 1. Protoilludane and protoilludane-derived sesquiterpene families.

importance of protoilludane as a scaffold in related sesquiterpene families but also explains the vast number of sesquiterpenes containing the protoilludane skeleton that have been isolated. However, humulene can be converted into various sesquiterpenes by different cyclization strategies and it should be mentioned that these protocols might occur side by side.[5]

The biosynthetic pathway discussed here has been verified by several labelling studies with humulene, farnesyl pyrophosphate and other intermediates.[12,13] Additionally, the interconversion of different protoilludane-derived sesquiterpenes containing labelled material has been demonstrated. These biosynthetic studies are not the main focus of this review article, however, so no further details are given at this point.

Isolation and Biological Properties

A vast number of sesquiterpenes containing the protoilludane skeleton have been isolated since the isolation of illudol from *Clitocybe illudens* in 1967,[14] and interest in this class of natural products still continues. Several of these sesquiterpenes possess promising biological properties; examples include pasteurestins A and B, which have been considered as lead structures in the quest for new antibiotics.[15,16]

A comprehensive overview of all known protoilludanes and structurally related L-shaped sesquiterpenes containing a 5/6/4-ring motif isolated to date, along with information relating to their biological properties, is provided in the Supporting Information.

Syntheses

This section summarizes syntheses of protoilludanes and related sesquiterpenes, as well as syntheses of natural products with protoilludanes as synthetic intermediates. Finally, four examples of unfinished approaches that afforded highly advanced materials are presented.

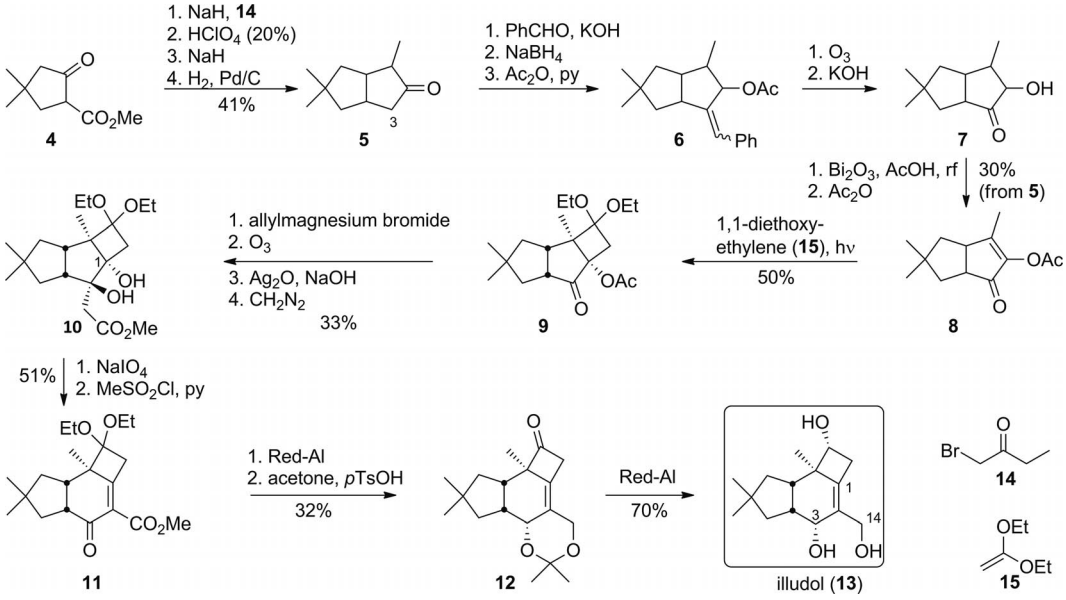
Throughout this section emphasis is placed on the key strategy of the synthetic routes and different approaches are compared where applicable. The numbering of carbon atoms in protoilludanes and related sesquiterpenes is not uniform. For all syntheses discussed here, the carbon numbering suggested by the authors of the corresponding publication has been adopted.

Syntheses of Protoilludanes and Related Sesquiterpenes

Illudol, Matsumoto, 1971

The first synthesis of racemic illudol (**13**), and at the same time the first synthesis of a naturally occurring protoilludane, was reported by Matsumoto in 1971 (Scheme 2).[17,18] The key steps in this seminal contribution are a [2+2] cycloaddition to establish the cyclobutane moiety and a subsequent ring expansion reaction to construct the cyclohexane ring.

Treatment of keto ester **4** with bromomethyl ethyl ketone (**14**) was followed by decarboxylation and intramolecular aldol condensation. The bicyclic unsaturated reaction product was reduced by catalytic hydrogenation and ketone **5** was obtained in fair overall yield. Next, oxygenation at C3 (illudol numbering) was achieved by treatment of ketone **5** with benzaldehyde, with formation of the kinetic α-phenylmethylidene ketone, and acetate **6** was obtained by reduction of the ketone. Ozonolytic cleavage of the double bond and saponification of the acetate delivered hydroxyketone **7**, which was oxidized and acetylated to afford **8** as precursor for the key [2+2] cycloaddition reaction. Irradiation of a mixture of **8** and 1,1-diethoxyethylene (**15**) es-



Scheme 2. Matsumoto's synthesis of illudol (**13**).

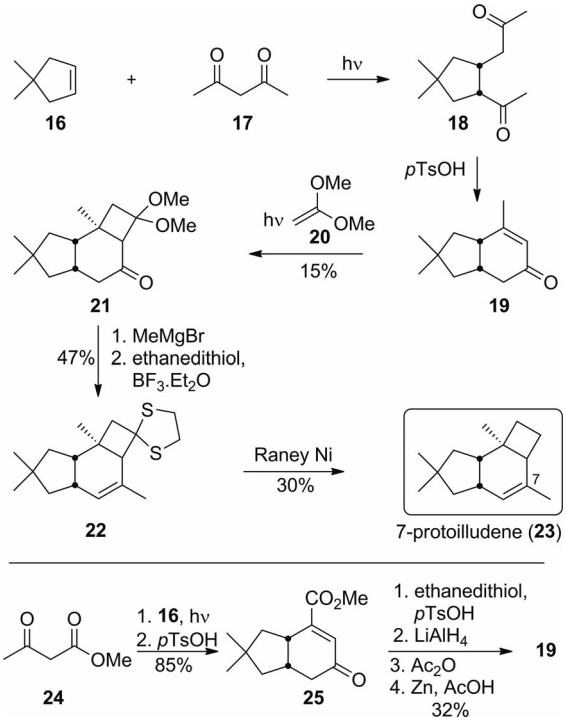
tablished the desired four-membered ring and tricyclic ketone **9** was isolated in 50% yield as a single isomer.

Addition of allylmagnesium bromide to tricyclic ketone **9** stereoselectively occurred from the less hindered α-face and methyl ester **10** was obtained after ozonolytic cleavage of the double bond, oxidation of the resulting aldehyde with silver oxide and treatment with diazomethane. With diol **10** in hand, the stage was set for the second key step, namely the ring expansion, which was achieved by periodate cleavage of the vicinal diol and a subsequent aldol reaction to establish the protoilludane skeleton. Mesylation of the C1-hydroxy functionality and subsequent elimination delivered protoilludane **11** in fair yield. With this sequence the dual purpose of the Grignard reaction becomes obvious. The addition of allylmagnesium bromide prepares the compound for the periodate cleavage but also introduces the C14-hydroxymethyl moiety of illudol.

The synthesis of illudol (**13**) was completed by reduction of the methyl ester and the ketone, removal of the diethyl acetal in **12** and subsequent stereoselective reduction of the resulting ketone to the corresponding secondary alcohol (Scheme 2).

7-Protoilludene, Takeshita, 1979

In 1979, Takeshita reported the synthesis of 7-protoilludene (**23**, Scheme 3) along with other higher oxygenated protoilludane sesquiterpenes.[19,20] The key steps in this synthetic protocol are [2+2] photocycloaddition reactions between 4,4-dimethylcyclopentene (**16**) and either acetoacetone (**17**) or β-keto ester **24**.



Scheme 3. Takeshita's synthesis of 7-protoilludene (**23**).

Irradiation of acetoacetone (**17**) and 4,4-dimethylcyclopentene (**16**) afforded diketone **18** through a [2+2] photocycloaddition with the enolized dicarbonyl moiety in **17**, and this was followed by opening of the intermediately formed four-membered ring.[21] On treatment with *p*-toluenesulfonic acid an aldol condensation reaction took place and diketone **18** cyclized to the α,β-unsaturated bicyclic ketone **19**, which served as a key intermediate in a [2+2] photocycloaddition reaction with freshly prepared 1,1-dimethoxyethene (**20**).

The reaction between **16** and **17** delivered the desired diketone in only marginal yields, however, so an alternative route to the α,β-unsaturated carbonyl compound **19** had to be devised in order to allow access to synthetically useful amounts of material. The procedure used on larger scale is shown at the bottom of Scheme 3 and utilized methyl acetoacetate (**24**) and 4,4-dimethylcyclopentene (**16**) as starting materials for the photocycloaddition reaction. Exposure of the reaction product to *p*-toluenesulfonic acid delivered bicyclic derivative **25** in 85% yield over two steps. The ester in **25** was removed by protection of the ketone as a thioacetal and subsequent treatment with $LiAlH_4$. The alcohol was then converted into the corresponding acetate and treated with zinc in acetic acid to establish the methyl group with concomitant cleavage of the thioacetal. The [2+2] photocycloaddition between α,β-unsaturated ketone **19** and 1,1-dimethoxyethene delivered tricyclic intermediate **21** in low yield but with complete regio- and stereocontrol.

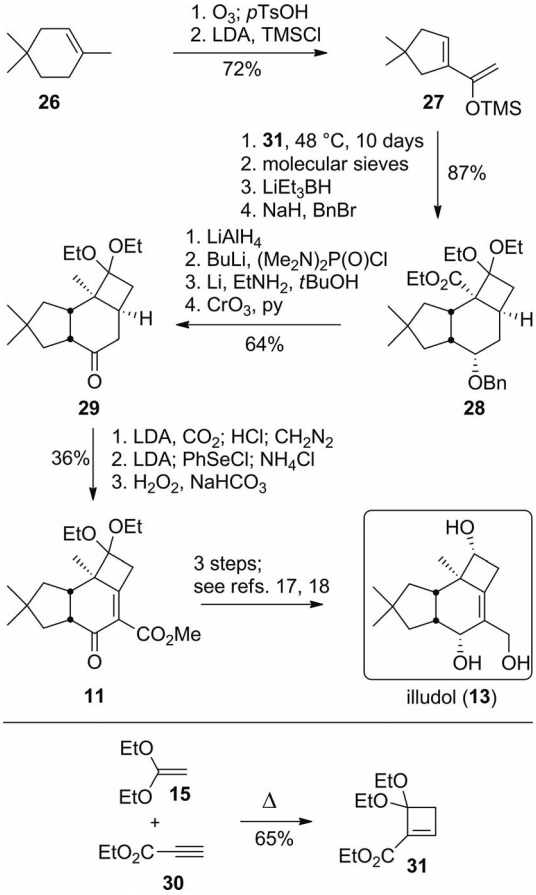
To complete the synthesis of 7-protoilludene (**23**) from **21** the C7-methyl group had to be introduced and the dimethylketal had to be removed. The ketone was therefore treated with methylmagnesium bromide, completing the construction of the protoilludane skeleton and, after elimination of water, establishing the correct substitution pattern on the B-ring of the sesquiterpene. Treatment of the reaction product with ethanedithiol under Lewis acid catalysis conditions and reduction of the thioacetal with Raney nickel delivered the desired 7-protoilludane (**23**).

Takeshita prepared several different higher oxygenated protoilludyl sesquiterpenoids for biological essays. The strategy applied to these synthetic efforts is based on the same key steps, however, so further elaboration of this topic is omitted here.[19,20]

Illudol, Semmelhack, 1980

In 1980, Semmelhack published a formal synthesis of illudol based on a Diels–Alder reaction as the key step.[22,23] One year later, the synthesis of fomannosin[23,24] by the same strategy was reported. The synthesis of **13** is outlined in Scheme 4.

Intermediate **27** served as the diene component in the highly stereoselective key Diels–Alder cycloaddition reaction. The compound was prepared by ozonolytic cleavage of 1,4,4-trimethylcyclohexene (**26**) and a subsequent condensation reaction and trapping of the enolate with trimethylsilyl chloride. Cyclobutene **31** was employed as dienophile in the cycloaddition reaction. Treatment of this highly strained compound, obtained through a [2+2] cycloaddition

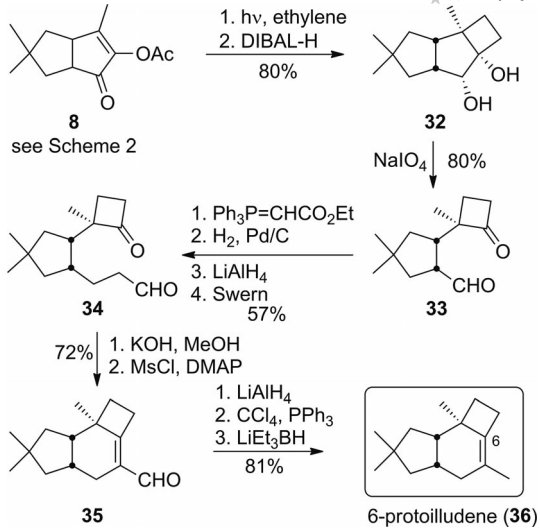


Scheme 4. Semmelhack's synthesis of illudol (**13**).

between diethoxyethylene (**15**) and ethyl propynoate (**30**), with diene **27** cleanly afforded the desired protoilludane skeleton on heating at 48 °C for a period of 10 days followed by hydrolysis of the silyl enol ether under basic conditions. Reduction of the ketone and protection of the corresponding secondary alcohol as the benzyl ether gave the highly advanced intermediate **28** in high overall yield. The ethyl ester in **28** was reduced to a methyl group by the procedure published by Ireland in 1972.[25] Because this protocol also requires the utilization of lithium metal, the benzyl protecting group was removed and ketone **29** was obtained after oxidation with chromium(VI). Carboxylation of the kinetically favored enolate of **29** with carbon dioxide and conversion of the free acid into the corresponding methyl ester was followed by installation of the C1–C2 double bond by selenoxide elimination to generate **11**, which had been an intermediate in Matsumoto's synthesis (Scheme 2).

6-Protoilludene, Furukawa, 1985

Interest in the biosynthetic pathway of humulene-derived sesquiterpenes motivated Furukawa to carry out the synthesis of 6-protoilludene (**36**, Scheme 5).[26] The strategy of Furukawa's synthesis is closely related to (and based on) Matsumoto's synthesis of illudol (**13**, Scheme 2).[17]



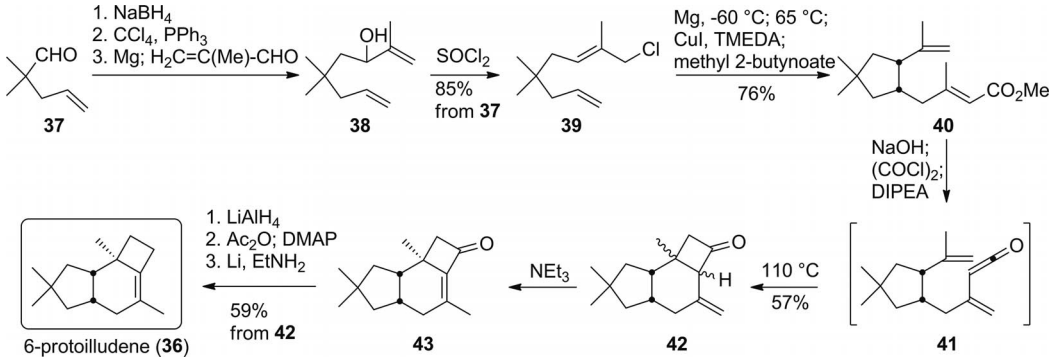
Scheme 5. Furukawa's synthesis of 6-protoilludene (**36**).

Matsumoto's keto acetate **8** was irradiated in the presence of ethylene and the photocycloadduct was subjected to DIBAL-H reduction to afford diol **32** in high overall yield. Periodate cleavage of the diol to give keto aldehyde **33** was followed by a C2-chain elongation by Wittig methodology to afford aldehyde **34**. The protoilludane skeleton was established through intramolecular aldol condensation of keto aldehyde **34** and subsequent elimination of the tertiary alcohol via the mesylate. To complete the synthesis of **36** the aldehyde function in **35** was reduced to the methyl group by a standard three-step sequence.

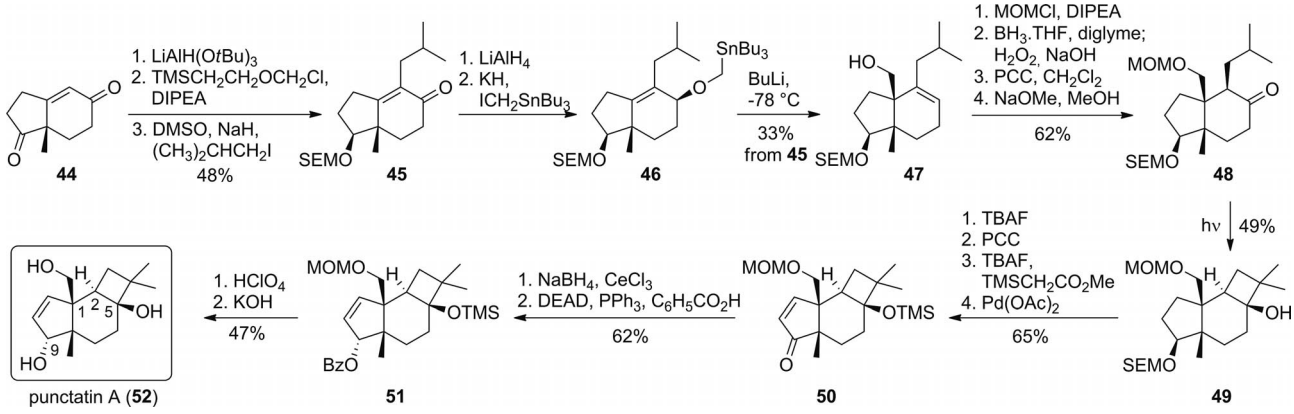
6-Protoilludene, Oppolzer, 1985

Oppolzer contributed to the field of protoilludanes with the synthesis of 6-protoilludene (**36**), published in 1985.[27] The key step in this short and highly efficient route is an intramolecular type-I magnesium ene-reaction[28,29] followed by an intramolecular [2+2] cycloaddition of a ketene intermediate.

Reduction of aldehyde **37** (Scheme 6) followed by chlorination under Appel conditions and subsequent Grignard reaction with methacrolein afforded dienol **38**. Treatment of this allylic alcohol with thionyl chloride gave the desired rearranged allylic chloride **39**, which served as substrate for the magnesium ene-reaction. Activated magnesium was added to the reaction mixture at –60 °C, after which the solution was heated at 65 °C for 24 hours. The resulting Grignard reagent was quenched with methyl but-2-ynoate to generate methyl ester **40** in high yield. Saponification, formation of the acid chloride and elimination of HCl led to ketene **41**, which underwent an intramolecular [2+2] cycloaddition to give protoilludane **42** in fair yield as a 4:1 mixture of *syn* and *anti* adducts. The *exo*-methylene double bond was shifted into conjugation and the synthesis of the sesquiterpene was achieved after reductive removal of the carbonyl functionality.



Scheme 6. Oppolzer's synthesis of 6-protoilludene (**36**).



Scheme 7. Paquette's synthesis of punctatin A (**52**).

Punctatin A, Paquette, 1986

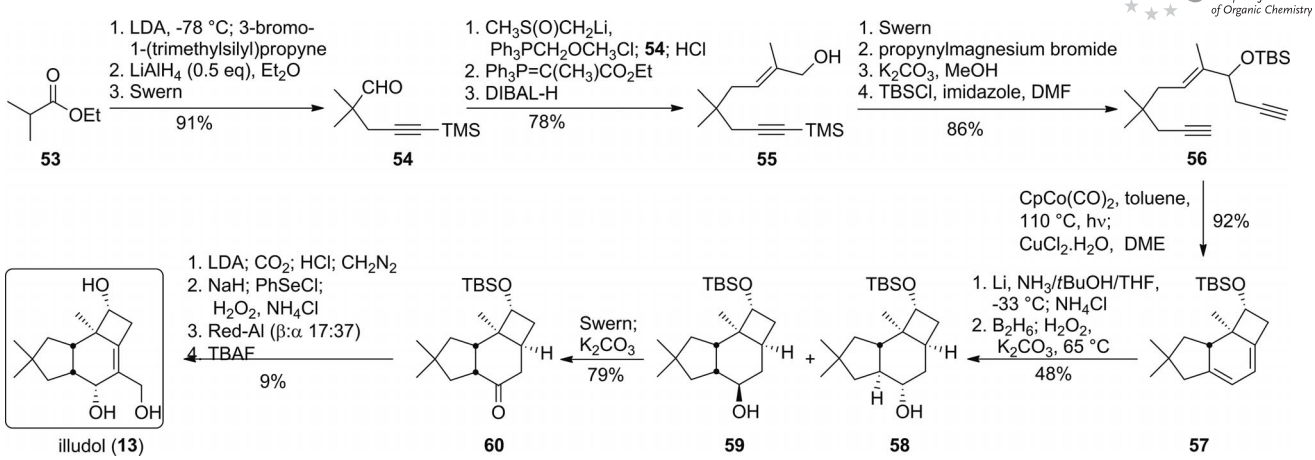
Paquette contributed to the field of 5/6/4-ring tricyclic sesquiterpenes with the synthesis of the antibiotic punctatin A (**52**).[30,31] The synthesis is outlined in Scheme 7. The key step is a Norrish type II photoreaction for the construction of the four-membered ring.

Regio- and stereoselective reduction of optically pure Hajos–Parrish ketone (**44**), followed by protection of the secondary hydroxy functionality and alkylation of the thermodynamically favored enolate with 1-iodo-2-methylpropane, afforded ketone **45** in fair overall yield. Treatment of **45** with $LiAlH_4$ exclusively gave the corresponding β-alcohol, which was alkylated with (iodomethyl)tributyltin to provide stannylmethyl ether **46**, which in turn served as precursor for a [2,3] sigmatropic rearrangement with complete transfer of chirality (**47**). Next, ketone **48** was prepared for the key photoreaction. Protection of the homoallylic alcohol and a subsequent hydroboration/oxidation protocol regioselectively delivered the requisite C5 alcohol. Oxidation and base-catalyzed epimerization afforded the thermodynamically more stable ketone epimer **48** with the correct stereochemistry at C2. Irradiation of ketone **48** gave cyclobutane **49** in fair yield. With the complete 5/6/4-ring skeleton in hand, the only remaining synthetic operation was incorporation of the cyclopentene double bond. Deprotection of the SEM ether was followed by oxidation of the secondary alcohol, *O*-silylation with (trimethylsilyl)acetate and subsequent palladium-mediated oxidation (**50**). Luche reduction, correction of the C9-stereochemistry through a Mitsunobu inversion (**51**) and deprotection concluded Paquette's synthesis of punctatin A (**52**). An analogous strategy was applied to punctatin D, which differs only in the stereochemistry at C9.

Illudol, Vollhardt, 1991

The third synthesis of racemic illudol (**13**) was published by Vollhardt in 1991.[32] The key strategy in this synthesis is the cobalt-mediated [2+2+2] cycloaddition between two alkynes and one olefin, applied to a relatively complex target structure for the first time. The outcome of the reaction was therefore uncertain and the entire synthesis had pioneering character.

The synthesis of the key intermediate started with alkylation of 2-methylpropanoate **53** with 3-bromo-1-(trimethylsilyl)propyne as outlined in Scheme 8. The ester was then converted into the corresponding aldehyde **54** by a reduction/oxidation sequence. One-carbon homologation and subsequent Wittig olefination delivered an α,β-unsaturated ester, which was reduced to yield primary alcohol **55** in good overall yield. Alcohol **55** was subjected to Swern oxidation conditions and converted into enediyne **56** by addition of propynylmagnesium bromide and subsequent TMS cleavage and silylation of the secondary alcohol.



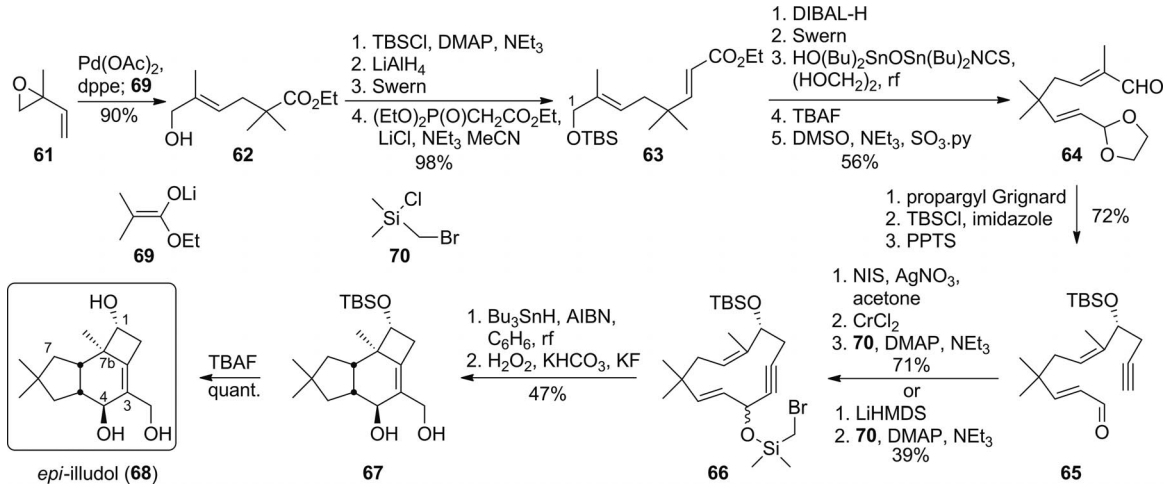
Scheme 8. Vollhardt's synthesis of illudol (**13**).

The key cobalt-mediated photocyclization reaction delivered tricyclic diene **57** with remarkable efficiency and complete stereoselectivity. Birch reduction of **57** removed the C1–C2 double bond to furnish the *cis*-fused ring system. The remaining C3–C4 double bond was removed by a regiospecific but, unexpectedly, not stereospecific hydroboration/oxidation sequence and alcohols **58** and **59** were obtained in a 2:1 ratio. This mixture of isomers was oxidized and the corresponding ketone was employed in a base-catalyzed isomerization and ketone **60** was obtained in high yield. The C2 hydroxymethyl functionality was introduced next by Semmelhack's protocol (Scheme 4)[22,23] to complete the synthesis of illudol (**13**).

epi-Illudol, Malacria, 1997

epi-Illudol (**68**, Scheme 9) was isolated in 1989 from *Clitocybe candidans*.[33] The synthesis by Malacria is based on the proposed biosynthetic pathway.[34] The key step is a well-established stereoselective 5-*exo*-*dig* radical cyclization of α-silyl radicals, initiating the cascade process to establish the protoilludane framework. With the concomitant formation of all three rings and the hydroxymethyl side chain the structure of **5** is ideally suited for the efficient application of this highly versatile radical cascade.

The palladium-catalyzed reaction between 1,2-epoxy-2-methylbut-3-ene (**61**) and the lithium enolate of isobutyrate (**69**) delivered alkene **62** in a 4:1 ratio of stereoisomers. The primary alcohol was protected as a silyl ether, after which the ester moiety was transformed into the corresponding aldehyde and the α,β-unsaturated ester was installed in nearly quantitative yield by means of a Horner–Wadsworth–Emmons reaction to afford **63**. Subsequently, the ester was reduced and converted into the corresponding acetal, after which the silyl group at C1 was cleaved, followed by oxidation of the primary alcohol to afford **64**. Addition of progargyl Grignard, silylation and cleavage of the acetal then afforded aldehyde **65**, which served as the scaffold for the formation of the 11-membered ring. This ring closure was achieved either by deprotonation of the alkyne with LiHMDS and subsequent addition to the carbonyl moiety or, because this protocol delivered the desired material only in low yield, in a three-step protocol including formation of the iodoalkyne followed by a NHK-coupling reaction. Both



Scheme 9. Malacria's synthesis of *epi*-illudol (**68**).

routes gave the desired material as a mixture of diastereomers in a ratio of 3:1. Silylation of the secondary alcohol with (bromomethyl)dimethylsilyl chloride (BMDMSCl, **70**) then afforded precursor **66** for the key radical cascade reaction.

When BMDMS ether **66** was subjected to radical reaction conditions, the cyclization cascade cleanly afforded the tricyclic [4.6.5]-framework. Tamao oxidation to remove the silyl tether gave **67** and cleavage of the TBS ether with TBAF concluded the synthesis of the basidomycete sesquiterpene **68**.

Interestingly, despite the fact that a mixture of diastereomers **66** was used in the tin-mediated radical cyclization protocol, no trace of illudol derivatives was observed. Malacria ascribes this finding to unfavorable interactions between the 4α-hydroxy and the 7b-methyl group during the radical transannular closure. Malacria was able to prepare the natural product in 18 synthetic steps and reported an overall yield of 6.5%.

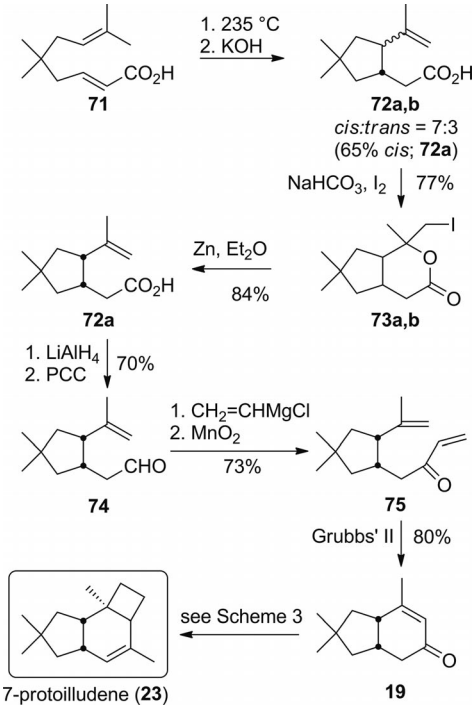
7-Protoilludene, Stenstrom, 2003

In 2003, a formal synthesis of 7-protoilludene (**23**) was reported by Stenstrom and co-workers.[35] Originally, Stenstrom had intended to construct the protoilludene skeleton through a thermally induced cycloaddition reaction between a phenylsulfonyl-substituted allene and an alkene as demonstrated by Padwa and co-workers.[36] This protocol, however, delivered a 4/5/5-ring system instead of the desired 4/6/5-protoilludene skeleton, so the approach was abandoned and the preparation of an intermediate utilized by Takeshita[19,20] in the synthesis of 7-protoilludene was chosen instead. The key step in Stenstrom's synthesis (Scheme 10) is a ring-closing metathesis (RCM) reaction to elaborate the six-membered ring present in the protoilludene system.

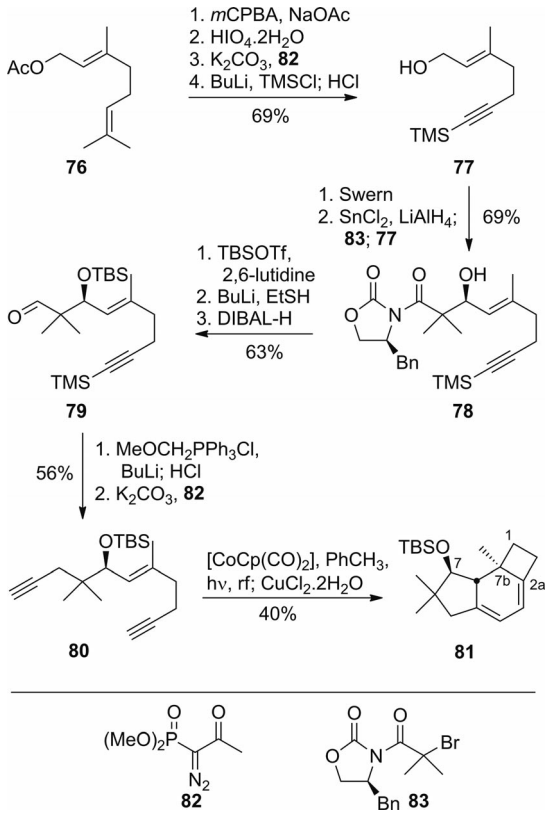
Acid **71**, which had been successfully employed in the synthesis of marasmane-type sesquiterpenes by Heathcock and co-worker,[37,38] was cyclized by means of an ene reaction at 235 °C to furnish an inseparable mixture of *cis* and *trans* isomers **72a** and **72b** in a 7:3 ratio. The separation of the stereoisomers was possible through formation of iodolactones **73a** and **73b**. Reduction of *cis*-iodolactone **73a** with zinc powder delivered the desired pure isomer **72a** with a *cis* relationship of the substituents. A reduction/oxidation sequence delivered aldehyde **74**, which was treated with vinylmagnesium bromide to give the secondary allylic alcohol, which was oxidized with manganese dioxide to afford enone **75**. RCM with the second-generation Grubbs catalyst cleanly delivered bicyclic α,β-unsaturated ketone **19**, which had previously been converted into 7-protoilludene (**23**) by Takeshita.[19,20] Stenstrom's formal synthesis thus improved the existing protocol with respect to the number of steps and overall yield.

Pasteurestins A and B, Mulzer, 2007

In 2007, Mulzer reported the synthesis and structural assignment of pasteurestin A and B.[15,16] Pasteurestins A (**97**, Scheme 13, below) and B (**88**, Scheme 12, below) were obtained by fermentation of *Agrocybe aegeritta* and were found to exhibit strong and selective activities against *Mannheimia haemolytica*, responsible for bovine respiratory disease. To establish the relative and absolute configurations

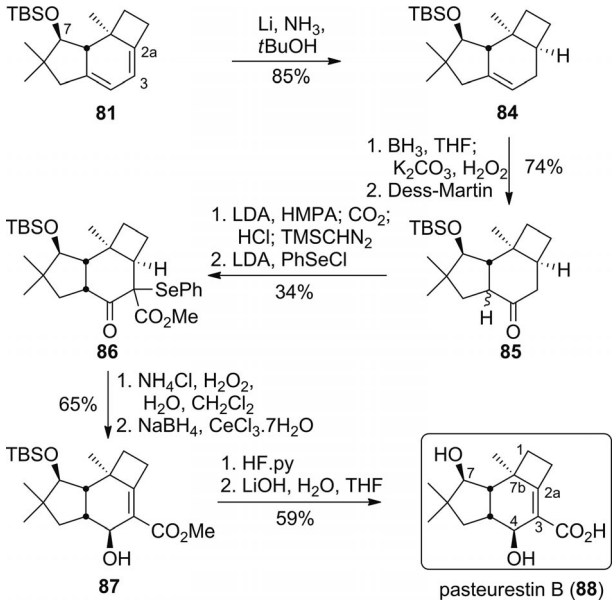


Scheme 10. Stenstrom's synthesis of 7-protoilludene (**23**).



Scheme 11. Mulzer's synthesis of pasteurestin B (**88**) – part 1.

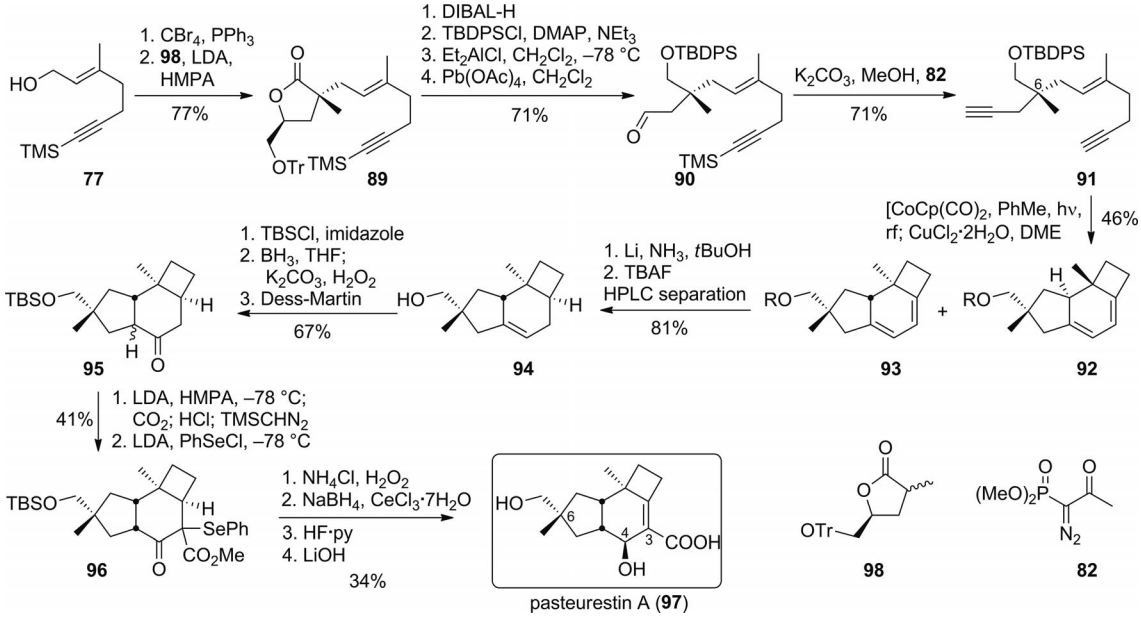
and to procure sufficient quantities for biological testing, a synthesis of **97** and **88**, based on the incorporation of a Co-mediated [2+2+2] photocycloaddition as the key step, was launched. The routes to **97** and **88** are outlined in Scheme 11, Scheme 12, and Scheme 13.



Scheme 12. Mulzer's synthesis of pasteurestrin B (**88**) – part 2.

The synthesis of pateurestrin B (**88**) was initiated with geranyl acetate (**76**) as a readily available starting material (Scheme 11). Epoxidation of the electron-rich double bond and subsequent periodate cleavage was followed by treatment of the resulting aldehyde with Bestmann–Ohira reagent (**82**), which after TMS protection of the terminal alkyne gave alcohol **77**. The hydroxy functionality was oxidized and a tin-mediated Reformatsky reaction then stereoselectively introduced the C7 hydroxy functionality with concomitant elaboration of the quarternary dimethyl moiety. In order to suppress unwanted side reactions, the reaction was carried out at –78 °C, in contrast to literature precedent. Interestingly, the stereochemical outcome of the reaction was found to be the opposite of that of reported examples and this discrepancy was ascribed to a fully complexed Nerz–Stormes–Thornton transition state.[39] The desired stereoselectivity was achieved by application of bromide **83** in the Reformatsky reaction, with aldehyde **79** being obtained after protection of the secondary alcohol and reductive cleavage of the auxiliary. The precursor for the Co-mediated cyclotrimerization reaction was obtained after C1-elongation of **79** by Wittig methodology and conversion of the newly formed aldehyde into the corresponding terminal alkyne with the Bestmann–Ohira reagent (**82**). Cyclotrimerization of enediyne **80**, closely related to intermediate **56** used by Vollhardt in the synthesis of illudol (**13**),[32] delivered tricyclic intermediate **81** with high diastereoselectivity, due to the proximity of the C7 stereocenter. The synthesis of pasteurestrin B (**88**) was completed analogously to Vollhardt's and Semmelhack's protocols; the route is outlined in Scheme 12. The final steps include Birch reduction of the highly strained C2a–C3 double bond to give **84**, a hydroboration/oxidation sequence to install the oxygen functionality at C4 (compound **85**), treatment of enolized **85** with CO_2 to introduce the C3 methoxycarbonyl group and the introduction of unsaturation by selenoxide elimination, followed by deprotection.

Inspired by the outcome of the highly diastereoselective cyclotrimerization reaction, Mulzer and co-workers also decided to prepare pasteurestrin A (**97**) by the above strategy. Although the stereogenic center is further from the site of the cycloaddition reaction, predominant formation of the desired diastereomer was expected.



Scheme 13. Mulzer's synthesis of pasteurestrin A (**97**).

Butyrolactone **98**, obtained from (*R*)-glycidol in two steps, served as the chiral starting material. As shown in Scheme 13, allylic alcohol **77**, which had also served as an intermediate in the synthesis of pasteurestin B, was converted into the corresponding bromide under Appel conditions and used for a stereoselective alkylation of butyrolactone **98**. Lactone **89** was then reduced and converted into aldehyde **90**, and enediyne **91** was finally obtained after C1-elongation with the Bestmann–Ohira reagent (**82**).

Exposure of enediyne **91** to cyclotrimerization conditions afforded **92** and **93** as a 3:4 mixture, showing that the chiral center in **91** is too far away from the reaction side to influence the stereochemical outcome of the cyclotrimerization efficiently. The inseparable mixture was used in the Birch reduction, after which HPLC separation gave diastereomerically pure **94**. The remaining steps to pasteurestin A were carried out in close analogy to the synthesis of pasteurestin B. The syntheses of these two basidomycete diterpenes allowed the assignment of the relative configurations. Additionally, biological activity testing confirmed high and selective activity of the sesquiterpenes against pathogenic strains of *Pasteurella multocida*.

Protoilludanes as Synthetic Intermediates

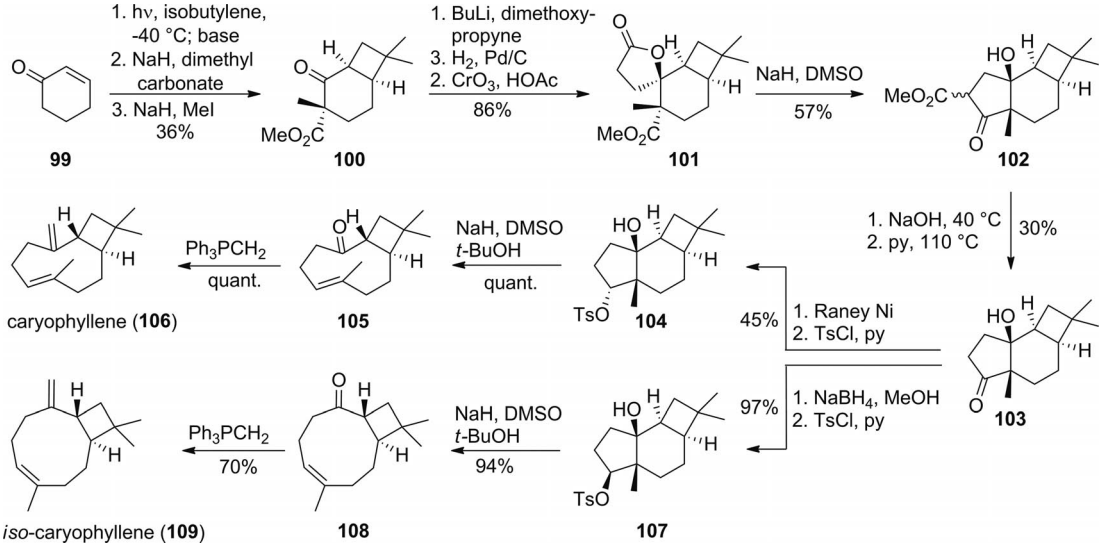
Caryophyllene, Corey, 1963

Caryophyllene (**106**, Scheme 14) is a bicyclic sesquiterpene and constituent of different essential oils. In 1963, Corey published a synthesis of the sesquiterpenes caryophyllene and isocaryophyllene,[40,41] one of the classics in the area of terpene synthesis. The key step in the preparation of these sesquiterpenes is a Grob fragmentation of a 5/6/4-fused ring intermediate in order to establish the nine-membered ring present in caryophyllene (**106**) and isocaryophyllene (**109**).[42] The synthesis is outlined in Scheme 14.

The synthesis of key intermediates **104** and **107** started with a [2+2] photocyclization reaction between cyclohexenone (**99**) and isobutylene, which regioselectively afforded the desired cycloadduct in high yield as mixture of *cis* and *trans* isomers. The undesired *trans* isomer was converted into the *cis*-fused derivative upon exposure of the mixture to base. Treatment of the ketone with sodium hydride and dimethyl carbonate afforded the corresponding keto ester, which was alkylated to afford bicyclic intermediate **100**. Next, the five-membered ring present in the protoilludyl intermediate was established. Addition of deprotonated dimethoxypropyne introduced the carbon chain required for construction of the cyclopentyl segment. Hydrogenation of the triple bond and subsequent oxidation to the corresponding carboxylic acid with Jones' reagent afforded lactone **101**, which gave keto ester **102**, possessing the 5/6/4-ring skeleton, through a Dieckmann condensation reaction. Saponification of the methyl ester and decarboxylation afforded ketone **103** as the common intermediate in the preparation of caryophyllene (**106**) and isocaryophyllene (**109**).

The *E* or *Z* trisubstituted double bonds of caryophyllene and isocaryophyllene, respectively, were elaborated through Grob fragmentations of tosylates **104** and **107**. Reduction of ketone **103** with sodium borohydride and subsequent tosylation of the secondary alcohol afforded tosylate **107**, with a *cis* relationship of the two hydroxy functionalities. On subjection to basic conditions, fragmentation product **108** with *Z* double bond geometry as present in isocaryophyllene (**109**) was obtained in excellent yield and the synthesis was completed by conversion of the ketone into the corresponding *exo*-methylene functionality through Wittig olefination.

After extensive screening of various reduction conditions, Raney Ni was found to deliver the desired diol with the *trans* relationship of the hydroxy groups necessary for the formation of the *E* trisubstituted double bond present



Scheme 14. Corey's syntheses of caryophyllene (**106**) and isocaryophyllene (**109**).

in caryophyllene. Tosylation (compound **104**) and Grob fragmentation gave ketone **105**, which was converted into caryophyllene (**106**) through a Wittig reaction in similar fashion as described for the preparation of isocaryophyllene.

Capnellene, Matsumoto, 1982

Matsumoto's synthesis of capnellene (**117**, Scheme 15) utilized a 5/6/4 ring system as intermediate. This was converted into the triquinane skeleton through a ring contraction/expansion reaction.[43] As outlined in Scheme 15, humulene oxide (**110**) was subjected to Lewis acid to afford tricyclic alcohol **111** in good yield.[44] Hydrogenation of the C1=C2 double bond was followed by oxidation of the secondary alcohol to the corresponding ketone with Jones' reagent. The ketone was treated with tosyl hydrazine and subsequently with butyllithium (Shapiro's conditions) to give alkene **112**. Epoxidation of the double bond in **112** was followed after desilylation by Lewis-acid-mediated rearrangement to the 5/6/4 ring system **113** as the major product in a mixture of three isomeric compounds. Hydrogenation of the highly strained cyclobutene ring and subsequent inversion of the hydroxy functionality by an oxidation/reduction sequence gave secondary alcohol **114**, which served as precursor for the key ring contraction/expansion reaction. Mesylation of the alcohol functionality and treatment with sodium acetate in acetic acid gave a mixture of triquinanes **115** and **116** in excellent overall yield. Acetate **115** could easily be converted into the desired alkene **116** by reductive removal of the ester, mesylation and elimination of the mesylate under basic conditions.

To complete the synthesis of capnellene, the double bond in **116** had to be shifted to the exocyclic position. Firstly, the C6=C7 double bond was isomerized by rhodium catalysis. Then, the trisubstituted olefin was epoxidized and treated with $LiAlH_4$ to afford the corresponding tertiary alcohol, which could be eliminated by heating of the substrate to reflux in a mixture of *N*-(1,1,2,3,3,3-hexafluoropropyl)diethylamine (HFPDEA) and *N*-(1,2,3,3,3-pentafluoropropenyl)diethylamine to afford capnellene (**117**) in fair yield.

Syntheses of Protoilludane Derivatives and Related Sesquiterpenes

Shirahama, 1989

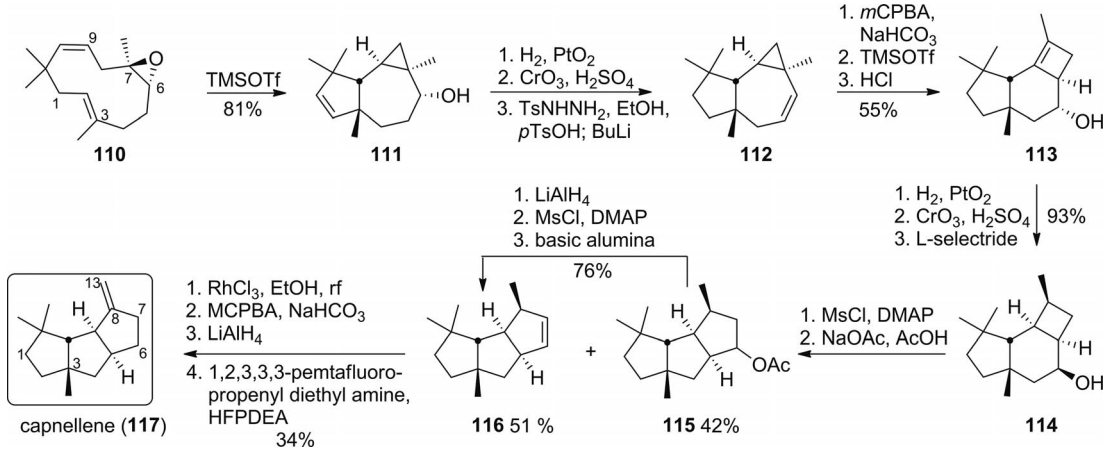
Shirahama presented a biomimetic approach towards 7(13)-protoilludene as outlined in Scheme 16.[45] In contrast with all other syntheses discussed here, this is the only route to this class of natural products that utilizes a ring contraction protocol to establish the 5/6/4 protoilludane system from an eight-membered ring.

Treatment of humulene (**3**) with mercuric nitrate and subsequent reductive demercuration afforded heterocycle **118** in fair yield.[46] Treatment with phosphorus tribromide followed by debromination and hydrogenolytic cleavage of the tetrahydrofuran moiety delivered cyclooctenol **119**. After masking with methyl oxalate, allylic oxidation with selenium dioxide and subsequent pyrolysis gave a mixture of isomeric aldehydes **120**, **121** and **122** in a ratio of 2:4:3. As shown in Scheme 16, Shirahama was able to convert alkenes **121** and **122** into the protoilludane derivative **126** by identical pathways.

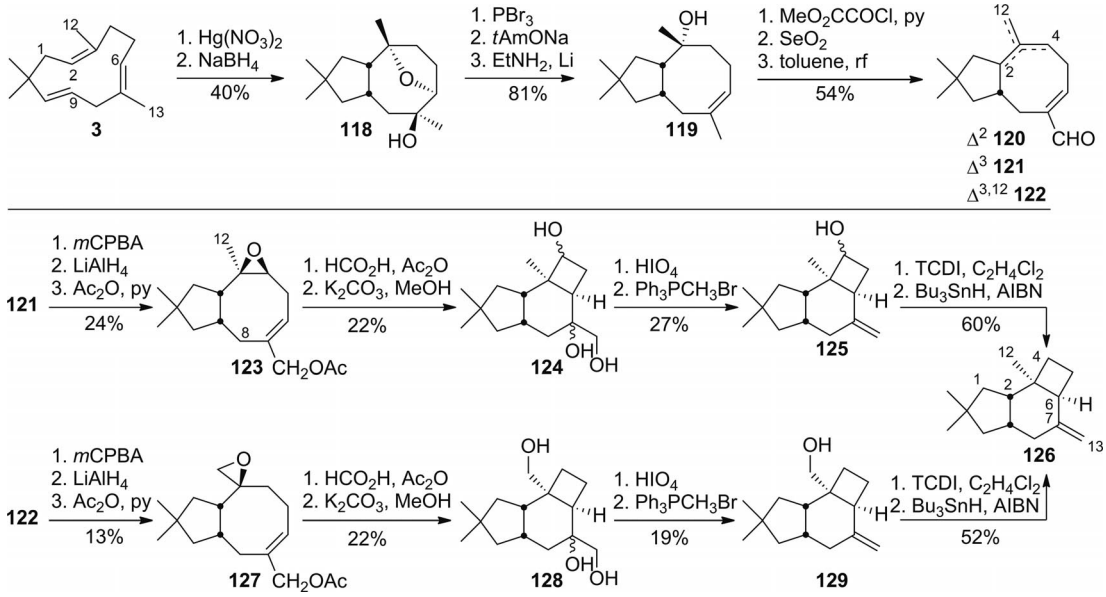
Epoxidation of the C3=C4 double bond in **121**, reduction of the carbonyl functionality and protection of the primary alcohol as an acetate delivered epoxide **123**, which was converted into protoilludane derivative **124** upon treatment with a mixture of formic acid and acetic anhydride and subsequent methanolysis. Periodate cleavage and Wittig olefination introduced the exocyclic double bond in **125**, after which the hydroxy moiety of the cyclobutane ring was removed in a Barton–McCombie protocol with 1,1′-thiocarbonyldiimidazole (TCDI) and tributyltin hydride. As described above, protoilludene **126** was also prepared from isomeric alkene **122** by the same reaction pathway.

Singh, 1993, 1998

In 1993,[47] and at full length in 1998,[48] Singh reported the preparation of various functionalized protoilludane skeletons with a photochemical sigmatropic 1,3-acyl shift as the key step. The route towards protoilludanes starting



Scheme 15. Matsumoto's synthesis of capnellene (**117**).



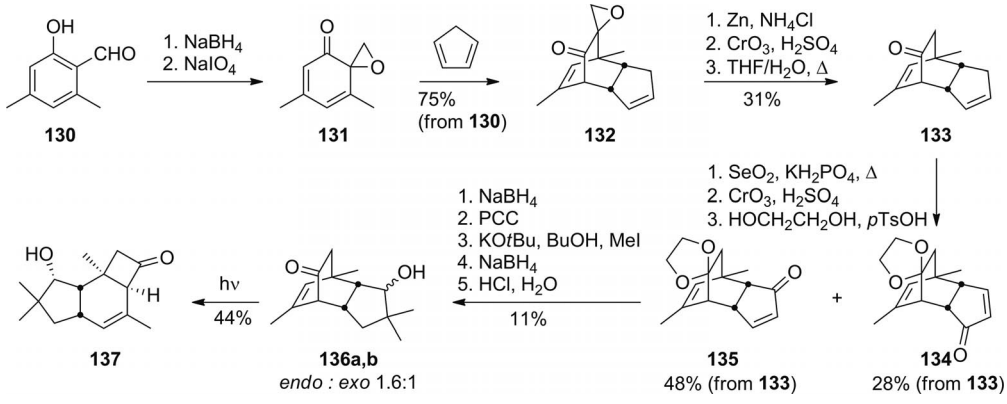
Scheme 16. Shirahama's synthesis of 7(13)-protoilludene (**126**).

from substituted salicyl aldehyde **130** is shown in Scheme 17.

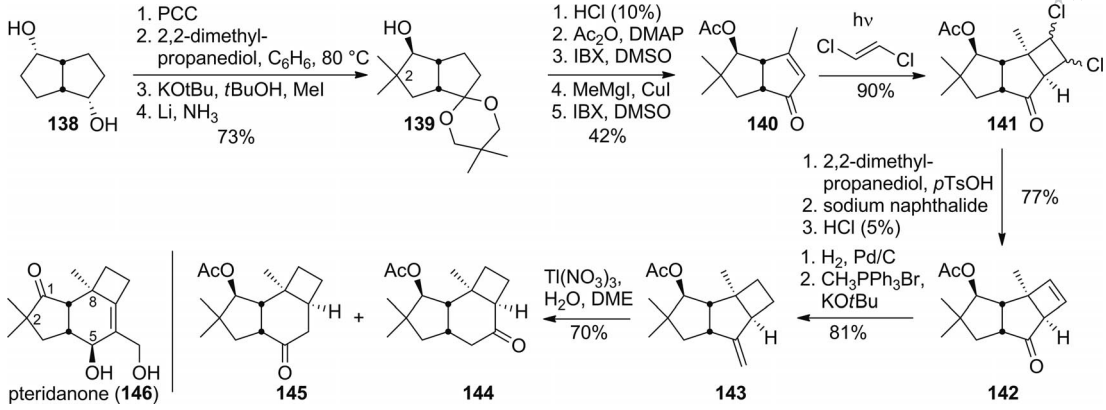
The synthesis of the *endo*-tricyclo[5.2.2.0^{2,6}]undecane system required for the key photochemical sigmatropic 1,3-acyl shift started with reduction of aromatic aldehyde **130** to the corresponding substituted salicyl alcohol, which on Becker–Adler oxidation gave spirocyclic keto epoxide **131**. This then acted as the diene component in a Diels–Alder cycloaddition reaction with cyclopentadiene to afford keto epoxide **132** in an excellent 75% yield from **130**. Next, the oxirane functionality, which served solely as an instrument to achieve dearomatization of the substituted salicyl alcohol, had to be removed to prepare the system for rearrangement to the desired tricyclic sesquiterpene skeleton. Regioselective reduction of the epoxide with zinc led to a primary alcohol, which was oxidized to the keto acid and decarboxylated to furnish ketone **133**.

Allylic oxidation of **133** with selenium dioxide afforded a regioisomeric mixture of allylic alcohols, which were converted into the α,β-unsaturated ketone. The carbonyl group on the ethano bridge was then protected as a ketal. At this stage, separation of the regioisomers was possible and ketone **135** could be further elaborated. The incorporation of the geminal dimethyl group required the reduction of the conjugated double bond in the five-membered ring. Treatment of **135** with sodium borohydride and subsequent re-oxidation of the alcohol was followed by bis-alkylation. Again, sodium borohydride reduction converted the ketone into the corresponding secondary alcohol and treatment with acid resulted in cleavage of the ketal protecting group. With epimeric alcohols **136a** and **136b** in hand, the stage was set for the key photochemical 1,3-sigmatropic acyl shift. Interestingly, irradiation of **136a** with a mercury vapor lamp in a quartz immersion well led to a complex mixture, whereas irradiation in a Pyrex immersion cleanly produced the desired tricyclic protoilludene skeleton in **137**.

This photochemical approach is readily applicable to the preparation of various protoilludane-derived sesquiterpenes, although the repeated oxidation/reduction sequences diminish the brevity and efficiency of the overall process.



Scheme 17. Singh's approach to substituted protoilludanes.



Scheme 18. Mehta's approach to pteridanone (**28**).

Mehta, 2003

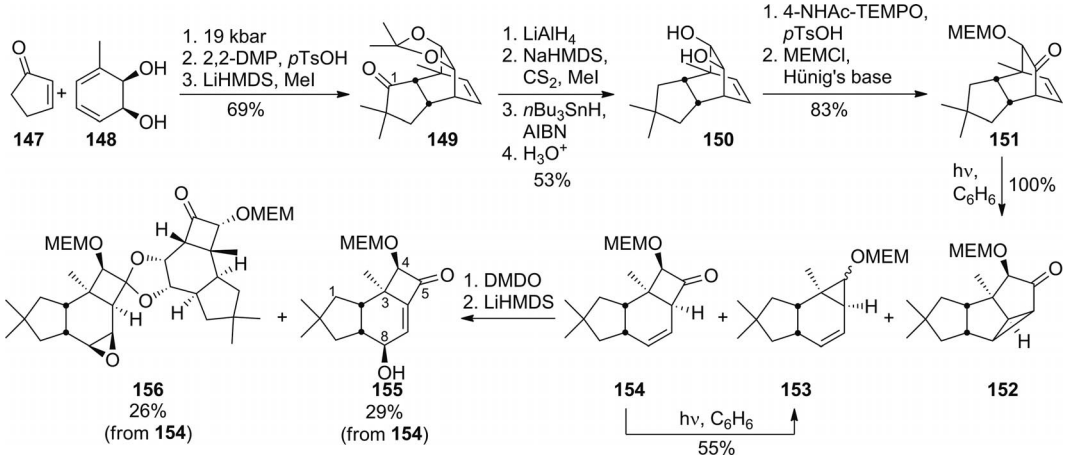
Mehta reported a route to pteridanone with a [2+2] photocycloaddition and a thallium(III)-mediated ring expansion reaction as key steps.[49] The approach is closely related to Matsumoto's protocol,[17] described above. Mehta's work is shown in Scheme 18.

PCC oxidation of *cis*-diol **138**, accessible from commercially available cycloocta-1,5-diene through Pd-catalyzed transannular cyclization,[50] was followed by monoketalization of the corresponding dione, after which treatment with potassium *tert*-butoxide and methyl iodide introduced a geminal dimethyl group at C2. Reduction of the ketone with lithium in liquid ammonia furnished **139**, with the hydroxy group in an *exo* position as the thermodynamically more stable alcohol epimer. The ketal protecting group was cleaved under acidic conditions, and after acetylation of the secondary alcohol, IBX oxidation afforded an enone suitable for a 1,4-conjugate addition with the cuprate derived from methylmagnesium bromide. The α,β-unsaturated system was restored through a second IBX oxidation to furnish enone **140** as the precursor for the [2+2] photocycloaddition. Irradiation of enone **140** and *trans*-1,2-dichloroethene afforded cyclobutane **141** in excellent yield as a mixture of diastereomers. Because direct dehalogenation could not be achieved successfully, the ketone was protected, after which treatment with sodium naphthalide resulted in reductive dehalogenation. The ketone was restored (**142**) and the cyclobutene ring was hydrogenated to furnish the saturated carbocycle. All ring expansion strategies tested on the ketone were found to be ineffective, so the substrate was converted into exocyclic ketone **143** by Wittig olefination in order to explore the scope of thallium(III) oxidation. When exocyclic alkene **143** was treated with thallium trinitrate in aqueous DME, the two regioisomeric ketones **144** and **145** (ratio of 2:1) were isolated. These could be converted into **146** by the Semmelhack/Matsumoto protocol described earlier.

Although reasonably short and direct, the main problem in Mehta's approach definitely lies in the unselective ring expansion method, which requires improvement before satisfactory syntheses can be carried out.

Banwell, 2004

Banwell reported an enantioselective route to the tricyclic protoilludane and marasmane framework starting from the biocatalytically derived cyclohexadiene-*cis*-diol **148**.[51] The approach discussed below and outlined in Scheme 19



Scheme 19. Banwell's approach to the protoilludane and marasmane frameworks.

is part of Banwell's ongoing interest in the synthesis of sesquiterpenes such as hirsutene and hirsutic acid,[52–54] as well as other natural products, from enantiomerically pure cyclohexadiene-*cis*-diols. The key steps are the Diels–Alder cycloaddition of the toluene-derived cyclohexadiene-*cis*-diol and cyclopentenone (**147**) and the photochemically induced formation of the 5/6/4 and 5/6/3 skeletons.

Whole-cell oxidation of toluene with the recombinant organism *Escherichia coli* JM109(pDTG601), which overexpresses toluene dioxygenase, delivered enantiomerically pure diol **148**, which served as starting material for the synthesis. Treatment of this diene with cyclopentenone (**147**) under high pressure (19 kbar) resulted in a Diels–Alder cycloaddition, and **149**[55] was isolated after protection of the diol moiety and installation of a geminal dimethyl group. The carbonyl functionality at C1 was then removed by reduction to the corresponding secondary alcohol. Barton–McCombie deoxygenation and cleavage of the acetonide moiety under acidic conditions gave diol **150**. Selective oxidation of the less hindered hydroxy group at the bridgehead was achieved with a sterically demanding TEMPO derivative and **151** was obtained after MEM protection of the remaining secondary alcohol. Irradiation of this key intermediate with a high-pressure mercury lamp gave a mixture of **152**, **153** and **154**, with the 5/6/4-fused ring system **154** as the predominant reaction product. The formation of **154** can be explained in terms of a 1,3-acyl shift, whereas the 5/6/3 ring system **153** requires a decarbonylation and **152** is the result of the familiar di-π-methane rearrangement. On further irradiation, **154** could be converted to **153** in 55% yield, indicating that this material served as an intermediate in the formation of the decarbonylated material. Epoxidation of **154** and subsequent treatment with LiHMDS afforded a mixture of alcohol **155** and dimer **156**. Banwell's preliminary synthetic efforts stopped at this point, with the perspective of further interesting applications of the advanced intermediates.

Conclusions

In summary, it has been shown that protoilludanes have been popular synthetic targets for many years. A multitude of approaches for the construction of the tricyclic framework, above all the annulation of the cyclobutane ring, have been developed. Straightforward [2+2] photocycloaddition has been a standard option throughout, although Diels–Alder or ketene olefin cycloaddition, cyclopropyl ring enlargement or free radical or cobalt mediated enediyne [2+2+2] cyclizations have emerged as surprisingly useful alternatives.

Supporting Information (see footnote on the first page of this article): A comprehensive overview of all known protoilludanes and structurally related L-shaped sesquiterpenes containing a 5/6/4-ring motif isolated to date, along with information concerning biological properties, is provided in Table S1.

Acknowledgments

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