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Applications of Friedel–Crafts reactions in total synthesis of natural products

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Over the years, Friedel–Crafts (FC) reactions have been acknowledged as the most useful and powerful synthetic tools for the construction of a special kind of carbon–carbon bond involving an aromatic moiety. Its stoichiometric and, more recently, its catalytic procedures have extensively been studied. This reaction in recent years has frequently been used as a key step (steps) in the total synthesis of natural products and targeted complex bioactive molecules. In this review, we try to underscore the applications of intermolecular and intramolecular FC reactions in the total syntheses of natural products and complex molecules, exhibiting diverse biological properties.

1. Introduction

Historically, the FC reactions are the well-established set of reactions initially discovered by Charles Friedel and James Crafts in 1877. In these reactions, certain substituents are attached on to a suitable aromatic ring.[1] Basically, Friedel–Crafts reactions imply two main sets of reactions. They are alkylation and acylation reactions. In fact, both types of such reaction proceed *via* the same mechanism, which is the typical reaction of aromatic compounds, electrophilic aromatic substitution.[2–5] FC alkylation comprises the alkylation of an appropriate aromatic ring using an alkyl halide, conventionally in the presence of a strong Lewis acid as the catalyst.[6] Commonly, anhydrous ferric chloride is used as a catalyst, in which the alkyl group initially attaches itself to the former site of the chloride ion.[7] Although this reaction enjoys the

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advantages already known for electrophilic aromatic substitution, it also suffers from the fact that the final product is more nucleophilic than the reactant, thus undesired over-alkylation may take place, giving unwanted side products. In addition, the reaction is limited to using tertiary carbon and secondary alkylating agents, or else the emerging carbocation (R^+) may be subjected to a known carbocation rearrangement.[7] Indeed, alkylations *via* FC reaction are not limited to using just alkyl halides. FC reactions can be successfully performed *via* the generation of any other appropriate intermediate, such as those carbocationic intermediates that are derived from alkenes in the presence of a protic acid, Lewis acid, enones, and epoxides. During the previous years of FC reactions, several other Lewis acids, such as BF_3, $BeCl_2$, $TiCl_4$, $SbCl_5$ or $SnCl_4$, have been proven to act as effective catalysts. Besides, strong Brønsted acids such as H_2SO_4 and HF, or super acids, such as $HF{\cdot}SbF_5$ and $HSO_3F{\cdot}SbF_5$, have also been used successfully and proven to accelerate the FC alkylation reaction. In spite of the great significance of FC alkylation in organic transformation, some major drawbacks and problems still exist, which must be circumvented. For example, the FC alkylation reaction requires stoichiometric or super stoichiometric amounts of a Lewis acid or Brønsted acid. Furthermore, since it needs toxic alkyl halides as a reagent, the formation of large quantities of salts as side products is proven to be inevitable. Thus, development of more eco-friendly strategies and economically feasible chemical processes for such an important reaction is still in great demand. The replacement of the alkyl chlorides by less harmful alkylating agents, for instance alcohols, has undoubtedly been a major development since in this case water is formed as a non-toxic by-product. More importantly, the utilization of activated double bonds and compounds such as styrenes have been found even more advantageous and operative, since no by products are generated at all.

The FC acylation reaction is actually the acylation of certain aromatic compounds. For the FC acylation reaction, acyl chlorides are used as common acylating agents. In this version of the FC reaction, frequently Lewis acid catalysts such as $AlCl_3$ can be used along with acid anhydrides as a suitable reagent. The reaction conditions for the FC acylation reaction are exactly as same as those for FC alkylation. It is worthwhile to know that the FC acylation reaction shows several advantages over the alkylation variant. Because of the electron-withdrawing nature of the carbonyl motif, the product, which is actually a ketone, is expectedly less reactive than the substrate, thus undesired multiple acylations do not take place. In addition, since the intermediate is not a carbocation, no rearrangement occurs as the generated carbonium ion is stabilized *via* a resonance structure in which the positive charge is located on the electronegative oxygen.

By definition, a natural product is a chemical compound or substance that originates from nature and is produced by a living organism.[8] In the more extensive sense, a naturally occurring compound implies any substance produced by a living organism.[9] Significantly, the total synthesis of natural products, including semi synthesis, is the state of art in synthetic organic chemistry and nowadays plays a key role in the development of organic chemistry as a whole by providing stimulating and useful and especially biologically active natural products as the target. Generally, the total synthesis of natural products is a non-commercial research activity, aimed at deeper understanding of the synthesis of a desired natural product scaffold and, more importantly, the development of more desirable new synthetic approaches. Natural products are also limited to the purified organic compounds isolated from natural sources that are originated by the pathways of primary or secondary metabolism. Many secondary metabolites are cytotoxic and have been chosen and modified through evolution for use as "chemical warfare" agents toward prey, predators, and competing organisms. The terminology of natural product has also been stretched for profitable purposes and thus refers to cosmetics, dietary supplements, and foods obtained from natural sources with no artificial ingredients as additives.[10–13] Natural products frequently show therapeutic benefit and many of them have been used as folk medicines for treating diseases for centuries and thus have given some knowledge about lead compounds for drug discovery.[14] Natural products can be categorized in accordance with their biological function, biosynthetic pathway, or source.

The applications of FC reactions (alkylation and acylation) in organic synthesis have been extensively studied and reviewed previously.[6,15–19] In continuation of our interest in applications

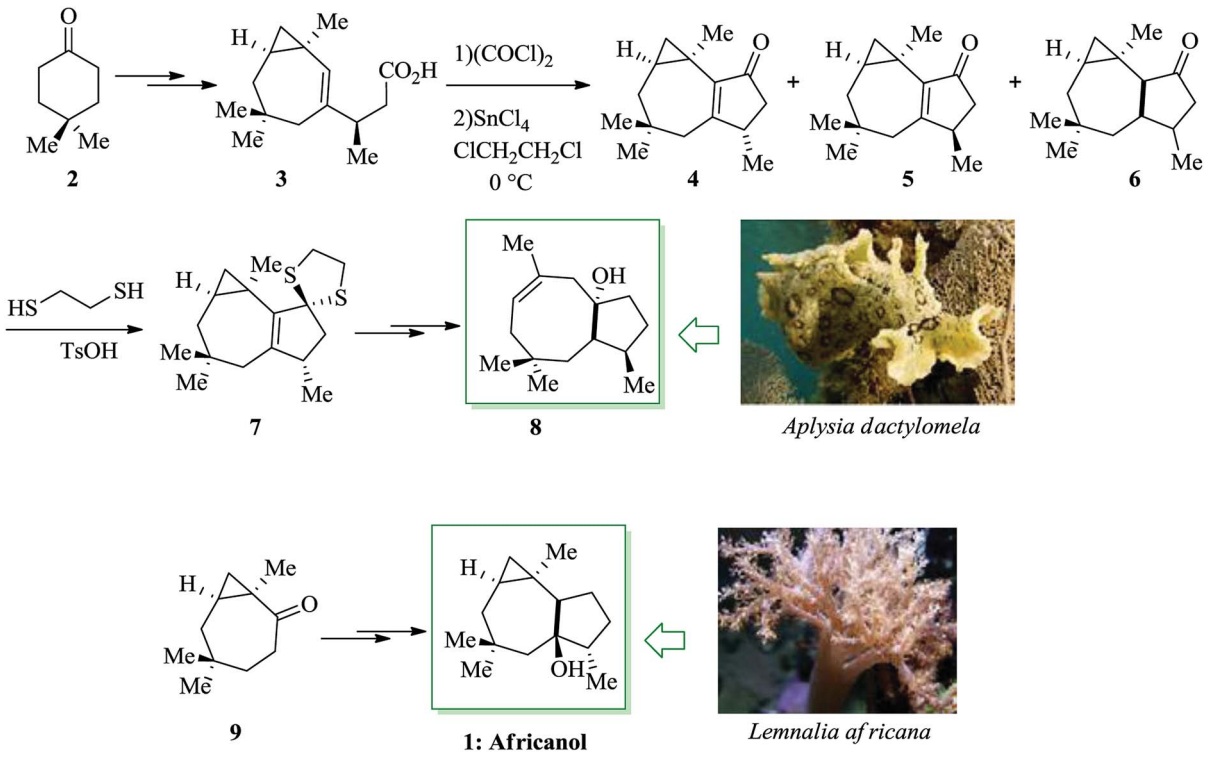


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Tayebeh Momeni was born in 1988 in Karaj, Iran. She received her BSc degree from Imam Khomeini International University in 2010 and her MSc degree from Tehran University under the direction of Professor Mehdi Ghandi in 2012 before moving to Alzahra University, where she became a PhD candidate in Professor Majid. M. Heravi's research group in 2015.

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Scheme 1 Total synthesis of africanol **1**.

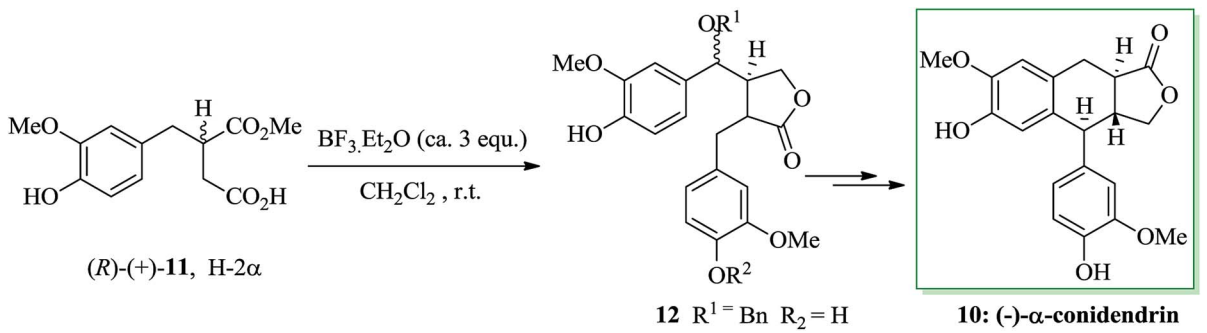
of name reactions[20–35] in the total synthesis of natural products, herein we try to underline the applications of both FC reactions in the total synthesis of naturally occurring compounds, showing diverse biological properties.

2. Applications of Friedel–Crafts in total synthesis of natural products

2.1. Intramolecular alkylation

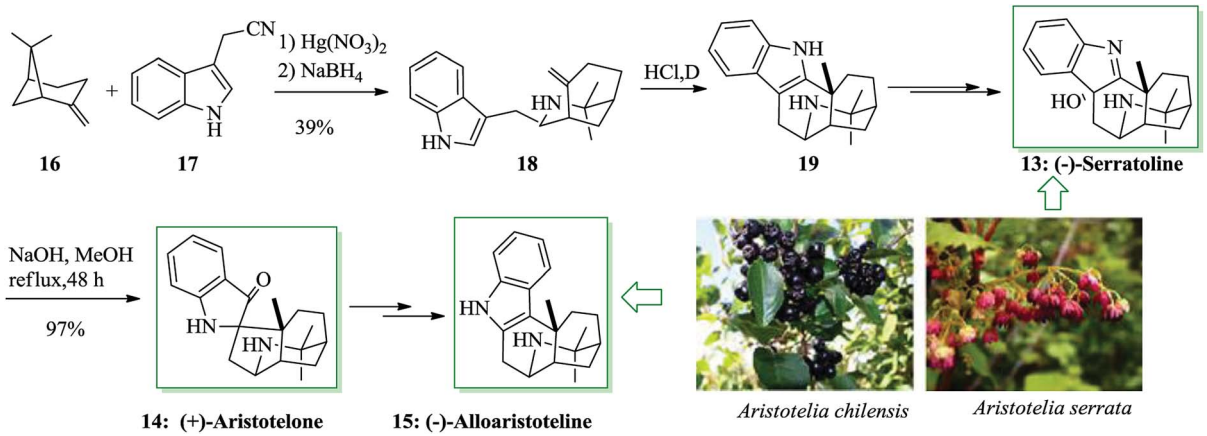
Dactylol, **8**, an irregular isoprenoid alcohol, was isolated from the Caribbean sea hare *Aplysia dactylomela* and its structure was identified in 1978 by Schmitz and co-workers.[36,37] The total synthesis of the marine sesquiterpenes africanol **1** and dactylol **8** was achieved from bicyclo[5.1.0]octane precursors. In this route, firstly, compound **2** gave carboxylic acid **3**, which was transformed into compound **7** *via* FC cyclization of its acid chloride and acid-mediated dithioketalization (after several steps). Compound **7** was converted into dactylol **8** after several steps. The configuration of the side chain Me substituent is detected to be proper in relation to dactylol **8** but reverse to that existing in africanol **1**. Subsequently, africanol **1** was provided from compound **9** upon several steps (Scheme 1).[38]

Most lactonic aryltetralin lignans, for example peltatins and podophyllotoxin, contain a similar common structure. α-Conidendrin was extracted from both wood[39] and waste sulfite liquor.[40] Boissin and co-workers developed the total synthesis of natural (−)-conidendrin **10**. Conidendrin **10** was provided in eight steps starting from the easily accessible and optically active hemisuccinic ester (*R*)-(+)-**11**. The latter gave the monobenzoxy intermediate **12** after several steps, including treatment

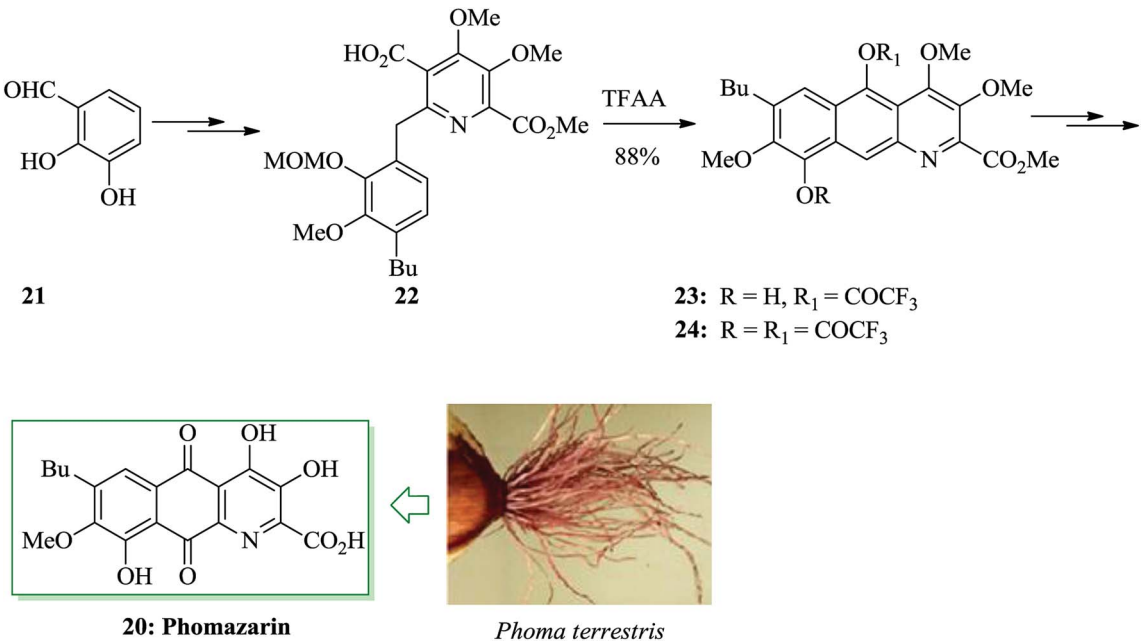


Scheme 2 Total synthesis of (−)-α-conidendrin **10**.

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Scheme 3 Total synthesis of natural products (−)-serratoline **13**, (+)-aristotelone **14** and (−)-alloaristoteline **15**.



Scheme 4 Total synthesis of phomazarin **20**.

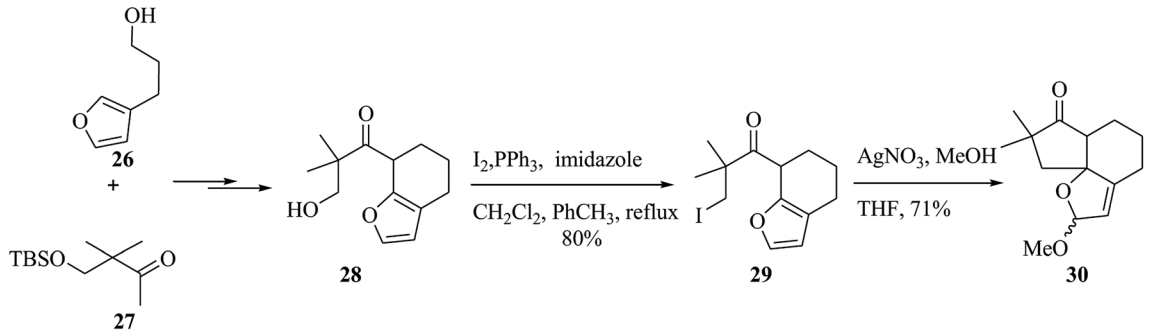
with $BF_3 \cdot Et_2O$ in dichloromethane at ambient temperature. The benzoxy group of **12** was actually found to be an excellent leaving group during intramolecular FC alkylation. As a result, (−)-α-conidendrin **10** was provided as the desired natural product from **12** in satisfactory yield (Scheme 2).[41]

The *Aristotelia* alkaloids (−)-serratoline **13**, (+)-aristotelone **14** and (−)-alloaristoteline **15** were extracted from *Aristotelia chilensis*. Serratoline was formerly extracted from *Aristotelia serrata*, a species native to New Zealand. Heathcock and co-workers reported the total synthesis of (−)-serratoline **13**, (+)-aristotelone **14** and (−)-alloaristoteline **15**. This approach starts from the reaction between (l*S*)-(−)-β-pinene **16** and 3-indolylacetonitrile **17** to afford (+)-makomakine **18**. Next, an intramolecular FC reaction provided (+)-aristotelone **19**, which upon two steps afforded alkaloid **13**. Subsequently, base-mediated skeletal rearrangement of **13** provided (+)-aristotelone **14**. Finally, alkaloid **14** gave (−)-alloaristoteline **15** upon several steps (Scheme 3).[42]

Phomazarin **20** is the most abundant and extensively studied aza anthraquinone that was extracted from cultures of *Phoma terrestris* Hansen (*Pyrenochaeta terrestris* Hansen) in 1940.[43] Boger and co-workers reported the total synthesis of phomazarin **20**. Initially 2,3-dihydroxybenzaldehyde **21** was converted into **22** after several steps. Compound **22** in the presence of TFAA cleanly led to FC closure of the B-ring and simultaneous MOM deprotection, affording a variable and inconsequential mixture of **23** and **24** with no detection of the intermediate bisphenol. Conditions were planned such that only the single mono-(trifluoroacetate) **23** (88%; TFAA) was obtained. Finally,

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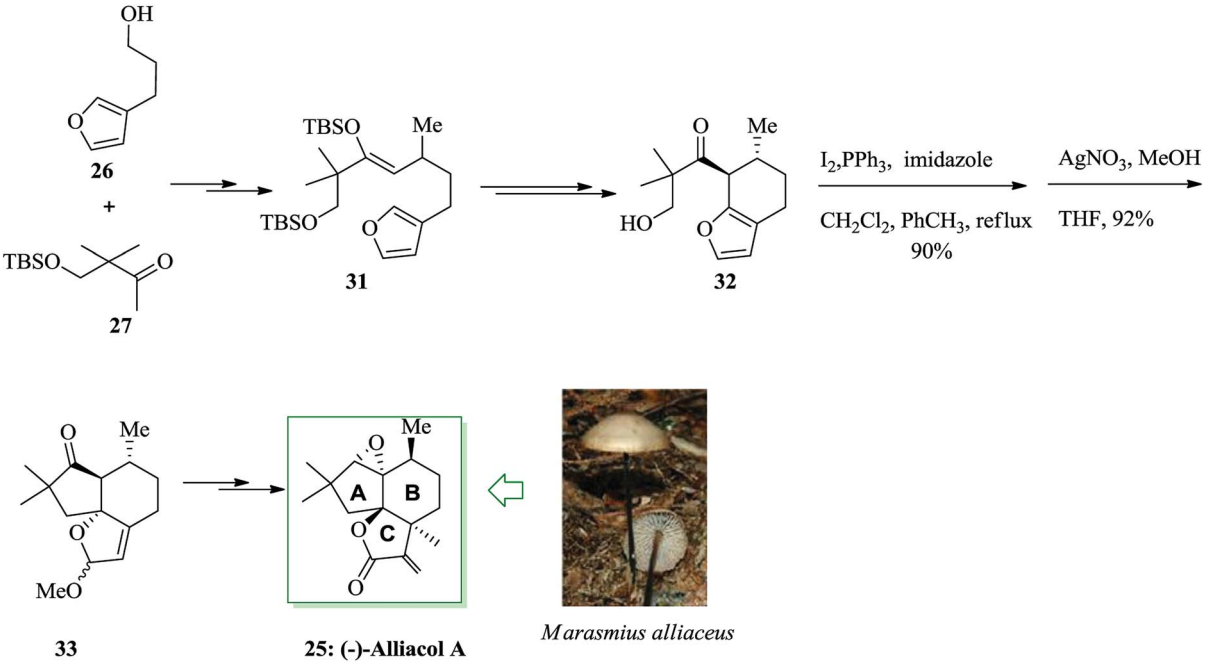
Scheme 5 The formation of the tricyclic product **30**.

compound **23** afforded phomazarin **20** upon several steps (Scheme 4).[44]

Alliacol A **25,** a sesquiterpene, was extracted in Europe from the culture broth of the fungus *Marasmius alliaceus*.[45] This molecule exhibits antimicrobial properties and prevents DNA synthesis in the ascetic form of Ehrlich carcinoma.[46,47] A tandem anodic coupling-FC alkylation methodology was applied to quickly complete the enantioselective synthesis of alliacol A. In this route, firstly, the reaction between compounds **26** and **27** afforded compound **28** after several steps. Then, it was tried to form the tricyclic unit of the desired naturally occurring compound. For this purpose, the alcohol in **28** was transformed into the relevant iodide, which was applied for either the FC alkylation or radical cyclization method. The FC reaction between iodide and $AgNO_3$ in MeOH gave a 71% yield of the corresponding tricyclic product **30** (Scheme 5).[48]

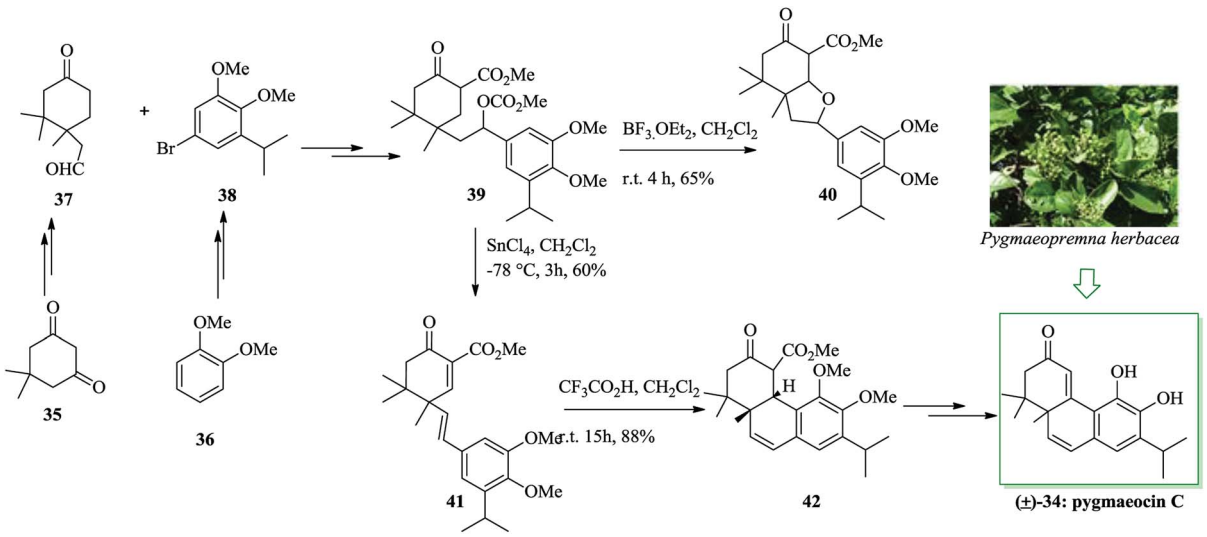
Subsequently, it was attempted to provide substrate **31** containing the B-ring Me group of alliacol A in place. Compounds **26** and **27** gave substrate **31** upon several steps. This compound provided the bicyclic product **32** upon two steps. Using the bicyclic product, the alcohol **32** was transformed into an iodide and the FC cyclization was finished. A 92% extracted yield of the tricyclic product **33** was provided from the FC reaction. Next, compound **33** was converted into (−)-alliacol A **25** upon several steps (Scheme 6).[48]

In 1990, Meng and co-workers for the first time reported the isolation of pygmaeocin C **34**,[49] a rearranged abietane diterpenoid, from the roots of *Pygmaeopremna herbacea* Moldenke. The initial total synthesis of pygmaeocin C **34**, in racemic form, was accomplished in 2005 by Liu and co-workers. Total synthesis of pygmaeocin C **34** was accomplished, starting from dimedone **35** in 14 steps with an overall yield of 4.6%. In this route, an intramolecular FC reaction was considered as a key step. Notably, keto aldehyde **37** was synthesized from dimedone **35** and also compound **38** was synthesized from veratrole **36** *via* several steps. In the following, the reaction of aldehyde **37** and bromide **38** gave the key intermediate **39**, upon several steps. It should be mentioned that compound **39** was subjected to

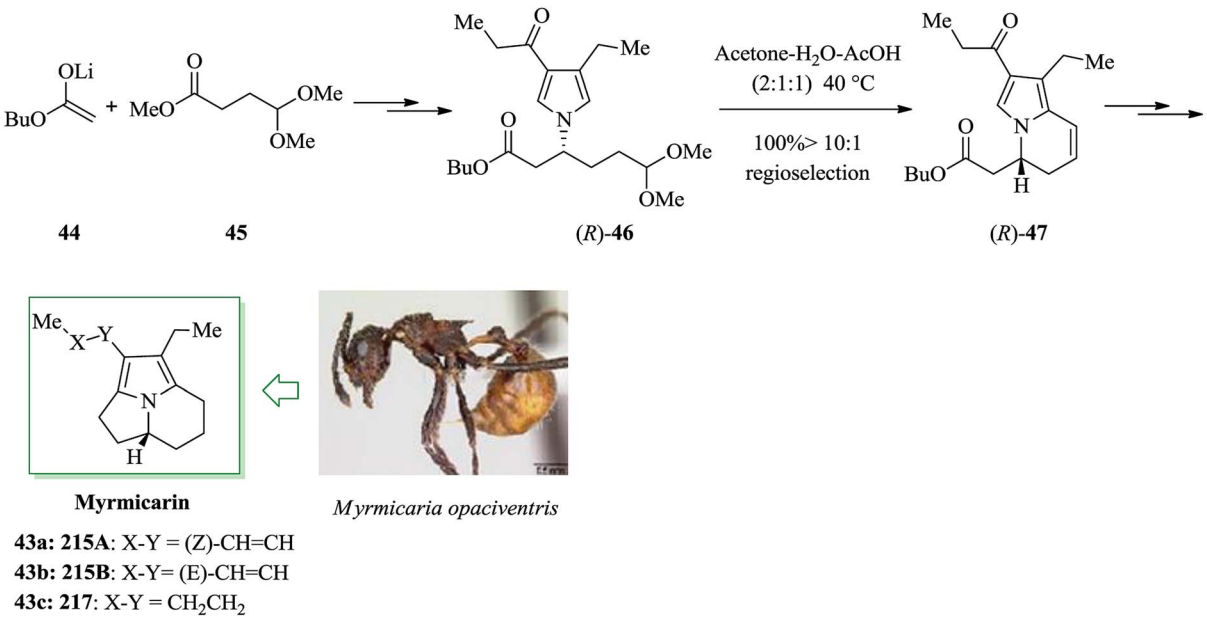


Scheme 6 Total synthesis of (−)-alliacol A **25**.

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Scheme 7 Total synthesis of pygmaeocin C **34**.



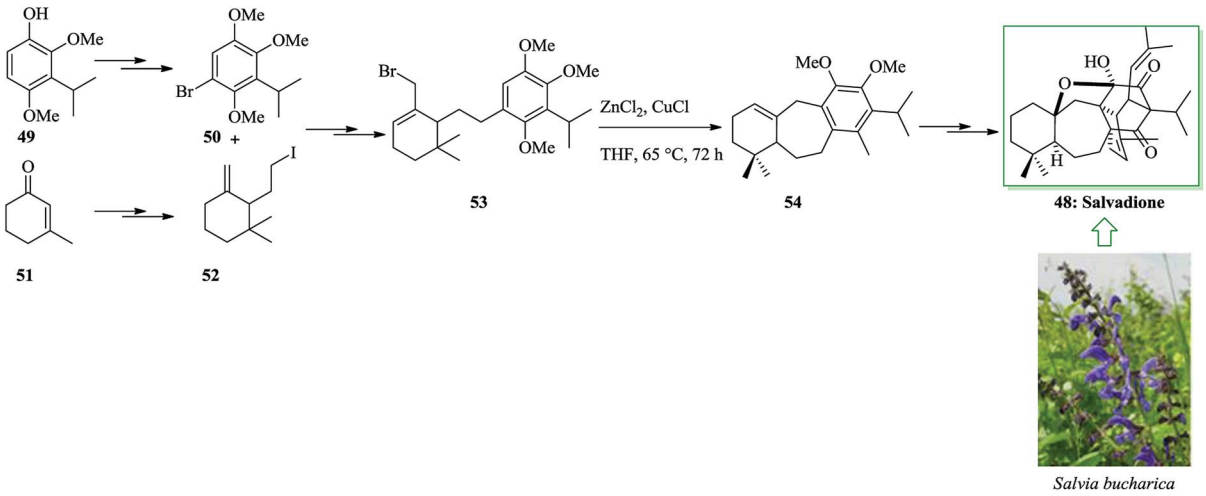
Scheme 8 Total synthesis of tricyclic myrmicarins **43a–c**.

a simple intramolecular FC alkylation to give the tricyclic system in the target product. Upon extensive study, it was found that the required cyclization could be obtained from olefin **41** with an extraordinary degree of efficiency. Upon treatment with trifluoroacetic acid (TFA), the latter was submitted to intramolecular FC reaction to afford an 88% yield of the corresponding cyclized product **42** as a result of double bond isomerization with subsequent ring closure. Finally, the tricyclic keto ester **42** was converted into pygmaeocin C **34** upon several steps (Scheme 7).[50]

The myrmicarins, a group of structurally intriguing alkaloids, were initially extracted from the poison gland secretions of the African ant species *Myrmicaria opaciventris*.[51,52] The pyrroloindolizine unit of myrmicarins **43a**, **43b**, and **43c** is a common structural scaffold found in various alkaloids. An asymmetric synthesis of a key dihydroindolizine intermediate **47** for the construction of myrmicarin alkaloids was developed in 2005 by Movassaghi and co-workers. Key conversions in this method contain a stereospecific Pd-mediated N-vinylation, a Cu-mediated asymmetric conjugate reduction, and a regioselective FC reaction. The synthesis of optically potent and isomerically pure samples of (4*aR*)-myrmicarins **43a**, **43b**, and **43c** and also their respective C4*a*-epimers was achieved using the above-mentioned protocol. Firstly, the lithium enolate **44** and methyl 4-(dimethoxy)-butyrate **45** were reacted to afford compound **46** in several steps. Next, the dihydroindolizine **47** was provided, which is a key intermediate for the construction of the myrmicarin alkaloids. A regioselective FC reaction of the

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Scheme 9 Total synthesis of salvadione **48**.

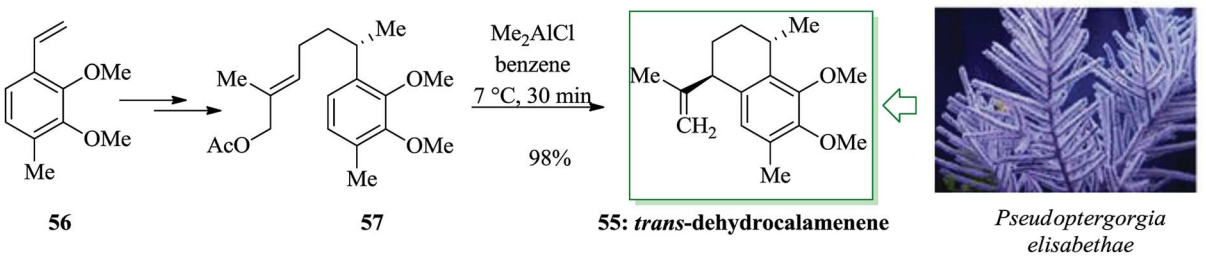
pyrrole ring upon Brønsted acid activation of the dimethoxyacetal **46** and removal of MeOH was achieved to provide the bicyclic vinyl pyrrole **47**. The optimized conditions (acetone–acetic acid–H_2O, 2 : 1 : 1, 40 °C) were recognized for the quantitative transformation of the β-pyrrolyl ester **46** to the bicyclic vinyl pyrrole to give the corresponding C7*a*-cyclization product **47**. Finally, compound **47** afforded isomerically pure tricyclic myrmicarins **43a–c** after several steps (Scheme 8).[53]

Ahmad and co-workers extracted and identified a remarkable polycyclic triterpene from *Salvia bucharica*, salvadione A **48**.[54] The tricyclic 6–7–6 unit structure of the triterpene salvadione **48** was provided using an effective method starting from the aryl bromide **50** (provided from cyclohexenone **51**) and the alkyl iodide **52** (provided from phenol **49**) containing a methylenecyclohexane group at the terminus. Notably, alkylation of **50** with the iodide **52** afforded the tethered system (allylic bromide) **53**. An intramolecular FC alkylation reaction of allyl bromide **53** provided compound **54** *via* cyclization in the presence of zinc chloride and copper(I) chloride in tetrahydrofuran. The synthesis of tricyclic compound **54** demonstrates a formal total synthesis of salvadione **48**. Finally, the tricycle **54** afforded salvadione **48** upon several steps (Scheme 9).[55]

Various aromatic diterpenes with a serrulatane or amphilectane framework have been recognized as bioactive metabolites from marine soft corals, particularly *Pseudopterogorgia elisabethae*.[56] Notable representatives of these compounds are the anti-inflammatory pseudopterosins,[57,58] the cytotoxic and antiviral helioporins,[59] and the pseudopteroxazoles.[60,61] Schmalz *et al.* in 2007 developed an effective and extremely enantioselective synthetic approach to calamenene **55**, a *trans*-1,4-difunctionalized tetralin derivative, in 6 linear steps and 57% overall yield initiating from **56**.[62] The reaction was initiated from compound **56**, which was converted into the corresponding allylic acetate **57** in moderate overall yield. The 1,4-*trans*-difunctionalized tetralin framework was selectively provided *via* a FC-type cationic cyclization reaction using Me_2AlCl as a "proton-scavenging" Lewis acid.[63] The envisioned *trans*-dehydrocalamenene **55** was provided in almost quantitative yield and with very moderate *de* (up to 10 : 1) (Scheme 10).[62]

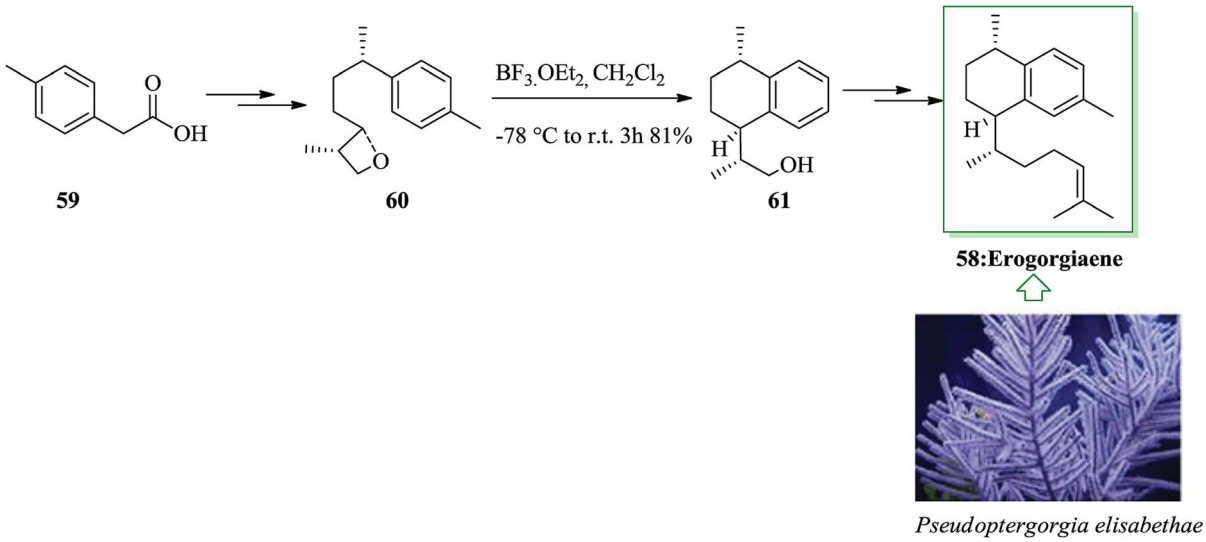
Erogorgiaene, extracted together with other diterpenes from the West Indian sea whip *Pseudopterogorgia elisabethae*, exhibits favorable anti-mycobacterial properties. A total synthesis of erogorgiaene **58** was developed in 16 steps with an overall yield of 8.2%. The synthesis was based on an extremely diastereoselective intramolecular FC reaction of an oxetane obtained through an enantioselective *syn* aldol coupling. In this route, firstly, easily accessible acid **59** was converted into oxetane **60** in high yield upon several steps. The essential intramolecular FC reaction of oxetane **60** was performed.[64] As expected, the reaction progressed easily, at room temperature, providing a single diastereomer **61**. Finally, alcohol **61** afforded erogorgiaene **58** upon several steps (Scheme 11).[65]

In 2005, Sattler and co-workers extracted and revealed a group of naturally occurring aromatic β-C-glycoside



Scheme 10 Total synthesis of *trans*-dehydrocalamenene **55**.

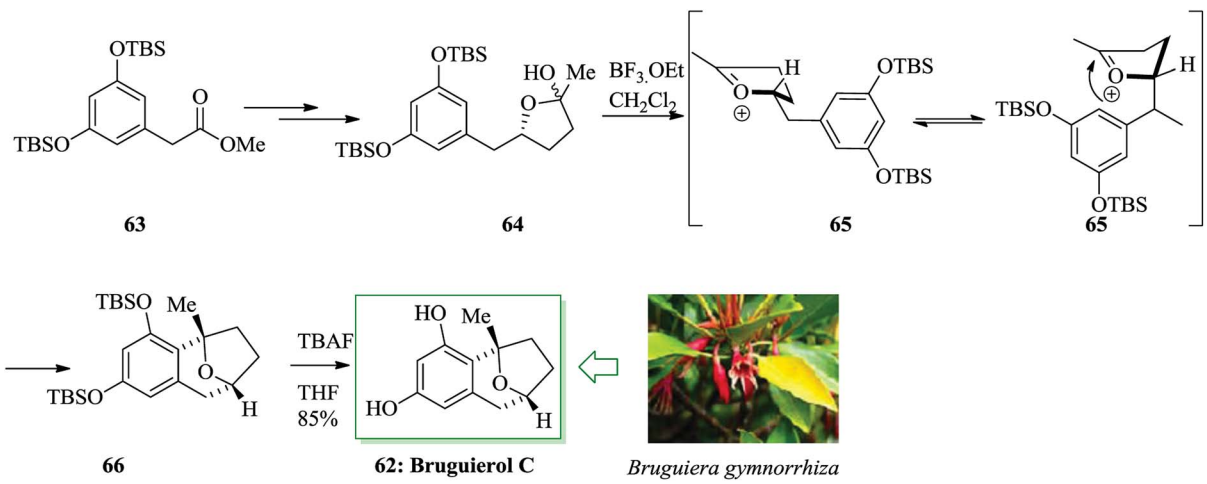
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Scheme 11 Total synthesis of erogorgiaene **58**.

compounds named bruguierols A–C from the stem of the *Bruguiera gymmorrhiza* mangrove tree.[66] In 2007, Jennings and co-workers demonstrated the initial total synthesis of bruguierol C **62** in 7 linear steps from compound **63**.[67] The main step was an intramolecular FC alkylation that eventually supplied the final natural product. For the synthesis of bruguierol C **62**, compound **63** was converted into lactol **64** after several steps. Lastly, an intramolecular trap of the incipient (emerging) oxocarbenium cation using a Marson-type FC alkylation[68] permitted the construction of the masked bruguierol C. The two-step reaction sequence including oxocarbenium construction to provide **65** and also intramolecular FC alkylation afforded the corresponding β-C-glycoside product **66**. Finally, compound **66** afforded the naturally occurring compound **62** in 85% yield (Scheme 12).[67]

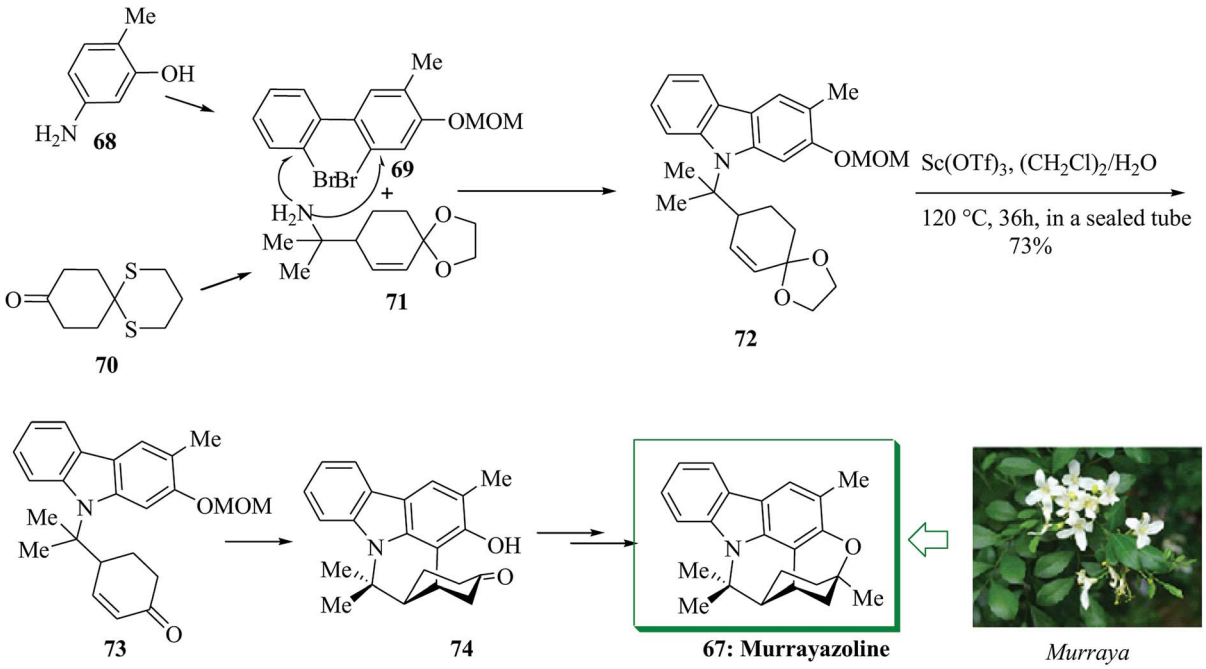
Murrayazoline **67**, found as mahanimbidine and curryangin, is a carbazole alkaloid extracted as a racemic or an optically active compound from the genus *Murraya*. Murrayazoline and its corresponding carbazole alkaloids were demonstrated to be have antiplatelet aggregation activity.[69] A structural explanation investigation demonstrated that murrayazoline is a hexa-heterocyclic alkaloid composed of *N*-functionalized carbazole, cyclohexane and dihydropyran constituents.[70,71] The total synthesis of (±)-murrayazoline **67** was developed in 2008 by Chida and co-workers.[72] The characteristic hexa-heterocyclic structure of **67** was generated using a combination of the intramolecular FC-type Michael addition reaction and palladium-mediated carbon–oxygen coupling reactions. Firstly, the two segments **69** and **71** were provided from 5-amino-2-methylphenol **68** and 1,5-dithiaspiro-[5,5]undecane-9-one **70**,[73] respectively, in several steps. Next they afforded the corresponding *N*-functionalized carbazole **72**. The reaction of **72** with scandium(III)triflate in water and dichloroethane induced the deprotection of the ethylene ketal substituent, the intramolecular FC-type Michael addition and the deprotection of the *O*-MOM group, affording pentacyclic ketone **74** in 73% yield.[74,75]



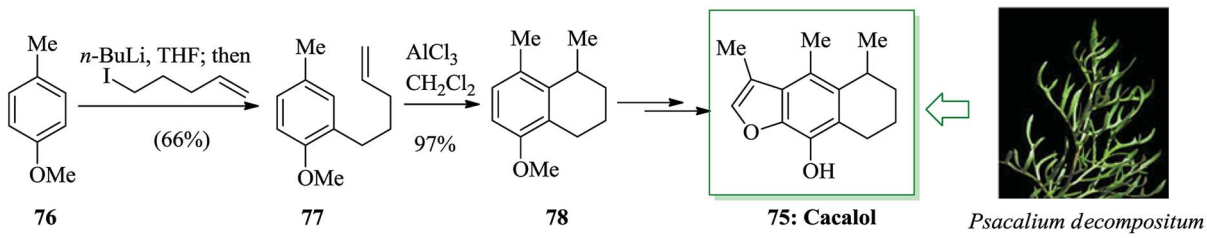
Scheme 12 Total synthesis of bruguierol C **62**.

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Scheme 13 Total synthesis of murrayazoline **67**.

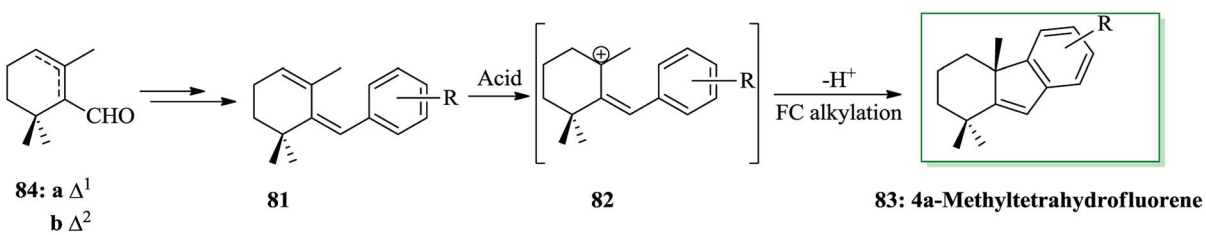


Scheme 14 Total synthesis of cacalol **75**.

Finally, compound **74** afforded (±)-murrayazoline **67** after several steps (Scheme 13).[72]

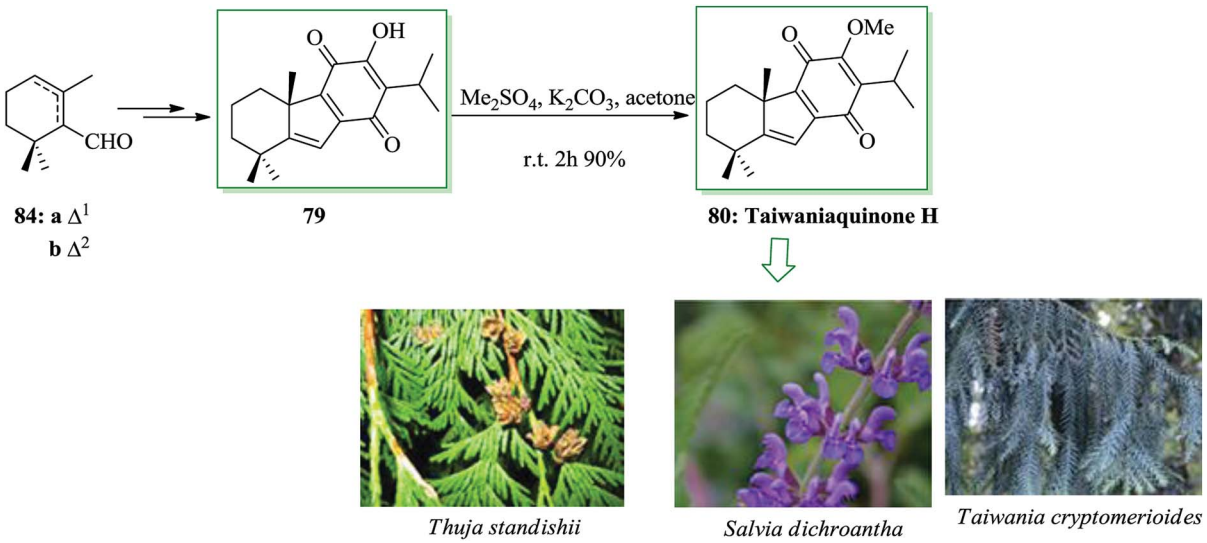
Cacalol **75**, a sesquiterpene naturally occurring compound, was extracted from the roots of the shrub *Psacalium decompositum* in northern Mexico,[76,77] that has antihyperglycemic,[78] anti-inflammatory,[79] antimicrobial,[79] and antioxidant[80] properties. A facile synthesis of cacalol **75** was established from 4-methylanisole **76** in seven steps and 21–25% overall yield. An intramolecular FC alkylation, Baeyer–Villiger oxidation and alkylation are the key reactions in this approach. The synthesis of cacalol **75** was started with *ortho*-lithiation[81] of 4-methylanisole **76** using *n*-butyllithium in tetrahydrofuran. This anion was alkylated with 5-iodo-1-pentene[82] to afford the alkene **77**. Subsequently, this molecule was cyclized *via* an intramolecular FC alkylation using $AlCl_3$ in dichloromethane to afford the tetralin **78**. Finally, compound **78** afforded cacalol **75** upon several steps (Scheme 14).[83]

Taiwaniaquinoids, a group of tricyclic diterpenoids containing a 4*a*-methyltetra- (and hexa-)hydrofluorene framework have been extracted from various East Asian conifers, for example, *Taiwania cryptomerioides*,[84,85] *Salvia dichroantha*,[86] and *Thuja standishii*.[87] They contain taiwaniaquinone H **80**[85] and dichroanone **79**.[86] A very significant pathway toward taiwaniaquinoids was reported in 2009 by Alvarez-Manzaneda and co-



Scheme 15 Synthesis of 4*a*-methyltetrahydrofluorene **83** framework.

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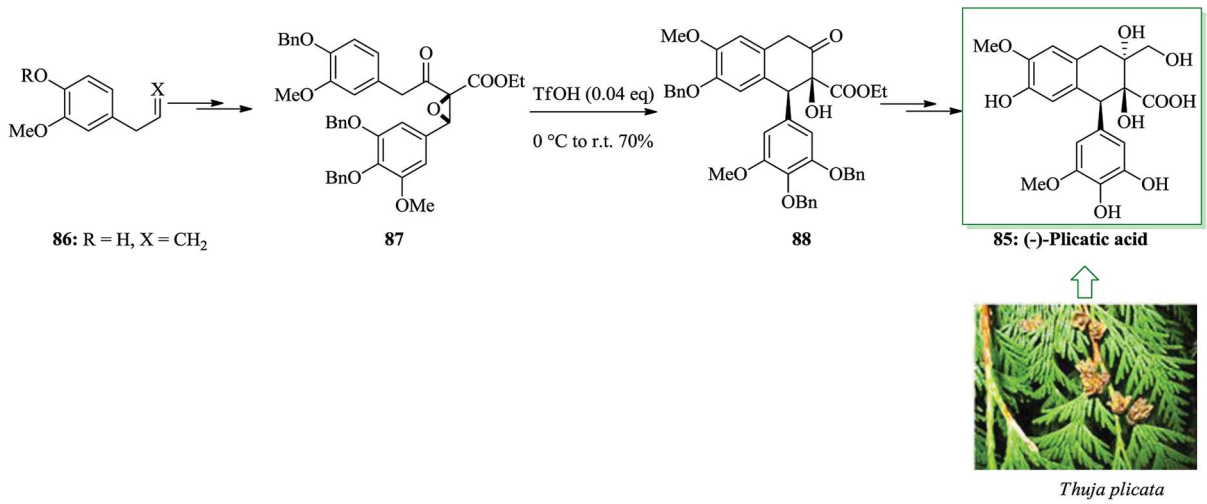
Scheme 16 Total synthesis of taiwaniaquinone H **80**.

workers. Key steps are the intramolecular FC alkylation reaction of an aryldiene and the degradative oxidation reaction of a methylenedioxy substituent. Using this strategy, (±)-dichroanone **79** (in three steps, 77% overall yield) and (±)-taiwaniaquinone H **80** (in four steps, 70% overall yield) were provided from α-**84a** or β-cyclocitral **84b**. This group designed a probable synthesis of taiwaniaquinoids. The key intermediate would be the aryldiene **81**, which resulted in the arylallyl cation **82** under acidic conditions, which, through a quick intramolecular FC alkylation, afforded the 4*a*-methyltetrahydrofluorene **83** framework (Scheme 15).[88]

β-Cyclocitral **84a** and α-cyclocitral **84b** afforded dichroanone **79** upon several steps. Then, the transformation of this quinone into taiwaniaquinone H **80** was achieved (Scheme 16).[88]

Plicatic acid was identified as the causative agent of occupational asthma.[89–91] Plicatic acid was extracted from western red cedar (*Thuja plicata*) in 1959 by Maclean and co-workers.[92] The initial enantioselective total synthesis of (−)-plicatic acid was achieved from eugenol in 12 steps and 14% overall yield. In this approach, a theoretically novel methodology containing an enantioselective epoxidation-intramolecular epoxy-ring-opening FC reaction sequence was performed for the asymmetric formation of a structurally complex 2,7′-cyclolignane framework. The synthesis was initiated from eugenol **86**, which was converted into epoxide **87** upon several steps. The key intermediate, α-hydroxy ketone **88**, was provided through an intramolecular FC reaction to open the epoxide ring in **86**. Noticeably, triflic acid (TfOH) efficiently improved the FC reaction. Finally, compound **88** provided (−)-plicatic acid **85** after several steps (Scheme 17).[93]

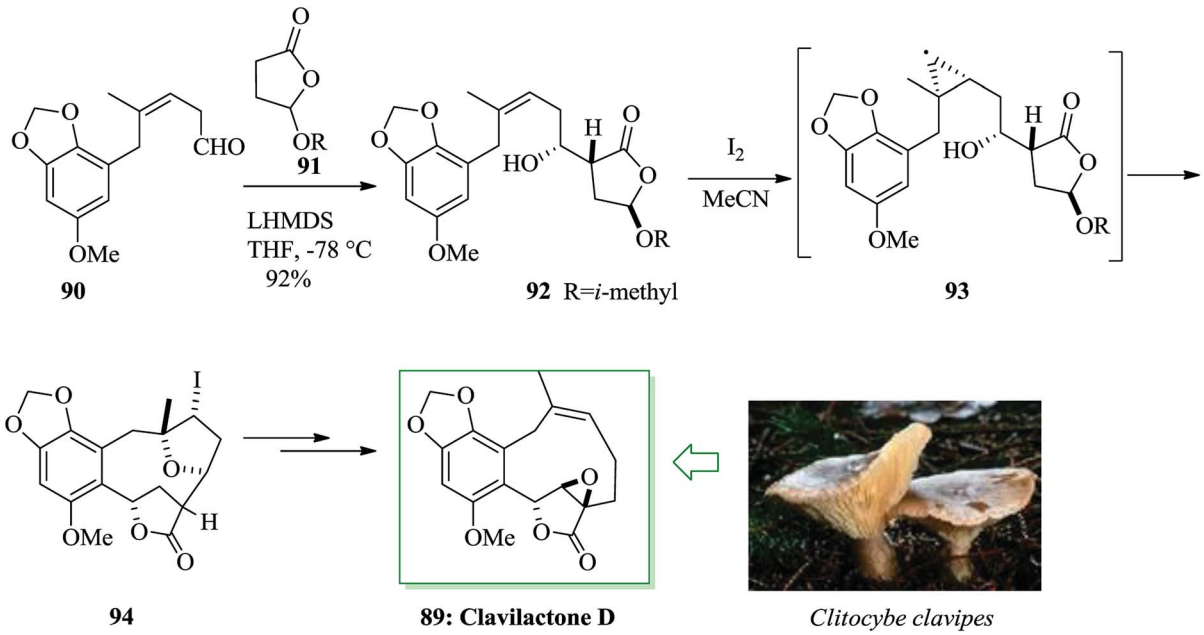
Clavilactone D **89**, a tyrosine kinase inhibitor,[94] was extracted from cultures of the fungus *Clitocybe clavipes*.[95] A method for the synthesis of clavilactone D was reported in 2009 by Yoshimitsu and co-workers.[96] This pathway uses sequential cyclization and FC cyclization to provide a polycyclic lactone fused



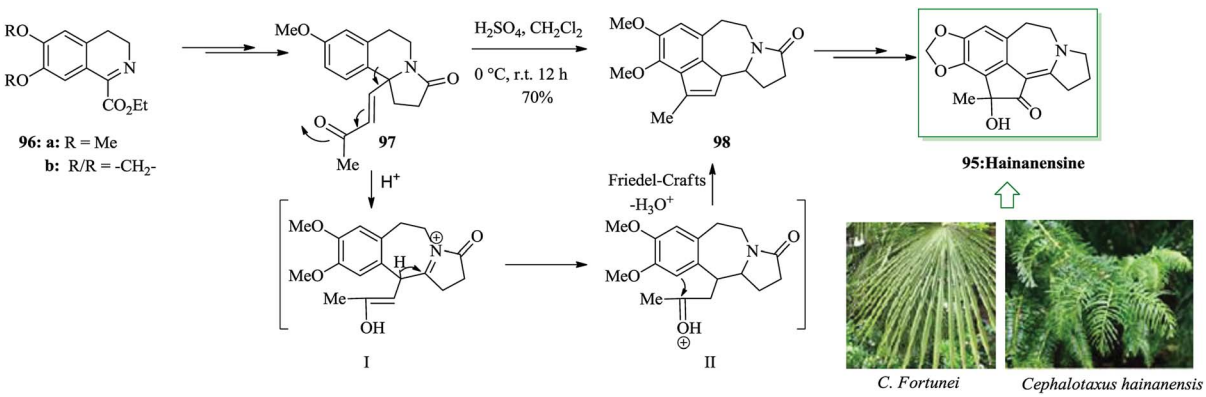
Scheme 17 Total synthesis of (−)-plicatic acid **85**.

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Scheme 18 Total synthesis of clavilactone D **89**.



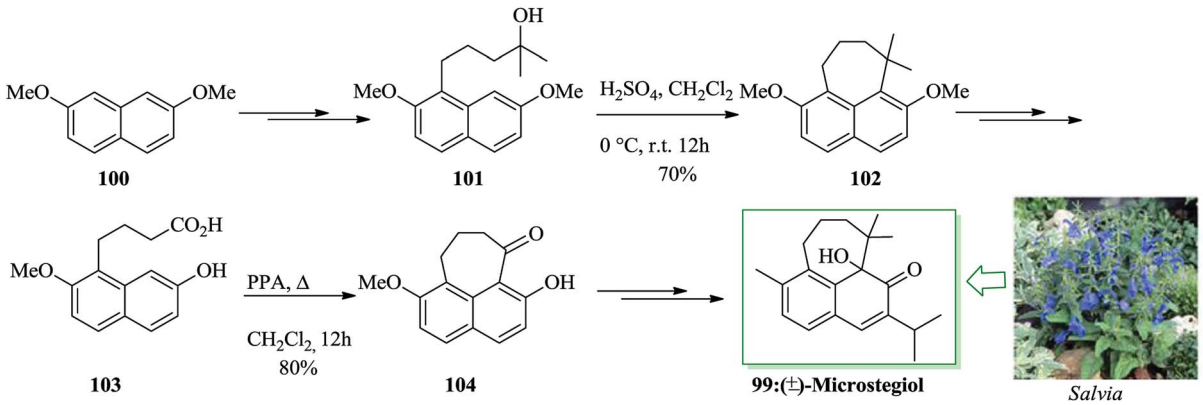
Scheme 19 Total synthesis of hainanensine **95**.

with an aromatic ring. Total synthesis of clavilactone D **89** was initiated from aldehyde **90**. In this route, substrate **92** was synthesized *via* the aldol reaction of chiral lactone **91**[97] with aldehyde **90**.[98] Next, iodo etherification followed *via* FC-type cyclization of alkenyl alcohol **92** with iodine gave the fused polycyclic compound **94**. Finally compound **94** provided clavilactone D **89** upon several steps (Scheme 18).[96]

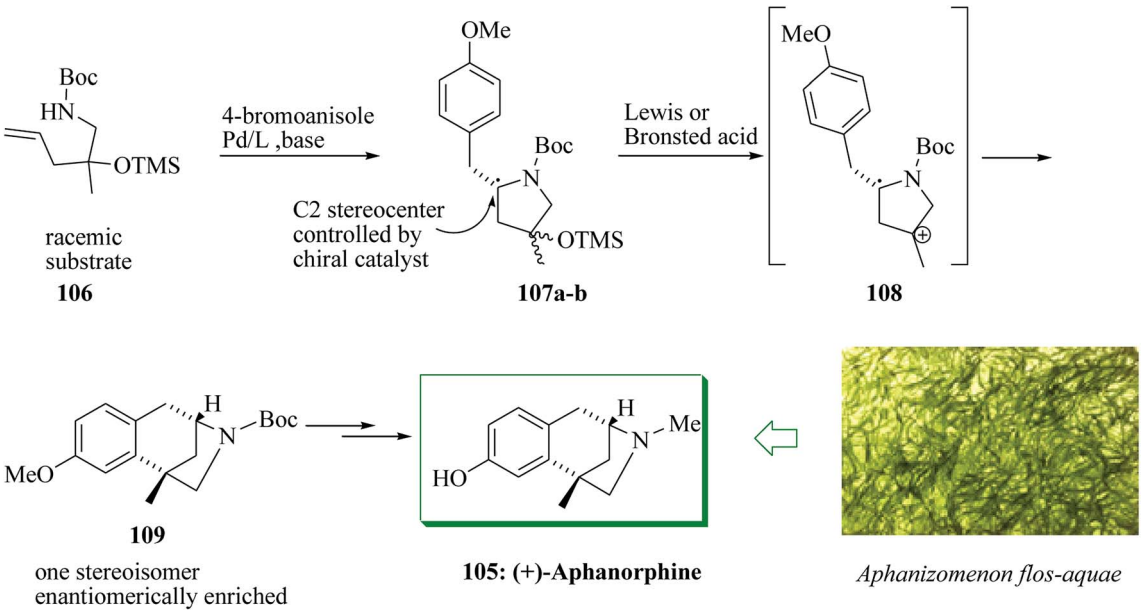
Hainanensine **95**, racemic, is a structurally distinctive minor alkaloidal constituent identified by Liang and Sun in 1981 from the antileukemia plants *Cephalotaxus hainanensis* and *C. fortunei*.[99] Hainanensine **95** contains marginal antitumor properties,[99] and also Yin *et al.* demonstrated that saturated derivatives and other structural analogues of **95** have demonstrated a series of remarkable biological properties.[100] A simple total synthesis of hainanensine **95** through an efficient acid-catalyzed rearrangement/FC annulation cascade, was developed. Relying on this method, initially, enone **97** was synthesized from 3,4-dihydroisoquinoline **96** after several steps. Upon refluxing enone **97** in formic acid, compound **98** was provided. Seemingly, the construction of rearranged annulation product **98** resulted from more FC-type cyclization-dehydration of the initial ring-expansion intermediates **I** and **II**. Subsequently, compound **98** provided hainanensine **95** upon several steps (Scheme 19).[101]

A rearranged abietane including the cyclohepta[*de*]naphthalene nucleus, microstegiol **99**,[102–107] was extracted from roots of a wide range of plants of the genus *Salvia*. Microstegiol itself was exhibited to contain antileukemic and modest antibacterial properties.[102,105–107] For the total synthesis of microstegiol **99**, firstly 2,7-dimethoxynaphthalene **100** was converted into compound **101** upon several steps. Exposing tertiary alcohol **101** to sulfuric acid in dichloromethane induced its transformation to 7,7-dimethyltetra-hydrocyclohepta[*de*]naphthalene **102** (70% yield).[108] Next, compound **102** afforded compound **103** upon

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Scheme 20 Total synthesis of (±)-microstegiol **99**.



Scheme 21 Enantioselective total synthesis of (+)-aphanorphine **105**.

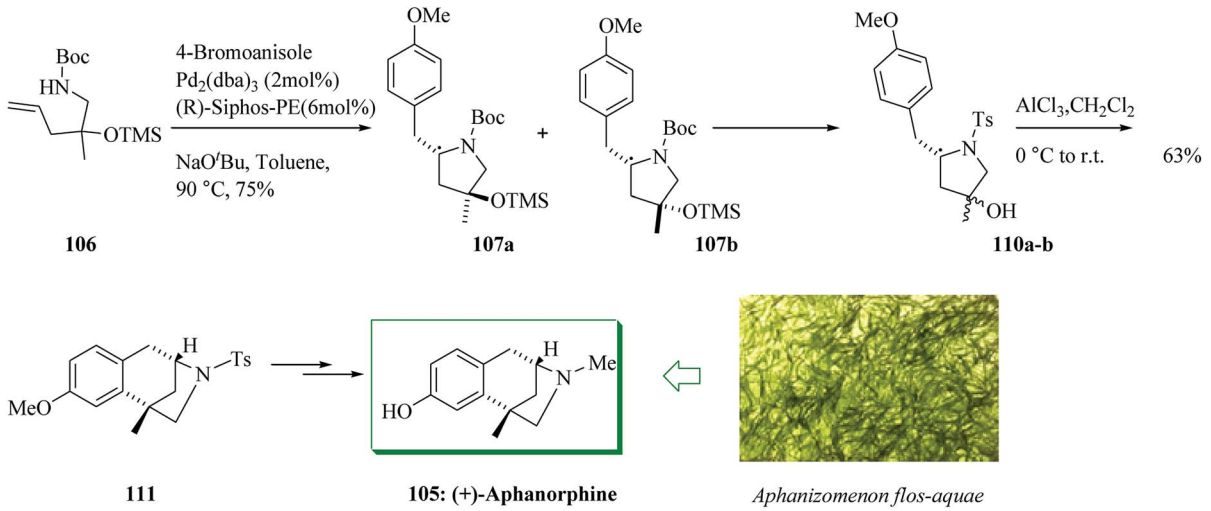
several steps. Subsequently, **103** using polyphosphoric acid (PPA) in dichloromethane under reflux conditions was transformed to **104** with 80% yield. Afterwards, compound **104** led to the construction of (±)-microstegiol **99** in 64% yield upon several steps (Scheme 20).[108]

The tricyclic alkaloid aphanorphine was extracted from the blue-green alga *Aphanizomenon flos-aquae* by Clardy and Shimizu in 1988.[109] Aphanorphine shares common structural features with other bioactive benzomorphan alkaloids, for example eptazocine, pentazocine and morphine.[110–114] A short enantioselective synthesis of (+)-aphanorphine **105** was accomplished in 10 steps and 13% overall yield. A racemic γ-aminoalkene derivative was converted into a 1 : 1 mixture of enantiomerically enriched diastereomers employing an enantioselective palladium-mediated carboamination. Next, this mixture was transformed into an enantiomerically enriched masked aphanorphine derivative *via* a FC reaction to make a quaternary all-carbon stereocenter. The catalyst-controlled enantioselective palladium-mediated carboamination reaction of racemic substrate **106** was applied to set the C2 stereocenter of pyrrolidines **107a,b**, thus affording a mixture of enantiomerically enriched diastereomers. Subsequently, this mixture of diastereomers was transformed to **109** in a FC alkylation that proceeded through intermediate carbocation **108**, and formed the all-carbon quaternary stereocenter in an enantio-convergent carbon–carbon bond-forming stage. A two-step sequence of reduction and demethylation was used to transform **109** to aphanorphine (Scheme 21).[115]

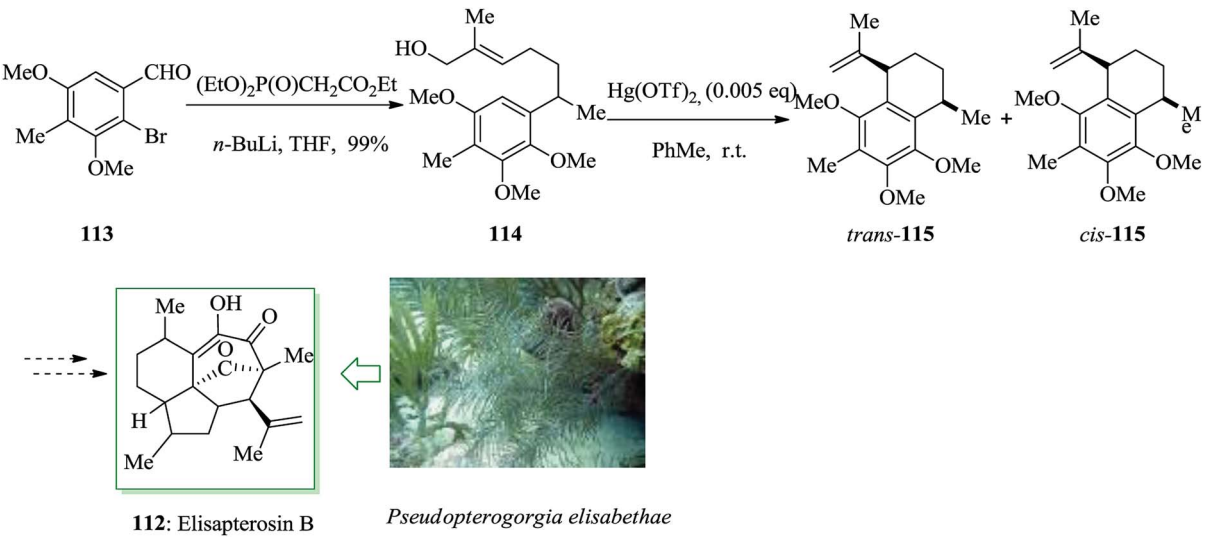
The coupling reaction of **106** and 4-bromoanisole was explored for asymmetric alkene carboamination reactions.

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Scheme 22 Total synthesis of (+)-aphanorphine **105**.



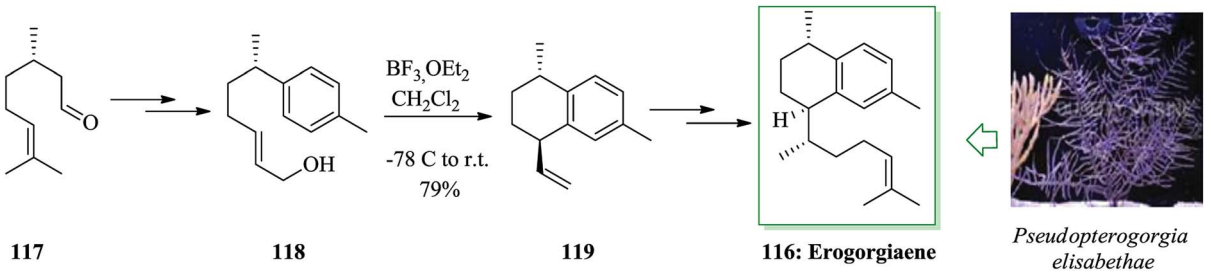
Scheme 23 Total synthesis of elisapterosin B **112**.

Based on the optimal conditions, this transformation gave a 1 : 1 mixture of diastereomers **107a** and **107b**, which afforded **110a,b**. The enantio-convergent intramolecular FC alkylation reaction of the mixture of diastereomers **110a,b** afforded **111** in 63% yield.[114] Meanwhile, the transformation of **107a,b** to **109** failed. The *N*-tosylated derivative **111** formerly acted as an intermediate in Zhai's syntheses of aphanorphine.[114,116] Afterwards, compound **111** was converted into (+)-aphanorphine **105** upon several steps (Scheme 22).[115]

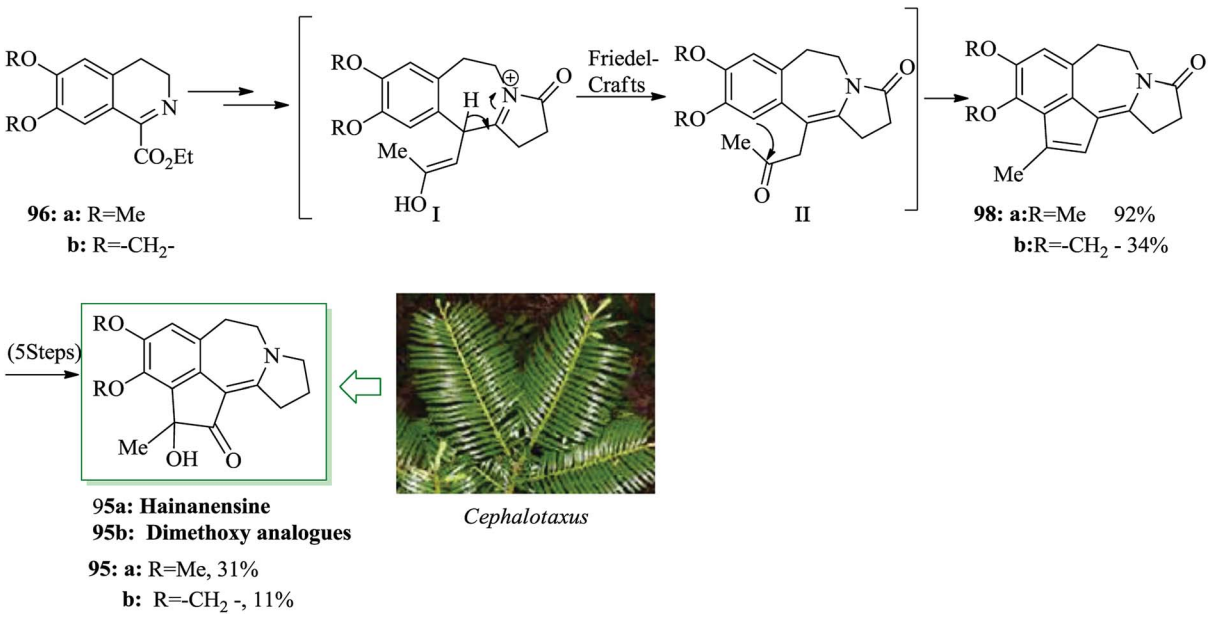
Elisapterosin B **112** was extracted from the gorgonian coral *Pseudopterogorgia elisabethae* and exhibited antitubercular properties, preventing the growth of *Mycobacterium tuberculosis* H37Rv.[117] As part of a method toward the formation of the antitubercular agent elisapterosin B, it was synthesized from two chiral, non-racemic olefinic substrates and their diastereoselective ring closure, achieved in the presence of Hg salts. In this pathway, the synthesis was initiated from aldehyde **113**,[118] which was converted into **114** upon several steps. The asymmetric construction of **115** was achieved through an intramolecular FC alkylation reaction of **114**. Harmata and coworkers synthesized elisapterosin B **112** by employing benzothiazine chemistry along with $Hg(OTf)_2$-mediated diastereoselective intramolecular FC alkylation (Scheme 23).[119]

Erogorgiaene **116**, together with other structurally relevant diterpenes, has been extracted[120] from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*. The formal total synthesis of the antitubercular agent erogorgiaene has been accomplished in 12 steps with an overall yield of 14.2%, initiating from (*S*)-(−)-citronellal **117**. This synthetic method includes an enamine-catalyzed 1,4-addition, an aldol condensation, dehydrogenation, a Wittig olefination reaction, intramolecular FC cyclization, TEMPO-BAIB-catalyzed oxidation, and Evans auxiliary-induced diastereoselective methylation. In this route, total synthesis of erogorgiaene **116** was started from

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Scheme 24 Total synthesis of erogorgiaene **116**.



Scheme 25 Total synthesis of hainanensine **95a** and its dimethoxy analogue **95b**.

(*S*)-(−)-citronellal **117**, which was converted into allylic alcohol **118** upon several steps. Next, compound **118** was exposed to intramolecular FC cyclization reaction[62,119] with $BF_3 \cdot OEt_2$ in dry CH_2Cl_2 to provide bicyclic compound **119** in 79% yield with moderate *de* (8 : 1). Afterwards, erogorgiaene **116** was provided from compound **119** upon several steps (Scheme 24).[121]

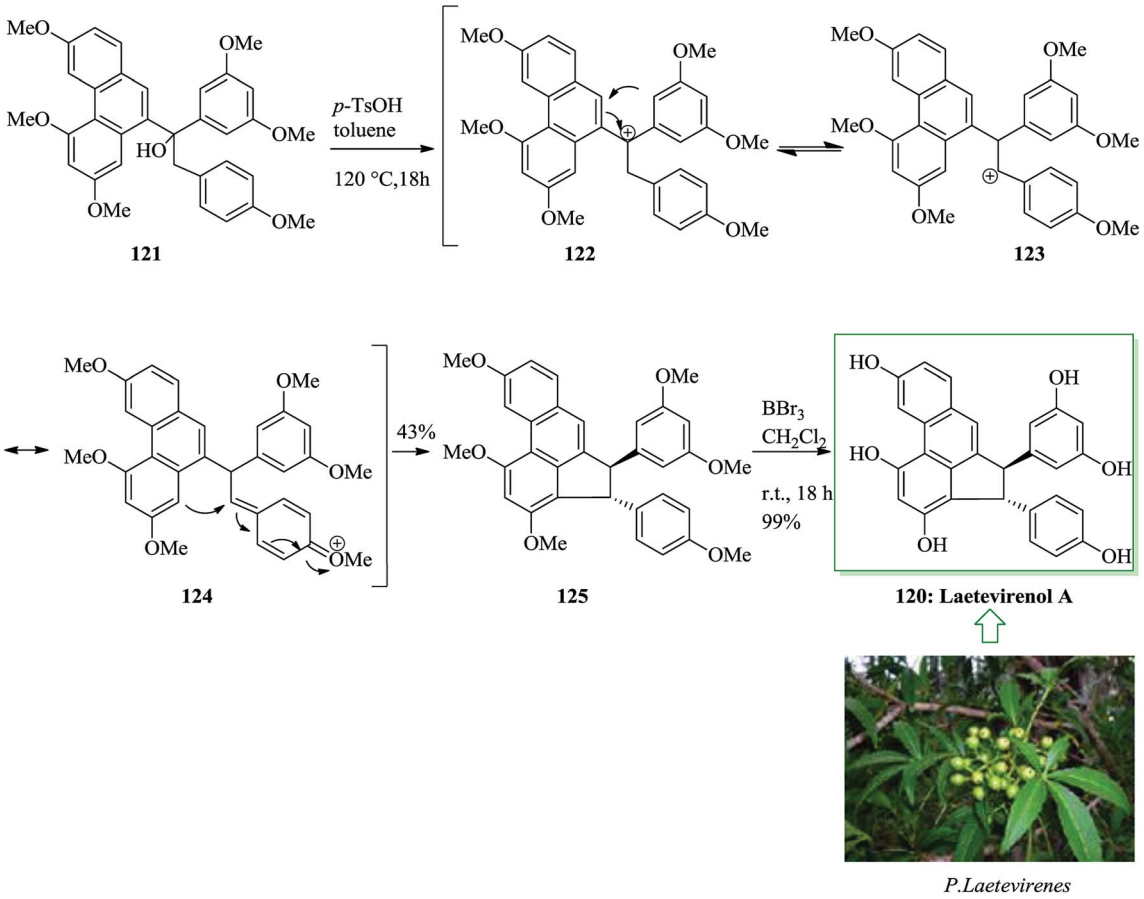
The *Cephalotaxus* genus is a member of the *Cephalotaxaceae* group of conifers. They are a fruitful source of several naturally occurring compounds, especially terpenoids (abietanes, troponoids) and alkaloids (cephalotaxine esters), which often exhibit medicinal activities, particularly in the anticancer area.[122] An uncommon rearrangement-annulation cascade has been demonstrated by Li and co-workers for the total synthesis of hainanensine **95a** and its dimethoxy analogue **95b**.[101] Initially, isoquinolines **96a**/**96b** provided the intermediate **I** followed by FC cyclization on the residual ketone **II** toward tetracyclic intermediates **98a** and **b**. Five more steps were necessary to attain hainanensine **95a** and its dimethoxy analogues **95b** (Scheme 25).[123]

Laetevirenol A **120**, together with laetevirenol B–E, was extracted from the stems and roots of *Parthenocissus laetevirens* in 2008 by Pan and co-workers.[124] Laetevirenol A exhibits potent antioxidant properties, probably because of the existence of a phenanthrene scaffold serving as a free radical scavenger.[125–133] The one-pot dehydration/FC alkylation of **121** with *p*-toluenesulfonic acid in toluene provided the corresponding *trans*-cyclized product **125** as a single isomer. Finally, global demethylation of **125** with boron tribromide in dichloromethane afforded laetevirenol A **120** in quantitative yield (Scheme 26).[134]

The *Leucetta* alkaloids, a class of 2-aminoimidazole alkaloids,[135] were extracted from sponges of the *Clathrina* and *Leucetta* groups.[136–138] Structurally, these alkaloids include at least one oxygenated benzyl group. Kealiinines A–C **126a–c**[139] were extracted by the Proksch group in 2004, together with naamidine H and naamine G. It should be mentioned that no biological activity has been stated by Proksch for **126b** and **126c**,[139] but kealiinine A **126a** was found to be potent in the brine shrimp toxicity test.[139] Concise total syntheses of the *Leucetta*-obtained alkaloids, kealiinines A–C, were achieved through an intramolecular FC dehydration sequence of a bis benzylic diol. For the synthesis of kealiinine C **126c**, the diol **128c** was synthesized from 1-methyl-4,5-diiodoimidazole **127** upon several steps. Pleasantly, the reaction between unpurified **128c**

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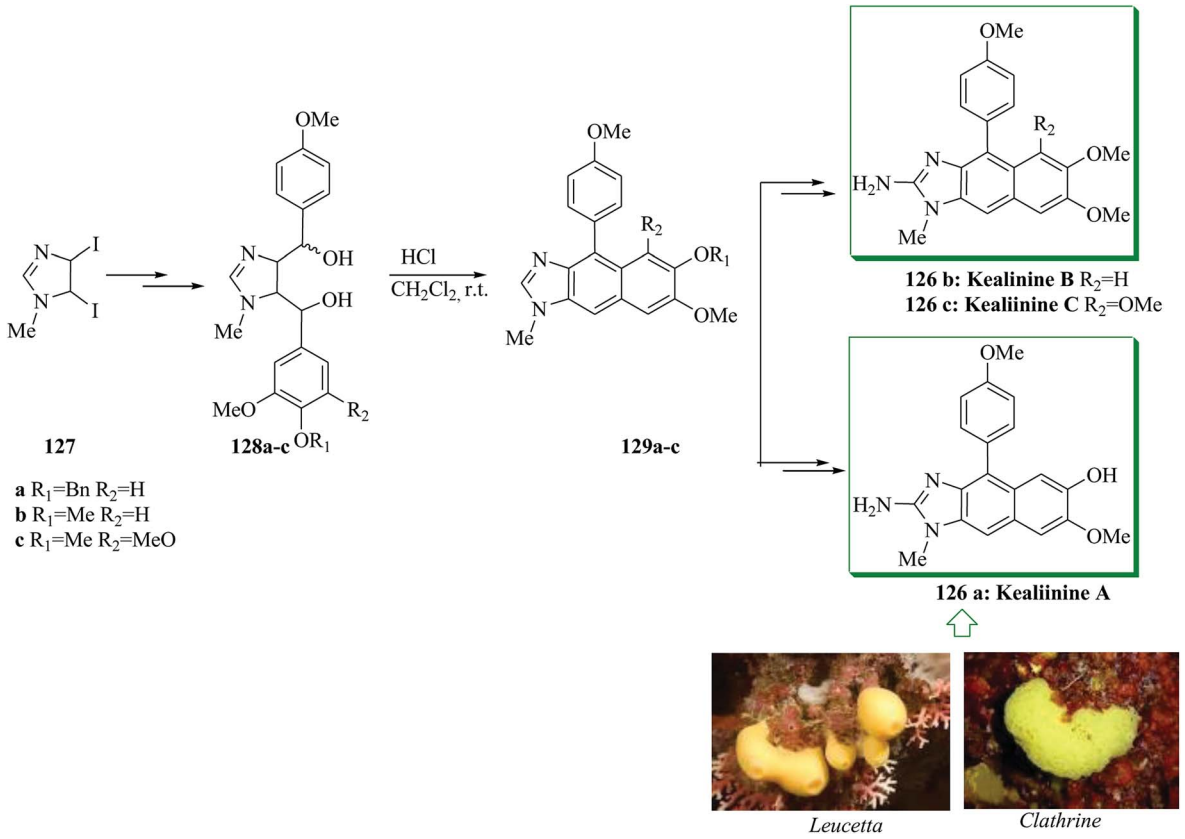
Scheme 26 Total synthesis of laetevirenol A **120**.

and hydrochloric acid led to an intramolecular FC cyclization-dehydration sequence to give the naphthimidazole **129c**. Subsequently, compound **129c** provided kealiinine C **126c** upon several steps. Next, it was tried to make the other two group members, kealiinine A **126a** and B **126b**. Their syntheses follow largely the similar methodology, simply substituting the suitable benzaldehyde for **126a** and **126b**, affording the target products after seven steps with 11% overall yield and six steps with 21% overall yield, respectively, starting from compound **127** (Scheme 27).[140]

The dibenzo[*a*,*d*]cycloheptene scaffold is a kind of polycyclic framework that occurs broadly in various naturally occurring compounds.[141,142] One of the most direct approaches for the formation of this scaffold is the intramolecular FC acylation reaction.[143,144] Another common synthetic pathway is the equivalent acid-mediated FC alkylation reaction of olefins.[145] The natural diptoindonesin D **130** and pauciflorial F **131** have been extracted from the acetone extract of the tree bark of *Hopea dryobalanoides*[146] and the stem barks of *Vatica pauciflora*[147] respectively. Yang and co-workers established an efficient method for the construction of several dibenzo[*a*,*d*] cycloheptenes through FC alkylation reaction. Furthermore, utilizing this approach as the main stage, this group demonstrated short and valuable pathways to form diptoindonesin D **130** and pauciflorial F **131**. The formation of diptoindonesin D **130** and pauciflorial F **131** was started with the construction of the biaryl alcohol **134** from the lithiated form of the Me-masked resveratrol bromide **132** and 3,5-dimethoxy benzaldehyde **133**.[148] With this key intermediate as the substrate, directly, the polyfunctionalized indene **135** was obtained in the presence of trifluoromethane sulfonic anhydride (Tf_2O) as a catalyst *via* FC alkylation reaction. Next, oxidation reaction of compound **135** followed *via* deprotection afforded paucifloral F. On the other hand, compound **134** provided ketone **136** with 90% yield.[149] Then, the carbocyclic unit structure of diptoindonesin D **130** was constructed through FC alkylation reaction, providing **137** in 76% yield. Upon oxidation and deprotection of **137**, the target natural diptoindonesin D **130** was provided (Scheme 28).[150]

Delle Monache *et al.* described the extraction of a dihydrophenanthrapyrane natural product from the root of *Clusia paralycola*, paralycolin A, that shows cytotoxicity against P388 cells and KB.[151] The structurally relevant natural product cedrelin A **138** was extracted from the bark of *Cedrelinga catenaeformis* Duke by Kakisawa *et al.* in 1991.[152] Paralycolin B has been extracted merely as a methylated derivative **139** upon reaction of a resultant mixture of paralycolin A and paralycolin B with diazomethane. Furthermore, these naturally occurring compounds usually contain an isopropenyl substituent at the

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Scheme 27 Total synthesis of kealiinines A–C **126a–c**.

10-position of the 9,10-dihydrophenanthrene framework. Hamada and co-workers in 2013 demonstrated the initial asymmetric total syntheses of cedrelin A and methylated paralycolin B, employing mediated enantioselective intramolecular FC allylic alkylation reaction of phenols as the main step.[153] Total synthesis of cedrelin A **138** was initiated from aldehyde **140**,[154] which was transformed into allyl carbonate derivative **141** upon several steps. Next, the mediated enantioselective intramolecular FC allylic alkylation of **141** was examined. With 1.5 equiv. of potassium acetate, the reaction progressed easily to give compound **142** in 98% yield (94% extracted yield) with 66% enantioselectivity. Finally, intermediate **142** has been converted into cedrelin A **138** in 74% yield (12 steps from **140** and 16.5% overall yield) (Scheme 29).[153]

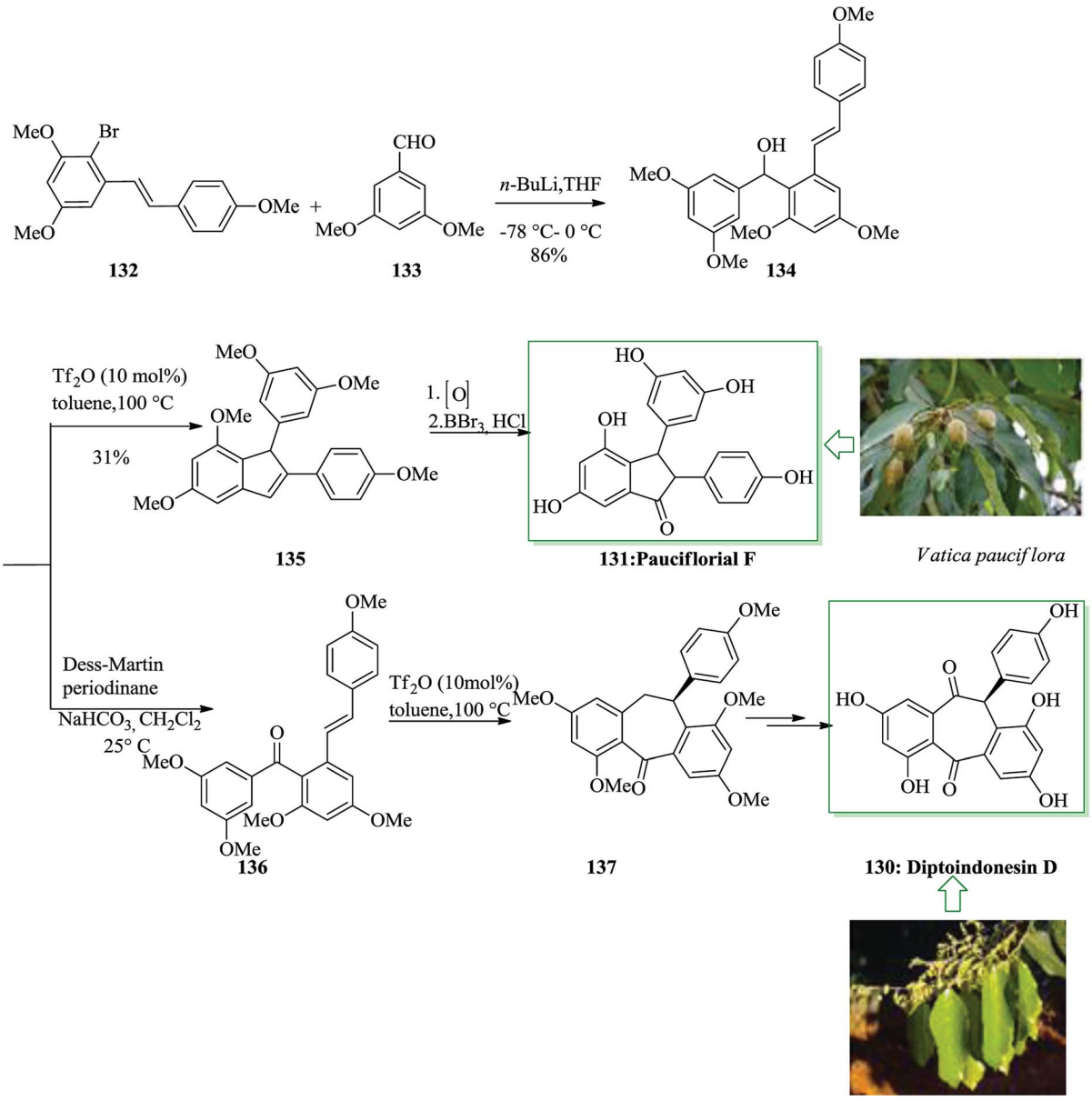
Subsequently, the asymmetric total synthesis of methylated paralycolin B **139** was accomplished. First, compound **144** was synthesized from 6-bromoveratraldehyde **143** upon several steps. Enantioselective intramolecular FC allylic alkylation reaction of **144** using $Pd(dba)_2$ and (*R*,*R*)-chiral ligand in dichloromethane/methanol mixed solvent afforded **145** in 98% yield with 92% enantioselectivity. Finally, compound **145** provided methylated paralycolin B **139** in 92% yield (10 steps from **143** and 35.2% overall yield) (Scheme 30).[154]

Members of the genera *Ligularia*, *Euryops*, *Senecio*, and *Psacalium* of the *Asteraceae* group are generally dispersed plants rich in furanoeremophilane compounds.[155–157] This group of sesquiterpenes includes a linearly fused C_6–C_6–C_4O tricyclic (C_{12}) scaffold having three methyl groups linked to the 4, 5, and 11 positions. An asymmetric total synthesis of the furanoeremophilane sesquiterpene (+)-9-oxoeuryopsin **146** was reported from 2-methyl-2-cyclohexen-1-one **147** in 7% overall yield. This method was accomplished in seven facile synthetic reactions involving conjugate addition-enolate trapping, imidazoylthiocarbonylation reaction, bisdethiocarbonylation, masked cyanohydrin construction-hydrolysis, dehydration, alkaline hydrolysis, and also FC cyclization. The total synthesis of **146** was initiated from 2-methyl-2-cyclohexen-1-one, which was converted into acid **148** upon several steps. Next, the crude acid **148** was transformed into (+)-9-oxoeuyopsin **146** in 59% overall yield *via* an intramolecular FC cyclization using tin(IV) chloride as the Lewis acid of the spontaneously provided acid chloride (PCl_5 in benzene at room temperature) (Scheme 31).[158]

Compound **149**, an unnamed quinone methide diterpenoid, was initially extracted from the root bark of *Bobgunnia madagascariensis*.[159] A convergent pathway was established to form an antifungal tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid **149** and analogues. In 2013, Yang and co-workers finished the total synthesis of the antifungal tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid **149**. A Stille reaction was applied to introduce the allyl substituent as a protected 2-hydroxyethyl side chain. This group established a BBr_3-catalyzed one-pot bis-demethylation/intramolecular FC alkylation reaction to make the tricyclic molecular framework and then completing the total synthesis of **149**.[160] Compounds **149** and **155** exhibited active

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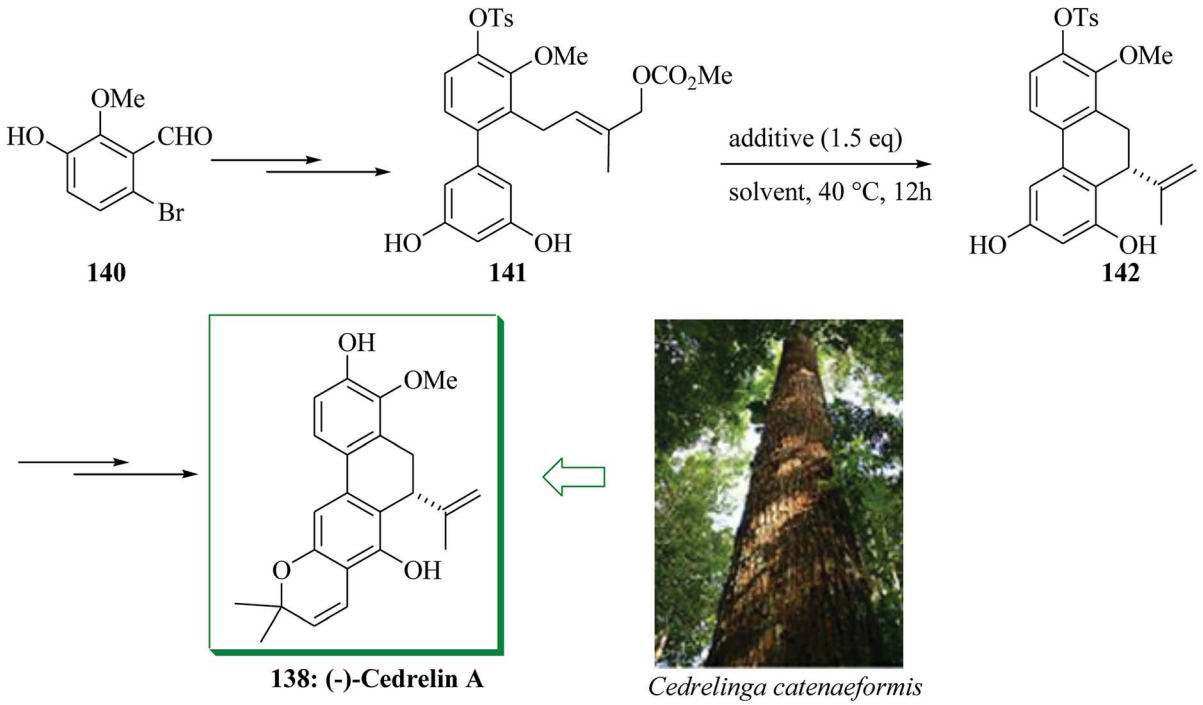
Scheme 28 Total synthesis of diptoindonesin D **130** and pauciflorial F **131**.

cytotoxicity against several strains of pathogenic yeasts tested, but etherification of the 2-hydroxyethyl group resulted in significantly attenuated activity. This total synthesis began from commercially available bromobenzene, which in four steps is converted into 3,4-dimethyoxytoluene **150**.[161] The latter after several steps gave the primary alcohol **151**. The application of the BBr_3-catalyzed one-pot reaction resulted in the completion of the synthesis of **149**. Therefore, reaction of **150** with BBr_3 resulted in bis-demethylation and cyclization in a one-pot manner to generate a tricyclic catechol that, upon oxidation with Ag_2O, afforded **149**. Selective monoetherification of **149** with dimethoxymethane afforded the analogue **152** (Scheme 32).[160]

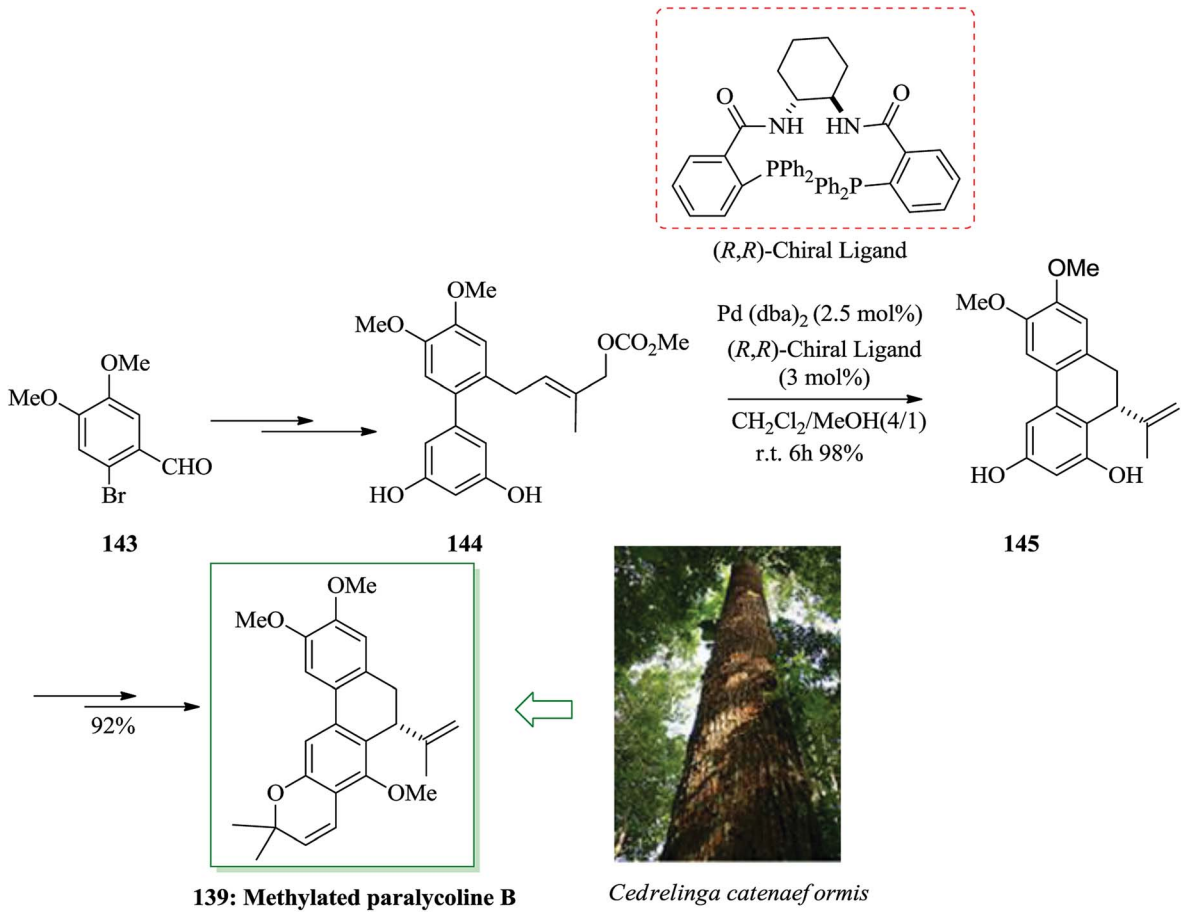
The same group synthesized analogue **155** from carboxylic acid **153**.[160] Compound **153** afforded enone **154** upon several steps. Compound **155** was provided *via* BBr_3-catalyzed bis-demethylation and intramolecular FC alkylation followed by oxidation of the resulting catechol with Ag_2O in one-pot fashion. Compounds **149** and **155** were found to be particularly effective against all yeast strains, including *Candida krusei*, *Candida glabrata*, and *Candida parapsilosis* strains (Scheme 33).[161]

Dimeric epipolythiodiketopiperazine alkaloids are an intriguing group of fungal metabolites notable for their complex molecular scaffolds and biological properties.[162,163] (+)-Bionectins A **156** and C **157**[164] were extracted in 2006 by Zheng and co-workers from fungi of the *Bionectra byssicola* species. (+)-Bionectins A (+)-**156** showed important bacteriostatic activity against methicillin-resistant and quinolone-resistant *Staphylococcus aureus* Gram-positive eubacteria. The

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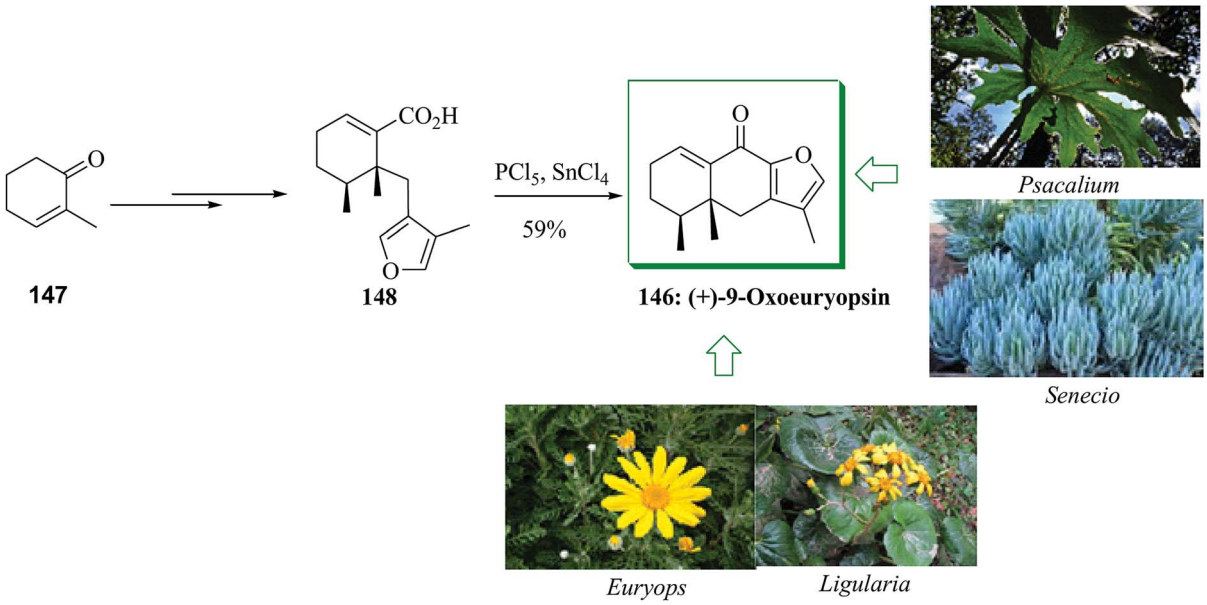
Scheme 29 Total synthesis of cedrelin A **138**.



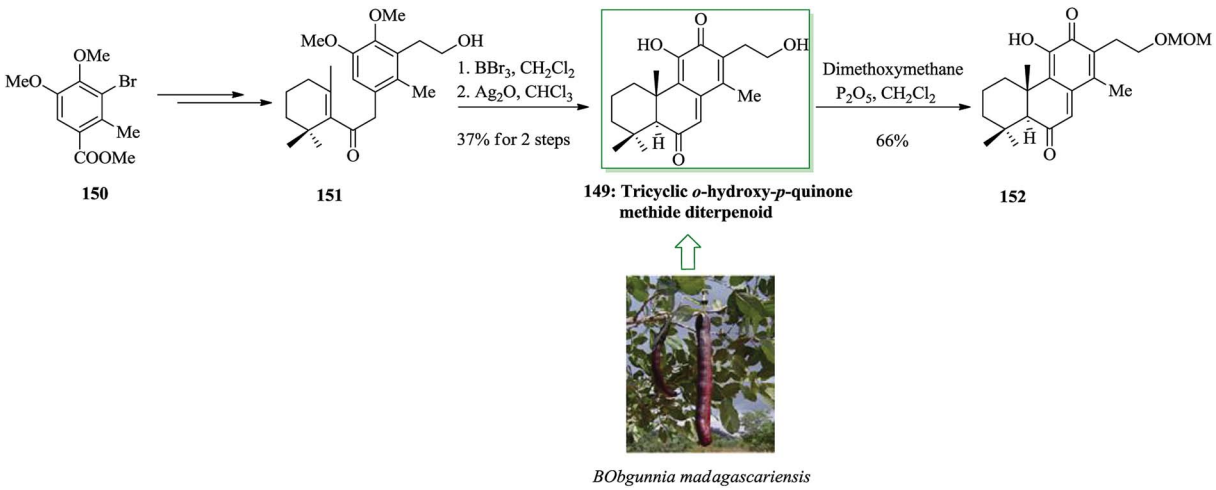
Scheme 30 Total synthesis of methylated paralycolin B **139**.

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Scheme 31 Total synthesis of (+)-9-oxoeuyopsin **146**.

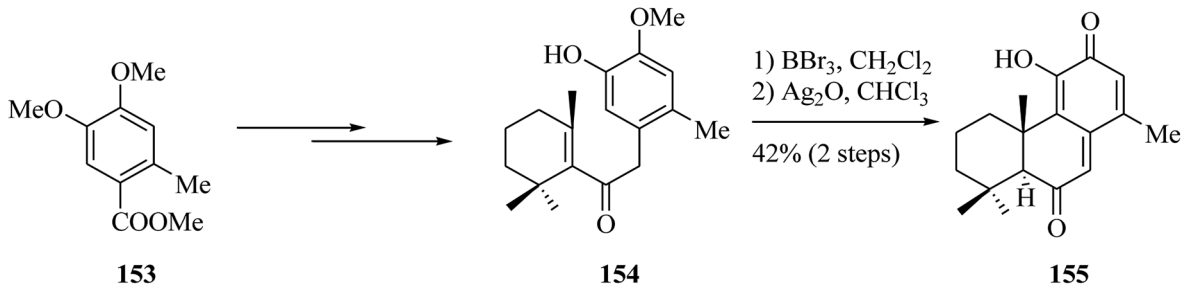


Scheme 32 Total synthesis of tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid **149** and analogues.

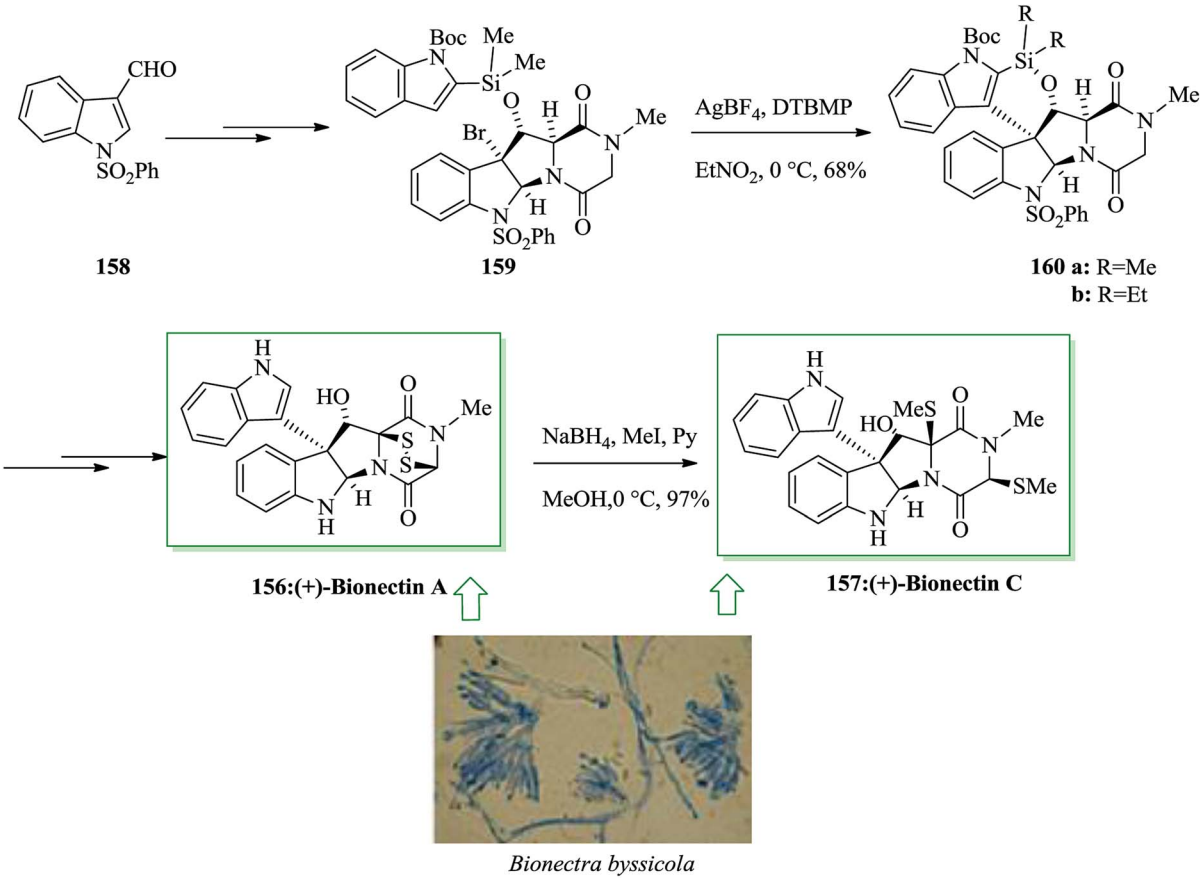
short and effective total synthesis of (+)-bionectins A and C was developed by Movassaghi and co-workers in 2013. This route leading to the total synthesis of these naturally occurring compounds features a new and scalable approach for the synthesis of erythro-β-hydroxytryptophan amino acid. It involves an intramolecular FC reaction of a silyl-tethered indole and a new mercaptan reagent for epipolythiodiketopiperazine (ETP) synthesis that can be unraveled under very mild conditions. Based on this approach, firstly indole-3-carboxaldehyde **158** was converted into the corresponding silyl-tethered indole adduct **159** in 74% yield in several steps. Gratifyingly, a silver-catalyzed intramolecular FC reaction progressed easily in nitroethane to give the C3-(3′-indolyl)-silacyclic product **160a** in 68% yield. The structure of a diethyl silyl variant **160b**, provided during optimization studies, was confirmed *via* X-ray analysis. Compound **160a** gave the target natural product (+)-bionectin A **156** in 81% yield after several steps. Reductive methylation of (+)-bionectin A **156** with $NaBH_4$ and methyl iodide in pyridine and MeOH gave (+)-bionectin C **157** in 97% yield (Scheme 34).[165]

Ammosamides A–C are marine alkaloids that were initially extracted from the marine *Streptomyces* strain CNR-698 by Fenical and co-workers in 2009.[166] Except for ammosamide D, these natural products have a characteristic pyrroloquinoline unit framework, in which the tricyclic structure contains a pyrrole scaffold bridging the C4 and C5 positions of a quinoline ring system.[167,168] Ammosamides A and B exhibit important cytotoxicity against human colon adenocarcinoma HCT-116 cells.[166] A total synthesis of ammosamide B **161**, a member of the pyrroloquinoline alkaloid group extracted from marine *Streptomyces*, was developed. The characteristic unit tricyclic

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Scheme 33 Total synthesis of product **155**.



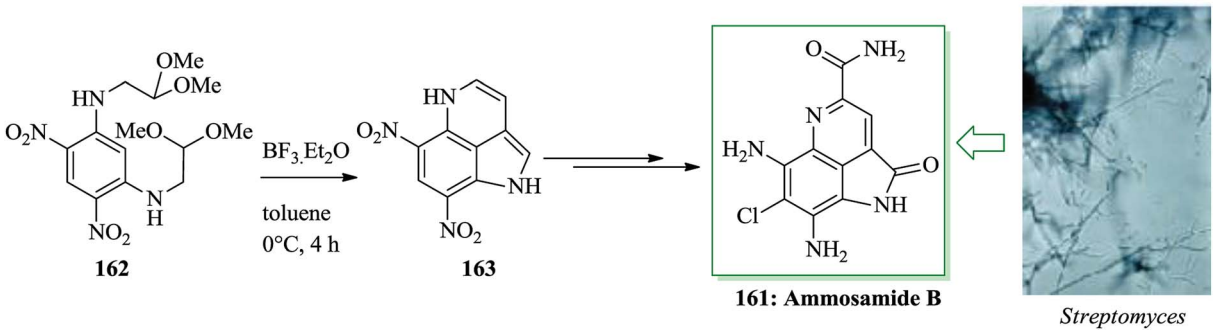
Scheme 34 Total synthesis of (+)-bionectins A **156** and C **157**.

structure of **161** was generated through a unique, tandem FC reaction sequence to transform the symmetric tetra-amino functionalized benzene derivative **162** into the tricyclic pyrroloquinoline product **163**. The reaction was initiated with an acid-promoted tandem FC reaction of the diamino and dinitro functionalized benzene derivative **162** to form the tricyclic pyrroloquinoline **163**. The required substrate **162** was easily synthesized from *m*-dichlorobenzene in a two-step sequence.

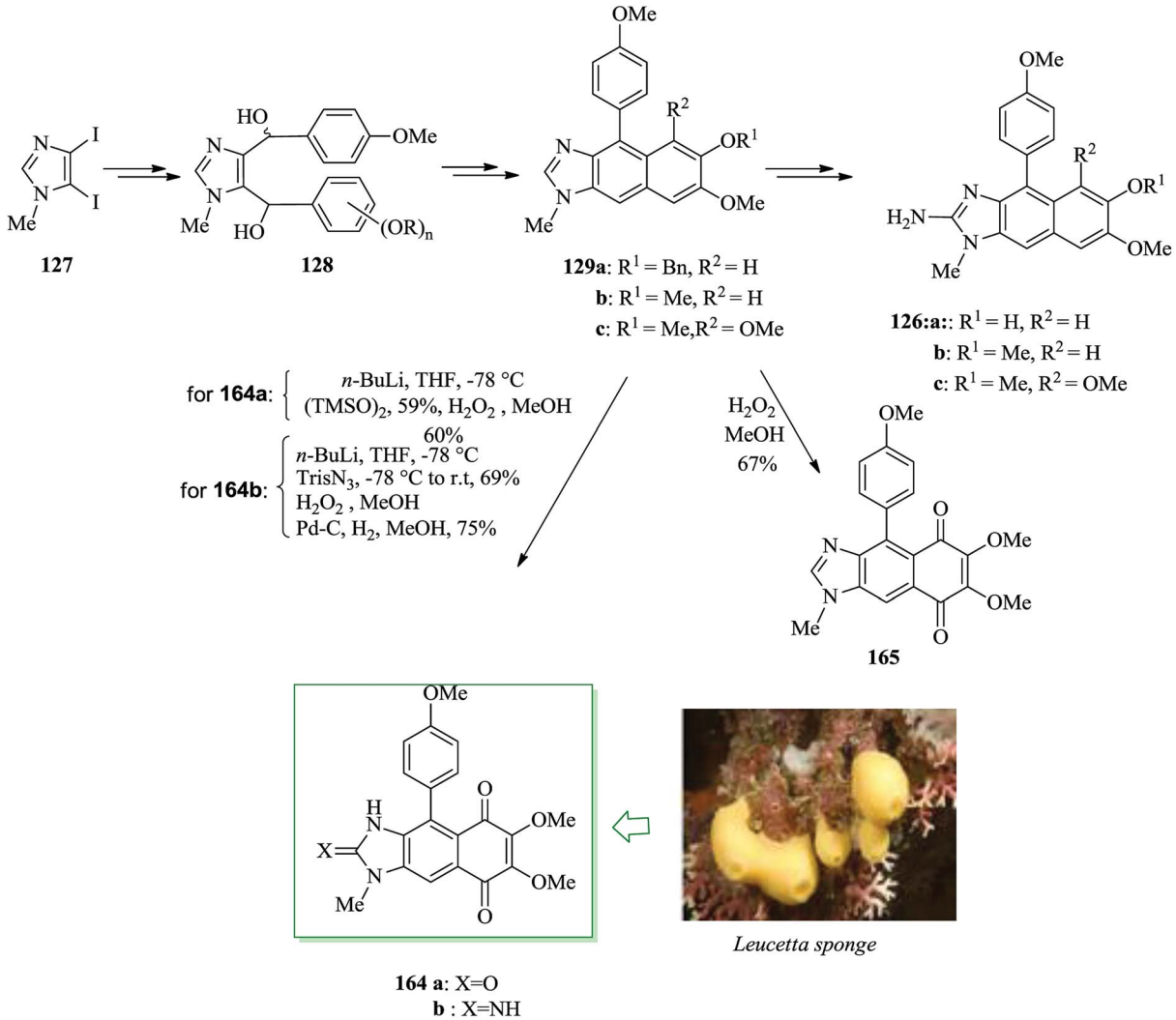
Subsequently, a number of acids were applied to examine the tandem FC reaction and the results demonstrated that the reaction improved in the presence of trifluoroacetic acid (TFA) but does not provide either of the anticipated FC products, only an unidentified oligomeric material. Reactions using the Lewis acids aluminium chloride and titanium tetrachloride also resulted in the construction of insoluble oligomers and no reaction (**162** was recovered quantitatively) happened once the less reactive Lewis acids zinc chloride, tin tetrachloride and $Yb(OTf)_3$ were used. The remarkable observation that an indole (side-product) was provided in 52% yield when $BF_3 \cdot Et_2O$ in dichloromethane was used provided the motivation for a broader investigation of solvent effects on this method. When CH_3CN or THF was utilized in the presence of $BF_3 \cdot Et_2O$ as the solvent for the improvement of the reaction, insoluble oligomers were provided. In contrast, tricyclic pyrroloquinoline **163**, *via* tandem FC product, produced the expected product in 35% isolated yield once toluene was applied as the solvent. While

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Scheme 35 Total synthesis of ammosamide B **161**.

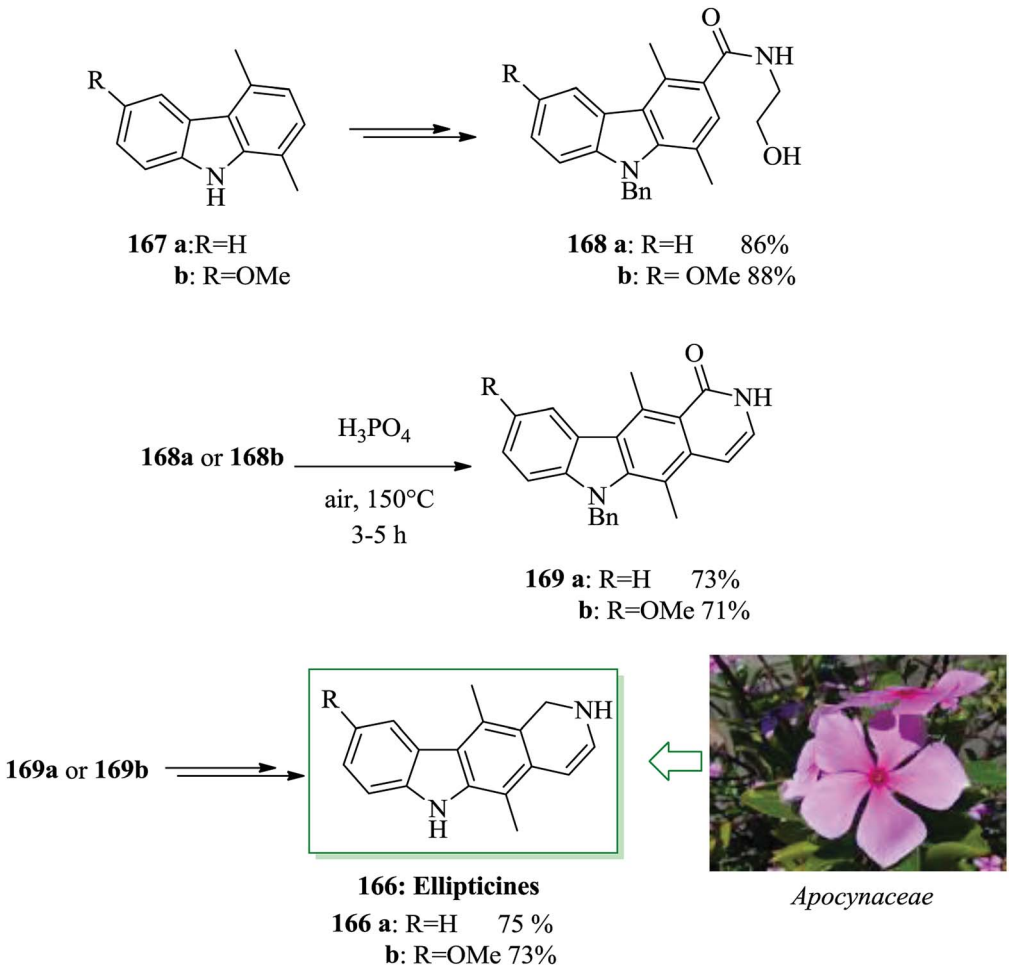


Scheme 36 Total synthesis of kealiiquinone A **164a** and the 2-amino congener **164b**.

this reaction was low yielding, it was performed efficiently and no significant side products were detected by TLC analysis. Hence, the poor yield of **163** is probably owing to its insolubility during the work-up and purification processes. Consequently, Nagasawa decided to apply the optimal reaction conditions ($BF_3 \cdot Et_2O$ in toluene) performing the conversion of **162** to **163** in the synthetic pathway to form ammosamide B **161** and skipped the purification stage. A tandem FC reaction of **162** promoted by $BF_3 \cdot Et_2O$ in toluene led to the formation of compound **163**. Next, ammosamide B **161** was provided after several steps (Scheme 35).[169]

Marine sponges provide a wide range of structurally unique secondary metabolites with remarkable biological properties.[170,171] Clardy and Scheuer initially extracted kealiiquinone

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Scheme 37 Total synthesis of ellipticines **166a** and **166b**.

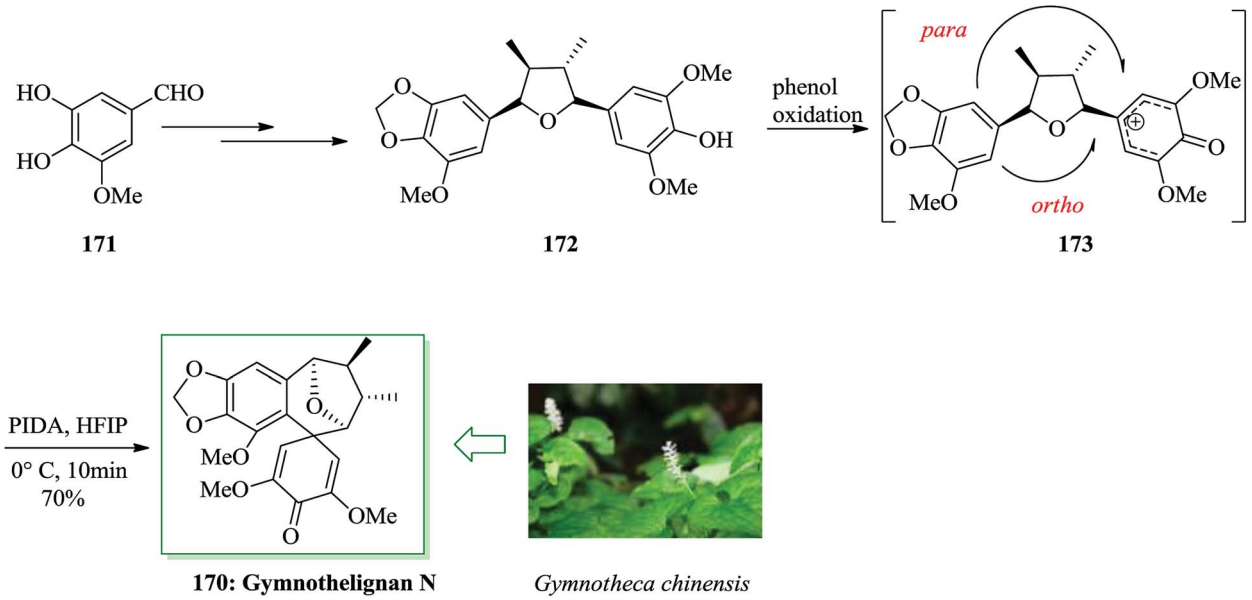
164a from a *Leucetta*-obtained sponge containing a unique imidazobenzoquinone scaffold.[172] Compound **164a** exhibited cytotoxicity, with potentially a unique mechanism of action.[173] Schmitz reported the isolation of 2-deoxy-2-aminokealiiquinone **164b**, but no bioactivity has been reported for this molecule.[174] A brief synthesis for kealiiquinone **164a** and 2-deoxy-2-aminokealiiquinone **164b** was reported in 2013 by Lovely and co-workers. Advanced intermediates including the full naphthimidazole scaffold are generated *via* FC reaction followed by oxidation. Total synthesis of **164a** and **164b** was started from diiodoimidazole **127**, which was converted into **128** in several steps the latter undergoes sequential FC reaction/dehydration to give compound **129**.[140] Subsequently, compound **129** provided kealiiquinone A **164a** and the 2-amino congener **164b** (Scheme 36).[175]

Natural products belonging to the pyrido[4,3-*b*]carbazole group of alkaloids are well represented in the chemical literature.[176–185] Since the first extraction of ellipticine **166a** and 9-methoxyellipticine **166b** in 1959 by Goodwin and co-workers,[177] several other compounds in this group have been extracted from *Apocynaceae* plants.[178] The antineoplastic activity of ellipticine has been developed largely because of the importance of DNA intercalation and inhibition of topoisomerase II.[181] Nagarajan and co-workers in 2014 achieved an convenient synthesis of ellipticine **166a** and 9-methoxyellipticine **166b** in 7 steps with 23% and 25% overall yields, respectively.[186] This synthetic method uses a key phosphoric acid-catalyzed FC cyclodehydration for the generation of the pyridine unit. Total synthesis began from 1,4-dimethylcarbazoles (**167a** and **167b**). In this approach, phosphoric acid-catalyzed FC cyclodehydration was employed as a key step for the construction of pyrido[4,3-*b*]carbazole alkaloids. This synthesis was started from 1,4-dimethylcarbazoles **167a** and **167b** and afforded the corresponding amides **168a** and **168b** after several steps. Amides **168a** and **168b**, were subjected to the critical FC cyclodehydration with subsequent pyridine ring construction. Compounds **168a** and **168b** in the presence of phosphoric acid provided dihydropyridocarbazolones **169a** and **169b** in 73% and 71% yields, respectively. Finally, compounds **169a** and **169b** were converted into ellipticines **166a** and **166b** after several steps (Scheme 37).[186]

In 2012, Xu and co-workers extracted various tetrahydrofuran-type lignans, gymnothelignans A–O, from *Gymnotheca chinensis* Decne, a broadly applied perennial

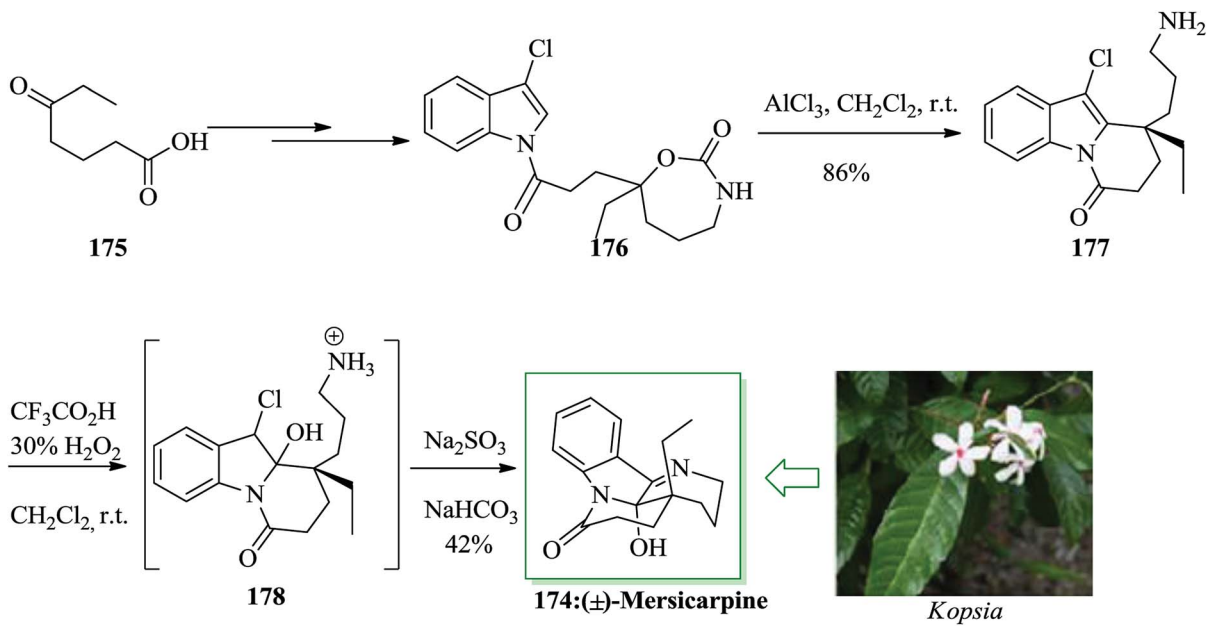
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Scheme 38 Total synthesis of gymnothelignan N **170**.

Chinese herb of *Saururacese*.[187] Among them, gymnothelignan N attracted the interest of the authors owing to its unique 10,11-benzospiro[5.6]dodec-13,15-dien-14-one scaffold across a tetrahydrofuran ring, which is extraordinary in lignans. Total synthesis of gymnothelignan N **170** was achieved in 13 steps from 5-hydroxyvanilin **171** in 6.7% overall yield. In this approach, a *syn* Evans aldol reaction, an intramolecular hydrogenative dehydration reaction, and a phenol oxidative dearomatization/FC reaction were considered as the key steps. Total synthesis was started from 5-hydroxyvanilin **171**, which was converted into compound **172** *via* several steps. Using the key intermediate **172**, the step was performed to generate the critical bioinspired oxidative FC reaction. However, there are many cases of phenol oxidative dearomatization/FC reaction used in natural product synthesis;[188–191] in this substrate, it is considered to be challenging for two aspects. The first one is the desired intramolecular FC reaction, which happens across the tetrahydrofuran ring to generate the seven-membered ring with an all-carbon quaternary center as linkage, while the presumed cation intermediate **173** is constructed *in situ*. The second one is the site selectivity of the FC reaction. The *para* and *ortho* positions of the methoxyl substituent are in competition in this reaction.[190,191] Hence, the usual phenol oxidation hypervalent iodine(III) reagents, for example iodobenzene diacetate (PIDA),

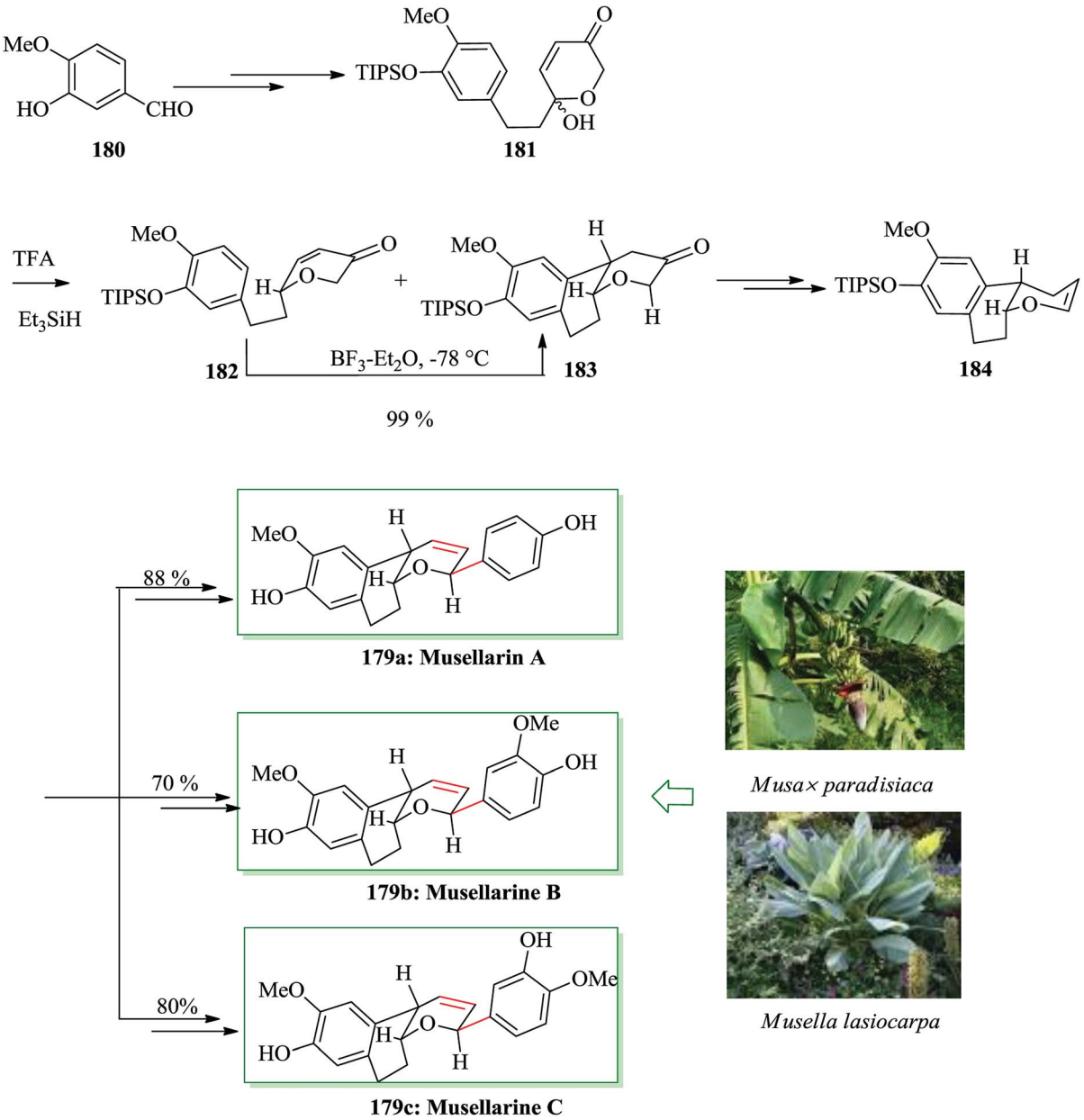


Scheme 39 Total synthesis of mersicarpine **174**.

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were considered and PIDA in hexafluoroisopropyl alcohol (HFIP) resulted in the FC product in 70% yield. The selectivity of the *ortho*/*para* ratio was found to be 2.6/1. The *ortho* FC product, so-called gymnothelignan N **170**, could be extracted using careful flash chromatography employing dichloromethane/methanol as the eluent system. Thus, the total synthesis of gymnothelignan N **170** was achieved upon several steps from 5-hydroxyvanilin **171** in 6.7% overall yield (Scheme 38).[192]

Mersicarpine **174**, a structurally fascinating monoterpene indole alkaloid, was extracted from the *Kopsia* species of plants by Kam and co-workers in 2004.[193] This uncommon tetracyclic natural product contains a typical seven-membered cyclic imine and a δ-lactam around a completely functionalized hemiaminal stereogenic center. A short total synthesis of mersicarpine **174** was accomplished using a cyclic carbamate for the construction of a tertiary carbocation. The main step includes intramolecular FC alkylation with this carbocation for the formation of a quaternary carbon center and a subsequent oxidation and cyclization cascade for the generation of a seven-membered cyclic imine. This approach permitted for a rapid synthesis of mersicarpine from a simple intermediate employing straightforward chemical operations in a one-pot fashion. The total synthesis of mersicarpine **174** was initiated from compound **175**, which afforded compound **176** upon several steps. The key FC alkylation reaction was employed in the total synthesis of mersicarpine. In this route, compound **176** was reacted with $AlCl_3$, a mixture of trifluoroacetic acid and H_2O_2 *via* FC reaction to provide the product **177** in 86% yield. Upon oxidation of **177**



Scheme 40 Total synthesis of musellarins A–C **179a–c**.

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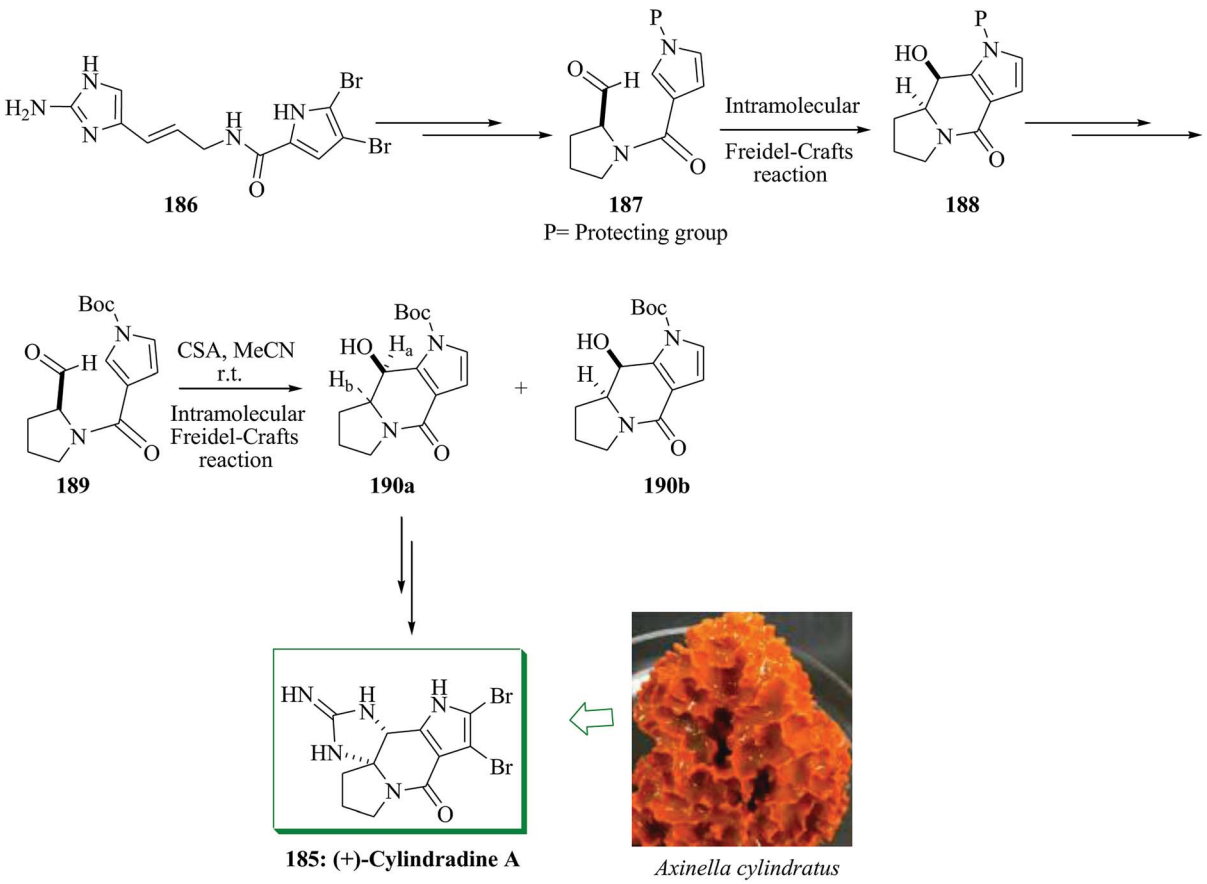
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and acidity optimization with Na_2SO_3/$NaHCO_3$, mersicarpine **174** was provided in 42% yield. As a result, the natural product was obtained in 25% overall yield (Scheme 39).[194]

Naturally occurring diarylheptanoids, a group of secondary plant metabolites,[195,196] exhibit active biological properties, for example anticancer, antioxidant, antibacterial, anti-osteoporosis, antifungal and antihepatotoxicity activity.[195,196] Among them, musellarins A–C represent an uncommon structural group owing the presence of the rare bicyclic tetrahydropyran scaffold. Musellarin A was extracted in 2002 by Kinghorn[197] and co-workers from hybrid plant fruits of *Musa x paradisiaca* in Peru.[197,198] In 2014, Tong and co-workers reported the first total syntheses of musellarins A–C in 15–16 steps.[199] The key synthetic features are an Achmatowicz rearrangement, a Kishi reduction, and FC cyclization to make the tricyclic scaffold and Heck coupling reaction of aryldiazonium salts to introduce the aryl substituent into the dihydropyran in a 2,6-trans method in the last step of the synthesis. Total syntheses of musellarins A–C were started from isovanillin **180**, which was converted into dihydropyranone hemiacetal **181**. Kishi reduction of **181** with a combination of trifluoroacetic acid and triethylsilane afforded a 2 : 1 mixture of dihydropyranone **182** and a surprising FC cyclization adduct **183** in 78% combined yield. In this step the intramolecular FC cyclization reaction of dihydropyranone **182** happened in the presence of $BF_3 \cdot Et_2O$ to give the tricyclic compound **183**. Compound **183**, after several steps, afforded the key intermediate enol ether **184**. Finally, compound **184** was converted into musellarins A–C in 88%, 70% and 80% yields upon several steps (Scheme 40).[199]

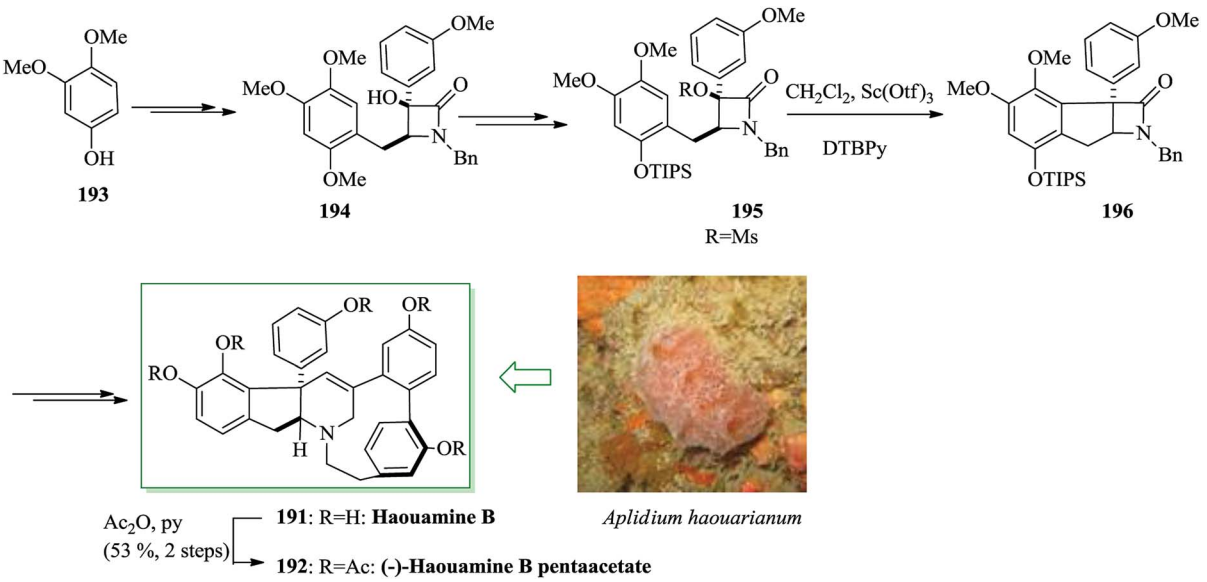
Polycyclic pyrrole-imidazole alkaloids (PIAs) are oroidin-obtained marine naturally occurring compounds[200,201] with various and complex frameworks. Most of these alkaloids exhibit multiple biological properties, including immunosuppressive, antitumor and adrenoceptoragonistic properties.[202,203] Nagasawa and co-workers in 2014 developed a total synthesis of (+)-cylindradine A through intramolecular FC-type cyclization reaction of pyrrole-aldehyde and oxidative cyclization of tricyclic pyrrolopyrrolidine–guanidine with hypervalent iodine to make the cyclic guanidine structure involving the *N*,*N*-aminal scaffold.[204] The total synthesis of cylindradine A was initiated from oroidin **186**, which was converted into **187** in several steps. Compound **187** containing aldehyde and 4-carbamoylpyrrole functional substituents gave compound **188** *via* an intramolecular FC-type reaction. Next, compound **188** was converted into **189** after several steps. The FC adduct **190** was provided in 82% yield as a diastereomeric mixture in a ratio of *ca.* 7 : 1 (**190a** : **190b**) *via* reaction of **189** with camphorsulfonic acid (CSA). Subsequently, (+)-cylindradine A **185** was provided from compound **190a** in 58% yield upon several steps (Scheme 41).[204]

Haouamines were extracted from a tunicate, *Aplidium haouarianum*, on the southern coast of Spain by Zubía and co-workers in 2003.[205] Structurally, haouamines have unique



Scheme 41 Total synthesis of (+)-cylindradine A **185**.

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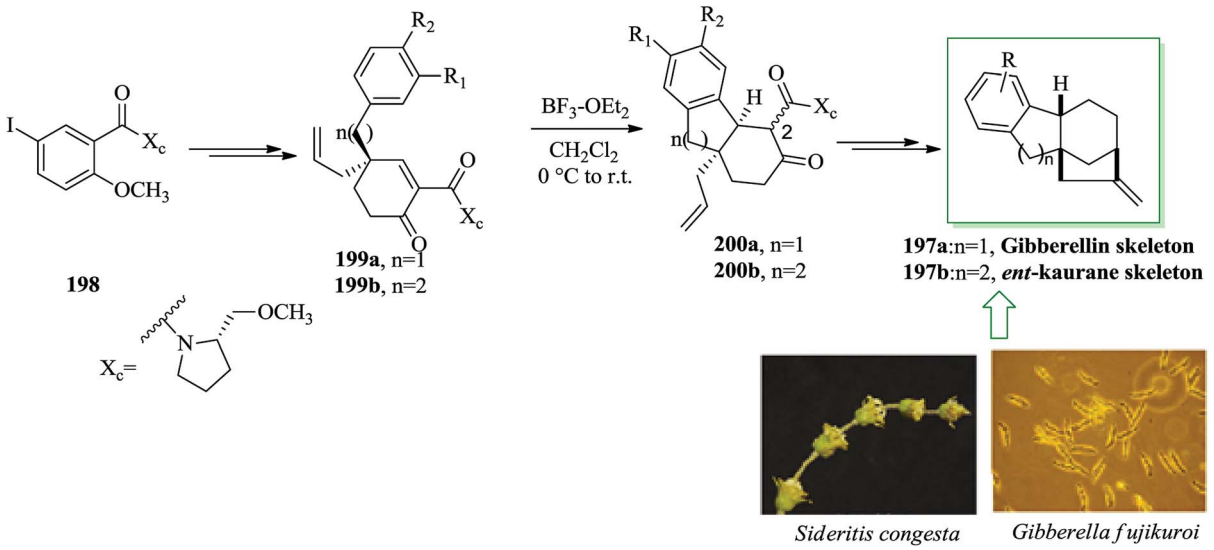


Scheme 42 Total synthesis of (−)-haouamine B **191** and haouamine B pentaacetate **192**.

the scandium(III) triflate-catalyzed intramolecular FC alkylation were applied to make the uncommon indane-fused β-lactam **196**. In this route, an intramolecular McMurry coupling reaction was considered as the key step. Tokuyama and co-workers initiated the synthesis of (−)-haouamine B from 3,4-dimethoxyphenol **193**, which after several steps was transformed into substrate **194**. To avoid the unanticipated cyclization, the benzyl group was changed to the more bulky TIPS substituent with the intention of reducing the nucleophilicity of the oxygen atom and a range of Brønsted/Lewis acids were explored. Upon hydrogenolysis of the benzyl ether, introduction of the TIPS substituent followed by mesylation of the tertiary alcohol gave substrate **195** for the FC alkylation. Compound **195** gave indeno-β-lactam **196**. The reaction was accomplished using 2,6-di-*tert*-butylpyridine (DTBPy). The corresponding compound **196** was provided in 80% yield with the labile TIPS substituent remaining intact. Finally, compound **196** afforded (−)-haouamine B **191** and haouamine B pentaacetate **192** after several steps (Scheme 42).[206]

Gibberellin[207] and *ent*-kaurane derivatives,[208] are naturally occurring diterpene compounds,[209] having a complex tetracyclic molecular framework presenting a bicyclo[3.2.1]octane system.[210,211] Both gibberellins and *ent*-kauranes contain remarkable biological properties. Notably, the gibberellins were found to be plant hormones and growth regulators.[212–214] Gibberellins were initially extracted from the fungus *Gibberella fujikuroi* and *ent*-kaurane diterpenoids were also extracted from the whole plant *Sideritis congesta* P. H. Davis & Hub.-Mor.[215]

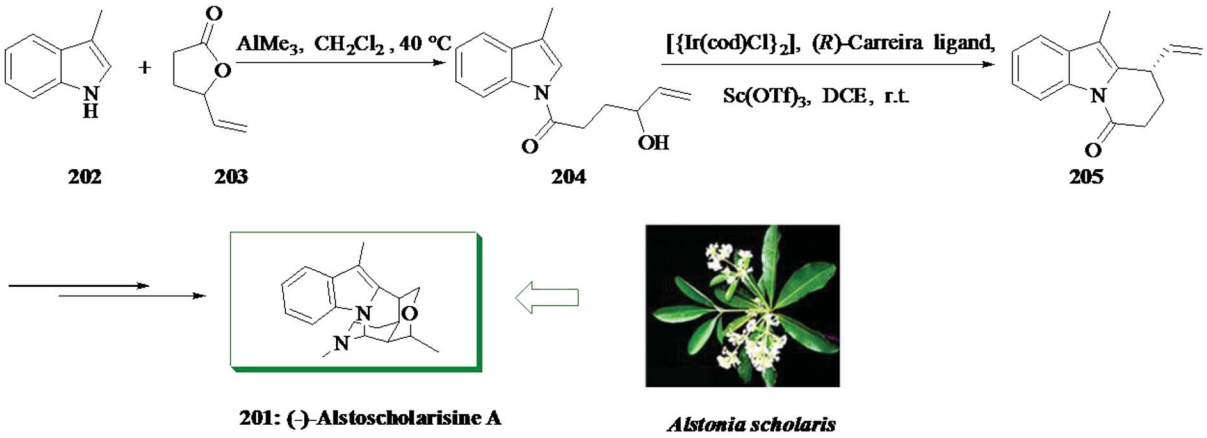
Malachowski and co-workers in 2015 developed an approach for the formation of tricarbocyclic scaffold *via* an extension of



Scheme 43 Total synthesis of gibberellins **197a** or *ent*-kauranes **197b**.

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Scheme 44 Total synthesis of (−)-alstoscholarisine A **201**.

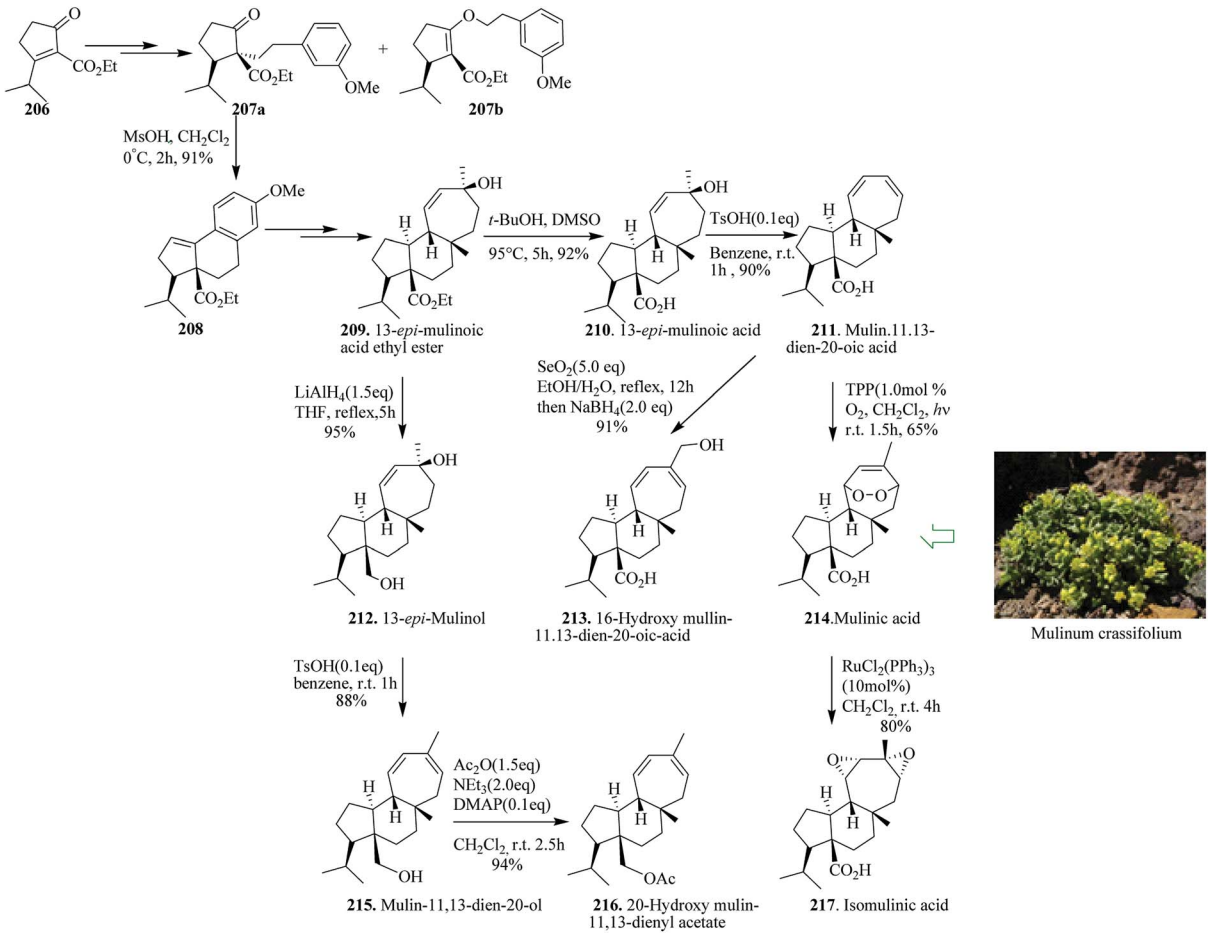
the asymmetric Birch–Cope sequence along with intramolecular FC alkylation reaction.[216] An asymmetric method for the synthesis of the tetracarbocyclic framework of the gibberellins **197a** or the *ent*-kauranes **197b** was demonstrated by the same group.[216] There is a tetracarbocyclic ring system in the unit of both the gibberellins and the *ent*-kauranes **197b**. The asymmetric formation of tetracyclic diterpene frameworks began from the 5-iodo-salicylate derivative **198**. Upon several steps, compounds **199a** and **199b** were produced. Conversion of these products, **199a** and **199b**, into the tetracarbocyclic scaffold of the gibberellins **197a** or *ent*-kauranes **197b** was achieved *via* FC alkylation in the presence of $BF_3 \cdot Et_2O$, which was clearly one of the most charming conjugate additions of an aromatic nucleophile to a cyclohexenone electrophile.[217,218] The cyclization happened to generate the *cis* isomers **200a** and **200b**, but most of the products were isolated as C-2 epimers, usually as a 1 : 1 mixture. Finally, the tetracarbocyclic framework of the gibberellins **197a** or *ent*-kauranes **197b** was obtained from **200a** and **200b** upon several steps (Scheme 43).[216]

The alstoscholarisines[219] are some fascinating monoterpenoid indole alkaloids having a complex pentacyclic structure extracted from *Alstonia scholaris* by Luo and co-workers. In 2016, Liang and co-workers reported an asymmetric total synthesis of (−)-alstoscholarisine A **201** in 10 steps.[220] This group demonstrated a short and highly asymmetric total synthesis of (−)-alstoscholarisine A **201**, an extracted monoterpenoid indole alkaloid having important bioactivity in promoting adult neuronal stem cells proliferation. A highly asymmetric (99% ee), intramolecular iridium-mediated FC alkylation reaction between indole **204** and a secondary allylic alcohol was used to create the first stereogenic center upon which the other three contiguous chiral centers were easily set through an extremely enantioselective tandem 1,4-addition and aldol reaction. Firstly, an acylation reaction between 3-methylindole **202** and 4-vinylbutyrolactone **203** was achieved using trimethylaluminium,[221] providing secondary allylic alcohol **204** in 75% yield. Catalytic enantioselective FC alkylation reaction of **204** with the combination of [{Ir(cod)Cl}$_2$], (*R*)-carreira ligand[222–224] and Lewis acid scandium(III) triflate effectively afforded tricycle **205** in 75% yield with 99% ee. The latter was converted into (−)-alstoscholarisine A **201** in several steps (Scheme 44).[220]

Terpenoids are structurally intriguing molecules with fascinating biological properties.[225] For instance, mulinane diterpenoids, initially extracted in 1990 from the Chilean shrub *Mulinum crassifolium*, have been applied as traditional folk medicine for the treatment of illnesses, for example, diabetes and bronchial and intestinal disorders.[226–232] Enantioselective total synthesis of mulinane diterpenoids has been accomplished. In this strategy, an intramolecular FC reaction and Birch reduction were considered as the key steps. Based on this pathway, Xie and co-workers in 2017 reported the divergent asymmetric total synthesis of seven mulinane diterpenoids, namely, 13-*epi*-mulinolic acid (**210**, 12 steps, 18% overall yield), mulin-11,13-dien-20-oic acid (**211**, 13 steps, 17% yield), mulinic acid (**214**, 14 steps, 11% yield), isomulinic acid (**217**, 15 steps, 8.6% yield), 16-hydroxy mulin-11,13-dien-20-oic acid (**213**, 14 steps, 15% yield), mulin-11,13-dien-20-ol (**215**, 13 steps, 15% yield), and 20-hydroxy mulin-11,13-dienyl acetate (**216**, 14 steps, 14% yield), along with two analogues, namely, 13-*epi*-mulinol (**212**, 12 steps, 17% yield) and 13-*epi*-mulinolic acid ethyl ester (**209**, 11 steps, 20% yield), from easily accessible cyclopentenone **206**.[236]

Total synthesis began from 3-isopropyl-2-(ethoxycarbonyl) cyclopentenone **206**. Compound **206** gave C-alkylation product **207a** in 65% yield, together with a 20% yield of the unanticipated O-alkylation product **207b** in several steps. Reaction of **207a** with methanesulfonic acid led to an intramolecular FC reaction that afforded tricyclic compound **208** in 91% yields. Subsequently, compound **208** gave 13-*epi*-mulinolic acid ethyl ester **209** upon several steps. Using compound **209**, the same group accomplished the enantioselective total synthesis of mulinane diterpenoids through late-stage functional modification or functionalization. Therefore, the synthesis of seven mulinane diterpenoids from the "biogenic precursor" **209** was initially achieved in several steps. The latter was then converted to various natural products, 13-*epi*-mulinolic acid **210**,[233] mulin-11,13-dien-20-oic acid **211**,[234] mulinic acid **214**[226] isomulinic acid **217**,[226] 16-hydroxymulin-11,13-dien-20-oic acid **213**,[235] 13-

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Scheme 45 Total synthesis of 13-*epi*-mulinolic acid ethyl ester **209**, 13-*epi*-mulinolic acid **210**, mulin-11,13-dien-20-oic acid **211**, 13-*epi*-mulinol **212**, 16-hydroxymulin-11,13-dien-20-oic acid **213**, mulinic acid **214** mulin-11,13-dien-20-ol **215**, 20-hydroxy mulin-11,13-dienyl acetate **216** and isomulinic acid **217**.

epi-mulinol **212**, mulin-11,13-dien-20-ol **215**[229] and 20-hydroxy mulin-11,13-dienyl acetate **216** (Scheme 45).[236]

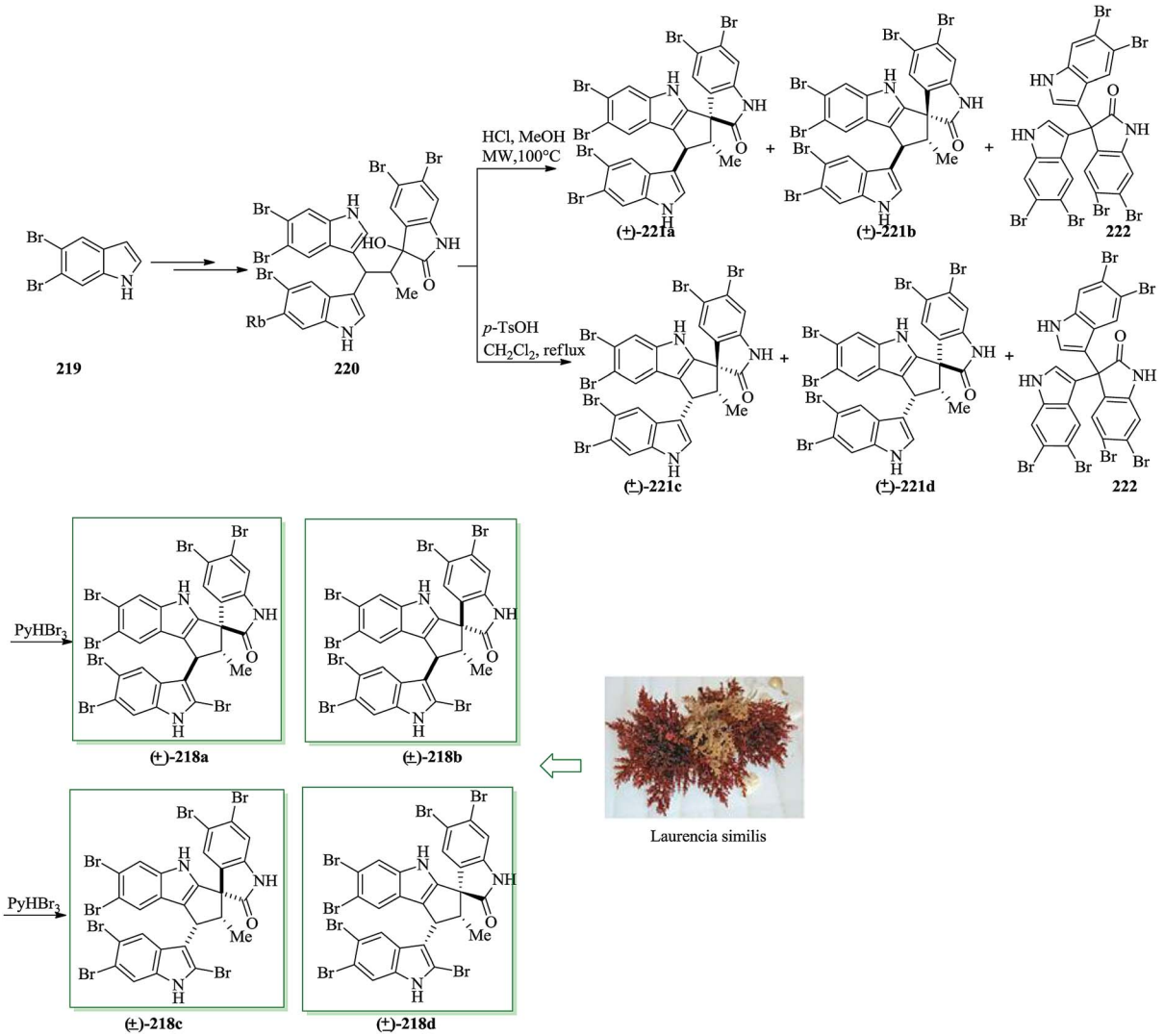
Similisines A [(+)-**218a**] and B [(−)-**218a**], extracted from *Laurencia similis* in 2013, are the first example of polybrominated spiro-trisindole alkaloids fused to a five-member ring.[237] Similisines A and B are trisindole alkaloids that feature a unique polybrominated [5,5] spirooxindole scaffold fused to a five-membered ring. The first total synthesis of similisines A and B, a pair of unprecedented polybrominated spiro-trisindole enantiomers and all their stereoisomers was achieved in 6 steps from 5,6-dibromoindole **219**. In this method, an intramolecular FC cyclization was considered as the key step. Total synthesis of similisines A, B and their stereoisomers started with the construction of trisindole **220**, which was obtained from 5,6-dibromoindole **219** upon several steps.[238] The five-membered spirocyclic framework of **221** was generated from trisindole **220** *via* intramolecular FC cyclization. Treatment of **220** with HCl in methanol under microwave irradiation (MWI) provided two racemic isomers (±)-**221a** (8% yield) and (±)-**221b** (8% yield), along with the unexpected trisindole **222** in 10% yield. Although the other two corresponding racemic isomers (±)-**221c** and (±)-**221d** were detected only in trace amounts, when trisindole **220** was reacted with *p*-TsOH in DCE under reflux, racemic isomers (±)-**221c** and (±)-**221d** were provided in 7% and 16% yields, respectively, along with trace amounts of racemic (±)-**221a** and (±)-**221b**. In this case, the unanticipated trisindole **222** was also provided in 10% yield. Therefore, both the racemic stereoisomers (±)-**221a**–(±)-**221d** could be obtained *via* two above-mentioned different conditions. Using the key (±)-**221a**–(±)-**221d**, the synthesis of similisines A, B and their stereoisomers was accomplished. Bromination of (±)-**221a**–(±)-**221d** with pyridinium tribromide[239,240] afforded the corresponding racemic compounds of (±)-**218a** (85%), (±)-**218b** (81%), (±)-**218c** (85%), and (±)-**218d** (83%), respectively. On the other hand, (±)-**218a** was identified to be a racemic mixture of natural similisines A and B (Scheme 46).[237]

2.2. Intermolecular alkylations

Brasiliquinones A–C, unique cytotoxic benz(*a*)anthraquinones usually found as angucyclines, were initially extracted from pathogenic species of *Nocardia*. Most of the angucycline antibiotics contain a Me substituent at C-3 while brasiliquinones A–C contain an Et substituent at C-3 providing a unique class of angucyclines. Brasiliquinones B and C are more effective than brasiliquinone A against L I210 tumor cells.[241] Brasiliquinone B

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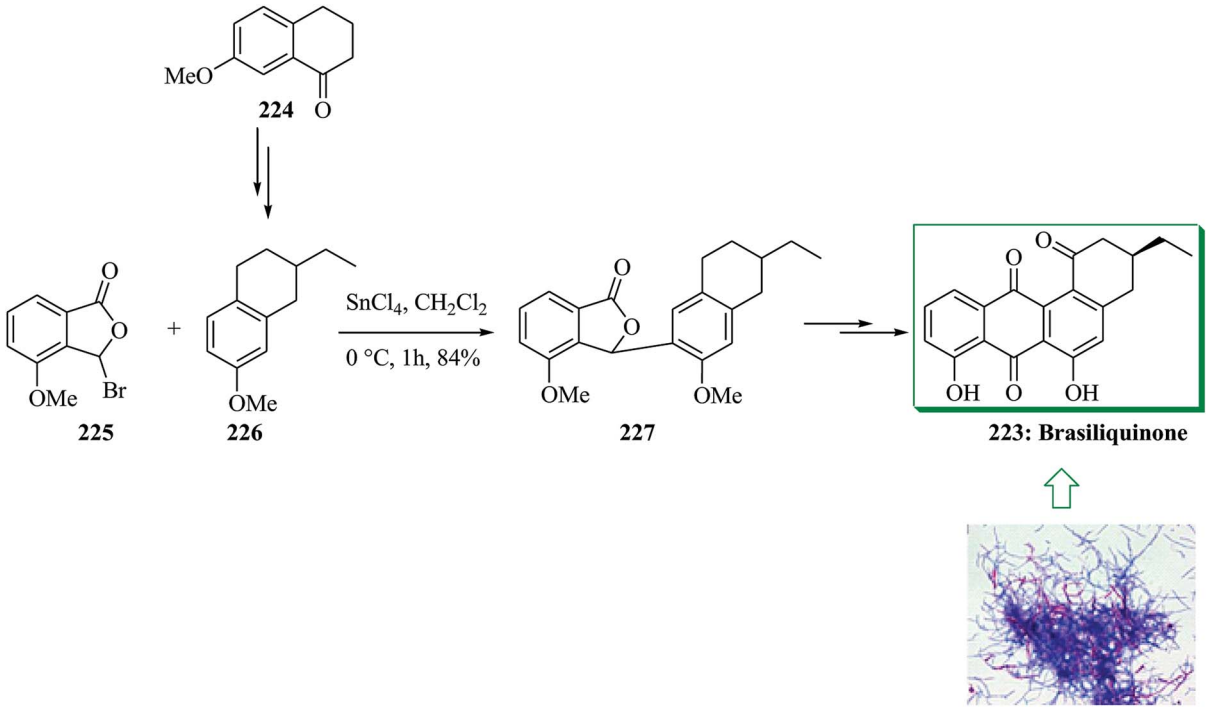
Scheme 46 Total synthesis of racemic compounds of (±)-**218a**, (±)-**218b**, (±)-**218c**, and (±)-**218d**.

223 has been obtained from 7-methoxy-L-tetralone in several steps making use of an FC alkylation reaction as a main stage. Initially, 7-methoxy-L-tetralone **224** gave the relevant tetralin derivative **226** after several steps. FC alkylation reaction of **226** with 3-bromo-4-methoxyphthalide **225** using $SnCl_4$ gave the lactone **227** regiospecifically. Finally, compound **227** provided (+)-brasiliquinone B **223** upon several steps (Scheme 47).[242] Deshpande and co-workers in 2002 also used this method for the synthesis of (±)-brasiliquinone B **223**.[243]

Methyl 3-(2,4,5-trimethoxyphenyl)propionate **228** has been extracted from the root bark of *Cordia alliodora*, demonstrating excellent larvicidal and antifungal properties in biological tests.[244] Tamariz *et al.* in 2004 developed a one-step synthesis of the antifungal and larvicidal natural product methyl 3-(2,4,5-trimethoxyphenyl)propionate **228** by the reaction between 1,2,4-trimethoxybenzene with **230** under MWI.[245] Even though methyl acrylate **230** failed to afford the desired product **228** under these conditions, the use of *sym*-tetrach loroethane[246] as the solvent at 80 °C for 1 week afforded **228** in 37% yield. The reaction time was shortened to 8 h and the yield improved using MWI (200 W) with the same mixture in a Teflon screw-capped glass tube at 80 °C, affording **228** in 66% yield. The construction of **228**, at the present time, is the shortest synthesis of this biologically potent natural product, since the previously reported synthesis, beginning from β-asarone or asaraldehyde, provided **228** in three steps (Scheme 48).[247]

Podophyllotoxin **231** and its derivatives are significant members of the lignan group of naturally occurring compounds.[248] The biological properties of podophyllotoxin have generated strong attention in the development of synthetic pathways to this natural product.[249,250] Bach and co-workers in 2008 reported a six-step total synthesis of enantiomerically pure (−)-podophyllotoxin starting from the Taniguchi lactone **203** in 35% overall yield, using iron(III)-mediated FC alkylation as a key step.[251] The synthesis was started from the Taniguchi lactone **203**, which is accessible in enantiomerically pure form from 2-

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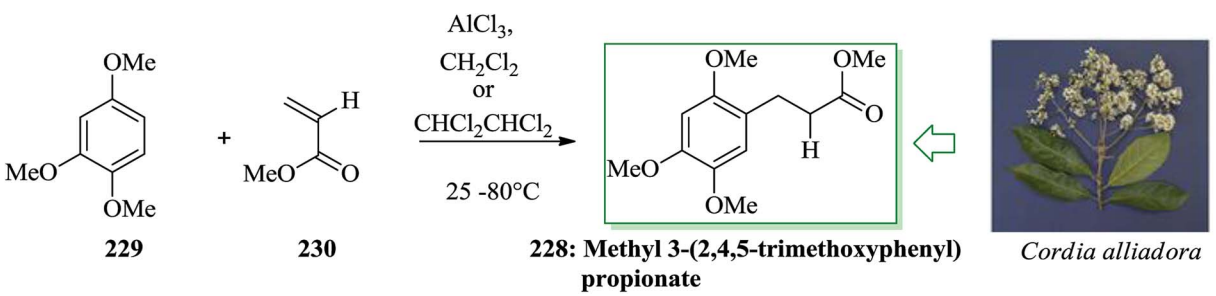


Scheme 47 Total synthesis of brasiliquinone B **223**.

butyne-1,4-diol in two steps with a subsequent conventional resolution[252] or in six steps *via* an asymmetric iridium-mediated allylation.[253] An aldol reaction with aldehyde **232** gave **233** with high stereoselectivity with respect to the stereogenic center at the α position of the lactone. Compound **233** was reacted with **234** (X = OH) under the optimized reaction conditions ($FeCl_3$ in dichloromethane) to afford the FC alkylation reaction product **235** in 99% yield. Finally, alcohol **233** afforded (−)-podophyllotoxin **231** upon several steps. This synthesis demonstrated that a stereogenic center in the β position to an ester or lactone scaffold can be generated diastereoselectively *via* a Lewis acid-mediated S_{N^1} reaction if a stereogenic center is already present in the α position (Scheme 49).[251]

Haplophytine **236** is the major indole alkaloid known in the dried leaves of the Mexican plant *Haplophyton cimicidum* and was first extracted by Snyder *et al.* in 1952.[254–256] The right-half segment is a hexacyclic aspidosperma alkaloid group, so-called aspidophytine, that is provided by the acidic degradation of (+)-haplophytine.[257] Fukuyama and co-workers in 2009 reported the initial total synthesis of (+)-haplophytine **236** demonstrating the simple assembly of tricyclic ketone **238** *via* the intramolecular Mannich reaction. FC alkylation reaction and Fischer indole synthesis were considered as the key steps. For the synthesis of (+)-haplophytine **236**, initially, tricyclic ketone **238** was synthesized from **237** after several steps. Using the key tricyclic ketone **237**, this group attempted the synthesis of the left-hand segment. 7-Benzyloxyindole **239** was converted into iodoindolenine **240** upon several steps. Next, the FC alkylation reaction progressed easily and provided the corresponding coupling product **242** as the major isomer in nearly a 2.4 : 1–2 : 1 diastereoselectivity. In the following, compound **242** afforded **243** after several steps. Finally, hydrazine **243** and ketone **239** provided (+)-haplophytine **236** upon several more steps (Scheme 50).[258]

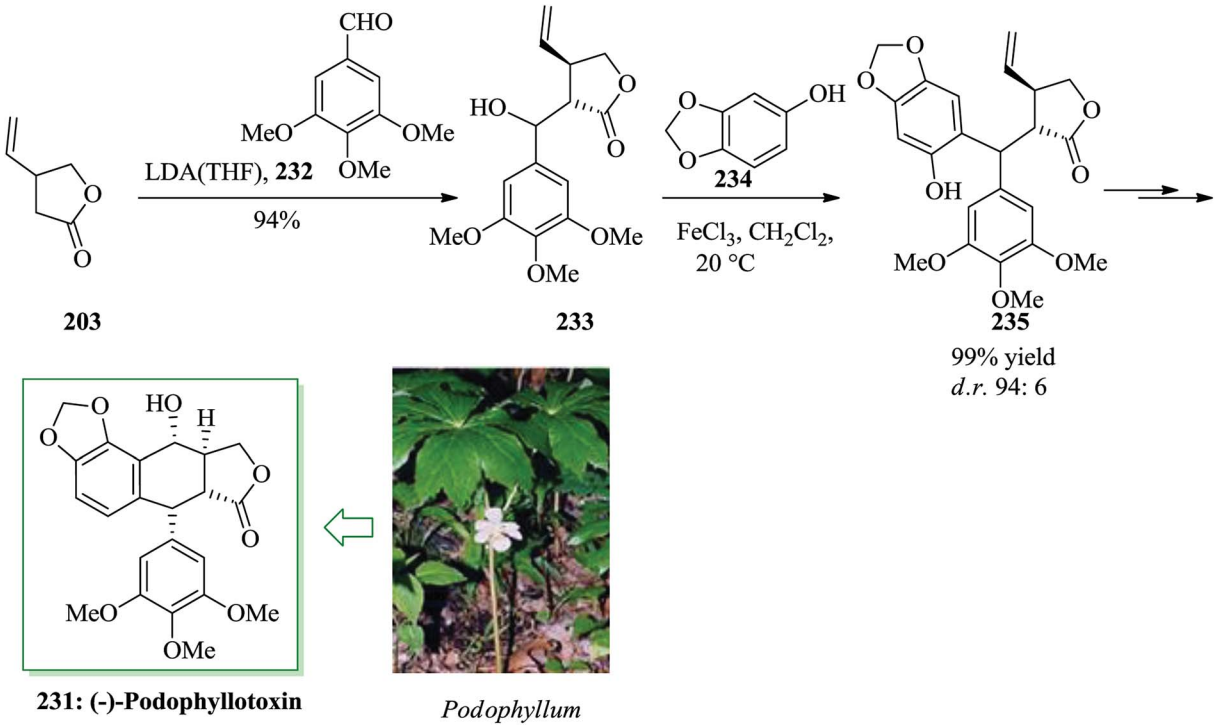
Polyphenolic natural products represent a large and growing group of structurally varied compounds exhibiting an extensive series of biological properties.[259,260] In 2006, Tan and co-workers revealed the structure and cytotoxic activities against a panel of



Scheme 48 Total synthesis of methyl 3-(2,4,5-trimethoxyphenyl)propionate **228**.

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Scheme 49 Total synthesis of (−)-podophyllotoxin **231**.

selected cancer cell lines of hopeanol **245**, a polyphenol secondary metabolite extracted from the bark of *Hopea exalata*.[261] A subsequent investigation of *H. hainanensis* led to the isolation of the structurally related hopeahainol A **244**. The total synthesis and biological evaluation of the resveratrol-obtained naturally occurring compounds products hopeanol **244** and hopeahainol A **245** in their racemic and antipodal forms were carried out. In this method, an intramolecular FC reaction and a Grob-type fragmentation were considered as the key steps. It was examined for building the quaternary center of hopeahainol A **244** and hopeanol **245** with appropriate appendages. In the first incursion, the synthesis of the simple triaryl methyl ester **250** *via* an intermolecular FC-type reaction containing tertiary alcohol **247** as the main substrate and phenol **249** as the external nucleophile was attempted. Therefore, dimethyl oxalate **246** provided the tertiary alcohol methyl ester **247** in 66% overall yield. Satisfyingly, treatment of a solution of tertiary alcohol **247** and phenol **249** in dichloromethane in the presence of excess *p*-TsOH·H_2O resulted in the construction of the desired product **250** in high yield (97%), probably *via* the intermediacy of carbocation **248** (Scheme 51a). Then, the feasibility of synthesizing the more relevant and advanced model system **257** was attempted. In this case, the corresponding tertiary alcohol methyl ester substrate **253** was synthesized from methyl glyoxalate derivative **251** by addition of Grignard reagent **252** (81% yield). The latter underwent a smooth FC-type reaction with resorcinol **255** providing the desired tetracyclic model system **257** (90% yield), probably *via* transient intermediate carbocation **254** and diphenolic methyl ester **256**. The latter apparently undergoes spontaneous lactonization under the optimized reaction conditions (Scheme 51b).[141]

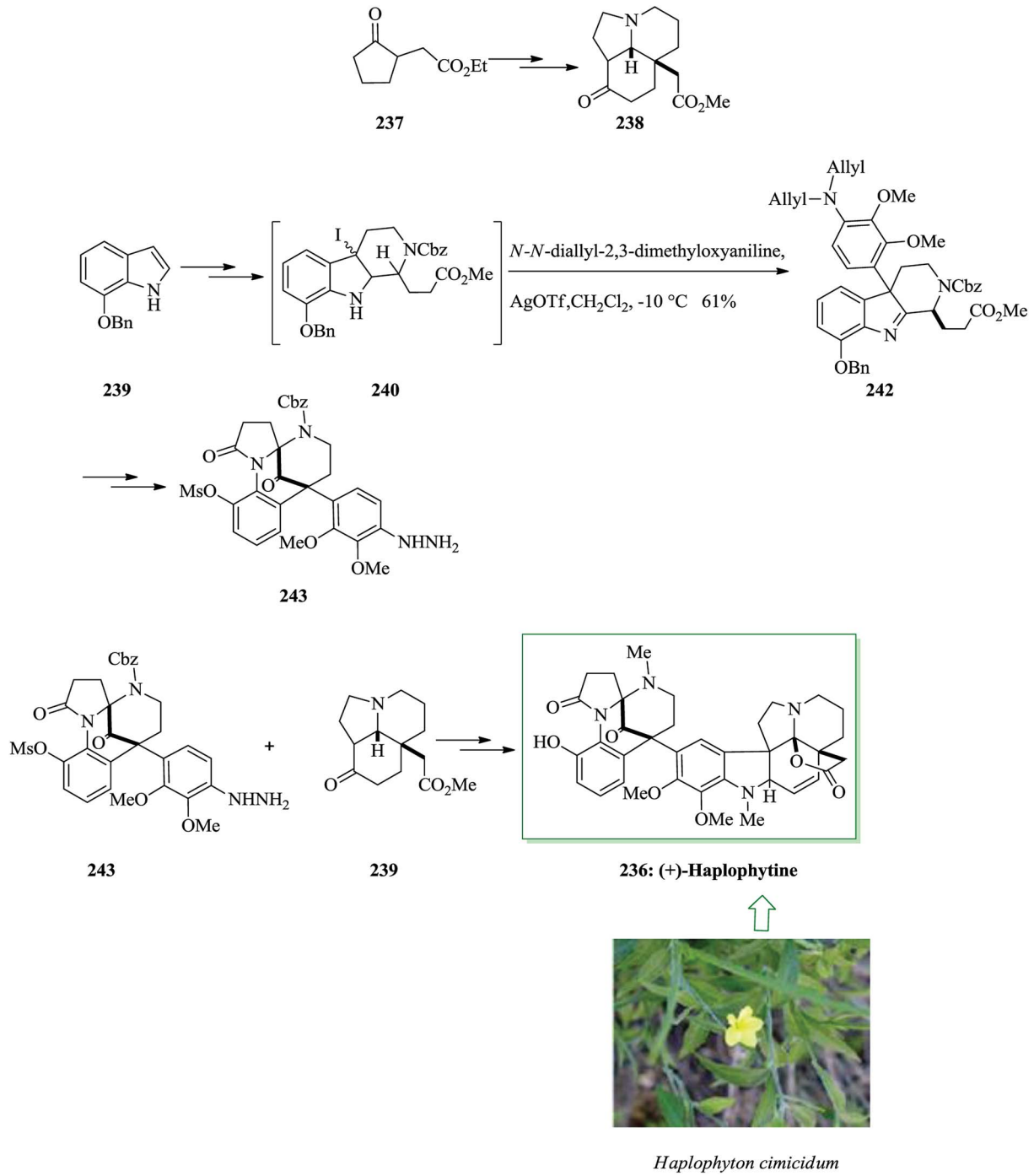
The successful formation of model system **257** (comprising four of the six ring systems of hopeahainol A) provided motivation for the next logical step, which was to attempt to use an established approach to assemble the entire carbon framework of hopeahainol A **244**. Using protected nucleophilic partner **258** in the FC reaction with tertiary alcohol methyl ester **253** gave regioisomeric product **260** in 80% yield (Scheme 52).[141]

Next, a simple model study directed toward the formation of model system **263** was designed. Thus, methyl glyoxalate **251** provided tertiary alcohol **261** upon several steps. Treatment of the latter with $BF_3 \cdot Et_2O$ in dichloromethane led to the construction of the corresponding FC reaction product **263** in 86% yield. It is suggested that compound **263** probably formed *via* generation of intermediate **262** (Scheme 53).[141]

Then, the next phase of the campaign was provided by the initial formation of the diphenolic γ-lactone **268** and/or **269** *via* hydroxyester **265**. The aldehyde **264** provided diphenolic hydroxyester **265** upon several steps. Treatment of **265** (~1 : 1 *dr*) with $BF_3 \cdot Et_2O$ in dichloromethane at room temperature provided diastereomeric products **268** and **269** (86% yield, ~1 : 1.3 *dr*) *via* FC reaction. Compounds **268** and **269** were probably formed *via* diastereomeric transition states **266** and **267**, respectively (Scheme 54).[141]

Compounds **268** and **269** provided epoxide **270** in several steps. Intramolecular FC reaction of epoxide **270** (~1 : 1 *dr*) resulted in the formation of two diastereomeric cyclized products **274** (major) and **273** (minor) in ~2 : 1 ratio in the presence of tin(IV) chloride in dichloromethane in 62% yield. Finally, compounds **272** and **273** provided (−)-hopeahainol A **244** in

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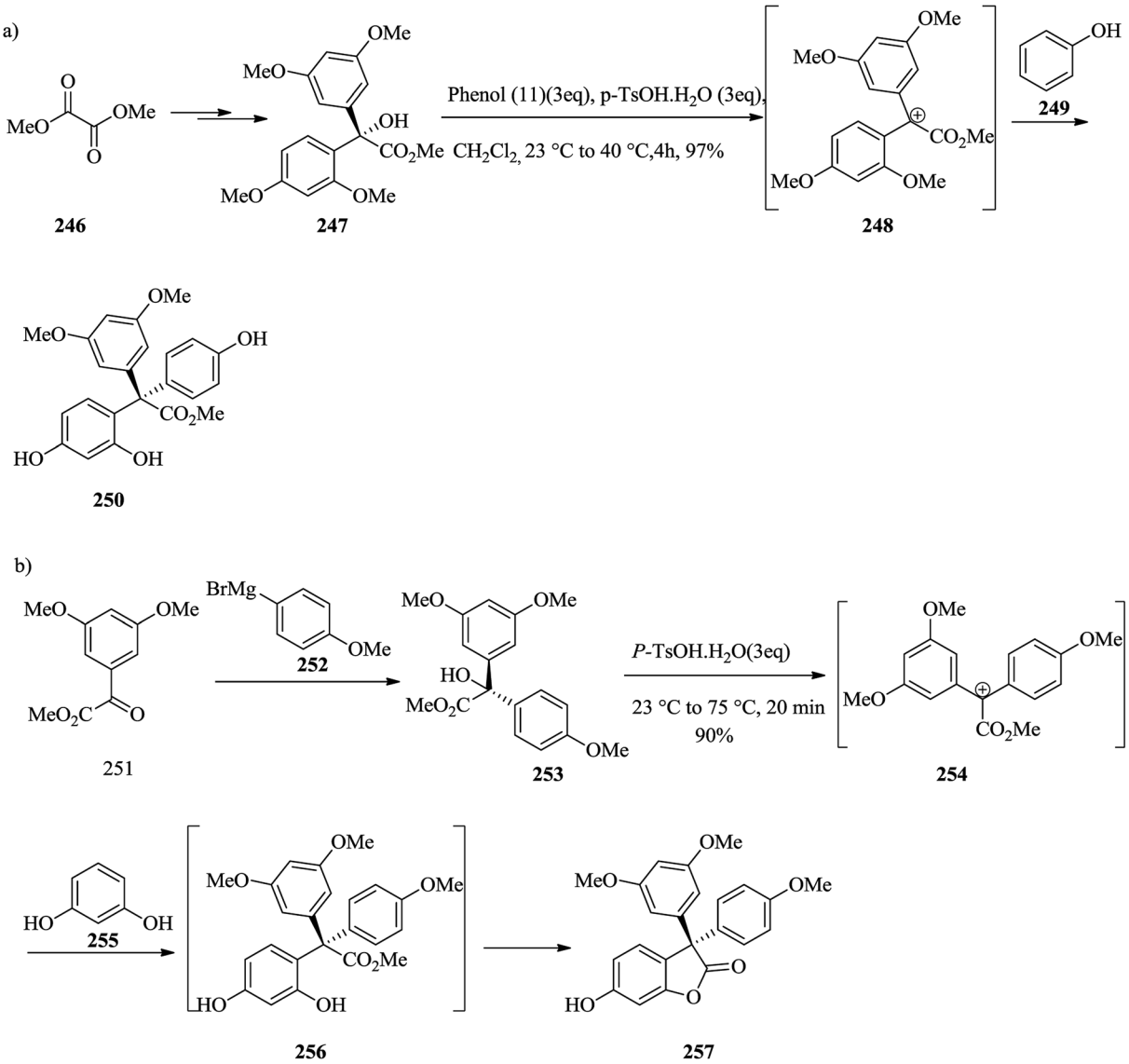
Scheme 50 Total synthesis of (+)-haplophytine **236**.

84% overall yield after several steps. Subsequently, (−)-hopeahainol A **244** was transformed into (−)-hopeanol (−)-**245** *via* several steps (Scheme 55).[141]

Dictyodendrins were initially extracted in 2003 by Fusetani and Matsunaga from the marine sponge *Dictyodendrilla verongiformis* collected from Nagashima Island in Southern Japan.[262] These compounds contain the highly functionalized pyrrolo[2,3-*c*]carbazole moiety. Tokuyama and co-workers in 2010 reported the first total synthesis of dictyodendrin A **275** and B **276** using an unprecedented one-pot benzyne-catalyzed indoline construction/cross-coupling sequence, employing transmetalation to Cu species.[263] In this route, for the synthesis of **275**, initially, *para*-nitrophenol **277** afforded **278** after several steps. The latter initially underwent FC alkylation reaction with **279** in the presence of AgOTf. Then upon pinacolborylation at the bromo group of **278**, the azidephenyl group was introduced *via* Suzuki–Miyaura coupling to afford **281**. Finally, azide **281** was converted into dictyodendrin A **275** in 8.2% overall yield over 21 steps, starting from *para*-nitrophenol **277** (Scheme 56).[263]

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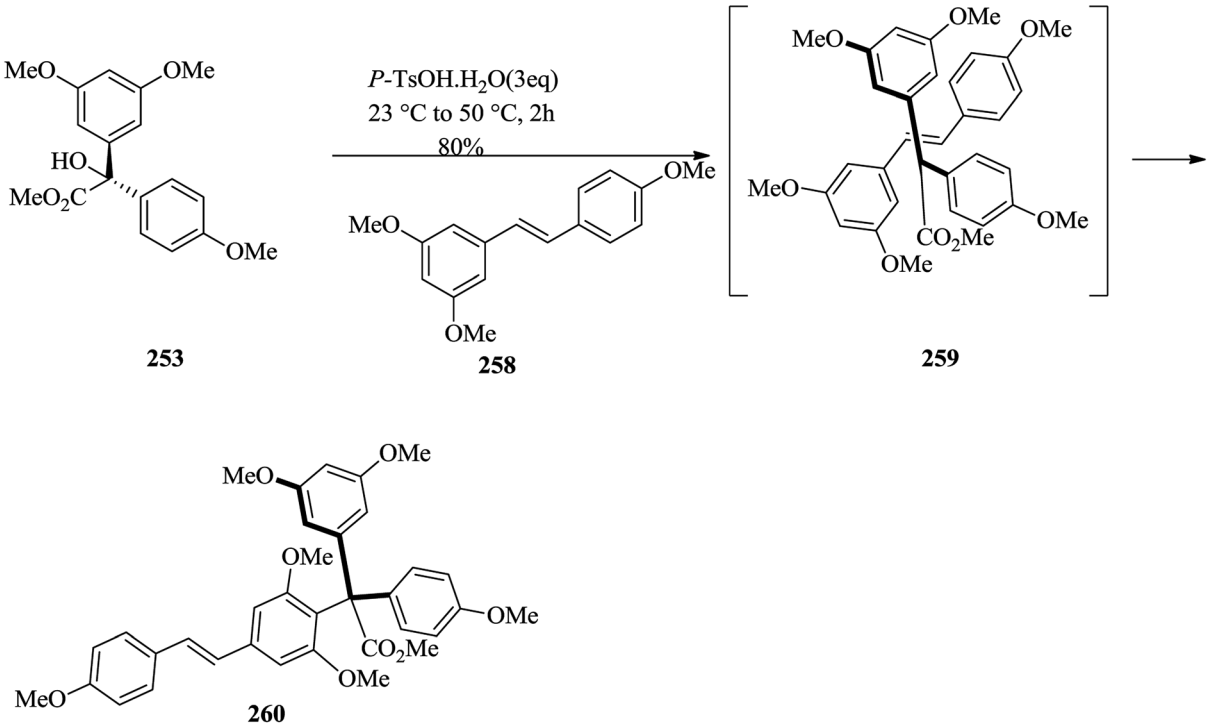
Scheme 51 Total synthesis of triaryl methyl ester **250** and tetracyclic model system **257**.

Subsequently, total synthesis of dictyodendrin B **276** was successfully achieved in 12% overall yield starting from *para*-nitrophenol **277**. By using bromoindole **278**, regioselective FC acylation occurred in the presence of zinc chloride[264] to afford **283**, which was converted into dictyodendrin B **276** in seven steps (Scheme 57).[263]

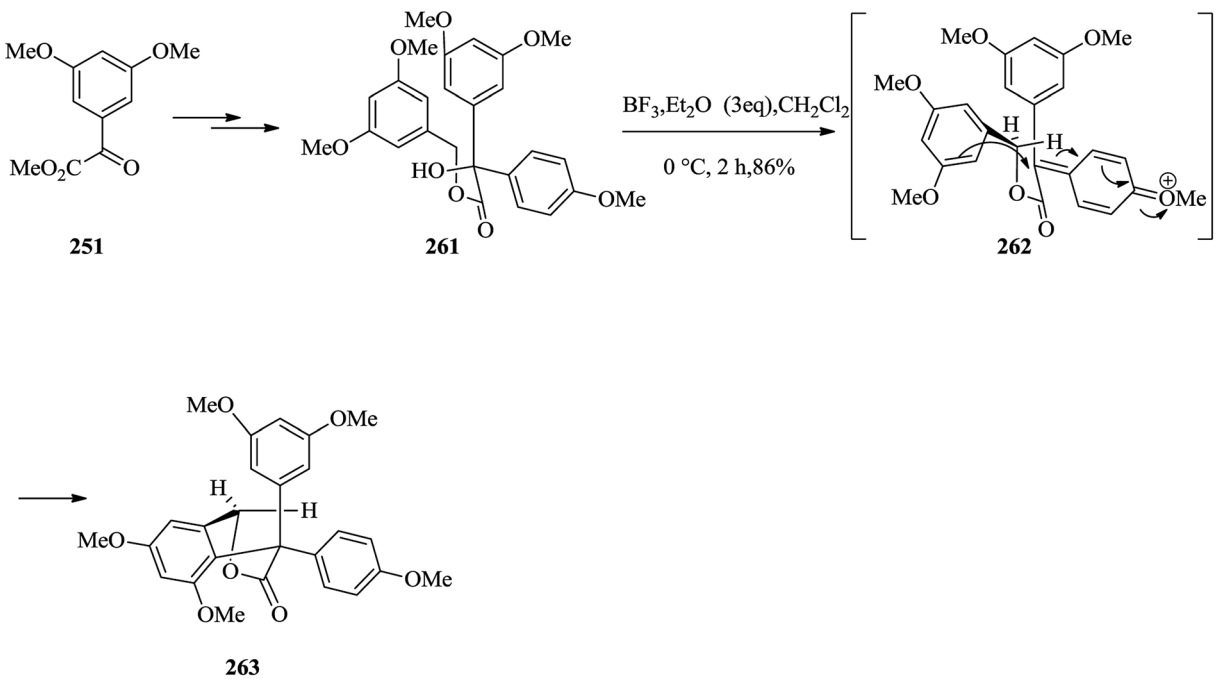
(−)-Ardeemin **284a** and (−)-acetylardeemin **284b** were extracted in 1993 from the fungus *Aspergillus fischerii*.[265] (−)-Acetylardeemin **284b** is one of the most active preventers of multidrug resistance.[266,267] Total synthesis of multidrug-resistant inhibitors (−)-ardeemin **284a**, acetylardeemin **284b**, and (−)-formylardeemin **285** was accomplished, starting from bromopyrroloinoline **286** in 10 steps by Song and co-workers in 2012. The key step includes direct alkylation of **286** with prenyl tributylstannane **287** to provide **288** through a silver-promoted enantioselective FC reaction. Significant installation of the isoprenyl substituent provided a good overall yield for this FC reaction. Firstly, direct isoprenylation of bromopyrroloindoline **286** with **287** gave **288** through the FC reaction in the presence of silver perchlorate, **287**, and caesium carbonate. Based on optimal reaction conditions, the main intermediate **288** was generated from **286** in 91% yield in a single step, leading to the total synthesis of **284** and **285**. Next, compound **288** gave (−)-formylardeemin **285** upon several steps. Deformylation of **285** with aqueous sodium hydroxide in methanol afforded (−)-ardeemin **284a** in 85% yield. (−)-Acetylardeemin **284b** was obtained from **284a** employing an already reported method (Scheme 58).[266]

Epipolythiodiketopiperazine alkaloids, a structurally varied group of secondary fungal metabolites, exhibit a broad range of biological properties, including antiviral, antifungal, antibiotic, and cytotoxic activities.[268,269] It is noteworthy that these mycotoxins were characterized by identification of a bridged polysulfide linkage across the cyclic dipeptide substructure.[270–276]

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Scheme 52 The formation of compound **260**.

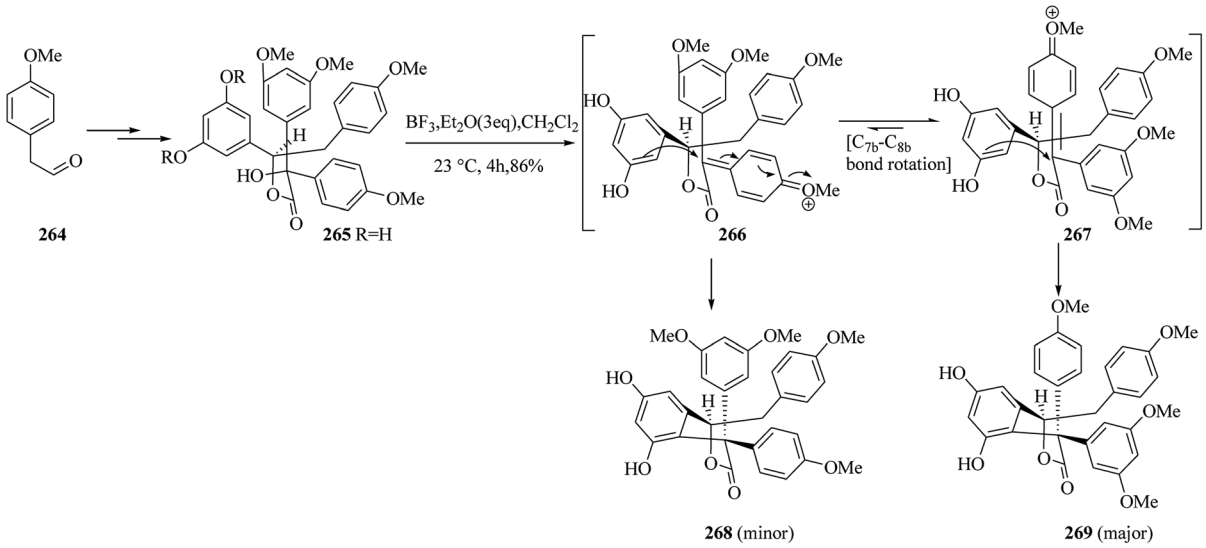


Scheme 53 The formation of product **263**.

(+)-Gliocladin B **289**,[277,278] a new epidithiodiketopiperazine, and (+)-gliocladin C **290**, an atypical non-thiolated triketopiperazine, were extracted by Usami and co-workers in 2004 from a strain of *Gliocladium roseum* OUPS-N132. (+)-Gliocladins show remarkable cytotoxicity against the murine P388 lymphocytic leukemia cellline.[277] A short and asymmetric total synthesis of (+)-gliocladin B and C was developed in 2012 by Movassaghi and co-workers. The unified synthesis of (+)-gliocladins B **289** and C **290** was started from the bromocyclization of diketopiperazine (−)-**291**[276,279] in just three steps starting from *N*-Boc-L-tryptophan and sarcosine methyl ester. Compound **291** reacted with bromine to give *endo*-tetracyclic bromide (+)-**292** in 75% yield

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Scheme 54 The formation of products **268** and **269**.

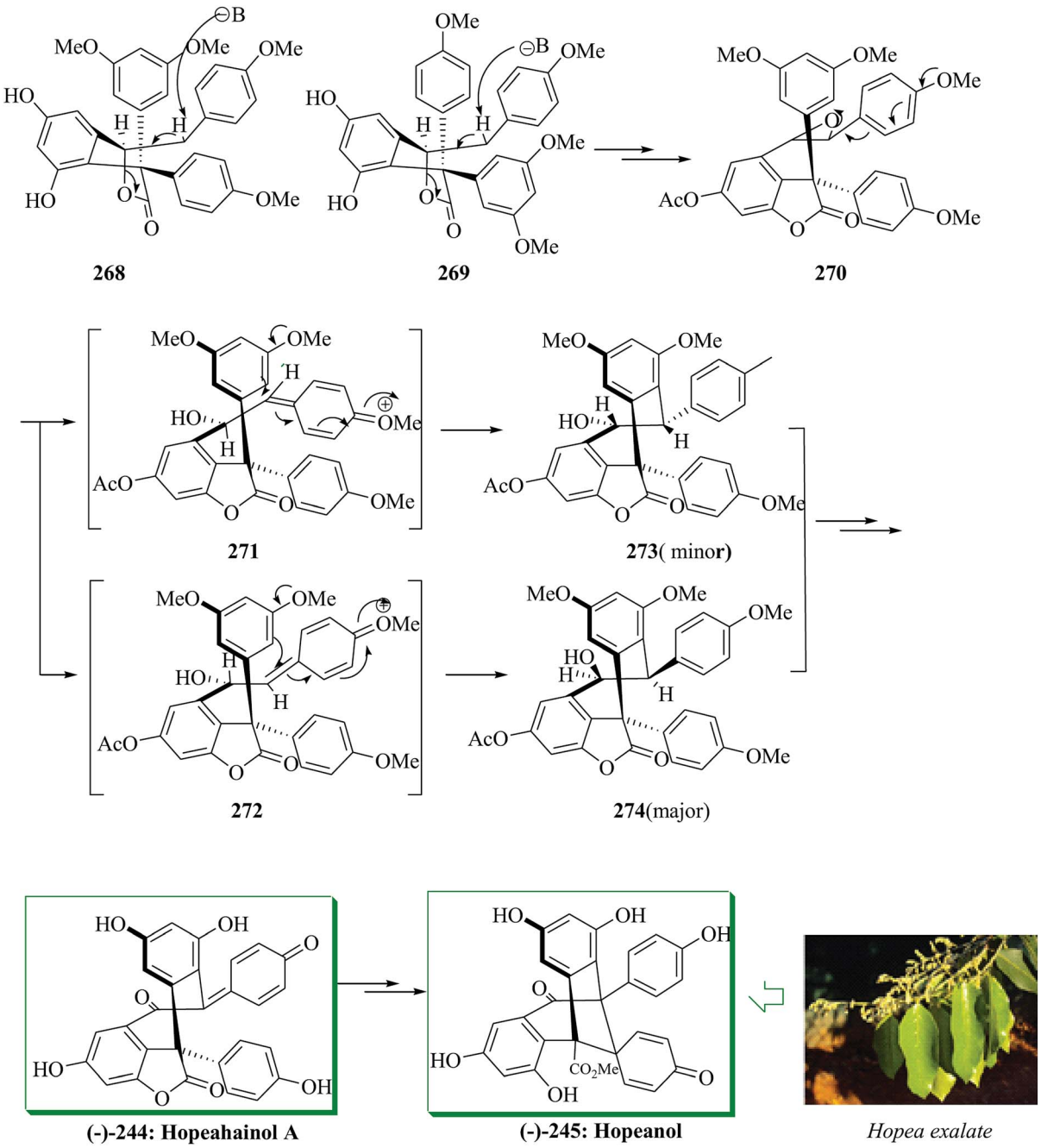
(*endo*-diastereomer). Significantly, coupling of bromide (+)-**292** with indole **293** promoted by $AgBF_4$ in nitroethane proceeded smoothly to give the corresponding C3-(3′-indolyl)hexahydropyrroloindole (+)-**294** in 83% yield. 5-Bromo-1-triisopropylsilylindole **293** was shown to be a significant nucleophile for the corresponding regio- and stereo-selective FC-type reaction. Finally, (+)-**294** provided (+)-gliocladin B **289** and C **290** after several steps (Scheme 59).[280]

Licorice is a popular food additive applied as a sweetener in chewing gums, tobaccos, and candies, and is also one of the most broadly applied medicinal herbs having anticancer[281,282] antiparasitic,[283] antibacterial,[284] superoxide-scavenging[285] and antioxidant properties.[286] Seven chalcones, licochalcones A–E and G and the closely related compound echinatin, have been extracted and identified from the root of *Glycyrrhiza inflata* (licorice),[287,288] except for the artificial synthetic licochalcone F.[289] Among these reported chalcones, licochalcone C shows higher cytotoxicity compared to the analogous licochalcone B.[281] In addition, licochalcone C exhibits remarkable inhibitory activity against the PTP1B enzyme.[290] Wang and co-workers reported a concise, four-step synthesis of licochalcone C **295a** and its regioisomer, tentatively called licochalcone H **295b**, *via* acid-catalyzed Claisen–Schmidt condensation reaction as a main step. Initially, a key intermediate, 2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde **298a**, was synthesized from the reaction between 2,4-dihydroxybenzaldehyde **296** and 3-hydroxy-3-methyl-1-butene **297**. Lewis acid-promoted FC alkylation of **297** in dioxane using $BF_3 \cdot OEt_2$ as a catalyst gave **298.** In this approach, the electron-rich aromatic ring attacked the electrophile in the presence of the Lewis acid catalyst, $BF_3 \cdot OEt_2$, and 3-hydroxy-3-methyl-1-butene **297**, followed by aromatization of the benzene ring to provide the desired compound **298a** in 18% yield based on recovery of 2,4-dihydroxybenzaldehyde (70%). The other regioisomer **298b** was provided as a major product in 38% yield, probably because of the desirable alkylation of the sterically less demanding C-5 in the FC reaction. Finally, compounds **298a** and **298b** gave **295a** and **295b** in 52 and 67% yield, respectively (Scheme 60).[291]

(±)-Yuehchukene **299**, a unique dimeric indole alkaloid, was initially extracted as a racemate from the roots of *Murraya paniculata* (L.) Jack and other related *Murraya* species.[292,293] Yuehchukene exhibits remarkable anti-implantation property in hamsters and rats. A concise total synthesis of yuehchukene was successfully accomplished through organocatalytic FC alkylation reaction of indole to a sterically encumbered α-alkyl enal with excellent *ee*s (up to 96%) as the vital step. It should be mentioned that a racemization method during the subsequent cyclization steps of the conjugate adduct to yuehchukene has been detected. In this route, at the beginning of exploring feasibility, a FC conjugate addition of dienecarbaldehyde **300** and indole **301** was successfully performed to provide the conjugate addition adduct **304**. The best result was obtained in the reaction between two equivalents of **300** and indole **301** in the presence of trifluoroacetic acid in dichloromethane at room temperature, which gave **303** in 22% yield. Various acid additives have been examined with the catalyst **302**[294] in this reaction, and the best result was obtained under the optimized reaction conditions, affording a 26% yield of the desired product **304** (*trans*/*cis* = 73 : 27) with 60% *ee* of the trans adduct. The absolute configuration of this FC alkylation adduct has been identified to be (1*S*, 2*R*). Next, yuehchukene **299** was provided through alkylation-cyclization of adduct **304** (93% *ee*) using indole **301** in 36% yield (Scheme 61).[295]

Several natural and synthetic heterocyclic quinones have shown significant biological properties, including antiprotozoan, antitumoral, and antibiotic properties.[296,297] Many of these compounds contain antineoplastic chemotherapeutic activities.[298] Quinones, a group of molecules known in various drugs, were applied in the clinical therapy of solid tumors.[299] Ellipticine was extracted from the leaves of *Ochrosia elliptica* Labill.[300] Ellipticine quinone **305**[301,302] is an essential synthetic intermediate in the Gribble synthesis of ellipticines, which

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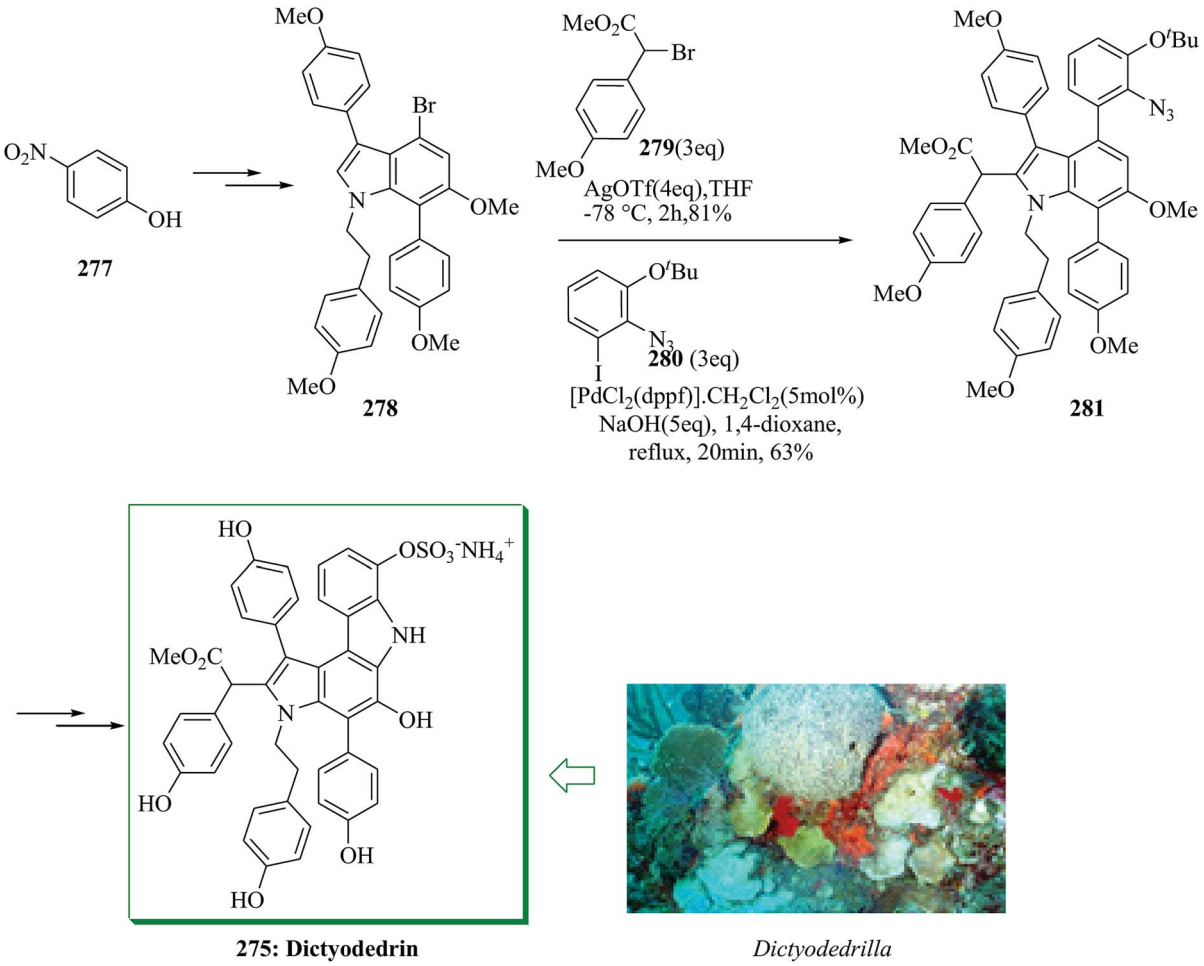
Scheme 55 Total synthesis of (–)-hopeahainol A **244** and (–)-hopeanol **245**.

display antitumor activity.[303] A straightforward pathway for the synthesis of biologically potent ellipticine quinones was developed in 2014 by Nagarajan and co-workers. The key steps included are FC hydroxyalkylation with subsequent oxidation followed by directed *ortho*-lithiation of indole-2-carboxylate esters with functionalized quinoline and pyridine carboxaldehydes. For the synthesis of ellipticine quinone **305**, firstly, compound **306** and pyridine-3-carboxaldehyde **307** were reacted to afford **308** as acid under FC hydroxyalkylation reaction. The acid **308** was directly transformed into ellipticine quinone **305** using LiTMP in 43% yield (Scheme 62).[304]

Studying the extract of leaves of *P. adunctum* by Orjala and co-workers[305] resulted in the extraction of natural adunctin E.[305] A wide range of naturally occurring compounds, namely methyllinderatin **310** and linderol A **312**, were extracted from the fresh bark of *Lindera umbellata* by Ichino[306] and Mimaki and co-workers,[307] respectively. In 2007, Portet and co-workers[308] extracted hostmanin A **309** together with methylinderatin **310**, adunctin E **311** and relevant naturally occurring compounds from the leaves of *Piper hostmannianum*. Methyllinderatin **310** exhibited antibacterial effects toward *M. luteus* and also exhibited potent antiplasmodial activity against chloroquine sensitive and resistant strains of *Plasmodium falciparum*.

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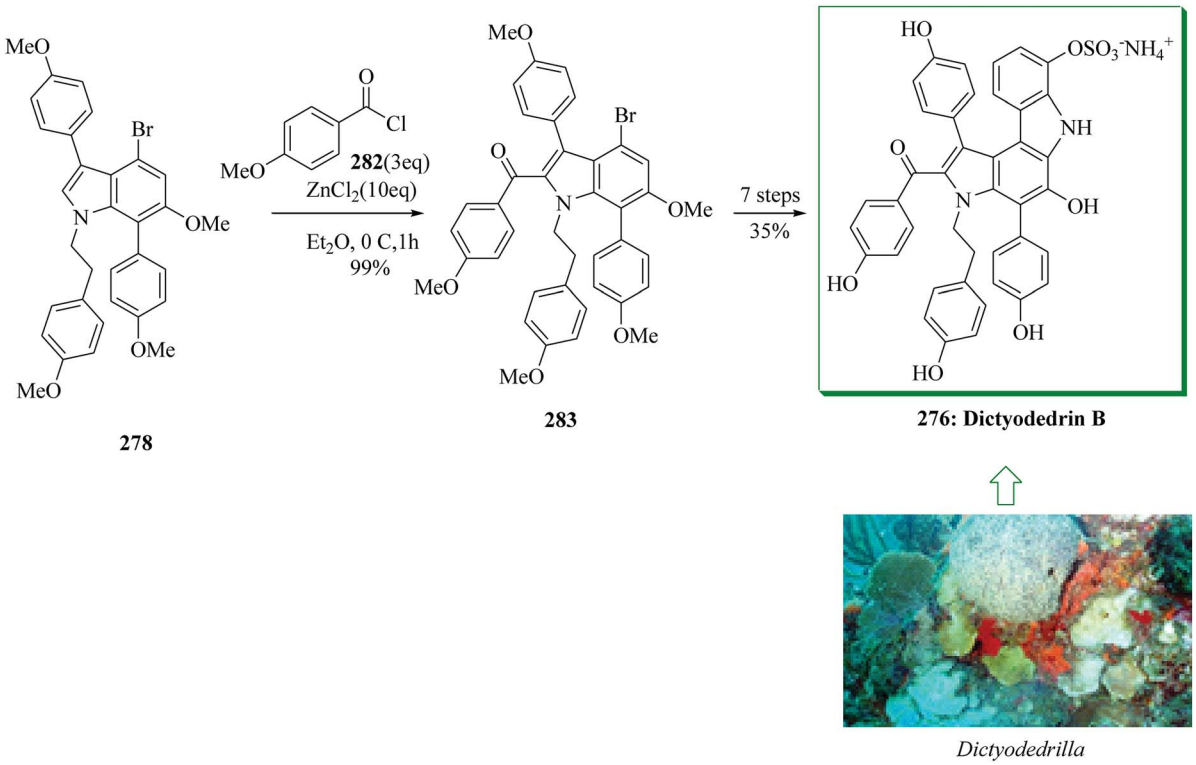
Scheme 56 Total synthesis of dictyodendrin A **275**.

(−)-Linderol A **312** inhibited melanin biosynthesis of cultured B-16 melanoma cells without providing any cytotoxicity in the cultured cells.[307] Adunctin E **311** and linderol A **312** have four contiguous stereocenters. Dethe *et al.* in 2015 reported[309] protecting group free,[310, 311] short and asymmetric total synthesis of (+)-hostmanin A **309**, (+)-methyllinderatin **310**, (+)-linderol A **312** and adunctin E **311**. A one-step method was established for the asymmetric synthesis of hexahydrodibenzofuran derivatives employing a modified FC reaction. The established approach was used for the synthesis of a wide range of naturally occurring compounds involving (+)-hostmanin A, (+)-methyllinderatin, and (−)-linderol A. For the synthesis of these natural products, the diastereoselective modified FC reaction was used,[312, 313] which included two needed constituents, dihydrochalcone derivative **314** and alcohol **315**. The desired chalcone derivative **314** was provided from acetophenone derivative **313** upon several steps. Using the required segments, the stage was set to examine the key FC coupling reaction of a mixture of **314** and **315** using $BF_3 \cdot OEt_2$, which resulted in rapid construction of the extremely regio- and diastereo-selective coupling product methyllinderatin **310** in 91% yield with >20 : 1 diastereomeric ratio (only major diastereomer is depicted in Scheme 63). Moreover, one-step synthesis of (+)-hostmanin A **309** has been accomplished. Therefore, the reaction of dihydrochalcone derivative **314** and alcohol **315** using *p*-toluenesulfonic acid under reflux in toluene provided (+)-hostmanin A **309** as a single diastereomer with 79% yield, whose spectral data and optical rotation were identical to those reported for the natural product.[308] Then, the total synthesis of (−)-linderol A **312** and adunctin E **311** was explored, which were finally obtained from methyllinderatin **310** upon several steps through various pathways.[309]

2.3. Intramolecular acylation

The benzo[*c*]phenanthridine alkaloid nitidine was first extracted from the root bark and root wood of *Zanthoxylum nitidum*, a woody climber that grows in most areas of Hong Kong.[314] A unique method for the total synthesis of benzophenanthridine alkaloids is presented in the context of the construction of the antileukemic agent nitidine chloride **316**. 4,5-Dimethoxyhomophthalic anhydride **317** was reacted with a solution of 3,4-methylenedioxybenzylidenemethylamine **318**, which after other steps gave compound **319**. Intramolecular FC acylation reaction of **319** with poly(phosphoric acid) afforded the tetracyclic ketone **320**. Next, compound **320** gave nitidine, separated

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Scheme 57 Total synthesis of dictyodendrin B **276**.

as the chloride **316** in 47% yield, along with a 24% yield of the hydrogenolysis product **321** (Scheme 64).[315]

Anthraquinones as naturally occurring compounds extracted from both plants[316] and insects[317] have stirred up the interest of synthetic organic chemists as significant synthetic targets. Erythroglaucin **322a** has been extracted from species of *Cortinarius* while catenarin **322b** was first extracted from cultures of *Helminthosporium catenarium*. The regiospecific, concise, and effective synthesis of the natural anthraquinones erythroglaucin **322a** and catenarin **322b** was successfully achieved. The synthesis of erythroglaucin **322a** and catenarin **322b** was achieved through generation of *ortho*-metalated *N*,*N*-diethylbenzamide as an intermediate. Firstly, 3,5-dimethoxy-*N*,*N*-diethylbenzamide **323** afforded a high yield of the *o*-benzylbenzoic acid **324** upon several steps, which under mild FC cyclization in the presence of trifluoroacetic anhydride[318,319] afforded the anthracenol **325**. NMR and IR spectral analysis disclosed evidence for a concentration-dependent anthracenol **325a** and anthracenone **325b** equilibrium. Finally, compound **325** gave catenarin **322a** and erythroglaucin **322b** in 22% and 29% overall yields, respectively (Scheme 65).[320]

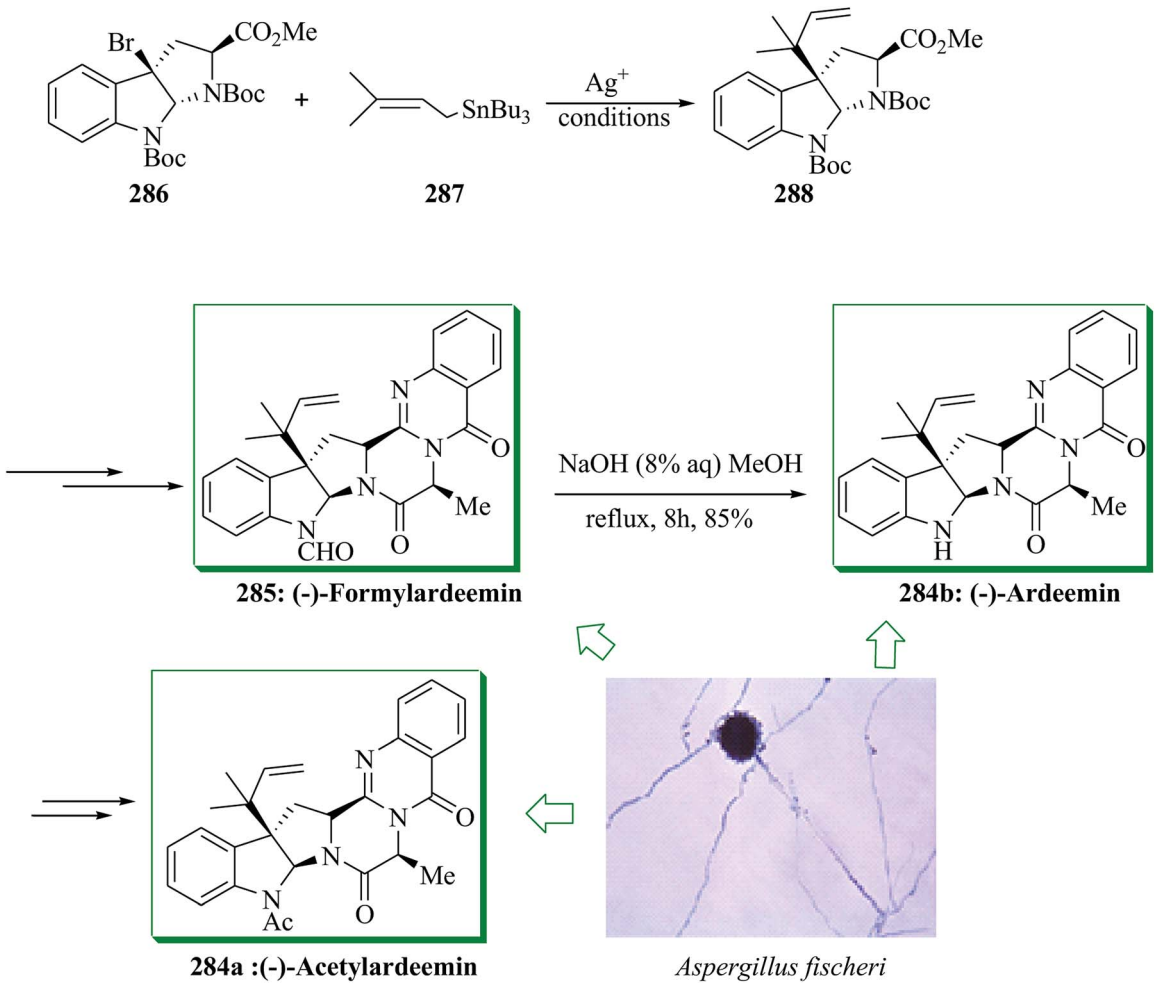
Interleukin-8 (IL-8), a chemoattractant for neutrophils, is provided by macrophages and endothelial cells.[321] IL-8 is implicated in a broad series of acute and chronic inflammatory disorders.[322] Frondosins A–D were recently extracted from the sponge *Dysidea frondosa*. In these compounds, the unifying architectural theme is the existence of bicyclo[5.4.0]undecane ring systems in the context of permuted linkages to several hydroquinone-based scaffolds.[323] Frondosin B **326**[324] includes a benzofuran ring system fused to a nor-sesquiterpenoid (14-carbon) scaffold. A concise synthesis of (±)-frondosin B **326**, an interleukin-8 receptor antagonist, was accomplished from 5-methoxysalicylaldehyde **327**. The seven-membered ring in ketone **329**, the common intermediate for both syntheses, was made *via* FC reaction. This method was initiated from 5-methoxysalicylaldehyde **327**, which provided carboxylic acid **328** upon several steps. Fortunately, the critical FC reaction could be performed. Therefore, reaction of **328** with oxalyl chloride and reaction of the resultant acid chloride with $SnCl_4$ afforded the corresponding ketone **329** in moderate yield.[325] Finally, compound **329** was converted into (±)-frondosin B **326** after several steps (Scheme 66).[326]

Various sesquiterpene metabolites have been identified from species of gorgonians.[327] These compounds show remarkable biological properties, including antifungal, cytotoxicity and immunostimulatory activity.[328] Echinofuran **330**,[329] a type of furanosesquiterpenoid tetrahydrolinderazulene, was extracted from the gorgonian *Echinogorgia praelonga* in 1992.[330] The initial total synthesis of (±)-echinofuran **330** was achieved in 12 steps with overall yield of 0.55%. The synthesis of **330** was accomplished using 3-methyl-4-(trimethylsilyl)furan **331** as a precursor. A Suzuki coupling reaction and a Lewis acid-catalyzed FC cyclization reaction were the main steps in the formation of the desired ring system **333** (Scheme 67).

For the synthesis of (±)-echinofuran **330**, next, benzyl ether **335** was obtained starting from 1,3-cyclopentanedione **334**, after several steps. Saponification of **335** with sodium hydroxide was followed instantaneously, without more purification, by a FC

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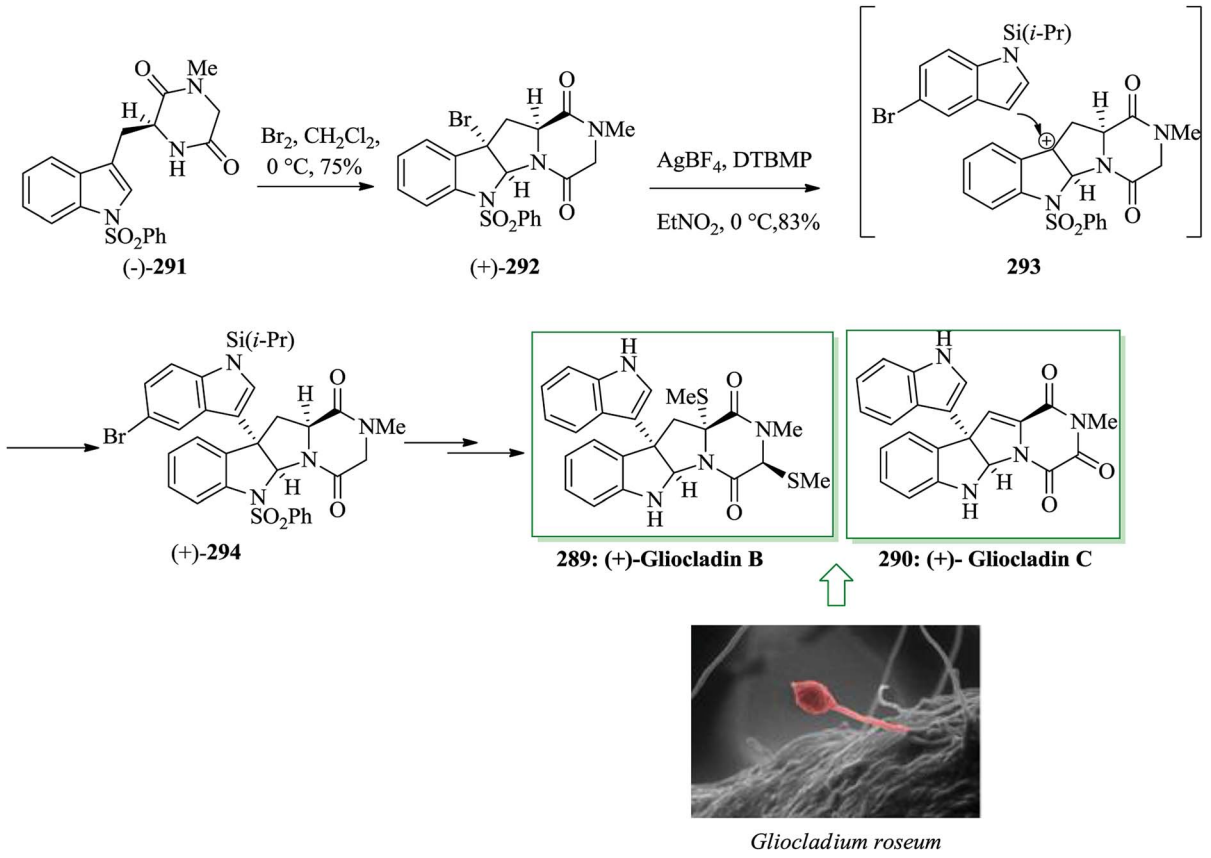
Scheme 58 Total synthesis of (–)-ardeemin **284a**, (–)-acetylardeemin **284b** and (–)-formylardeemin **285**.

cyclization reaction, providing **336**. Finally, compound **336** was converted into (±)-echinofuran **330** upon several steps (Scheme 68).[331]

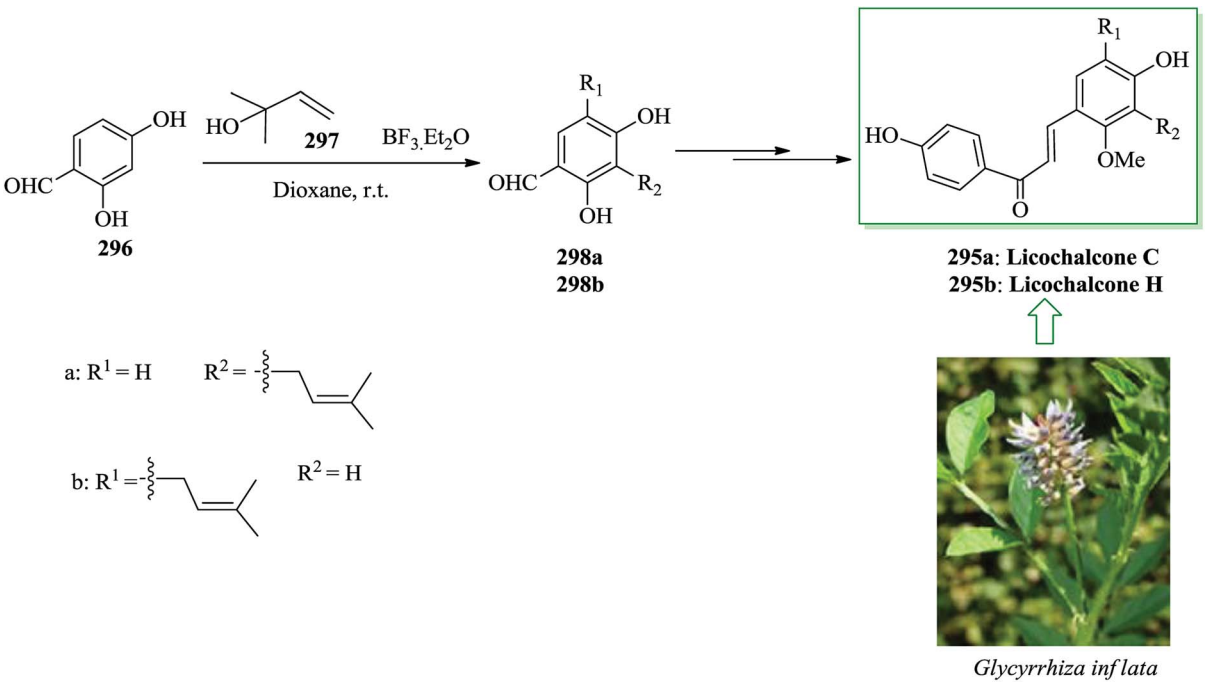
Preussomerins A–F were the first members of this group to be reported[332] and preussomerins G–L are the most recent additions.[333] Structurally, all the preussomerins contain two naphthalene nucleus linked by three oxygen atoms, providing a bis-spiroacetal system. This significant head-to-tail trioxabicyclo[3.3.1]nonane core is a unique natural product unit. The synthesis of newly extracted members of the preussomerin group, preussomerins K and L (4% overall yields in both cases), was demonstrated by Taylor *et al.*[334] The main stages are the functionalization of a 2-arylacetal anion, one-pot FC cyclization-deprotection and reductive opening of epoxides. The total synthesis was commenced from methoxyphenol **338**, which afforded the diacid **339** in several steps. The next step of the synthesis was FC cyclization reaction of the diacid **339**. Upon activating of the latter as the acid chloride by a homogenous solution of aluminium chloride in nitromethane, the corresponding FC adduct **340** was obtained. However, if the reaction was permitted to stand for longer time in the presence of excess aluminium chloride, two new compounds, identified as **341a** and **341b**, started forming, demonstrating that upon a quick cyclization, the remaining Lewis acid gradually mediated the removal of the phenolic methoxy groups. Lastly, compound **341b** gave preussomerin L **336** and preussomerin K **337** through a different multi-step synthesis (Scheme 69).[334]

Preussomerin F was extracted from the coprophilous fungus *Preussia isomera* by Gloer and co-workers in 1990.[335] Preussomerin K was also extracted independently by Isaka *et al.* from a lichenicolous fungus *Microsphaeropsis* sp. BCC 3050.[336] All of the preussomerins exhibit pronounced antifungal activity as well as preventing Gram-positive bacteria. All the members of the preussomerin group are characterized by the same key structural aspect, containing the naphthalene units linked by three oxygen atoms, providing a bis-spiroacetal functionality. Taylor and co-workers in 2004 developed and reported the first total synthesis of the racemic natural products preussomerin F (3% overall yield, 13 steps) and preussomerins K and L (4% overall yields in both cases, 11 and 10 steps, respectively) from cheap and simply accessible initiating precursors *via* the usage of a straightforward, non-biomimetic methodology including the functionalization of 2-arylacetal anions, simultaneous one-pot FC cyclization-deprotection and substrate-regiocontrolled hydrogenation as the key steps. The total synthesis of the racemic naturally occurring compounds preussomerins F, K

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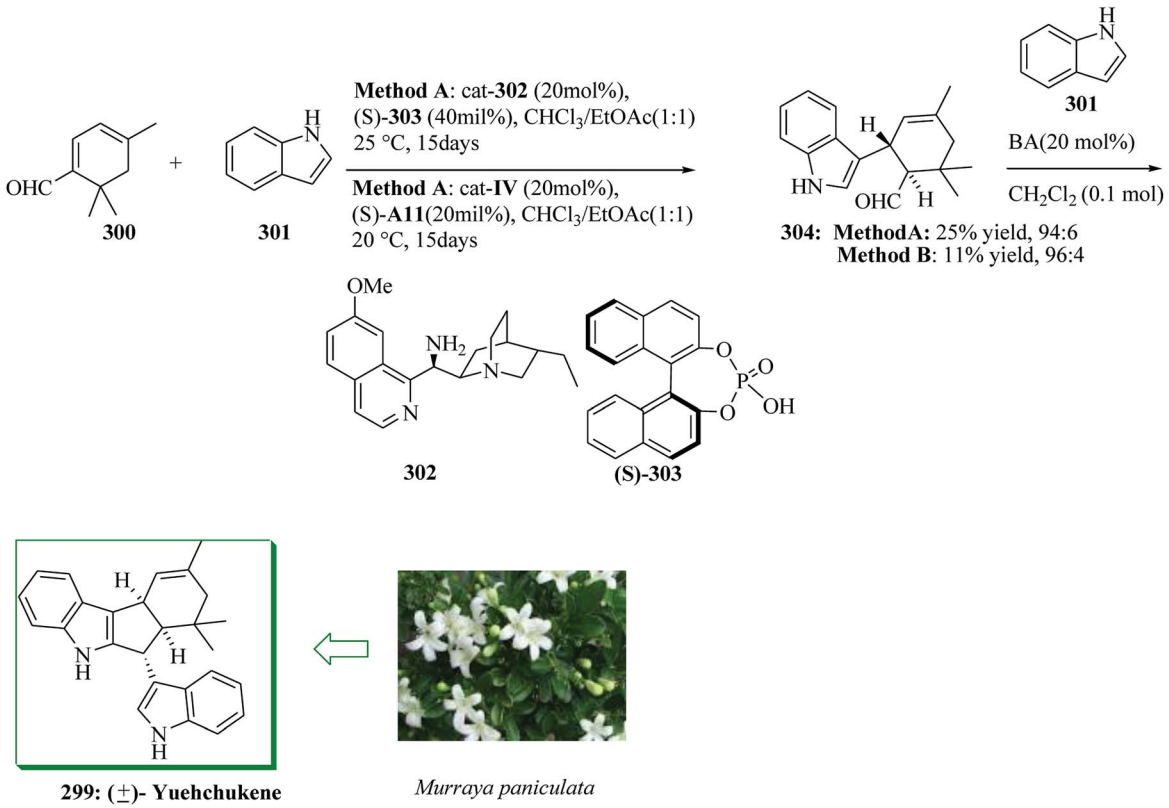
Scheme 59 Total synthesis of (+)-gliocladin B **289** and C **290**.



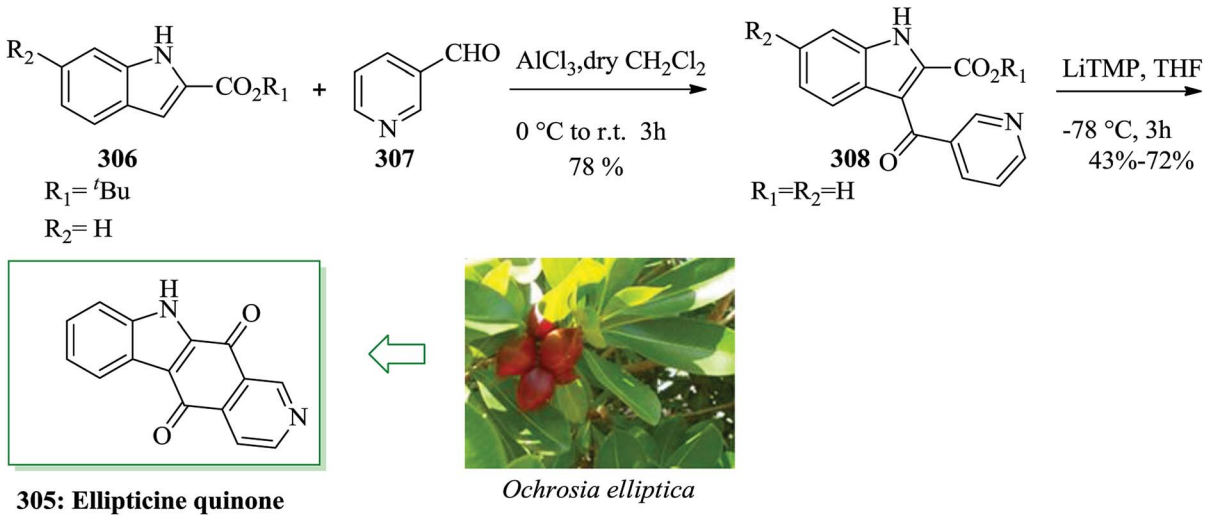
Scheme 60 Total synthesis of licochalcone C **295a** and its regioisomer licochalcone H **295b**.

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Scheme 61 Total synthesis of yuehchukene **299**.

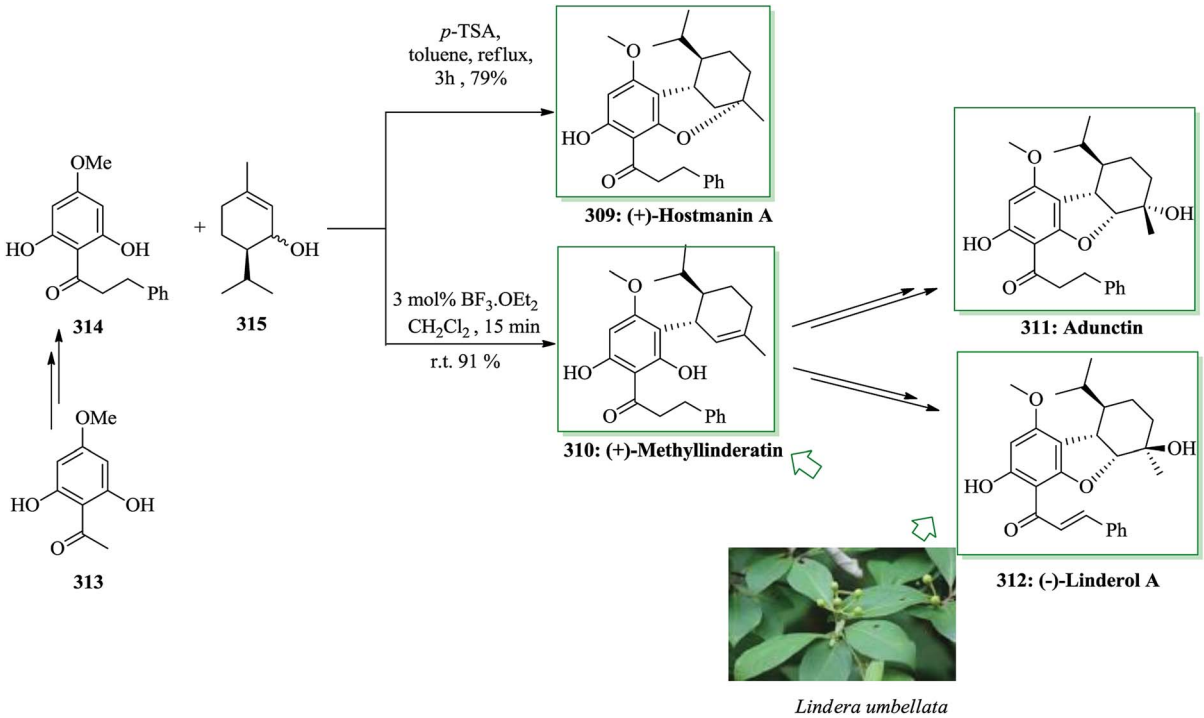


Scheme 62 Total synthesis of ellipticine quinone **305**.

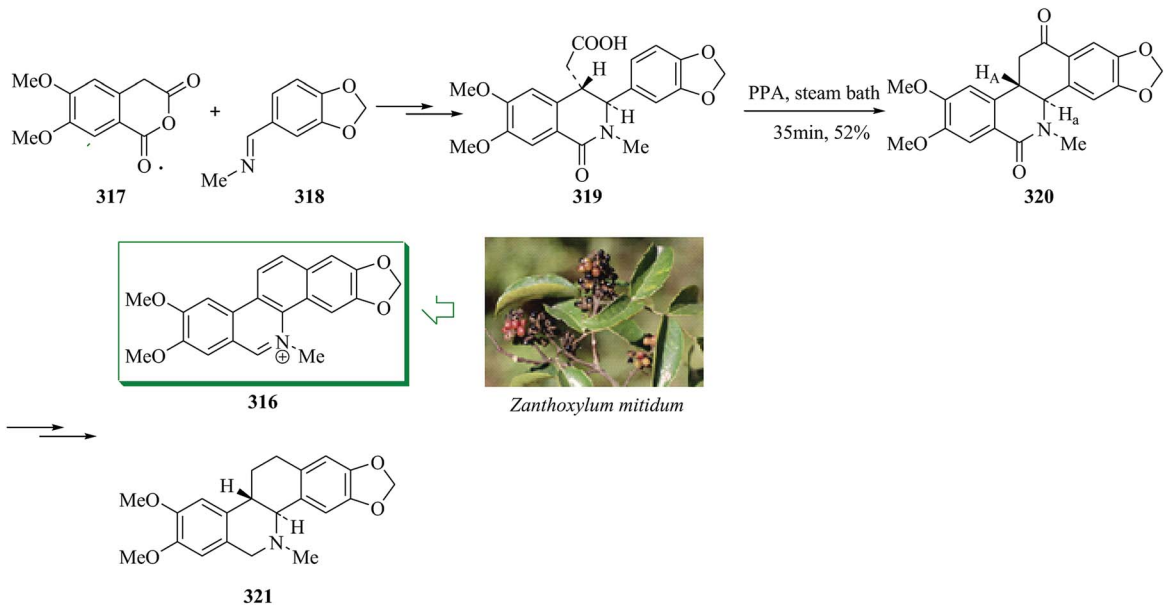
and L started from 4-methoxyphenol, which was transformed into the diacid **339** in several steps. Then the reaction of diacid **339** with a homogenous solution of aluminium chloride in nitromethane at ambient temperature provided the corresponding FC adduct **340** in satisfactory yield (75%). However, if the reaction was permitted to stand for a longer time in the presence of an excess of aluminium chloride, two new compounds, characterized as **341a** and **341b**, started to appear, demonstrating that after a fast cyclization, the lasting Lewis acid gradually removed the phenolic methoxy substituents. Finally, compound **341b** gave preussomerins F, K and L upon several steps (Scheme 70).[337]

The search for phytoalexins in *Musa* over the years led to the isolation and structural identification of 9- and 4-phenylphenalenones and related compounds, for example dimeric phenylphenalenones, phenylnaphthalic anhydrides, perinaphthenones, and an oxabenzochrysenone.[338] 4-Methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone) **343**, a subunit

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Scheme 63 Total synthesis of (+)-hostmanin A **309**, (+)-methyllinderatin **310**, (+)-linderol A **312** and adunctin E **311**.



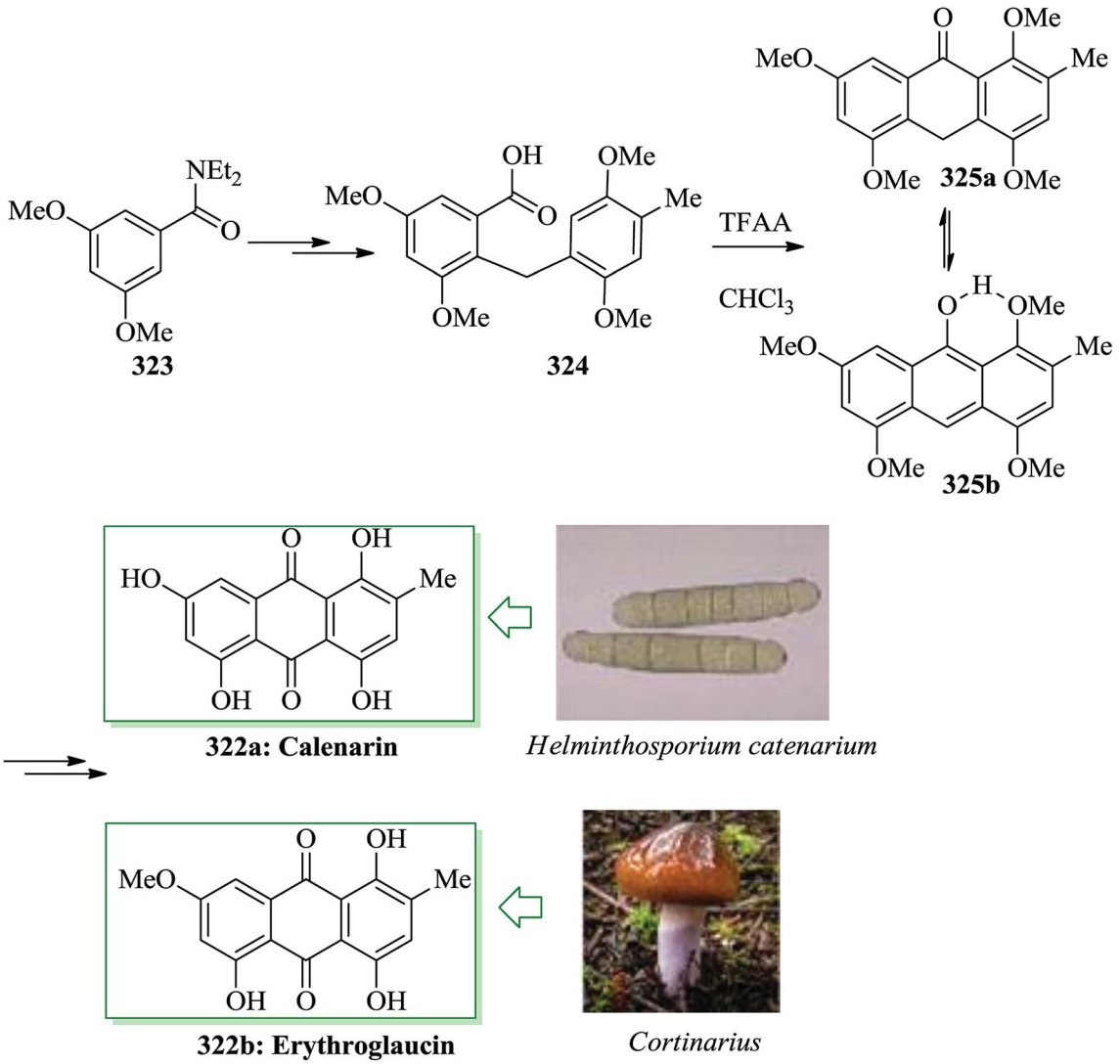
Scheme 64 The formation of compounds **316** and **321**.

known in some *Musa* phytoalexins and relevant naturally occurring compounds from *Haemodoraceae*, was obtained *via* a Heck–Fujiwara coupling reaction and a FC acylation as the carbon–carbon bond-forming reactions. It was actually synthesized from 2-methoxynaphthalene in five steps with an overall yield of 36%. The formation of 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **343**) and other perinaphthenones alike was achieved *via* the cyclization of *b*-1-naphthylpropanoic acids provided by the malonic ester synthesis, employing 4-methoxynaphthalenes **344** as the starting material.[339] Based on this method, 4-methoxynaphthalene gave **345** upon several steps. Compound **345** was cyclized employing FC reaction conditions and gave 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone) **343** as the sole product in 48% yield (Scheme 71).[340]

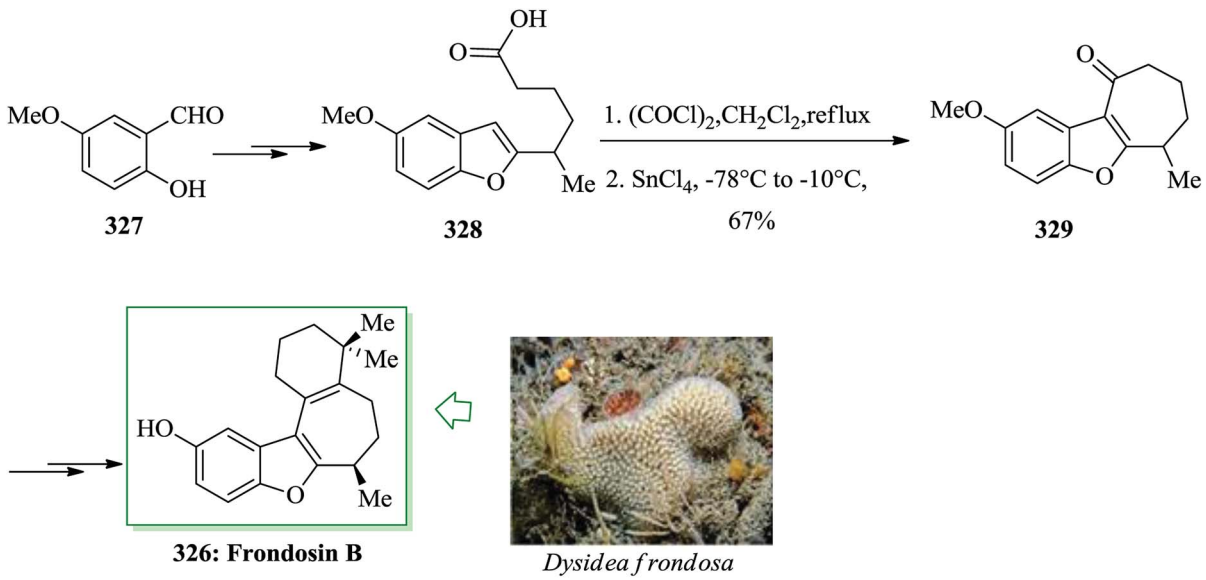
Xestodecalactone C **346** was extracted from the fungus *Penicillium* cf. *montanense*, which in turn was extracted from *Xestospongia exigua*. This molecule is structurally related to

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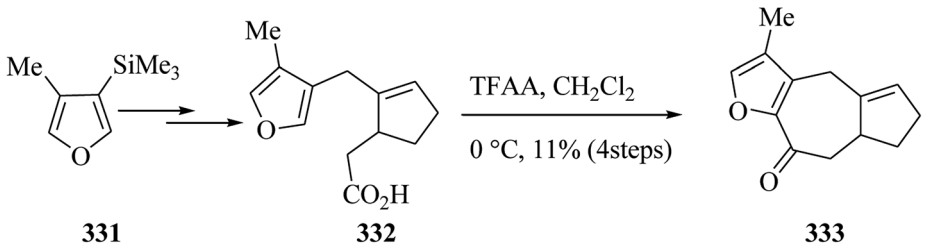


Scheme 65 Total synthesis of catenarin **322a** and erythroglaucin **322b**.

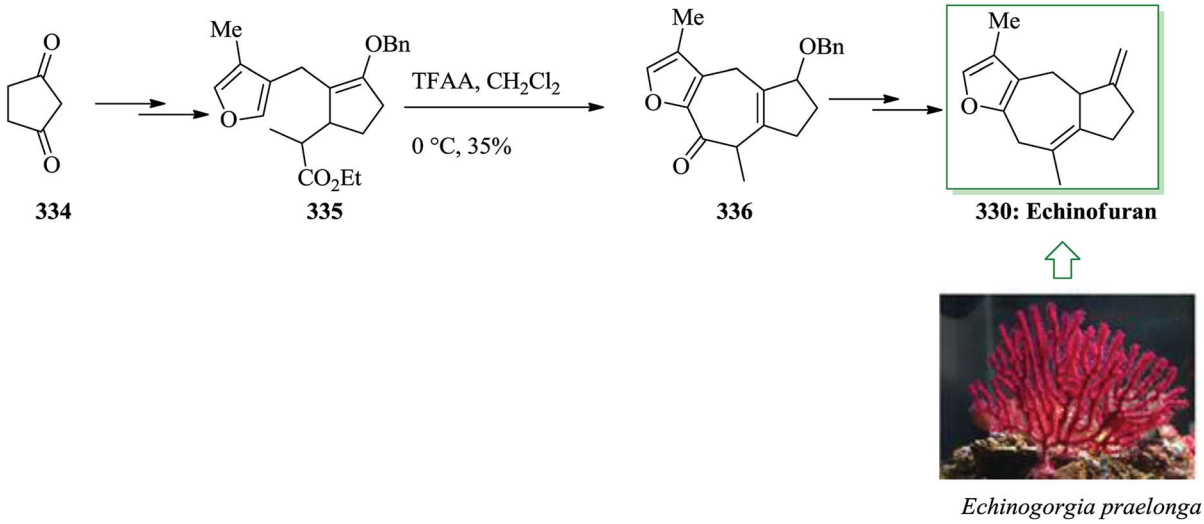


Scheme 66 Total synthesis of (±)-frondosin B **326**.

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Scheme 67 The formation of compound **333**.



Scheme 68 Total synthesis of (±)-echinofuran **330**.

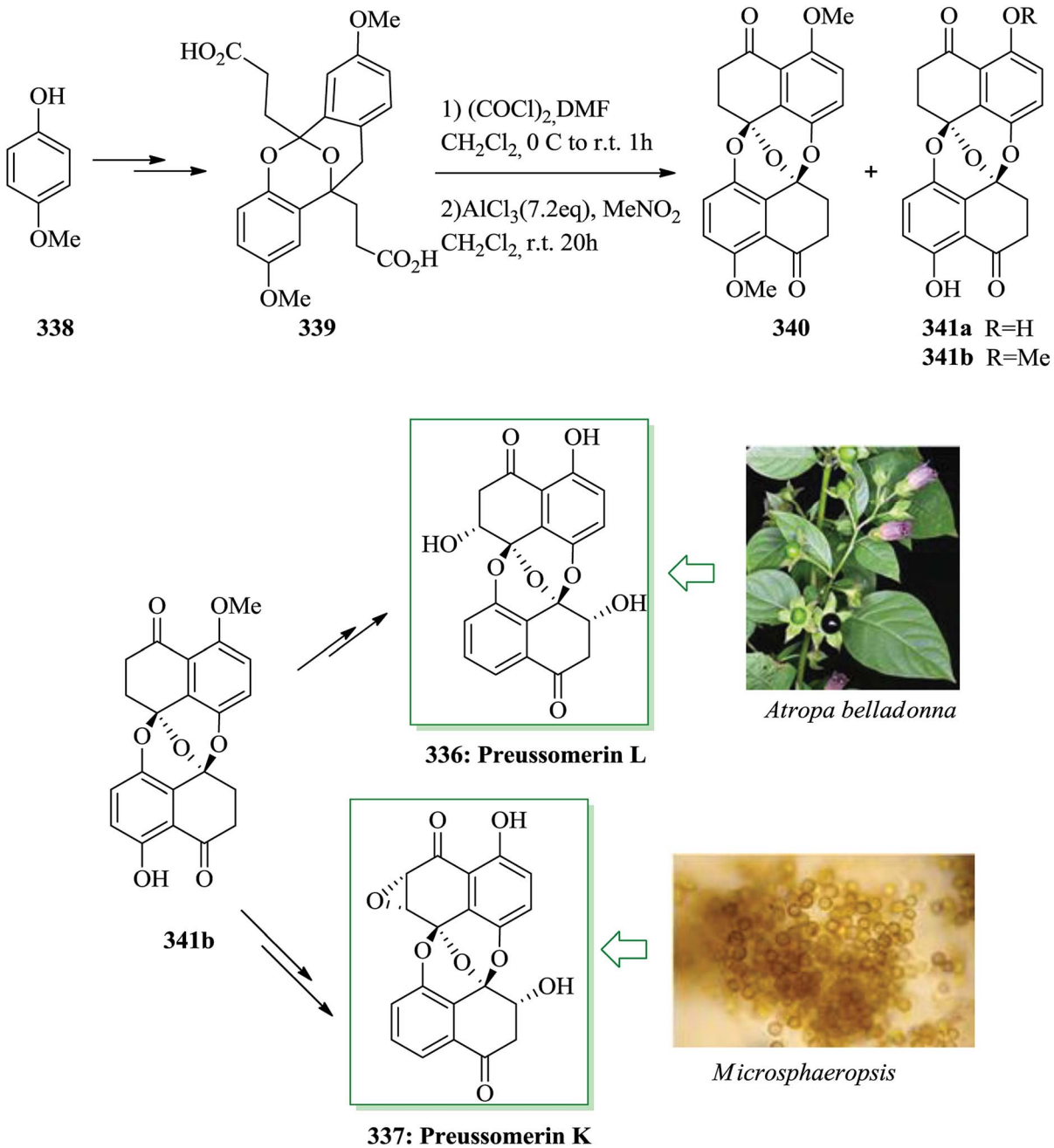
a wide range of compounds extracted from terrestrial fungi, involving sporostatin **347**. Sporostatin (M5032, **347**), extracted from the fungus *Sporormiella* sp., is an inhibitor of cyclic adenosine 3′,5′-monophosphate phosphodiesterase.[341] Total synthesis of xestodecalactone C and *epi*-sporostatin was developed in 10 steps using Prins cyclizations, Mitsunobu reaction and intramolecular FC acylation reaction. This method is convergent and extremely enantioselective. The synthesis of xestodecalactone **346** and *epi*-sporostatin **347** was started with chiral homoallyl alcohol **349**. The starting material **349** was synthesized in two steps from *S*-(−)-benzyl glycidyl ether **348**. Next, compound **349** was converted into acid **350** after several steps. The corresponding macrolide **351** was provided in 41% yield *via* intramolecular FC reaction of the carboxylic acid **350** in the presence of a mixture of trifluoroacetic acid and trifluoroacetic acid anhydride.[342,343] Demethylation reaction of **351** with freshly synthesized AlI_3 afforded the target molecule **346**[344,345] in 96% yield, whereas the same reaction at ambient temperature provided **347** in 94% yield.[342,343] Finally, compound **351** afforded **346** and **347** in 96% and 94% yield, respectively (Scheme 72).[346]

The aaptamines, first found in nature by Nakamura and coworkers in 1982,[347] are marine alkaloids that include a benzo[*de*][1,6]naphthyridine scaffold.[348,349] The aaptamine group involves aaptamine **352**, first extracted from an Okinawan specimen of *Aaptos aaptos*. The aaptamines exhibit various remarkable biological properties. Owing to their antagonistic effects on β-adrenergic receptors, a cardiac property was found for **352**.[350,351] A formal total synthesis of the marine alkaloid aaptamine **352** has fruitfully been accomplished *via* the development of a new methodology to provide 2,3,3*a*,4,5,6-hexahydroaaptamine **356**. This alternative access to **356** has been achieved in eight steps and in 11% overall yield, with quinolin-4-one **355** as a key intermediate. The synthesis was started from market-accessible 2,3-dimethoxybenzoic acid **353**, which after several steps afforded acid **354**. Then, acid **354** was exposed to FC-type acylation reaction with excess PPE in toluene to obtain **355** in 95% yield. Finally, after several steps, intermediate **355** afforded 2,3,3*a*,4,5,6-hexahydroaaptamine **356**, which is an intermediate for the synthesis of aaptamine **352** (Scheme 73).[352]

Sporostatin (M5032, **347**), extracted from the fungus of *Sporormiella* sp., is an inhibitor of cyclic adenosine 3′,5′-monophosphate phosphodiesterase (cAMP-PDE),[353] composed of a ten-membered macrolide derivative with a 1,3-dihydroxybenzene ring. A simple and effective total synthesis of sporostatin was achieved in five steps beginning from (*S*)-propylene oxide **357**. In this method, esterification, cross-metathesis, and intramolecular FC reaction were known as the key steps. Total synthesis of sporostatin (M5032, **347**) was started from (*S*)-propylene oxide **357**, which afforded the relevant α,β-unsaturated carboxylic acid **358** after several steps. Then, the macrolide **359** was obtained in 41% yield when the carboxylic acid **358** was exposed to an intramolecular FC

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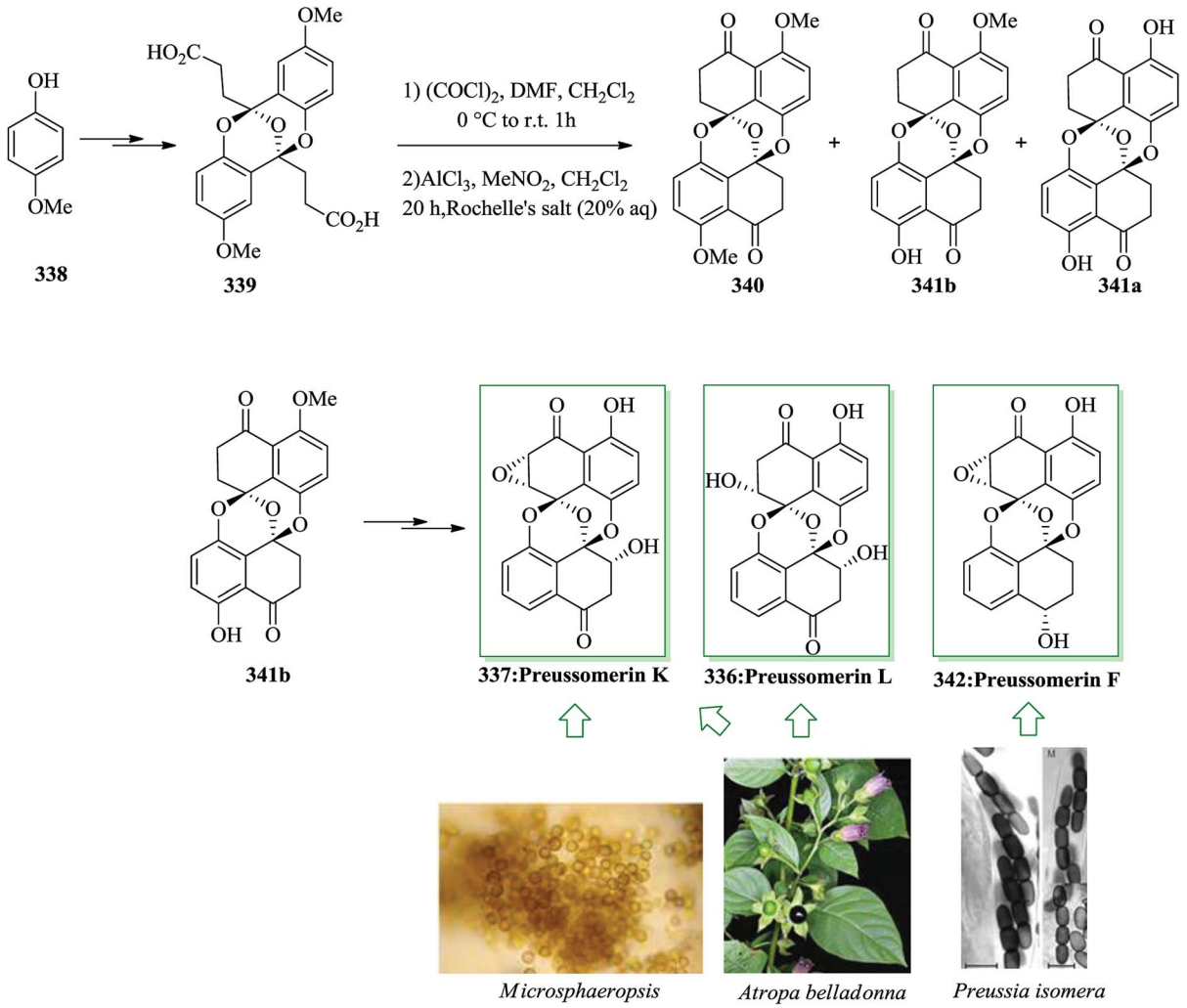
Scheme 69 Total synthesis of preussomerin L **336** and preussomerin K **337**.

reaction with a mixture of trifluoroacetic acid and trifluoroacetic anhydride.[344,354–356] Deprotection of the MeO substituents of **359** employing freshly synthesized AlI_3 (ref. 357–359) provided the final product **347** in 94% yield (Scheme 74).[360]

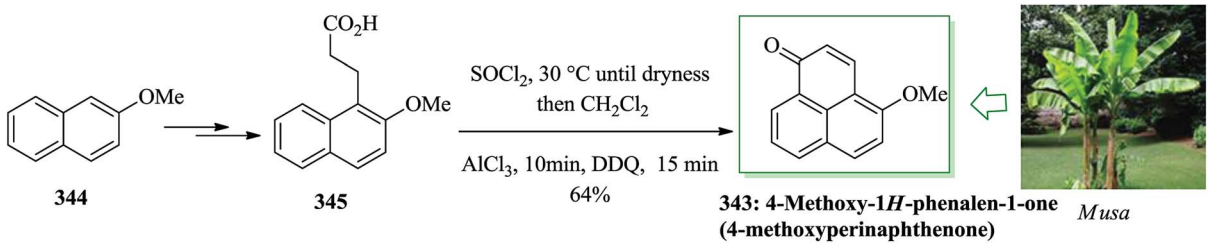
In 2002, 10-membered macrolides fused to the 1,3-dihydroxybenzene ring, for example xestodecalactones A, B, and C **346,** were extracted from the fungus *Penicillium* cf. *mantanense* obtained from the marine sponge *Xestospongia exigua*.[358] Xestodecalactones A–C exhibited antifungal and antibacterial properties.[361] A simple and extremely effective enantioselective total synthesis of xestodecalactone C **346**, a polyketide natural product, was accomplished using Keck's asymmetric allylation reaction, an iodine-induced electrophilic cyclization, and an intramolecular FC acylation as key steps. The synthesis of xestodecalactone C **346** was initiated from propane-1,3-diol, which was protected with *p*-methoxybenzyl (PMB) bromide to provide the relevant propan-1-ol **360.** Next, compound **360** gave the acid **361** in several steps. The corresponding macrolide **362** was obtained in 40% yield *via* an intramolecular FC acylation reaction of the carboxylic acid **361** using $CF_3COOH/(CF_3CO)_2O$[346] Finally, compound **362** was transformed into the desired natural product **346** after several steps (Scheme 75).[362]

The curvularins are octaketides composed of a 12-membered macrolide framework fused to a 1,3-dihydroxybenzene scaffold. (11β)-11-Methoxycurvularin **363** is a member of the curvularin group extracted from the mycelium of the hybrid strain ME 005

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Scheme 70 Total synthesis of preussomerins L **336**, K **337** and F **342**.



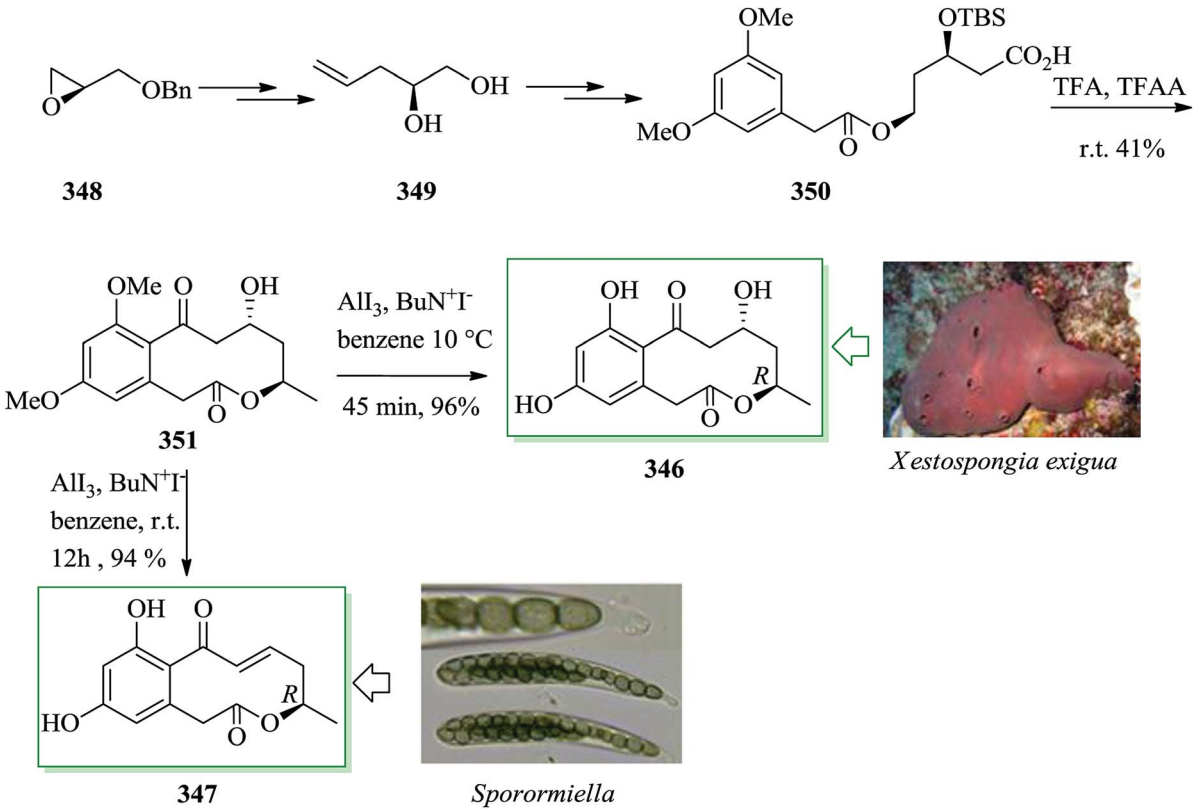
Scheme 71 Total synthesis of 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone) **343**.

obtained from *Penicillium citreoviride* 4692 and 6200 (ref. 363) that demonstrated significant cytotoxicity toward a panel of four human-cancer cell lines.[364] A simple and extremely effective enantioselective total synthesis of (11β)-11-methoxycurvularin **363** was accomplished in 2010 by Venkateswarlu and co-workers.[365] The synthesis was started with a Cu-catalyzed regioselective ring opening of (2*S*)-2-methyloxirane **357**, a Keck enantioselective allylation and intramolecular FC acylation as key steps. In this strategy, oxirane **357** was used as the starting material, which was converted into compound **364** upon several steps. The corresponding macrolide **365** was obtained in 41% yield *via* intramolecular FC reaction of the carboxylic acid **364** in the presence of $CF_3COOH/(CF_3CO)_2O$. Next, demethylation of **365** using freshly synthesized AlI_3 afforded the natural product **363** in 96% yield (Scheme 76).[365]

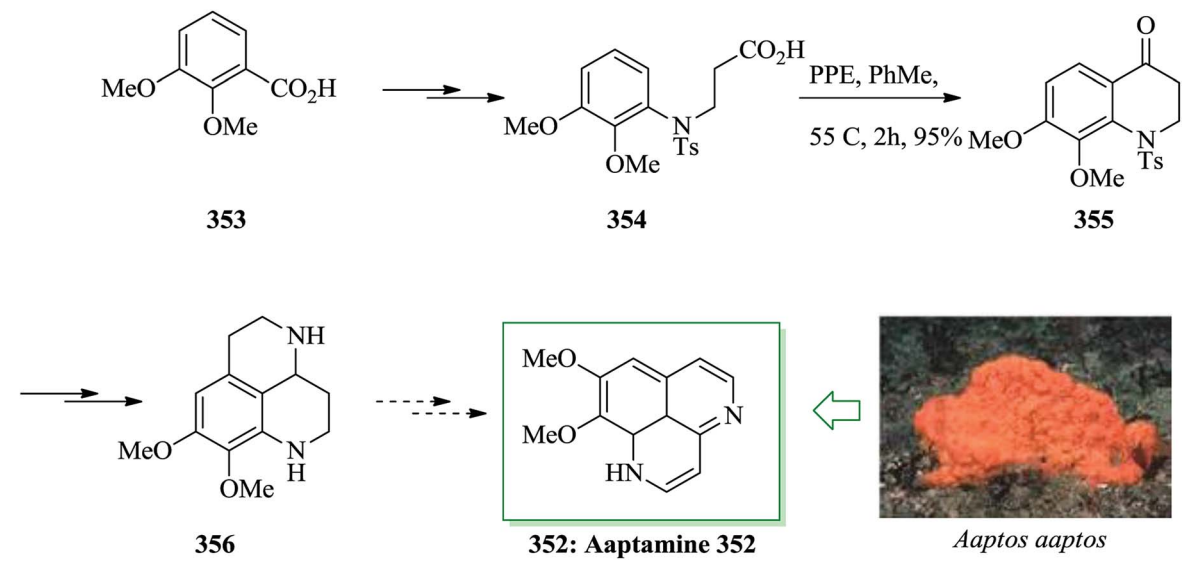
Dipterocarpaceae is a rich source of a wide range of biologically potent oligostilbenoids.[366,367] Not surprisingly, many remarkable pharmacological functions of this group were also identified, including antifungal, anti-inflammatory, antibacterial, and anticancer properties.[368–371] Isolation of a novel

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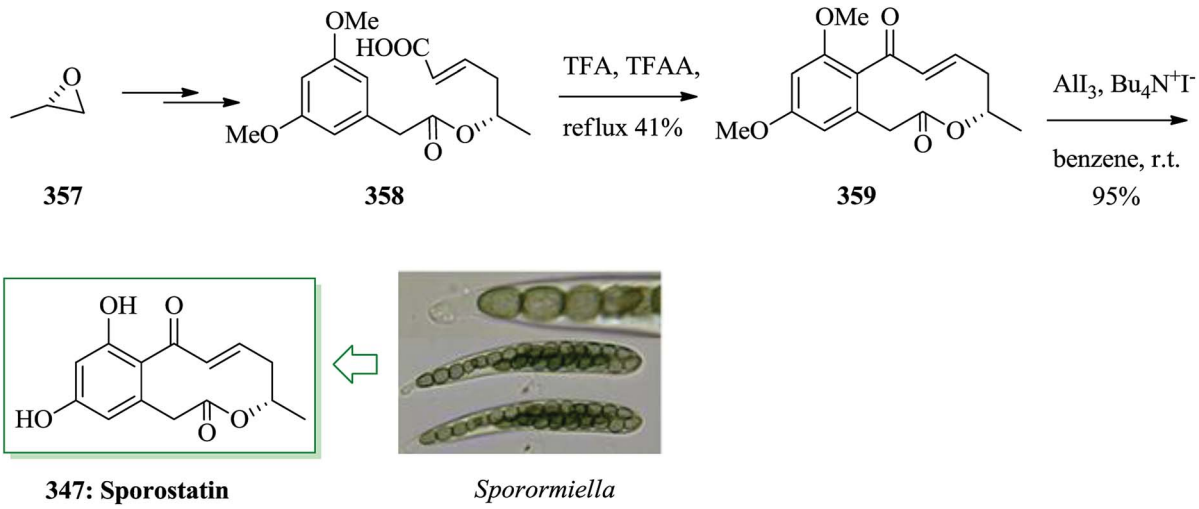
Scheme 72 Total synthesis of sporostatin **347**.



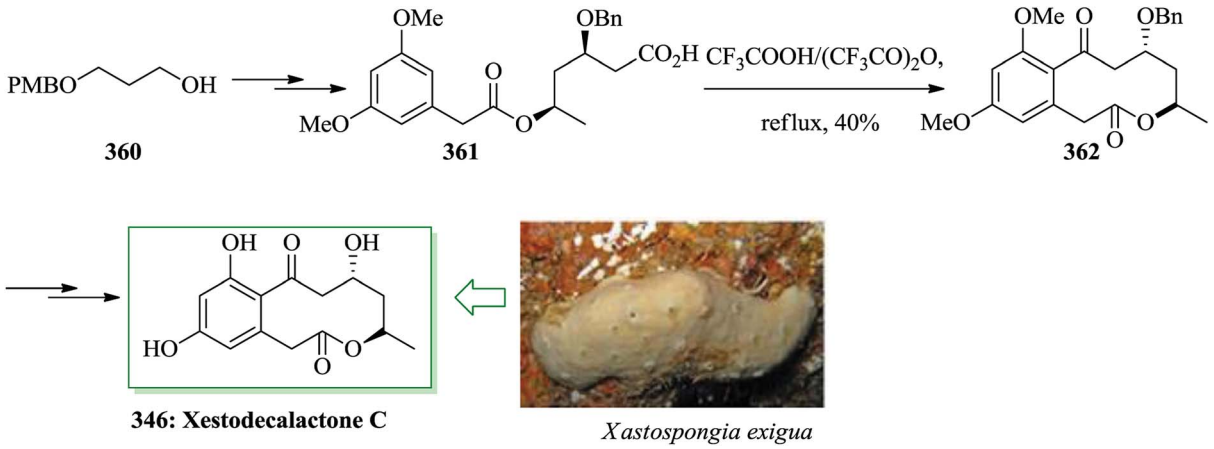
Scheme 73 Total synthesis of aaptamine **352**.

oligostilbenoid containing strong cytotoxicity, diptoindonesin G, from the tree bark of *Hopea mengarawan* was demonstrated by Syah *et al.*[372] This natural product exhibits active immunosuppressive properties.[373] A very significant total synthesis of diptoindonesin G **366** was developed using a domino dehydrative cyclization/intramolecular FC acylation/regioselective demethylation reaction of aryloxyketone **371** in the presence of boron trichloride, in which the tetracyclic 6*H*-anthra[1,9-*bc*] furan-6-one framework was generated through the 3-arylbenzofuran in a one-pot fashion. Accordingly, a coupling reaction of **367** and **368** took place, which was followed by dehydrative cyclization and subsequent direct arylation at the C2 position of the benzofuran scaffold to afford the key intermediate **369**. The latter was then transformed into compound **370** upon

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Scheme 74 Total synthesis of sporostatin **347**.



Scheme 75 Total synthesis of xestodecalactone C **346**.

treatment with NaOH and then TFAA by intramolecular FC acylation reaction. Upon treatment with BBr_3 the latter was converted into G **366** in 93% yield (Scheme 77).[374]

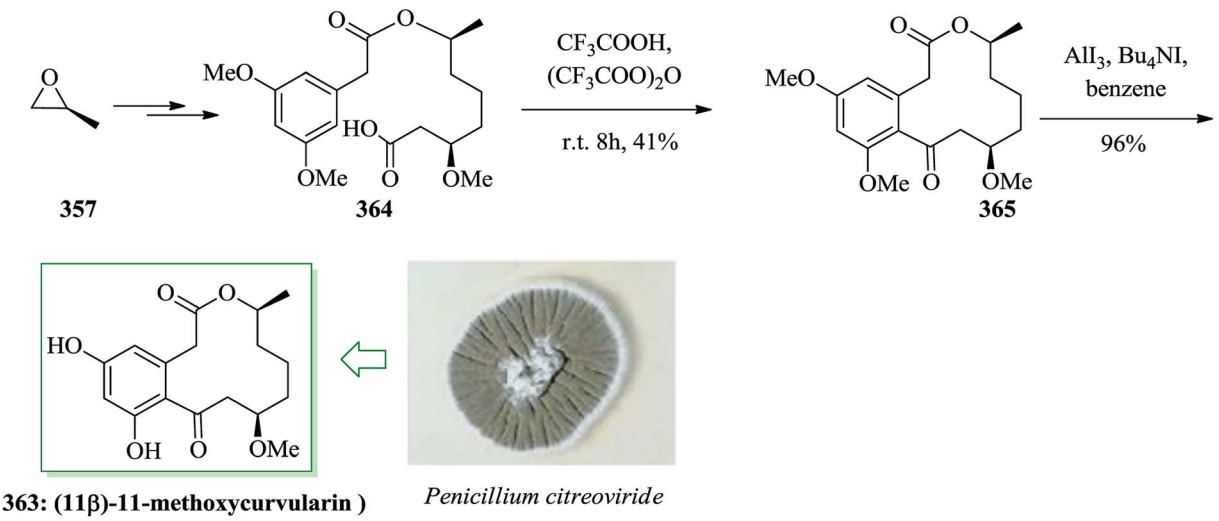
The same strategy was applied for the synthesis of diptoindonesin G **366** using compound **371** instead of **370** as the precursor. Compound **371** was treated with BCl_3 in CH_2Cl_2 to give the demethylated compound **372** in 95% yield.[375–378] Finally, the latter was transformed into the desired natural product diptoindonesin G **366** upon several steps (Scheme 78).[374]

Kinamycin antibiotics[379,380] have been extracted from of *Streptomyces murayamaensis* culture broth[381,382] with antitumor and antiviral properties.[382] The structure was at first identified as *N*-cyanobenzo[*b*]carbazoloquinone. The structure of so-called 'prekinamycin' extracted by Gould was revised to, temporarily, diazobenzo[*b*]fluorene **373**.[383] This compound with the structure **373** was extracted as a metabolite provided by *S. murayamensis* mutant MC2 (ref. 384) and finally named as prekinamycin.[385] Total synthesis of prekinamycin **373** was accomplished through Suzuki coupling reaction of naphthaleneboronic acid and a bromobenzene derivative, intramolecular FC reaction of 2-(naphthalen-2-yl)benzoic acid, and diazotization in ten steps starting from 3,5-dimethylphenol **374**, in 7% yield. Initially, 3,5-dimethylphenol **374** was converted into carboxylic acid **375** upon several steps. The intramolecular FC reaction of **375** with $(CF_3CO)_2O$[386] or $POCl_3/K_2CO_3$ (ref. 387) in a one-pot fashion resulted in a complex mixture. Transformation of acid **375** to acid chloride **376**, followed by intramolecular FC reaction in the presence of tin(IV) chloride, afforded the key MOM-deprotected benzo[*b*]fluorenone **377** in merely 4% yield. Finally, compound **377** was transformed into the desired natural product prekinamycin **373** in 47% yield (Scheme 79).[388]

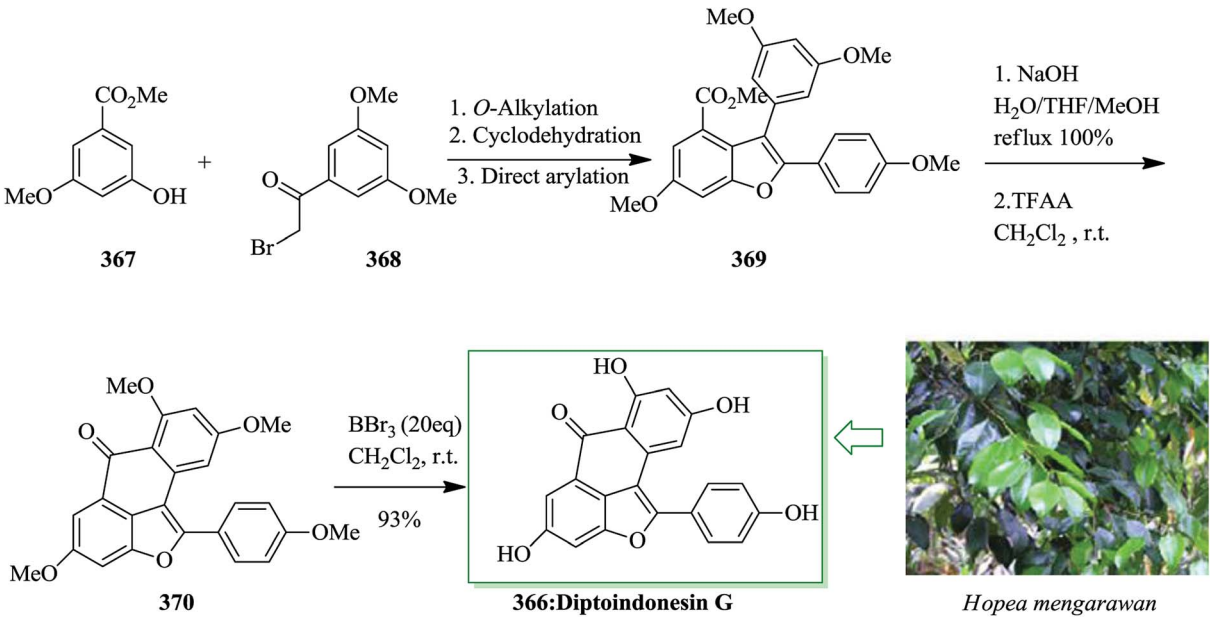
Diazobenzofluorene is a naturally occurring compound, classified as a group of structurally complex molecules bearing a tetracyclic (ABCD) scaffold along with a diazo group. Some epoxykinamycins contain FL-120B and the closely related FL-120B′ **378**.[389] Monomeric diazobenzofluorenes were found to exhibit antitumor activity. Enantioselective synthesis of FL-120B′ was accomplished employing Sharpless asymmetric epoxidation, Stille cross-coupling, and intramolecular FC

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Scheme 76 Total synthesis of (11β)-11-methoxycurvularin **363**.



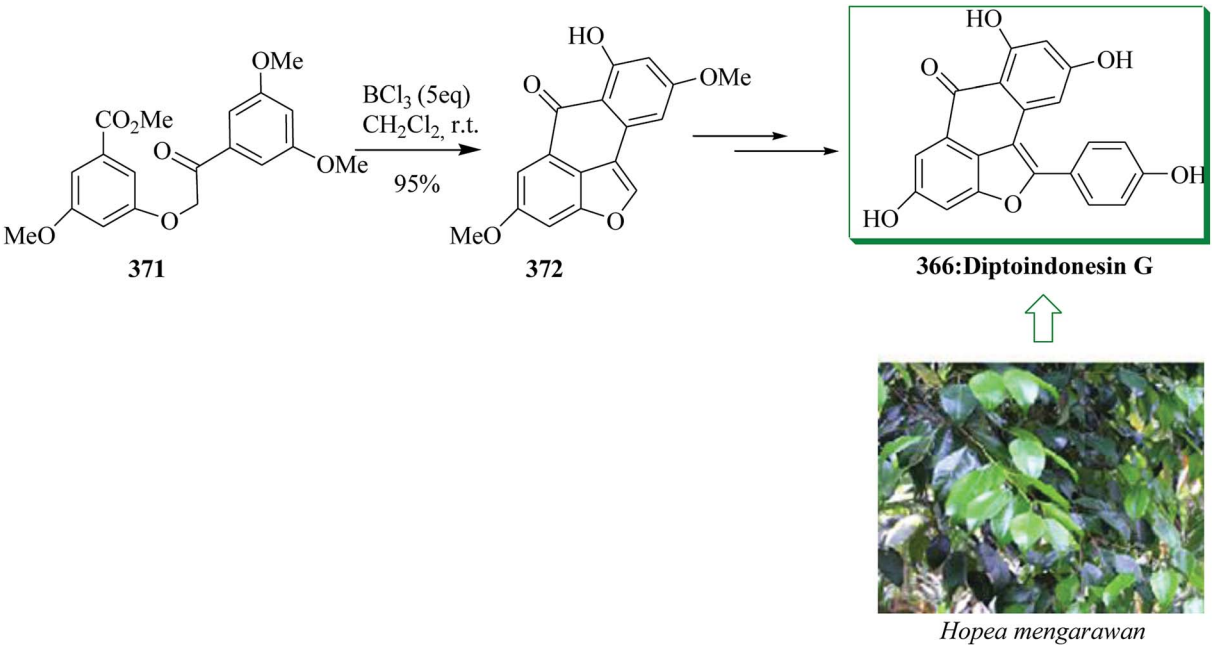
Scheme 77 Total synthesis of diptoindonesin G **366**.

reactions as key steps. The synthesis of FL-120B′ represents the first total synthesis of an epoxide-comprising, diazobenzofluorene natural product. Firstly, quinone **379** gave carboxylic acid **380** upon several steps. Then, carboxylic acid **380** in the presence of trifluoroacetic anhydride (TFAA) underwent an intramolecular FC acylation, affording the corresponding ketone **381**. Finally, ketone **381** was transformed into FL-120B′ **378** after several steps (Scheme 80).[390]

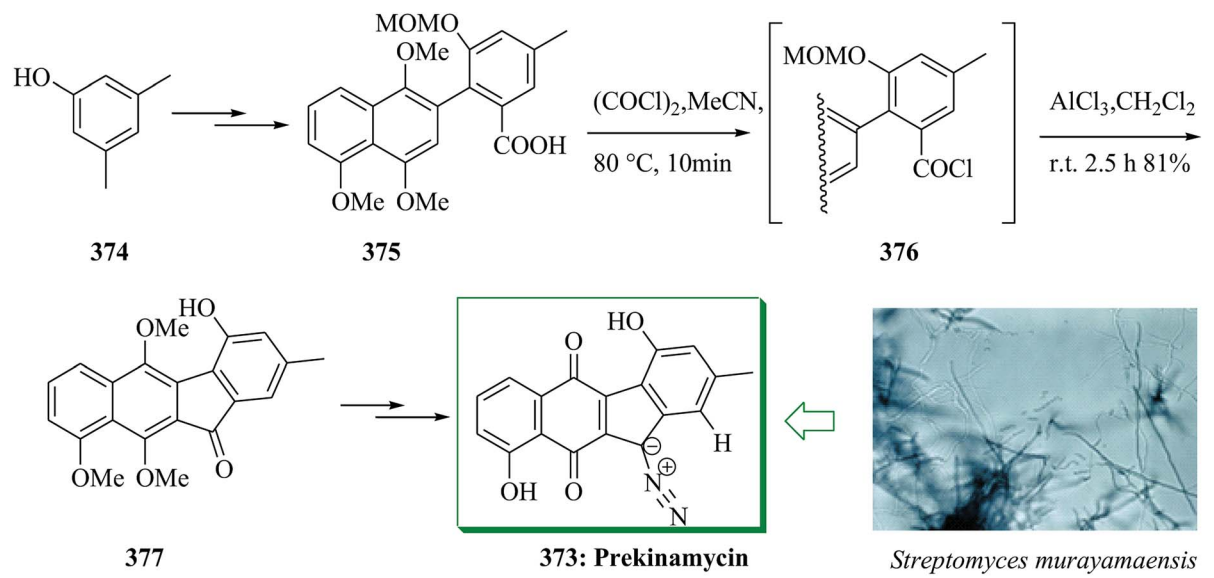
The trikentrins **382** and **384** were extracted from the marine sponge *Trikentrion flabelliforme* by Capon[391] and exhibited antibacterial properties. In a concise total synthesis of (+)-*cis*-trikentrin A, initially 4-ethyl-7-vinylindole underwent nickel(II)-mediated enantioselective hydrovinylation to afford the desired 2-but-3-enyl derivative **384a** in excellent yield (99%) and high *ee* (96%). Compound **384a** was converted into the corresponding carboxylic acid **385a** in several steps. The latter was subjected to an intramolecular FC reaction and a Wittig reaction affording the *exo*-methylene compound **387a** in about 70% yield from the acid **385a**. Subsequently, compound **387a** was converted into the natural product (+)-*cis*-trikentrin **382** after several steps. Noticeably, synthesis of a more complex natural product, (+)-*cis*-trikentrin B, demonstrates the application of the hydrovinylation product, **384b**, and a late-step functionalization of a 6,8-dimethylcyclopent[*g*]indole nucleus. Employing the aforementioned protocol, **384b** was transformed into (+)-*cis*-trikentrin-B **383** after several steps (Scheme 81).[392]

Amaryllidaceae isocarbostyril alkaloids have been attractive synthetic targets for organic synthetic chemists during the last two decades.[393,394] The isolation of *trans*-dihydronarciclasine **388** from the Chinese medical plant *Zephyranthes candida* was

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Scheme 78 Total synthesis of diptoindonesin G **366**.



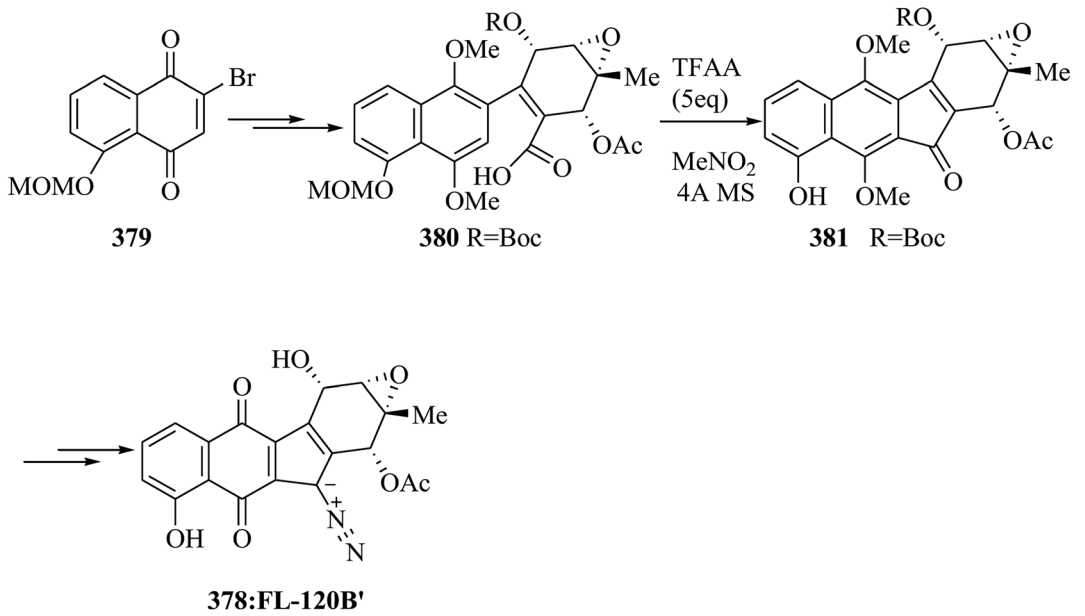
Scheme 79 Total synthesis of prekinamycin **373**.

demonstrated in 1990.[395] An extremely enantioselective and effective total synthesis of *trans*-dihydronarciclasine **388** in an entirely substrate-controlled strategy from easily accessible chiral starting materials was developed in which the desired target **388** was obtained in 16% overall yield. The total synthesis of *trans*-dihydronarciclasine **388** was commenced by preparing triacetate **390** from the enantiomerically enriched allylic alcohol **389** *via* several steps. Using 1.1 equivalents of Tf_2O and 1.5 equivalents of 2-chloropyridine, and heating at 35 °C, the product **392** was obtained with very high regioselectivity (12.5 : 1) and in 76% yield. After two steps, the desired target (+)-**388** was obtained (Scheme 82).[396]

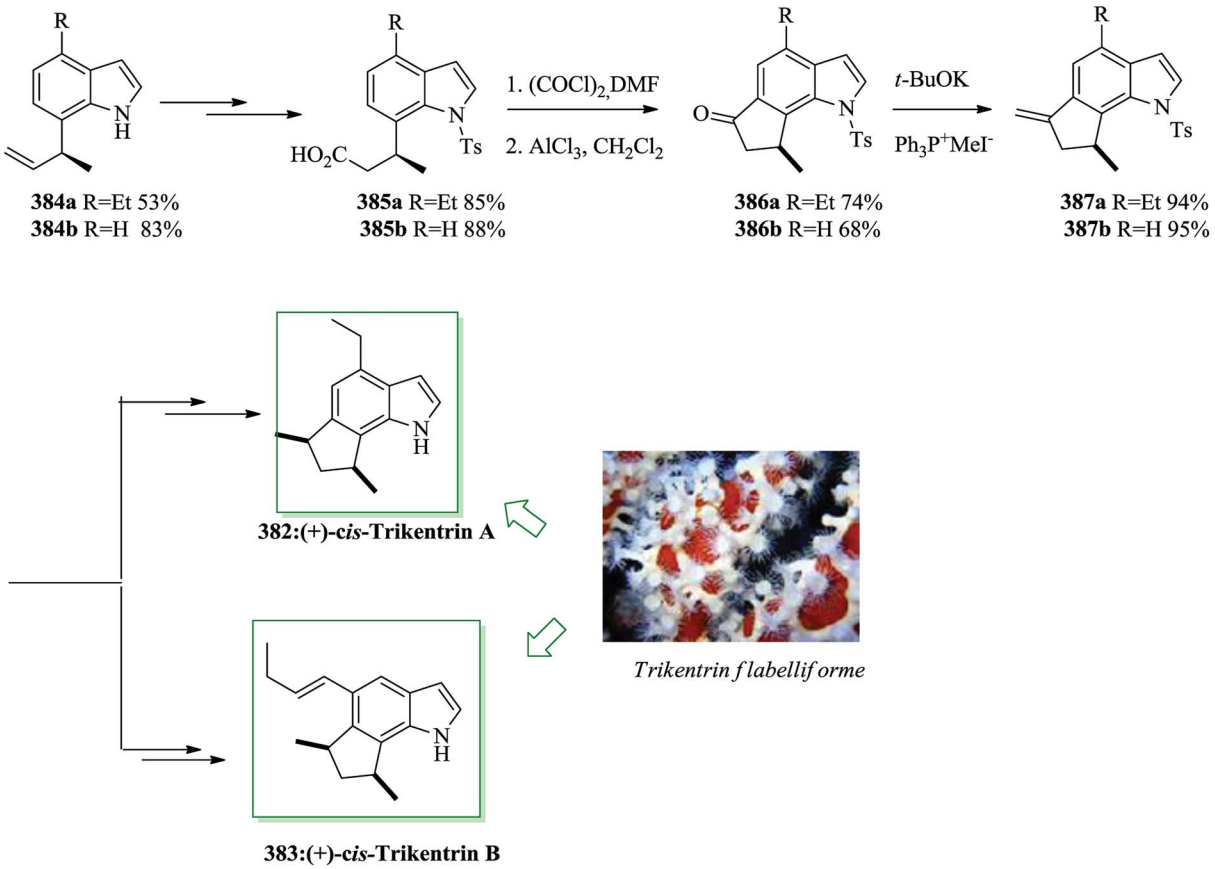
Colchicine,[397,398] extracted from *Colchicum autumnale*, is a cytostatic drug that strongly binds to tubulin, the main constitutive protein of microtubules.[399] Colchicine and its structural analogues, for example allocolchicine[400] and combretastatin A-4,[401] symbolize promising lead structures for the development of new anticancer agents addressing the colchicine binding site of tubulin.[402,403] and 5,6,7-trimethoxy-4-(1-methyl-1*H*-indol-6-yl)-2*H*-chromen-2-one,[404] respectively that were known to prevent microtubule assembly *in vitro* at nanomolar concentrations. Schmalz and co-workers in 2012 provided a unique group of indole-comprising allocolchicine analogues. Using 3,4,5-trimethoxy-phenylpropionic acid **394**,

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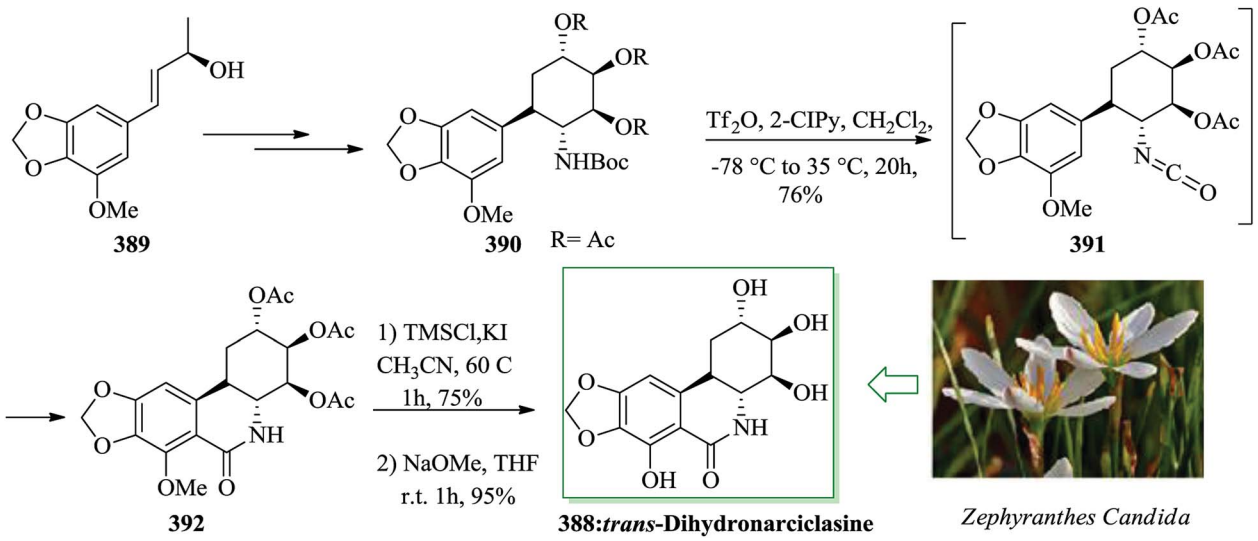
Scheme 80 Total synthesis of FL-120B′ **378**.



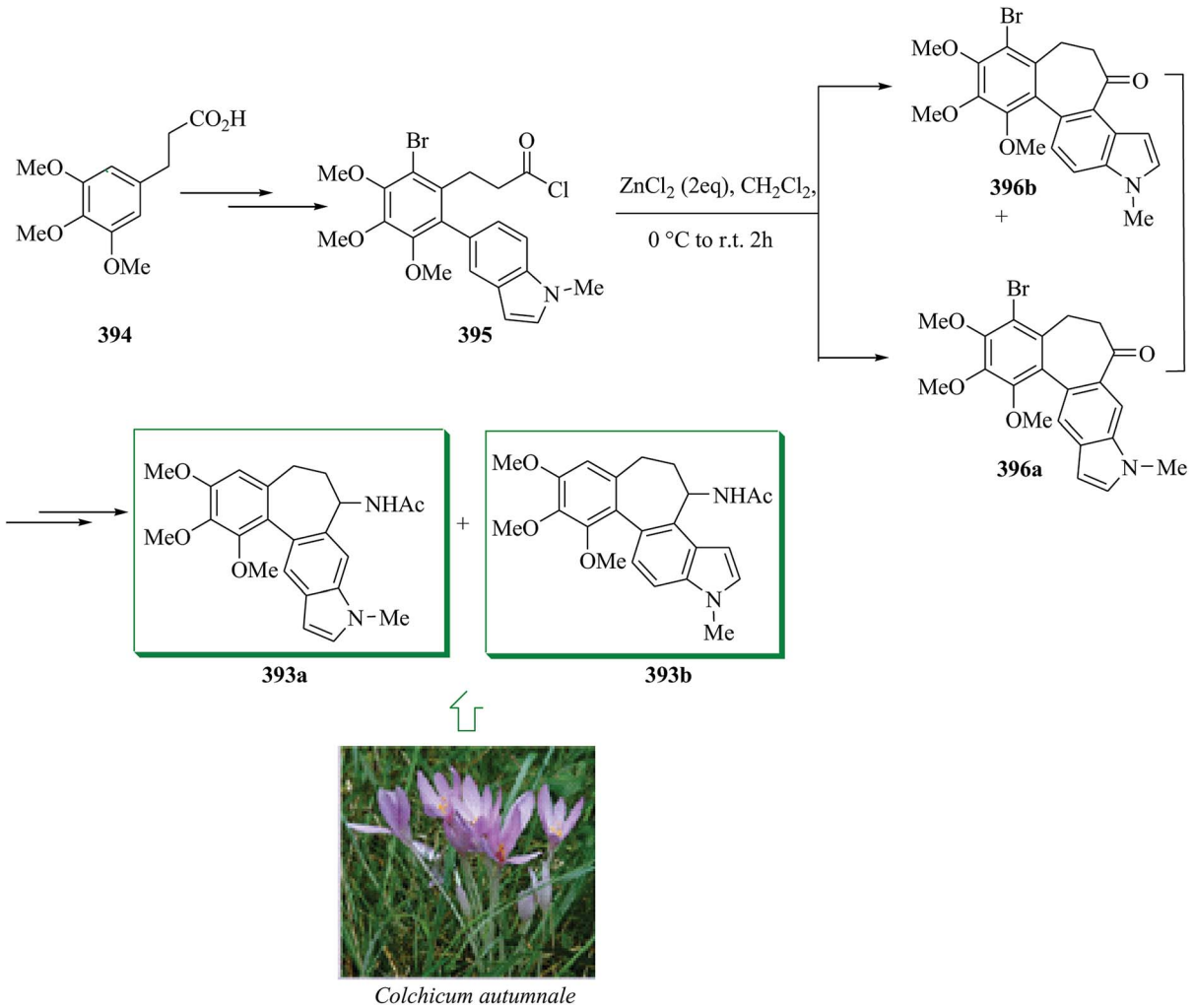
Scheme 81 Total synthesis of (+)-*cis*-trikentrin **382** and (+)-*cis*-trikentrin-B **383**.

the target compounds *rac*-**393a** and *rac*-**393b** were obtained in 11 steps with overall yields of 14% and 3%, respectively, through a Suzuki cross-coupling reaction and a FC cyclization reaction as the key carbon–carbon bond-forming reactions. Firstly, 3,4,5-trimethoxyphenylpropionic acid **394** afforded a clear solution including acid chloride **395** upon several steps.

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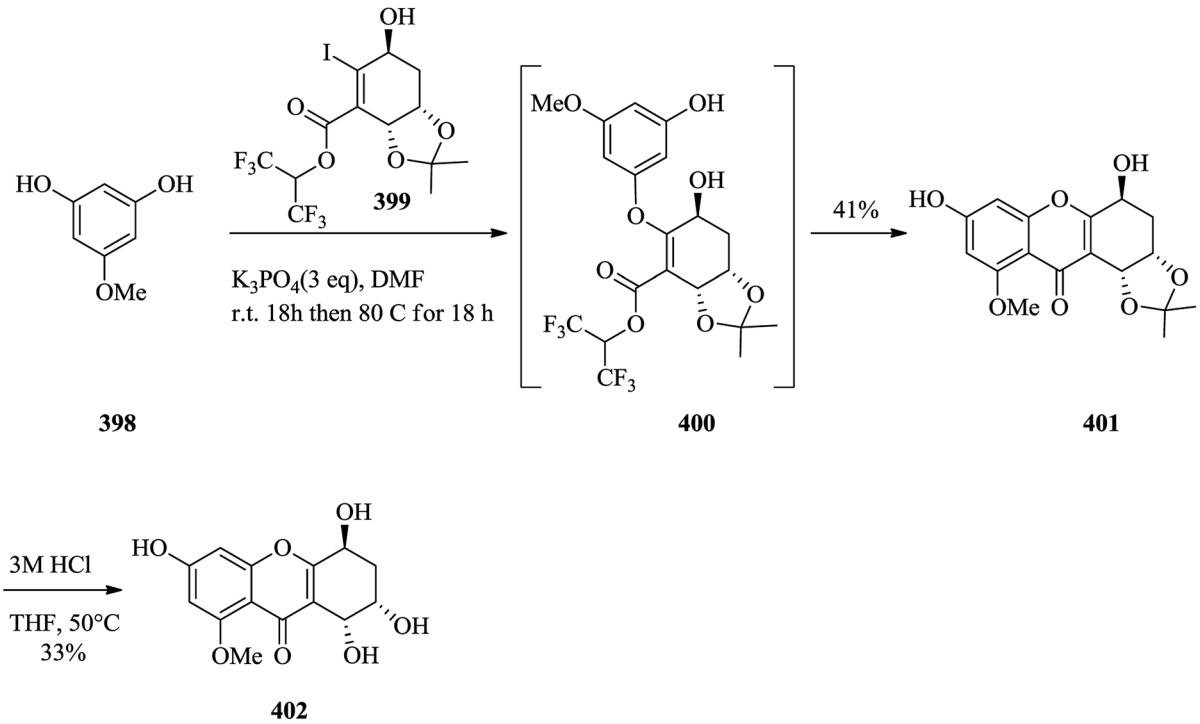
Scheme 82 Total synthesis of *trans*-dihydronarciclasine **388**.



Scheme 83 Total synthesis of allocolchicinoids *rac*-**393a** and *rac*-**393b**.

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Scheme 84 The formation of the simplified kibdelone tetrahydroxanthone analogue **402**.

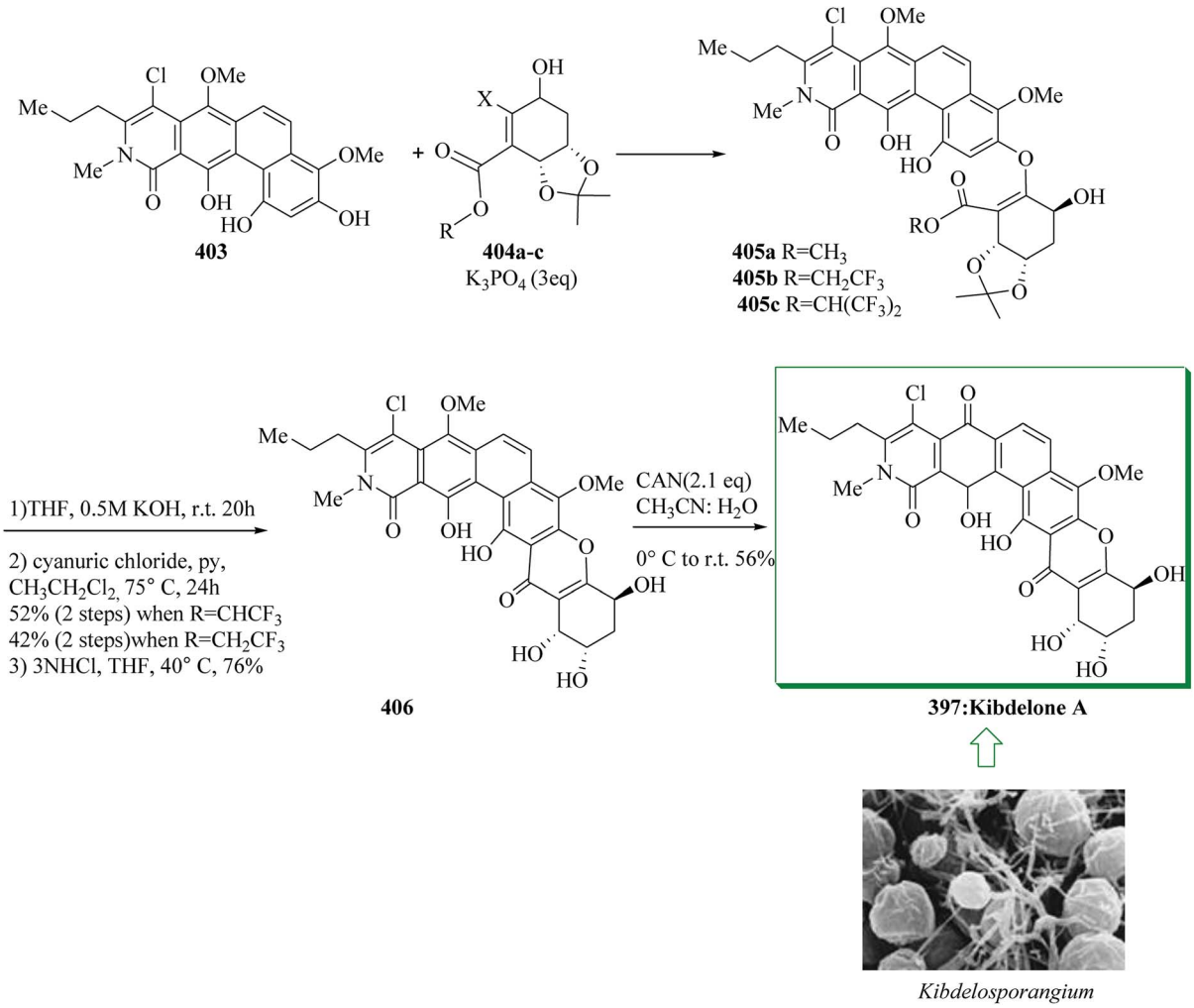
In a first attempt to induce the projected FC cyclization, $ZnCl_2$ was added to a crude solution of **395** in dichloromethane at ambient temperature. The corresponding ketones **396a** and **396b** were obtained in merely 5% yield (as a 4 : 1 mixture). Finally, compounds **396a** and **396b** provided the indole-obtained allocolchicinoids *rac*-**393a** and *rac*-**393b**, respectively, after several steps (Scheme 83).[405]

The kibdelones are a unique group of bioactive heterocyclic polyketides provided by a rare soil actinomycete, *Kibdelosporangium* sp. (MST-108465). Significantly, kibdelones A–C were found to be active at low nanomolar concentrations against tumor cell lines.[406] The total synthesis of kibdelone A **397** was achieved through In(III)-mediated arylation of a heterocyclic quinone monoketal and iodine-catalyzed oxidative photochemical electrocyclization. A one-pot oxa-Michael/FC method was tried using monomethoxy phloroglucinol **398**[407] to produce the first simplified analogues of kibdelones. Under the optimal conditions, using the extremely activated HFIP ester **399** resulted in the finding that tetrahydroxanthone construction based on basic conditions was possible in a one-pot method, avoiding extraction of the acid- and heat-sensitive vinylogous carbonate **400**. Furthermore, the oxa-Michael reaction progressed in a site-selective manner at ambient temperature; however, the FC cyclization reaction needed heating to 60 °C using K_3PO_4 to provide tetrahydroxanthone **401** in 41% yield. The usage of base was needed for the FC cyclization reaction by the isolation of vinylogous carbonate **400** and its subsequent thermolysis in dimethylformamide (60 °C), which was shown to be unsuccessful. Final deprotection of **401** gave the simplified kibdelone tetrahydroxanthone analogue **402** (Scheme 84).[408]

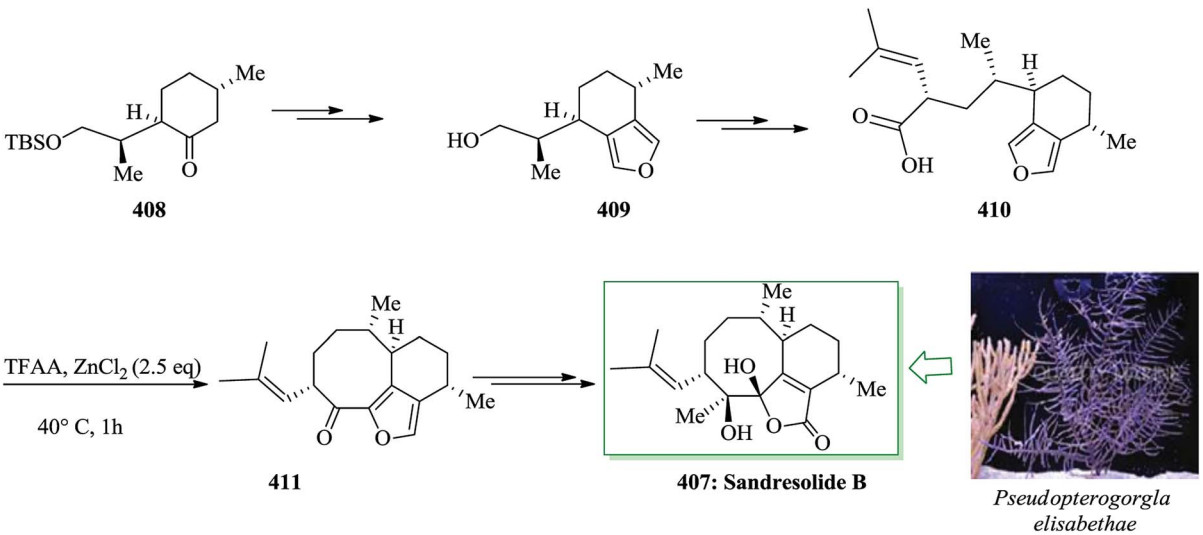
Then, total synthesis of the triol unit of kibdelone A **397** was examined. The reaction of **403** and **404a–c** gave the corresponding products **405a–c**. Additional FC cyclization was explored employing a one- or two-pot method with the naturally occurring compounds **405a–c** based on thermal, Lewis acid--mediated, and *N*-methylimidazole-improved conditions; however, in these cases merely initiating material, aromatized F-ring, or retro-Michael products were detected. Cyclization reaction was accomplished employing a two-step sequence through saponification/cyanuric chloride activation of vinylogous carbonates **405b** and **405c** in 52% and 42% yield over two steps, respectively. Lastly, deprotection of the acetonide scaffold of the F-ring and oxidation reaction of the B-ring employing ceric ammonium nitrate (CAN) in H_2O/acetonitrile gave kibdelone A **397** in moderate yield (Scheme 85).[408]

The Caribbean octocoral *Pseudopterogorgia elisabethae* is a chemically prolific species that has attracted the attention of scientists.[409] Sandresolide B **407**[410–412] was first reported in 1999.[413] The total synthesis of the diterpenoid sandresolide B from a common furan framework was achieved and reported in 2013 by Trauner and co-workers. Key stages contain Pd-catalyzed carbonylation, lanthanide mediated ring closure, Myers alkylation reaction, intramolecular FC acylation, photooxygenation, and a Kornblum–DeLaMare rearrangement.[414] Total synthesis of **407** was started from ketone **408**, which was converted into compound **409** upon several steps. Next, compound **409** afforded acid **410** upon several steps. Using the key acid **410**, the seven-membered ring of the sandersolides was provided through an intramolecular FC acylation reaction. Activation of the acid with trifluoroacetic anhydride followed by

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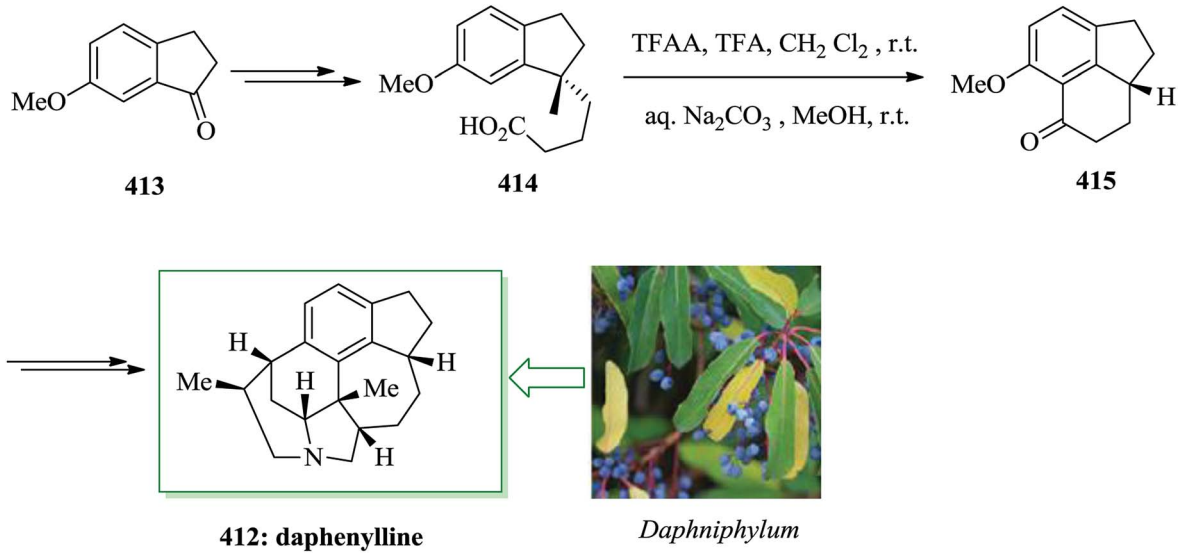
Scheme 85 Total synthesis of kibdelone A **397**.



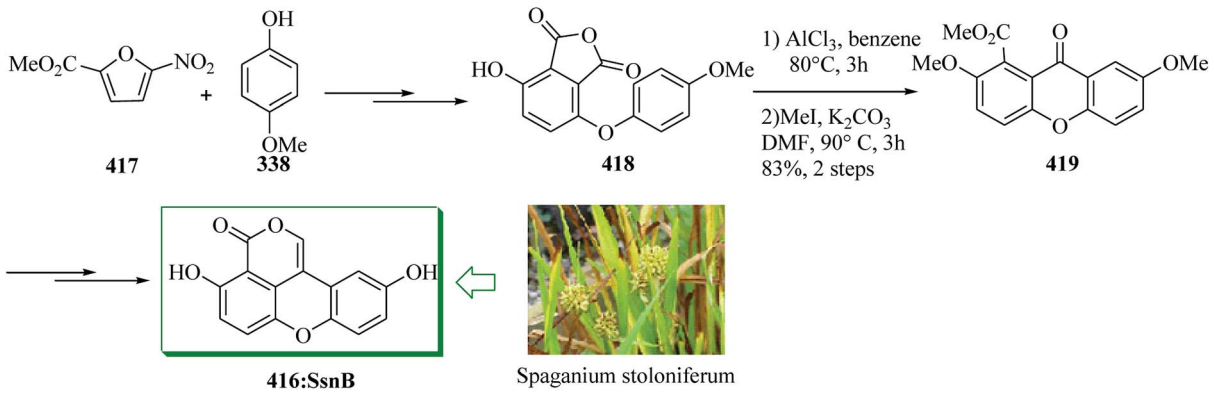
Scheme 86 Total synthesis of sandresolide B **407**.

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Scheme 87 Total synthesis of daphenylline **412**.



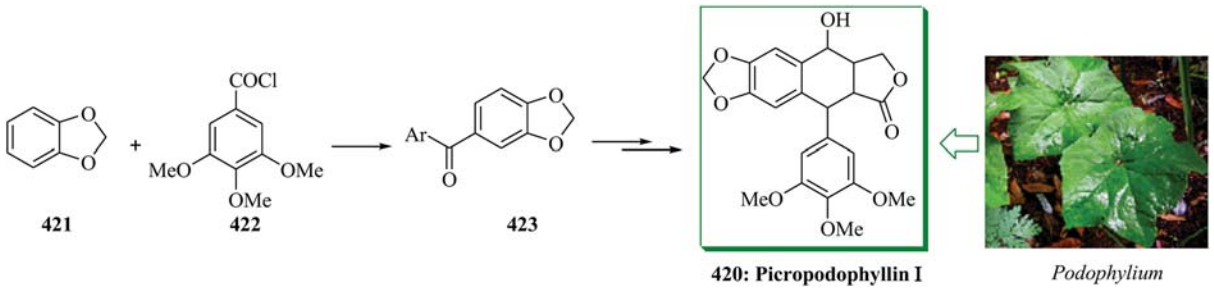
Scheme 88 Total synthesis of sparstolonin B (SsnB) **416**.

gentle heating with zinc chloride afforded the corresponding product **411**. It should be mentioned that short reaction times and stoichiometric $ZnCl_2$ were key to this ring closure. Finally, sandresolide B, **407**, was obtained from **411** in 51% yield over two seps (Scheme 86).[414]

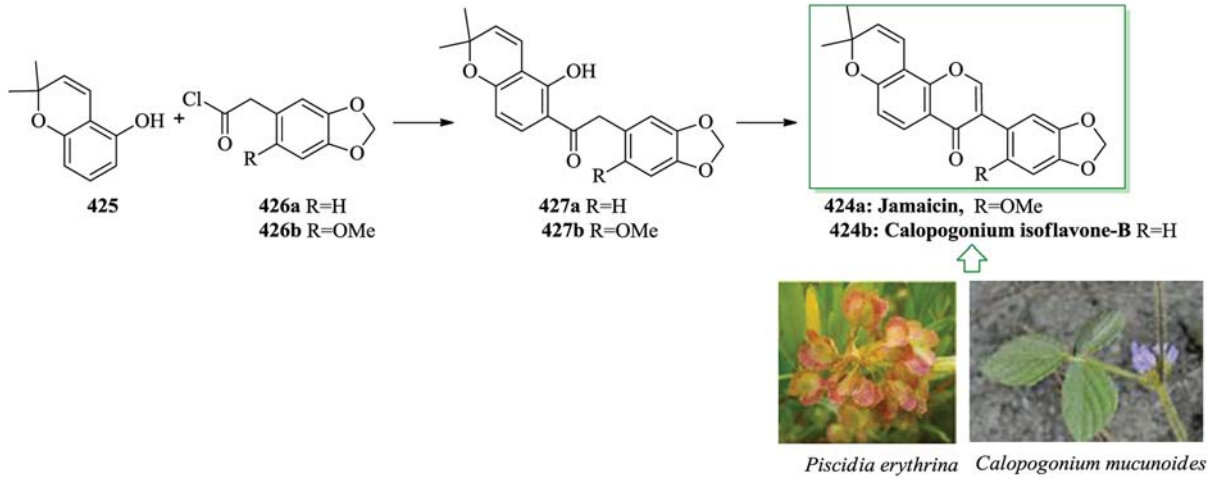
Daphenylline **412**, extracted from the fruit of *Daphniphyllum longeracemosum* by Hao and co-workers in 2009, is the first member of the *Daphniphyllum* alkaloids that includes a benzene ring in the unit structure.[415] Daphenylline contains a rearranged 22-norcalyciphylline A type framework,[416] the highly fused hexacyclic system of which has generated significant interest in the chemical community. Total synthesis of (−)-daphenylline, a hexacyclic *Daphniphyllum* alkaloid, was accomplished in 2016 by Fukuyama and co-workers.[417] In this approach, an asymmetric Negishi coupling reaction, an intramolecular FC reaction, Sonogashira coupling and Claisen rearrangement are considered as key steps. Total synthesis of (−)-daphenylline **412** was initiated from 6-methoxyindan-1-one **413**, which was converted into carboxylic acid **414** after several steps. Next, an intramolecular FC reaction of **414** was achieved by reaction with trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) to provide cyclic ketone **415**. Finally, daphenylline **412** was obtained after several steps (Scheme 87).[417]

In 2010, sparstolonin B (SsnB) **416** was first extracted from the Chinese herb *Spaganium stoloniferum* by Liang *et al.*[418] In 2015, Sun and co-workers reported that sparstolonin B can prevent high-fat-diet-induced obesity in rats, and also prevents LPS-induced production of MCP-1, interleukin-6, and tumor necrosis factor-α in 3T3-L1 adipocytes.[419] Shibata and co-workers in 2017 developed a unique method for the syntheses of sparstolonin B (SsnB) **416** with an overall yield of 38% over 10 steps from the affordable, market-accessible initiating precursor methyl 5-nitro-2-furoate. In this method, Diels–Alder reaction and intramolecular FC reaction were found as the key steps. Total synthesis of **416** was started with aromatic substitution of methyl 5-nitro-2-furoate with sodium 4-methoxybenzenolate as a nucleophile to afford the cyclic anhydride **419** in 95% yield. The intramolecular FC reaction of anhydride **419** in benzene afforded a mixture of the corresponding ester **420** and a side-product **420b**, provided *via* elimination of an *O*-

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Scheme 89 Total synthesis of picropodophyllin **420**.



Scheme 90 Total synthesis of jamaicin **424a** and calopogonium isoflavone-B **424b**.

of sparstolonin B (SsnB) **416** with an overall yield of 38% over 10 steps from the affordable, market-accessible initiating precursor methyl 5-nitro-2-furoate. In this method, Diels–Alder reaction and intramolecular FC reaction were found as the key steps. Total synthesis of **416** was started with aromatic substitution of methyl 5-nitro-2-furoate with sodium 4-methoxybenzenolate as a nucleophile to afford the cyclic anhydride **419** in 95% yield. The intramolecular FC reaction of anhydride **419** in benzene afforded a mixture of the corresponding ester **420** and a side-product **420b**, provided *via* elimination of an *O*-methyl substituent.[420] Without more purification, reaction of the product mixture with iodomethane afforded intermediate **420** in 83% yield over two steps. Lastly, compound **420** gave sparstolonin B (SsnB) **416** upon several steps (Scheme 88).[421]

2.4. Intermolecular acylation

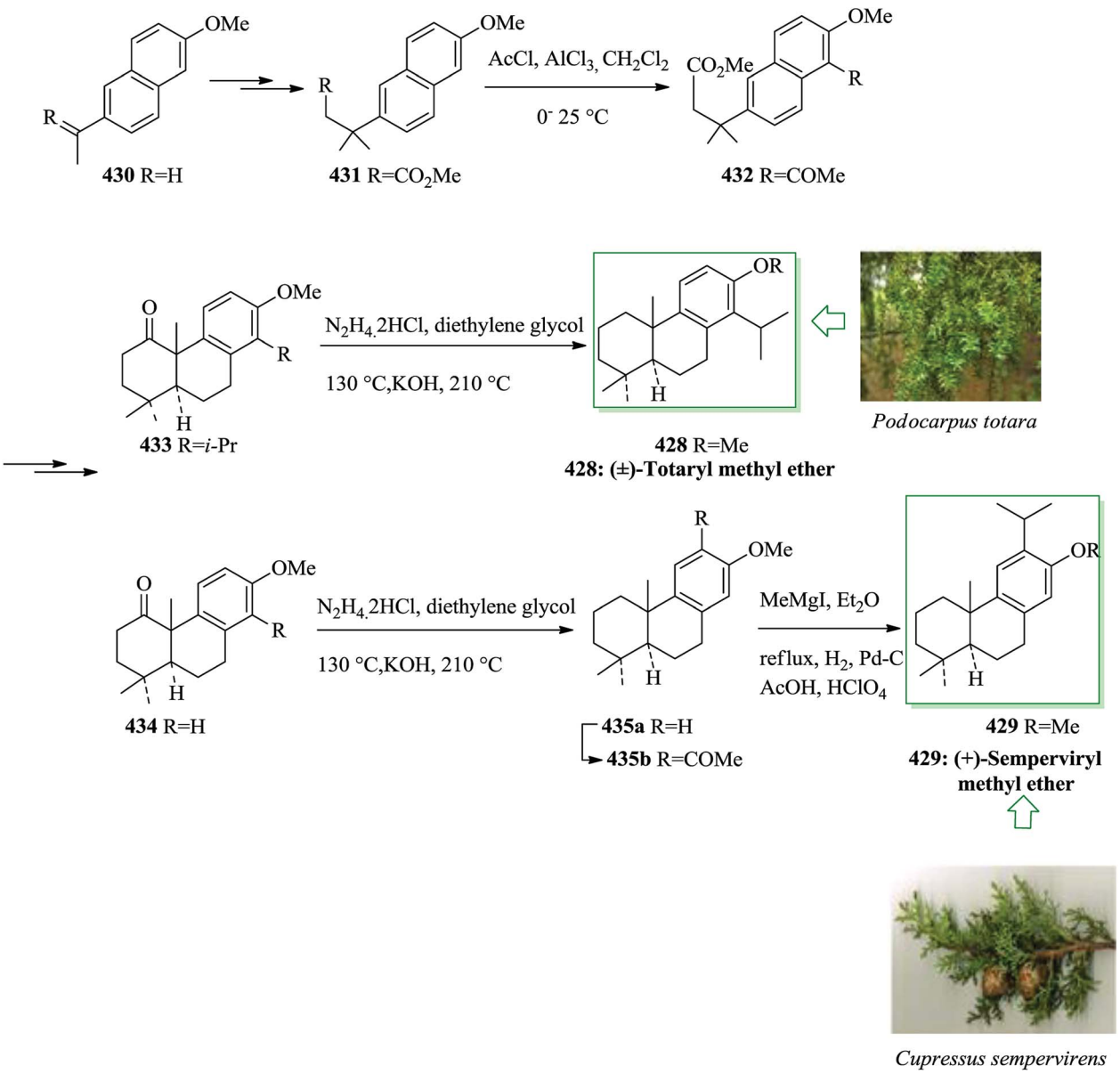
The lignan lactone picropodophyllin **420** has been obtained from various species of *Podophyllum*.[422,423] Gensler and co-workers demonstrated total synthesis of picropodopyllin. Initially, 3, 4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone **422** was synthesized from the FC reaction between methylenedioxybenzene **421** and trimethoxybenzoyl chloride **422**. Subsequently, compound **423** provided picropodophyllin **420** after several steps (Scheme 89).[424]

Isoflavones[425] are the most abundant subset of the flavonoid group of compounds, which also includes pterocarpans, rotenoids,[426] and coumestans.[427] Structurally, isoflavones are highly functionalized and oxygenated derivatives of 3-phenylchromans. Jamaicin **424a** has been extracted from *Piscidia erythrina* bark root.[428] Calopogonium isoflavone-B **424b** was extracted from ether extracts of *Calopogonium mucunoides* seeds. The FC acylation reaction has been examined on various acid-sensitive substrates. Based on the proper conditions of changing Lewis acids, solvents, and reaction temperatures, the acylation indeed occurred, therefore obviating the necessity for functional group protection-deprotection sequences. By the use of these methods, the naturally occurring isoflavones jamaicin **424a** and calopogonium isoflavone-B **424b** have been obtained. Jamaicin **424a** and calopogonium isoflavone-B **424b** have been obtained from the deoxybenzoin systems **427b** and **427a**, respectively, by any of a wide range of excellent formylation methodology.[429,430] These crucial and sensitive deoxybenzoins were synthesized directly *via* the FC acylation reaction between 2,2-dimethyl-5-hydroxychrom-3-ene **425** and a homologated piperonal-**426a** or sesamol-**426b** obtained acid halide (Scheme 90).[431]

The tricyclic diterpenes sempervirol and totarol incorporate a *trans*-fused octahydrophenanthrene core as the basic carbocyclic scaffold. Totarol includes a modified abietane framework and has been extracted as a major constituent of the heartwood

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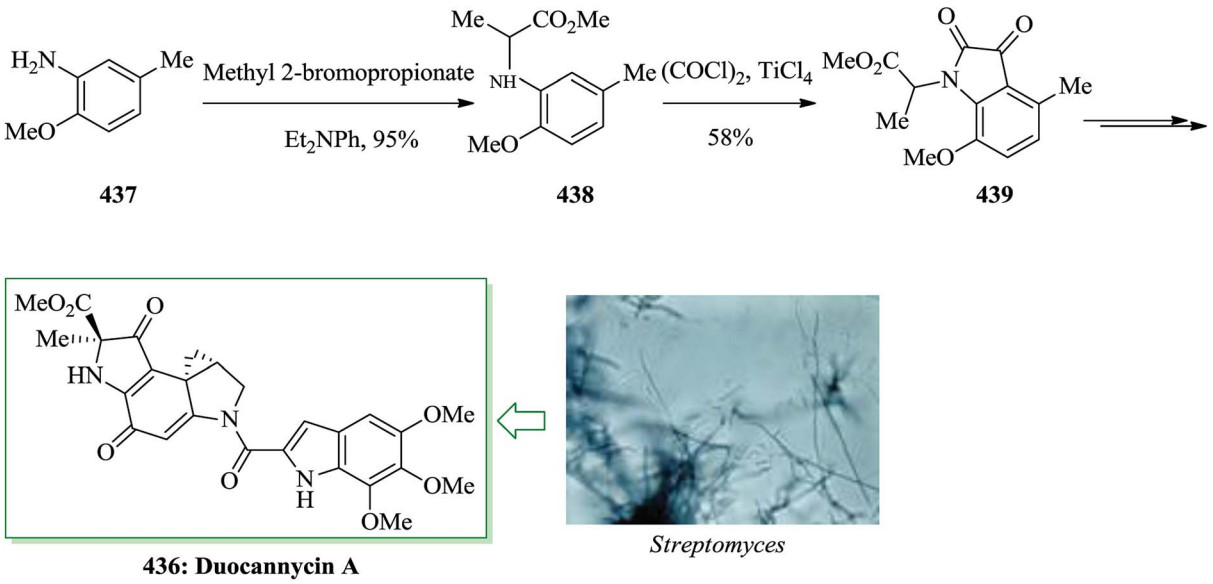
Scheme 91 Total synthesis of (±)-totaryl methyl ether **428** and (+)-semperviryl methyl ether **429**.

methoxynaphthalene afforded[435] a mixture of 6-acyl and 1-acyl derivatives. Compound **432** provided the *trans*-fused ketones **434** and **433** *via* several steps. Huang–Minlon reduction[436] of **433** gave (+)-totaryl methyl ether **428** in 84% yield. An analogous reduction of the ketone **434** provided octahydrophenanthrene **435a**. FC acylation reaction between **435a** and AcCl using tin(IV) chloride gave the methyl ketone **435b** as the only product in 80% yield. Reaction of **435b** with MeMgI and catalytic hydrogenolysis of the resulting carbinol in acetic acid with a few drops of perchloric acid gave (+)-semperviryl methyl ether **429** in 80% yield (Scheme 91).[434]

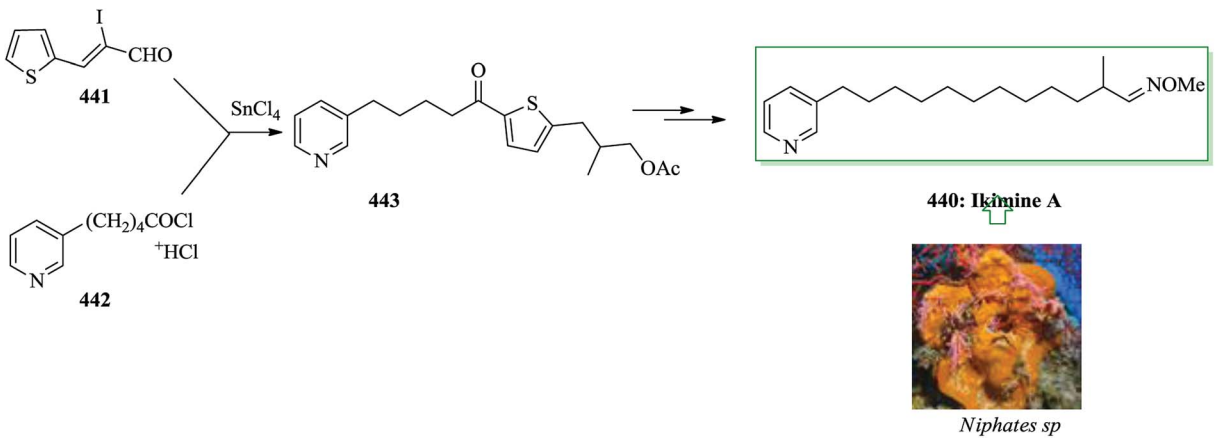
Duocannycin A **436** [437–439] extracted from *Streptomyces* sp. was found to be an enormously active antitumor antibiotic that is effective against several strains of experimental cancer cell lines. Total synthesis of **436** was accomplished using methoxycarbonylation of the C_4-position of the 5-aminoindoline by way of the isatin and subsequent Dieckmann cyclization to the methyl 2-methylindoxyl-2-carboxylate as key steps. Total synthesis of **436** was started from 6-methoxy-3-methylaniline **437**. Next, one carbon unit was introduced effectively using isatin derivative **439** obtainable *via* the FC reaction of *N*-alkyl derivative **438** with oxalyl chloride. Finally, compound **439** was converted into *dl*-**436** after several steps (Scheme 92).[440]

Ikimine A has been extracted from *Niphates* sp.[441] The cytostatic ikimine A **440** was synthesized *via* acylation of 2-methyl-3-(2-thiophene)-L-propylacetate **441**, reductive de-sulfurization, and functional group transformation to methyl branched racemic and nonracemic chiral 3-alkylpyridines. $SnCl_4$ mediated the acylation reaction between 2-methyl-3-(2-thiophene)-L-propylacetate **441** and the acid chloride **442** to afford the ketone

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Scheme 92 Total synthesis of duocannycin A **436**.



Scheme 93 Ikimine A (α-methyl-3-pyridinedodecanal-*O*-methyloxime) **440**.

443. Reaction with $TiCl_4$ or H_3PO_4 as FC catalysts or acylation reaction with *in situ* made acyl trifluoroacetates using phosphoric acid[442] afford lower yields. Lastly, compound **443** afforded ikimine A (α-methyl-3-pyridinedodecanal-*O*-methyloxime) **440** *via* several steps (Scheme 93).[443]

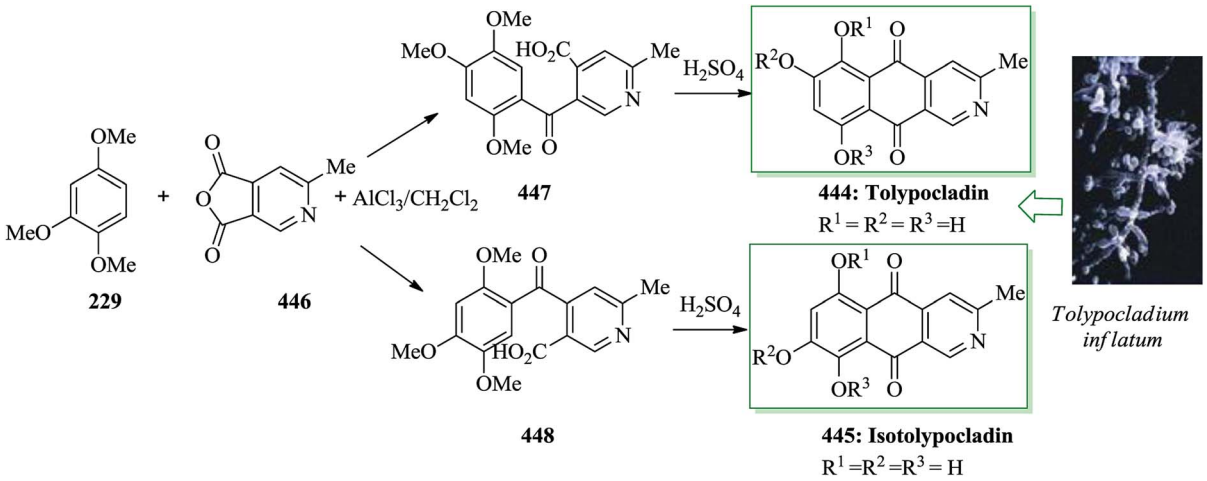
Tolypocladin **444** has been extracted from *Tolypocladium inflatum* DSM 915 and identified as 3-methyl-5,6(or 7),8-trihydroxy-2-aza-anthraquinone-(9,10).[444] Total synthesis of the microbial metabolite tolypocladin **444** and isomeric isotolypocladin **445** was developed through FC acylation reaction *via* the condensation of 2-aza-anthraquinone-(9,10) ring. The total synthesis was commenced by the reaction of 1,2,4-trimethoxy-benzene **229** and 2-methyl-pyridine 4,5-dicarboxylic acid anhydride **446** based on FC condition reactions. The resultant key products **447** and **448** can be separated though recrystallization. Therefore, cyclization and demethylation of the key products **447** and **448** using sulfuric acid afforded **444** (Scheme 94).[445]

(+)-Calanolide A,[446] initially extracted from the dried fruits and twigs of *Calophyllum lanigerum* var. *Austrocoriaceum*, is a non-nucleoside reverse transcriptase inhibitor currently in clinical trials as an anti-HIV agent. Zhang and co-workers in 2000 used an investigation method to perform the FC acylation reaction that was applied in the total synthesis of (+)-calanolide A **449**. A FC acylation reaction was applied to form 5,7-dihydroxy-4-propyl-8-propionylcoumarin **452** as a key intermediate for the formation of (+)-calanolide A. This reaction was performed by reacting 5,7-dihydroxycoumarin **450** with 1 equiv. of propionic anhydride aluminium chloride under reflux in dichloroethane (DCE). The optimal reaction conditions used 7 equiv. of aluminium chloride in 1.0 mL of nitromethane, with a predicted excellent yield (97%) (Scheme 95).[447]

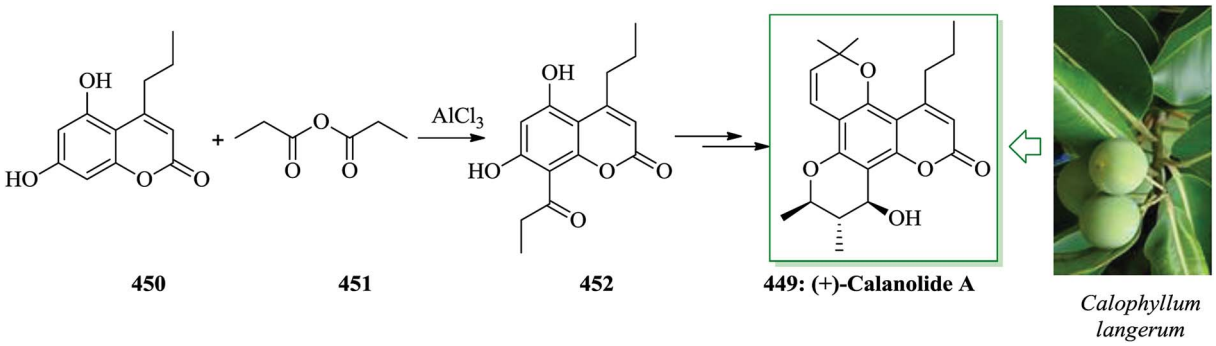
Kaempferol **453**[448,449] and other flavonoids have been found to be potential antitumor agents and human immunodeficiency virus (HIV) type 1 integrase inhibitors.[450] Kaempferol and its 3-*O*-glycoside derivatives were identified in several plants,

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Scheme 94 Total synthesis of tolypocladin **444** and isomeric isotolypocladin **445**.



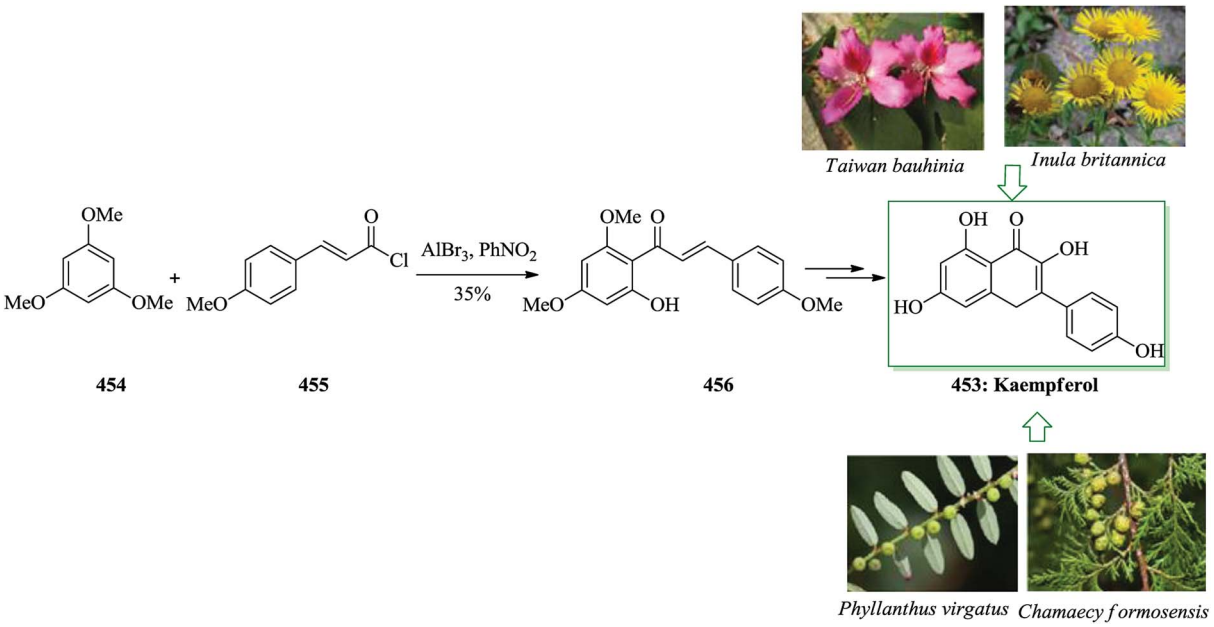
Scheme 95 Total synthesis of (+)-calanolide A **449**.

vegetables, fruits, and beverages, for example *Taiwan Bauhinia*,[451] *Chamaecyparis formosensis*,[452] *Inula britannica*,[453] French beans,[454] asparagus,[455] blueberries,[456] grape fruit juice,[457] teas,[458] and honey.[459] Kaempferol **453** was obtained in seven steps with 47% overall yield from 1,3,5-trimethoxybenzene **454**. Firstly, the FC reaction of trimethoxy benzene **454** and 4-methoxycinnamic acid chloride **455** with $AlBr_3$ as a catalyst provided *o*-hydroxychalcone **456** in 35% yield after several steps. Finally, compound **456** provided the corresponding product **453** upon several steps (Scheme 96).[460]

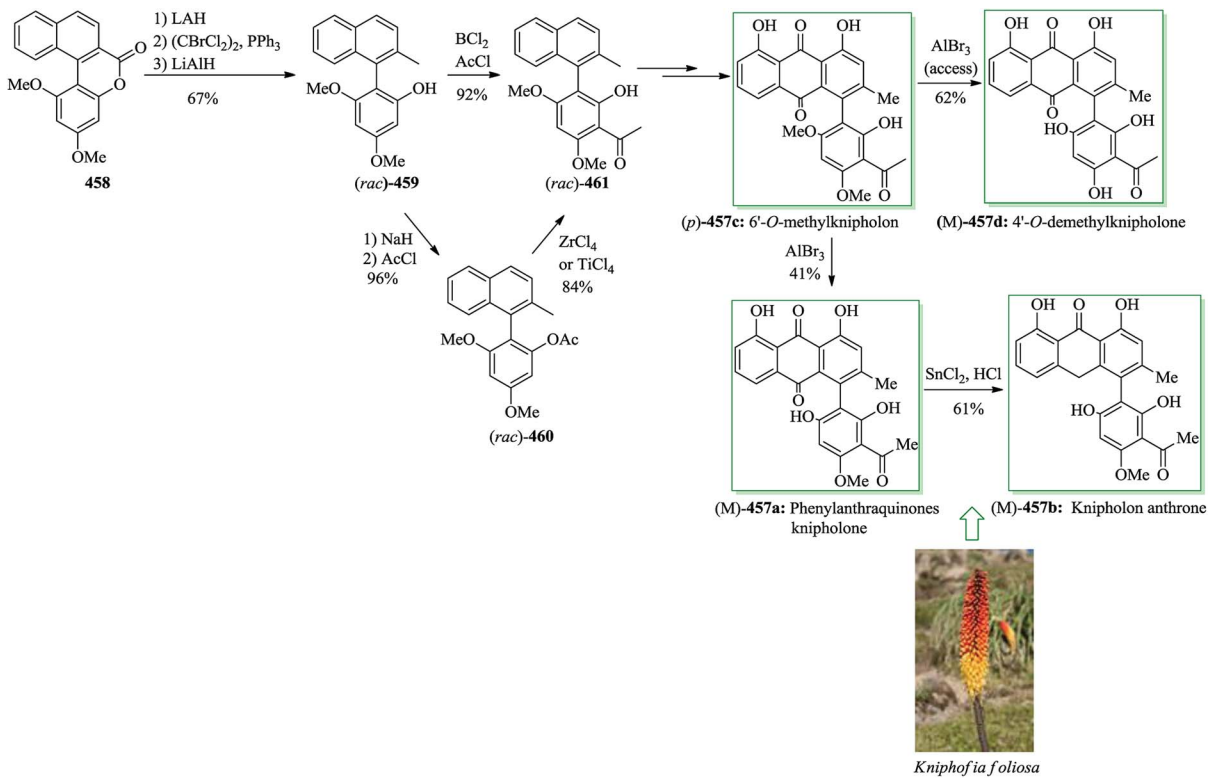
Several naturally occurring phenylanthraquinones, namely knipholone **457a**, knipholone anthrone **457b**, 6′-*O*-methylknipholone **457c** and 4′-*O*-demethylknipholone **457d**, demonstrated moderate to high antiplasmodial activity *in vitro* against *Plasmodium falciparum*,[461] the carrier of the most lethal malaria tropica. M-Knipholone **457a** has been extracted from *Kniphofia foliosa*.[462] Bringmann *et al.* in 2002 demonstrated the initial significant synthetic method toward natural knipholone-type phenylanthraquinones. Firstly, lactone **458** afforded the racemic biaryl **459**.[463] With this substrate, the introduction of the *C*-acetyl substituent succeeded both directly, *via* FC acetylation reaction, and in a two-step method, *via* an *ortho*-selective Fries reaction[464] on ester **461**, and afforded the *C*-acetyl compound **460** in moderate yields, without any removal of the methyl ether. Therefore, compound **460** afforded 6′-*O*-methylknipholone **457c**, the first natural phenylanthraquinone. Selective mono-*O*-demethylation of **457c** at C-6′ employing aluminium bromide afforded the target molecule knipholone **457a**, reduction of which afforded its anthrone **457b**. The fully *O*-demethylated derivative **457d** was obtained by employing aluminium bromide in excess (Scheme 97).[463]

The polycitones A **462** and B **463**, polybrominated pyrrole alkaloids, were extracted by Kashman *et al.*[465] from marine ascidians of the genus *Polycitor*. Polycitone A is an active inhibitor of retroviral reverse transcriptases and cellular DNA polymerases.[466] Polycitone B **463** was obtained in four steps from pyrrole dicarboxylic acid **464**, involving FC reaction of the desired acid chloride with anisole. The transformation of **462** into polycitone A **463** was accomplished in two steps through Mitsunobu alkylation of the pyrrolic NH group. Polycitone A was obtained in 18% overall yield and gave the probability of changing the groups on the pyrrole ring. This synthetic method was started from dicarboxylic acid **464**, which reacted with oxalyl chloride followed by elimination of the solvent and rigorous drying, which afforded the crude acid chloride **465.** Compound **465** was treated with anisole under FC reaction conditions to provide the diketone **466** in 66% yield. In the following, compound **466** afforded polycitone B **462** after

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Scheme 96 Total synthesis of kaempferol **453**.



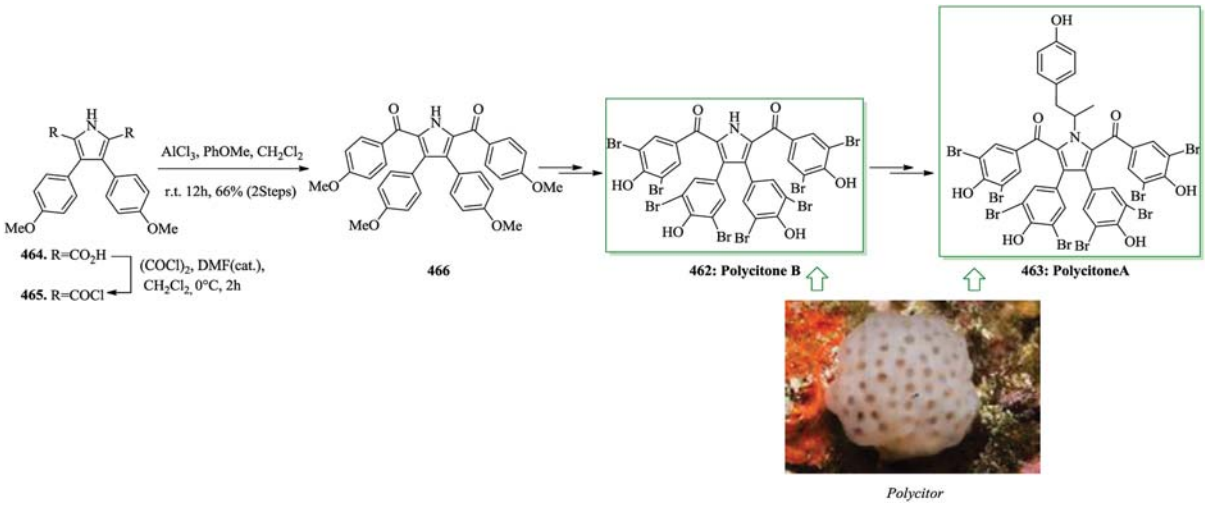
Scheme 97 Total synthesis of phenylanthraquinones knipholone **457a**, knipholone anthrone **457b**, 6′-*O*-methylknipholone **457c** and 4′-*O*-demethylknipholone **457d**.

several steps and then polycitone B **462** was transformed into polycitone A **463** after several steps (Scheme 98).[356]

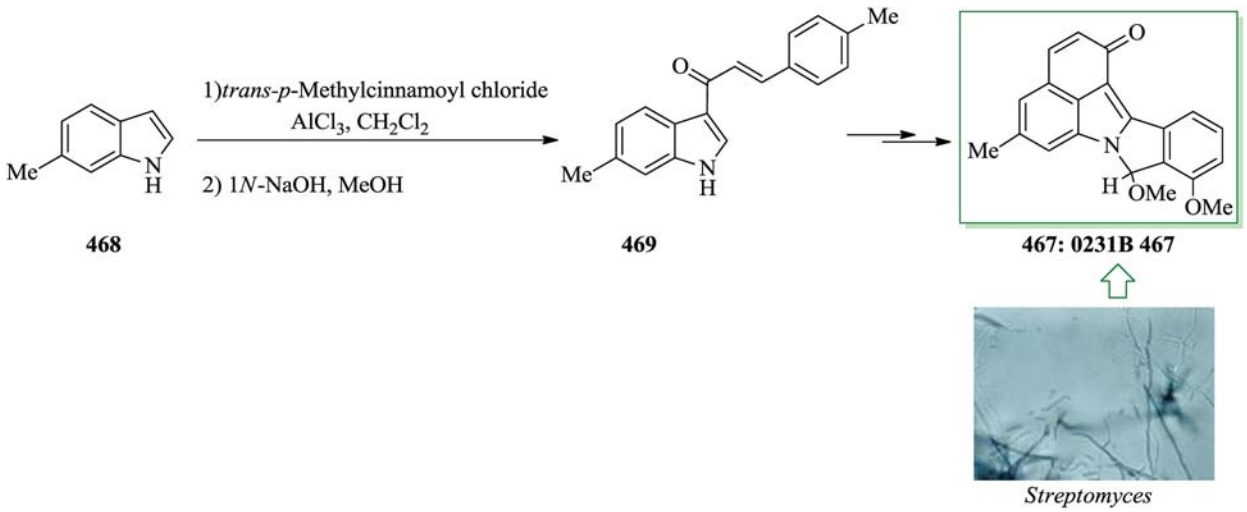
The unique inhibitors of 3α-hydroxysteroid dehydrogenase, 0231A and 0231B, have been extracted from a fermentation broth of *Streptomyces* sp. HKI0231.[467] These compounds are promising as lead structures for anti-inflammatory agents. 0231A and 0231B have a unique benz[*c*,*d*]indol-3(1*H*)-one scaffold in their molecules. Nakatsuka and co-workers in 2003

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Scheme 98 Total synthesis of polycitone B **462** and polycitone A **463**.



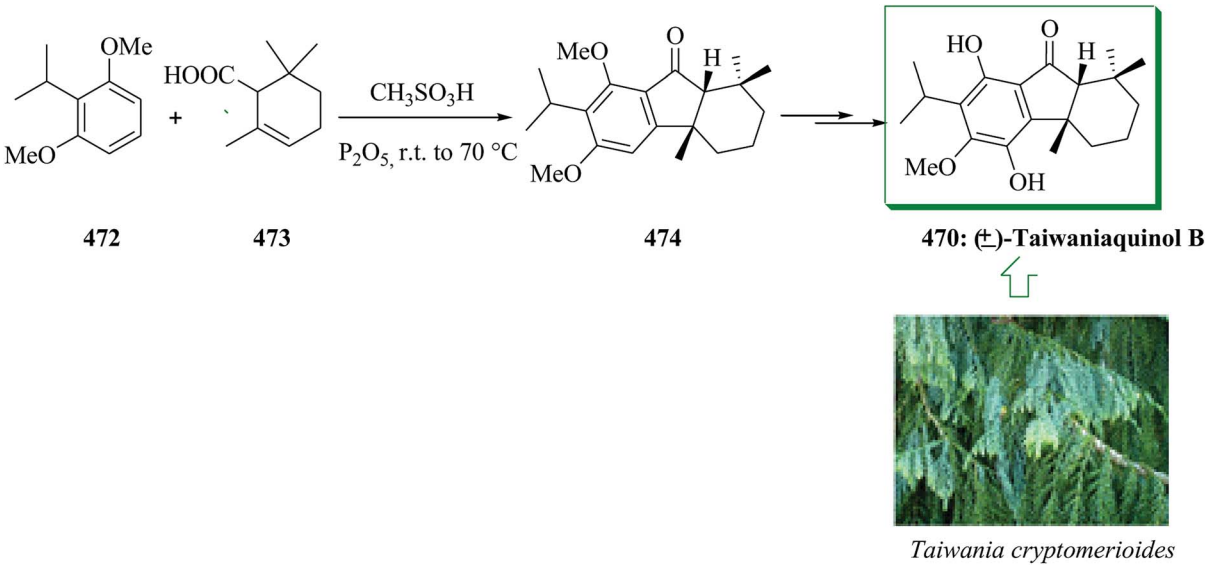
Scheme 99 Total synthesis of 0231B **467**.

conditions to provide the diketone **466** in 66% yield. In the following, compound **466** afforded polycitone B **462** after several steps and then polycitone B **462** was transformed into polycitone A **463** after several steps (Scheme 98).[356]

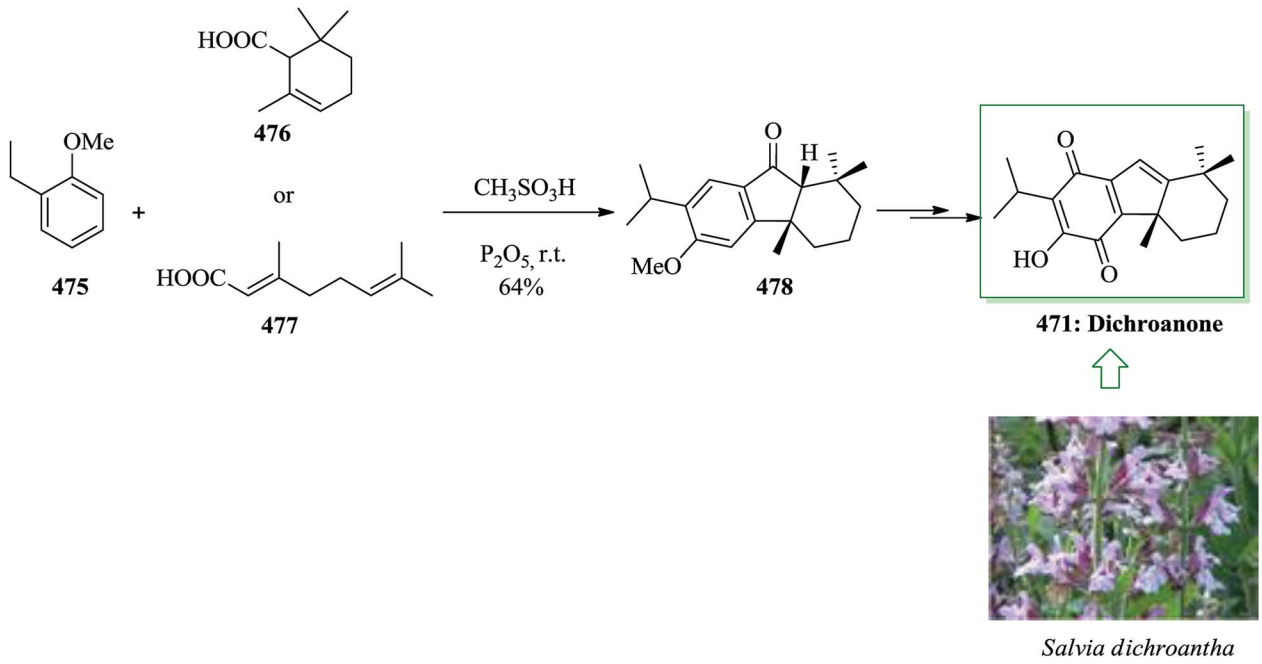
The unique inhibitors of 3α-hydroxysteroid dehydrogenase, 0231A and 0231B, have been extracted from a fermentation broth of *Streptomyces* sp. HKI0231.[467] These compounds are promising as lead structures for anti-inflammatory agents. 0231A and 0231B have a unique benz[*c*,*d*]indol-3(1*H*)-one scaffold in their molecules. Nakatsuka and co-workers in 2003 reported the synthesis of 0231B **467** in 10 steps (8.1% overall yield) from 6-methylindole **468**.[468] Upon masking the nitrogen with a pivaloyl group, the introduction of a *trans-p*-methylcinnamoyl group was achieved at the 3-position *via* FC acylation,[469] and subsequent de-protection of the pivaloyl group gave the *trans-p*-methylcinnamoyl derivative **469** in an 87% overall yield from **468**. Finally, compound **469** was converted into 0231B **467** upon several steps (Scheme 99).[468]

Various diterpenoids have the 4a-methyltetra- (and hexa-) hydrofluorene framework, for example, taiwaniaquinols A, B, and D and taiwaniaquinone D and H, as well as diverse structurally relevant diterpenoids. Dichroanone, dichroanal B, and standishinal were extracted from *Taiwania cryptomerioides*, *Salvia dichroantha* and *Thuja standishii*.[84,86,470] A significant acid-promoted domino FC acylation/alkylation reaction was known as the key step. Significantly, the formal total syntheses of diterpenoids (±)-taiwaniaquinol B **470** and (±)-dichroanone **471** were performed. Total synthesis of (±)-taiwaniaquinol B **470** was accomplished in 2008 by She and co-workers.[471] Total synthesis of **470** was accomplished from the reaction of 1,3-

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Scheme 100 Total synthesis of (±)-taiwaniaquinol B **470**.



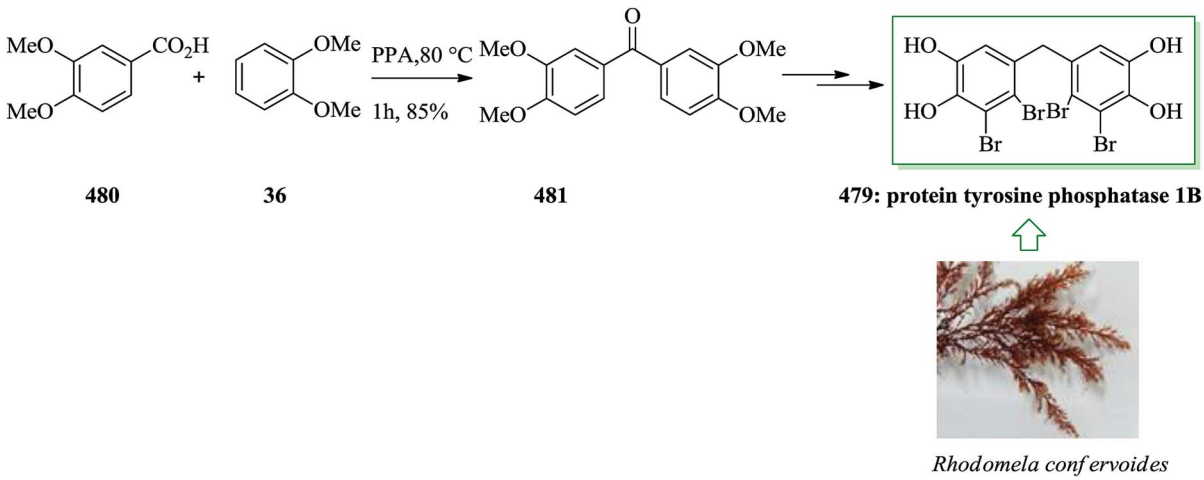
Scheme 101 Total synthesis of (±)-dichroanone **471**.

major isomer **478** was obtained by employing the domino FC acylation/alkylation reaction of compound **475** with geranic acid **477**, giving a 64% yield after purification by column chromatography. Finally, compound **478** afforded (±)-dichroanone **471** in several steps and its spectra were found to be identical with those formerly reported (Scheme 101).[86,471,472]

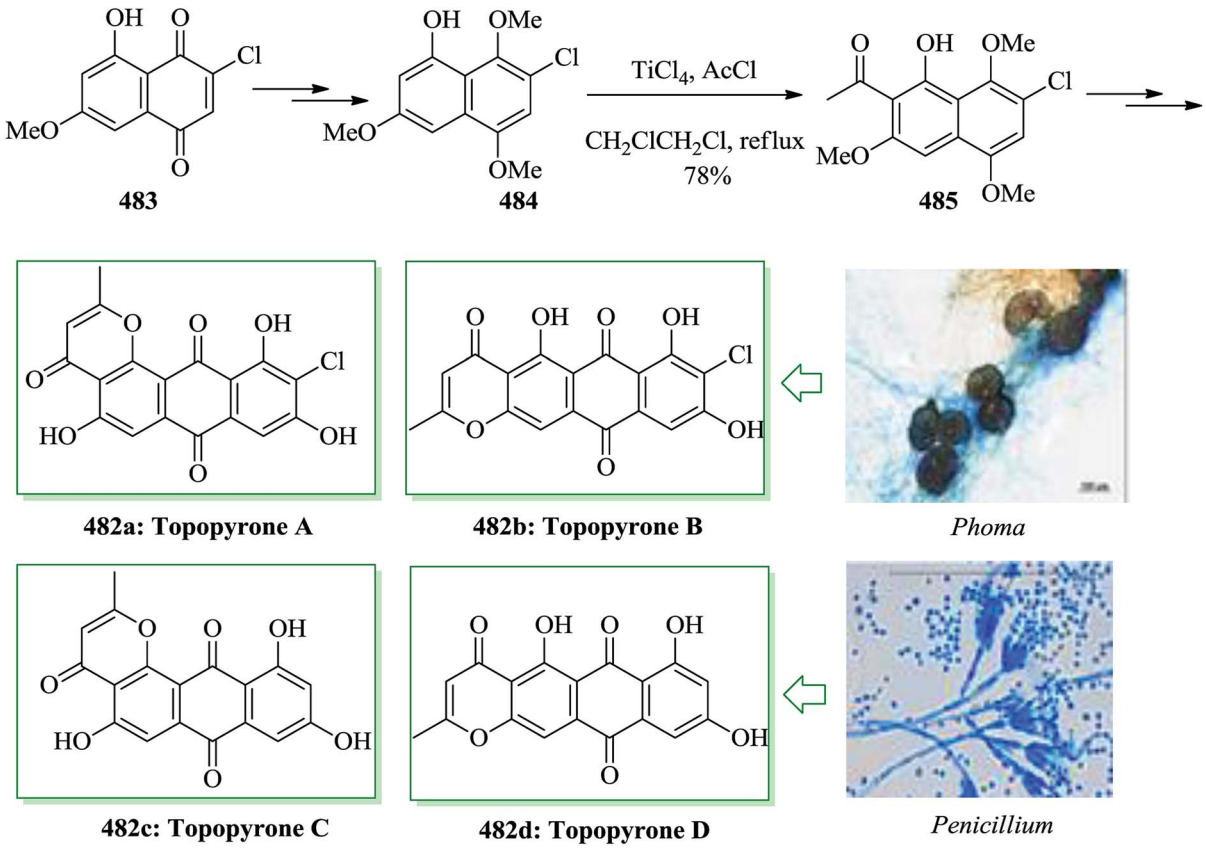
Protein tyrosine phosphatase 1B (PTP1B) has aroused intensive research interest because of its involvement in the insulin signaling cascade as a major negative regulator.[473] Bioassay-guided separation of the ethanol extract using a wide range of chromatographic techniques resulted in a series of bromophenols. One of them, named bis-(2,3-dibromo-4,5-dihydroxyphenyl)-methane, exhibited surprising inhibitory activity against PTP1B. Bis-(2,3-dibromo-4,5-dihydroxyphenyl)-methane **479**, which was extracted from red algae *Rhodomela confervoides*, was demonstrated as a natural bromophenol with important inhibition against PTP1B. Total synthesis of compound **479** was achieved with an overall yield of 24%. Initially, 3,4-dimethoxybenzoic acid **481** on reaction with 1,2-dimethoxybenzene **36** using polyphosphoric acid at 80 °C for one hour easily gave **481** in 85% yield.[474] Finally, compound **481**

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Scheme 102 Total synthesis of protein tyrosine phosphatase 1B (PTP1B).

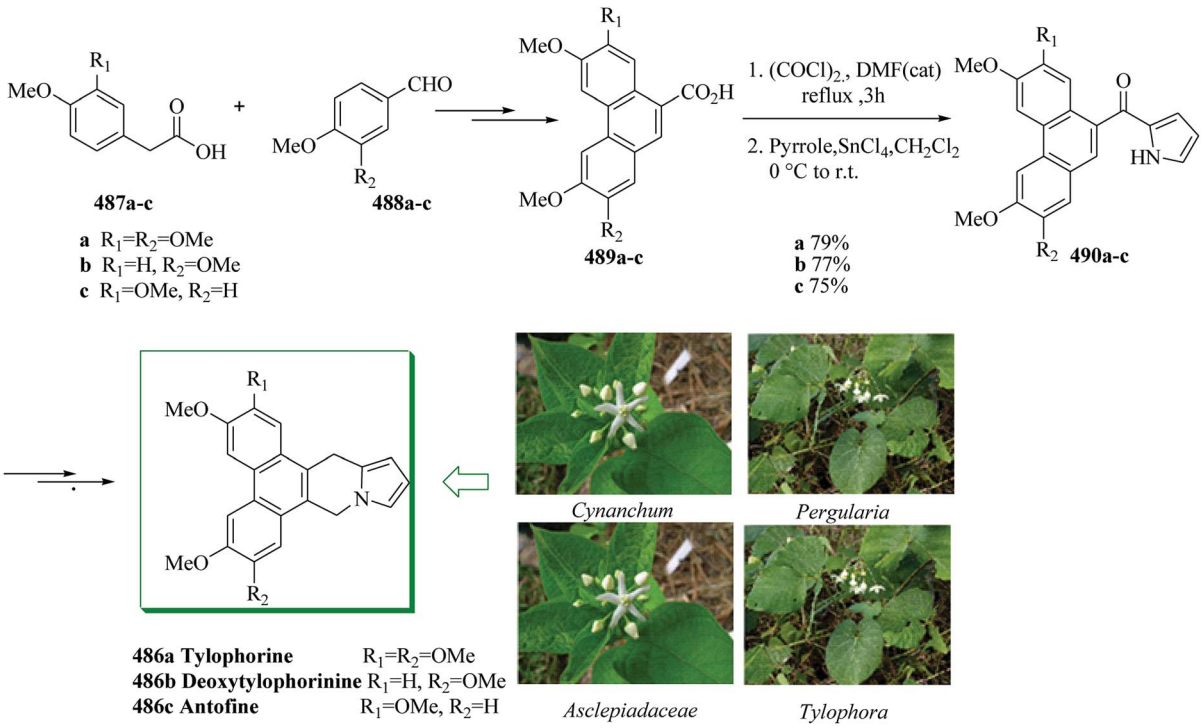


Scheme 103 Total synthesis of topopyrone A **482a**, B **482b**, C **482c** and D **482d**.

afforded compound **479** after several steps in 24% overall yield (Scheme 102).[475]

The topopyrones, a group of planar anthraquinone polyphenols, were identified by the orientation of the pyrone ring appended on one side as well as the presence or lack of a chlorine at C7. Topopyrones A **482a** and B **482b** contain a chloro group at C7, *i.e.*, that part of the molecule distant from the pyrone ring, while topopyrones C **482c** and D **482d** are unfunctionalized at C7. The topopyrones were extracted from the culture broths of two fungi, *Phoma* sp. BAUA2861 and *Penicillium* sp. BAUA4206. Particularly, topopyrones A, B, C, and D selectively inhibited the growth of yeast expressing human topoisomerase I. The topopyrones exhibit a unique group of extremely cytotoxic topoisomerase I poisons. Efficient total synthesis of all four naturally occurring members of this group was achieved in 2008 by Hecht *et al.*[476] Main steps are Diels–Alder reaction and a titanium-catalyzed *ortho*-directed FC acylation. For the synthesis of topopyrone A **482a**, B **482b**, C **482c**

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Scheme 104 Total synthesis of tylophorine **486a**, deoxytylophorinine **486b**, and antofine **486c**.

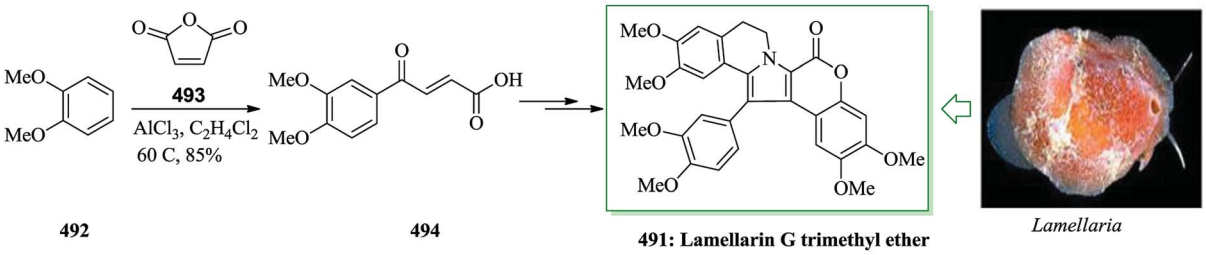
and D **482d**, initially quinone **483**[477] was converted into phenol **484** in several steps. At this point $TiCl_4$ was selected to perform regiocontrolled FC acylations. Actually, it was known that reaction of **484** in 1,2-dichloroethane with titanium tetrachloride and AcCl under reflux introduced the needed acyl side chain selectively at the *ortho* position giving **485** in 78% yield. Finally, compound **485** gave topopyrone A **482a**, B **482b**, C **482c** and D **482d** after several steps (*via* different routes) (Scheme 103).[476]

Phenanthroindolizidine alkaloids, extracted from *Pergularia*, *Cynanchum*, *Tylophora*, and some genera of the *Asclepiadaceae* group, show significant biological, pharmacological,[478,479] and antitumor properties.[480–483] (−)-Antofine **486c**, extracted from *Cynanchum komarovii*, exhibited high antiviral activity against the tobacco mosaic virus (TMV).[484,485] Wang *et al.* in 2008 reported the total synthesis of tylophorine **486a**, deoxytylophorinine **486b**, and antofine **486c** starting from pyrrole in 48%, 44%, and 46% overall yields, respectively.[486] In this route for the synthesis of phenanthroindolizidine alkaloids **486a**, **486b**, and **486c**, the reaction of benzeneacetic acid **487a–c** and aromatic aldehyde **488a–c** afforded phenanthrene-9-carboxylic acid **489a–c** *via* several steps. Then, the intermolecular FC acylation of the corresponding acyl chloride (synthesized by chlorination of acid **489a** with oxalyl chloride) and pyrrole was catalyzed by tin(IV) chloride to form pyrrolidine ring system **490a** under mild conditions in 79% yield. After three steps, the racemic tylophorine **486a** was provided. Thus, the shortest synthetic pathway to a large-scale construction of tylophorine **486a** was accomplished starting from pyrrole under mild conditions without any protecting group in 48% overall yield. This group demonstrated the construction of deoxytylophorinine **486b** and antofine **486c**. Deoxytylophorinine **486b** and antofine **486c** were obtained in 44% and 46% overall yields, respectively, in six steps including a Perkin condensation reaction, intramolecular oxidative coupling reaction of acids, chlorination of acids **489b,c**, and subsequent intermolecular FC reactions with pyrrole in one pot, deketonization of 2-acylpyrroles **490b,c**, catalytic hydrogenation of 2-alkylpyrroles, and Pictet–Spengler cyclomethylenation. The versatility and flexibility of this approach were exhibited by the large-scale construction of three representative phenanthroindolizidine alkaloids, tylophorine **486a**, deoxytylophorinine **486b**, and antofine **486c** (Scheme 104).[486]

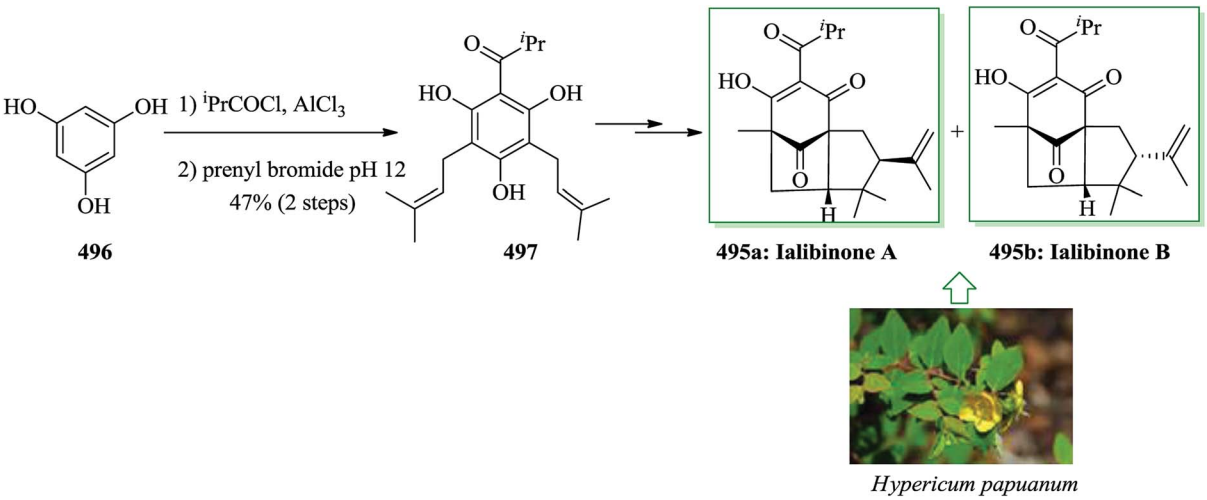
Lamellarin G, a marine natural product, includes a 5-oxa-6b-aza dibenzo[*a*,*i*]fluoren-6-one framework. Lamellarins were extracted from the prosobranch mollusk *Lamellaria* sp. and the ascidians.[487] Some of these lamellarins[488,489] show active biological properties,[490] for example cytotoxicity to a series of cancer cell lines, cell division inhibition, and immunomodulation. A modular synthesis of the lamellarin G trimethyl ether was established using various reactions in sequence, including FC acylation, esterification, haloarylation, and oxidative cyclization. This method provided the complete structure of lamellarin G trimethyl ether in four steps with 44% overall yield. Total synthesis of lamellarin G trimethyl ether was accomplished in 2009 by Yadav *et al.*[491] In this approach, 4-(3,4-dimethoxyphenyl)-4-oxo-but-2-enoic acid **494** was obtained from veratrole **492** and maleic anhydride *via* FC reaction.[492] Subsequently, compound **494** afforded the desired target product lamellarin G trimethyl ether **491** upon several steps (Scheme 105).[491]

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Scheme 105 Total synthesis of lamellarin G trimethyl ether **491**.



Scheme 106 Total synthesis of ialibinone A **495a** and ialibinone B **495b**.

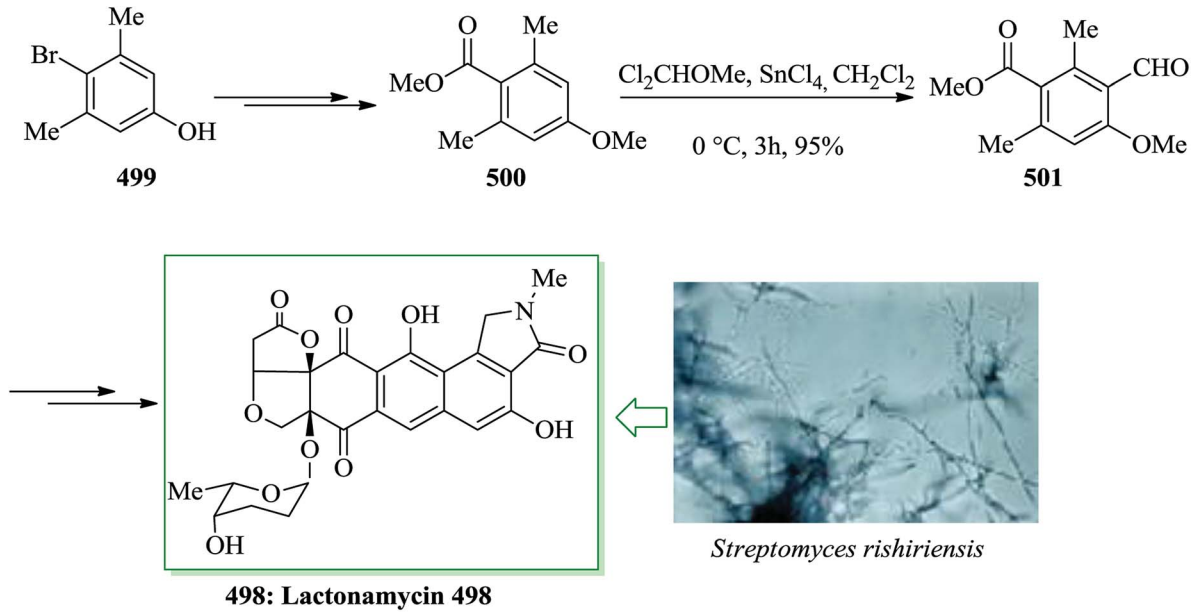
The epimeric ialibinones A and B **495**, uncommon types of PPAP, were extracted from the leaves of *Hypericum papuanum* by Sticher *et al.* in 2000.[493] They show antibacterial activity against cytotoxic against KB cell lines.[493,494] The tricyclic natural products ialibinone A and ialibinone B were synthesized as a 41 : 59 mixture in four steps starting from phloroglucinol. The synthetic sequence included acylation reaction of phloroglucinol through FC reaction, double prenylation, dearomatizing methylation, and oxidative free radical cyclization. Initially, the bis-prenylated acylphloroglucinol **497** was synthesized in two steps from phloroglucinol **496** *via* FC acylation reaction. Next, compound **497** provided the target natural products, ialibinone A **495a** and ialibinone B **495b**, as an inseparable mixture in 35% overall yield (Scheme 106).[495]

Lactonamycin **498**, extracted from a culture broth of *Streptomyces rishiriensis* MJ773-88K4, exhibited active antimicrobial properties against Gram-positive bacteria and vancomycin-resistant *Enterococcus* (VRE) as well as antitumor properties.[496,497] Structurally, compound **498** contains a hexacyclic system and a glycosidic bond at the *t*-alcohol.[497] The first total synthesis of lactonamycin **498** was accomplished in 2010 by Tatsuta *et al.*[498] The synthesis includes sequential intramolecular conjugate addition reaction of alcohols to the acetylenic ester, asymmetric glycosylation of the tertiary alcohol, and Michael–Dieckmann type cyclization with the thioester. The synthesis of lactonamycin **498** was started from 4-bromo-3,5-dimethylphenol **499**, that after two steps gave ester **500**.[499] Then, FC-type formylation reaction[500] of **500**, gave aldehyde **501**. Upon several steps, compound **501** gave lactonamycin **498** (Scheme 107).[498]

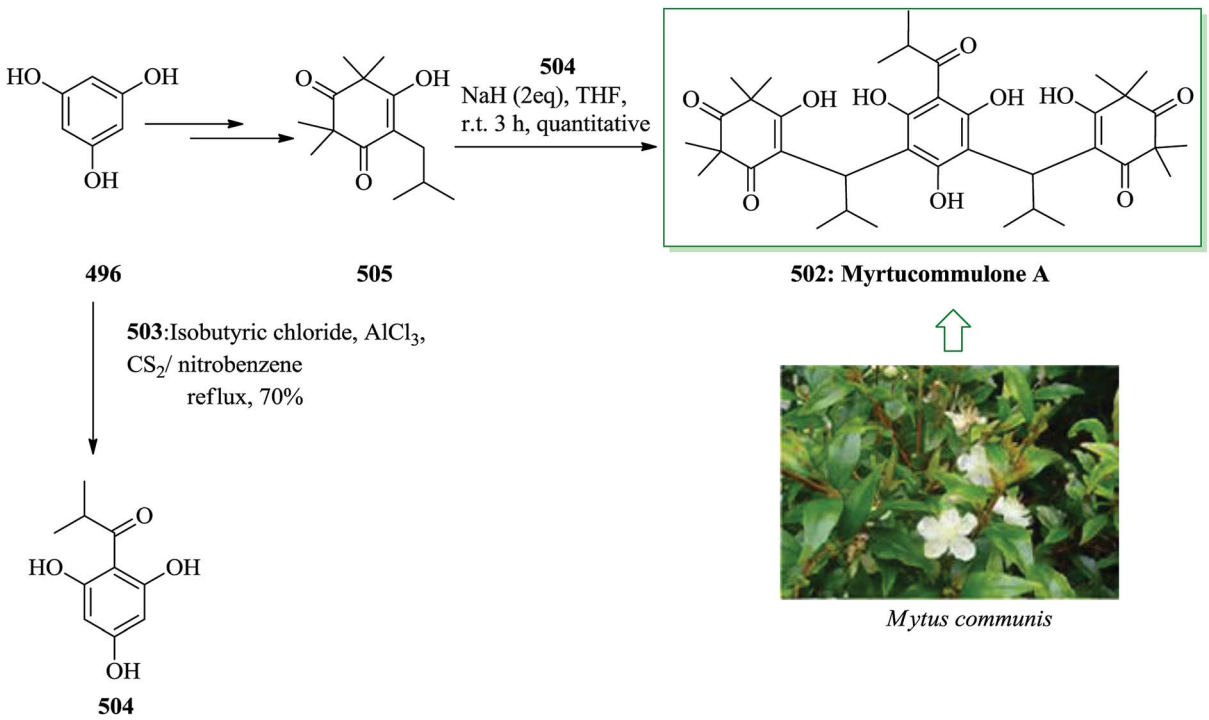
Myrtucommulone A **502** was developed in 1974 by Kashman *et al.* as a substance known in the common myrtle *Myrtus communis* L.[501] Jauch *et al.* in 2010 reported synthesis of myrtucommulone A **502** from isobutyryl phloroglucinol **504**, isobutyraldehyde, and syncarpic acid in one step. Isobutyryl phloroglucinol **504** is easily accessible *via* FC acylation of phloroglucinol **496** in 70–80% yield.[502,503] Compound **496** after three steps gave syncarpic acid.[504,505] Compound **503** is also accessible from **496** upon several steps. In this part, two acid-catalyzed FC alkylation reactions occurred consecutively in a one-pot reaction. Running the FC alkylation under basic conditions needed removal of the acid and extraction of **505** as a crude product prior to reaction with **504**, which had been deprotonated with two equivalents of sodium hydride in tetrahydrofuran. Finally, the synthesis of **502** was completed in three hours at ambient temperature in quantitative yield (Scheme 108).[506]

The tylophora alkaloids have obtained synthetic and medicinal attention owing to their panoply of biological properties, such as antibacterial, anticancer, antifungal, antiviral,

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Scheme 107 Total synthesis of lactonamycin **498**.

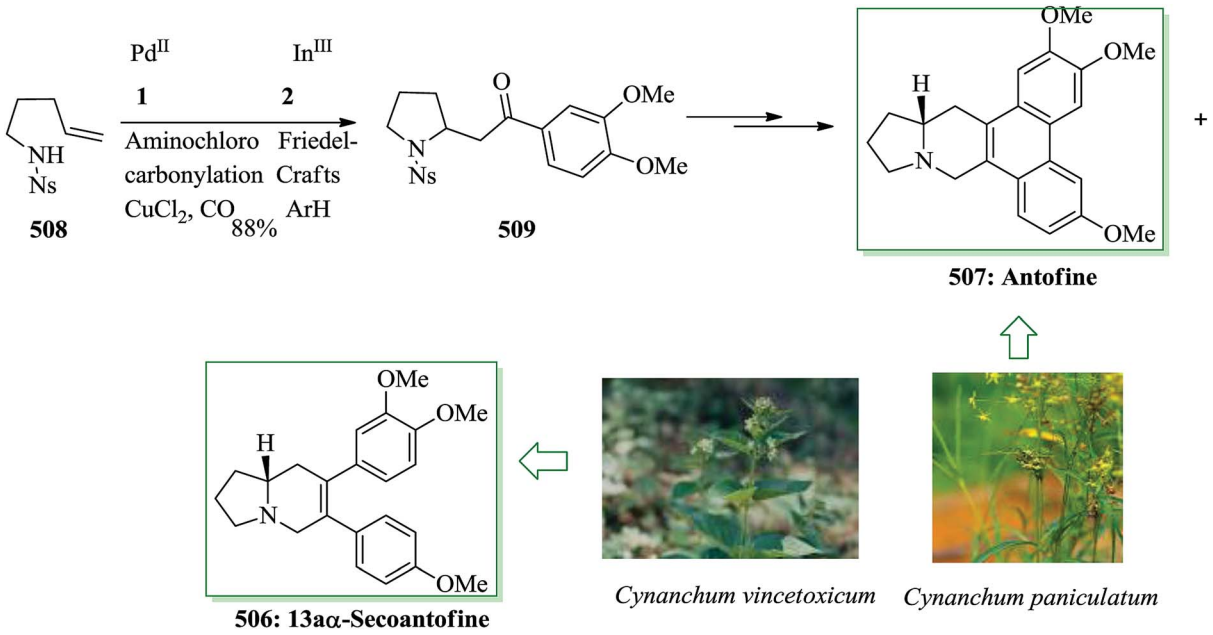


Scheme 108 Total synthesis of myrtucommulone A **502**.

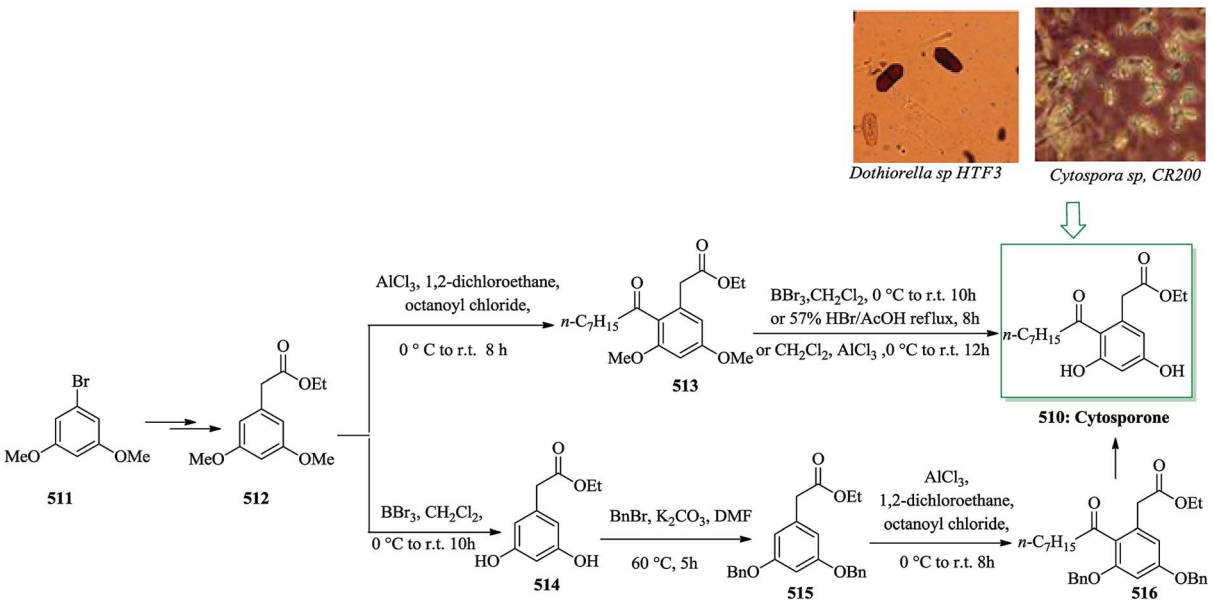
and anti-inflammatory properties.[507] Antofine and 13*aα*-secoantofine were extracted from the root of *Cynanchum paniculatum* Kitagawa (*Asclepiadaceae*)[508] and from aerial parts of *Cynanchum vincetoxicum*,[509] respectively.[510] A fast synthetic method to the tylophora alkaloids antofine and 13*aα*-secoantofine was achieved. The key step in this synthetic methodology was the multicatalytic aminochlorocarbonylation/FC acylation reaction of a protected 4-pentenyl amine to give a β-pyrrolidinyl ketone intermediate. Thus, after exposing the easily accessible nosyl protected alkenyl amine **508** and veratrole to aminochlorocarbonylation, it was gratifying to find that the β-pyrrolidinyl ketone **509** could be isolated in high yield. Finally, compound **509** afforded 13*aα*-secoantofine and antofine in 19% and 48% overall yield, respectively (Scheme 109).[511]

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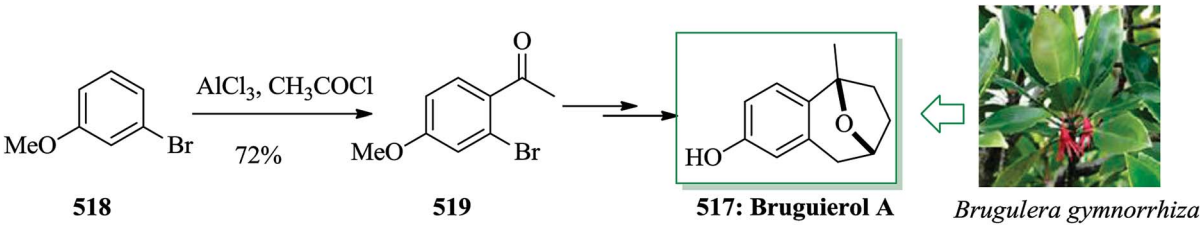
Scheme 109 Total synthesis of 13*aα*-secoantofine **506** and antofine **507**.



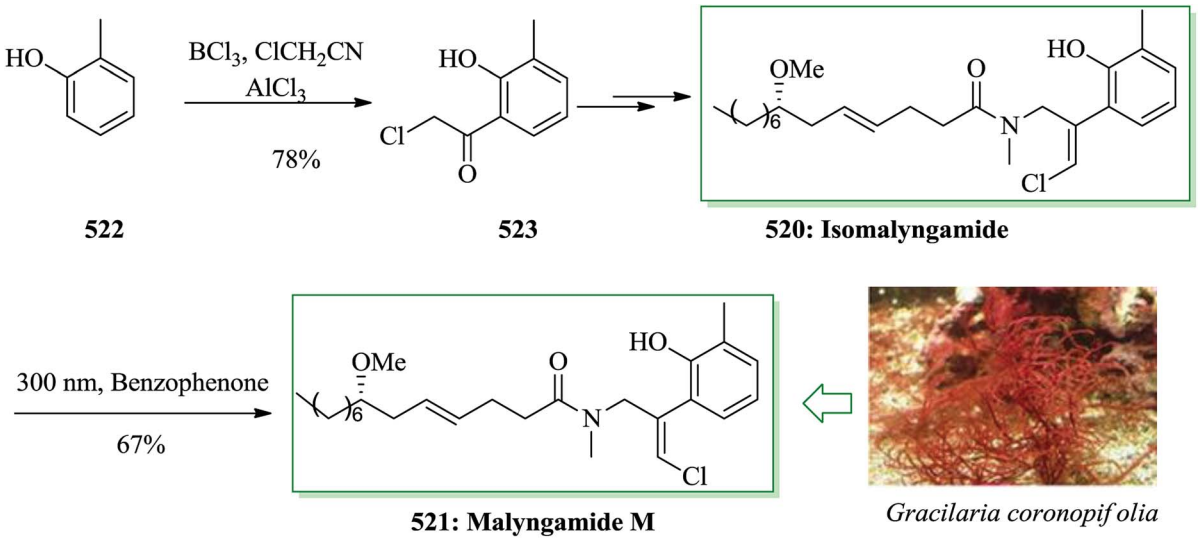
Scheme 110 Total synthesis of cytosporone B **510**.

Cytosporone B **510**, extracted from *Cytospora* sp. CR200 and *Dothiorella* sp. HTF3,[512] exhibits antibacterial activity.[512–515] The total synthesis of cytosporone B was achieved from 1-bromo-3,5-dimethoxybenzene. The key steps are sequential Grignard reaction and Lemieux-van Rudloff oxidation followed by a deprotection of the methyl aromatic ether to phenol and subsequent FC acylation. In this route, total synthesis of cytosporone B was started from 1-bromo-3,5-dimethoxybenzene **511**. Next, it was converted into the key intermediate **512** *via* three steps. Then, with the key intermediate **512** obtained by oxidation and esterification, the sequential FC acylation and deprotection were accomplished subsequently. The FC reaction progressed with 86% yield of the purified product. The ether in **512** was deprotected to phenol **514** using BBr_3, followed by etherification with benzyl bromide to provide the intermediate **515** (56% yield, two steps). The hydroxyl protection step was followed by an attempt at acylation of this protected phenol with octanoyl chloride catalyzed by aluminium chloride in 83%

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Scheme 111 Total synthesis of bruguierol A **517**.



Scheme 112 Total synthesis of isomalyngamide **520** and malyngamide M **521**.

yield. Finally, the debenzylation of ethyl 2-(3,5-bis(benzyloxy)-2-octanoylphenyl)acetate **516** under H_2 progressed very easily (95% yield) and very pure cytosporone B **510** was obtained (Scheme 110).[512]

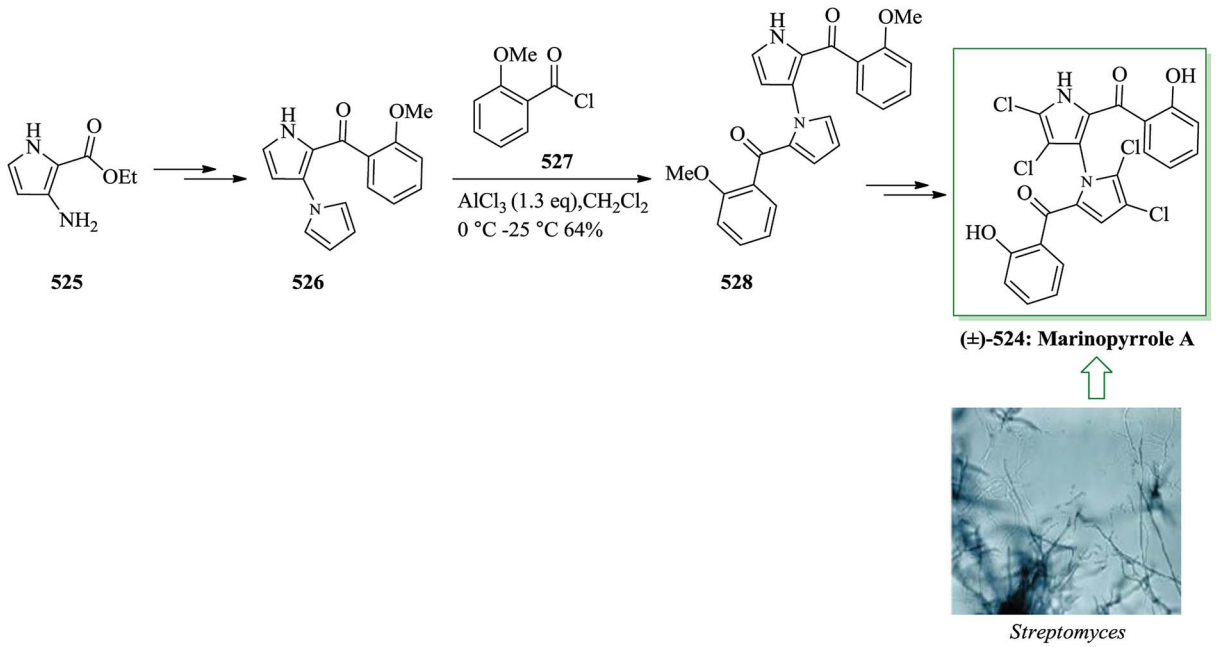
Bruguierol A **517** was extracted and identified by Sattler *et al.* from the stem of *Bruguiera gymnorrhiza* tree in 2005.[66] This natural product has a unique structure characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. Total synthesis of (±)-bruguierol A **517** was achieved in 10 steps and with an overall 16.8% yield. The embedded unique 8-oxabicyclo[3.2.1] octane unit framework in this natural product was generated through a novel $Sc(OTf)_3$-catalyzed intramolecular [3 + 2] cycloaddition of cyclopropane. The synthesis of bruguierol A **517** was achieved *via* FC acylation reaction of 3-bromoanisole **518** to give compound **519** in 72% yield.[516,517] Finally, (±)-bruguierol A **517** was synthesized after several steps from compound **519** (Scheme 111).

The malyngamides, usual metabolites of *Lyngbya majuscula*, are N-functionalized amides of long chain fatty acids. A subgroup of malyngamides contains a communal and remarkable terminal vinyl chloride functionality, for example malyngamides A, B, M, and isomalyngamides A, B, M. Malyngamide M **521** was extracted from the Hawaiian red alga *Gracilaria coronopifolia*.[518] It was the first example of a natural aromatized malyngamide that possesses a special terminal vinyl chloride substructure. The first concise and significant asymmetric synthesis of malyngamide M **521** was achieved in nine steps from *o*-cresol in 12% overall yield. The key steps included the Wittig reaction, FC acetylation, amidation, and isomerization reaction. The isomalyngamide M **520** was also obtained in 2010 by Cao *et al.*[519] In this pathway, total synthesis of malyngamide M **521** was started from *o*-cresol **522**. FC acetylation reaction of **522** with chloroacetonitrile using boron trichloride and aluminium trichloride afforded phenol **523** in 78% yield.[520] Next, after several steps, compound **523** gave isomalyngamide **520** in 83% yield. Finally, compound **520** was transformed into a mixture of **521**/*Z*-**521** (2.5 : 1) when exposed to UV light using benzophenone in dichloromethane for 8 h at room temperature.[521] Fortunately, the two isomers could be simply separated by flash chromatography over silica gel, and pure **521** was provided in 67% yield (Scheme 112).[519]

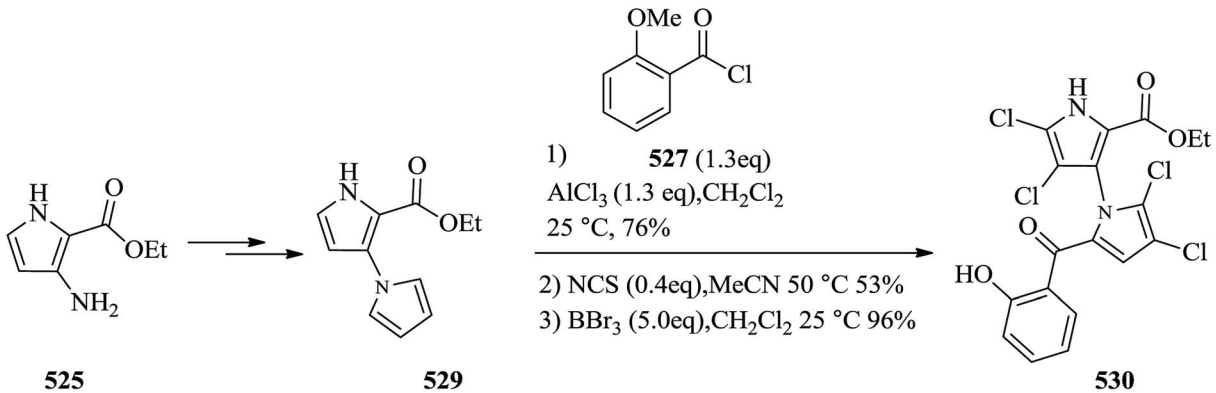
Marinopyrrole A **524** is an alkaloid endowed with promising antibiotic properties against methicillin-resistant *Staphylococcus aureus* (MRSA)[523] that was extracted from an obligate marine *Streptomyces*. This structurally uncommon molecule exists at room temperature as enantiopure M-(−)-atropisomers. Nicolaou *et al.* developed total synthesis of the antibiotic marinopyrrole A **524** in five steps and 16% overall yield from aminopyrrole **525**.[524] The synthesis of marinopyrrole (−)-**524** (natural) and (+)-**524** (unnatural) was started from aminopyrrole **525**, which was converted into tricycle **526** upon several steps. FC arylation reaction of **526** and acid chloride **527**, catalyzed by

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Scheme 113 Total synthesis of marinopyrrole A (±)-**524**.



Scheme 114 Total synthesis of mono-arylated marinopyrrole **530**.

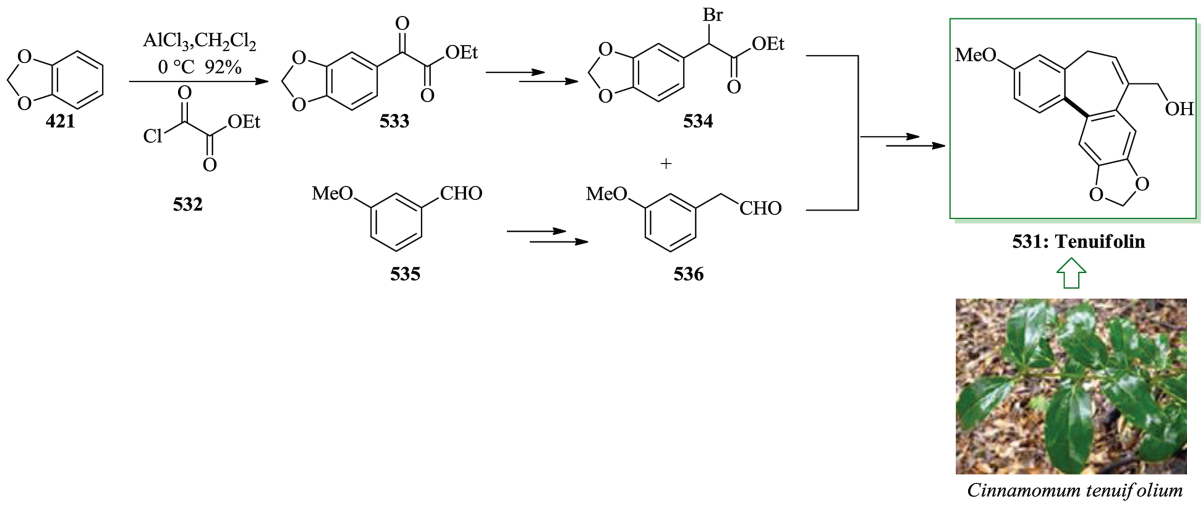
aluminium chloride in dichloromethane, resulted in the marinopyrrole unit structure **528** in 64% yield. Finally, compound **528** afforded racemic marinopyrrole A [(±)-**524**] *via* several steps (Scheme 113).[524]

In a similar method, mono-arylated marinopyrrole **530** was synthesized from bis-pyrrole **529** (obtained from compound **525**), *via* a three-step sequence containing a FC C-arylation with acid chloride **527**, *tetra*-chlorination with NCS in acetonitrile, and demethylation with BBr_3 in dichloromethane to provide the target product **530** in 39% overall yield (Scheme 114).[525]

Biaryl compounds, containing a 6,7,6-ring system, include a wide range of naturally occurring compounds and synthetic pharmaceuticals, for example alkaloids as well as cyclolignans. Several of them showed activity against various cancer cell lines. Lin *et al.* extracted a unique sesquiterpenoid, tenuifolin **531**, from the stems of *Cinnamomum tenuifolium*.[526] In the structure of **531** exists a similar moiety to allocolchicine and a preliminary bioassay indicated that **531** only exhibited weak anti-proliferative activity against tumor cell line DU145.[526] The first total synthesis of a sesquiterpenoid, tenuifolin **531**, was accomplished in seven linear steps from market-accessible benzodioxole **421**. A FC acylation reaction of **421** using ethyl 2-chloro-2-oxoacetate **532** gave compound **533** in 92% yield. Next, compound **533** was converted into bromoester **534** *via* several steps. Lastly, bromoester **534** and aldehyde **536** afforded tenuifolin **531** in excellent yield (91%) (Scheme 115).[527]

Dictyodendrins were extracted in 2003 by Fusetani and Matsunaga from the extracts of a Japanese marine invertebrate, the marine sponge *Dictyodendrilla verongiformis*, which was from Nagashima Island in Kagoshima, Japan. These compounds were the first marine alkaloids that contain inhibitory activity against telomerase.[528] A highly effective total synthesis of dictyodendrins A–E was accomplished. The synthesis demonstrates a novel benzyne-catalyzed one-pot indoline construction/cross-coupling sequence. Firstly, 2,6-dibromo-phenylethylamine **539** was transformed into the

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Scheme 115 Total synthesis of tenuifolin **531**.

pivotal indole **278** *via* removal of the Boc group, DDQ oxidation to the indole,[529] and attachment of apara anisylethyl group onto the nitrogen atom. Then, the stage was set for the installation of subunits on the indole 2-position for the synthesis of dictyodendrin A **275**, B **276**, and E **538**. 2-Acylindole derivative **283** was provided in almost quantitative yield through FC acylation reaction[264] with *para*-methoxybenzoyl chloride **282** and zinc chloride as a promoter (Table 1, entry 1). In contrast, installation of the *para*-anisyl-acetate group was needed for synthesis of dictyo-dendrin A **275** (Table 1, entry 2). It was found that silver triflate[530] was effective and the reaction progressed to afford the corresponding product **541** in high yield (Table 1, entry 3). To provide the intermediate to dictyodendrin E **538**, it was necessary to introduce the *para*-methoxybenzyl group onto the indole 2-position. Unfortunately, reaction with $ZnCl_2$ or silver triflate did not afford the corresponding product at all. It was assumed that the difficulty with *para*-methoxybenzylation was because of the high reactivity of *para*-methoxybenzyl chloride **540** and the presence of electron-rich aromatic rings in the substrate, which induce nonselective benzylation. Moreover, compound **278** afforded intermediates **541** and **542**. Finally, compound **541** provided the dictyodendrins upon several steps (Scheme 116).[531]

Table 1 The effect of various Lewis acids

Entry	RX	Lewis acid	Product	Yield [%]
1[a]	**282**	$ZnCl_2$	**283**	99
2[a]	**279**	$ZnCl_2$	**541**	—
3[b]	**279**	AgOTf	**541**	81
4[a]	**540**	$ZnCl_2$	**542**	Trace[c]
5[b]	**540**[d]	AgOTf	**542**	—

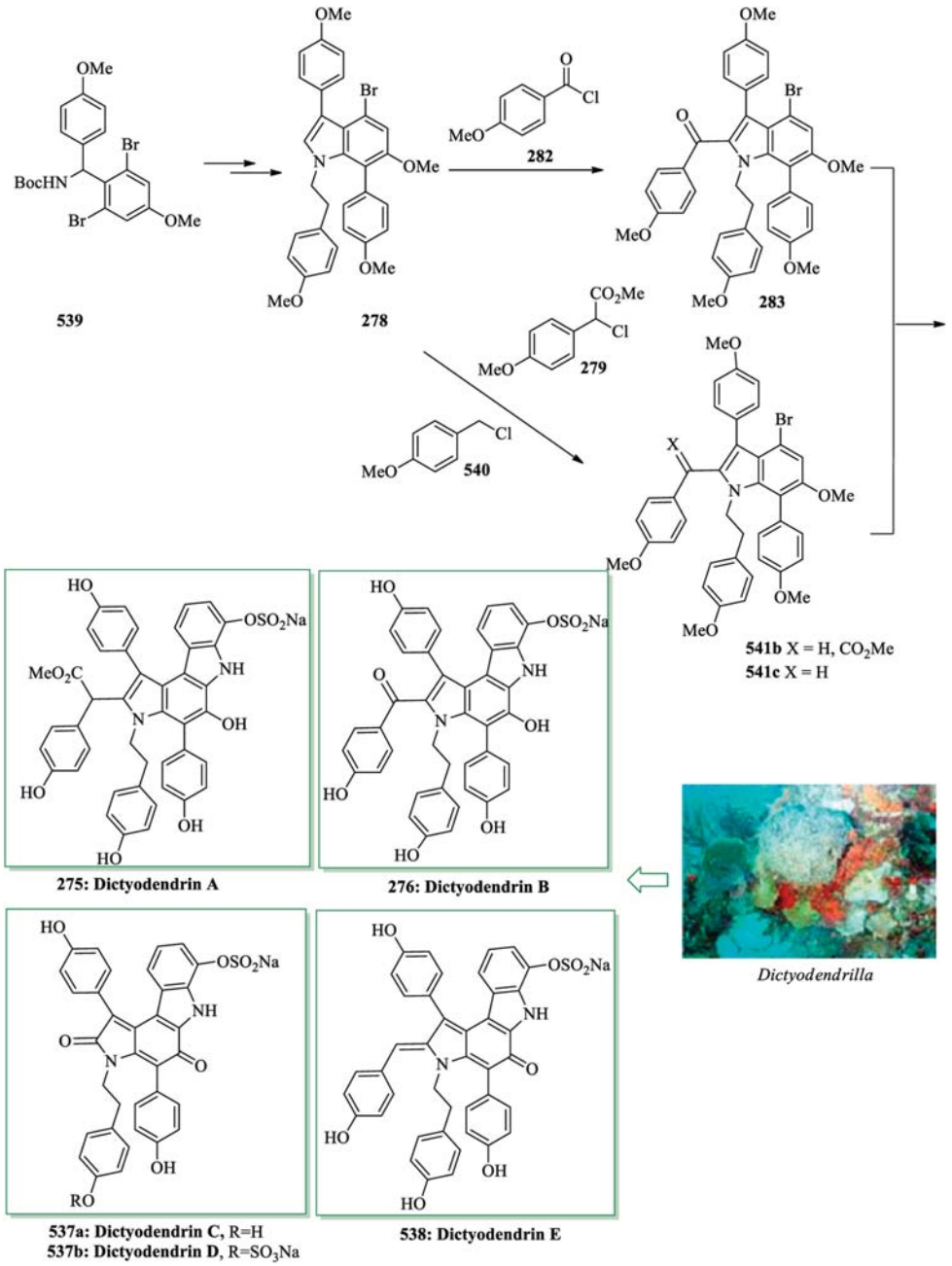
[a] Reaction condition: $ZnCl_2$ (10 equiv.), RX (2 equiv.), Et_2O, 0 °C. [b] Reaction condition: AgOTf (4 equiv.), RX (3 equiv.), THF, −78 °C. [c] Complex mixture. [d] **540** two equivalents. Reaction temperature: −78 to 0 °C.

Miles *et al.* extracted cadinane sesquiterpene lactones heritol **544**[532] and heritonin **543**[533] from the sap of the mangrove plant *Heritiera littoralis* in the Philippines, which were demonstrated to possess ichthyotoxicity in parts per million quantities to *Tilapia nilotica* fingerlings. Chavan *et al.* reported the highly diastereoselective total synthesis of racemic heritonin **543** and heritol **544** *via* intramolecular cyclization on a preprovided sensitive butenolide functionality from market-purchasable initiating precursors in eight and nine purification operation in 43% and 33% overall yield, respectively. Synthesis of heritol **544** and heritonin **543** was started with FC acylation reaction of *o*-cresol methyl ether **545** and allylacetyl chloride in CH_2Cl_2 at ambient temperature to provide the desired allylic keto compound **546** in 95% yield. Next, compound **546** was converted into acid **547** *via* several steps. Then, compound **547** provided the key intermediate tetralone **548** through intramolecular FC acylation in 95% yield (over two steps). Compound **548** afforded compound **549** *via* several steps. The latter was converted into heritonin **543** in 96% yield and lastly compound **543** gave heritol **544** in 80% yield (Scheme 117).[534]

Lysidicins A–C were extracted from *Lisidicie rhodostegia* Hance (*Fabaceae*) by Yu *et al.* in 2006[535] and the isolation of lysidicins D–H was reported by the same group in 2007[536] and 2010.[537] Meanwhile, among the lysidicin group, lysidicin A **553** has the most unique and complicated structure in which two acetals form a spiro[furan-furofuran] ring system. Watanabe *et al.* in 2012 reported the initial total synthesis of (±)-lysidicin A significantly through single and cascade Claisen rearrangements and FC acylation reaction with AgOTf.[538] In this method, the overall yield was 3.5% in 15 steps from diol **551**. The total synthesis was started from diol **551**, which was converted into benzyl ether **552** after several steps. Next, FC acylation reaction of **552** gave **553a** and **553b** in 27% and 35% yield (in two steps), respectively. Both **550a** and **550b** are regioisomeric compounds of lysidicin A; they were separately exposed to acid-mediated isomerization of the acetalic spiro[furan-furofuran] ring

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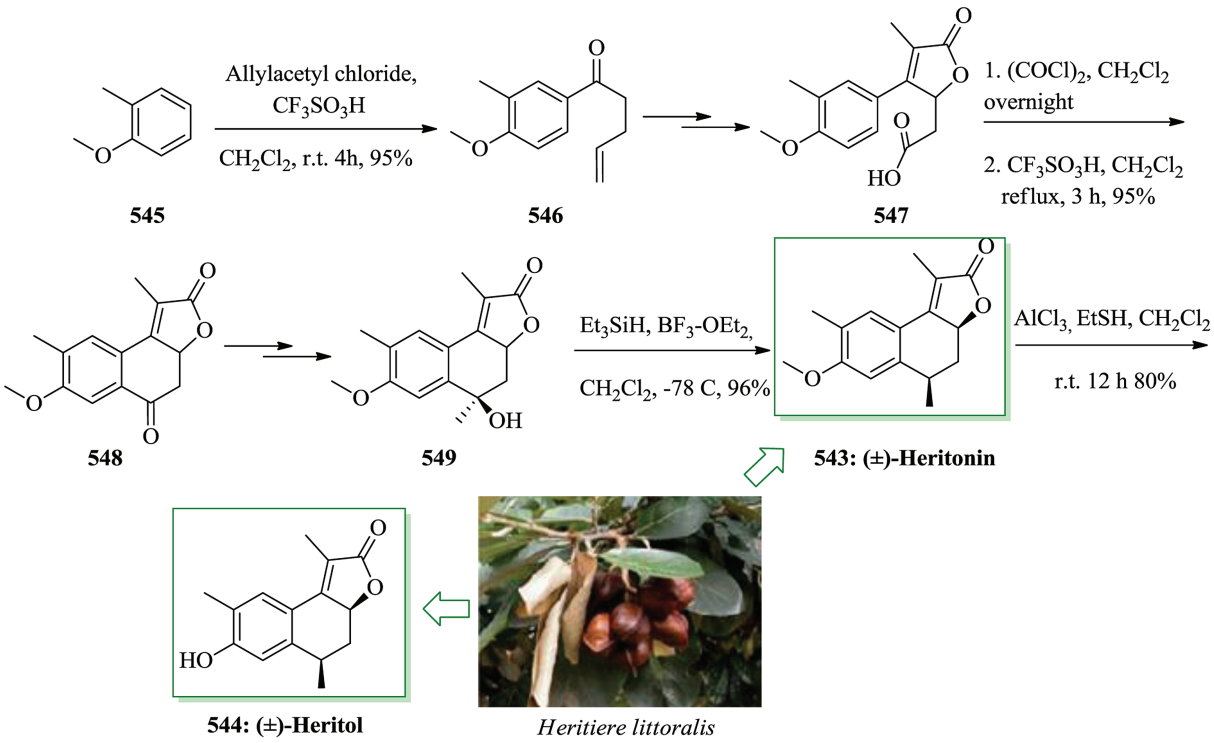


Scheme 116 Total synthesis of dictyodendrins A–E.

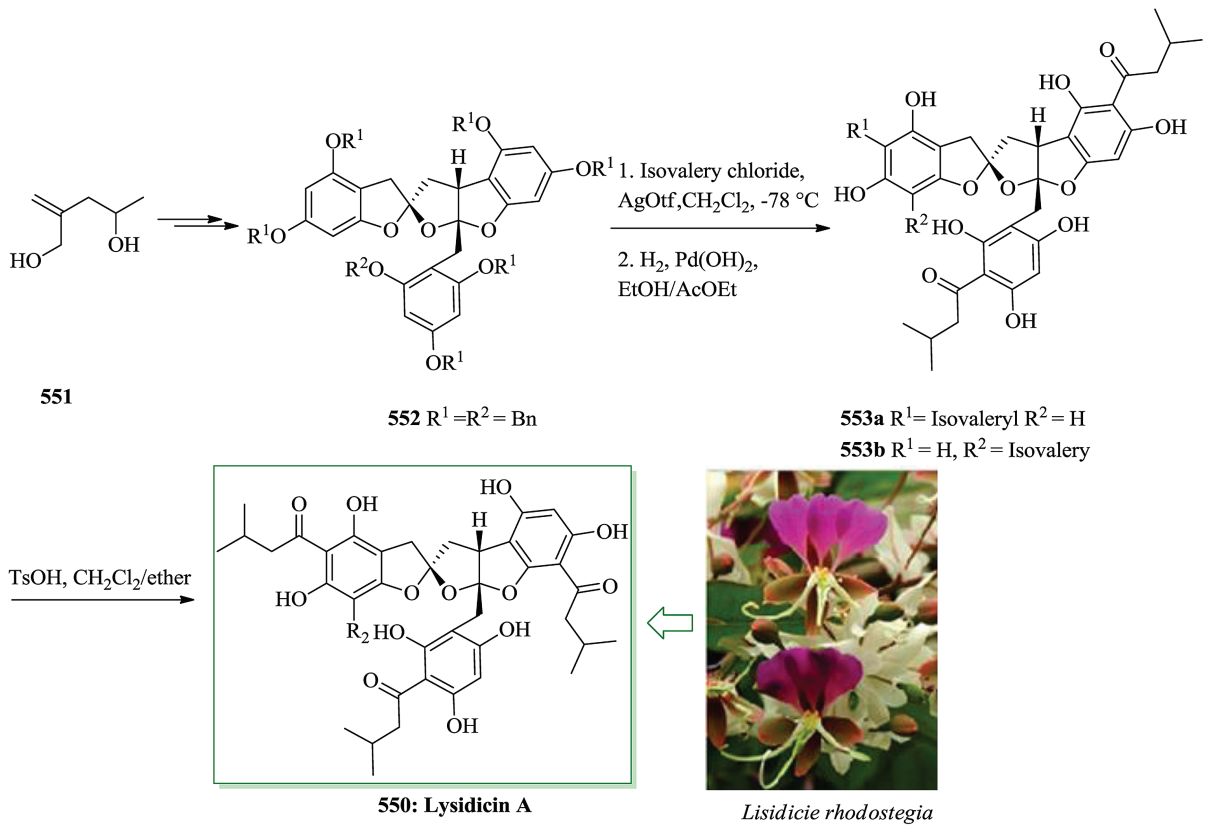
et al. in 2012 reported the initial total synthesis of (±)-lysidicin A significantly through single and cascade Claisen rearrangements and FC acylation reaction with AgOTf.[538] In this method, the overall yield was 3.5% in 15 steps from diol **551**. The total synthesis was started from diol **551**, which was converted into benzyl ether **552** after several steps. Next, FC acylation reaction of **552** gave **553a** and **553b** in 27% and 35% yield (in two steps), respectively. Both **550a** and **550b** are regioisomeric compounds of lysidicin A; they were separately exposed to acid-mediated isomerization of the acetalic spiro[furan-furofuran] ring system and finally total synthesis of (±)-lysidicin A **550** was achieved (Scheme 118).[538]

The cultivation of *Streptomyces armeniacus* under specific conditions resulted in the discovery of the armeniaspiroles, a unique group of compounds biosynthetically related to streptopyrroles.[539] Armeniaspiroles, a unique group of natural products extracted from *Streptomyces armeniacus*, are identified by a novel spiro[4.4]non-8-ene moiety. Several derivatives of armeniaspiroles were obtained *via* halogenation, alkylation, addition/removal or reduction. A total synthesis of the 5-chloro analogue of armeniaspirole A was achieved in a linear six-step sequence. 5-Chloro-armeniaspirole A shows moderate activity against a series of multidrug-resistant, Gram-positive bacterial pathogens. A biomimetic synthesis of the armeniaspirole unit was envisaged starting from **556**. The pyrrolo-phenone

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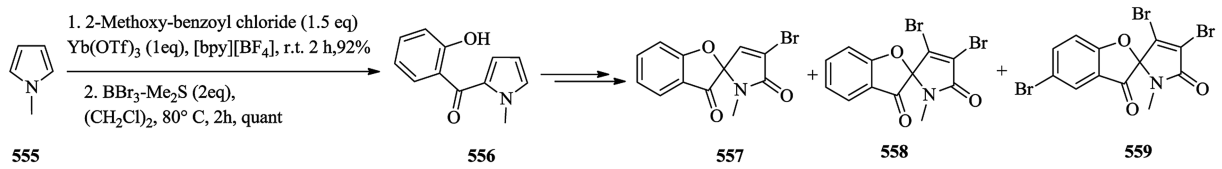
Scheme 117 Total synthesis of (±)-heritonin **543** and (±)-heritol **544**.



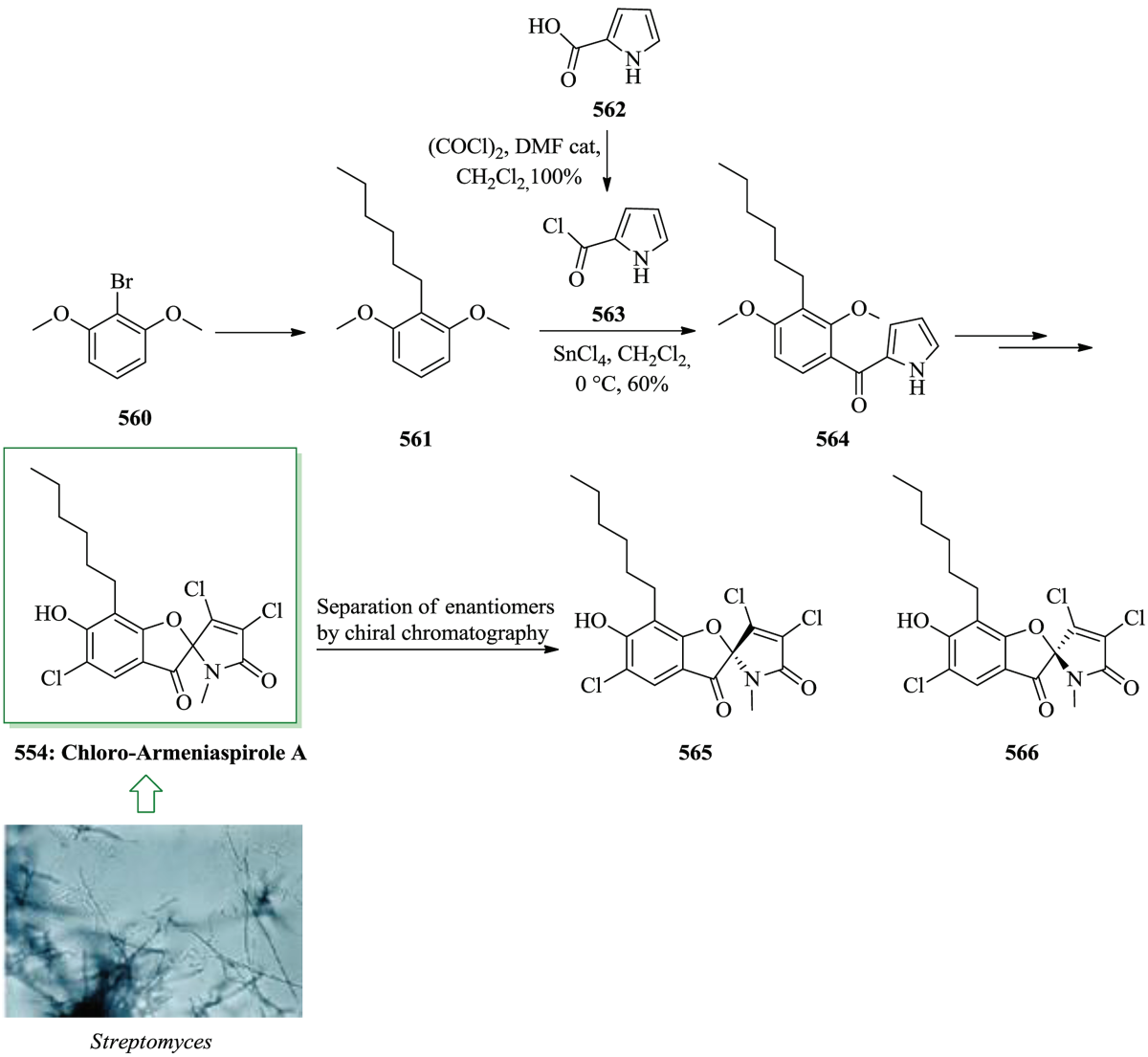
Scheme 118 Total synthesis of lysidicin A **550**.

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Scheme 119 Formation of a mixture of mono-, di- and tri-brominated products **557**, **558** and **559**.

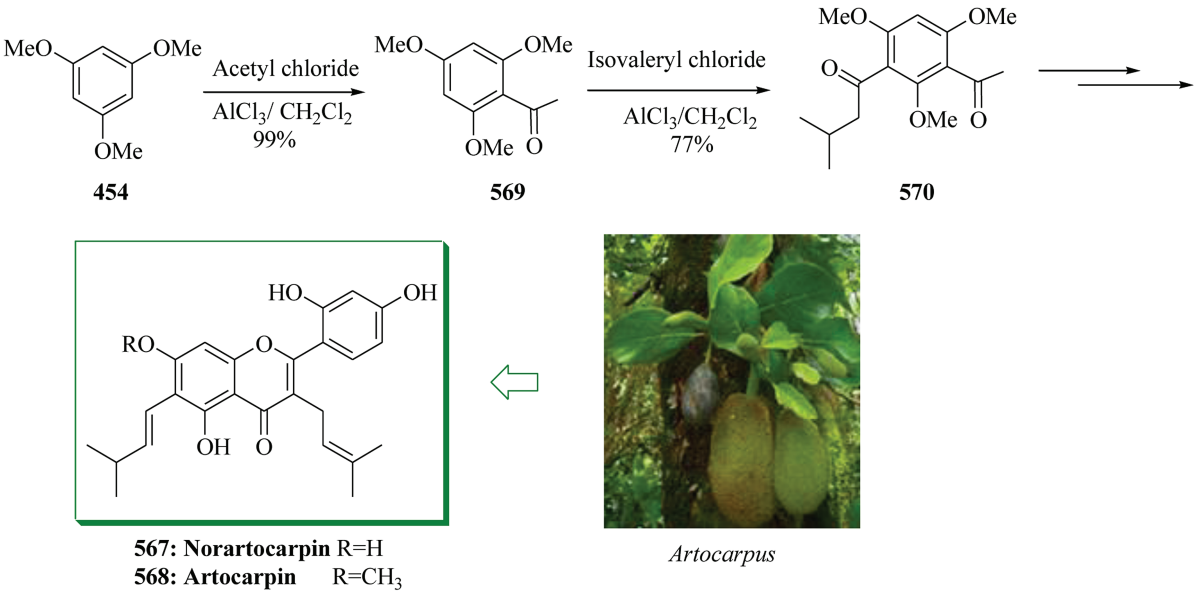


Scheme 120 Total synthesis of 5-chloro-armeniaspirol **554**.

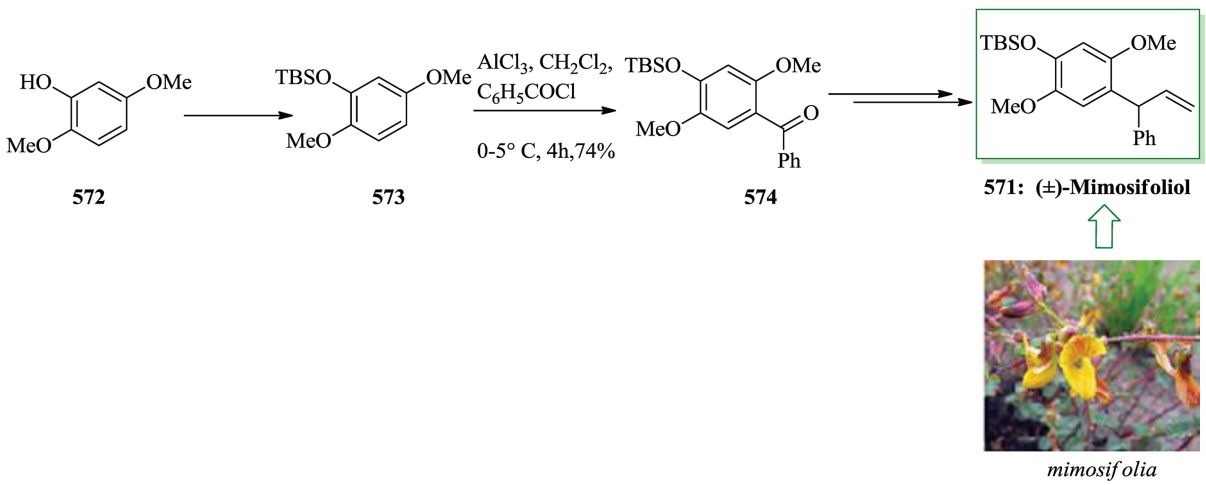
compound **564** in a satisfactory 60% yield. Compound **564** gave compound **554** in 72% yields after several steps. The two enantiomers of racemic 5-chloro-armeniaspirole A **554** were finally separated by chiral chromatography to afford enantiopure 5-chloro-armeniaspirole A **565** (*R*-configuration) and **566** (*S*-configuration).[540]

Norartocarpin **567** and artocarpin **568** are natural isoprenylated flavonoids isolated from the genus *Artocarpus*.[541–543] They have a wide range of remarkable biological properties, including inhibitor effects on melanin biosynthesis and 5α-reductase, as well as antibacterial and cytotoxic activity.[544] The total syntheses of norartocarpin and artocarpin, two biologically remarkable natural flavonoids with two regioisomeric isoprenyl side chains, were accomplished for the first time through a linear reaction sequence of 9 and 12 steps with overall yields of 14% and 3.5%, respectively, starting from 1,3,5-trimethoxybenzene. Starting from 1,3,5-trimethoxybenzene **454**, twice sequential FC acylation of **454** in CH_2Cl_2 with aluminium

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Scheme 121 Synthesis of norartocarpin **567** and artocarpin **568**.



Scheme 122 Total synthesis of (±)-mimosifoliol **571**.

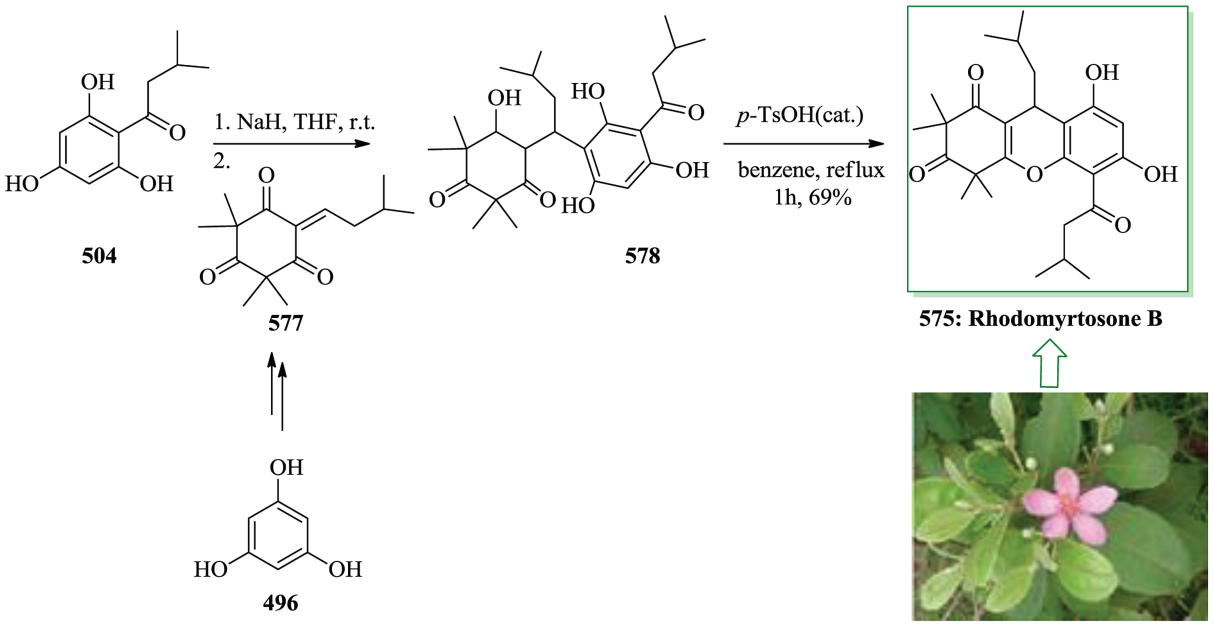
chloride using acetyl chloride and 3-methylbutanoyl chloride as the acylated reagents, respectively, gave the intermediate **570** in moderate yields (75% for two steps). In the course of FC acylation, the corresponding demethylation simultaneously happened, which may be related to the effect of two carbonyl groups at *ortho* positions. On the other hand, if the two FC reactions were accomplished in a reversed sequence, 2,4,6-trimethoxyacetylbenzene **569** rather than the desired target molecule **570** was obtained as the major product, *i.e.,* the isopentanoyl group was removed through reverse FC reaction during the second step. Finally, compounds **567** and **568** were obtained from **570** *via* several steps (Scheme 121).[545]

(+)-R-Mimosifoliol **571**, a neoflavonoid isolated from the rootwood of *Aeschynomene mimosifolia,* demonstrated weak activity in a DNA-strand scission assay.[546] Racemic (±)-mimosifoliol was obtained in 5 steps through an *o*-quinone methide intermediate and subsequently (+)-mimosifoliol was obtained through cycloaddition of the same intermediate with a chiral enol ether.[547] A two-step method was developed to vinylate the diarylmethanes at the bridging CH_2 with lateral lithiation and formylation followed by a Wittig reaction. This strategy was used in the racemic synthesis of the natural product mimosifoliol. Completion of the total synthesis of (±)-mimosifoliol needed a protected hydroxyl substituent. For this purpose, compound **572** was protected with a *tert*-butyldimethylsilyl group to afford **573**. The latter was acylated to provide ketone **574**. Careful control of the temperature of the FC reaction was needed to prevent accidental deprotection. Finally, compound **574** afforded (±)-mimosifoliol **571** after several steps (Scheme 122).[548]

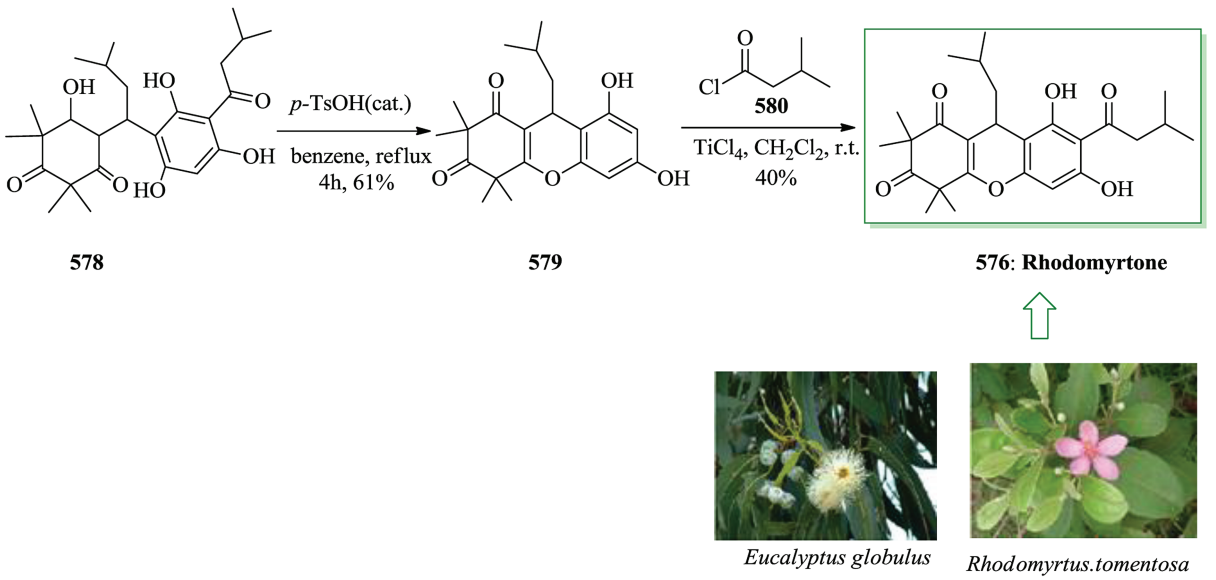
The flowering plant *Rhodomyrtus tomentosa* (Aiton) Hassk. of the group Myrtaceae is applied in Thailand to treat a wide range

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Scheme 123 Total synthesis of rhodomyrtosone B **575**.



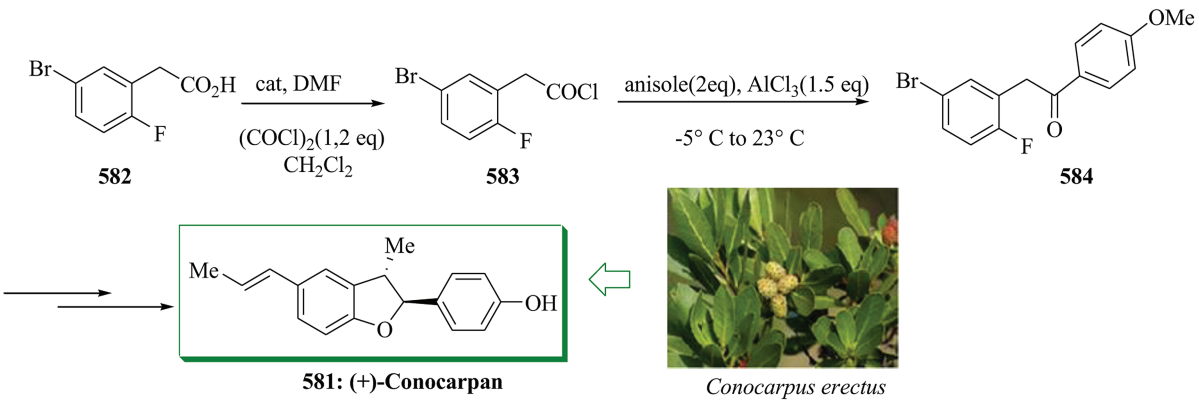
Scheme 124 Synthesis of rhodomyrtone **576**.

of ailments. Rhodomyrtone **576** was isolated from the ethanol extract. The same compound was extracted from the bark of small twigs of *Eucalyptus globulus* Labill, which is a member of the *Myrtaceae* group.[549,550] This acylphloroglucinol exhibits significant antibacterial activity. Additional acylphloroglucinols could be isolated from the leaves of *R. tomentosa*, which contain the isomer rhodomyrtosone B **575**.[551] In 2013, Maier *et al.* developed a concise synthesis of the isomeric acylphloroglucinols rhodomyrtosone B **575** and rhodomyrtone **576**.[552] In this pathway, for the synthesis of **575**, phloroglucinol **496** was converted into the cross-conjugated enedione **577** *via* several steps. Since enone **577** is prone to isomerization,[553] it was instantaneously treated with the enolate made *via* the reaction of acylphlorglucinol **504** with sodium hydride. In this way, a reasonable yield of the key intermediate **578** could be obtained. Refluxing a benzene solution of hydroxy ketone **578** in the presence of catalytic quantities of *p*-toluenesulfonic acid resulted in rhodomyrtosone B **575** in 69% yield (Scheme 123).[552]

The other isomer, the antibiotic rhodomyrtone **576**, was obtained from **578** through a sequence of acid-catalyzed cyclization, retro FC reaction, and reacylation (Scheme 124).[552]

8,5′-Neolignans having an 8-aryl-2,3-dihydrobenzofuran framework are the most plentiful natural products known in various groups of plants. These dihydrobenzofuran neolignans

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Scheme 125 Enantioselective synthesis of (+)-conocarpan **581**.

exhibit a wide range of biological activities, including cytotoxic, antiviral, and antifungal.[554,555] (+)-Conocarpan **581**, isolated from the wood of *Conocarpus erectus* by Hayashi and Thomson in 1975,[556] showed a range of biological activities, including insecticidal, antifungal, anti-inflammatory, and anti-trypanosomal.[557–559] The enantioselective synthesis of natural (+)-conocarpan was reported in 2013 by Chen *et al.*[560] The highlights of the synthesis are the asymmetric hydrogenation of prochiral ketones and intramolecular ring closure. Total synthesis of (+)-conocarpan **581** was started from 2′-fluoro-5′-bromophenyl acetic acid **582**. The acid was transformed into acid chloride **583** followed by FC reaction with a slight excess of anisole to provide ketone **584** in 92% yields over two steps. Subsequently, compound **584** provided (+)-conocarpan **581** in 84% yield (Scheme 125).[560]

Marmycin A, a unique angucycline analogue, was isolated by Fenical *et al.* in 2007 from the culture broth of a marine sediment-obtained actinomycete related to the genus *Streptomyces*. FC acylation and Dess–Martin oxidation were considered as the key steps in the synthesis of marmycin A **585**. In this route, firstly anthracen-1-amine **589** and glycal **588** gave the C1′ *N*-glycosidation product **590**. Next, *N*-trifluoroacetylation of **590** using TFAA/triethylamine followed by O-deprotection with ammonium resulted in a FC acylation product **591b** in 70% overall yield, other than the desired *N*-Boc product **591a**. Finally, compound **591b** provided compound **585** in several steps (Scheme 126).[561]

To confirm the FC acylation using $(CF_3CO)_2O$ and the nucleophilic addition occurring on the carbonyl group, diastereomeric *N*-glycosidation products **592** and **593** were reacted with $(CF_3CO)_2O$/triethylamine/DMAP and then ammonium to afford FC acylation products **594** and **595**, respectively, in 70% overall yield. Quaternary alcohols **586** and **587** were obtained from **594** and **595**, respectively, in 55% overall yield after several steps (Scheme 127).[561]

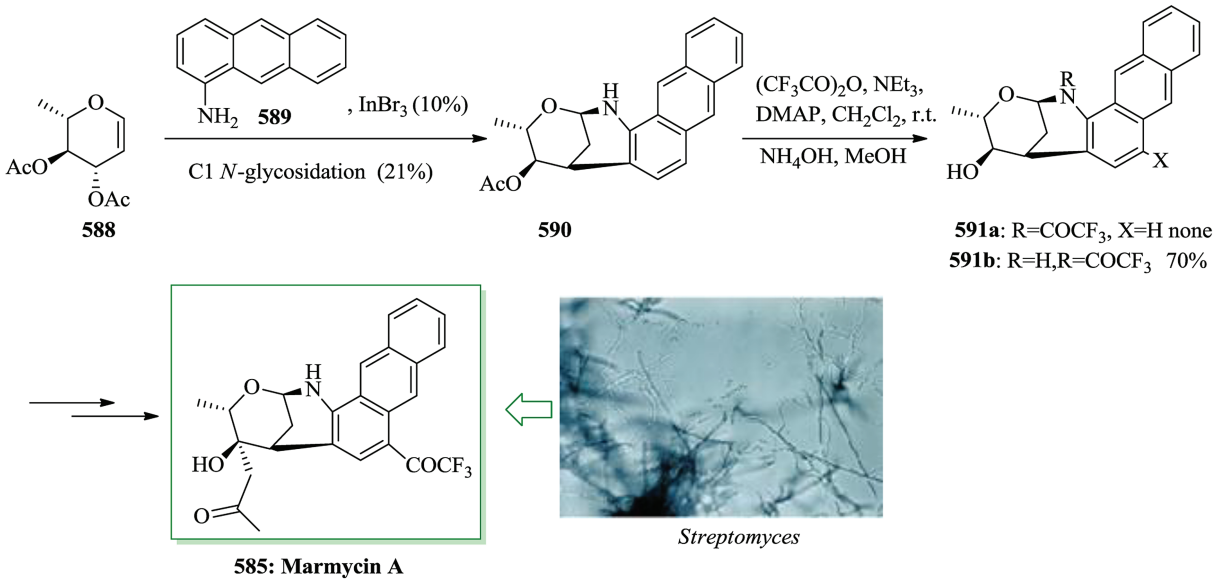
Marinamide **596** and its methyl ester **602** are two isoquinolinone alkaloids that were isolated from the metabolite of mixed fermentation of two mangrove endophytic fungi (strains no. 1924 and 3893) from the South China Sea. These two compounds were identified as 4-(2-pyrrolyl)-1-isoquinolone-3-carboxylic acid **596** and methyl 4-(2-pyrrolyl)-1-isoquinolone-3-carboxylate **602**, respectively. Compounds **596** and **602** exhibited significant antibacterial and[562] antitumor properties. The first total synthesis of isoquinolinone alkaloid marinamide **596** and its methyl ester **602** was developed in 2013 by Ji *et al.*[563] The key steps included a regioselective FC reaction of 1-benzyl-1*H*-pyrrole to generate the intermediate **601**. The synthesis of intermediate **601** is the key step for the formation of marinamide and its methyl ester, which included a regioselective FC acylation of 1-benzyl-1*H*-pyrrole to generate a 2-acylpyrrole derivative. Phthalic anhydride **597** afforded the acyl chloride **598** after several steps. Compound **598** reacted with **599**, which was obtained by reacting pyrrole **600** with benzyl bromide in anhydrous dimethyl sulfoxide, *via* the catalysis of zinc powder in toluene at ambient temperature to effectively give the key intermediate **601** in 68% yield.[564] Compound **601** gave the methyl ester of marinamide **602**.[565] Finally, hydrolysis of **602** with hydrochloric acid gave marinamide **596** (Scheme 128).[563]

The naphtho[2,3-*c*]furandiones (isofuranonaphthoquinones), a relatively small group of secondary metabolites with various biological properties, have been isolated from fungal, botanical, bacterial and insect sources. Monosporascone **603** was isolated from the fungus *Gelasinospora pseudoreticulata*.[566] Monosporascone is the only known isofuranonaphthoquinone with oxygenation at the 5 and 7 positions. The first total synthesis of the natural isofuranonaphthoquinone monosporascone **603** was exhibited in 2014 by Piggott *et al.*[567] The five-step synthesis established involves a silver acetylide–acid chloride coupling, domino Diels–Alder-retro-Diels–Alder reaction, and an intramolecular FC acylation reaction. Total synthesis of the natural product monosporascone **603** was accomplished in 57% yield overall. The synthesis of monosporascone **603** was started from the reaction of silver acetylide **605**[568] and acid chloride **604**,[569] which after four steps gave acid chloride **606**. Reaction of acid chloride **606** with five equivalents of aluminium chloride,[570] with an extended reaction period to permit selective demethylation of the perimethoxy group, gave monosporascone **603** in satisfactory yield (Scheme 129).[571]

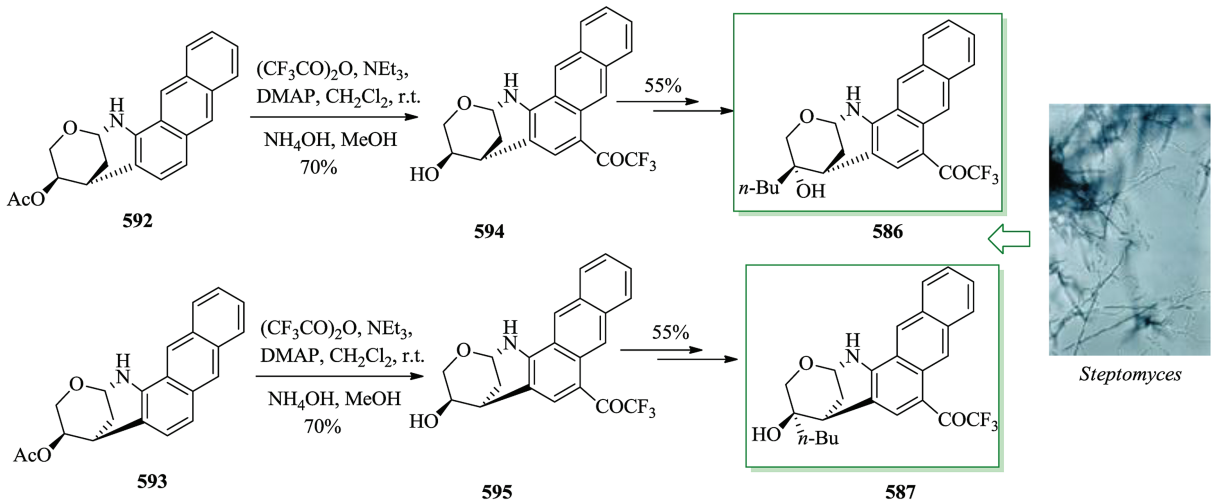
In 2006, Merck researchers reported the discovery of a unique and active antibiotic, (−)-platensimycin **607**, isolated from *Streptomyces platensis* strain MA7327, which originated

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Scheme 126 Total synthesis of marmycin A **585**.

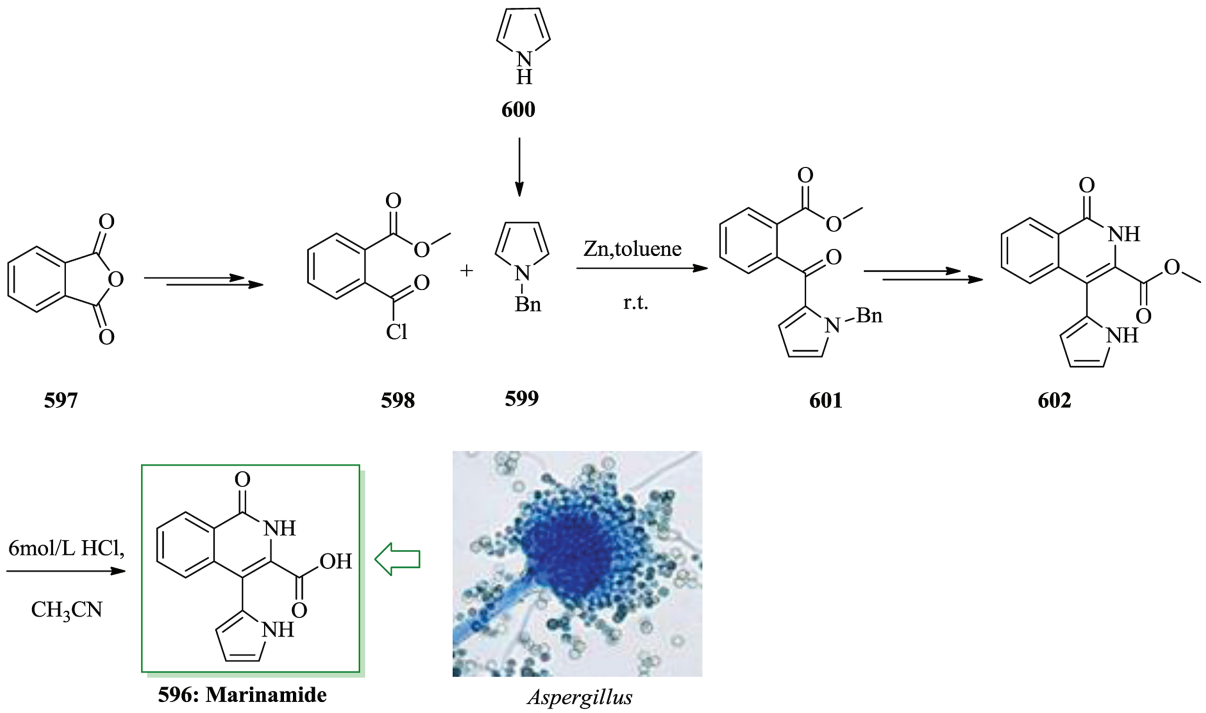


Scheme 127 The formation of quaternary alcohols **586** and **587**.

from South Africa.[572] Lear *et al.* developed its total synthesis *via* a four-step construction of the aromatic amine segment and an improved stereocontrolled assembly of the ketolide segment, (−)-platensic acid. Key synthetic advances contain a modified Lieben haloform reaction, a sterically controlled chemo- and diastereo-selective organocatalytic conjugate reduction and a bismuth(III)-mediated FC cyclization. The longest linear sequence is 21 steps with an overall yield of 3.8% from eugenol. In this approach, firstly, compound **608** was converted into lactol **609** *via* several steps. A practical limitation of this method is the excessive requirement for very toxic and ecologically harmful tin(IV)chloride to drive the FC arylation. Hence, $Bi(OTf)_3$ was found to be the most superior in reactivity and gave **610** in 94% yield. Subsequently, compound **610** was converted into the tetracyclic dienone **613** after several steps. Then, the Lewis acid-catalyzed cyclization of the *cis*-tosyl lactol **611**, which could be accessed directly from **608**, was explored. The reaction of **611** with tin(IV) chloride needed a greater excess (8–10 equiv.) to achieve a high-yielding FC transformation. Inspired by Bartoli, Sambri, and co-workers,[573] they eventually turned to lithium perchlorate as a cocatalyst to $Bi(OTf)_3$ to help drive the FC cyclization of **611**. The best catalytic combination of 5 mol% $Bi(OTf)_3$ with 3 equivalents of lithium perchlorate eventually provided **612** in 94% yield. Subsequently, compound **612** was converted into **613** *via* several steps and then compound **613** was transformed into **614** *via* several more steps (Scheme 130).[574]

A unique synthesis of the aromatic section of platensimycin **607** was accomplished. This synthesis was started with FC acylation of **615** with acetic acid in hot PPA to provide the acetophenone **616**. Next, compound **616** was converted into compound **617** *via* several steps (Scheme 131).[574]

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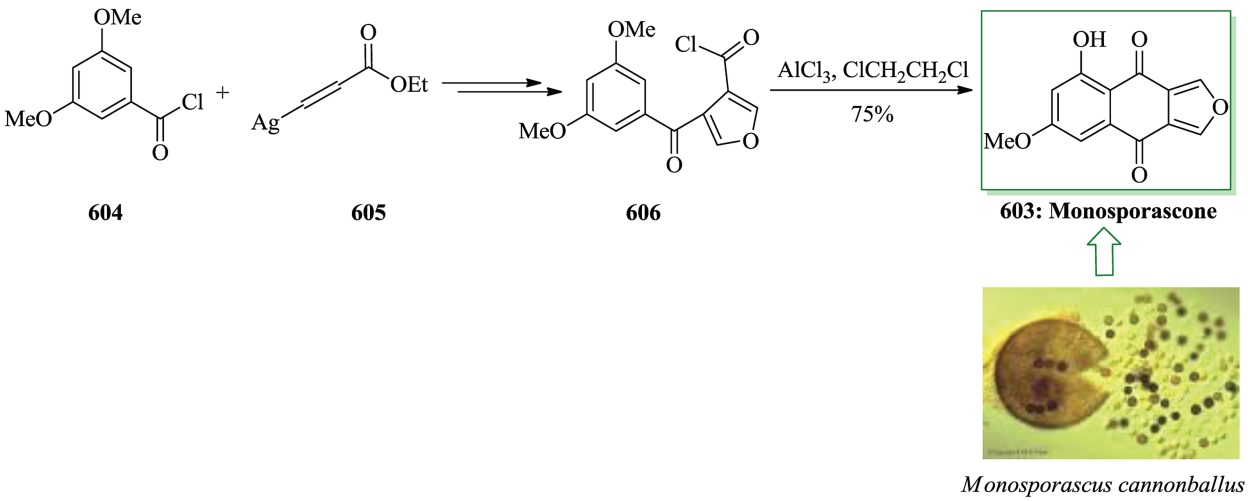


Scheme 128 Total synthesis of marinamide **596**.

Finally, platensic acid **614** and the aniline core **617** afforded (−)-platensimycin **607** in 60% yield upon several steps (Scheme 132).[574]

The natural product 2,4,6-trihydroxy-3-geranyl-acetophenone (tHGA) isolated from the medicinal plant *Melicope ptelefolia* was demonstrated to show lipoxygenase (LOX) inhibitory activity. It is known that LOX plays a significant role in inflammatory response as it catalyzes the oxidation of unsaturated fatty acids.[575,576] Shaari *et al.* in 2014 reported synthesis of tHGA analogues through simple FC acylation and alkylation reactions.[577] In this method, they reported the formation of 3-geranyl-1-(2′-methylpropanoyl)phloroglucinol **618**, a natural product known in *Hypericum empetrifolium*. Direct FC acylation of phloroglucinol **496** was achieved with isobutyryl chloride as the acylating agent using anhydrous $AlCl_3$ to provide compound **619**.[578] Subsequently, the geranyl scaffold was introduced through electrophilic substitution of geranyl bromide with anhydrous K_2CO_3 as the base in dry MeOH under reflux to afford the FC alkylation product **618** in satisfactory yield (19.5%) (Scheme 133).[577]

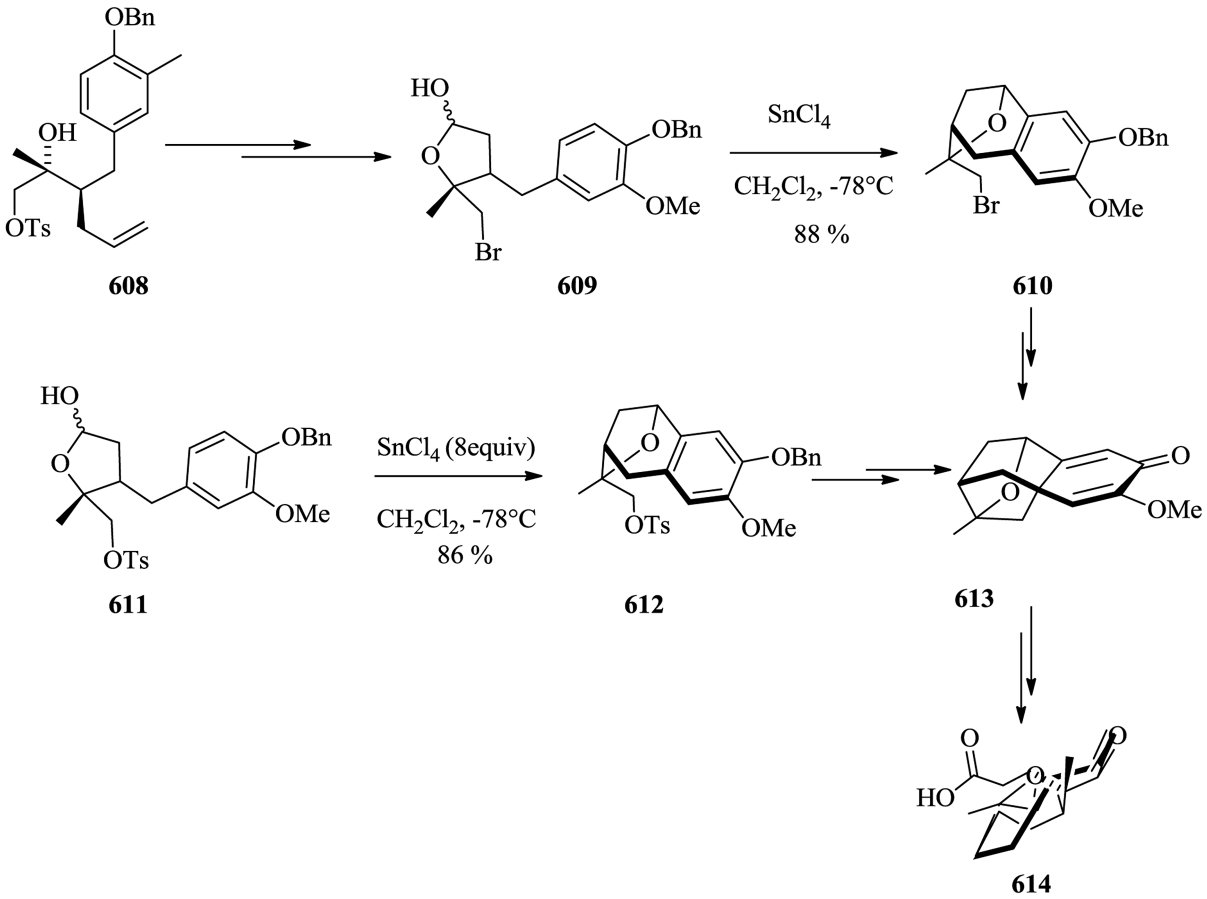
The merochlorins, a structurally uncommon group of four chlorinated meroterpenoids, have potent antimicrobial activity and were isolated from a marine strain of *Streptomyces* bacteria.[579] Merochlorin A **620** contains four contiguous stereocenters embedded in a bicyclo[3.2.1]octanone scaffold. The complex, polycyclic structures of merochlorins A, obtained from



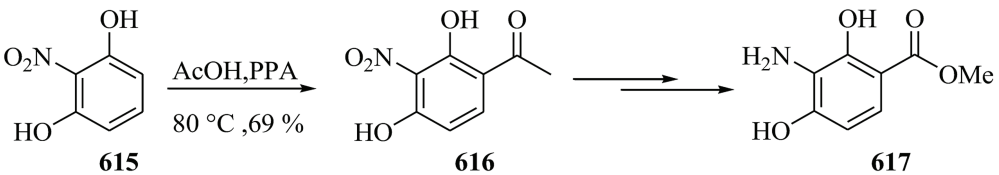
Scheme 129 Total synthesis of monosporascone **603**.

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Scheme 130 Total synthesis of compound **614**.



Scheme 131 The formation of compound **617**.

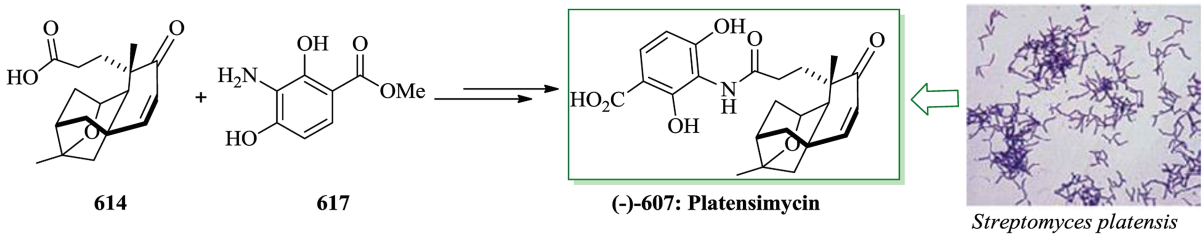
a unique terpene side chain, have aroused the interest of chemists.[580,581]

Total synthesis of merochlorin A was exhibited alongside the biosynthetic studies of George *et al.* in 2015.[582] Synthesis of merochlorin A **620** was started with a FC reaction of methyl 3,5-dimethoxyphenylacetate **621** and chloroacetyl chloride to afford ketone **623** in 56% yield. Finally, merochlorin A **620** was obtained from compound **623** in 42% yield *via* several steps (Scheme 134).[582]

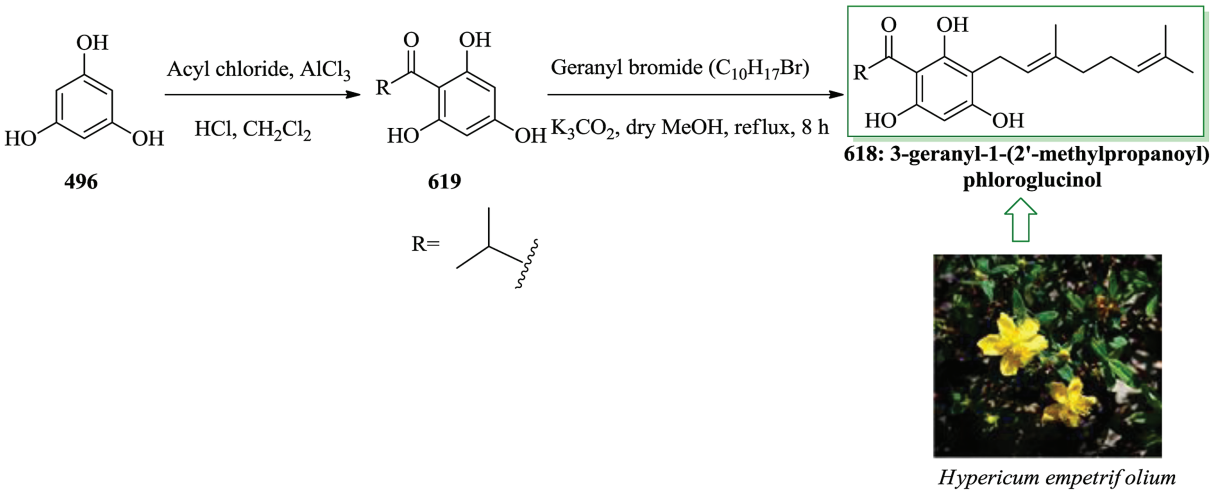
Curvulone B **624**, a *cis*-di functionalized tetrahydropyran natural product, is one of a wide range of relevant compounds isolated from the marine fungus *Curvularia* sp., which was isolated from the marine alga *Gracilaria folifera*.[583] A total synthesis of curvulone B was achieved using a FC reaction and a highly *cis*-selective intramolecular oxa-Michael addition. This synthetic method was accomplished in ten steps and 39% overall yield. Total synthesis of Curvulone B **624** was started from 3,5-dihydroxybenzoic acid **625**. Next, compound **625** afforded ester **626** upon several steps. The FC acylation reaction of ester **626** was performed with whole regioselectivity with a 2-chlorobenzyl protecting group to afford ketone **628** in 89% yields. Finally, ketone **628** afforded the target natural product **624** *via* several steps (Scheme 135).[584]

Triumphalone **629** and isotriumphalone **630**, highly oxidized monomeric phloroglucinols[585,586] with two stereogenic centers, were extracted from *Melaleuca triumphalis* by Brophy *et al.*[587] The first total synthesis of (±)-triumphalone was accomplished in 8 steps from phloroglucinol. Synthetic triumphalone was converted into (±)-isotriumphalone in one step. In this route, firstly phloroglucinol **496** was converted into **632** through the FC acylation reaction in 82% yield.[588] Subsequently, (±)-triumphalone **629** was provided from compound **632** *via* several steps and also compound **629** was transformed to (±)-isotriumphalone **630** in one step. An spontaneous change of **629** to

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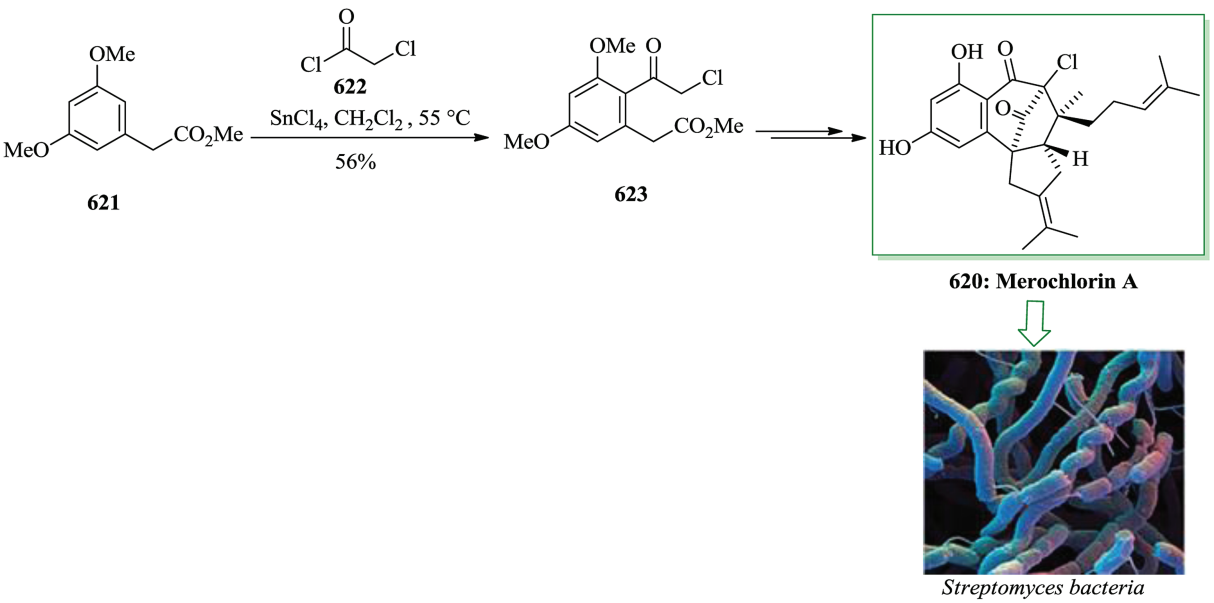
Scheme 132 Total synthesis of (−)-platensimycin **607**.



Scheme 133 Total synthesis of 3-geranyl-1-(2′-methylpropanoyl)phloroglucinol **618**.

630 was detected. The structure change gradually occurred to afford a 3 : 7 mixture of **629** and **630** upon standing for 24 months (Scheme 136).[589]

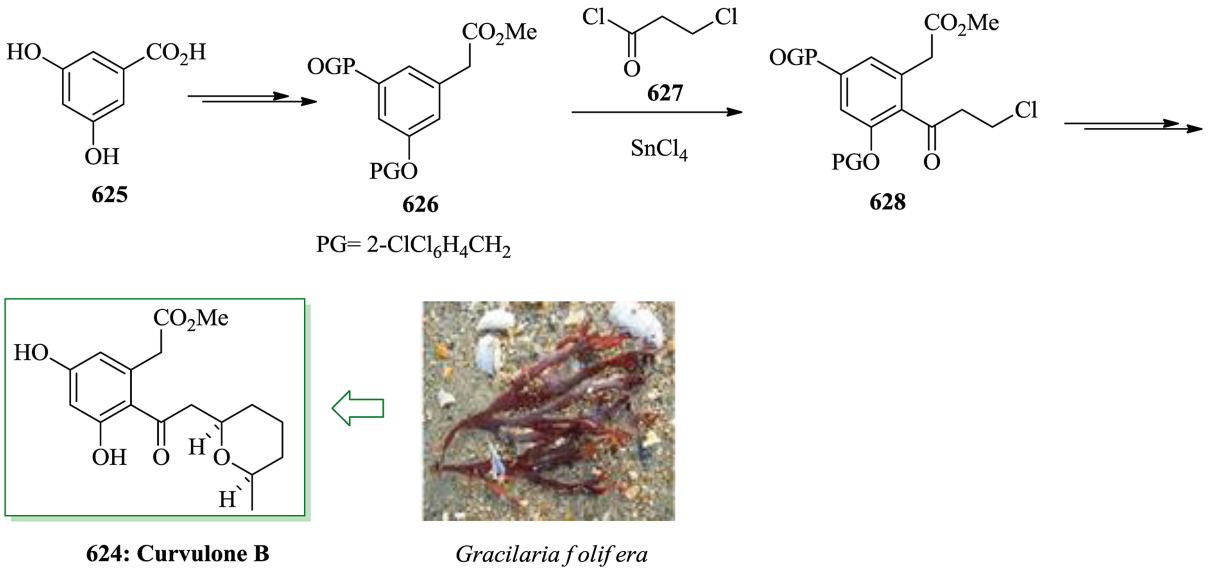
Flavonoids, a group of polyphenolic compounds that are abundant in plants,[590] include dietary components of potential importance to health.[591] In addition, flavanoids are emerging as a potentially significant unique group of pharmaceutical lead substrates.[590] Among the several classes of flavonoids, dihydrochalcones exhibit a series of biologically remarkable activities, including antioxidant,[592,593] antiinflammatory,[594] antileishmanial,[595] antidiabetic,[596] anticancer[597] and molluscidal[598] properties.[599] Peng *et al.* described the isolation and



Scheme 134 Total synthesis of merochlorin A **620**.

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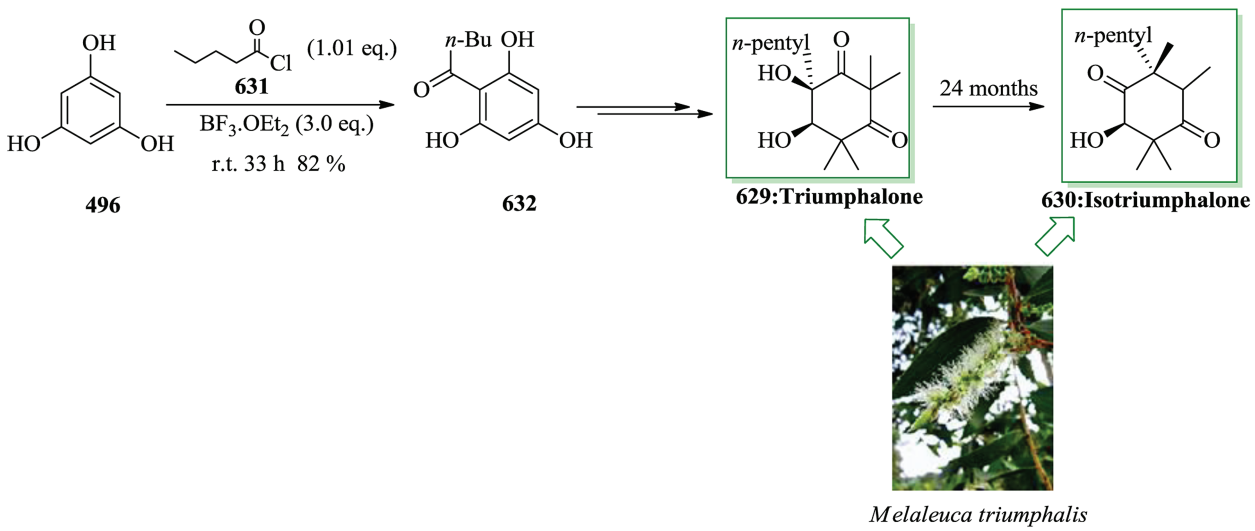


Scheme 135 Total synthesis of curvulone B **624**.

identification of a significant dihydrochalcone, named taccabulin E **633**, from extracts of the plant species *Tacca chantrieri* and *Tacca integrifolia*.[600] Spring *et al.* in 2015 reported the concise and divergent total synthesis of dihydrochalcone **633**,[601] which was started from catechol **634**. Next, FC acylation reaction of **634** permitted access to **635** in moderate yield.[602,603] Finally, compound **635** was converted into taccabulin E **633** in 94% yield upon several steps (Scheme 137).[601]

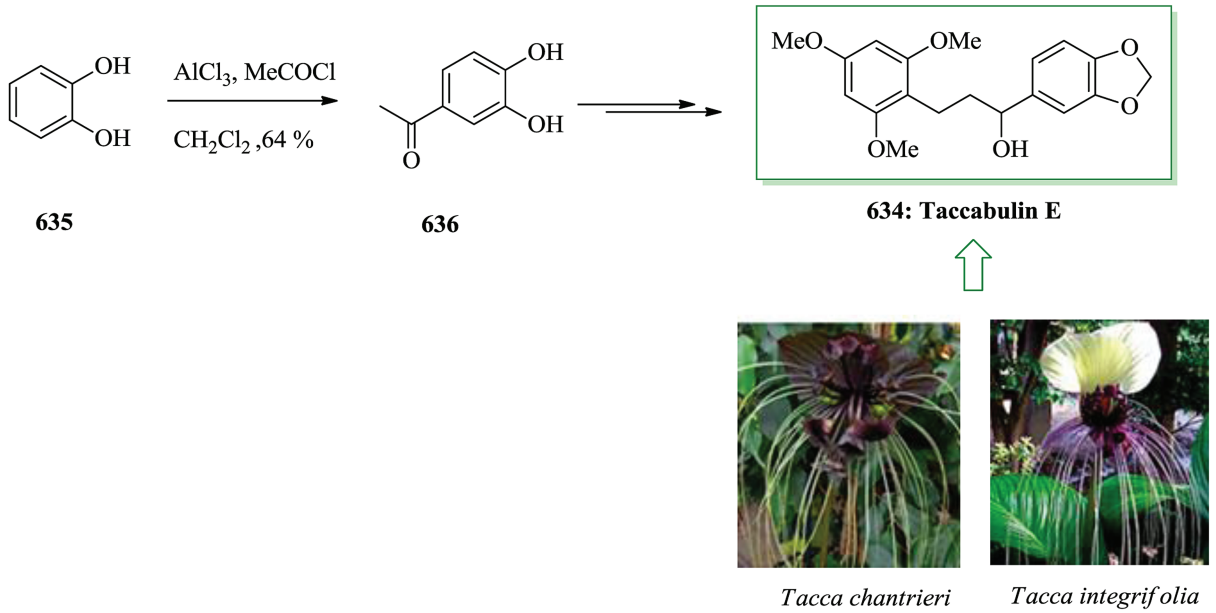
Diarylheptanoids, with two aryl groups at C(1) and C(7) of a C_7 chain, are a significant group of natural products isolated from nature.[604–608] Generally, diarylheptanoids are categorized into three groups comprising linear diarylheptanoids, macrocyclic biarylheptanoids, and macrocyclic diaryl ether heptanoids. Sun *et al.*[609] isolated two furan-cyclized diarylheptanoids, **637** and **638**, from rhizomes of *Alpinia officinarum Hance* (Zingiberaceae) as minor constituents and they were demonstrated to have satisfactory cytotoxicity against the IMR-32 human neuroblastoma cell line. Seçen *et al.* in 2015 reported a synthetic strategy for the formation of two natural diarylheptanoids, 2-benzyl-5-(2-phenylethyl)furan **637** and 2-methoxy-4-{[5-(2-phenyl-ethyl)furan-2-yl]methyl}phenol **638**.[610] Total synthesis of the natural product **637** was started from benzyl bromide **639**, which afforded 2-(2-phenylethyl)furan **640** *via* several steps. FC acylation of compound **640** with benzoyl chloride using aluminium chloride afforded ketone **641** in 73% yield. Finally, the reduction of **641** afforded **637** in 81% yield (Scheme 138).[610]

Then, this group used 2-(2-phenylethyl)furan **640** as the initiating precursor to form natural product **638**. In this route, compound **640** was reacted with 4-(acetyloxy)-3-methoxybenzoyl chloride **642** *via* FC reaction to afford ketone **643** in a satisfactory yield (59%). Subsequently, natural product **642** was

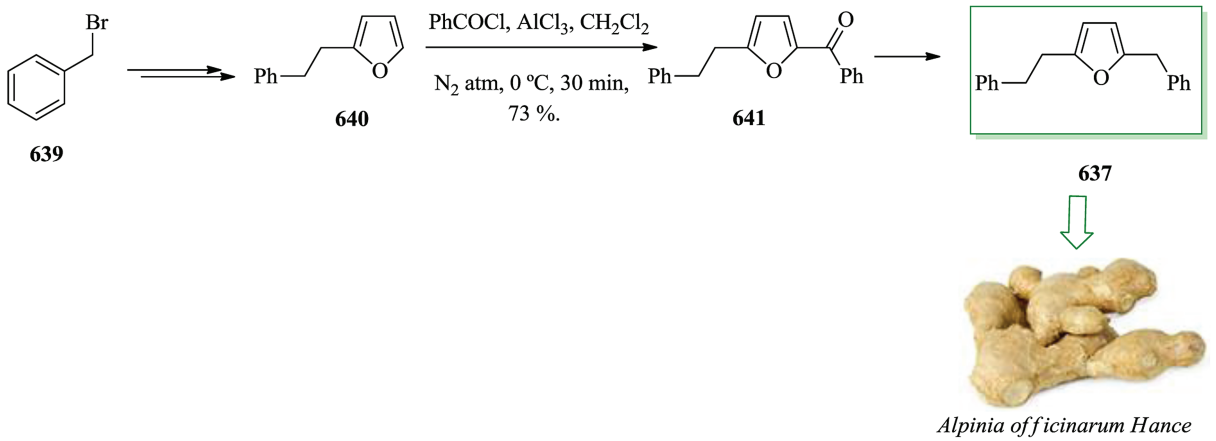


Scheme 136 Total synthesis of triumphalone **629** and isotriumphalone **630**.

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Scheme 137 Total synthesis of taccabulin E **633**.



Scheme 138 Total synthesis of furan-cyclized diarylheptanoid **637**.

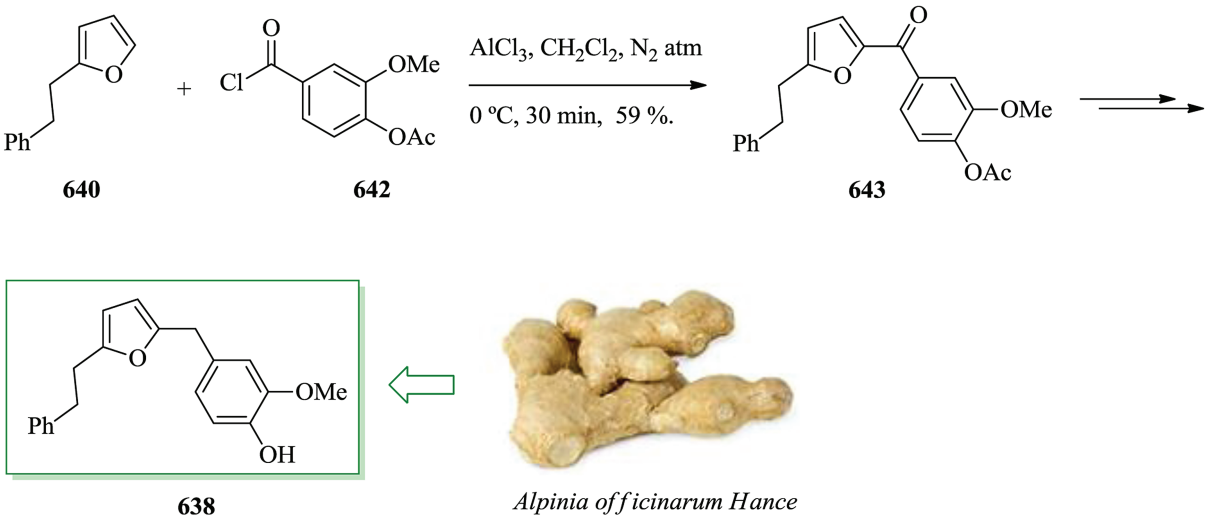
synthesized from compound **643** upon several steps (83%) (Scheme 139).[610]

Stigmatellin A and B, two unique antibiotics, were isolated from the gliding bacterium *Stigmatella aurantiaca*.[611] They are powerful inhibitors of electron transport in chloroplasts and mitochondria. The absolute configuration of Stigmatellin A was confirmed as (*S*,*S*,*S*,*S*) by chemical correlation.[612] A significant and enantioselective method for the formal total synthesis of stigmatellin A was developed in 2017 by Yadav *et al.*[613] The key steps included in this synthesis are desymmetrization, FC acylation reaction, regioselective demethylation, Baker–Venkataraman rearrangement and Grubbs cross-metathesis. Total synthesis of stigmatellin A was started from tetramethoxy benzene **645**. The FC acylation reaction of tetramethoxy benzene **645** with propanoyl chloride using aluminium chloride gave the corresponding ketone **646**.[614] Finally, compound **646** gave stigmatellin A **644** after several steps (Scheme 140).[613]

γ-Lycorane is an alkaloid isolated from the plants of the *Amaryllidacae* group.[615] Various methods for the synthesis of γ-lycorane **647** have been reported, despite, as several authors have pointed out, its apparent lack of useful pharmacological activities.[616,617] A total synthesis of γ-lycorane was accomplished using *N*-tosylpyrrole as a key framework. The synthesis uses both an intermolecular and an intramolecular FC reaction, and also an entirely diastereoselective hydrogenation of a late-step pyrrole intermediate. For the synthesis of γ-lycorane **647**, *N*-tosyl pyrrole **648** was subjected to an FC acylation reaction with succinic anhydride. The resulting acid **650** afforded the corresponding alcohol **651** *via* several steps. The reaction between alcohol **651** and amberlyst-15 easily afforded the corresponding FC product **652** in 82% yield by construction of the novel C–C bond at the α-position. Finally, compound **652** gave γ-lycorane **647** *via* several steps (Scheme 141).[618]

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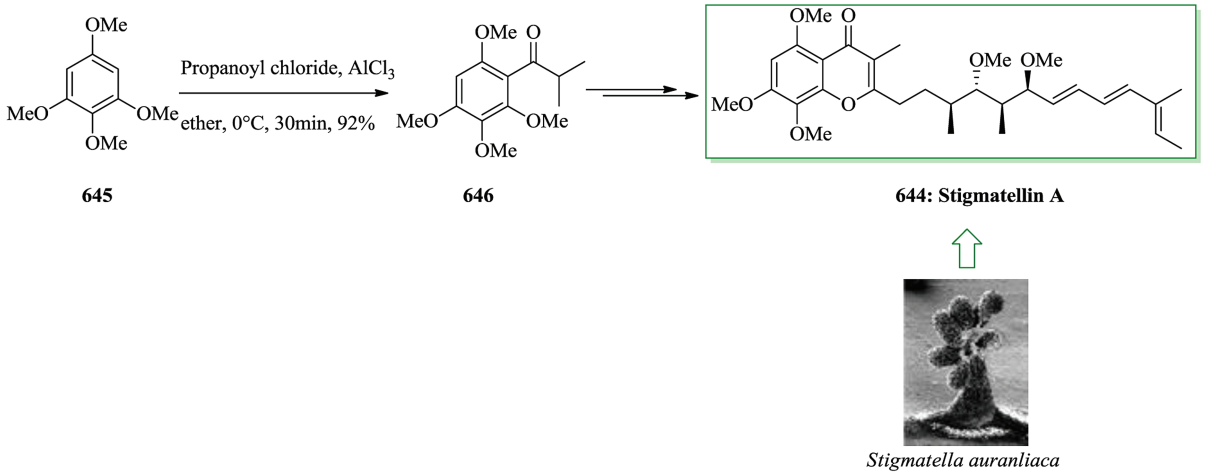
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Scheme 139 Total synthesis of furan-cyclized diarylheptanoid **638**.

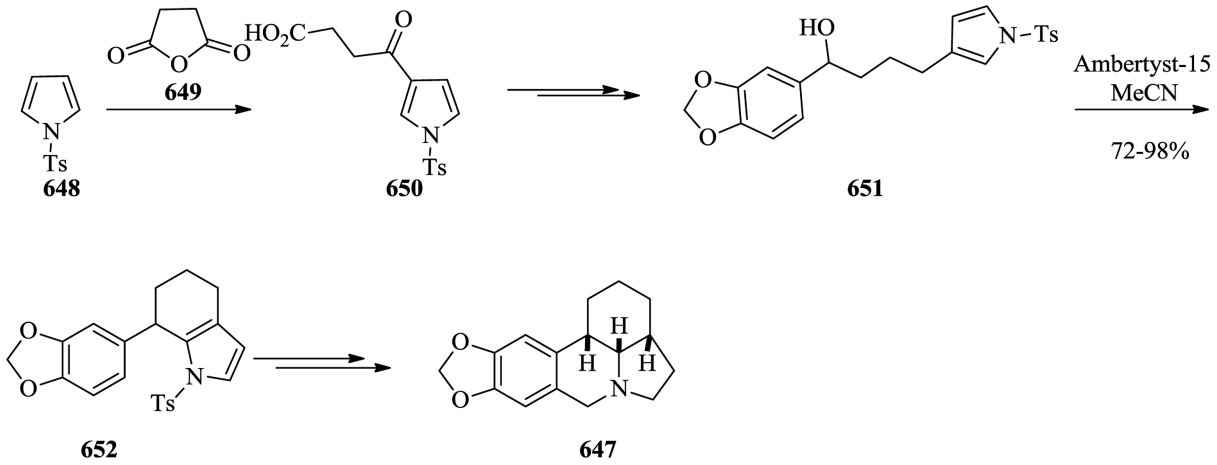
Calothrixin A and B are unique indolo[3,2-*j*]phenanthridine alkaloids that were isolated from *Calothrix* cyanobacteria in 1999.[619] These natural products show significant biological activities, for example antimalarial and anticancer, and they inhibit bacterial RNA polymerase.[620] The total synthesis of oxacalothrixin B, an isostere of the biologically significant carbazoloquinone alkaloid calothrixin B, was accomplished from 2-acetyl-3-methylbenzofuran. In this route, initially FC acylation reaction of 2-methylbenzofuran **654**[621] using CH_3COCl with tin(IV) chloride in dry dichloromethane at 0 °C gave 3-acetyl-2-methylbenzo[*b*]furan **655** in moderate yield. Next, compound **655** afforded oxacalothrixin B **653a–f** in moderate yields after several steps (Scheme 142).[622]

Coumarins constitute a significant group of heterocyclic compounds that are known as benzo-α-pyrones, wherein a pyran ring is fused with a benzene ring. Two unique geranylated coumarins, mammeasins C and D (**656** and **657**), were isolated together with 20 other coumarins.[623] Compounds **656** and **657** are rare coumarins, wherein a dioxaphenalene type scaffold is generated by attaching a pyran ring to the coumarin unit. Both these compounds exhibit active aromatase inhibitory activity comparable to that of aminoglutethimide, which was applied as a reference standard.[623] The first total synthesis of the geranylated pyranocoumarins, mameasins C **656** and D **657**, aromatase inhibitors isolated from the flowers of *Mammea siamensis*, was achieved in five steps, starting from phloroglucinol **496**. Based on this method, total synthesis of **656** and **657** was started from **496**, in which **496** was exposed to FC acylation with crotonyl chloride. This reaction gave the corresponding chromanone 5,7-dihydroxy-2-methylchroman-4-one **659**, albeit in a low yield of 31%. Next compound **659** provided pyranocoumarin **660** in 69% yield. FC acylation reaction of **660** with butyryl chloride or isobutyryl chloride was applied for the acylation of phenolic compounds,[506] and two regioisomers (**663**/**664**) in 4 : 1 and 5 : 1 ratio were provided. Finally, compounds **663a** and **663b** afforded the corresponding **656** and **657** in 23% and 15% yield after 2 steps, respectively. In addition, examining of the intermediates obtained in the synthetic route to **656** and **657** revealed that de-geranylated pyranocoumarins **663** and **664**

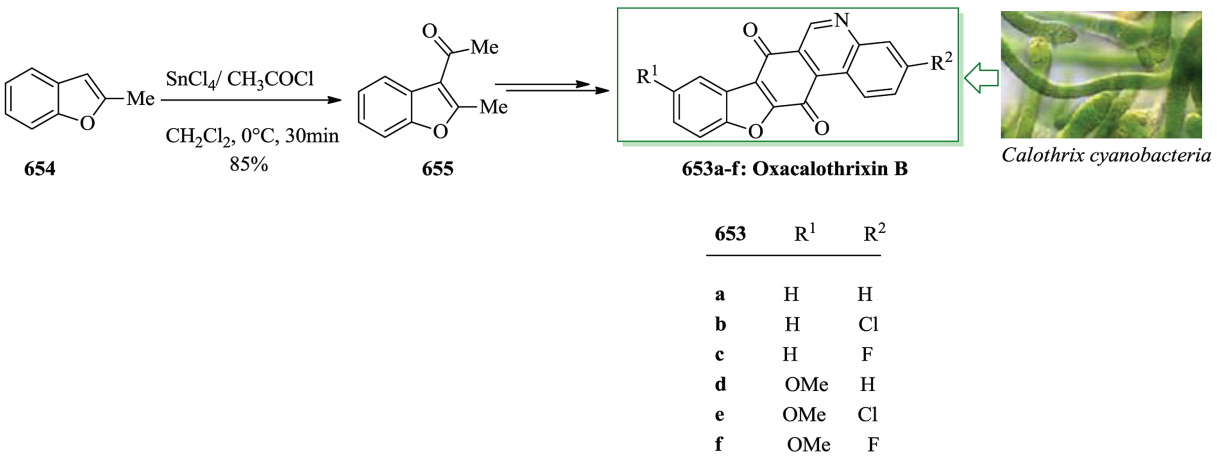


Scheme 140 Total synthesis of stigmatellin A **644**.

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Scheme 141 Total synthesis of γ-lycorane **647**.



653	R^1	R^2
a	H	H
b	H	Cl
c	H	F
d	OMe	H
e	OMe	Cl
f	OMe	F

Scheme 142 Total synthesis of oxacalothrixin B **653a–f**.

exhibit superior aromatase inhibitory activity as compared to the natural products **656** and **657** (Scheme 143).[624]

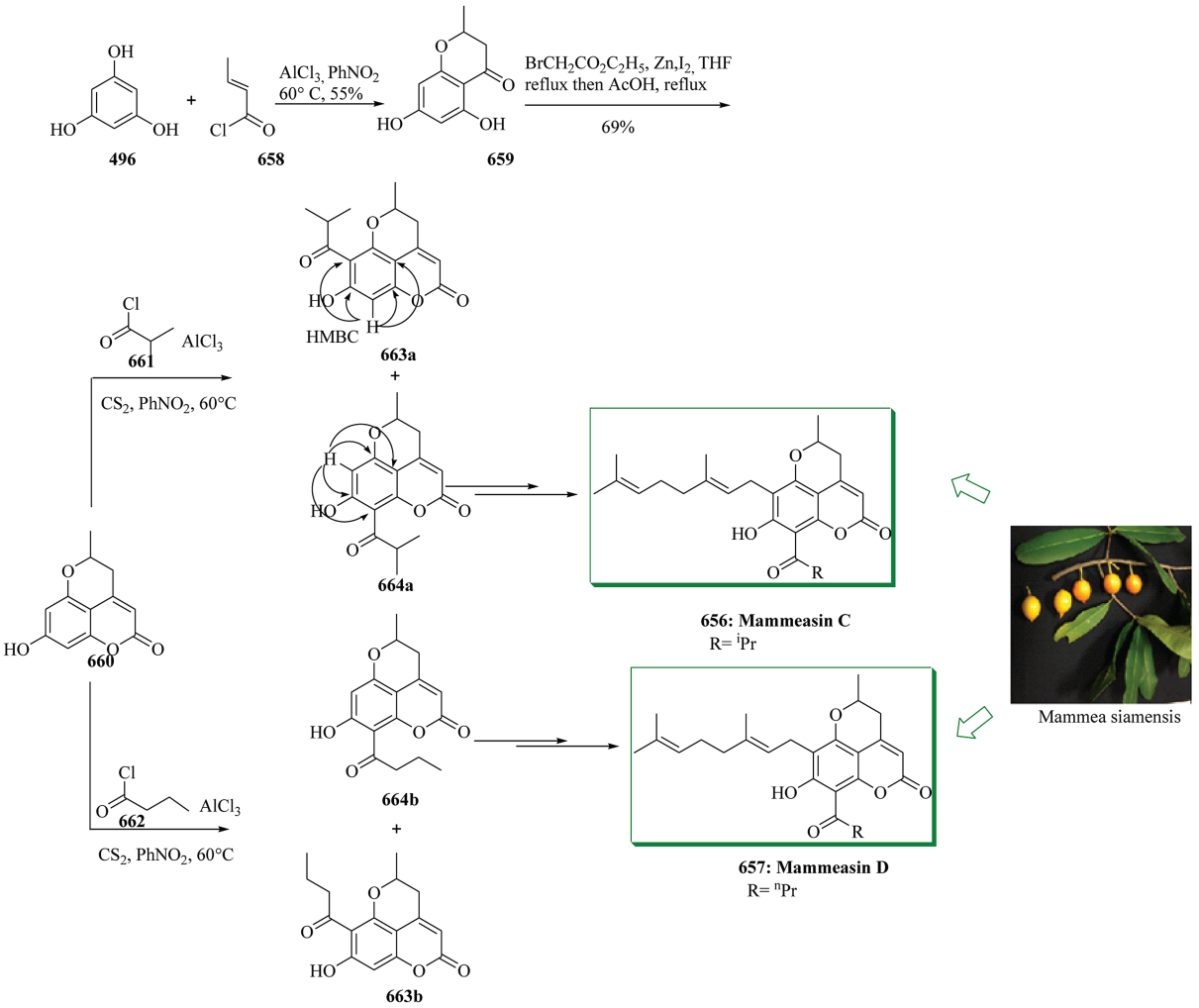
Isoflavone *C*-glycosides, in which the sugar scaffold is attached by a carbon–carbon bond directly to the isoflavone ring, are not simply hydrolyzed in acidic gastric juices, unlike O-glycosides and aglycone. These glycosides exhibit several biological properties, including radioprotective,[625] anti-myocardial ischemic,[626] mitogenic and colony-stimulating,[627] and antidiabetic[628] activities. Among these compounds, puerarin, which is known mainly in *Pueraria radix*, exhibits a strong anti-myocardial ischemic influence.[629] Two isoflavone C-glycosides (6-*tert*-butyl puerarin and 6-*tert*-butyl-4′-methoxypuerarin) were obtained using FC acetylation reaction and Vilsmeier–Haack cyclization in five steps with overall yields of 14.6% and 14.2%, respectively. Initially, *C*-glucosyl acetophenone **666** was converted into 2 *C*-β-D-glucopyranoside **667** after several steps. The key intermediate deoxybenzoin **669** was obtained from FC acetylation reaction of **667** using anhydrous $AlCl_3$ with a 63.6% yield.[630,631] Lastly, compound **669** gave 6-*tert*-butyl-4′-methoxypuerarin **665a** and 6-*tert*-butyl puerarin **665b** with 95.5% and 98.6% yields,[632,633] respectively (Scheme 144).[634]

2.5. Miscellaneous

With the increase in the advanced age population, neurodegenerative disorders, for example Alzheimer's and Parkinson's disease, are emerging as a major social issue, therefore resulting in great demand for new therapeutic drugs to prevent these diseases.[635] Significant efforts at searching for small-molecule-based natural products with neurotrophic activities resulted in the isolation of (−)-talaumidin **670** from Brazilian *Aristolochia arcuata* Masters.[636] Talaumidin and its analogues show important neurite outgrowth-promoting and neuroprotective activities in the primary cultured rat corticaland additionally in the hippocampal neurons.[636] The initial asymmetric total synthesis of neurotrophic (−)-talaumidin **670** was developed in 16 steps from 4-benzyloxy-3-methoxybenzaldehyde in *ca.* 10.7% overall yield. In this method, the key steps are Evans asymmetric *anti*-aldol reaction, hydroboration/oxidation and epimerization and FC arylation reaction. Total synthesis of

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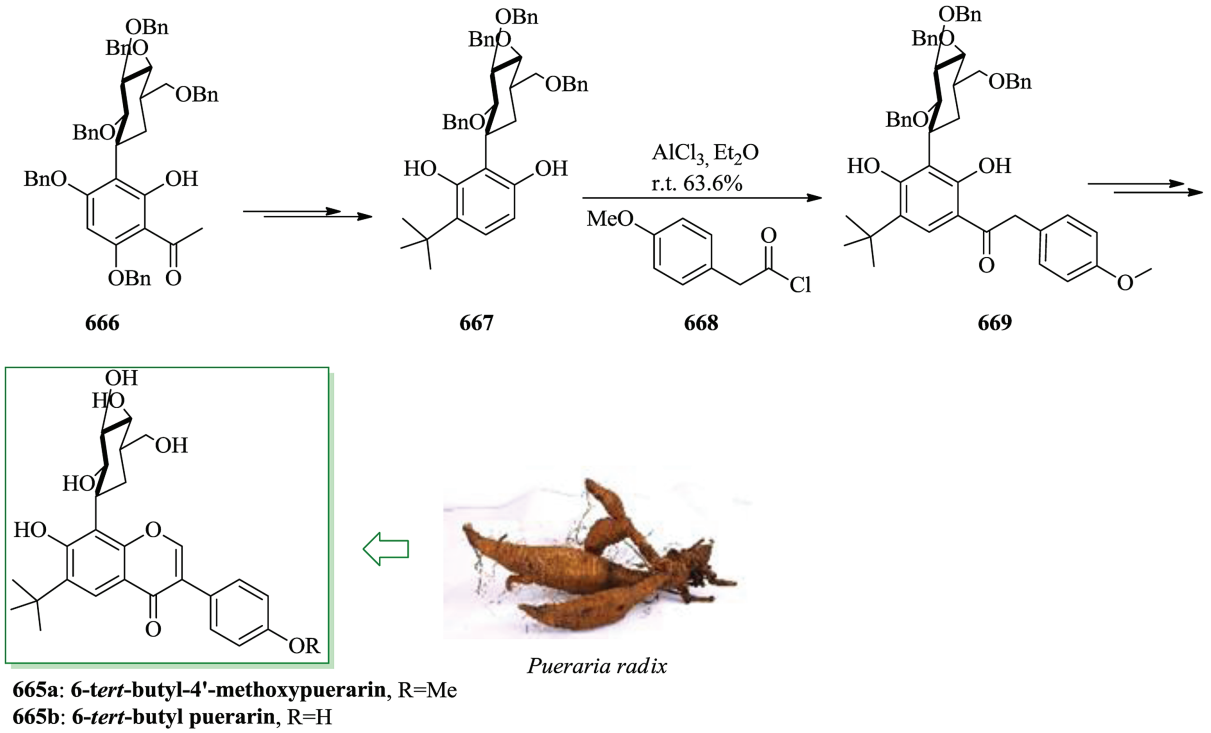
Scheme 143 Total synthesis of mammeasins C **656** and **657**.

(−)-talaumidin **670** was started from the reaction between 4-benzyloxy-3-meth-oxybenzaldehyde **671** and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone **672** to provide five-membered acetal **673** *via* several steps. Then, FC-type arylation reaction of **673** with 1,2-methylenedioxybenzene **421** using tin(IV) chloride in dichloromethane afforded only the corresponding (5*S*)-**675** in 89% yield along with 2% of talaumidin **670**. Finally, debenzylation of **675** with $Pd(OH)_2$ in ethanol provided (−)-(2*S*,3*S*,4*S*,5*S*)-**670** in 77% yield (Scheme 145).[637]

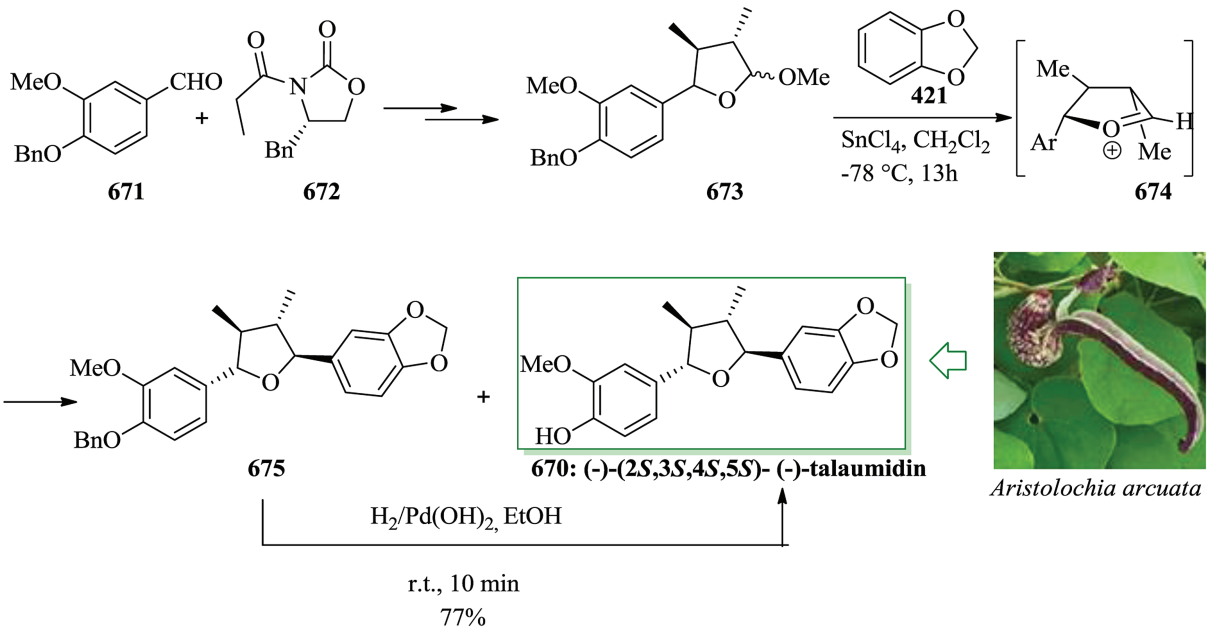
An oxidative FC reaction containing various aromatic compounds catalyzed by a hypervalent iodine reagent was accomplished by employing polyfunctionalized phenols. This reaction provided rapid access to extremely functionalized compounds, including a dienone, a quaternary carbon center, and an aromatic ring. The product's framework is found in various naturally occurring compounds. Based on this method, total synthesis of compounds belonging to the Amaryllidaceae alkaloids group, for example *O*-methyljoubertiamine, mesembrine, and its natural derivative the dihydro-*O*-methyl-sceletenone, was accomplished in eight/nine steps. The synthetic pathway to these molecules features a significant transformation on the basis of a Fukuyama and Michael-retro-Michael tandem method. The synthesis of **679** was started from 2,4,6-trimethylphenol **676**, which afforded compound **677** *via* several steps. Subsequently, reaction of compound **678a** or **678b** with TBAF leads in satisfactory yield to the bicyclic compound **679** with complete regioselectivity regarding the alkene, including the silyl substituent, the latter being subsequently removed under the reaction conditions. This oxidative FC reaction permits quick access to substituted synthons, including a quaternary carbon center, a dienone, and an aromatic scaffold, and various functionalities can be present on the side chain. Such an intermediate could provide some opportunity for total synthesis of different naturally occurring compounds. The most well-known belong to the group of *Amaryllidaceae* alkaloids (Scheme 146).[638]

Based on this method, two alkaloids of this group were synthesized. Mesembrine **680a** and *O*-methyljoubertiamine **681** are alkaloids present in *Sceletium tortuosum*. They were demonstrated to be very active serotonin reuptake inhibitors, potent at very low doses. The 4,5-dihydro-4′-*O*-methyl-sceletenone **680b** is a simpler natural derivative of mesembrine

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Scheme 144 Total synthesis of 6-*tert*-butyl-4′-methoxypuerarin **665a** and 6-*tert*-butyl puerarin **665b**.



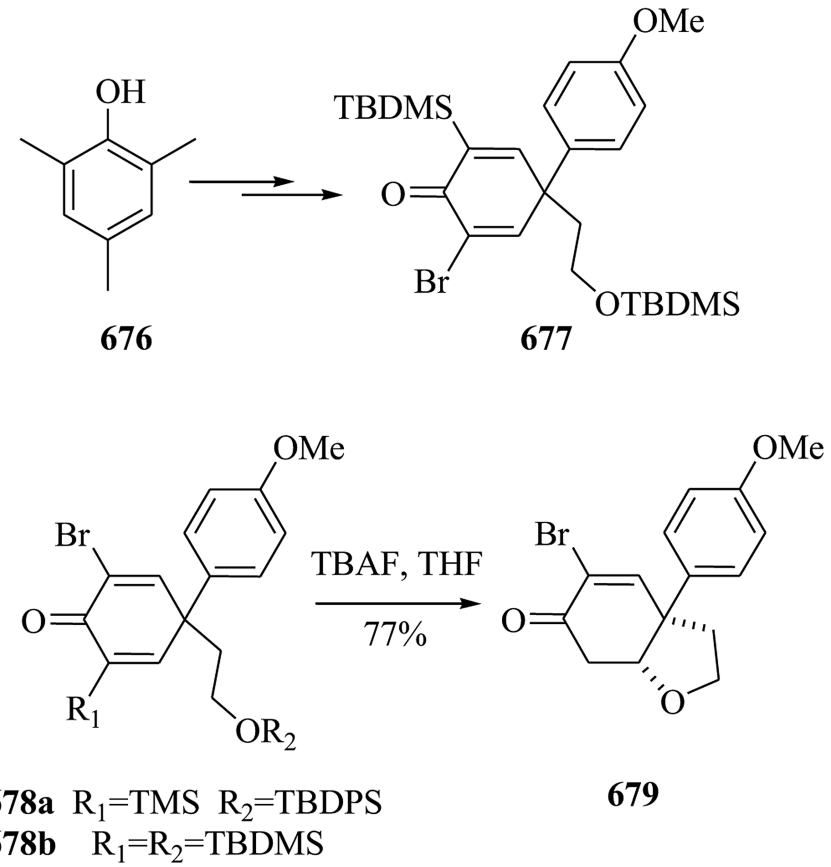
Scheme 145 Total synthesis of (−)-talaumidin **670**.

extracted from *Aptenia cordifolia*. Starting from 2-(4-hydroxyphenyl)ethanol **682**, total synthesis of mesembrine and 4,5-dihydro-4′-*O*-methylsceletenone was achieved *via* several steps in 86% yield. Furthermore, the transformation of 4,5-dihydro-4′-*O*-methylsceletenone, **680b**, into *O*-methyljoubertiamine **681** was accomplished by reaction with iodomethane (Scheme 147).[638]

(2)-Talaumidin **683** and (2)-galbelgin **684**, naturally occurring lignans, were isolated from *Aristolochia arcuata*[636] and *Piper futokadsura*.[639] They are 2,5-diaryl-3,4-dimethyl-tetrahydrofuran lignans.[640] Among them, (2)-talaumidin **683** demonstrated important neurotrophic activity in the primary culture of rat cortical neurons and could serve as a promising lead compound for the treatment of neurodegenerative disorders, for example

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Scheme 146 The formation of the bicyclic compound **679**.

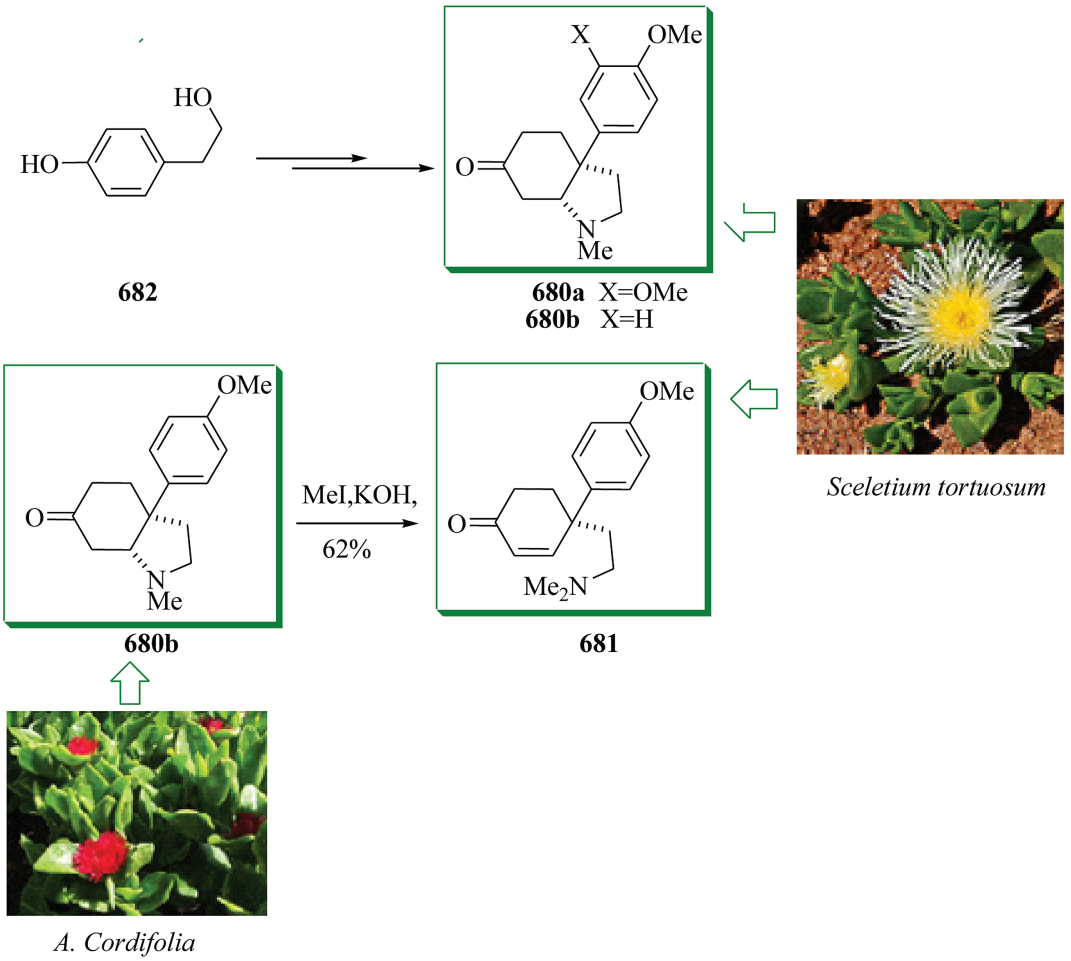
Alzheimer's and Parkinson's disease,[641] whereas (2)-galbelgin **684** exhibits anti-HBV activity.[642] (2)-Talaumidin **683** and (2)-galbelgin **684** were obtained starting from 4-pentenoic acid with an overall yield of about 17.8 and 16.9%, respectively. The key steps contain an Evans asymmetrical anti-aldol reaction, TBS protection, hydroboration, oxidation, and FC arylation. Firstly, 4-pentenoic was converted into **686** *via* several steps. Next, the methyl acetal **686** was transformed into 2,5-diaryl-3,4-dimethyltetrahydrofuran *via* FC-type arylation reaction using tin(IV) chloride in dichloromethane.[637,643] The FC-type arylation reaction was performed with the epimerization at the C2 position of **686** to give 2,3-*trans*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **687a** and **687b** as a single diastereomer. Lastly, removal of the Bn protecting group in **687a** afforded (2)-talaumidin **683** (90%). Furthermore, the total synthesis of (2)-galbelgin **684** was achieved in two steps from the intermediate **687b** (Scheme 148).[644]

Extracts from the plants *Pycnanthus angolensis* and *Holostylis reniformis* were applied to treat malaria throughout Africa and Brazil, respectively.[645] Extracted lignans from these and other plants,[250] such as (−)-8′-*epi*-aristoligone **689**, have demonstrated promising antiplasmodial activity against a chloroquine-resistant strain of *Plasmodium falciparum*.[250] The development of a unique one-pot oxidative [3,3] rearrangement/FC arylation reaction permitted the fast and stereocontrolled synthesis of several tetralone- and naphthyl-type lignan natural products with antimalarial activity. For the synthesis of **689** and **688**, initially hydrazine **691** serves as a linchpin for the reaction of aryl aldehyde **690** with arene **693** *via* initial construction of hydrazone **692**, which is followed by a hypervalent-iodide oxidative [3,3] rearrangement/FC arylation in one-pot fashion to provide benzhydryl derivative **694**. Next, *via* several steps, the one-pot oxidative [3,3] rearrangement/FC arylation of **695** with 1,2-dimethoxybenzene **36** progressed with complete chirality transfer to provide benzhydryl **696** in 77% yield. Subsequently, compound **696** was transformed into (−)-8′-*epi*-aristoligone **689** in 28% yield and (−)-cyclogalgravin **688** in 73% yield *via* several steps (Scheme 149).[646]

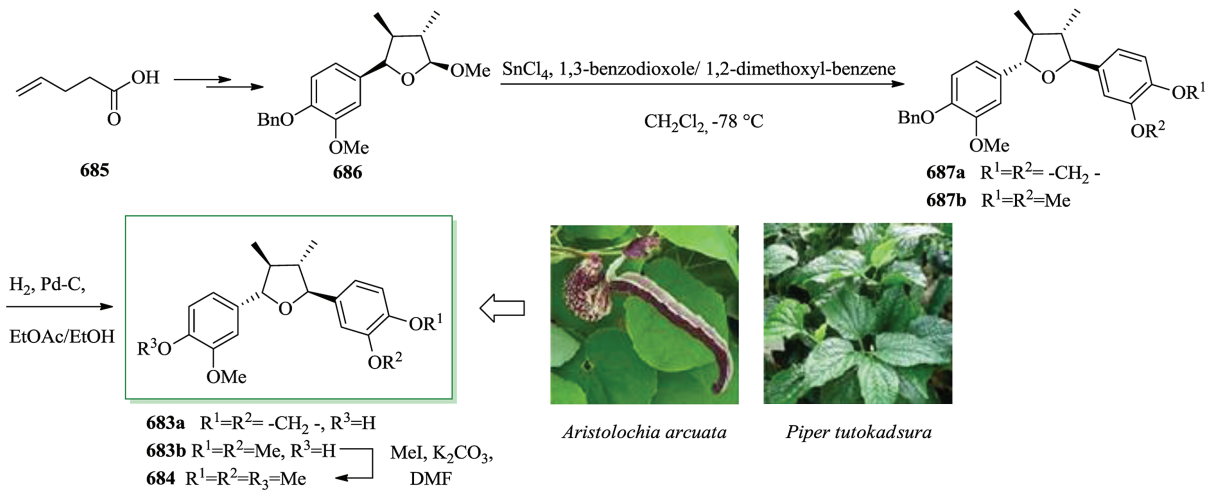
Based on this method, the total synthesis of **697** and **698** was achieved as follows. Construction of hydrazone **699** from piperonal followed *via* oxidative [3,3] rearrangement and FC arylation reaction with 1,2-dimethoxybenzene **36** resulted in the formation of diastereomeric benzhydryl **700** (80% yield, 5 : 1 d.r.). Next, the final two natural products, (−)-8′-*epi*-aristotetralone **698** and (−)-pycnanthulignene B **697**, were synthesized in 43% and 70% yield, respectively, from compound **700** *via* several steps (Scheme 150).[646]

Santalin Y occurs in "red sandalwood", the hardwood of *Pterocarpus santalinus*. The yellow pigment santalin Y was isolated by Nohara *et al.* in 1995 as a minor component.[647] A biomimetic total synthesis of santalin Y, a structurally complex but racemic natural product, was developed in 2015 by Strych *et al.* Santalin Y was obtained *via* seven steps (longest linear

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Scheme 147 The formation of 4,5-dihydro-4′-*O*-methylsceletenone **680b** into *O*-methyljoubertiamine **681**.



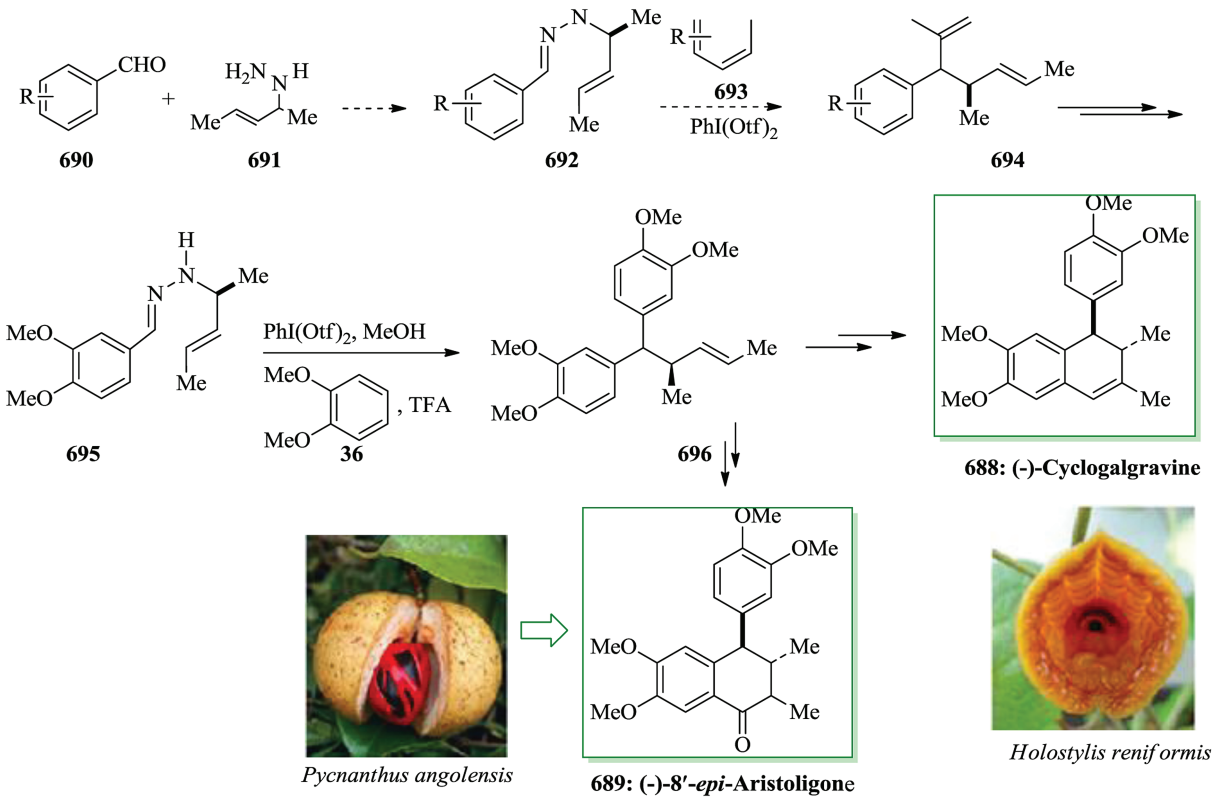
Scheme 148 Total synthesis of (2)-talaumidin **683** and (2)-galbelgin **684**.

sequence) and in 8% overall yield. The key steps were a (3 + 2) cycloaddition reaction and an intramolecular FC reaction. The total synthesis of santalin Y was started from isoflavylium ion **702**, which was converted into a tetrahydrofuran intermediate **703** *via* several steps. Next, a subsequent intramolecular FC cyclization provided santalin Y (Scheme 151).[648]

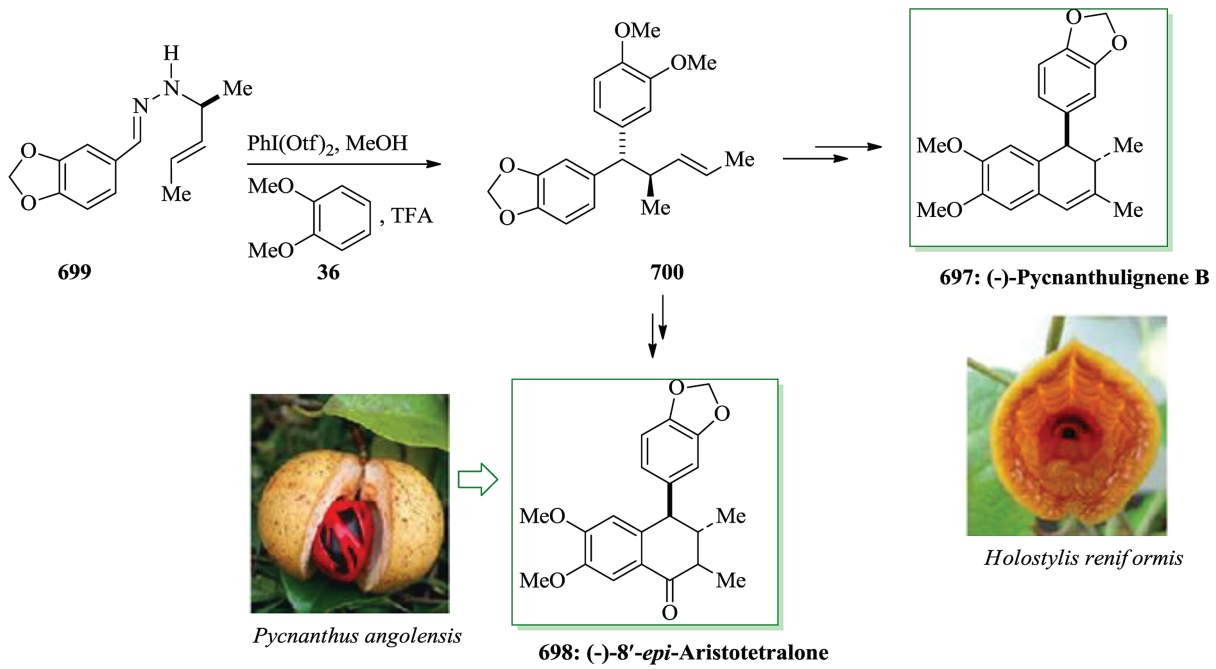
Epipolythiodiketopiperazine alkaloids represent a structurally complex and biologically potent group of secondary fungal

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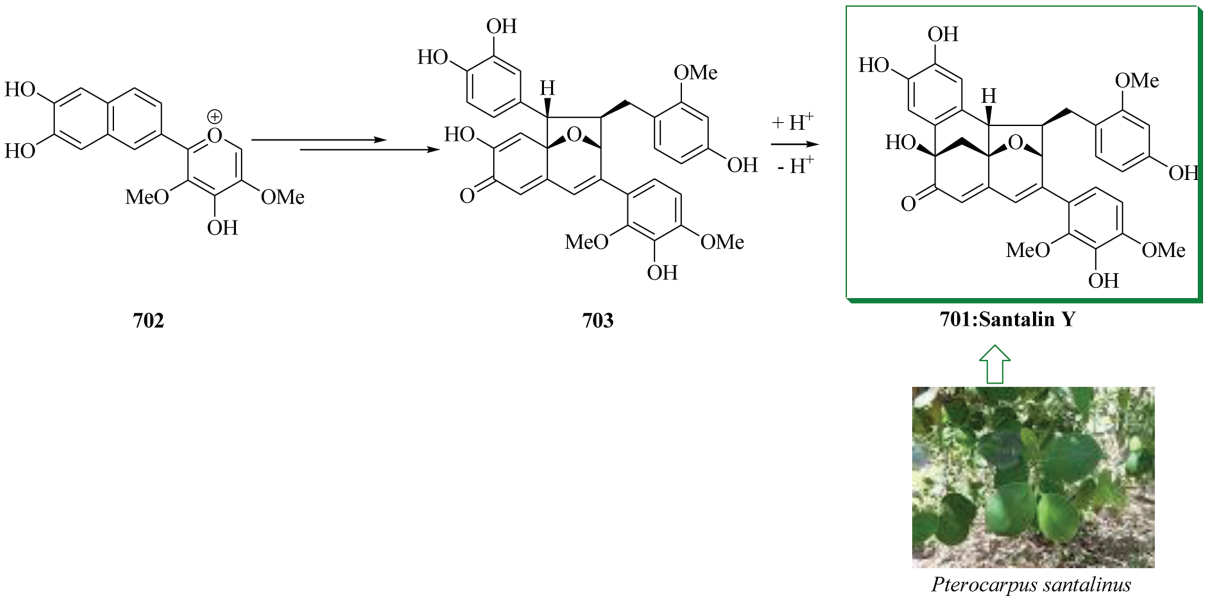
Scheme 149 Total synthesis of (–)-cyclogalgravin **688** and (–)-8′-*epi*-aristoligone **689**.



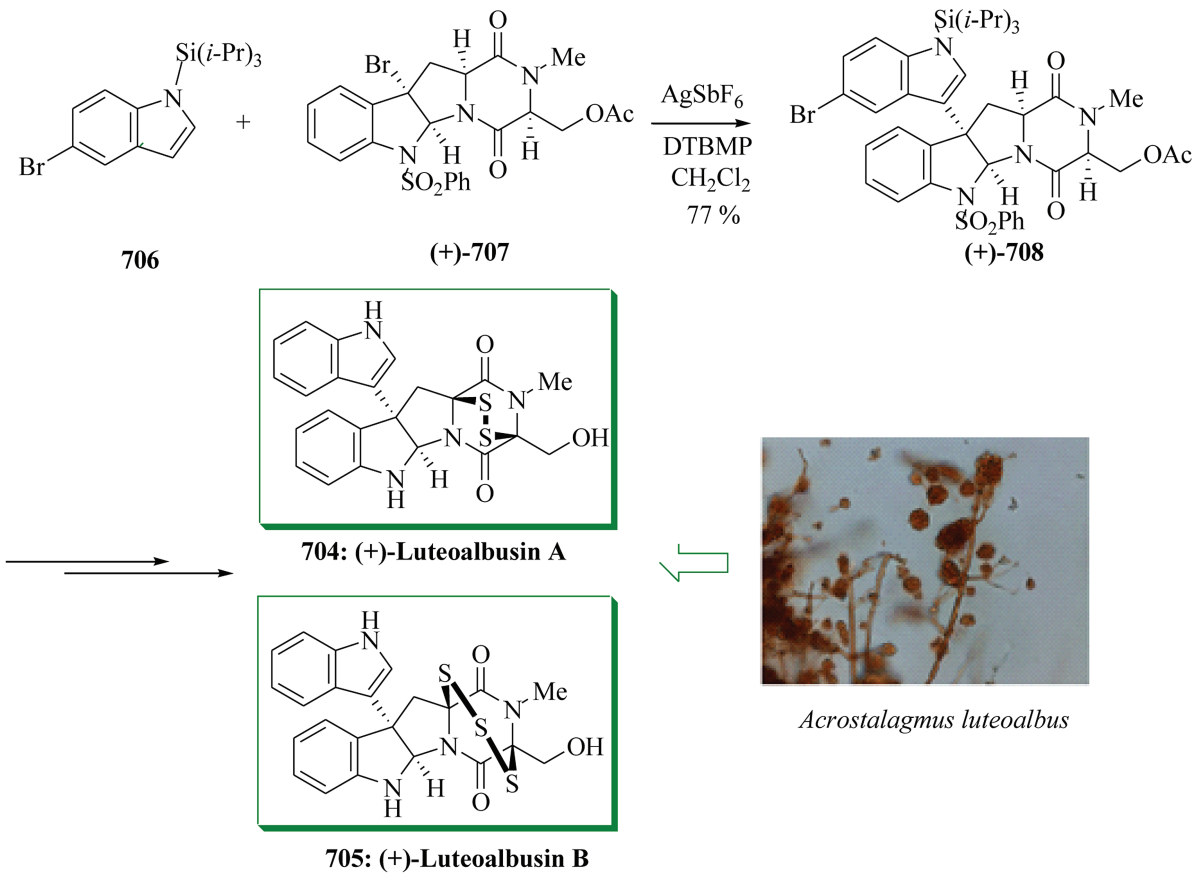
Scheme 150 Total synthesis of (–)-pycnanthulignene B **697** and (–)-8′-*epi*-aristotetralone **698**.

metabolites.[162,268,649] Several members of this group of natural products share a cyclo-tryptophan unit and an eponymous epipolythiodiketopiperazine (ETP) substructure. Among them, (+)-luteoalbusin A **704** and (+)-luteoalbusin B **705** were isolated from the marine fungi *Acrostalagmus luteoalbus* SCSIO F457. The first total synthesis of (+)-luteoalbusins A and B was developed in 2015 by Movassaghi *et al.*[650] The total synthesis of alkaloids (+)-**704** and (+)-**705** was started with the Ag-catalyzed

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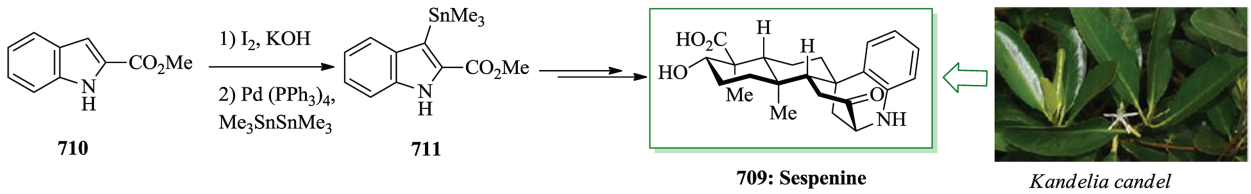
Scheme 151 Total synthesis of santalin Y **701**.



Scheme 152 Total synthesis of (+)-luteoalbusin A **704** and (+)-luteoalbusin B **705**.

FC arylation of diketopiperazine (+)-**707**. Reaction of a solution of C3-bromo diketopiperazine (+)-**707** in CH_2Cl_2 with indoles **706** and silver(I) hexafluoroantimonate using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) gave the corresponding C3-indolylhexacycle (+)-**708** in 77% yield. Lastly, compound **708** produced (+)-luteoalbusins A **704** and B **705** *via* several steps (Scheme 152).[650]

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Scheme 153 Total synthesis of sespenine **709**.

In 2011, Ding *et al.* identified sespenine **709**, which is a structurally uncommon polycyclic molecule isolated from *Streptomyces* sp. HKI0595.[651] Li *et al.* in 2016 reported a ten-step (the longest linear sequence) synthesis of this molecule from market-accessible precursors.[652] Sharpless enantioselective epoxidation, Stille–Miyata coupling reaction and Prins cyclization/FC/retro FC were considered as the key steps. Total synthesis of sespenine **709** was started from methyl indole-2-carboxylate **710**. Initially, the feasibility of FC-type allylation at the C3 position of **710** was investigated.[653,654] In this pathway, stannane **711** was synthesized from **710** through a two-step sequence described by Routier *et al.*[655] Iodination based on basic conditions gave the desired C3 iodide, which was transformed to **711** *via* a methodology-mediated stannylation [$Pd(PPh_3)_4$, $Me_3SnSnMe_3$]. Afterwards, sespenine **709** was obtained after several steps (Scheme 153).[652]

3. Conclusion

In conclusion, in this review, we tried to underscore the significance and importance of the FC reaction as an old reaction with a new and interesting perspective owing to its applications in the important and new field of total synthesis of naturally occurring compounds. We showed how this old reaction can play an important and key role in the total synthesis of natural products proven to exhibit diverse biological activities. Indeed, nowadays, the FC reaction is considered as one of the most significant basic reaction classifications in the total synthesis of the most important class of natural products. The important compounds from biological points of views are totally synthesized *via* a pathway including at least one step involving this old but useful FC reaction as a key step. As a result, the FC reaction as an old but extremely useful reaction is frequently applied in the total synthesis of natural products, particularly those with various biological activities.

Conflicts of interest

There are no conflicts to declare.

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