

Cite this: *RSC Adv.*, 2018, 8, 40061

Received 3rd September 2018

Accepted 3rd November 2018

DOI: 10.1039/c8ra07325b

rsc.li/rsc-advances

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

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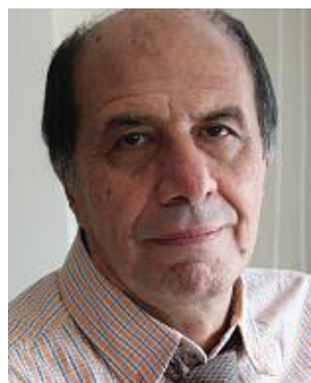
Over the years, Friedel–Crafts (FC) reactions have been acknowledged as the most useful and powerful synthetic tools for the construction of a special kind of carbon–carbon bond involving an aromatic moiety. Its stoichiometric and, more recently, its catalytic procedures have extensively been studied. 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 $H_2SO_4 \cdot F \cdot SbF_5$, 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

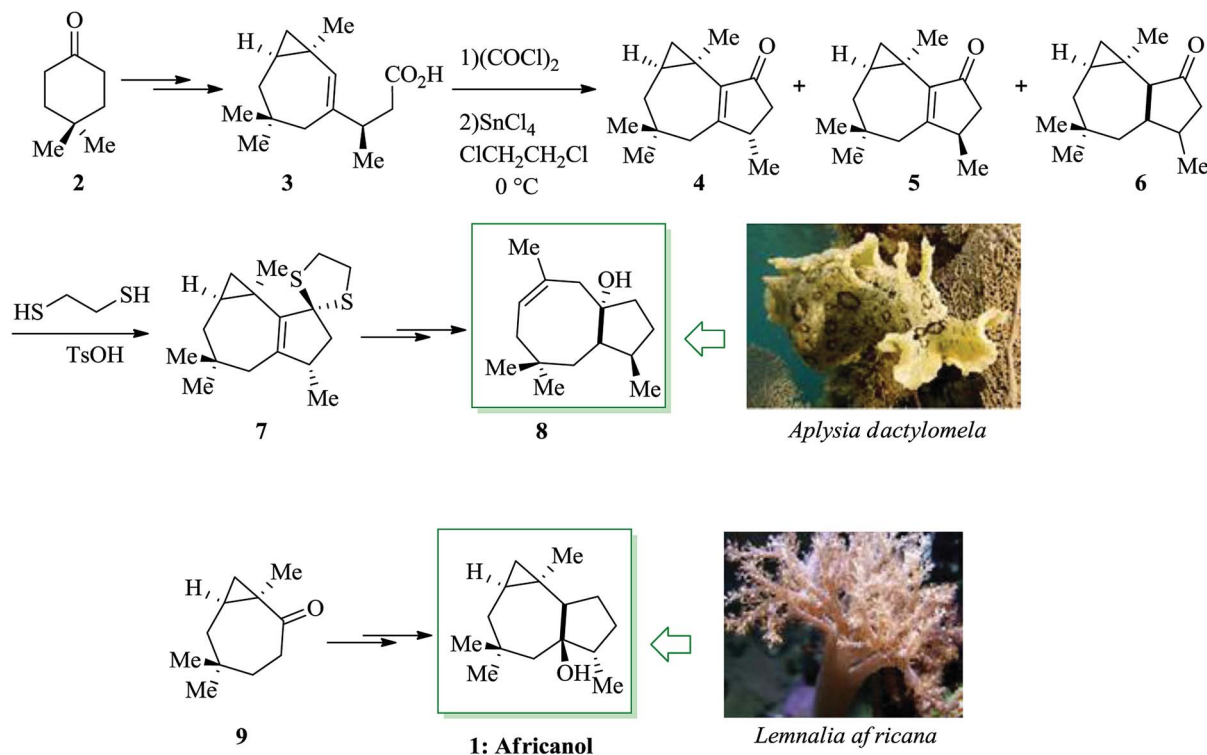


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Scheme 1 Total synthesis of africanol 1.

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.

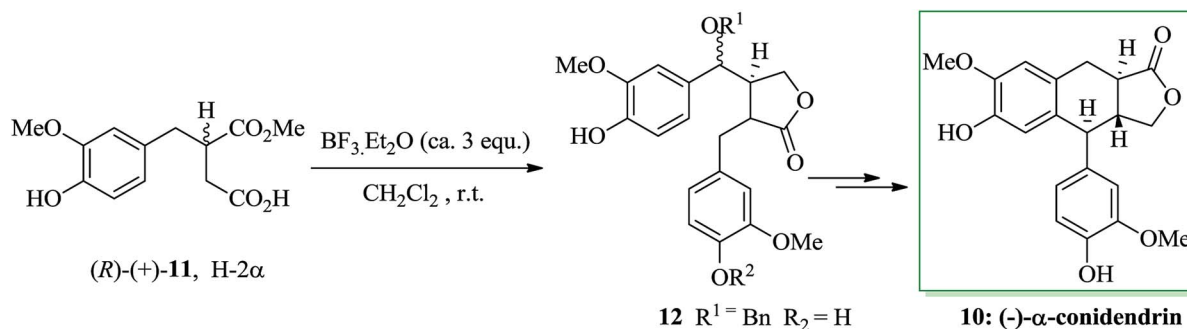
2. Applications of Friedel–Crafts in total synthesis of natural products

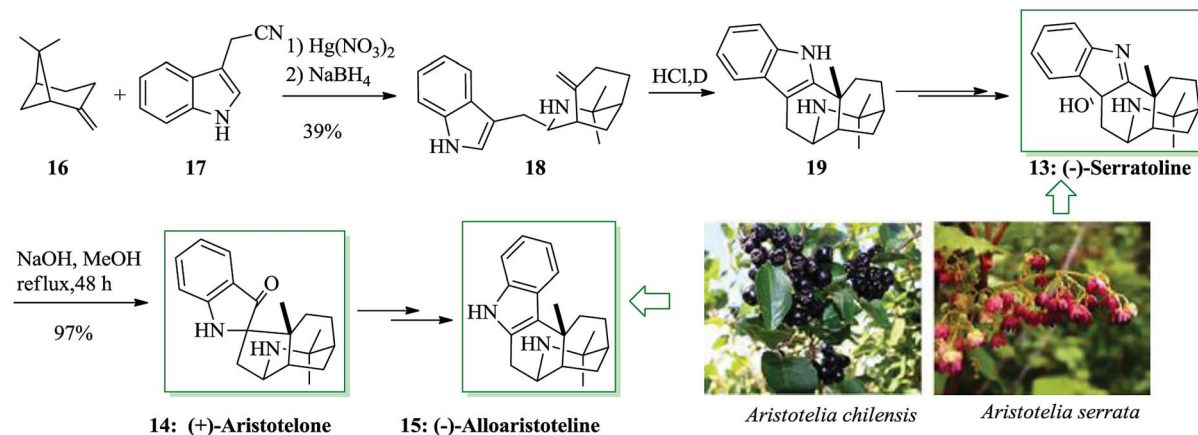
2.1. Intramolecular alkylation

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

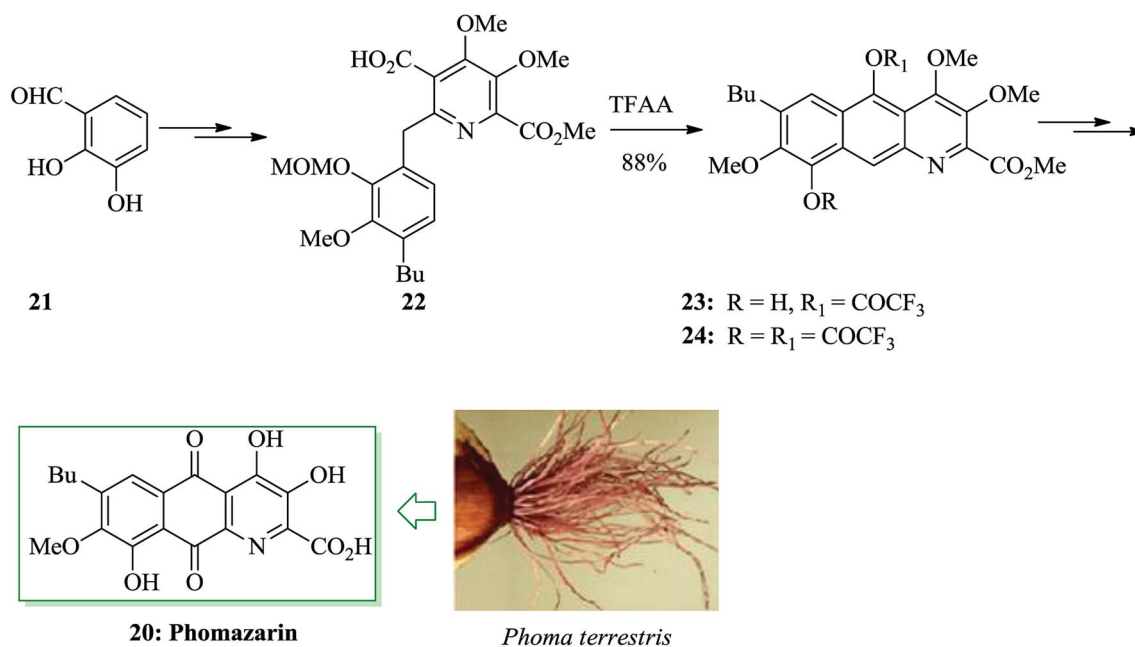
transformed into compound **7** via FC cyclization of its acid chloride and acid-mediated dithioetherization (after several steps). Compound **7** was converted into dactylol **8** after several steps. The configuration of the side chain Me substituent is detected to be proper in relation to dactylol **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 wood³⁹ 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**.



Scheme 3 Total synthesis of natural products (-)-serratoline 13, (+)-aristolone 14 and (-)-alloaristolone 15.



Scheme 4 Total synthesis of phomazarin 20.

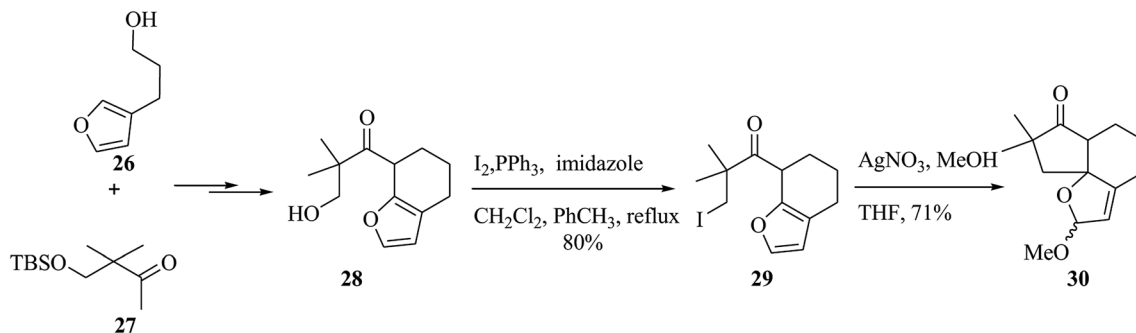
with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane at ambient temperature. The benzyloxy group of 12 was actually found to be an excellent leaving group during intramolecular FC alkylation. As a result, (-)- α -conidendrin 10 was provided as the desired natural product from 12 in satisfactory yield (Scheme 2).⁴¹

The *Aristotelia* alkaloids (-)-serratoline 13, (+)-aristolone 14 and (-)-alloaristolone 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, (+)-aristolone 14 and (-)-alloaristolone 15. This approach starts from the reaction between (1S)-(-)- β -pinene 16 and 3-indolylacetonitrile 17 to afford (+)-makomakine 18. Next, an intramolecular FC reaction provided (+)-aristolone 19, which upon two steps afforded alkaloid 13. Subsequently, base-

mediated skeletal rearrangement of 13 provided (+)-aristolone 14. Finally, alkaloid 14 gave (-)-alloaristolone 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,





Scheme 5 The formation of the tricyclic product 30.

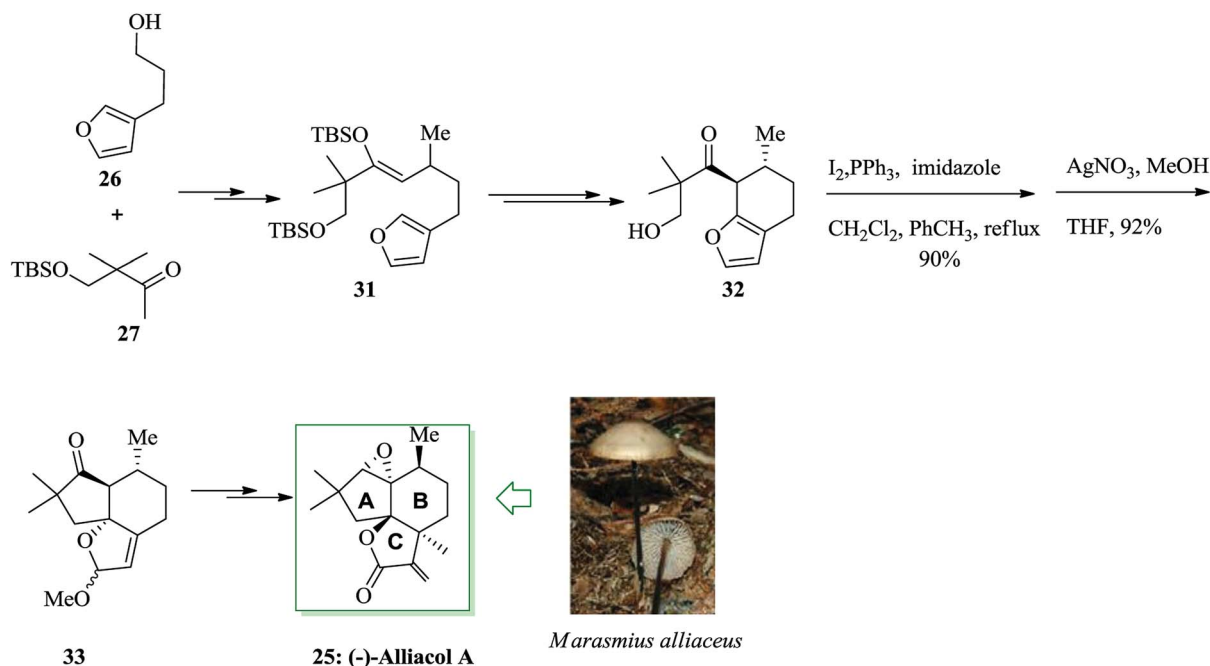
compound 23 afforded phomazarin 20 upon several steps (Scheme 4).⁴⁴

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 AgNO₃ 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.

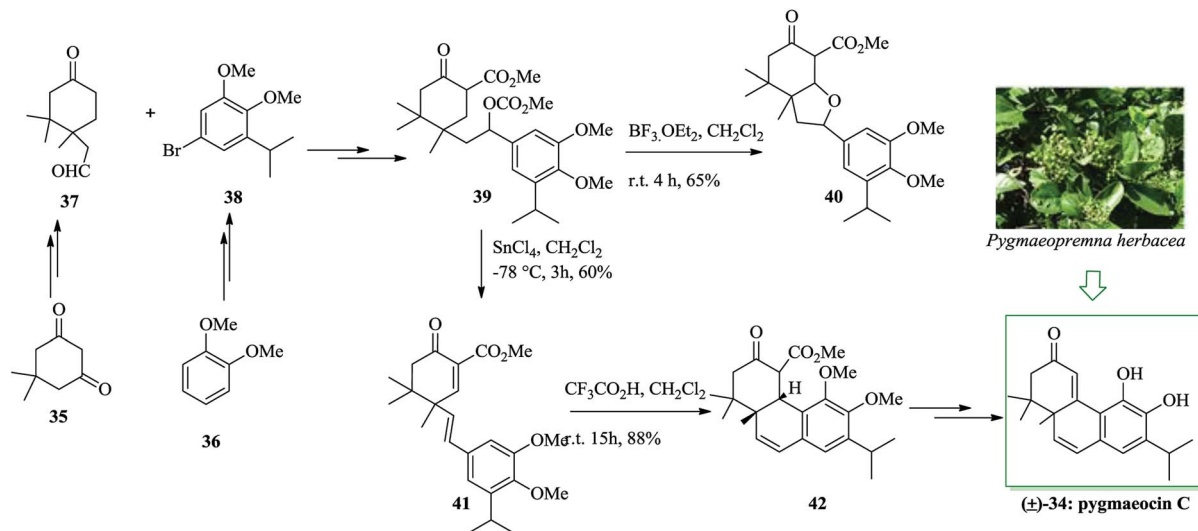
This compound provided the bicyclic product 32 upon two steps. Using the bicyclic product, the alcohol 32 was transformed into an iodide and the FC cyclization was finished. A 92% extracted yield of the tricyclic product 33 was provided from the FC reaction. Next, compound 33 was converted into (–)-alliacol 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

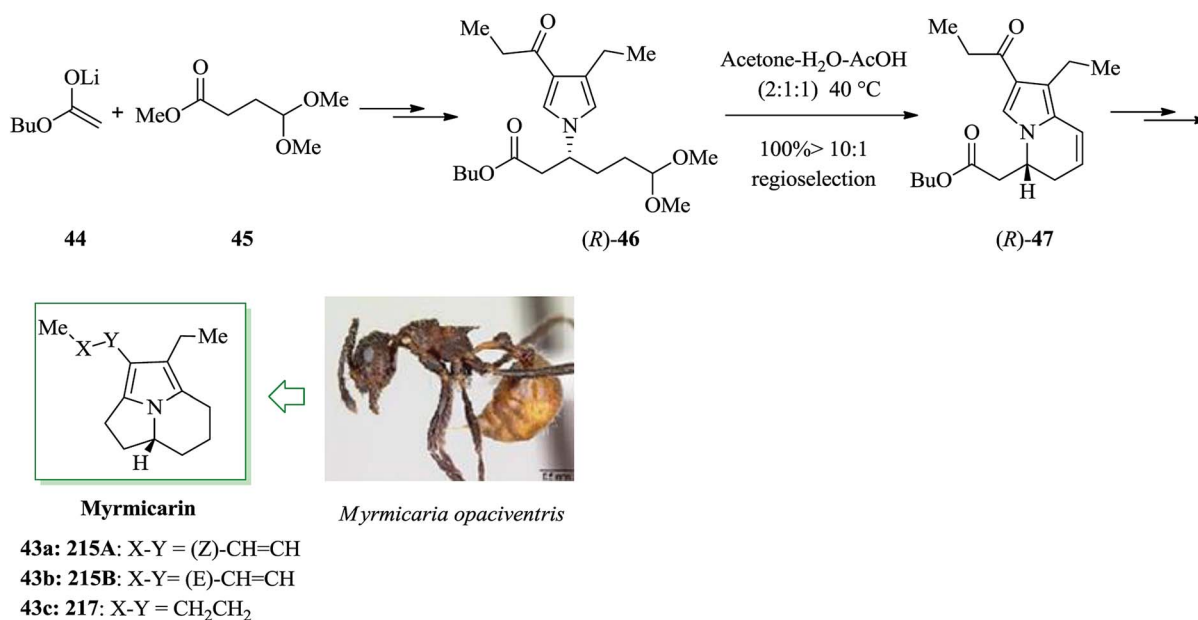


Scheme 6 Total synthesis of (–)-alliacol A 25.





Scheme 7 Total synthesis of pygmaeocin C 34.



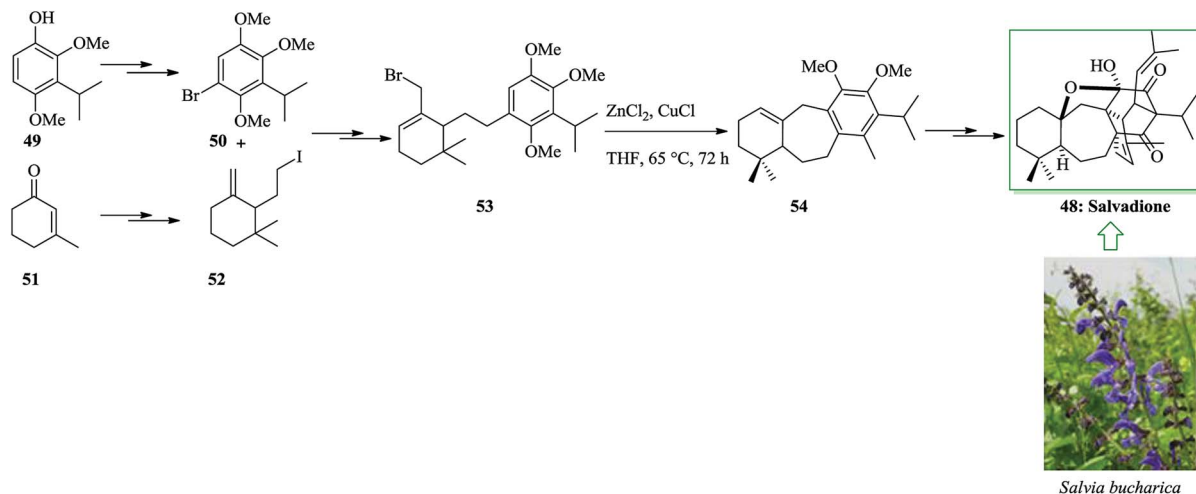
Scheme 8 Total synthesis of tricyclic myrmicarins 43a–c.

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 *Myrmecaria opaciventris*.^{51,52} The pyrrolindolizine 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 myrmecarin alkaloids was developed in 2005 by Movassaghi and co-workers. Key conversions in this method contain a stereospecific Pd-mediated N-xylation, a Cu-mediated asymmetric conjugate reduction, and a regioselective FC reaction. The synthesis of optically potent and isomerically pure samples of (4*a*R)-myrmecarins **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 myrmecarin alkaloids. A regioselective FC reaction of the





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 (acetic acid–H₂O, 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 α -cyclization product **47**. Finally, compound **47** afforded isomerically pure tricyclic myrmicarinins **43a–c** after several steps (Scheme 8).⁵³

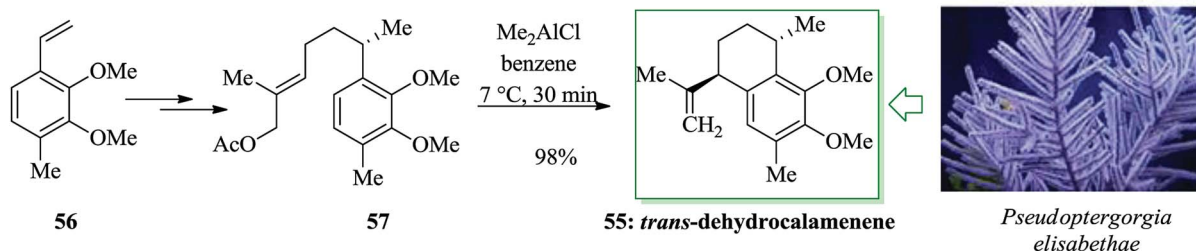
Ahmad and co-workers extracted and identified a remarkable polycyclic triterpene from *Salvia bucharica*, salvadione A **48**.⁵⁴ The tricyclic 6–7–6 unit structure of the triterpene salvadione **48** was provided using an effective method starting from the aryl bromide **50** (provided from cyclohexenone **51**) and the alkyl iodide **52** (provided from phenol **49**) containing a methyl-encyclohexane 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 tricyclic **54** afforded salvadione **48** upon several steps (Scheme 9).⁵⁵

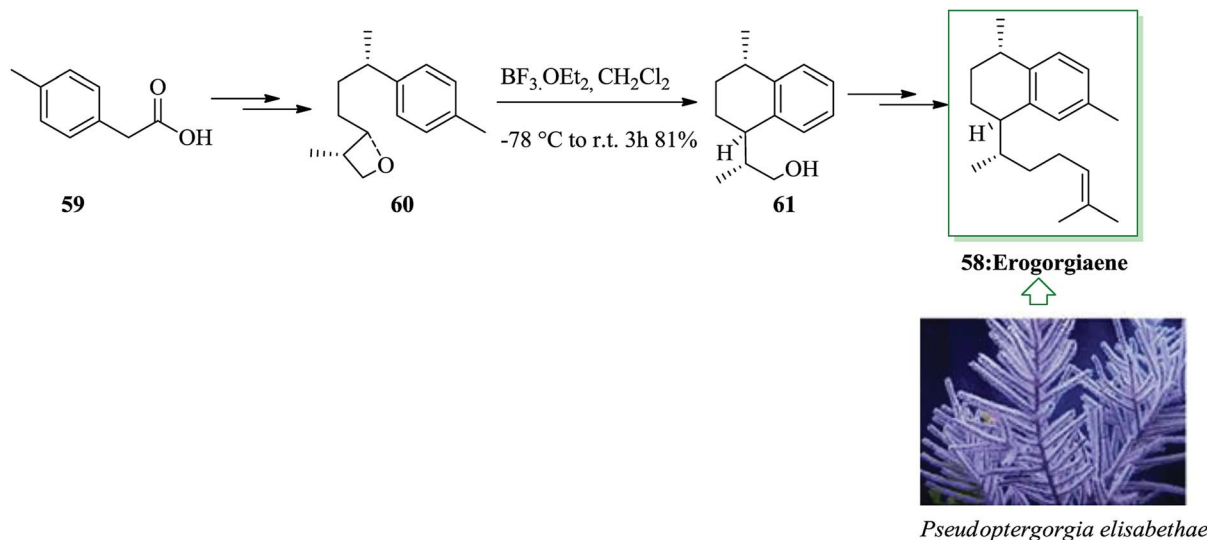
Various aromatic diterpenes with a serrulatane or amphilectane framework have been recognized as bioactive metabolites from marine soft corals, particularly *Pseudopterogorgia elisabethae*.⁵⁶ Notable representatives of these compounds are the anti-inflammatory pseudopteropsins,^{57,58} the cytotoxic 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 Me₂AlCl 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.

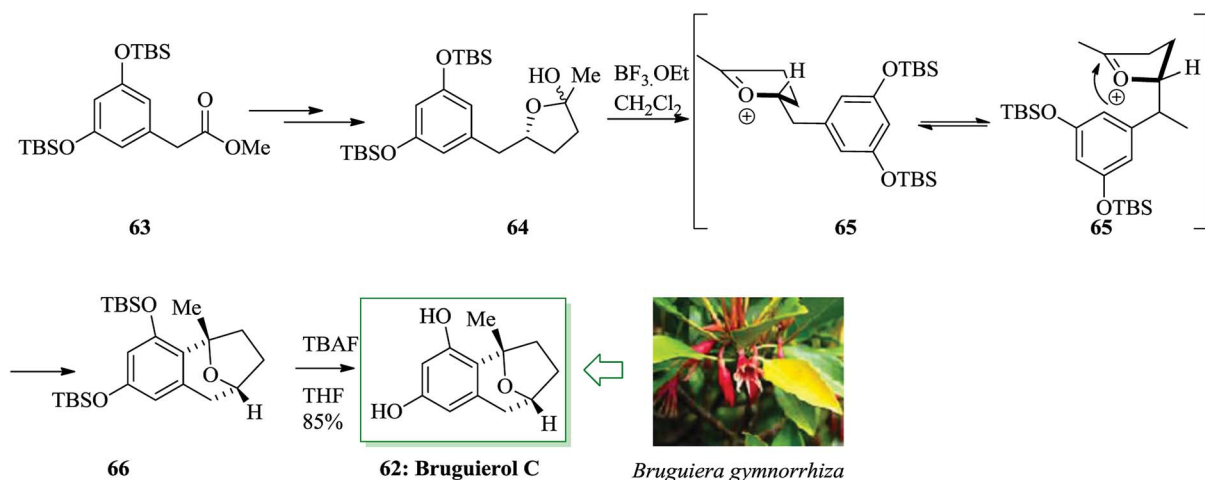


Scheme 11 Total synthesis of erogorgiaene 58.

compounds named bruguierols A–C from the stem of the *Bruguiera gymnorhiza* 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 alkylation⁶⁸ 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

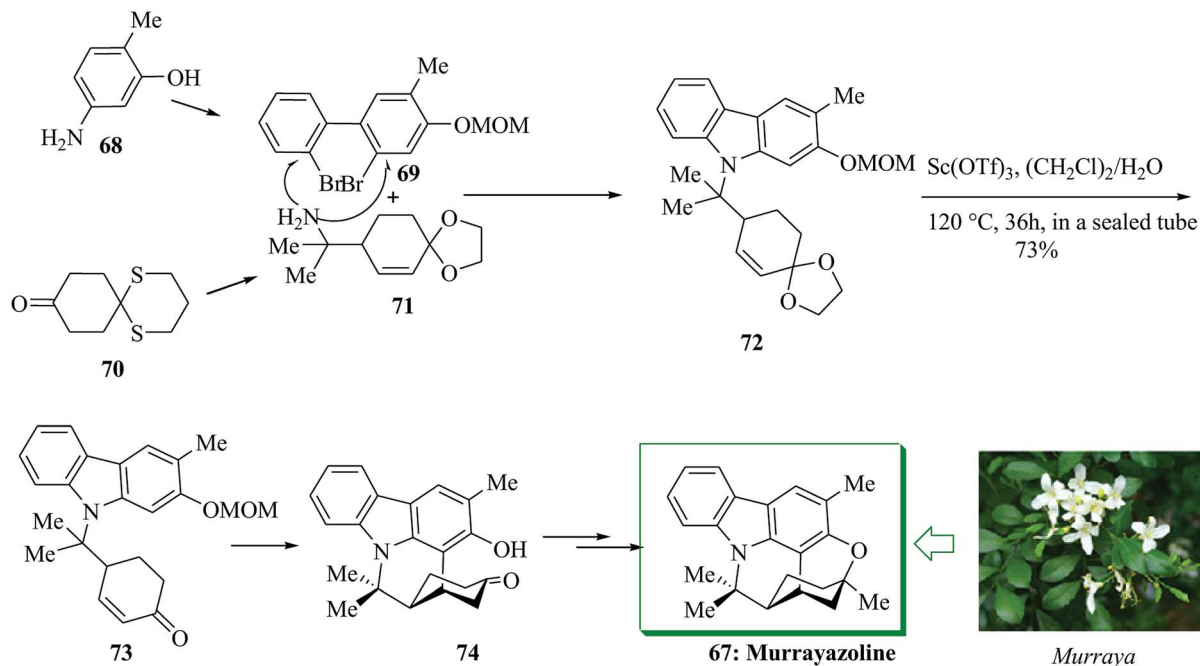
Murrayazoline 67, found as mahanimbidine and curryangin, is a carbazole alkaloid extracted as a racemic or an optically active compound from the genus *Murraya*. Murrayazoline and

its corresponding carbazole alkaloids were demonstrated to be 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 (\pm)-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}

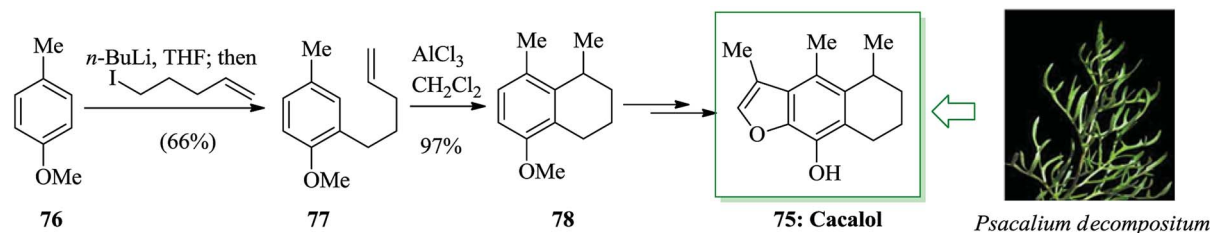


Scheme 12 Total synthesis of bruguierol C 62.





Scheme 13 Total synthesis of murrayazoline 67.



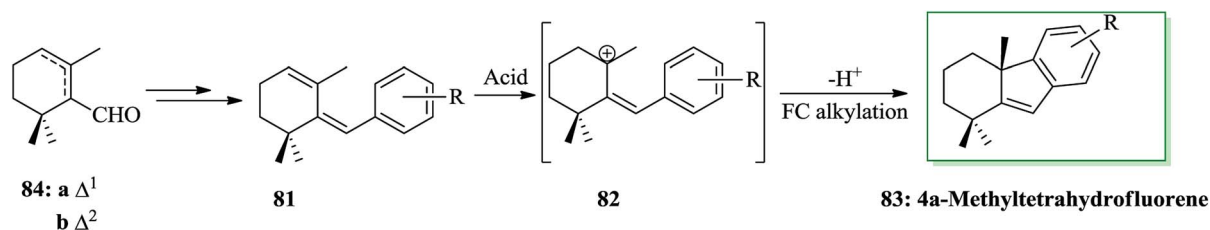
Scheme 14 Total synthesis of cacalol 75.

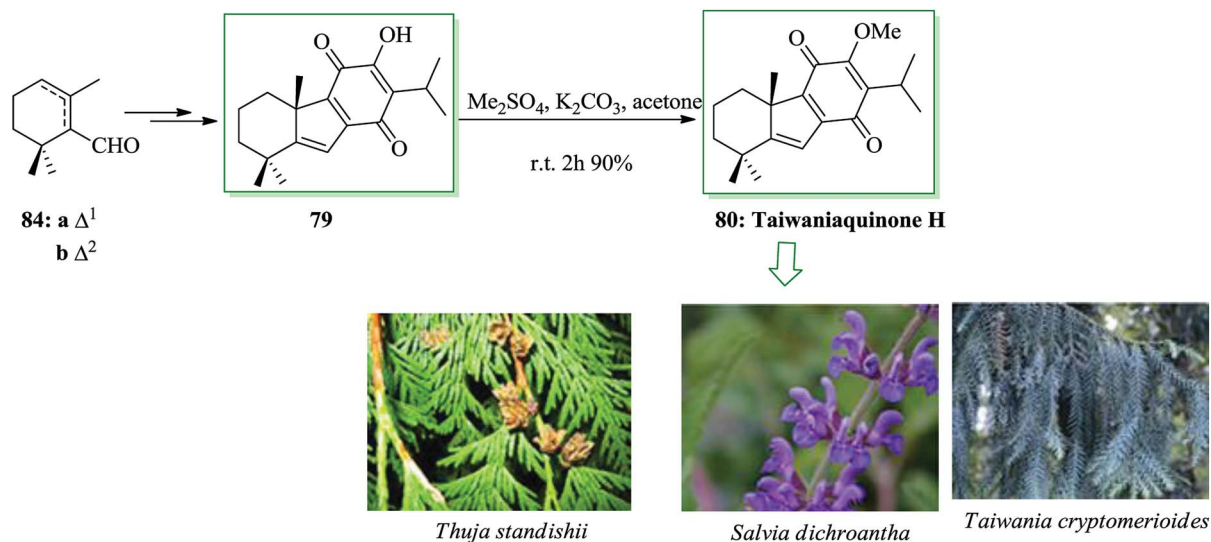
Finally, compound **74** afforded (\pm)-murrayazoline **67** after several steps (Scheme 13).⁷²

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 antioxidant⁸⁰ 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*-lithiation⁸¹ of 4-methylanisole **76** using *n*-butyllithium in tetrahydrofuran. This anion

was alkylated with 5-iodo-1-pentene⁸² to afford the alkene **77**. Subsequently, this molecule was cyclized *via* an intramolecular FC alkylation using AlCl₃ 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 **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.



Scheme 16 Total synthesis of taiwaniaquinone H 80.

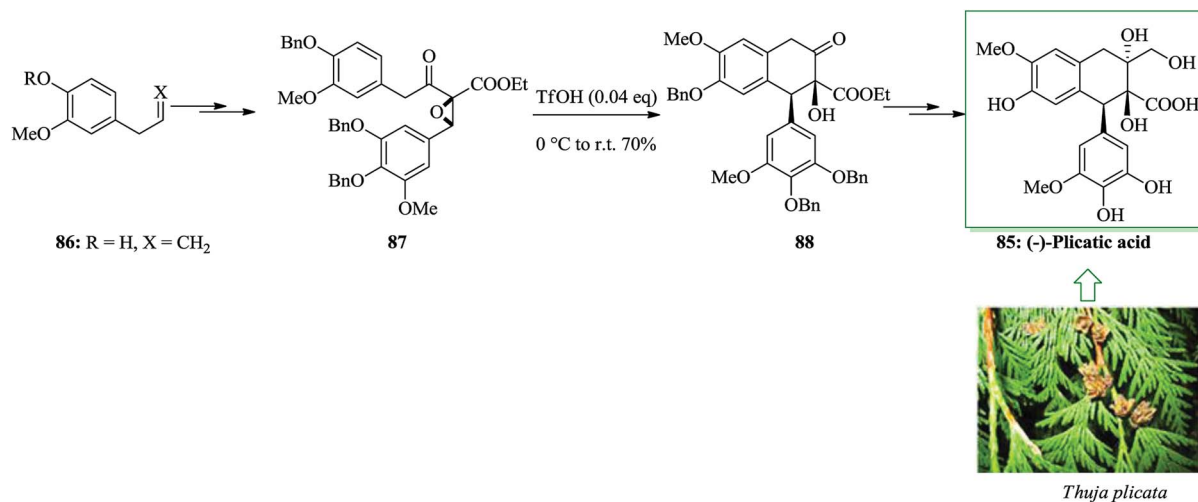
workers. Key steps are the intramolecular FC alkylation reaction of an aryldiene and the degradative oxidation reaction of a methylenedioxy substituent. Using this strategy, (\pm)-dichroanone **79** (in three steps, 77% overall yield) and (\pm)-taiwaniaquinone H **80** (in four steps, 70% overall yield) 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

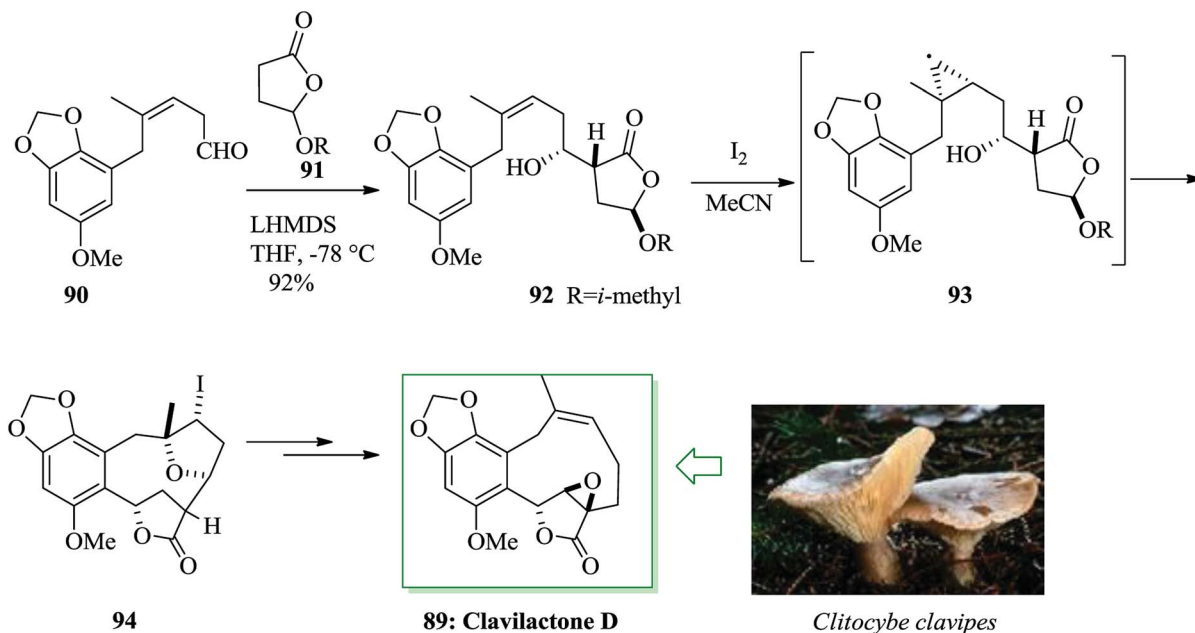
was achieved from eugenol in 12 steps and 14% overall yield. In this approach, a theoretically novel methodology containing an enantioselective epoxidation-intramolecular epoxy-ring-opening FC reaction sequence was performed for the asymmetric formation of a structurally complex 2,7'-cyclo lignane framework. 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

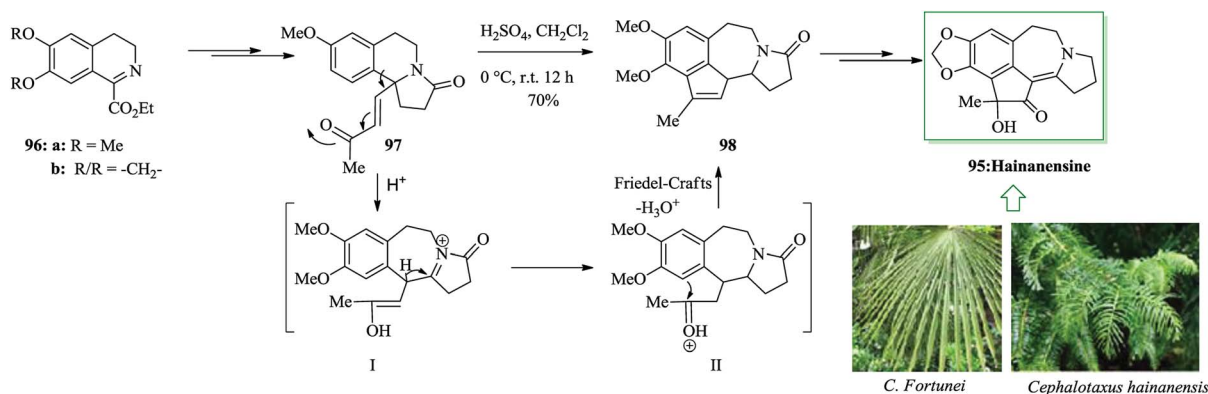


Scheme 17 Total synthesis of (–)-plicatic acid 85.





Scheme 18 Total synthesis of clavilactone D 89.



Scheme 19 Total synthesis of hainanensine 95.

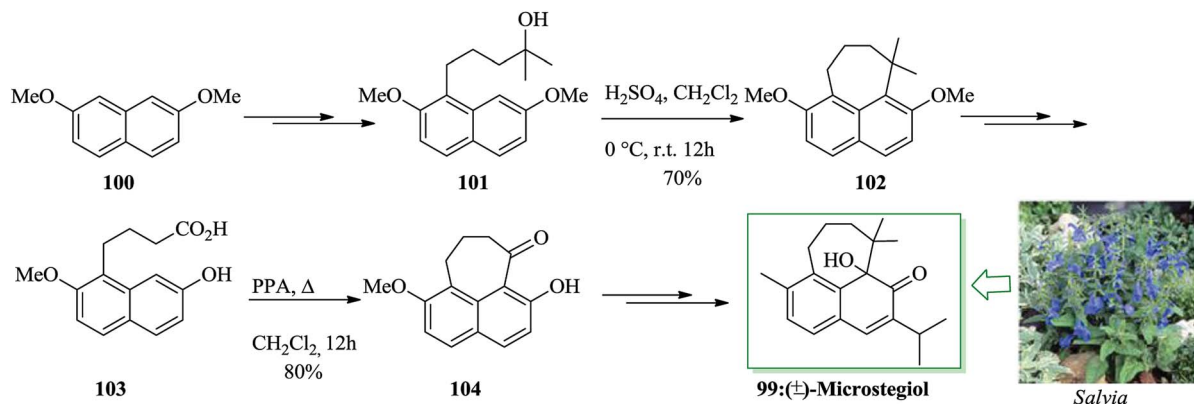
with an aromatic ring. Total synthesis of clavilactone D **89** was initiated from aldehyde **90**. In this route, substrate **92** was synthesized *via* the aldol reaction of chiral lactone **91**⁹⁷ with aldehyde **90**.⁹⁸ Next, iodo etherification followed *via* FC-type cyclization of alkenyl alcohol **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

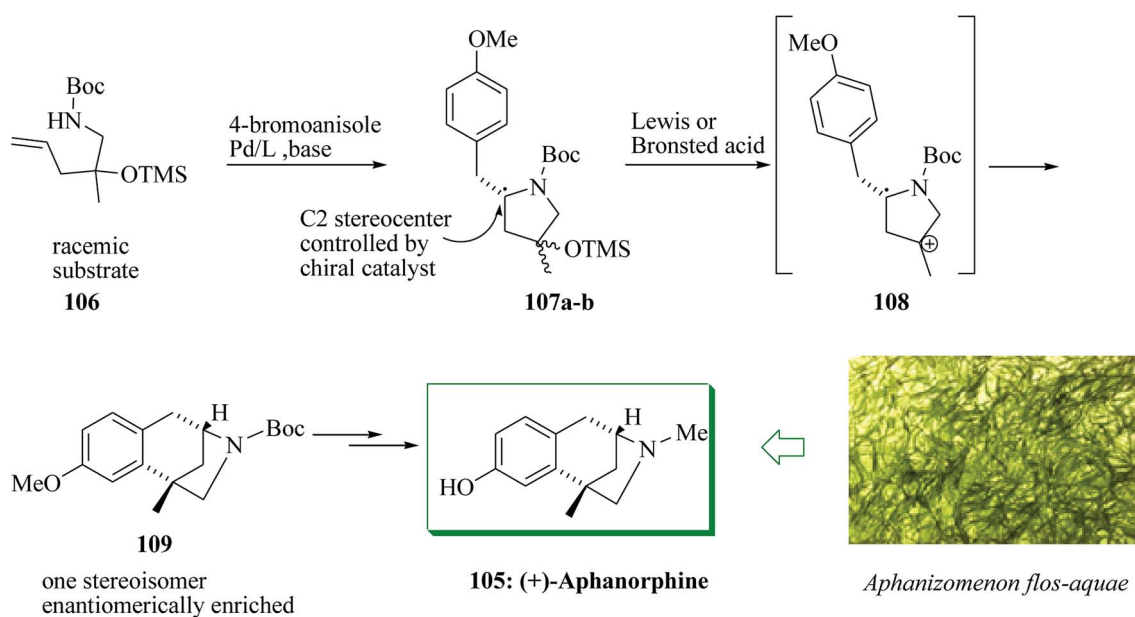
synthesized from 3,4-dihydroisoquinoline **96** after several steps. Upon refluxing enone **97** in formic acid, compound **98** was provided. Seemingly, the construction of rearranged annulation product **98** resulted from more FC-type cyclization-dehydration of the initial ring-expansion intermediates **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





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



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

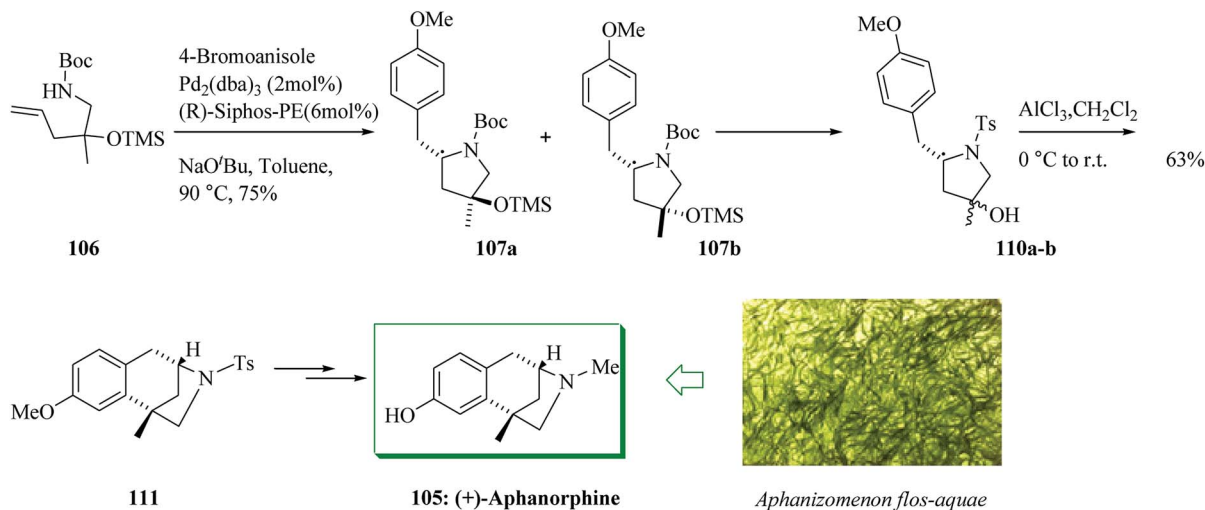
several steps. Subsequently, **103** using polyphosphoric acid (PPA) in dichloromethane under reflux conditions was transformed to **104** with 80% yield. Afterwards, compound **104** led to the construction of (±)-microstegiol **99** in 64% yield upon several steps (Scheme 20).¹⁰⁸

The tricyclic alkaloid aphanorphone was extracted from the blue-green alga *Aphanizomenon flos-aquae* by Clardy and Shimizu in 1988.¹⁰⁹ Aphanorphone shares common structural features with other bioactive benzomorphan alkaloids, for example eptazocine, pentazocine and morphine.^{110–114} A short enantioselective synthesis of (+)-aphanorphone **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

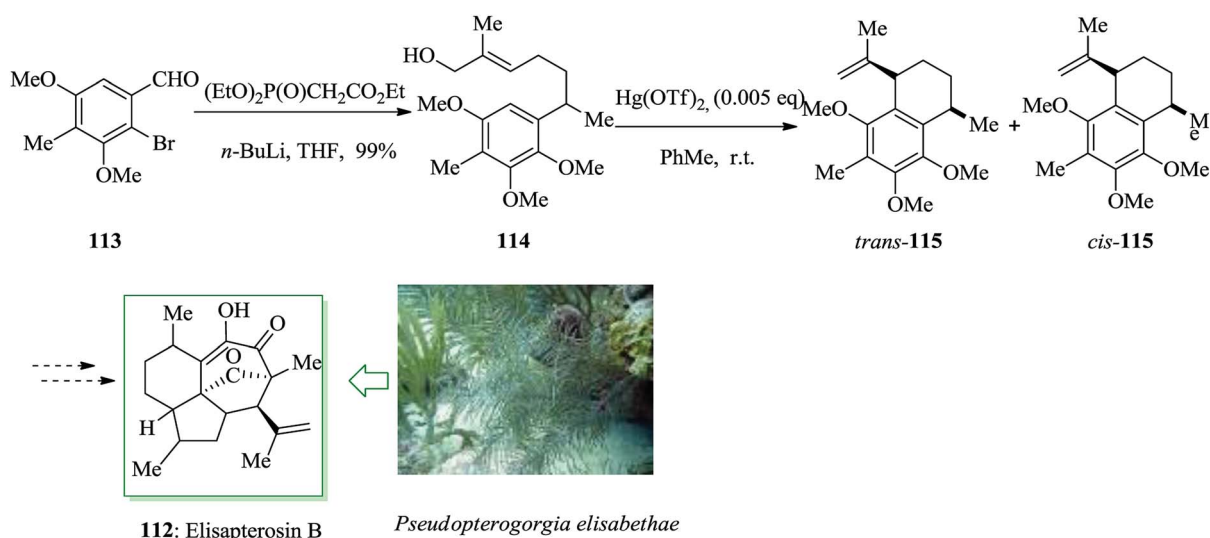
mixture was transformed into an enantiomerically enriched masked aphanorphone derivative *via* a FC reaction to make a quaternary all-carbon stereocenter. The catalyst-controlled enantioselective palladium-mediated carboamination reaction of racemic substrate **106** was applied to set the C2 stereocenter 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 aphanorphone (Scheme 21).¹¹⁵

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





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



Scheme 23 Total synthesis of elisapterosin B 112.

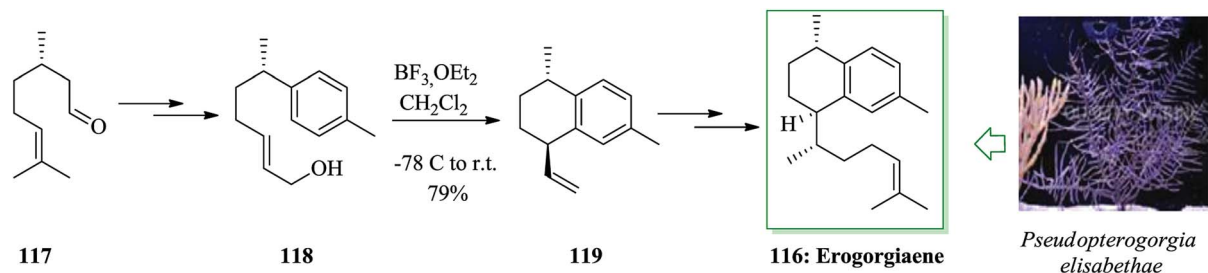
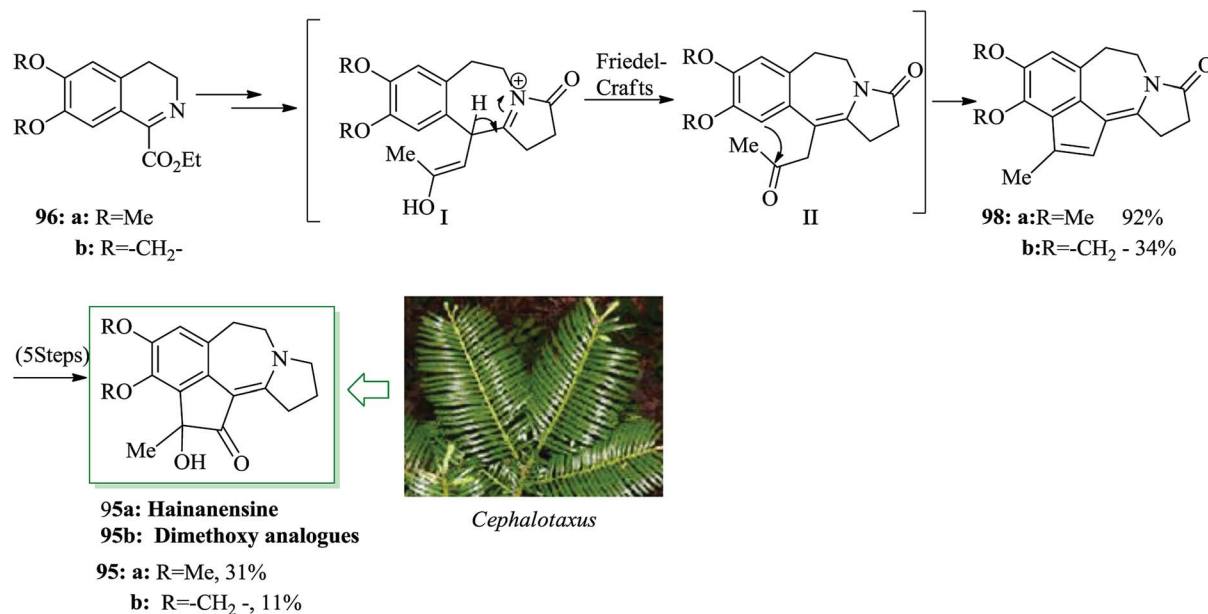
Based on the optimal conditions, this transformation gave a 1 : 1 mixture of diastereomers **107a** and **107b**, which afforded **110a,b**. The enantio-convergent intramolecular FC alkylation reaction of the mixture of diastereomers **110a,b** afforded **111** in 63% yield.¹¹⁴ Meanwhile, the transformation 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 co-workers 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 extracted¹²⁰ 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



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 $\text{BF}_3 \cdot \text{OEt}_2$ 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

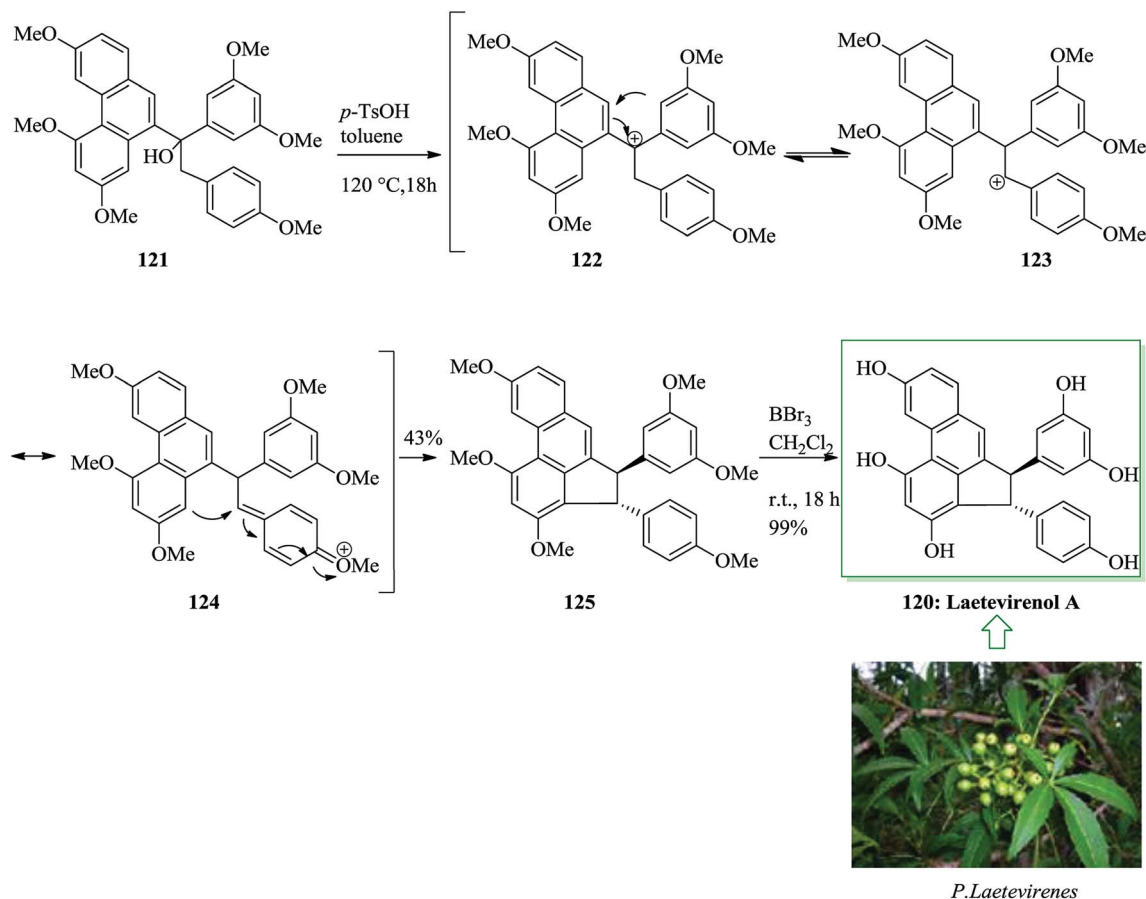
The *Cephalotaxus* genus is a member of the *Cephalotaxaceae* group of conifers. They are a fruitful source of several naturally occurring compounds, especially terpenoids (abietanes, tropenoids) and alkaloids (cephalotaxine esters), which often exhibit medicinal activities, particularly in the anticancer 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 naamine 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-diidoimidazole **127** upon several steps. Pleasantly, the reaction between unpurified **128c**





Scheme 26 Total synthesis of laetevirenol A 120.

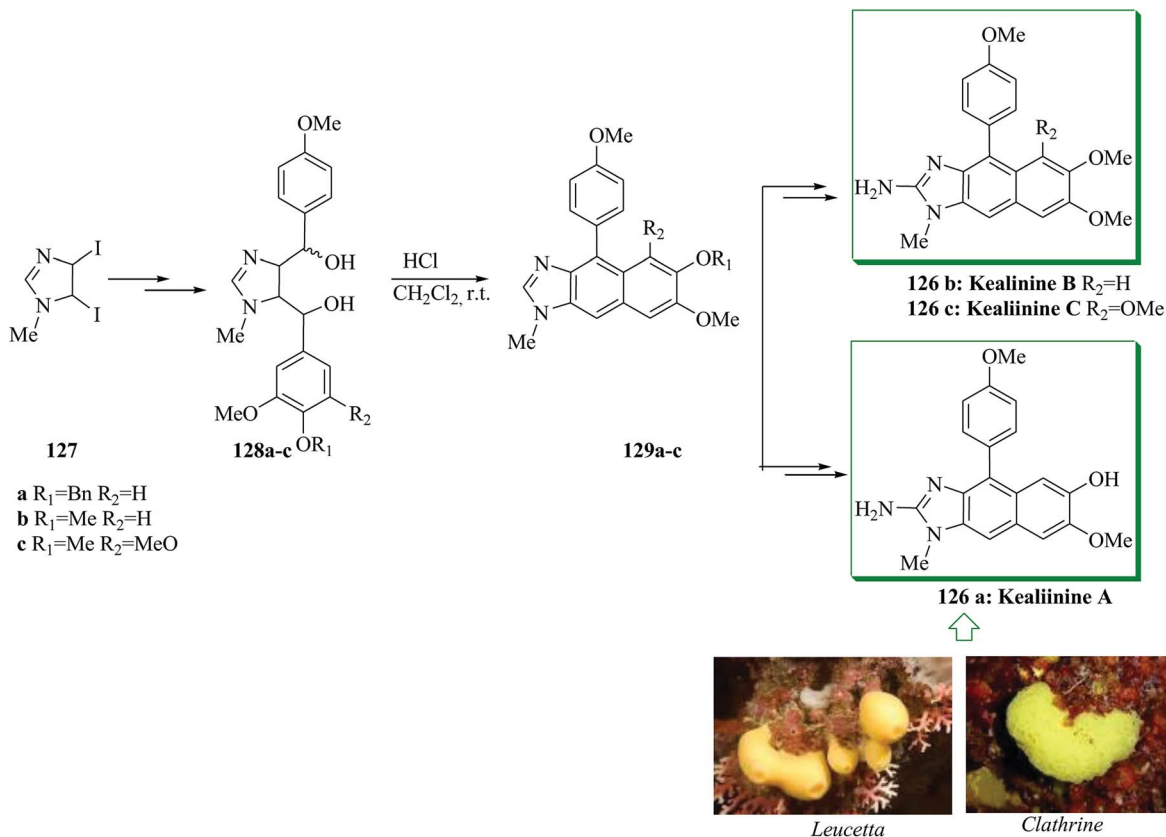
and hydrochloric acid led to an intramolecular FC cyclization-dehydration sequence to give the naphthimidazole **129c**. Subsequently, compound **129c** provided kealiinine C **126c** upon several steps. Next, it was tried to make the other two group members, kealiinine A **126a** and B **126b**. Their 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 diptoinonesin D **130** and paucifloral 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 diptoinonesin D **130** and

paucifloral F **131**. The formation of diptoinonesin D **130** and paucifloral 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 (Tf₂O) 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 diptoinonesin D **130** was constructed through FC alkylation reaction, providing **137** in 76% yield. Upon oxidation and deprotection of **137**, the target natural diptoinonesin D **130** was provided (Scheme 28).¹⁵⁰

Delle Monache *et al.* described the extraction of a dihydrophenanthropyrene 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 cate-naeformis* 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





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

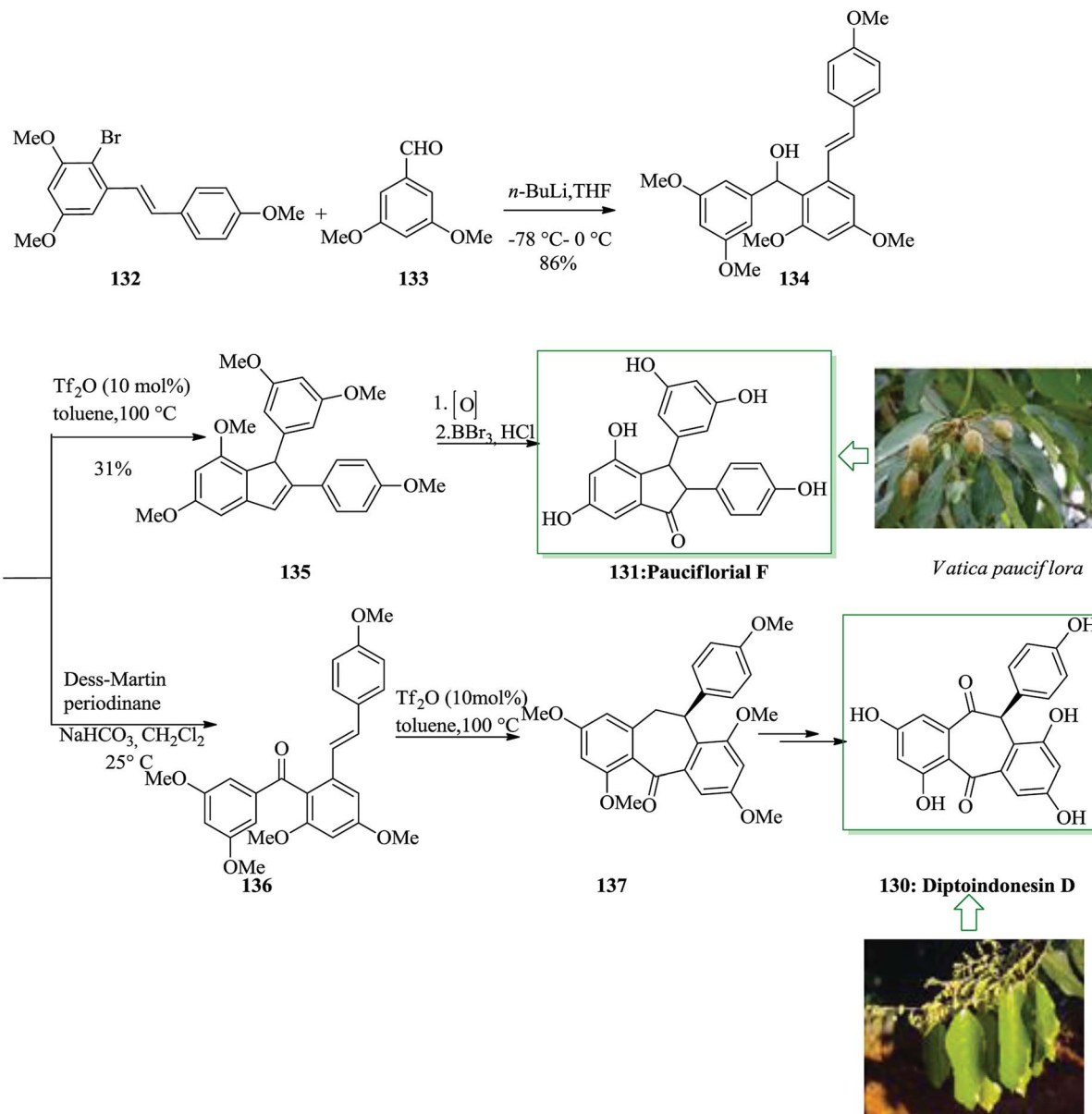
Subsequently, the asymmetric total synthesis of methylated paralycolin B 139 was accomplished. First, compound 144 was synthesized from 6-bromoveratraldehyde 143 upon several steps. Enantioselective intramolecular FC allylic alkylation reaction of 144 using $Pd(dba)_2$ and (*R,R*)-chiral ligand in dichloromethane/methanol 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 *Psalidium* 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-oxoeryopsin 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, imidazolylthiocarbonylation 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-oxoeryopsin 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





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

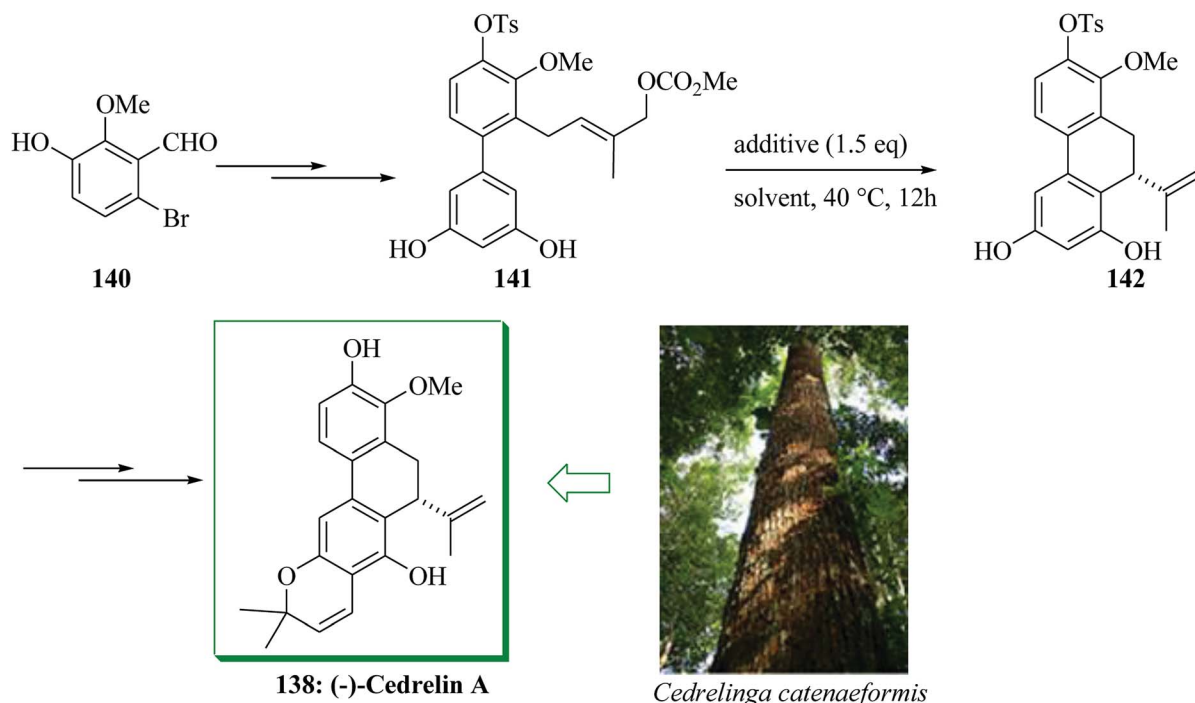
cytotoxicity against several strains of pathogenic yeasts tested, but etherification of the 2-hydroxyethyl group resulted in significantly attenuated activity. This total synthesis began from commercially available bromobenzene, which in four steps is converted into 3,4-dimethoxytoluene **150**.¹⁶¹ The 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

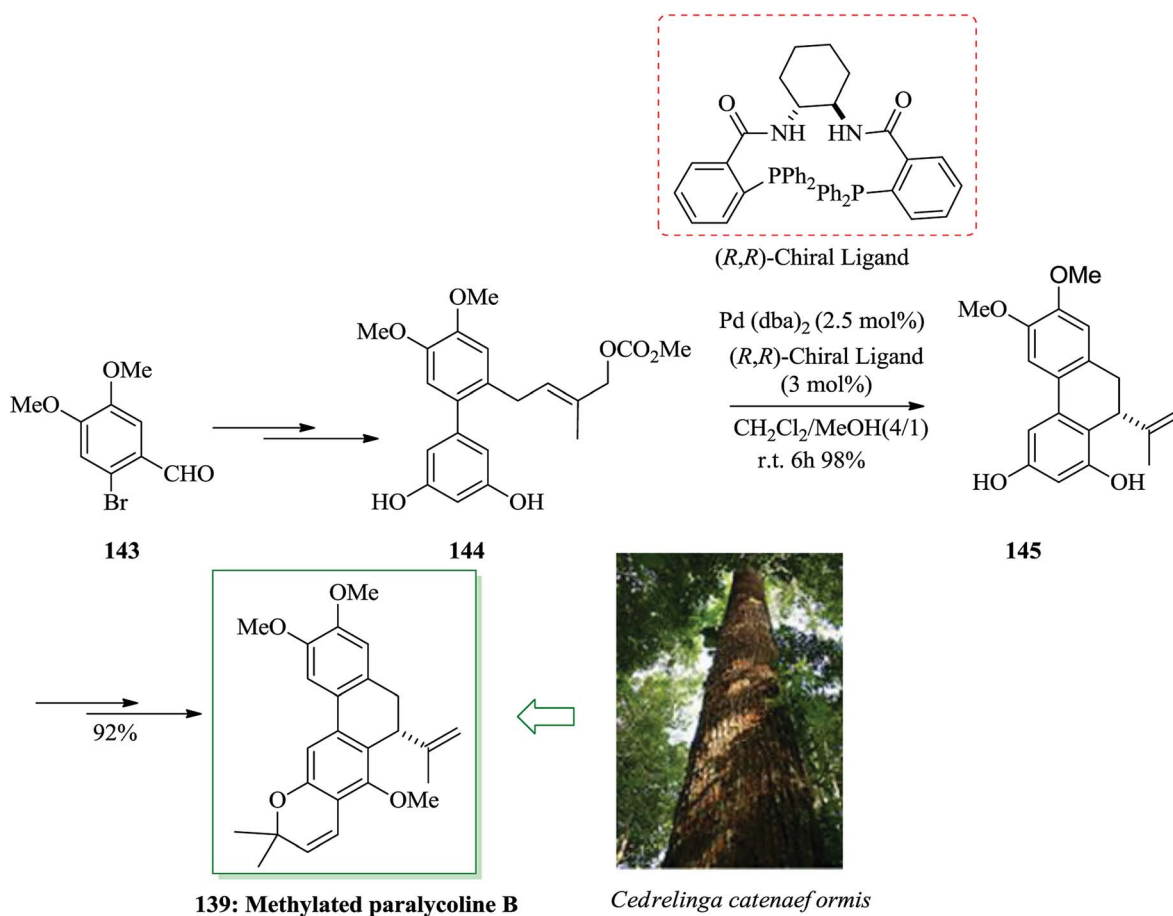
steps. Compound **155** was provided *via* BBr_3 -catalyzed bis-demethylation and intramolecular FC alkylation followed by oxidation of the resulting catechol with Ag_2O in one-pot fashion. Compounds **149** and **155** were found to be particularly effective against all yeast strains, including *Candida 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

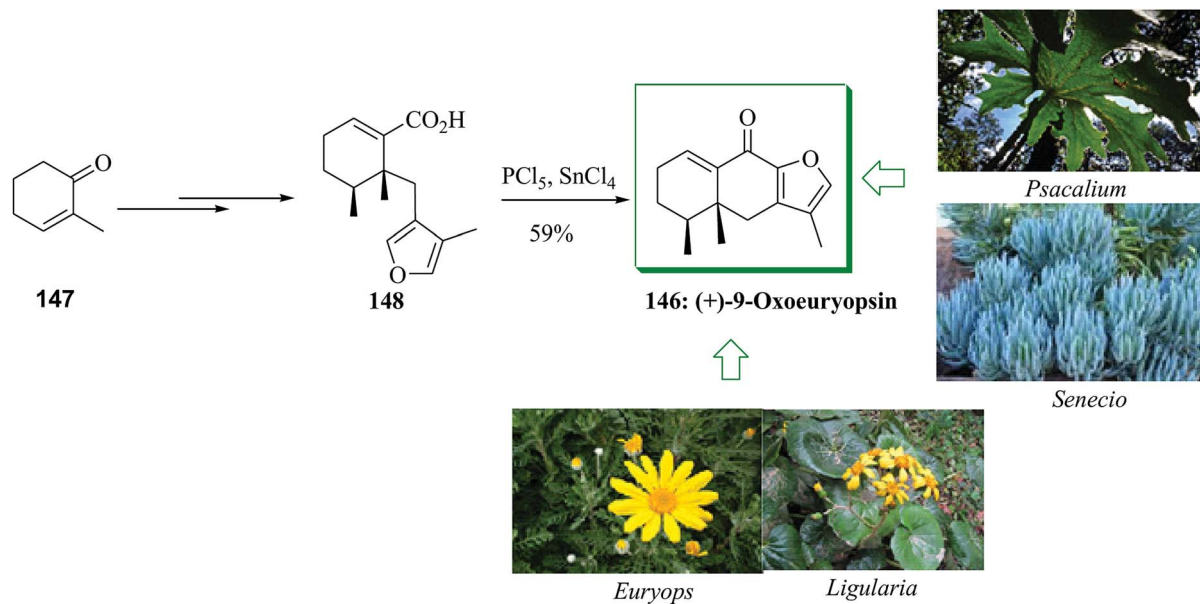




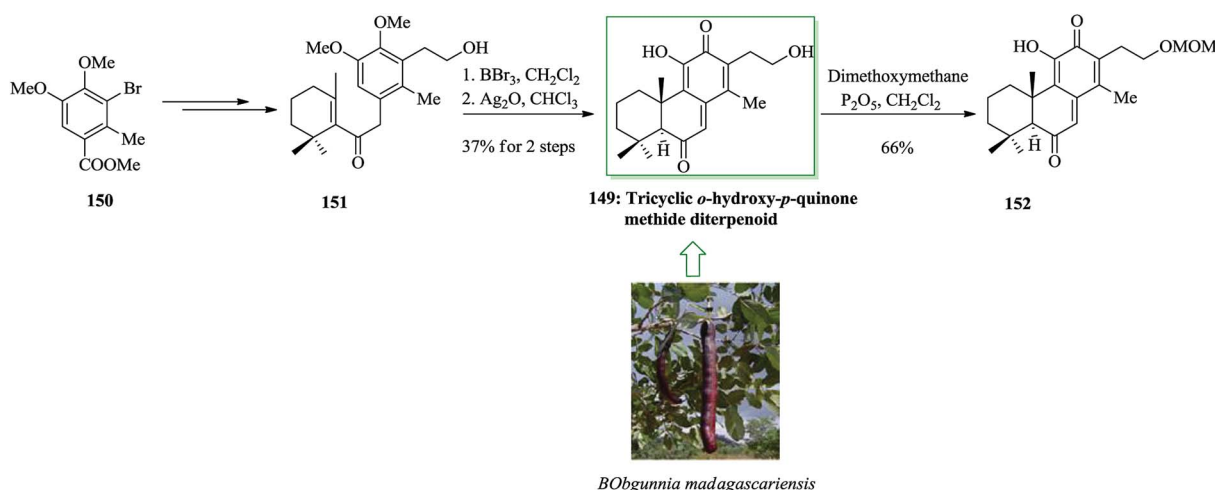
Scheme 29 Total synthesis of cedrelin A 138.



Scheme 30 Total synthesis of methylated paralycolin B 139.



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

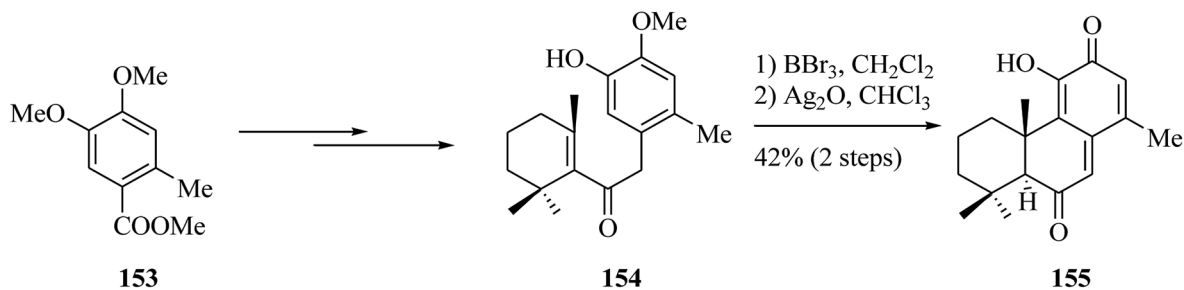
Scheme 32 Total synthesis of tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid 149 and analogues.

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.

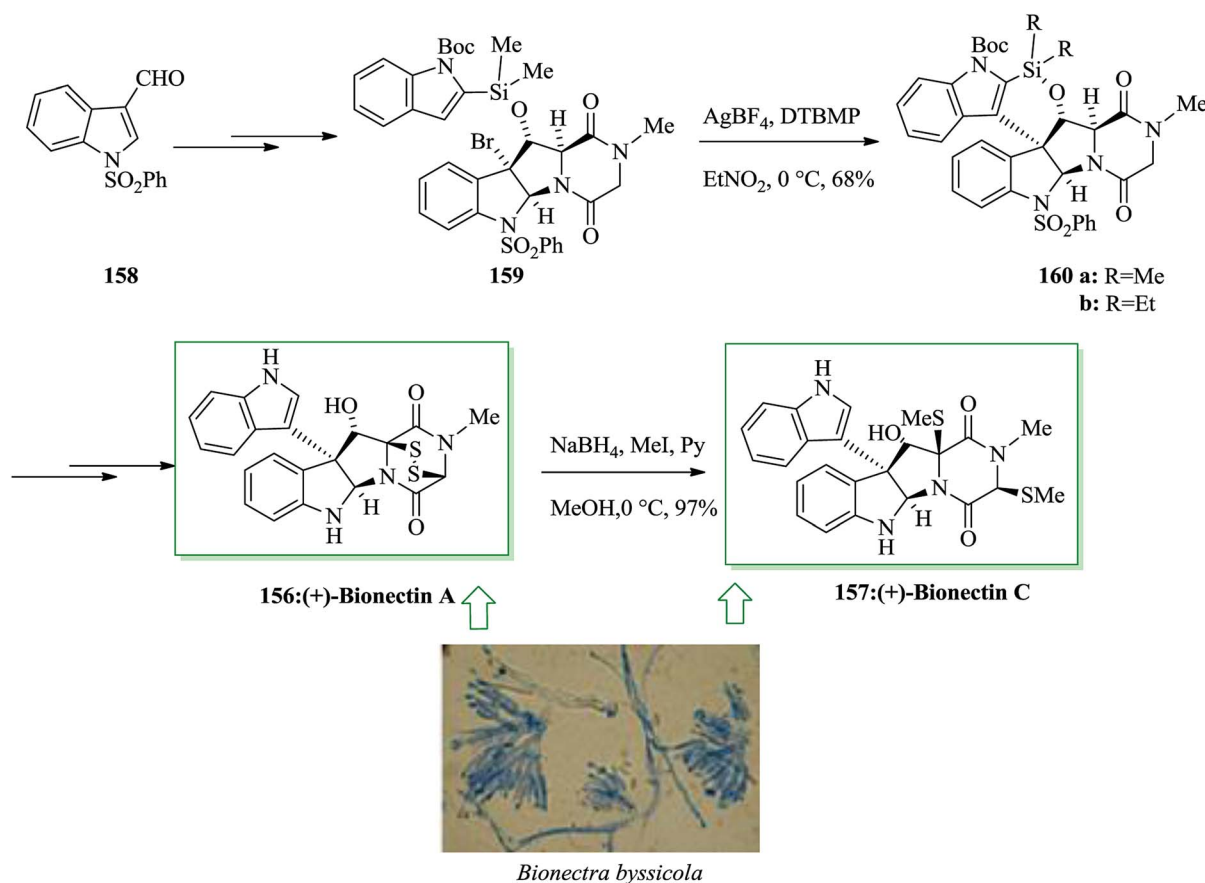
Compound 160a gave the target natural product (+)-bionectin A 156 in 81% yield after several steps. Reductive methylation of (+)-bionectin A 156 with NaBH_4 and methyl iodide in pyridine and MeOH gave (+)-bionectin C 157 in 97% yield (Scheme 34).¹⁶⁵

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





Scheme 33 Total synthesis of product 155.



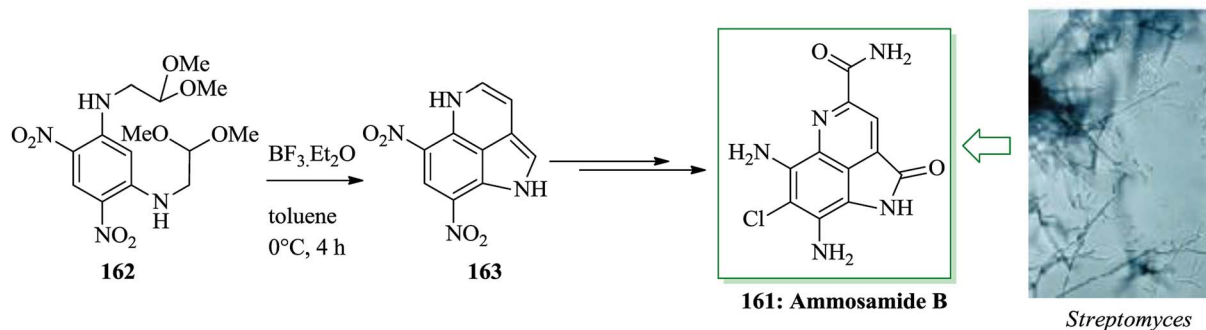
Scheme 34 Total synthesis of (+)-bionectins A 156 and C 157.

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.

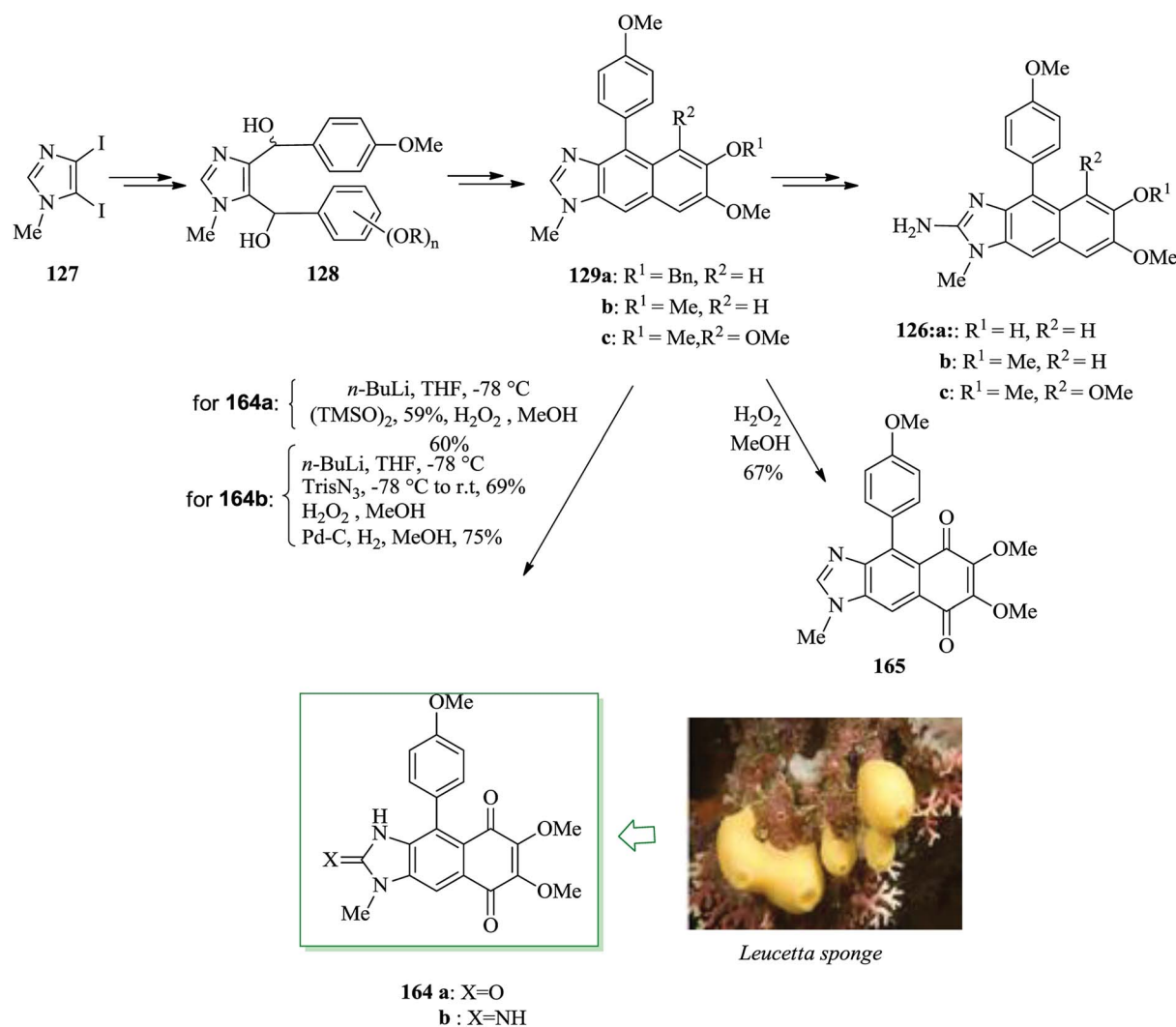
Subsequently, a number of acids were applied to examine the tandem FC reaction and the results demonstrated that the reaction improved in the presence of trifluoroacetic acid (TFA) but does not provide either of the anticipated FC products, only an unidentified oligomeric material. Reactions using the 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 BF₃·Et₂O in dichloromethane was used provided the motivation for a broader investigation of solvent effects on this method. When CH₃CN or THF was utilized in the presence of BF₃·Et₂O 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





Scheme 35 Total synthesis of ammosamide B 161.



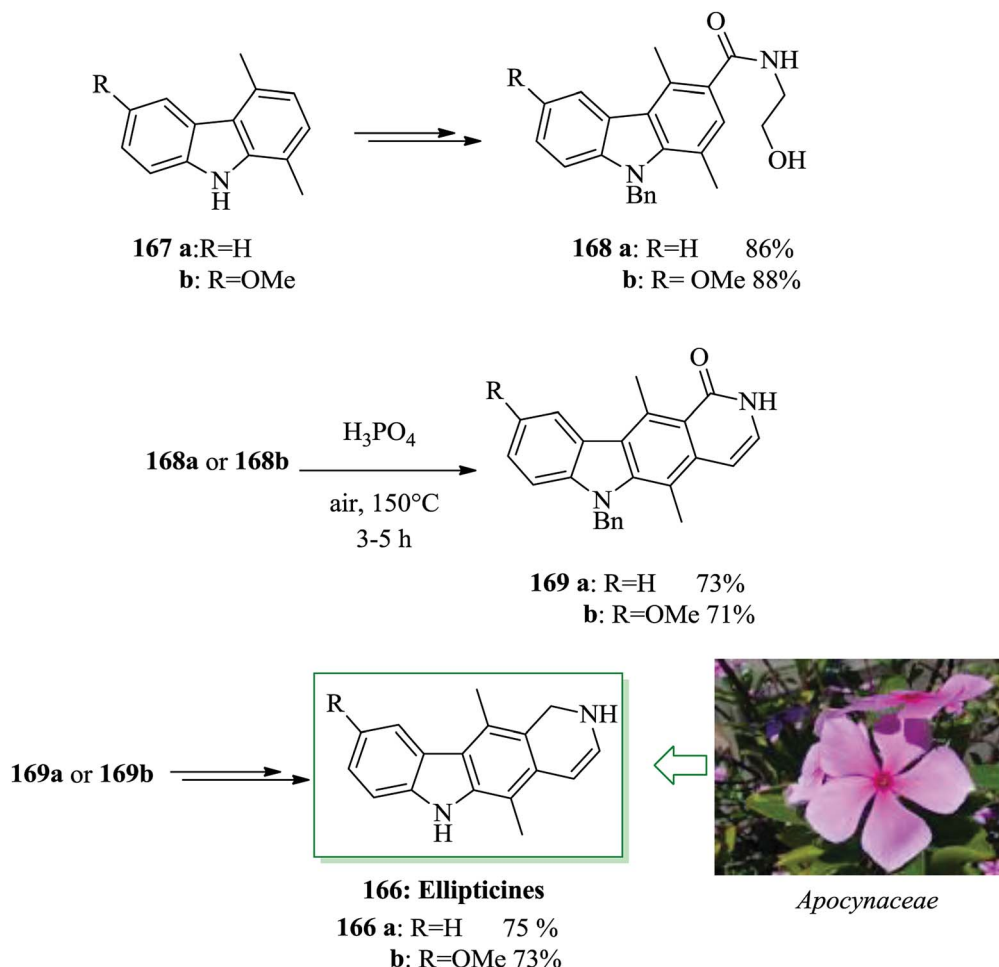
Scheme 36 Total synthesis of kealiiquinone A 164a and the 2-amino congener 164b.

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 ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 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



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

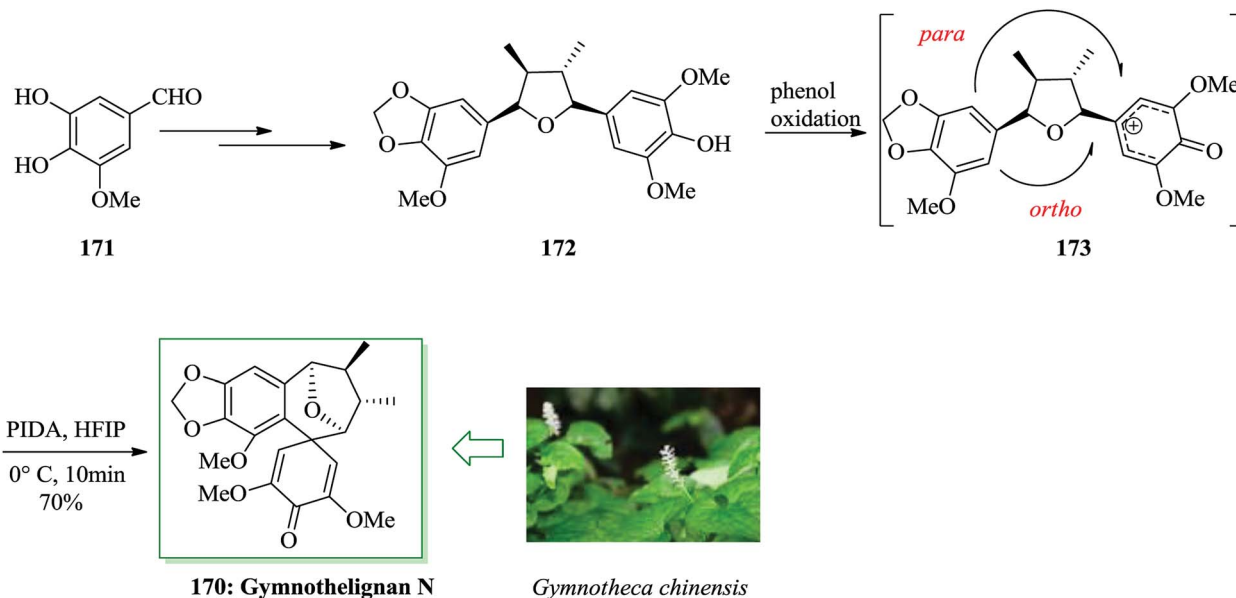
164a from a *Leucetta*-obtained sponge containing a unique imidazobenzoquinone scaffold.¹⁷² Compound **164a** exhibited cytotoxicity, with potentially a unique mechanism of action.¹⁷³ Schmitz reported the isolation of 2-deoxy-2-aminokealiiquinone **164b**, but no bioactivity has been reported for this 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 diiodimidazole **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 a 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

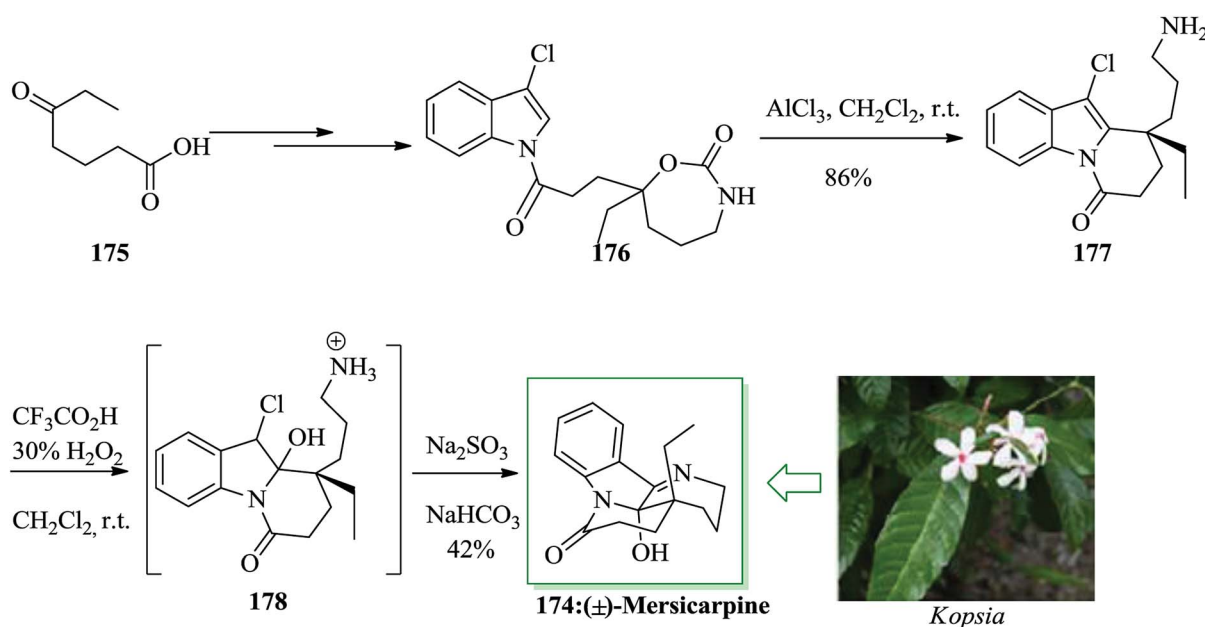




Scheme 38 Total synthesis of gymnothelignan N 170.

Chinese herb of *Saururaceae*.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-hydroxyvanillin 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-hydroxyvanillin 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),



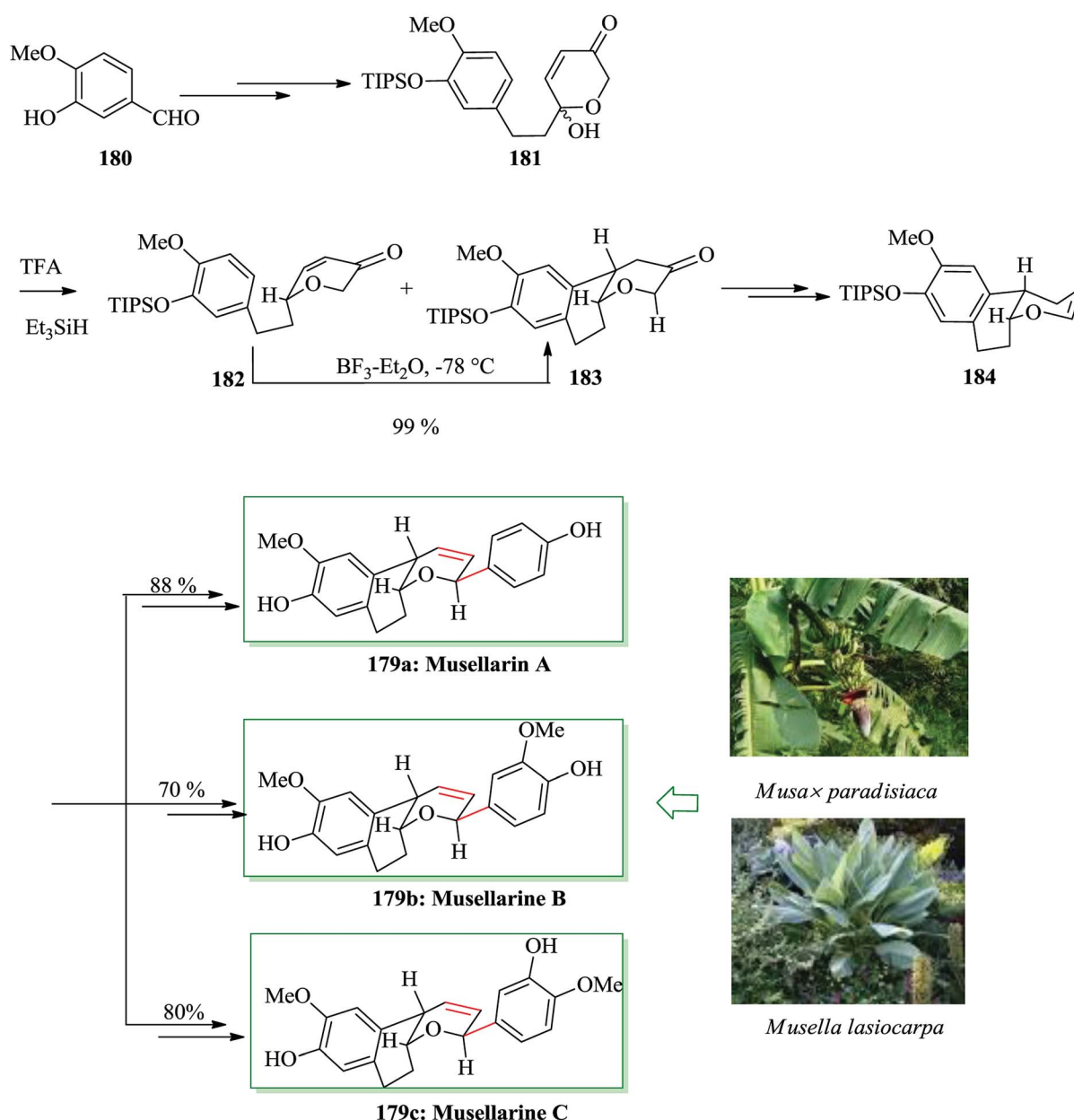
Scheme 39 Total synthesis of mersicarpine 174.



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-hydroxyvanillin **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**.



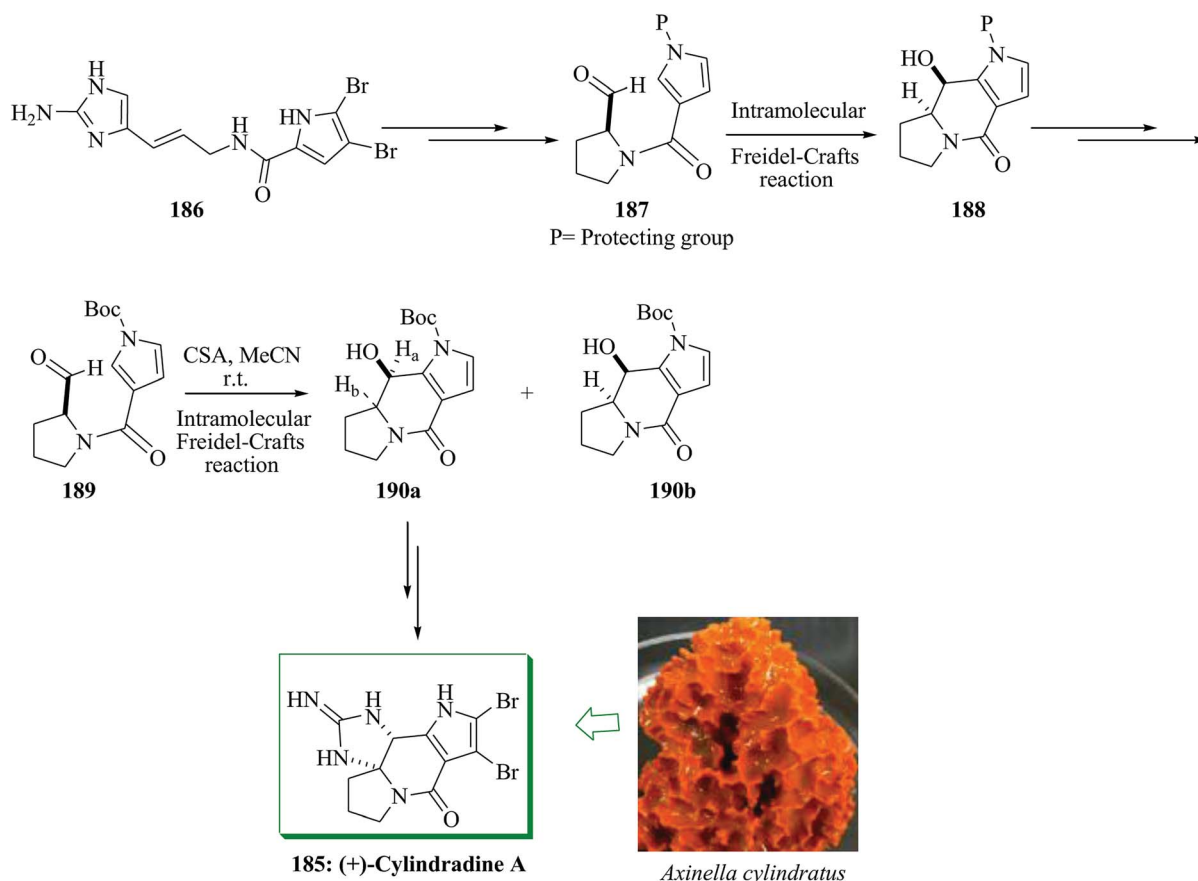
and acidity optimization with $\text{Na}_2\text{SO}_3/\text{NaHCO}_3$, merciscarpine **174** was provided in 42% yield. As a result, the natural product was obtained in 25% overall yield (Scheme 39).¹⁹⁴

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 Kinghorn¹⁹⁷ 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 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

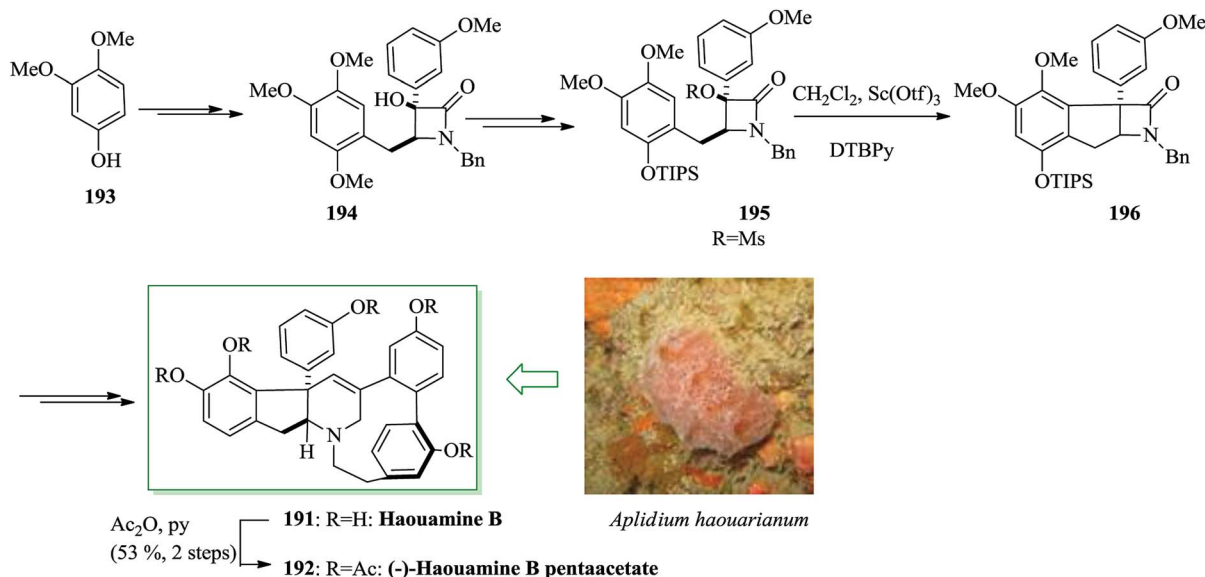
Polycyclic pyrrole-imidazole alkaloids (PIAs) are oroidin-obtained marine naturally occurring compounds^{200,201} with various and complex frameworks. Most of these alkaloids exhibit multiple biological properties, including immunosuppressive, antitumor and adrenoceptoragonistic properties.^{202,203} 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**.





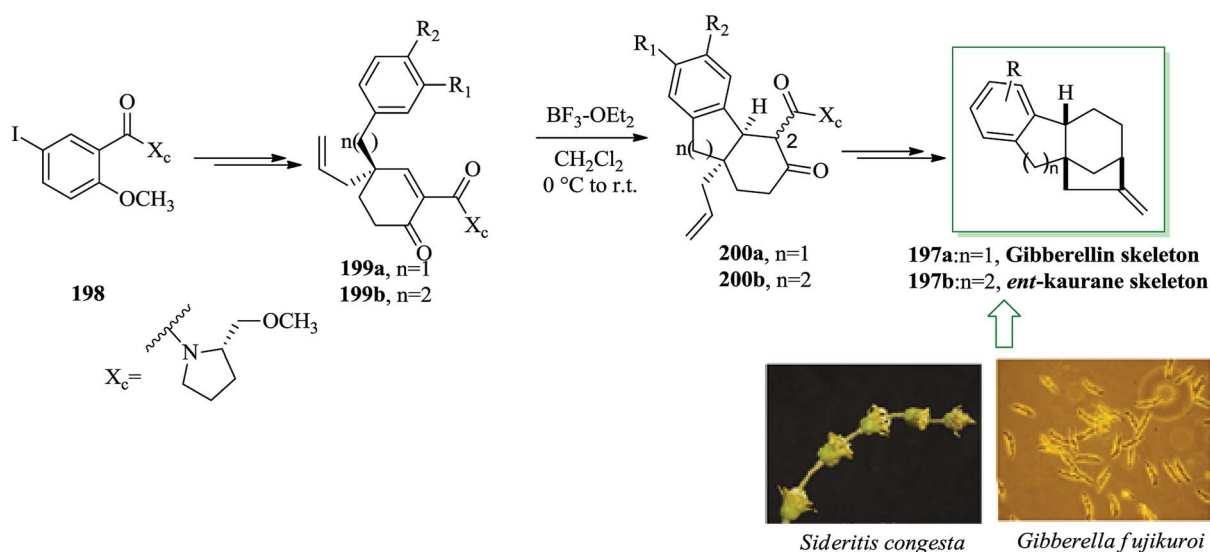
Scheme 42 Total synthesis of (-)-haouamine B 191 and haouamine B pentaacetate 192.

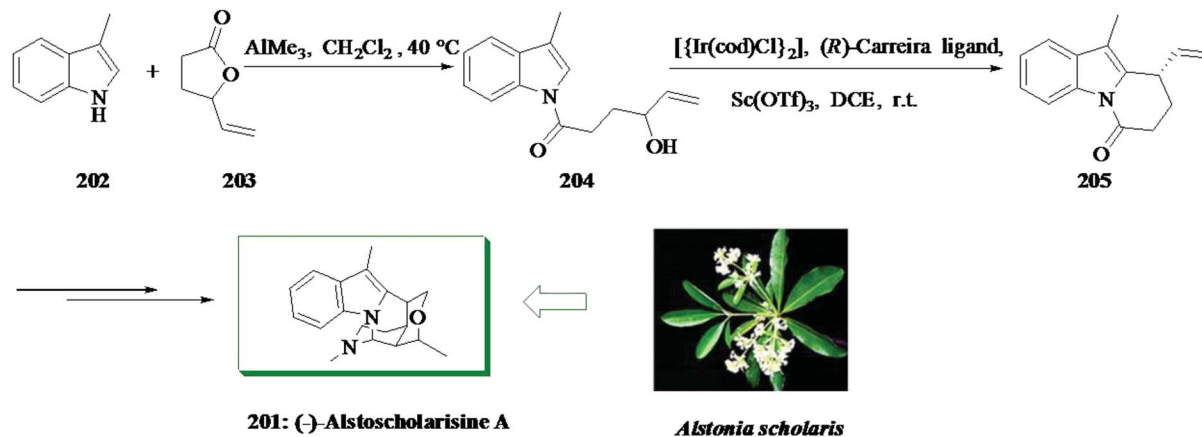
the scandium(III) triflate-catalyzed intramolecular FC alkylation were applied to make the uncommon indane-fused β -lactam **196**. In this route, an intramolecular McMurry coupling reaction was considered as the key step. Tokuyama and co-workers initiated the synthesis of (-)-haouamine B from 3,4-dimethoxyphenol **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

Gibberellin²⁰⁷ 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 tricycyclic scaffold *via* an extension of

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



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 tetracyclic framework of the gibberellins **197a** or the *ent*-kauranes **197b** was demonstrated by the same group.²¹⁶ There is a tetracyclic 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 tetracyclic scaffold of the gibberellins **197a** or *ent*-kauranes **197b** was achieved via FC alkylation in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 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 tetracyclic framework of the gibberellins **197a** or *ent*-kauranes **197b** was obtained from **200a** and **200b** upon several steps (Scheme 43).²¹⁶

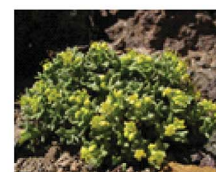
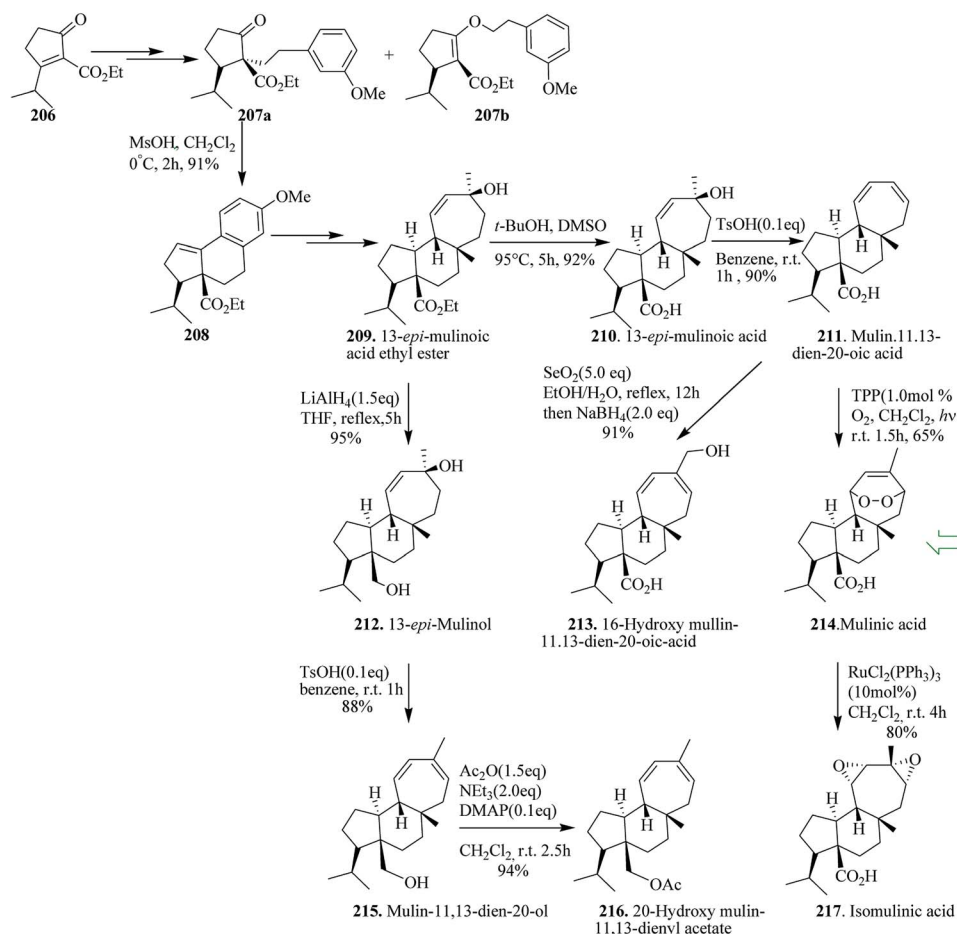
The alstoscholarisines²¹⁹ are some fascinating mono-terpenoid indole alkaloids having a complex pentacyclic structure extracted from *Alstonia scholaris* by Luo and co-workers. In 2016, Liang and co-workers reported an asymmetric total synthesis of (-)-alstoscholarisine A **201** in 10 steps.²²⁰ This group demonstrated a short and highly asymmetric total synthesis of (-)-alstoscholarisine A **201**, an extracted mono-terpenoid 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 trimethylaluminum,²²¹ providing secondary allylic alcohol **204** in 75% yield. Catalytic enantioselective FC alkylation reaction of **204** with the combination of $[\{\text{Ir}(\text{cod})\text{Cl}\}_2]$, (*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-





Mulinum crassifolium

Scheme 45 Total synthesis of 13-*epi*-mulinic acid ethyl ester **209**, 13-*epi*-mulinic 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

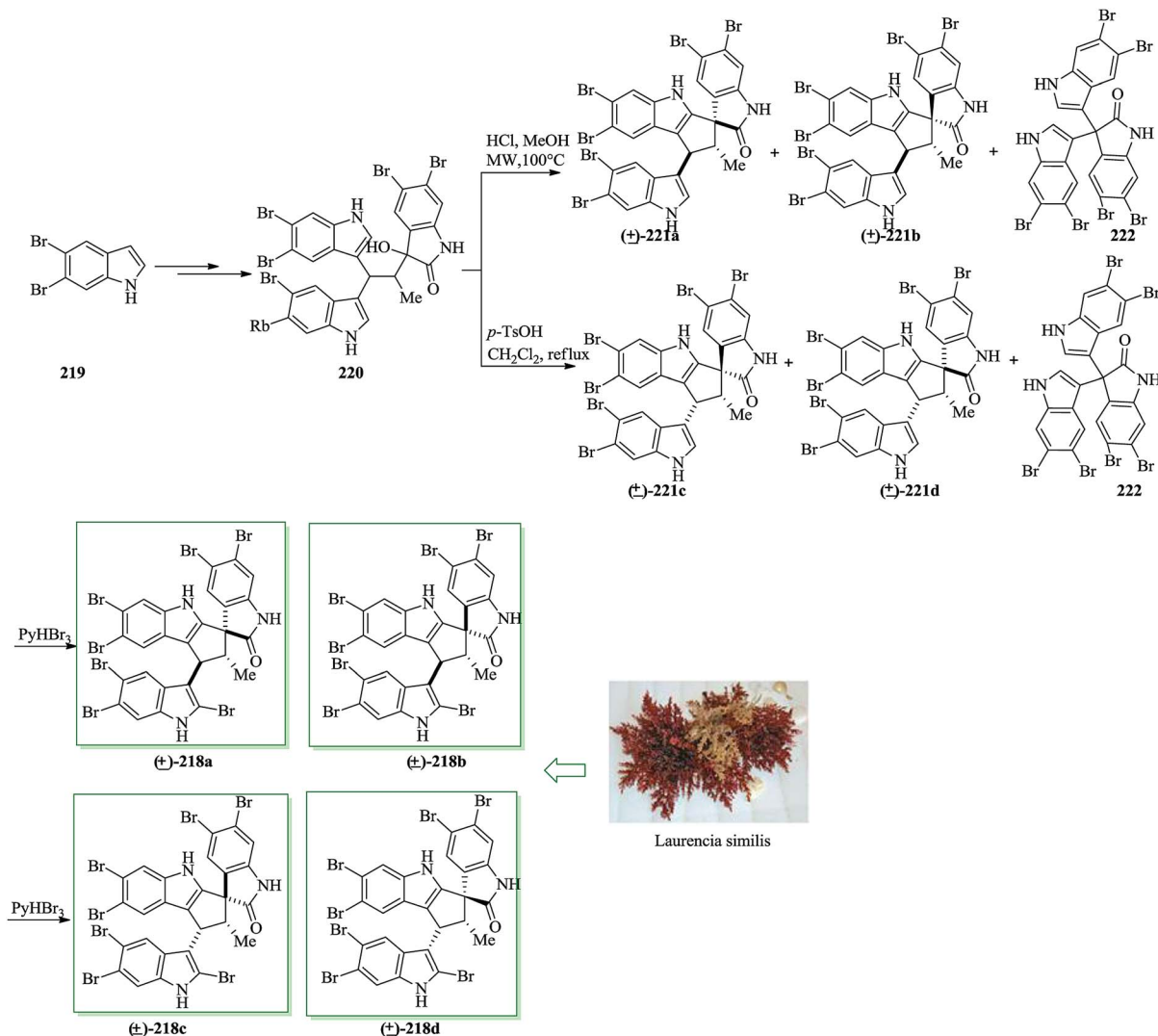
Similisines A [(+)-**218a**] and B [(−)-**218a**], extracted from *Lau-rencia similis* in 2013, are the first example of polybrominated spiro-trisindole alkaloids fused to a five-member ring.²³⁷ Similisines A and B are trisindole alkaloids that feature a unique polybrominated [5,5] spirooxindole scaffold 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





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

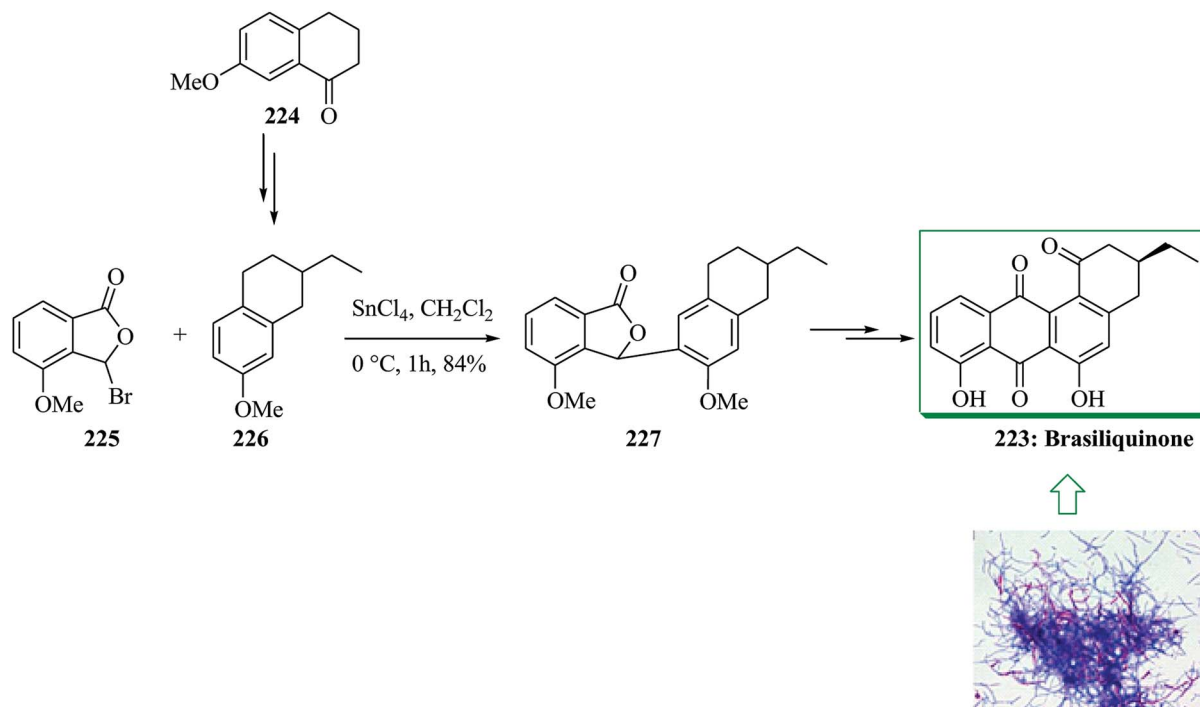
223 has been obtained from 7-methoxy-*L*-tetralone in several steps making use of an FC alkylation reaction as a main stage. Initially, 7-methoxy-*L*-tetralone **224** gave the relevant tetralin derivative **226** after several steps. FC alkylation reaction of **226** with 3-bromo-4-methoxyphthalide **225** using SnCl₄ 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*-tetrachloroethane²⁴⁶ 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-





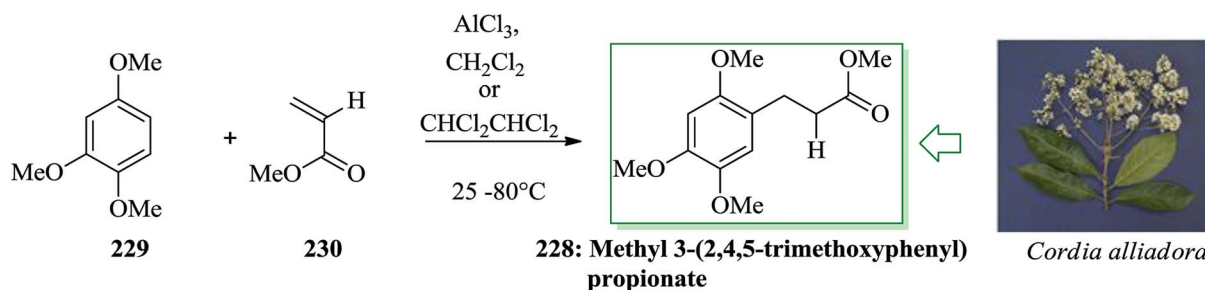
Scheme 47 Total synthesis of brasiliquinone B 223.

butyne-1,4-diol in two steps with a subsequent conventional resolution²⁵² 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 (–)-podo-phyllotoxin 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 $\text{S}_{\text{N}}1$ 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 cimidum* 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

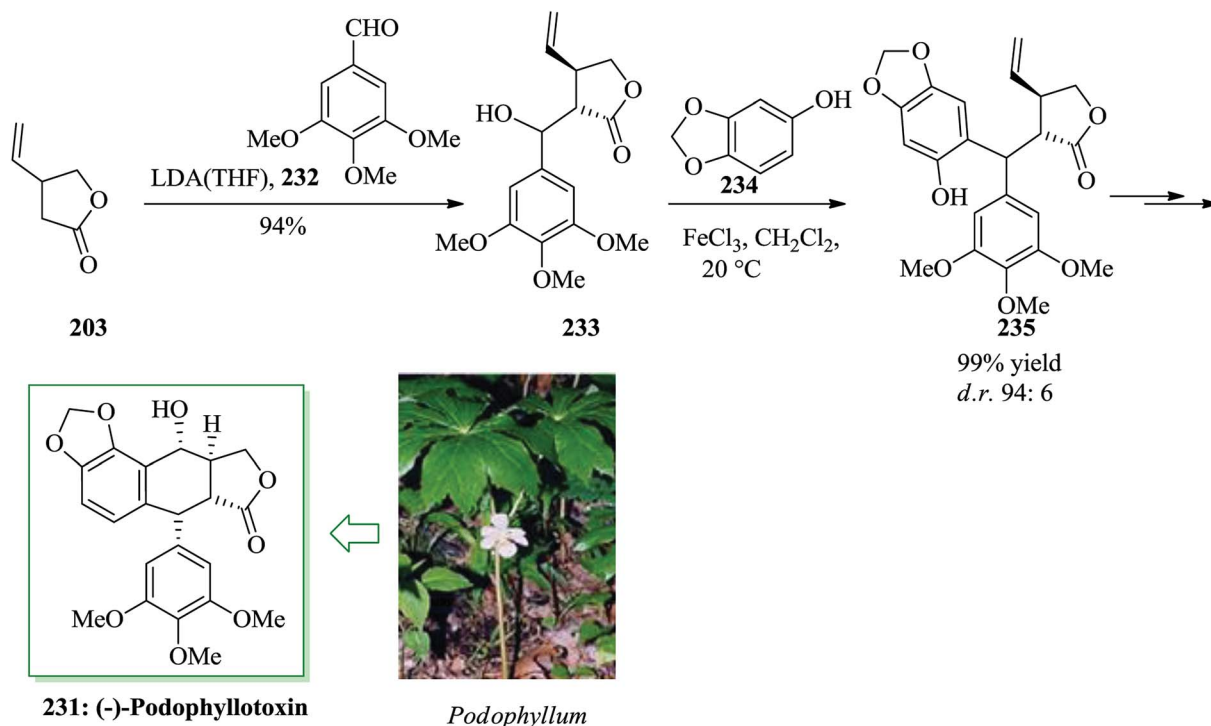
reported the initial total synthesis of (+)-haplophytine 236 demonstrating the simple assembly of tricyclic ketone 238 *via* the intramolecular Mannich reaction. FC alkylation reaction and Fischer indole synthesis were considered as the key steps. For the synthesis of (+)-haplophytine 236, initially, 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-Benzoyloxyindole 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.





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

selected cancer cell lines of hopeanol **245**, a polyphenol secondary metabolite extracted from the bark of *Hopea exaltata*.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·H₂O 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

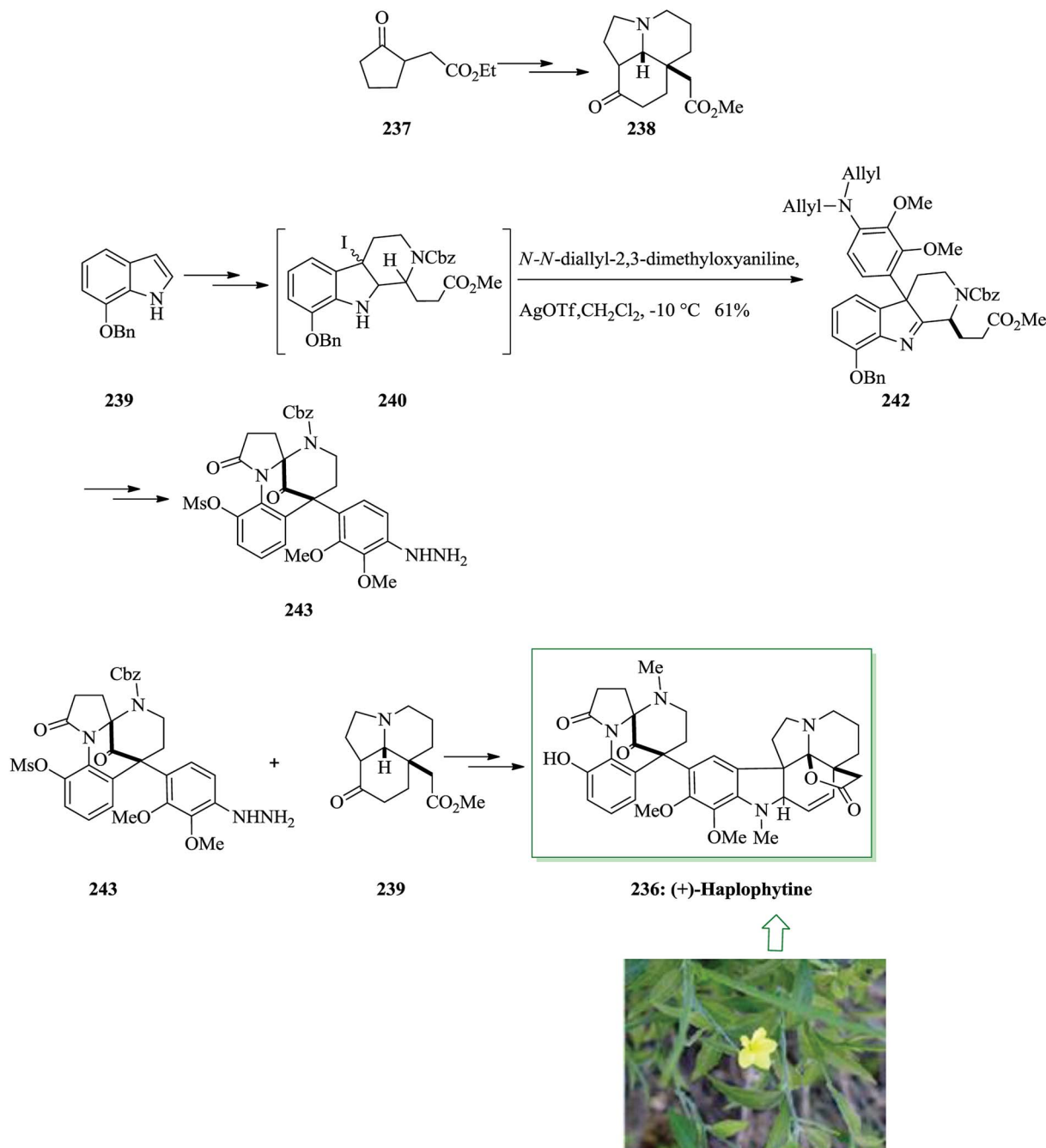
The successful formation of model system **257** (comprising four of the six ring systems of hopeahainol A) provided motivation for the next logical step, which was to attempt to use an established approach to assemble the entire carbon framework of hopeahainol A **244**. Using protected nucleophilic 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 BF₃·Et₂O 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 BF₃·Et₂O 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





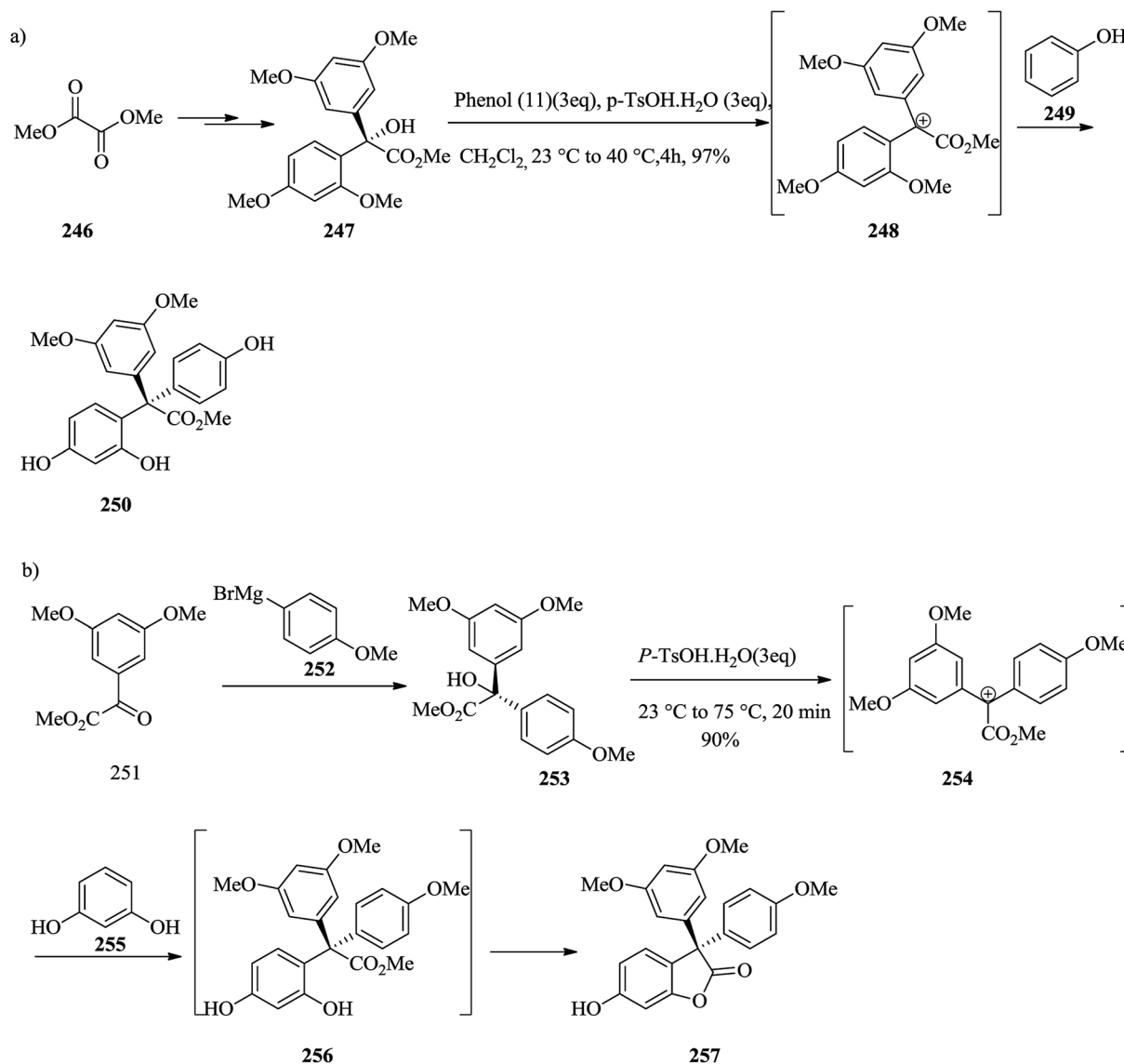
Scheme 50 Total synthesis of (+)-haplophytine 236.

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





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

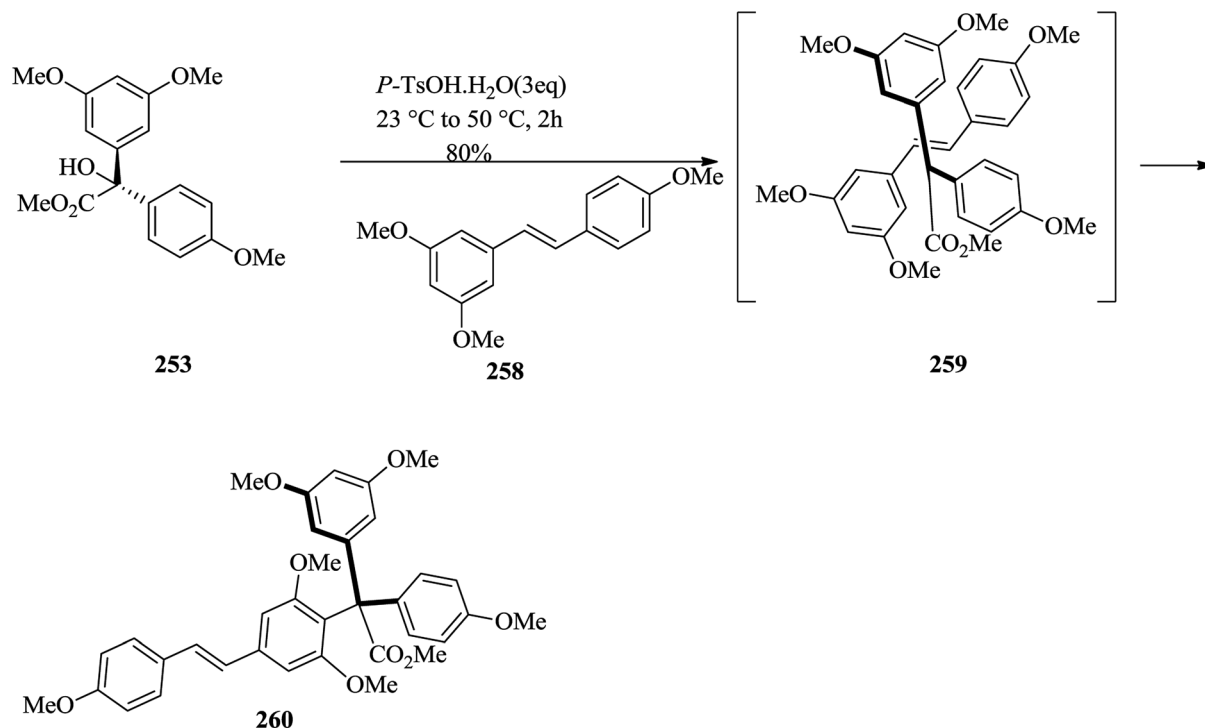
Subsequently, total synthesis of dictyodendrin B 276 was successfully achieved in 12% overall yield starting from *para*-nitrophenol 277. By using bromoindole 278, regioselective FC acylation occurred in the presence of zinc chloride²⁶⁴ to afford 283, which was converted into dictyodendrin B 276 in seven 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 bromopyrrolinoline 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

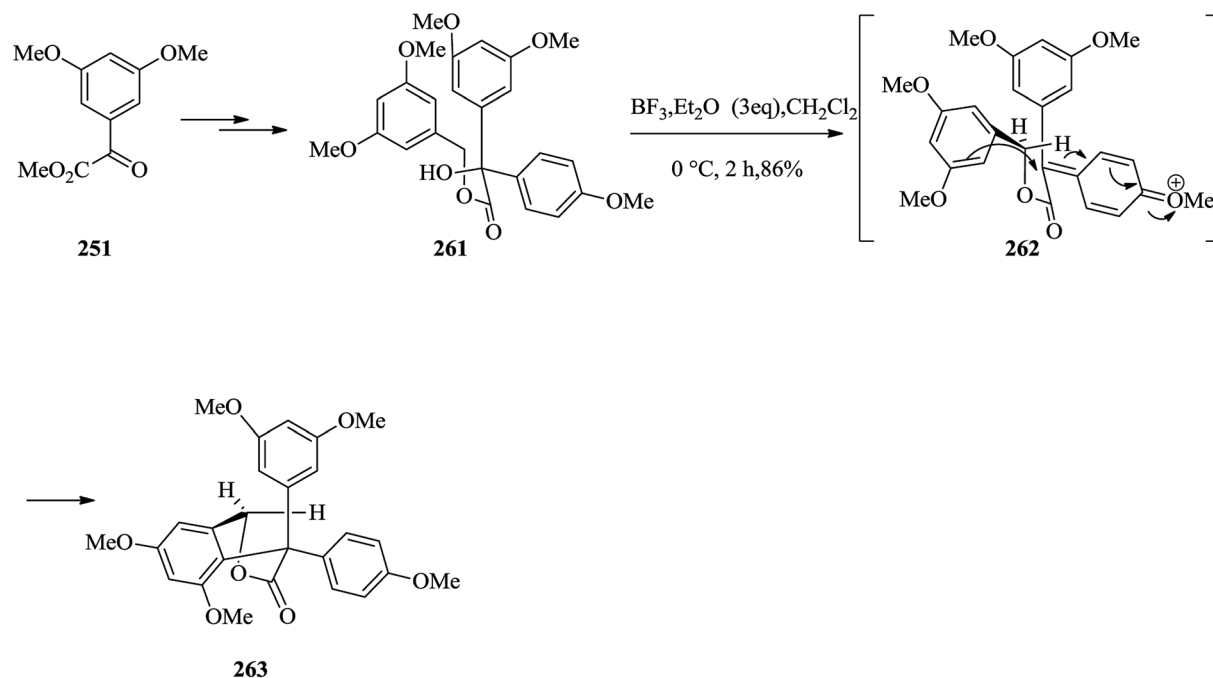
reaction. Firstly, direct isoprenylation of bromopyrrolinoline 286 with 287 gave 288 through the FC reaction in the presence of silver perchlorate, 287, and caesium carbonate. Based on optimal reaction conditions, the main intermediate 288 was generated from 286 in 91% yield in a single step, leading 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





Scheme 52 The formation of compound 260.

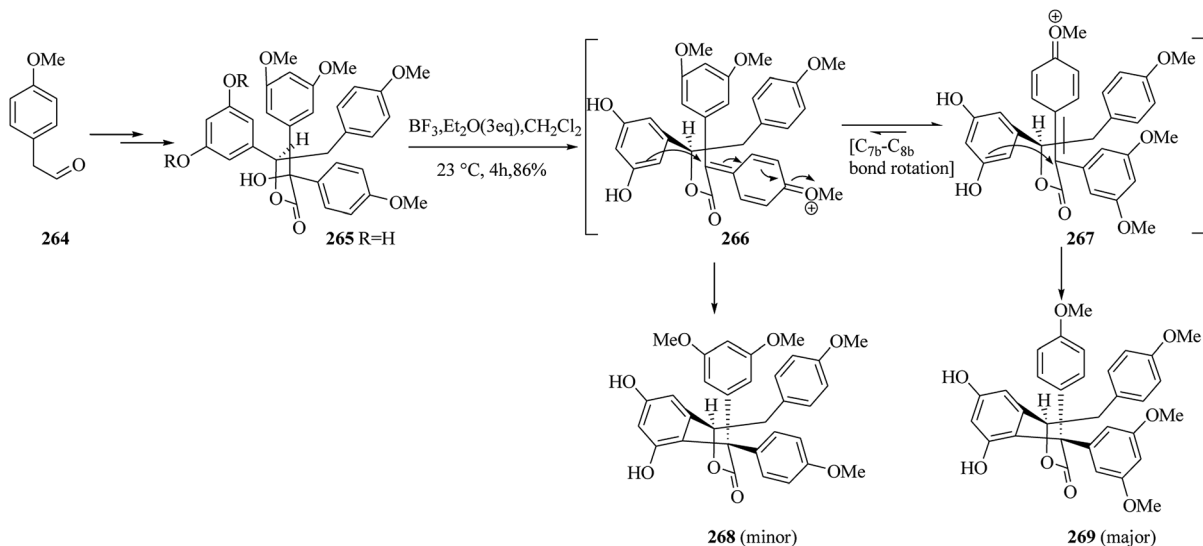


Scheme 53 The formation of product 263.

(+)-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





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)hexahydro-pyrroloindole (+)-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

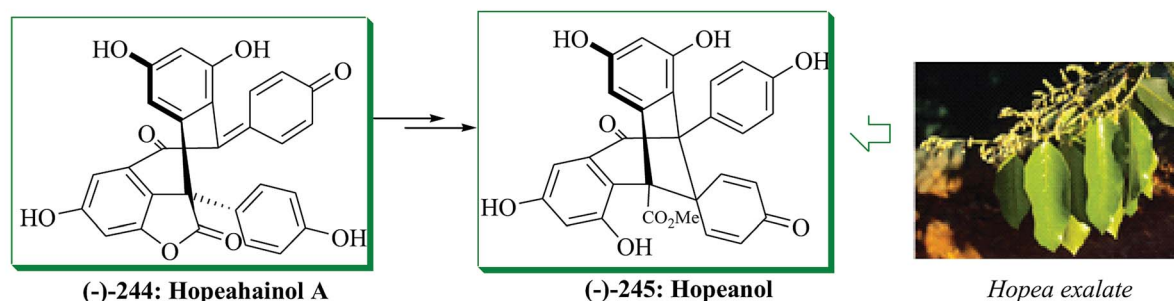
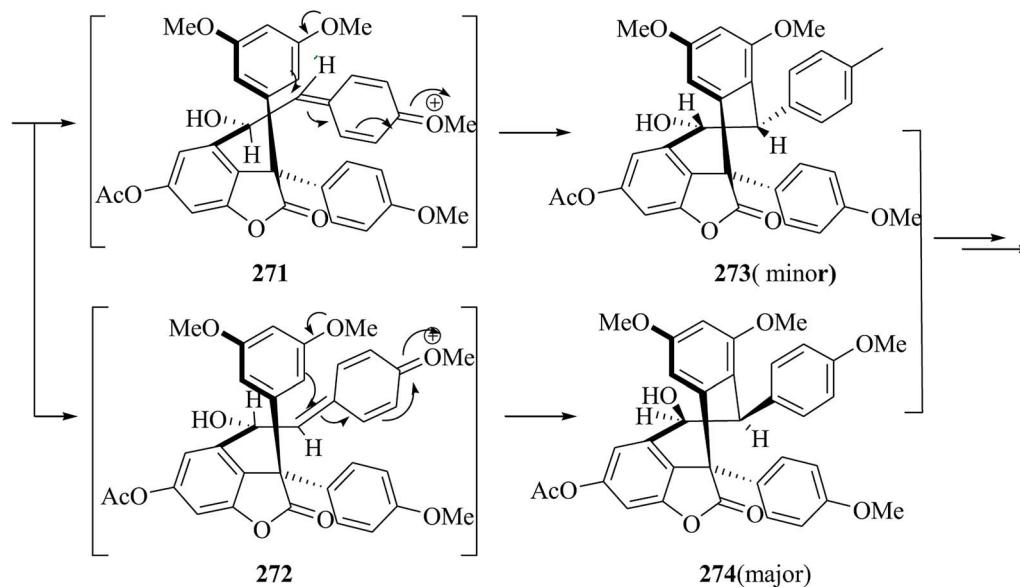
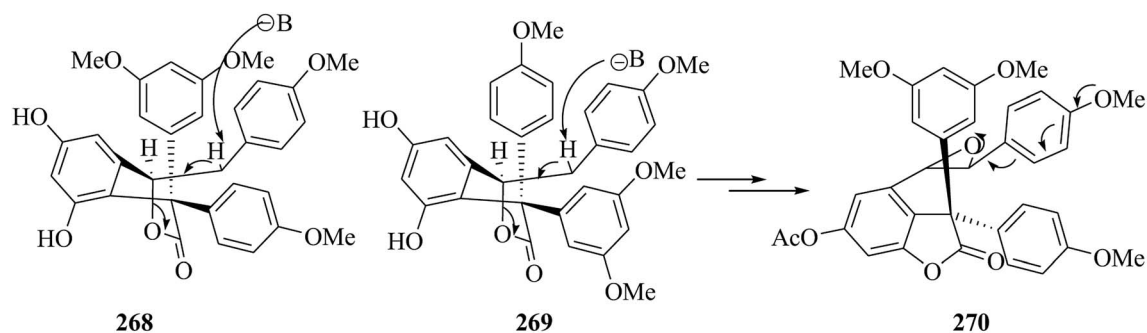
Licorice is a popular food additive applied as a sweetener in chewing gums, tobaccos, and candies, and is also one of the most broadly applied medicinal herbs having anticancer^{281,282} antiparasitic,²⁸³ antibacterial,²⁸⁴ superoxide-scavenging²⁸⁵ and antioxidant properties.²⁸⁶ Seven chalcones, licochalcones 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 $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst gave 298. In this approach, the electron-rich aromatic ring attacked the electrophile in the presence of the Lewis acid catalyst, $\text{BF}_3 \cdot \text{OEt}_2$, 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 *ees* (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 302²⁹⁴ 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 anti-protozoan, 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



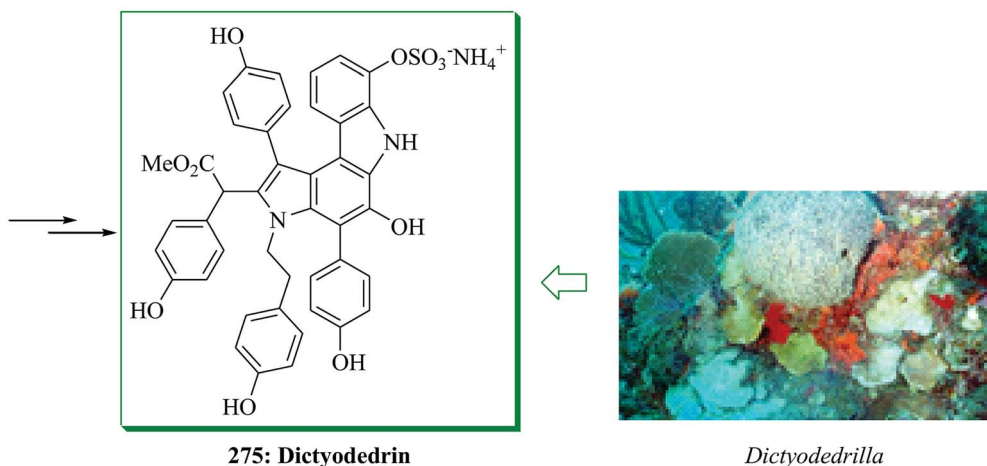
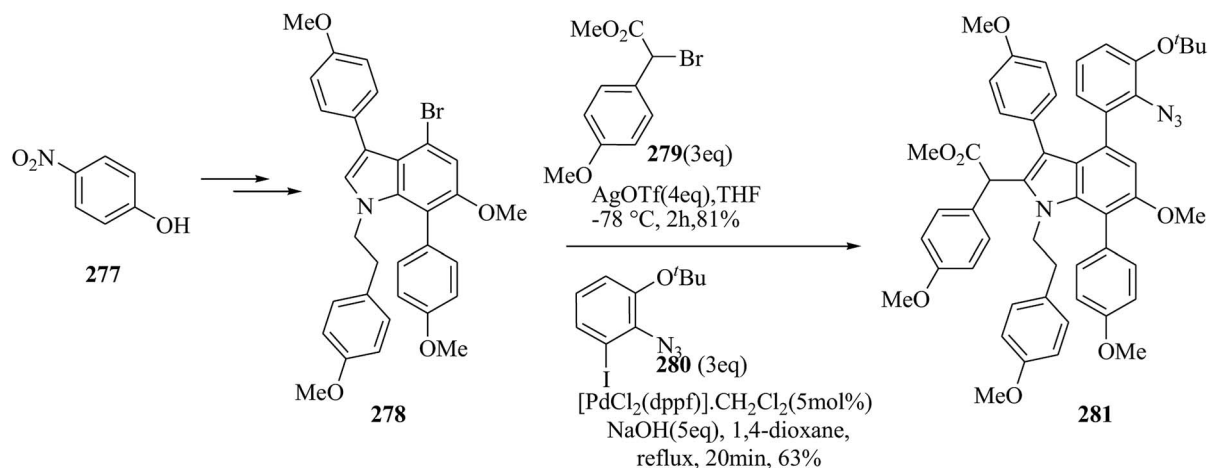


Scheme 55 Total synthesis of (-)-hopeahainol A 244 and (-)-hopeanol 245.

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-workers³⁰⁵ resulted in the extraction of natural adunctin E.³⁰⁵ A wide range of naturally occurring compounds, namely methylinderatin 310 and linderol A 312, were extracted from the fresh bark of *Lindera umbellata* by Ichino³⁰⁶ and Mimaki and co-workers,³⁰⁷ respectively. In 2007, Portet and co-workers³⁰⁸ extracted hostmanin A 309 together with methylinderatin 310, adunctin E 311 and relevant naturally occurring compounds from the leaves of *Piper hostmannianum*. Methylinderatin 310 exhibited antibacterial effects toward *M. luteus* and also exhibited potent antiplasmodial activity against chloroquine sensitive and resistant strains of *Plasmodium falciparum*.





Scheme 56 Total synthesis of dictyodendrin A 275.

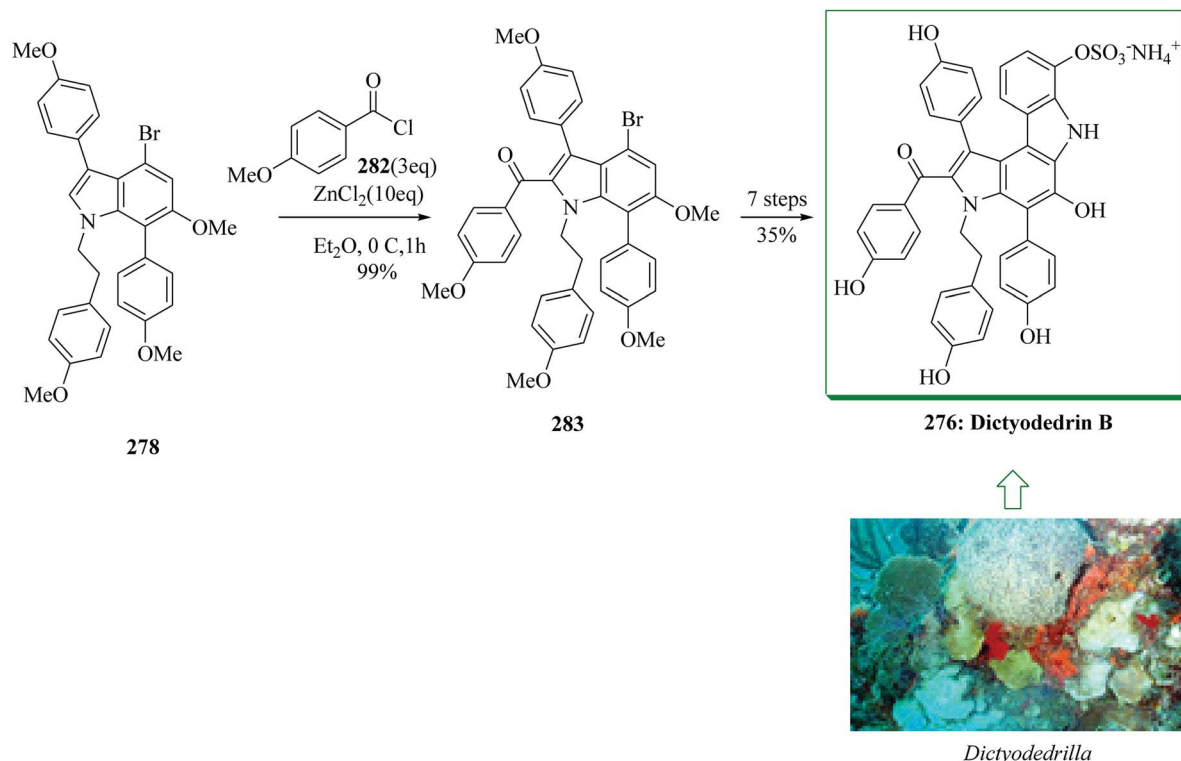
(–)-Linderol A **312** inhibited melanin biosynthesis of cultured B-16 melanoma cells without providing any cytotoxicity in the cultured cells.³⁰⁷ Adunctin E **311** and linderol A **312** have four contiguous stereocenters. Dethe *et al.* in 2015 reported³⁰⁹ protecting group free,^{310, 311} short and 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 $\text{BF}_3 \cdot \text{OEt}_2$, 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-methylenedioxybenzylidene methylamine **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





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 plants³¹⁶ and insects³¹⁷ have stirred up the interest of synthetic organic chemists as significant synthetic targets. Erythroglaucon **322a** has been extracted from species of *Cortinarius* while catenarin **322b** was first extracted from cultures of *Helminthosporium catenarium*. The regioselective, concise, and effective synthesis of the natural anthraquinones erythroglaucon **322a** and catenarin **322b** was successfully achieved. The synthesis of erythroglaucon **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 erythroglaucon **322b** in 22% and 29% overall yields, respectively (Scheme 65).³²⁰

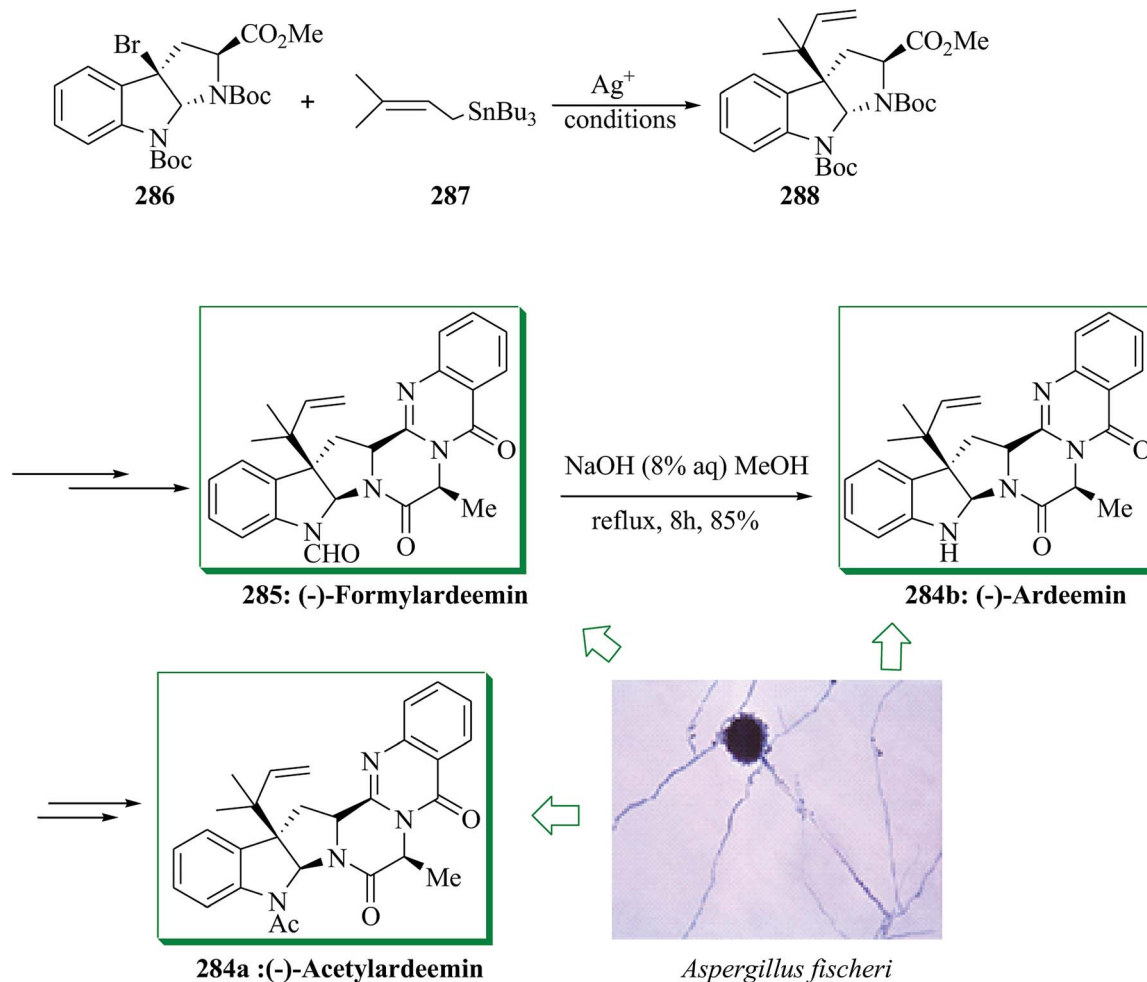
Interleukin-8 (IL-8), a chemoattractant for neutrophils, is provided by macrophages and endothelial cells.³²¹ IL-8 is implicated in a broad series of acute and chronic inflammatory disorders.³²² Frondosins A–D were recently extracted from the sponge *Dysidea frondosa*. In these compounds, the unifying 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 SnCl₄ 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





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

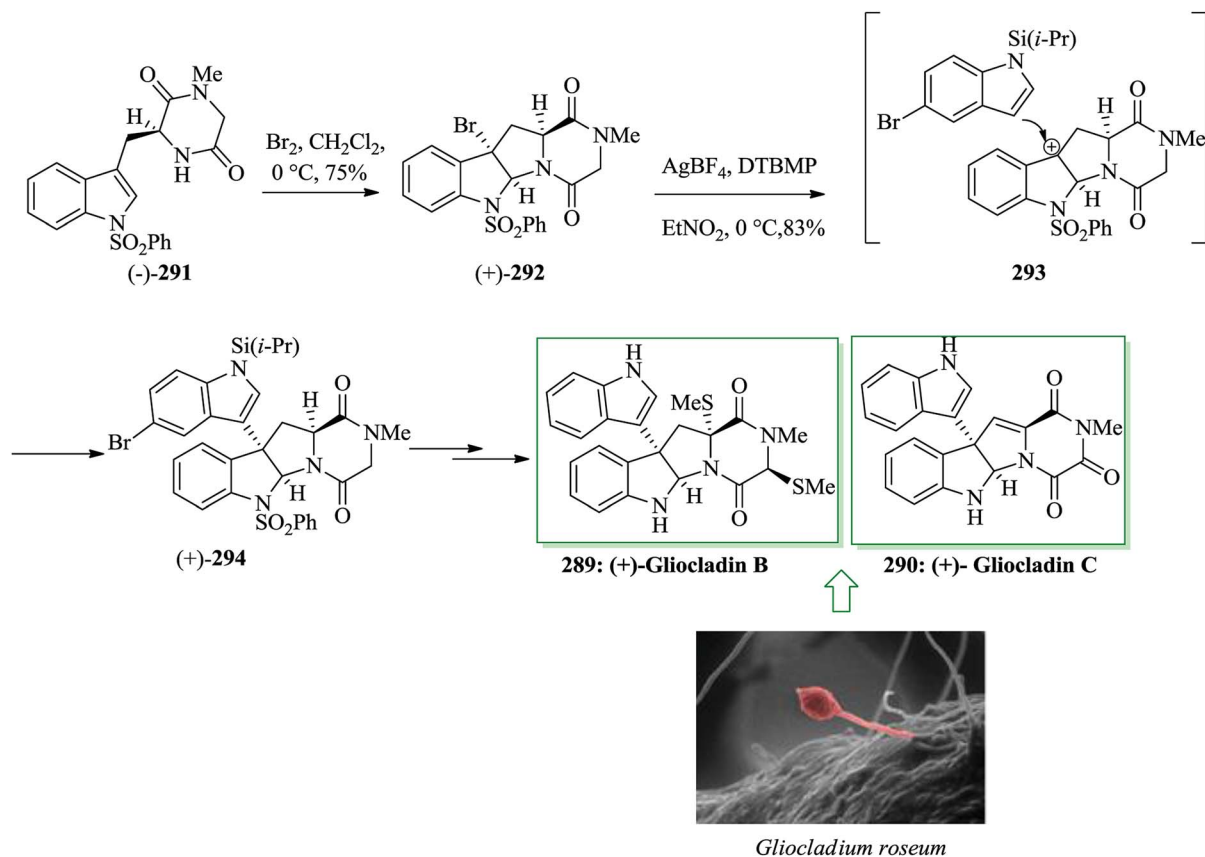
cyclization reaction, providing 336. Finally, compound 336 was converted into (\pm)-echinofuran 330 upon several steps (Scheme 68).³³¹

Preussomerins A–F were the first members of this group to be reported³³² 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

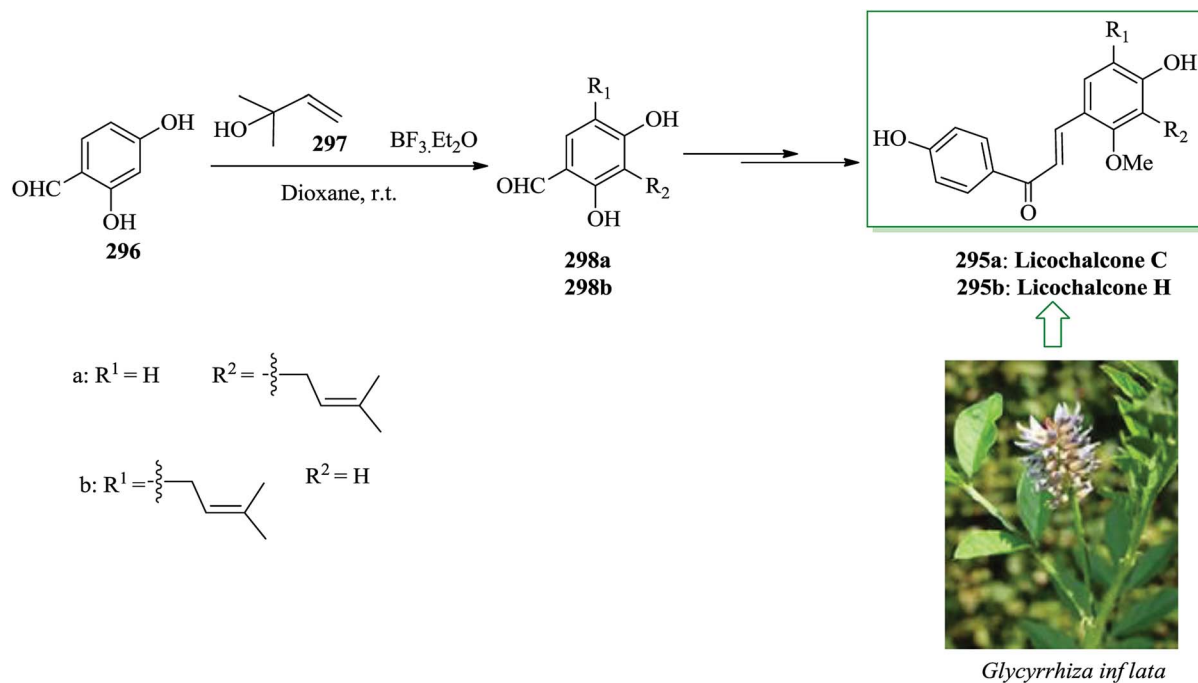
cyclization, the remaining Lewis acid gradually mediated the removal of the phenolic methoxy groups. Lastly, compound 341b gave preussomerin L 336 and preussomerin K 337 through a different multi-step synthesis (Scheme 69).³³⁴

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

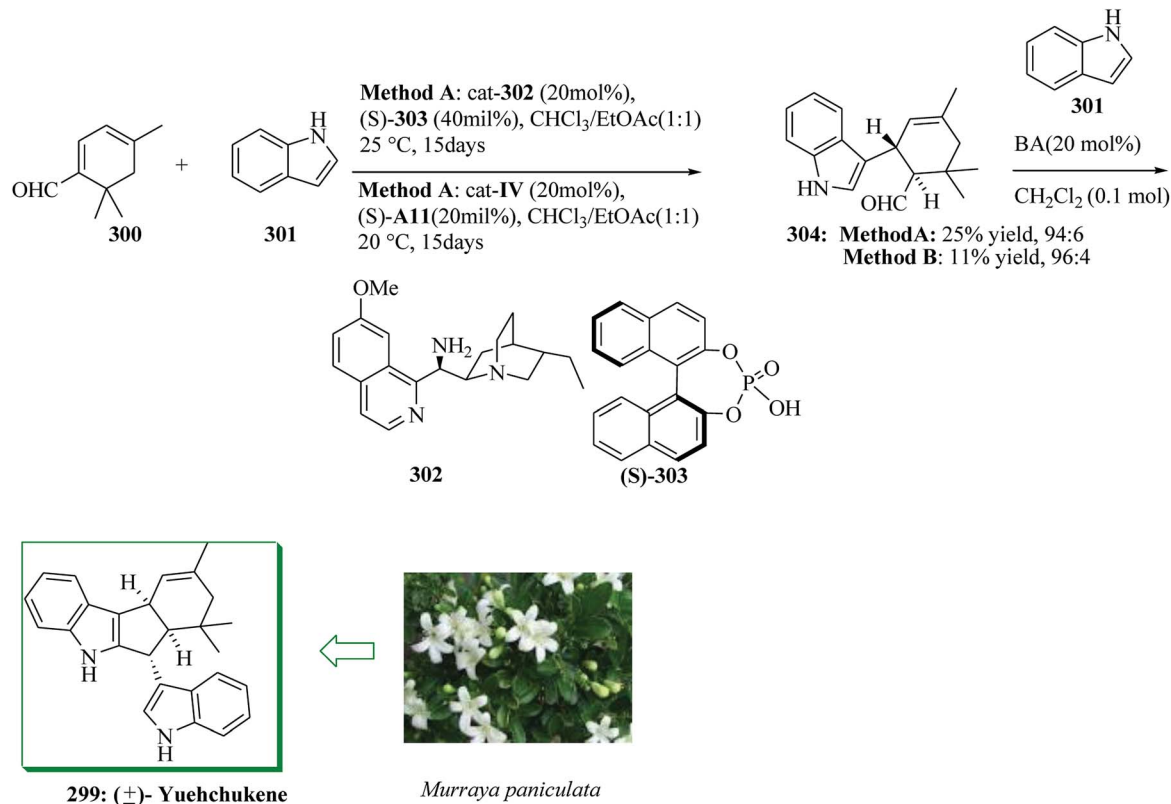




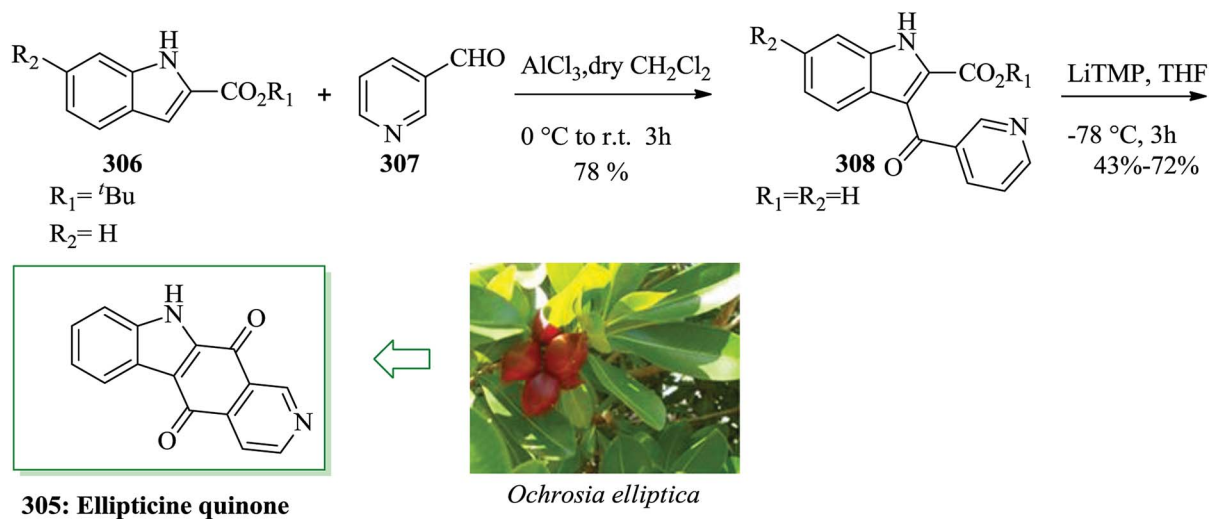
Scheme 59 Total synthesis of (+)-gliocladin B 289 and C 290.



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



Scheme 61 Total synthesis of yuehchukene 299.



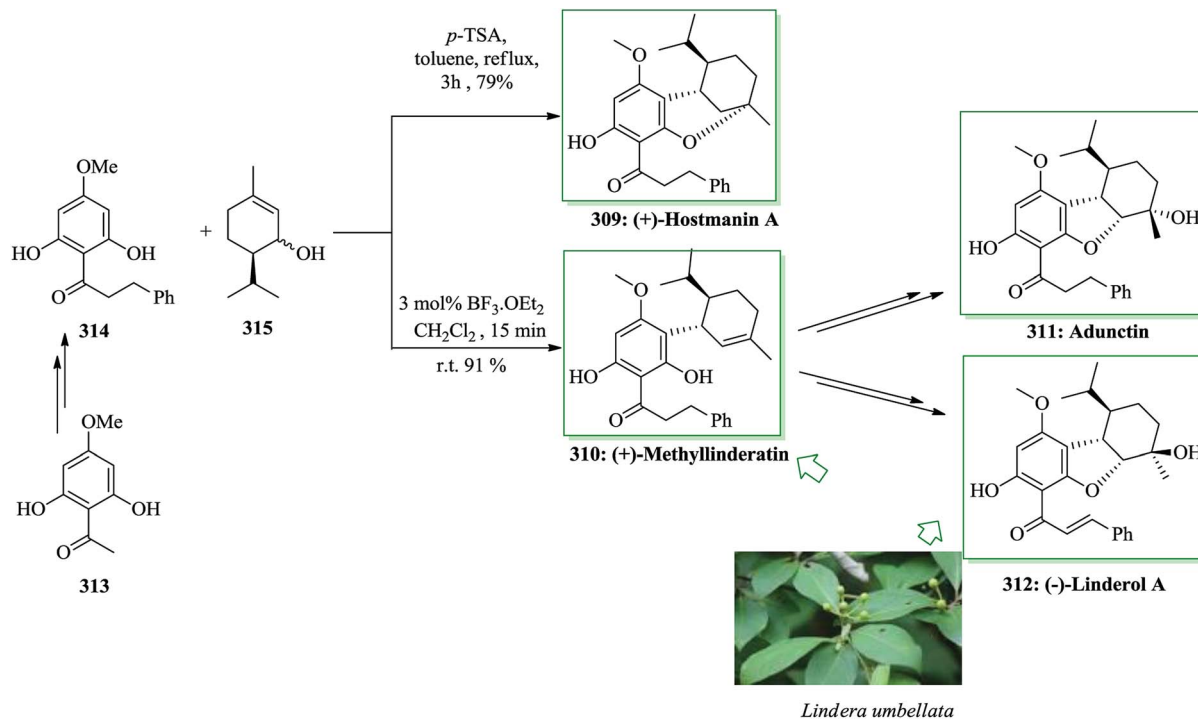
Scheme 62 Total synthesis of ellipticine quinone 305.

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

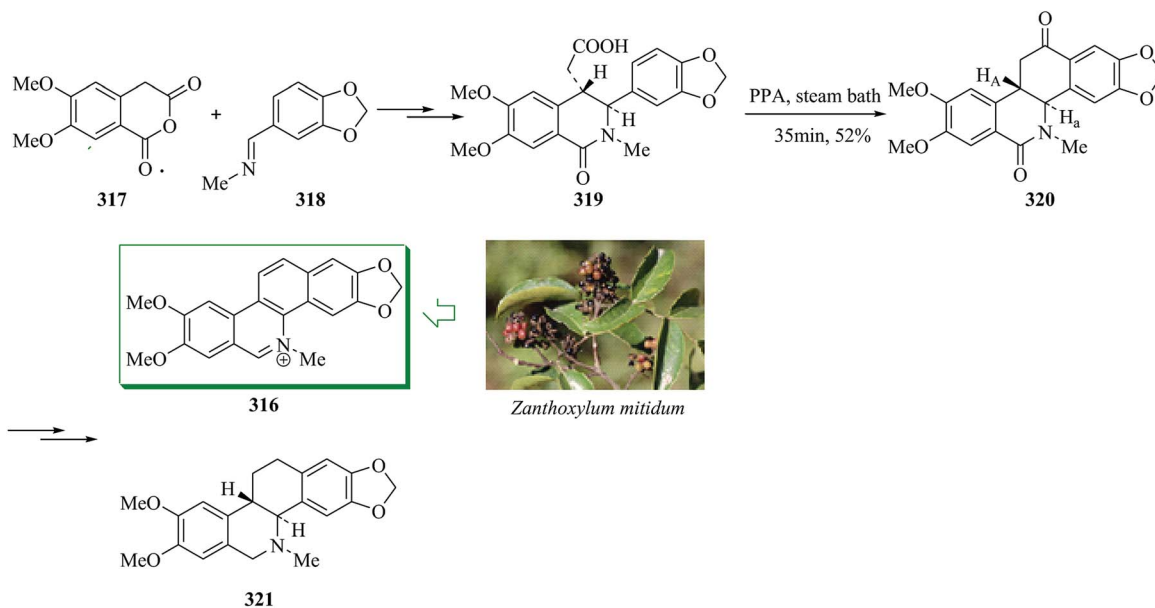
acid gradually removed the phenolic methoxy substituents. Finally, compound **341b** gave preussomerins F, K and L upon several steps (Scheme 70).³³⁷

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, phenyl-naphthalic anhydrides, perinaphthenones, and an oxabenzochrysenone.³³⁸ 4-Methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone) **343**, a subunit





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



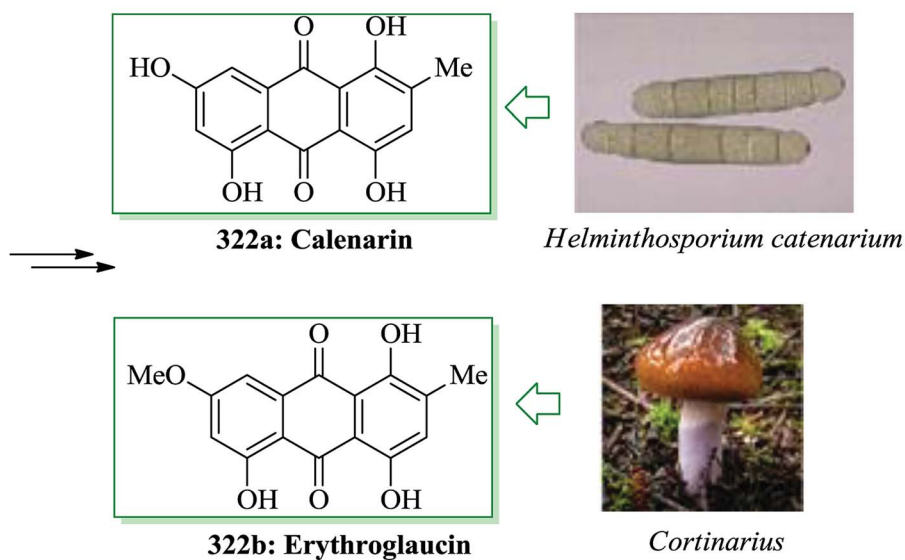
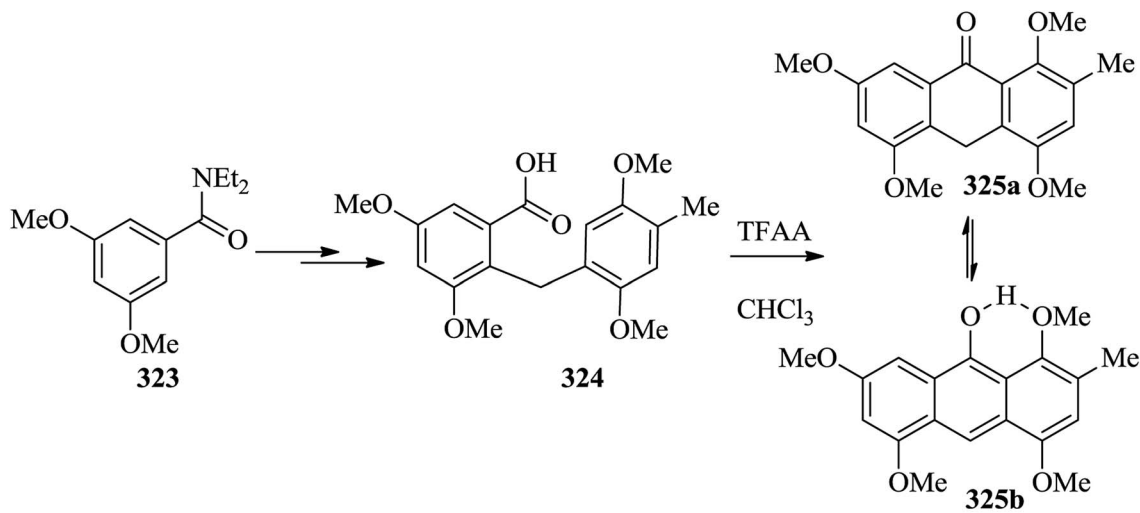
Scheme 64 The formation of compounds 316 and 321.

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,

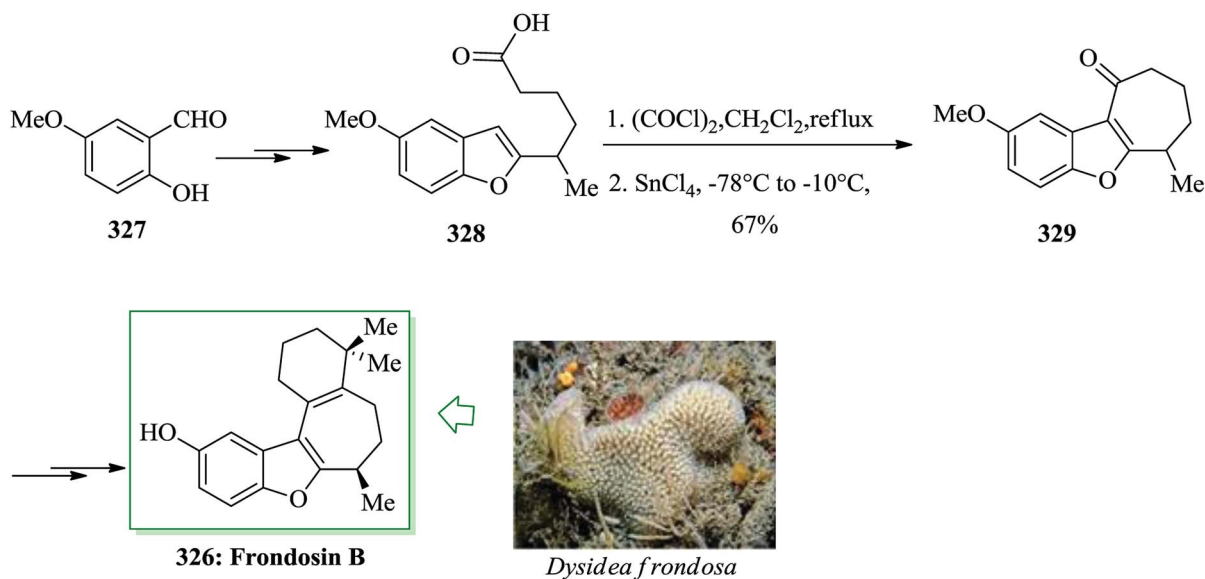
employing 4-methoxynaphthalenes 344 as the starting material.³³⁹ Based on this method, 4-methoxynaphthalene gave 345 upon several steps. Compound 345 was cyclized employing FC reaction conditions and gave 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone) 343 as the sole product in 48% yield (Scheme 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



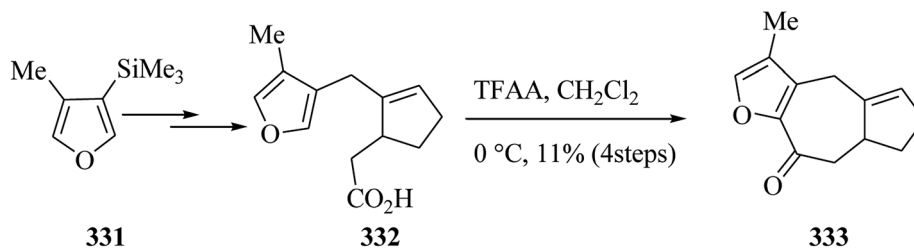


Scheme 65 Total synthesis of catenarin 322a and erythroglauclin 322b.

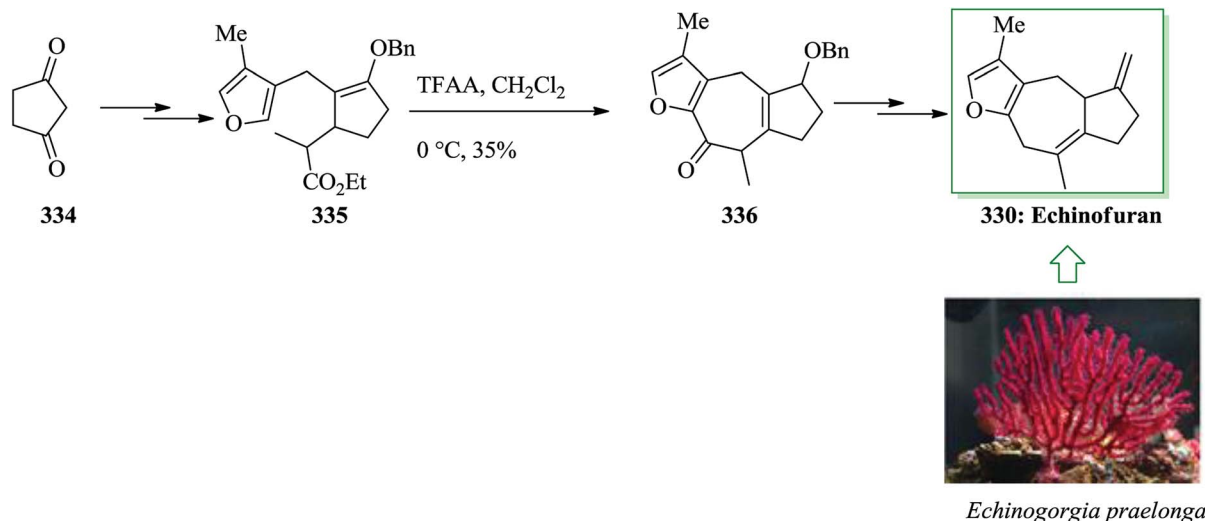


Scheme 66 Total synthesis of (±)-frondosin B 326.





Scheme 67 The formation of compound 333.



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

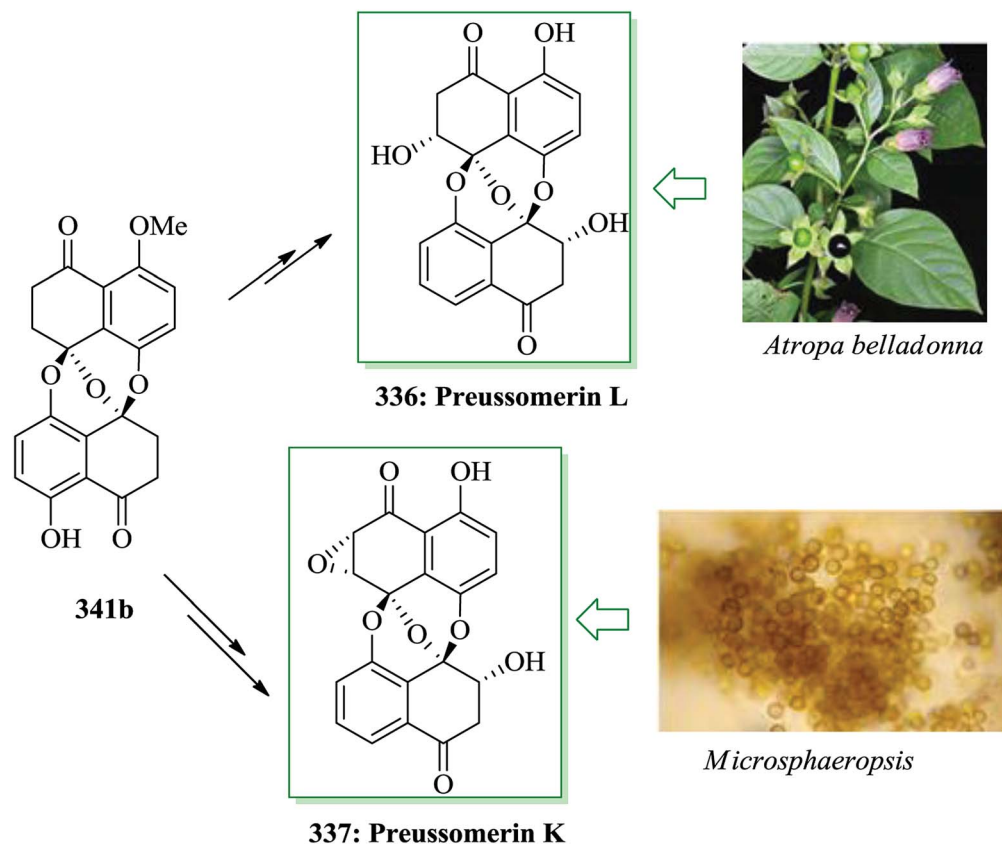
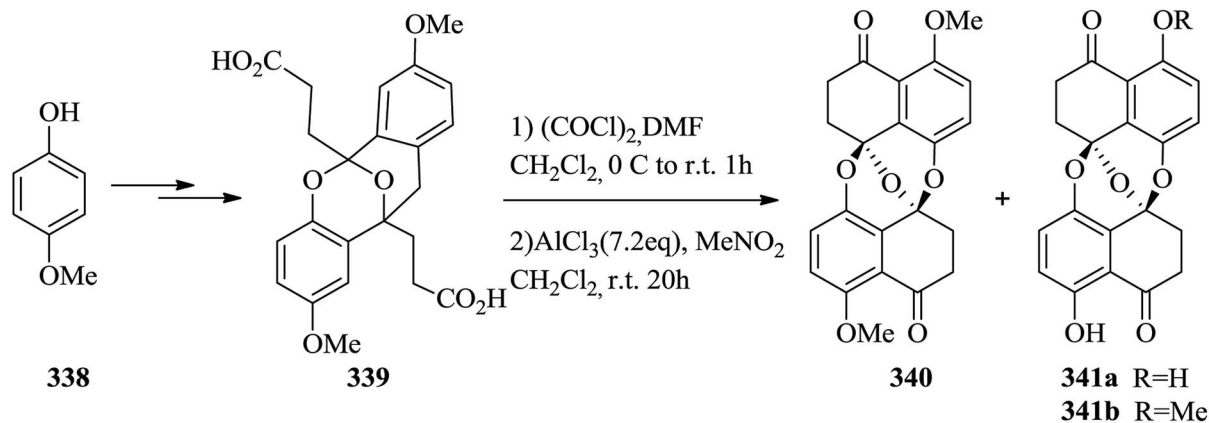
a wide range of compounds extracted from terrestrial fungi, involving sporostatin 347. Sporostatin (M5032, 347), extracted from the fungus *Sporormiella* sp., is an inhibitor of cyclic adenosine 3',5'-monophosphate phosphodiesterase.³⁴¹ Total synthesis of xestodecalactone C and *epi*-sporostatin was 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 AlI₃ 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 co-workers 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





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

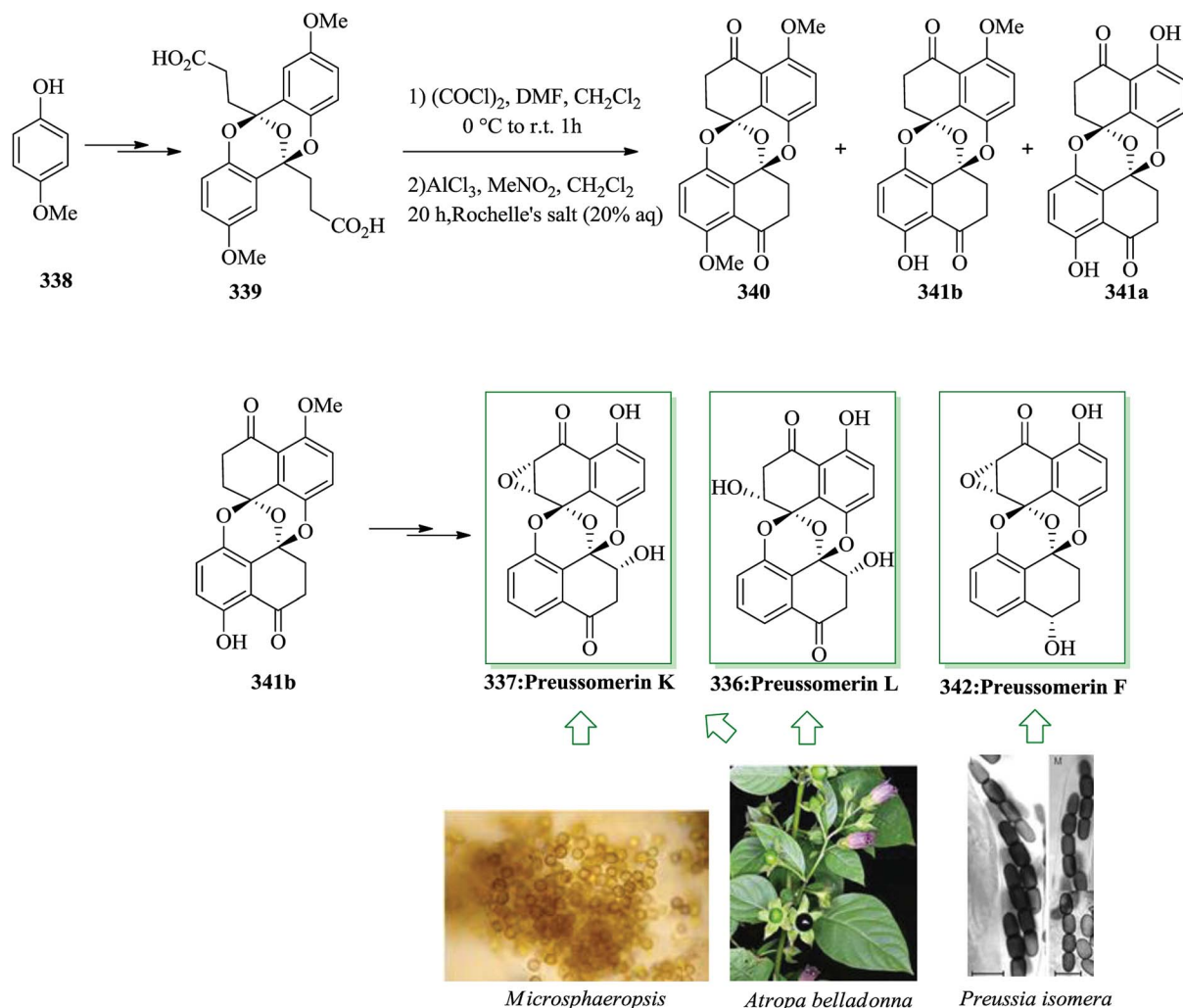
reaction with a mixture of trifluoroacetic acid and trifluoroacetic anhydride.^{344,354–356} Deprotection of the MeO substituents of 359 employing freshly synthesized AlI_3 (ref. 357–359) provided the final product 347 in 94% yield (Scheme 74).³⁶⁰

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

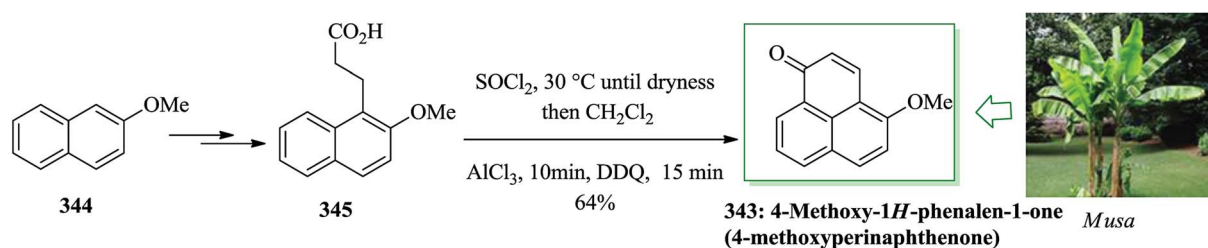
intramolecular FC acylation as key steps. The synthesis of xestodecalactone C 346 was initiated from propane-1,3-diol, which was protected with *p*-methoxybenzyl (PMB) bromide to provide the relevant propan-1-ol 360. Next, compound 360 gave the acid 361 in several steps. The corresponding macrolide 362 was obtained in 40% yield *via* an intramolecular FC acylation reaction of the carboxylic acid 361 using $\text{CF}_3\text{COOH}/(\text{CF}_3\text{CO})_2\text{O}$.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. (11 β)-11-Methoxycurvularin 363 is a member of the curvularin group extracted from the mycelium of the hybrid strain ME 005





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



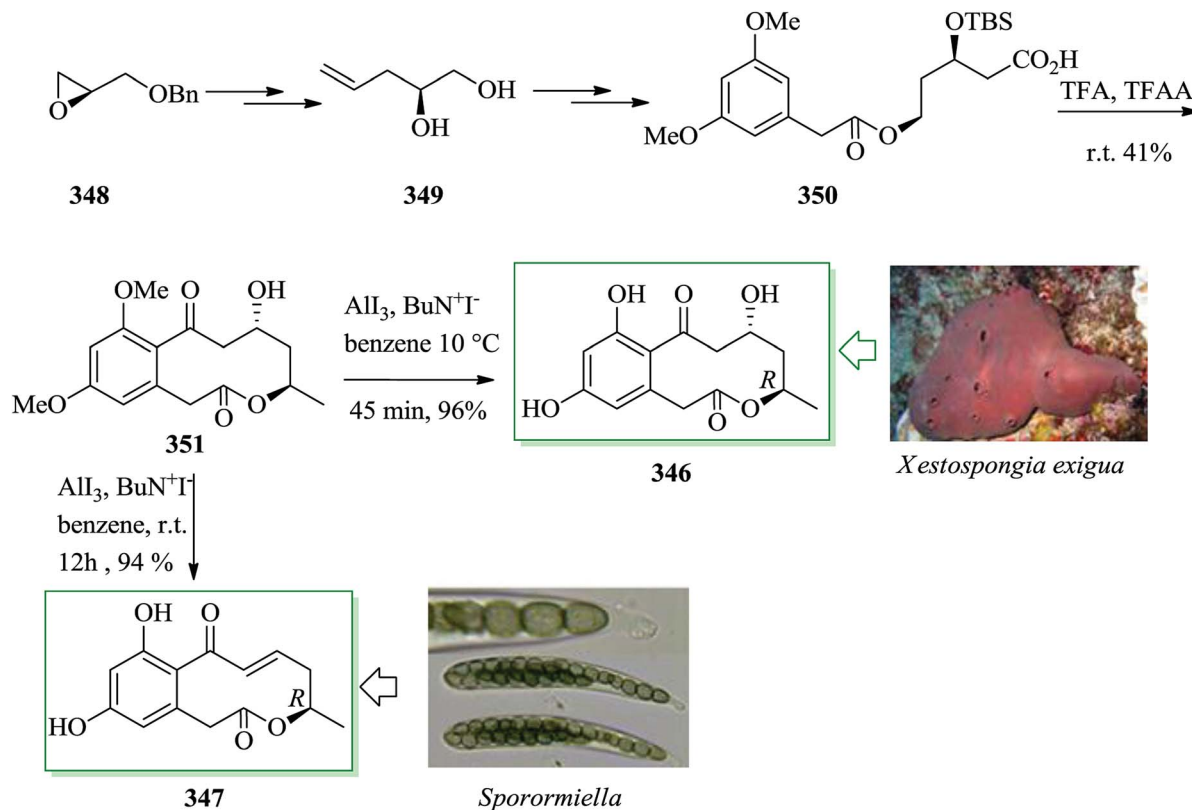
Scheme 71 Total synthesis of 4-methoxy-1H-phenalen-1-one (4-methoxyperinaphthenone) 343.

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 (11 β)-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**

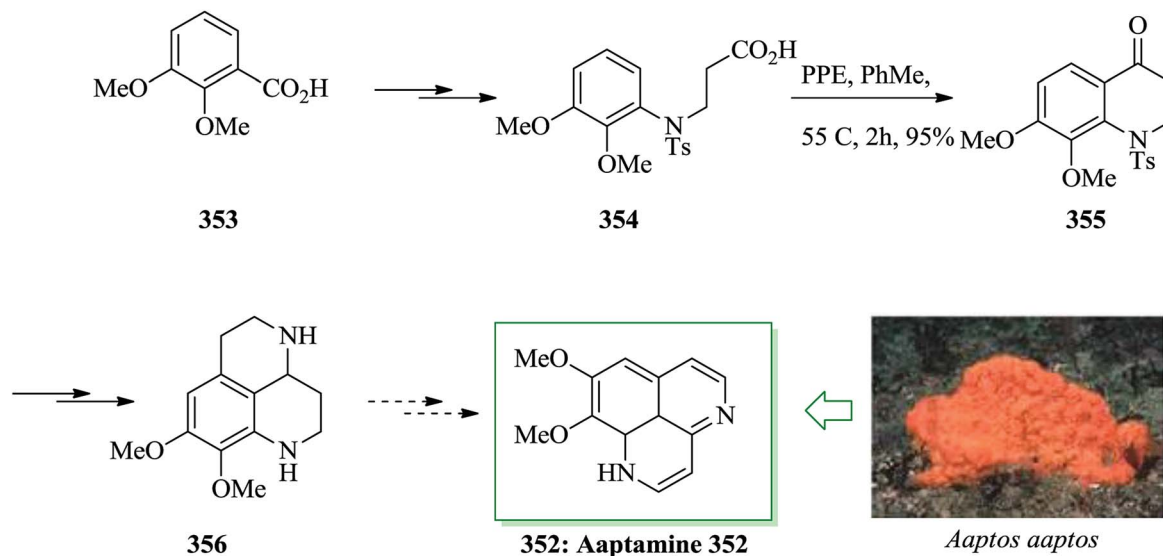
upon several steps. The corresponding macrolide **365** was obtained in 41% yield *via* intramolecular FC reaction of the carboxylic acid **364** in the presence of $\text{CF}_3\text{COOH}/(\text{CF}_3\text{CO})_2\text{O}$. Next, demethylation of **365** using freshly synthesized AlI_3 afforded the natural 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





Scheme 72 Total synthesis of sporostatin 347.

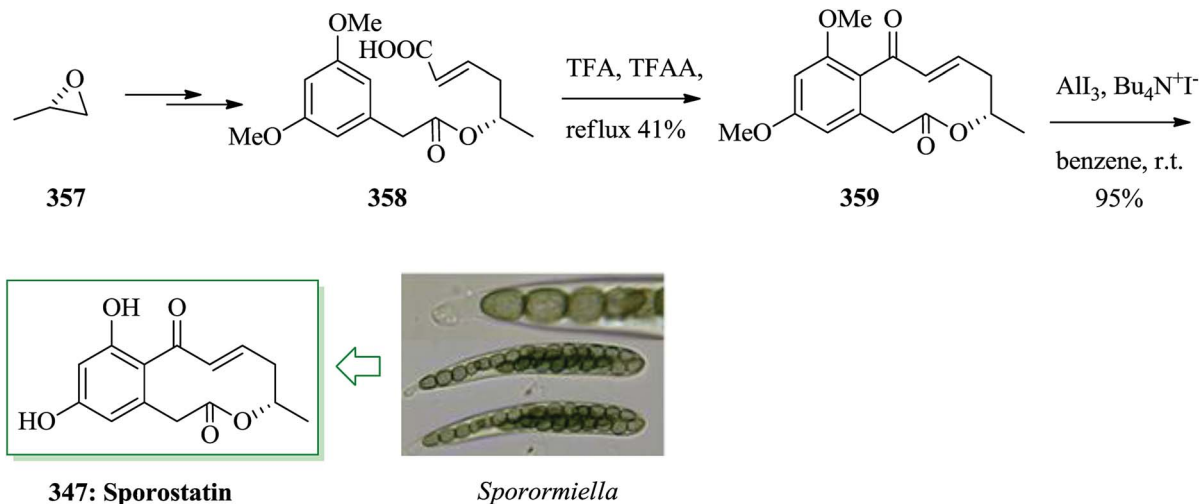


Scheme 73 Total synthesis of aptamine 352.

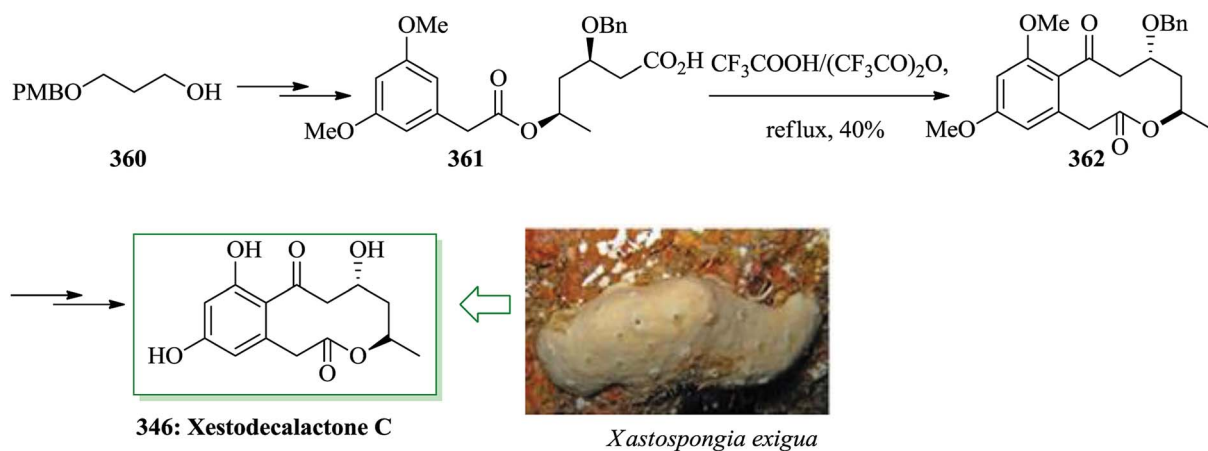
oligostilbenoid containing strong cytotoxicity, diptoindonesin G, from the tree bark of *Hopea mengarawan* was demonstrated by Syah *et al.*³⁷² This natural product exhibits active immunosuppressive properties.³⁷³ A very significant total synthesis of diptoindonesin G **366** was developed using a domino 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





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

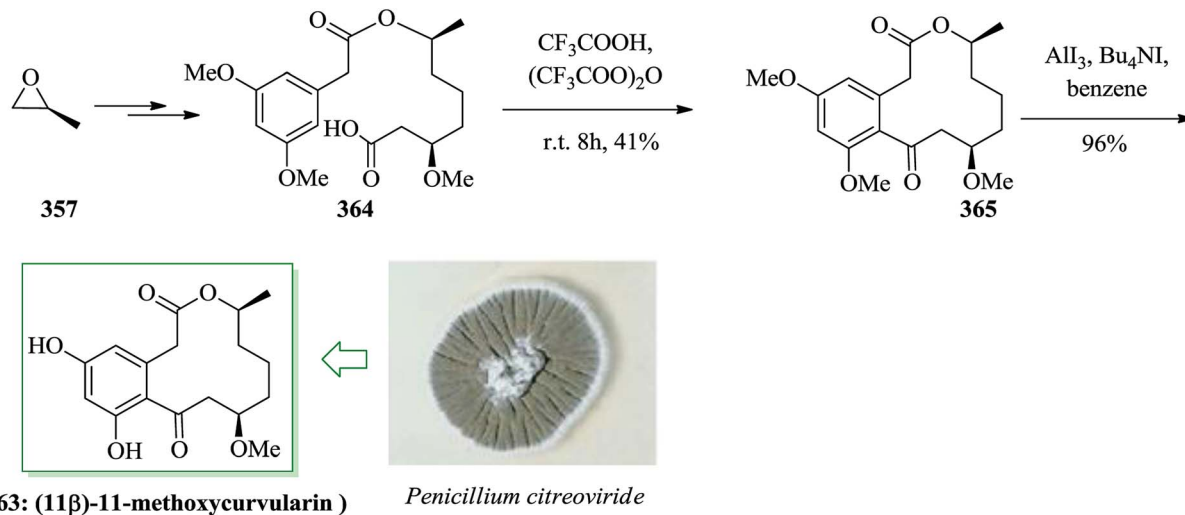
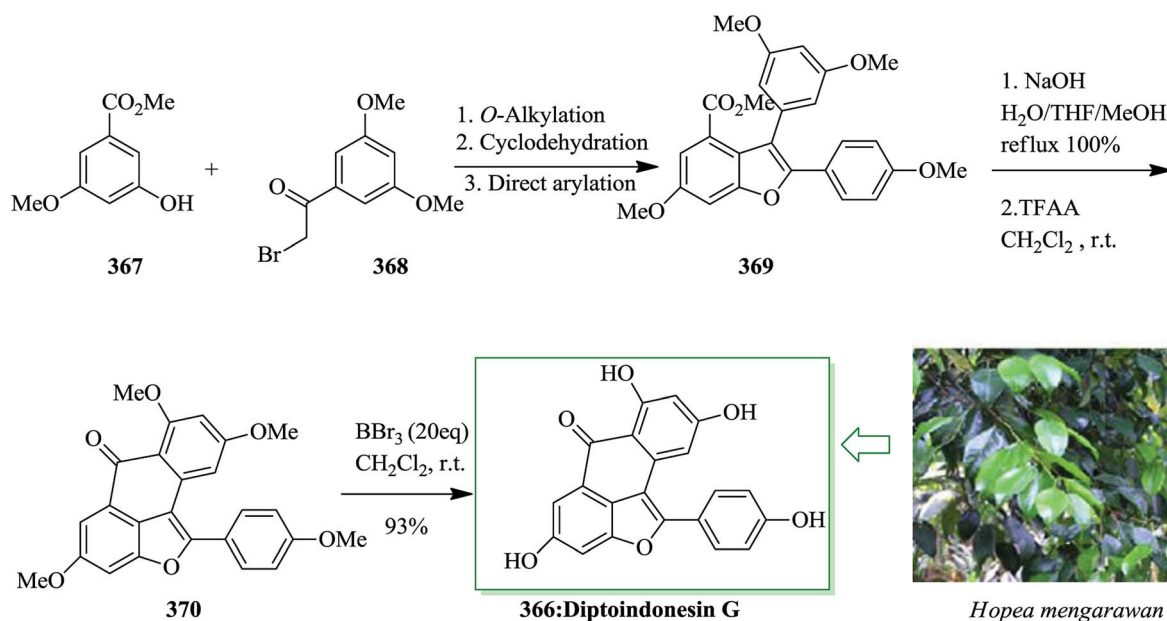
The same strategy was applied for the synthesis of diptoindonesin G 366 using compound 371 instead of 370 as the precursor. Compound 371 was treated with BCl_3 in CH_2Cl_2 to give the demethylated compound 372 in 95% yield.^{375–378} Finally, the latter was transformed into the desired natural product 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 $(\text{CF}_3\text{CO})_2\text{O}$ ³⁸⁶ or $\text{POCl}_3/\text{K}_2\text{CO}_3$ (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-protected 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

Diazobenzo[*b*]fluorene 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 diazobenzo[*b*]fluorenes were found to exhibit antitumor activity. Enantioselective synthesis of FL-120B' was accomplished employing Sharpless asymmetric epoxidation, Stille cross-coupling, and intramolecular FC



Scheme 76 Total synthesis of (11β)-11-methoxycurvularin **363**.Scheme 77 Total synthesis of diptoindonesin G **366**.

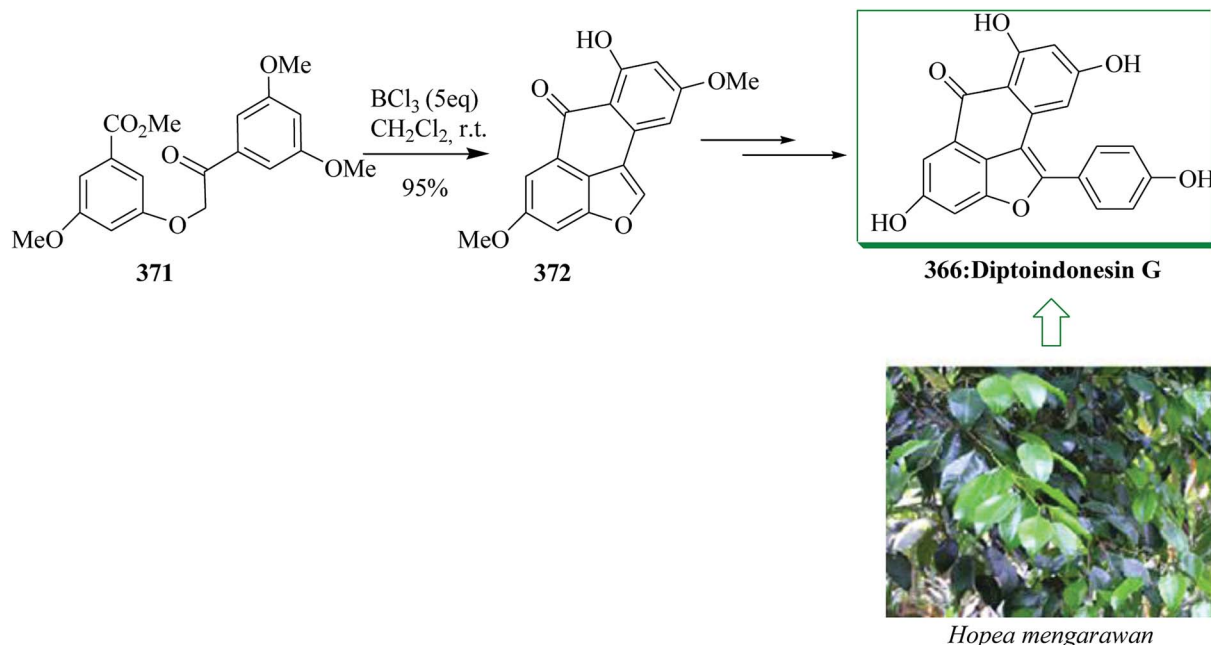
reactions as key steps. The synthesis of FL-120B' represents the first total synthesis of an epoxide-comprising, diazobenzo-fluorene natural product. Firstly, quinone **379** gave carboxylic acid **380** upon several steps. Then, carboxylic acid **380** in the presence of trifluoroacetic anhydride (TFAA) 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 *Trikenrion flabelliforme* by Capon³⁹¹ 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

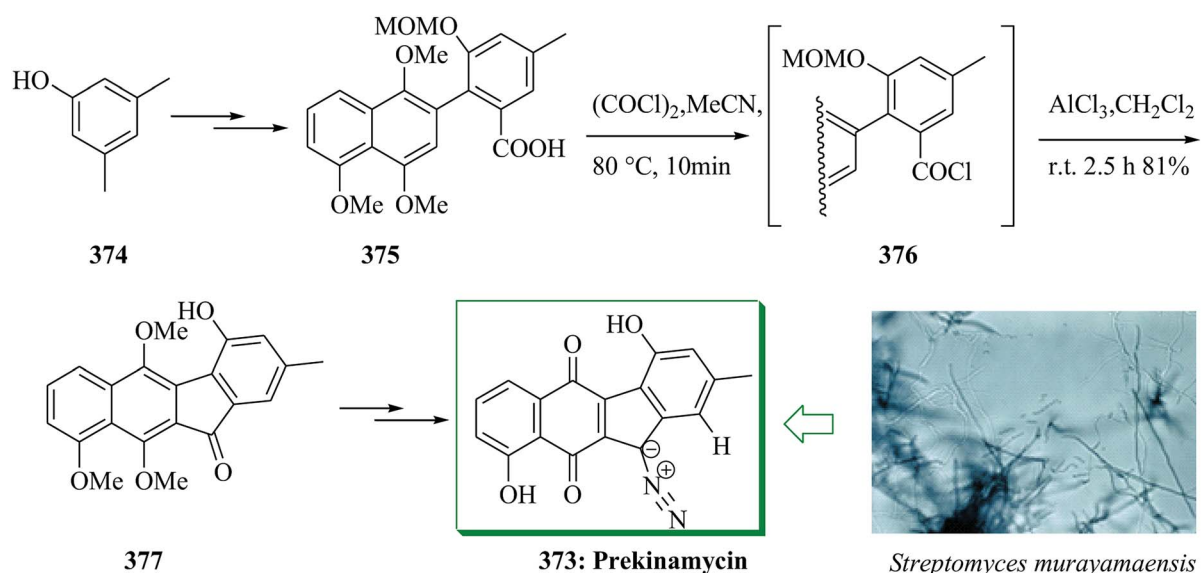
carboxylic acid **385a** in several steps. The latter was subjected to an intramolecular FC reaction and a Wittig reaction affording the *exo*-methylene compound **387a** in about 70% yield from the acid **385a**. Subsequently, compound **387a** was converted into the natural product (+)-*cis*-trikentrin **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 isocarboxtyril alkaloids have been attractive synthetic targets for organic synthetic chemists during the last two decades.^{393,394} The isolation of *trans*-dihydonarciclasine **388** from the Chinese medical plant *Zephyranthes candida* was





Scheme 78 Total synthesis of diptoindonesin G 366.

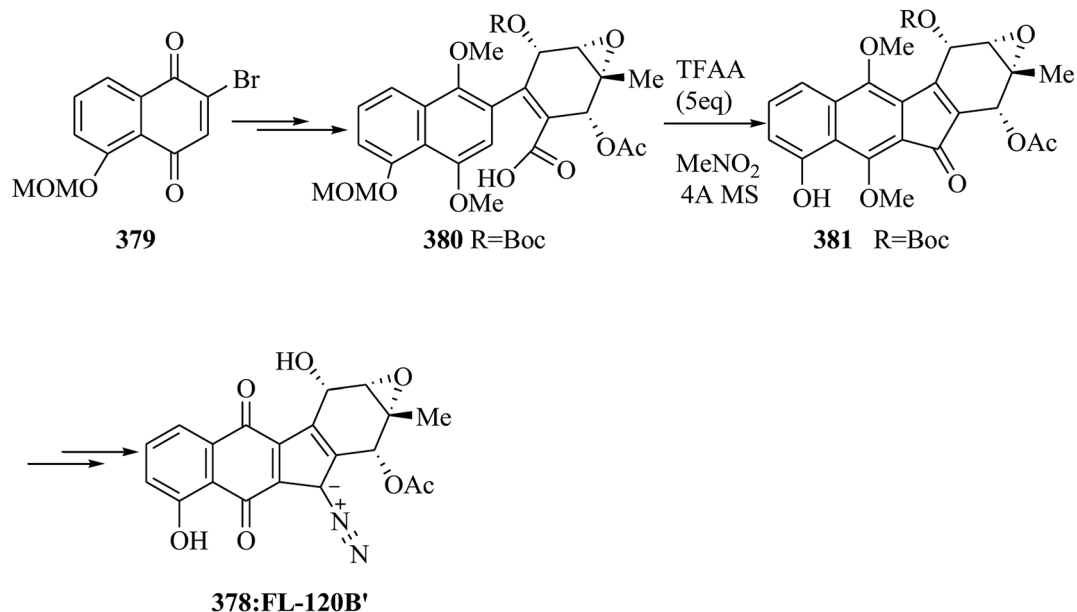


Scheme 79 Total synthesis of prekinamycin 373.

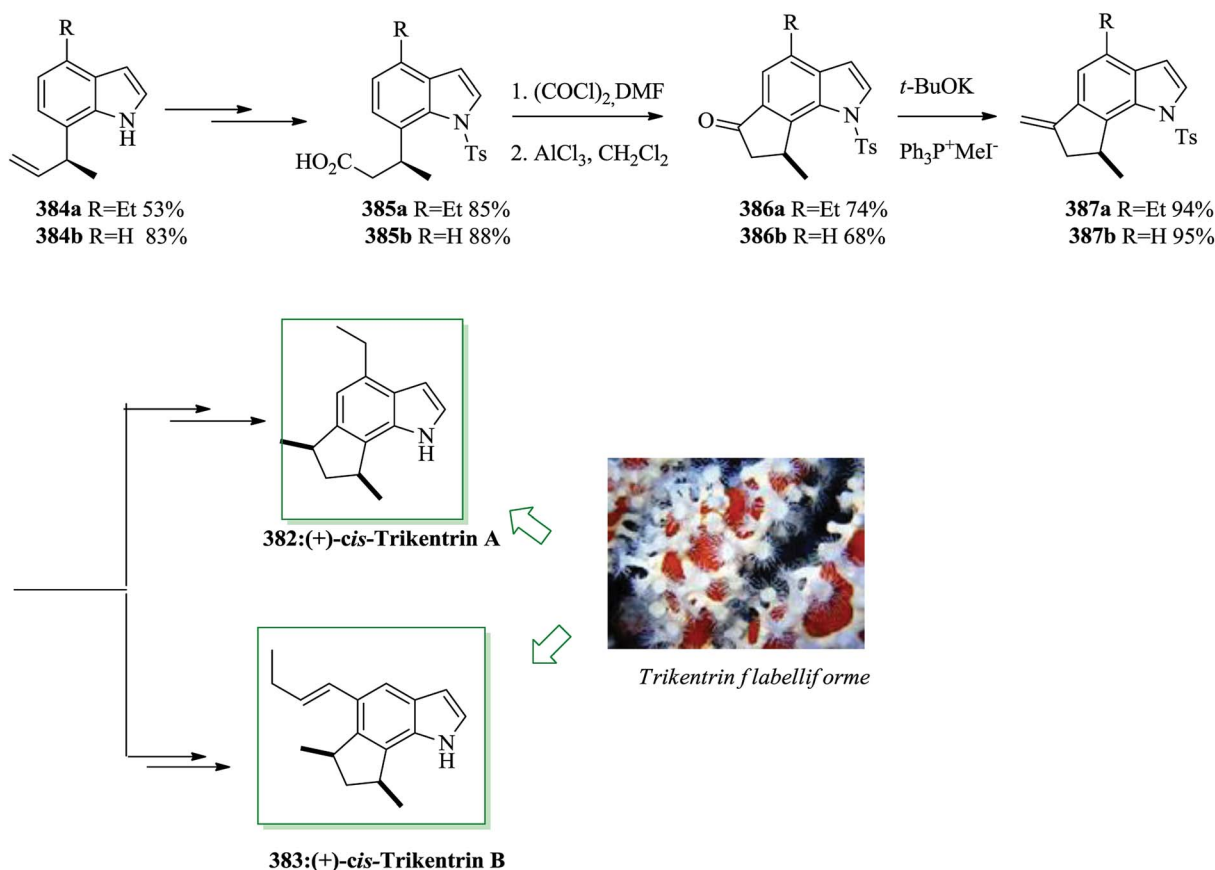
demonstrated in 1990.³⁹⁵ An extremely enantioselective and effective total synthesis of *trans*-dihydronarciclasine **388** in an entirely substrate-controlled strategy from easily accessible chiral starting materials was developed in which the desired target **388** was obtained in 16% overall yield. 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 Tf₂O 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 allocolchicine⁴⁰⁰ 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**,





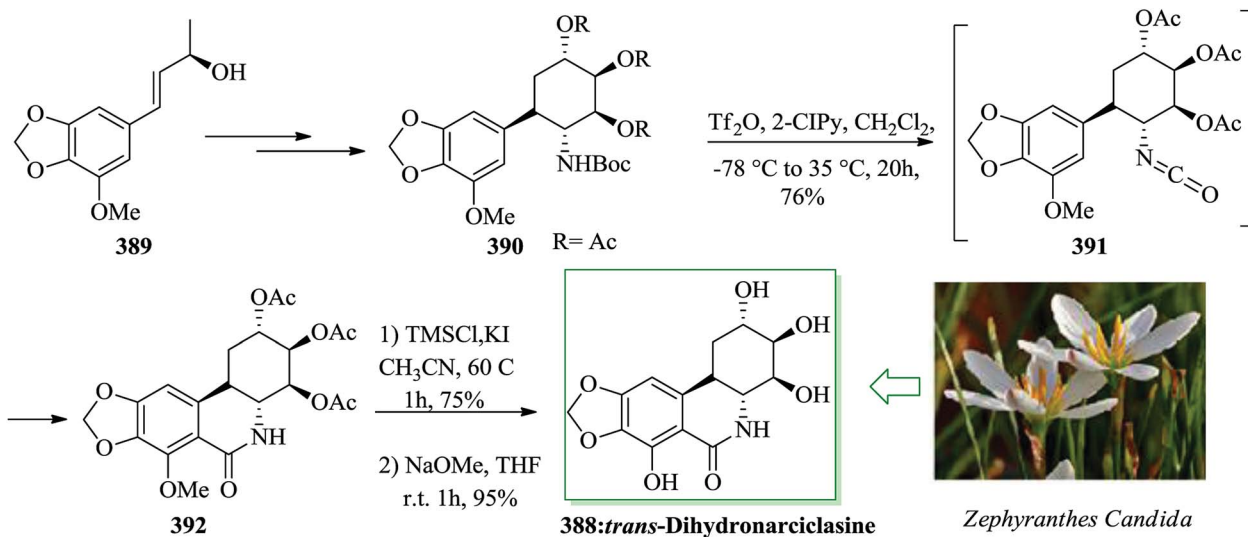
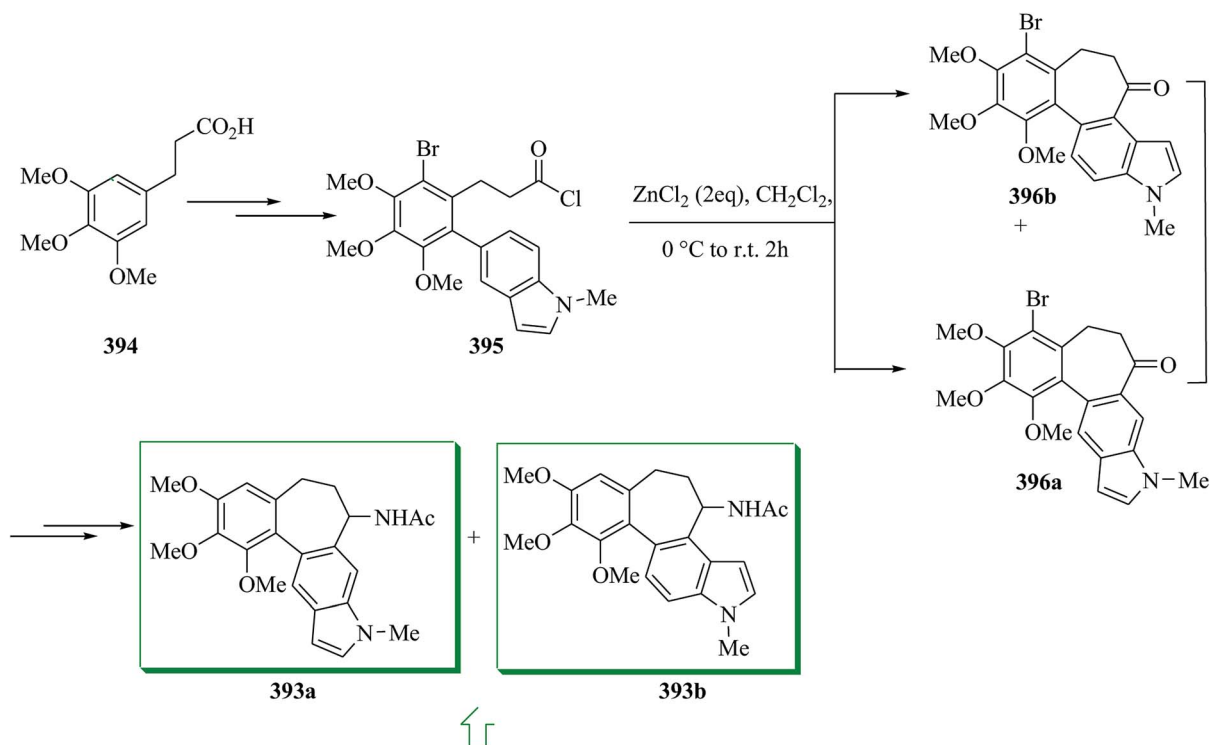
Scheme 80 Total synthesis of FL-120B' 378.

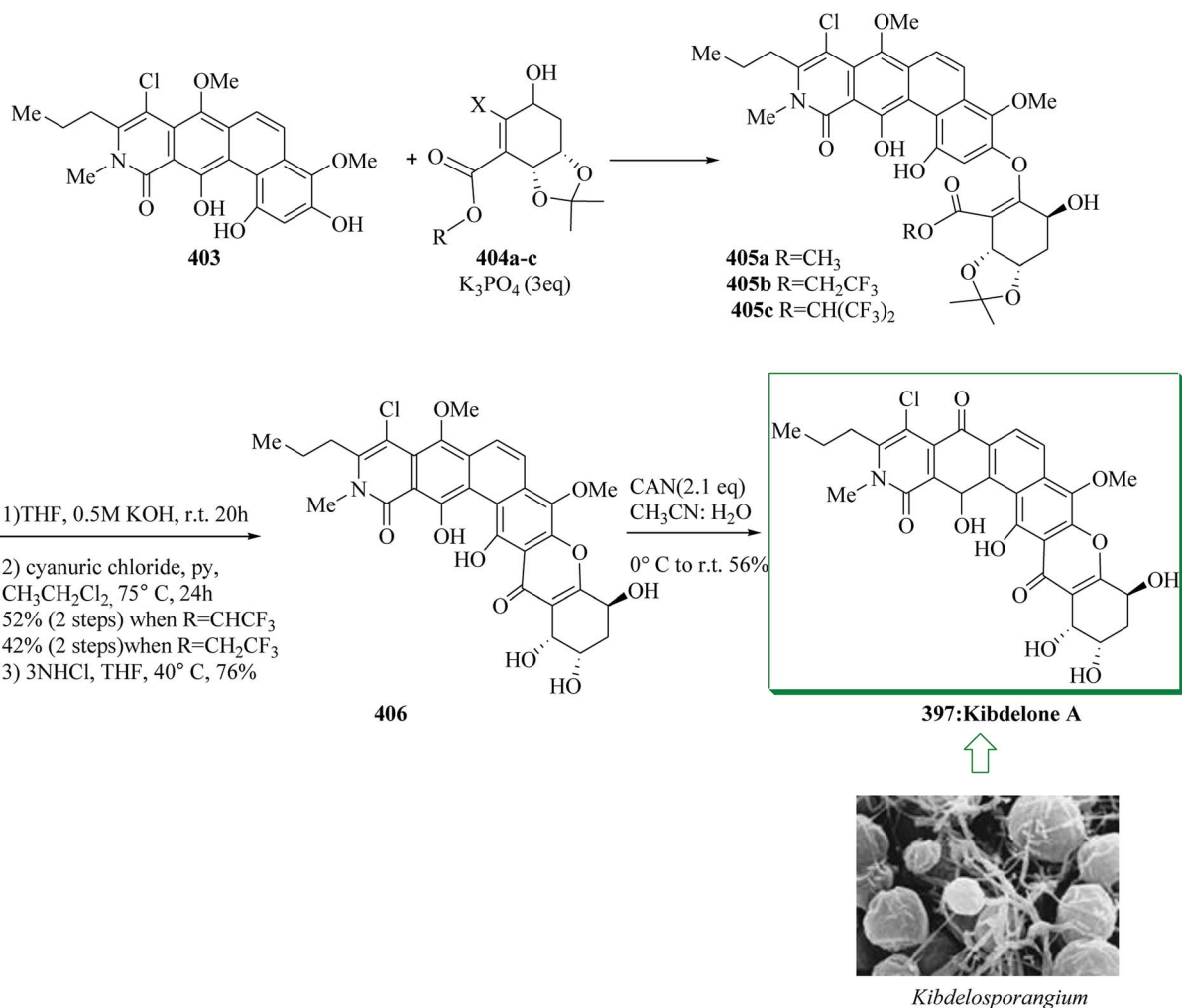
Scheme 81 Total synthesis of (+)-*cis*-trikentrin 382 and (+)-*cis*-trikentrin-B 383.

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

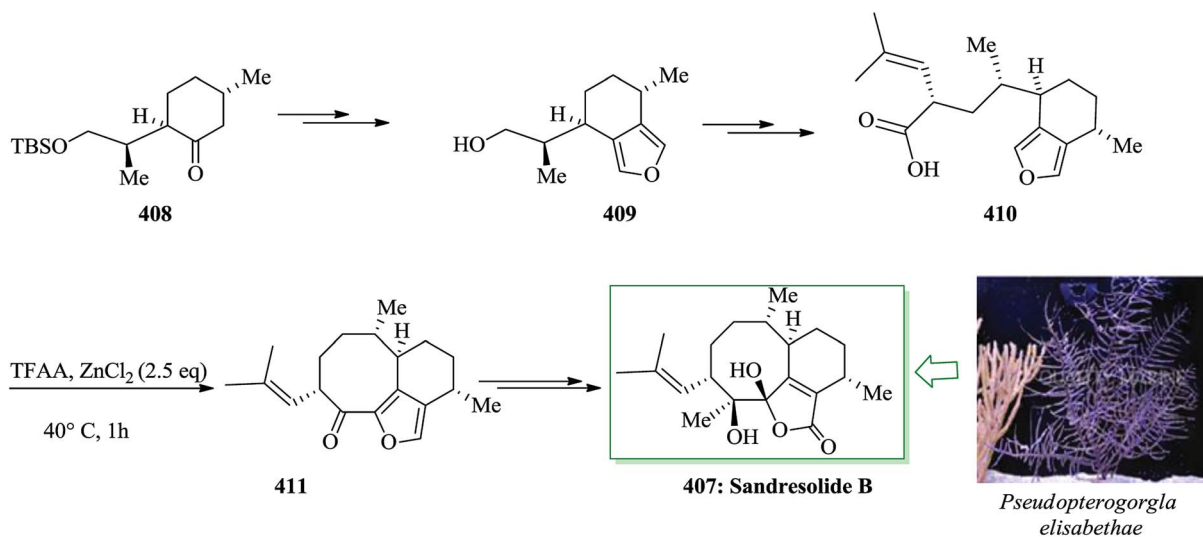
reaction as the key carbon-carbon bond-forming reactions. Firstly, 3,4,5-trimethoxyphenylpropionic acid 394 afforded a clear solution including acid chloride 395 upon several steps.



Scheme 82 Total synthesis of *trans*-dihydronarciclasine **388**.Scheme 83 Total synthesis of allocolchicinoids *rac*-**393a** and *rac*-**393b**.

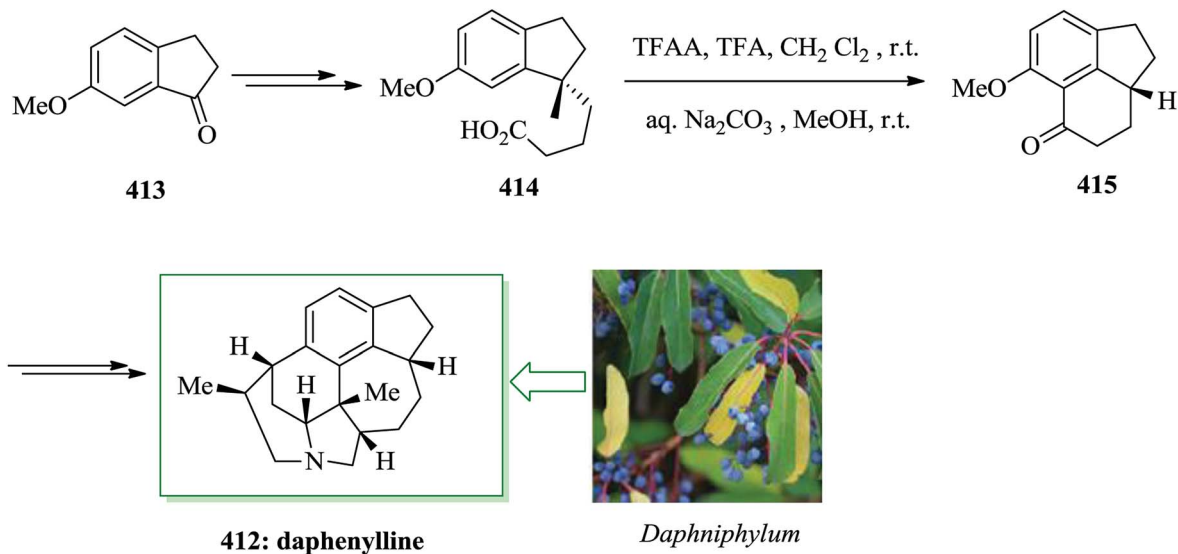


Scheme 85 Total synthesis of kibelone A 397.

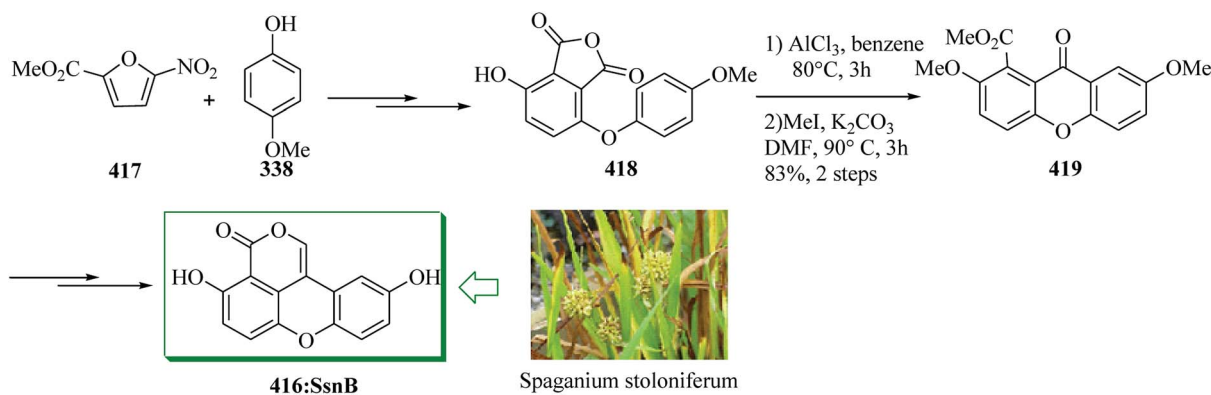


Scheme 86 Total synthesis of sandresolide B 407.





Scheme 87 Total synthesis of daphenylline 412.



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

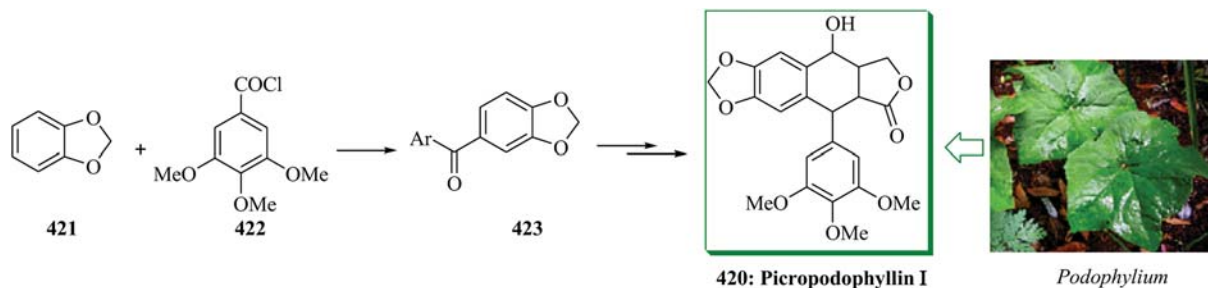
gentle heating with zinc chloride afforded the corresponding product **411**. It should be mentioned that short reaction times and stoichiometric ZnCl_2 were key to this ring closure. Finally, sandresolide B, **407**, was obtained from **411** in 51% yield over two steps (Scheme 86).⁴¹⁴

Daphenylline **412**, extracted from the fruit of *Daphniphyllum longracemosum* 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

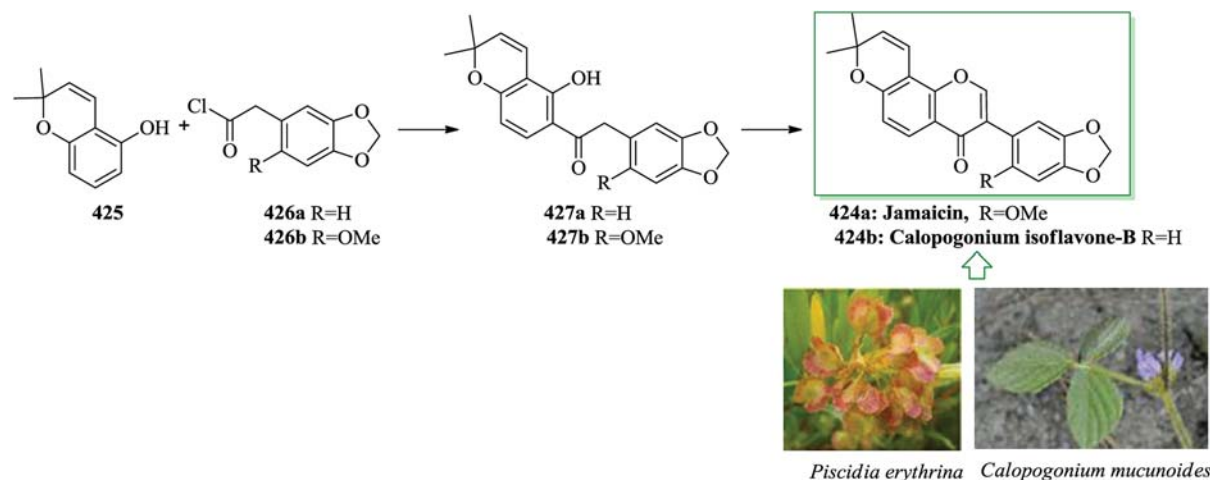
trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) to provide cyclic ketone **415**. Finally, daphenylline **412** was obtained after several steps (Scheme 87).⁴¹⁷

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 **420a** and a side-product **420b**, provided *via* elimination of an *O*-





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

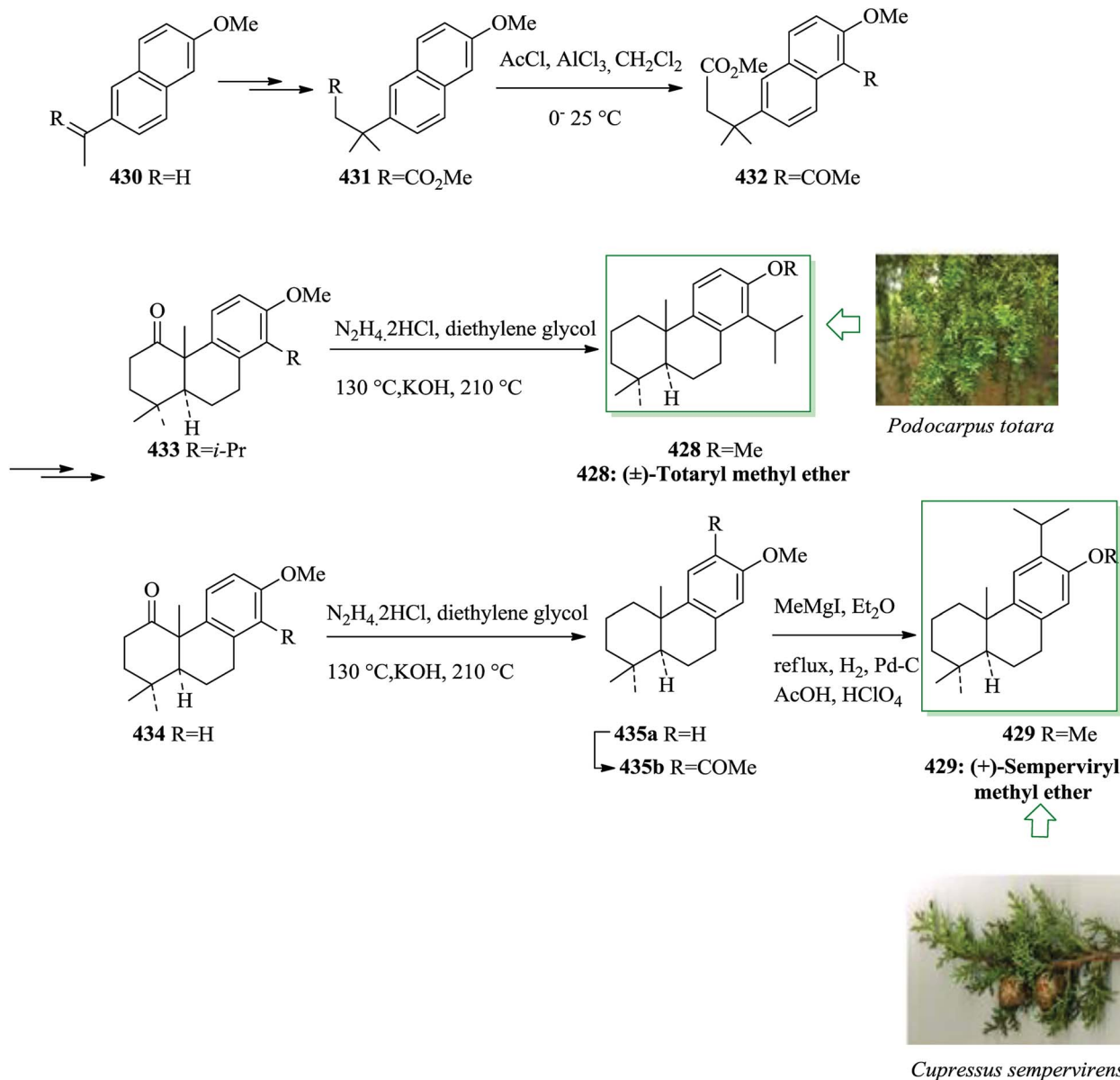
2.4. Intermolecular acylation

The lignan lactone picropodophyllin **420** has been obtained from various species of *Podophyllum*.^{422,423} Gensler and co-workers demonstrated total synthesis of picropodophyllin. 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

Isoflavones⁴²⁵ are the most abundant subset of the flavonoid group of compounds, which also includes pterocarpan, 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 deoxybenzoin systems 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 sempervirrol 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





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

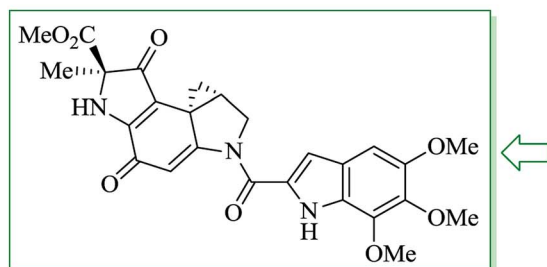
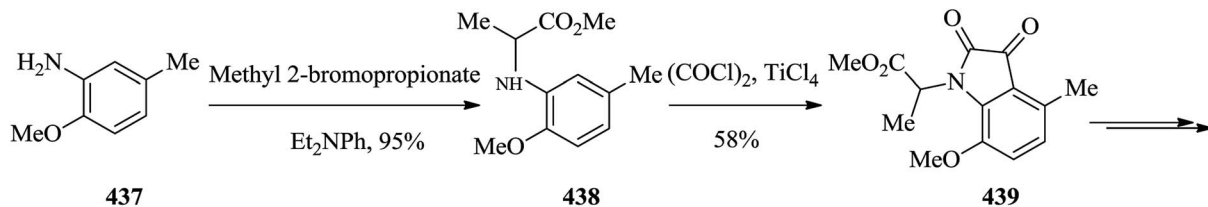
methoxynaphthalene afforded⁴³⁵ a mixture of 6-acyl and 1-acyl derivatives. Compound 432 provided the *trans*-fused ketones 434 and 433 *via* several steps. Huang–Minlon reduction⁴³⁶ of 433 gave (+)-totaryl methyl ether 428 in 84% yield. An analogous reduction of the ketone 434 provided octahydrophenanthrene 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

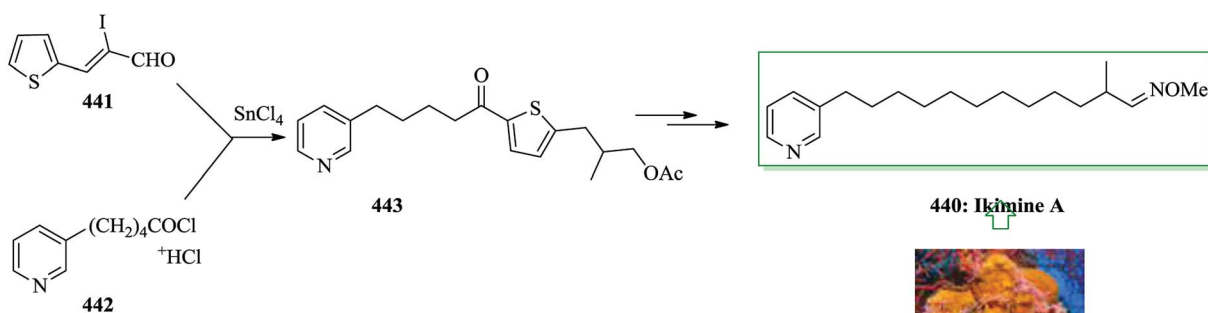
methoxycarbonylation of the C₄-position of the 5-aminoindoline by way of the isatin and subsequent Dieckmann cyclization to the methyl 2-methylindoxyl-2-carboxylate as key steps. Total synthesis of 436 was started from 6-methoxy-3-methylaniline 437. Next, one carbon unit was introduced effectively using 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. SnCl₄ mediated the acylation reaction between 2-methyl-3-(2-thiophene)-L-propylacetate 441 and the acid chloride 442 to afford the ketone



**436: Duocannycin A***Streptomyces*

Scheme 92 Total synthesis of duocannycin A 436.

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

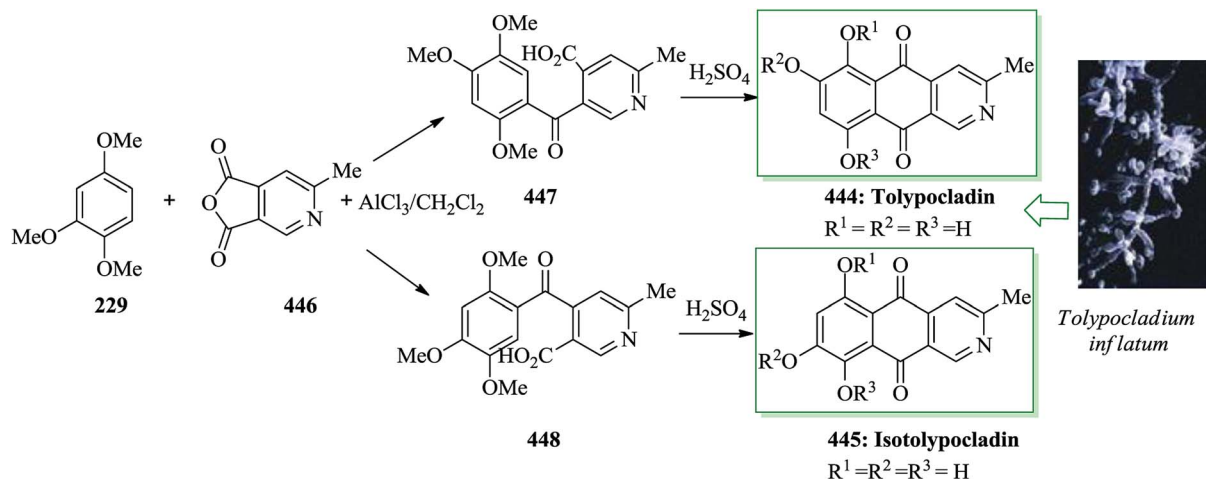
443. Reaction with TiCl_4 or H_3PO_4 as FC catalysts or acylation reaction with *in situ* made acyl trifluoroacetates using phosphoric acid⁴⁴² afford lower yields. Lastly, compound **443** afforded ikimine A (α -methyl-3-pyridinedodecanal-*O*-methyloxime) **440** via several steps (Scheme 93).⁴⁴³

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 through recrystallization. Therefore, cyclization and demethylation of the key products **447** and **448** using sulfuric acid afforded **444** (Scheme 94).⁴⁴⁵

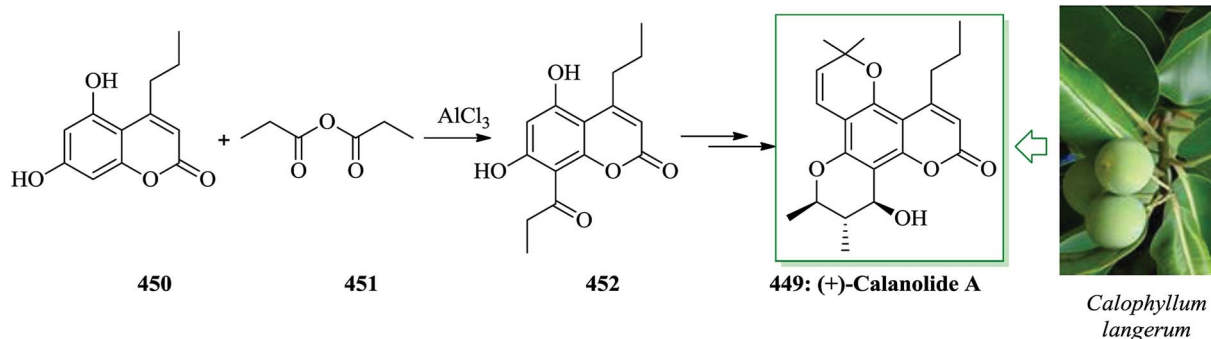
(+)-Calanolide A,⁴⁴⁶ initially extracted from the dried fruits and twigs of *Calophyllum lanigerum* var. *Austrocoriaceum*, is a non-nucleoside reverse transcriptase inhibitor currently in clinical trials as an anti-HIV agent. Zhang and co-workers in 2000 used an investigation method to perform the FC 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,





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



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

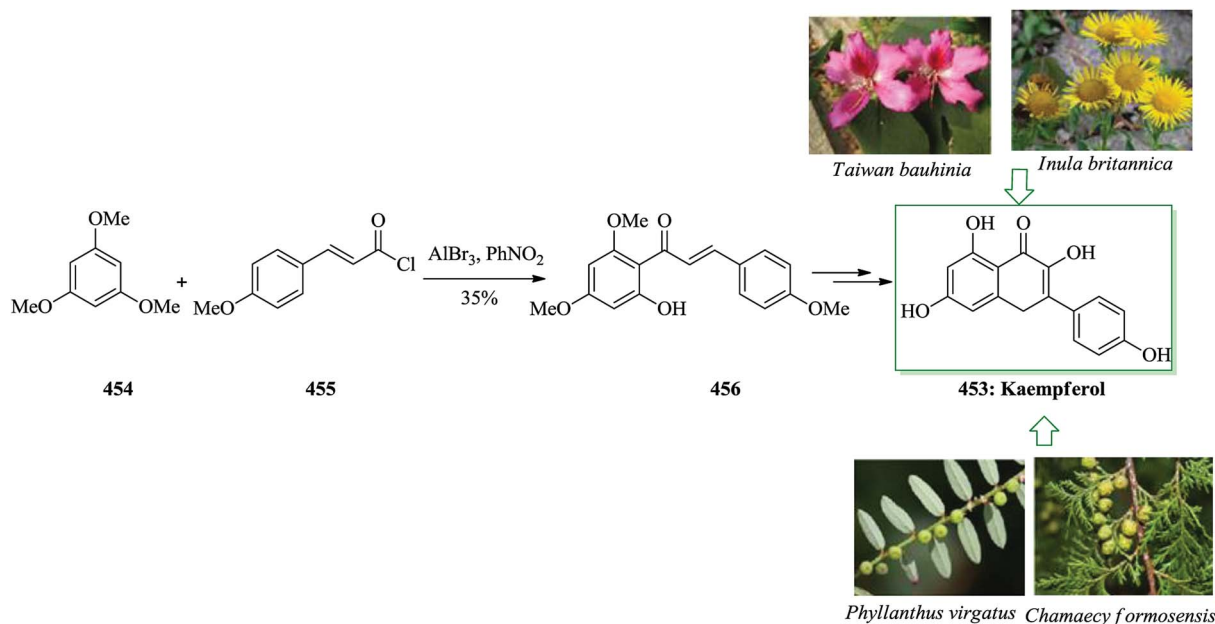
vegetables, fruits, and beverages, for example *Taiwan Bauhinia*,⁴⁵¹ *Chamaecyparis formosensis*,⁴⁵² *Inula britannica*,⁴⁵³ French beans,⁴⁵⁴ asparagus,⁴⁵⁵ blueberries,⁴⁵⁶ grape fruit juice,⁴⁵⁷ teas,⁴⁵⁸ and honey.⁴⁵⁹ Kaempferol 453 was obtained in seven steps with 47% overall yield from 1,3,5-trimethoxybenzene 454. Firstly, the FC reaction of trimethoxybenzene 454 and 4-methoxycinnamic acid chloride 455 with AlBr₃ 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 reaction⁴⁶⁴ on ester 461, and afforded the *C*-acetyl compound 460 in moderate yields, without any removal of the

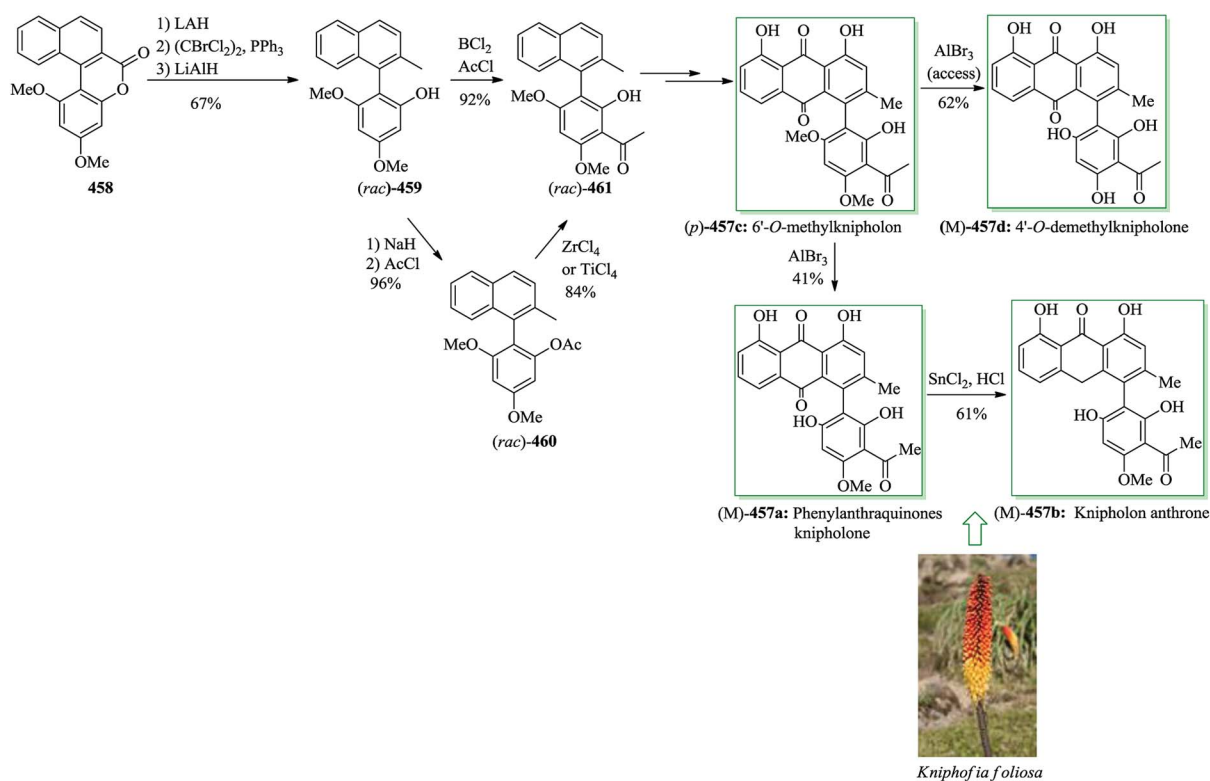
methyl ether. Therefore, compound 460 afforded 6'-*O*-methylknipholone 457c, the first natural phenylanthraquinone. Selective mono-*O*-demethylation of 457c at C-6' employing aluminium bromide afforded the target molecule knipholone 457a, reduction of which afforded its anthrone 457b. The fully *O*-demethylated 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





Scheme 96 Total synthesis of kaempferol 453.



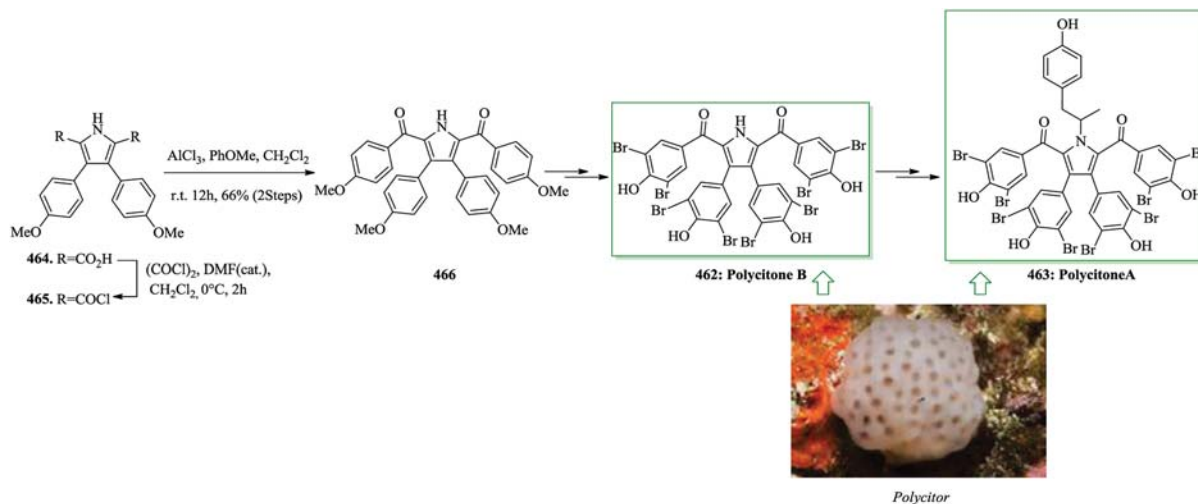
Scheme 97 Total synthesis of phenylanthraquinones knipholone 457a, knipholone anthrone 457b, 6'-O-methylknipholone 457c and 4'-O-demethylknipholone 457d.

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

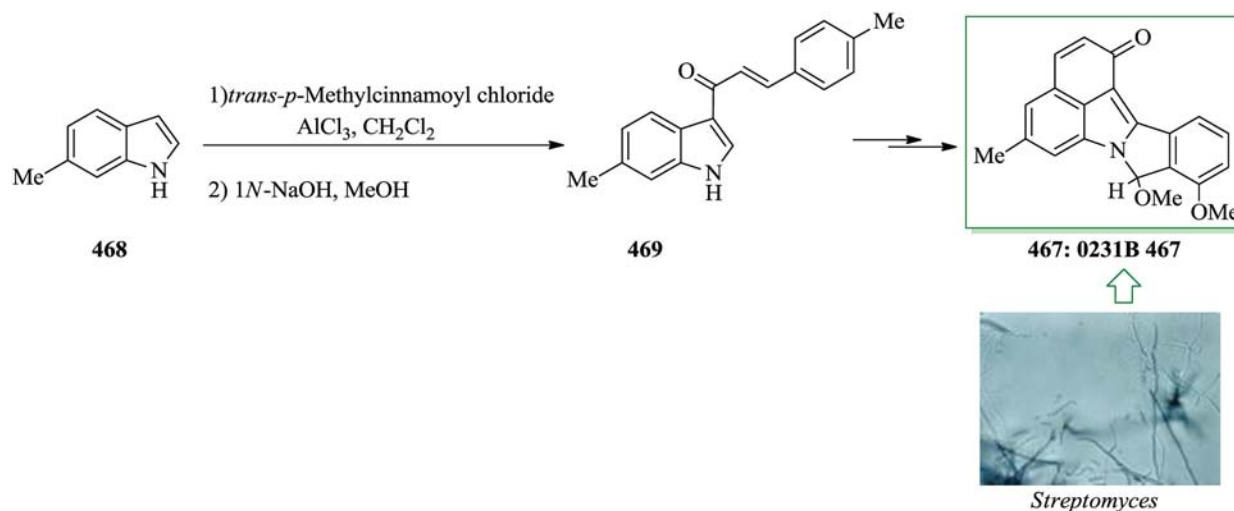
The unique inhibitors of 3α -hydroxysteroid dehydrogenase, 0231A and 0231B, have been extracted from a fermentation

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





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



Scheme 99 Total synthesis of 0231B 467.

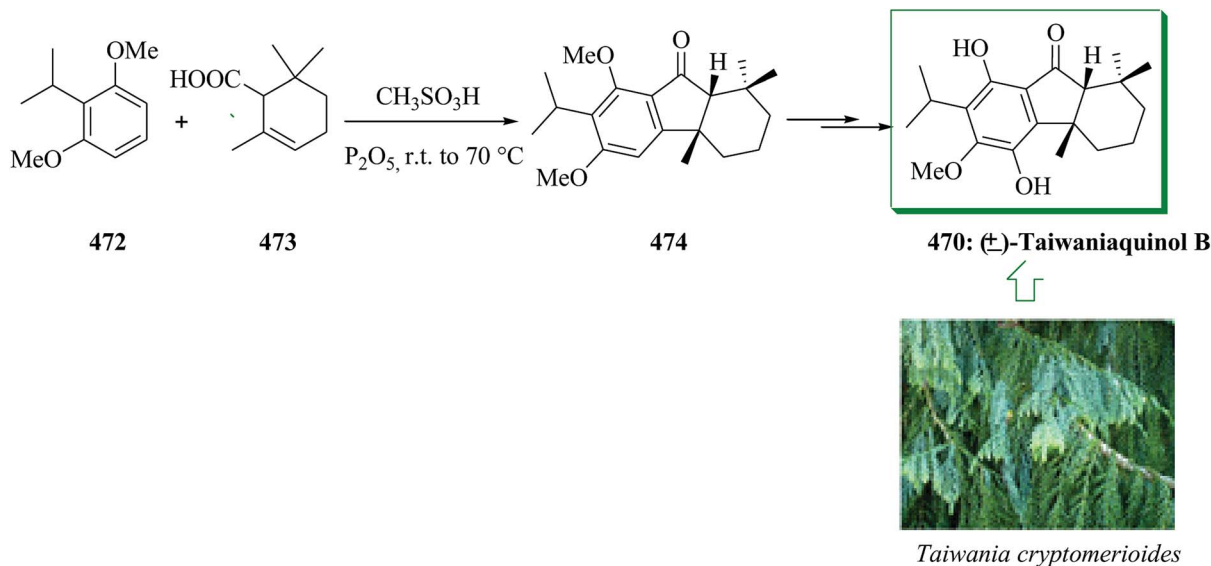
conditions to provide the diketone **466** in 66% yield. In the following, compound **466** afforded polycitone B **462** after several steps and then polycitone B **462** was transformed into polycitone A **463** after several steps (Scheme 98).³⁵⁶

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*-

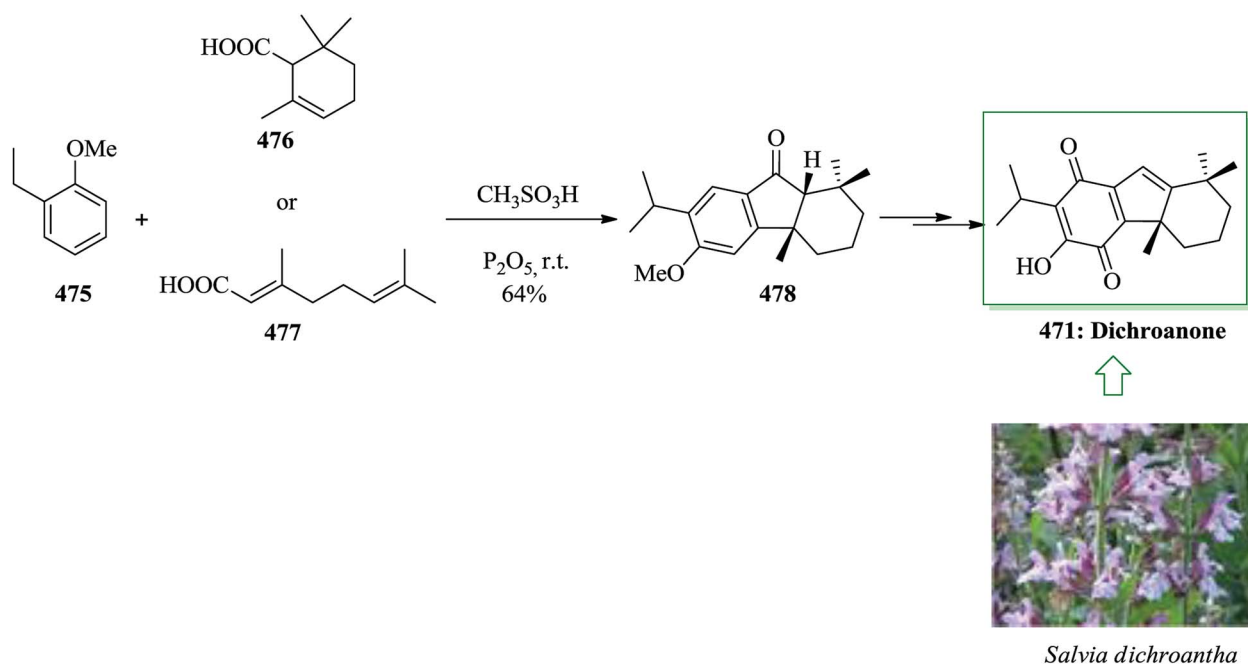
methylcinnamoyl derivative **469** in an 87% overall yield from **468**. Finally, compound **469** was converted into 0231B **467** upon several steps (Scheme 99).⁴⁶⁸

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 (\pm)-taiwaniaquinol B **470** and (\pm)-dichroanone **471** were performed. Total synthesis of (\pm)-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-





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



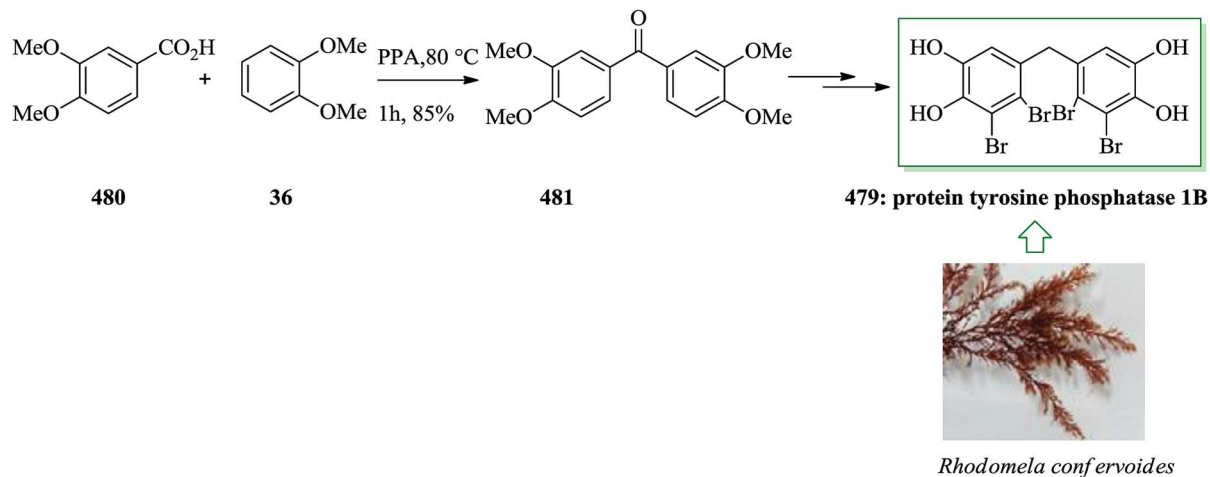
Scheme 101 Total synthesis of (±)-dichroanone 471.

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}

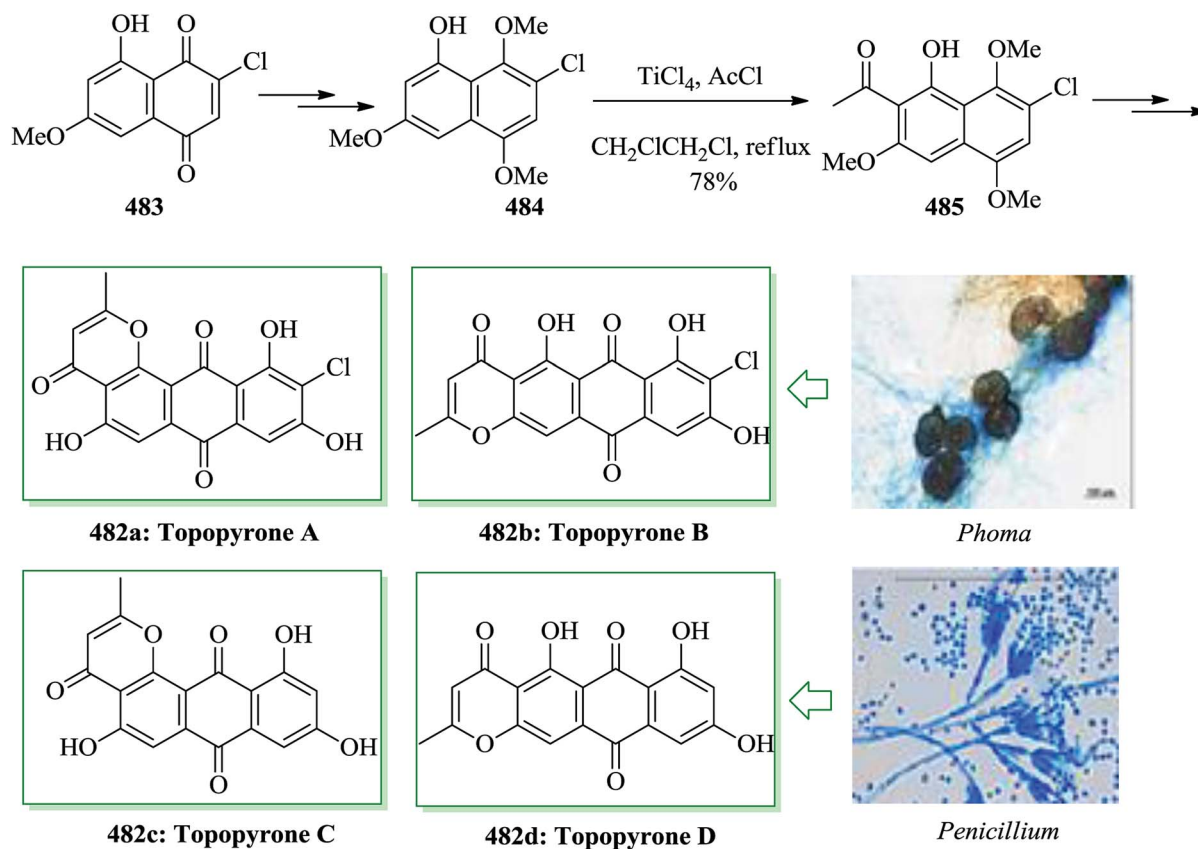
Protein tyrosine phosphatase 1B (PTP1B) has aroused intensive research interest because of its involvement in the insulin signaling cascade as a major negative regulator.⁴⁷³ Bioassay-guided separation of the ethanol extract using a wide range of chromatographic techniques resulted in a series of

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**





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

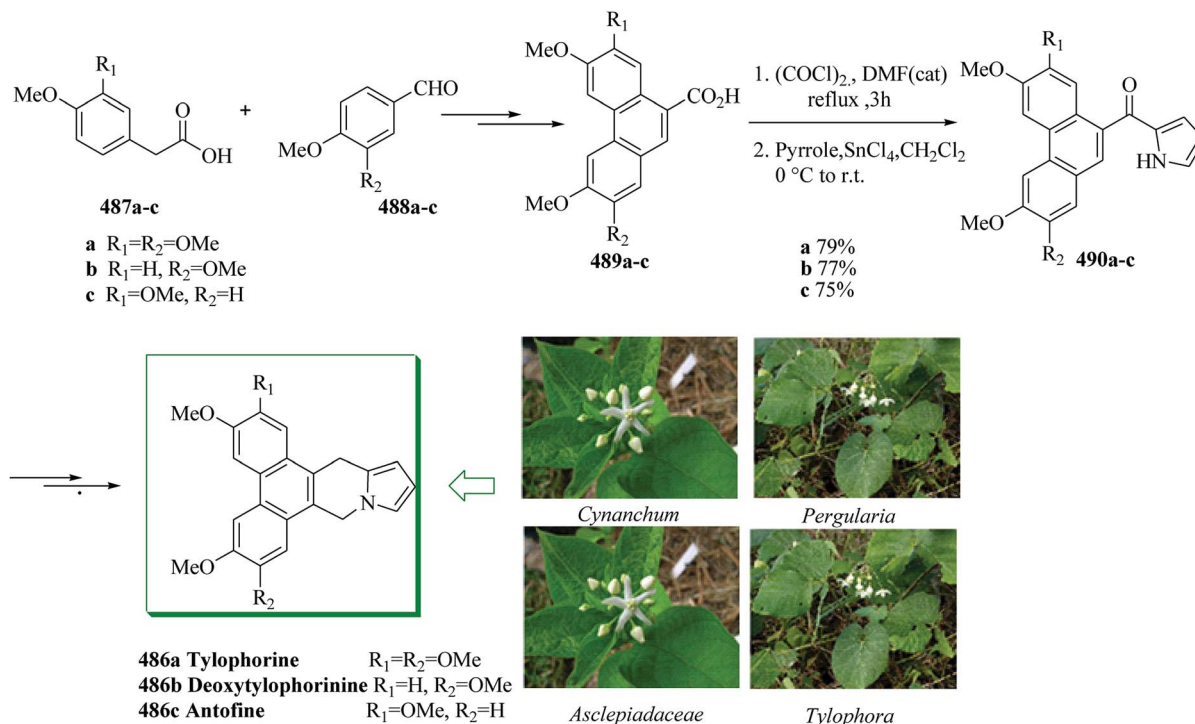
Scheme 103 Total synthesis of topopyrone A **482a**, B **482b**, C **482c** and D **482d**.

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 chlorine 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**





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

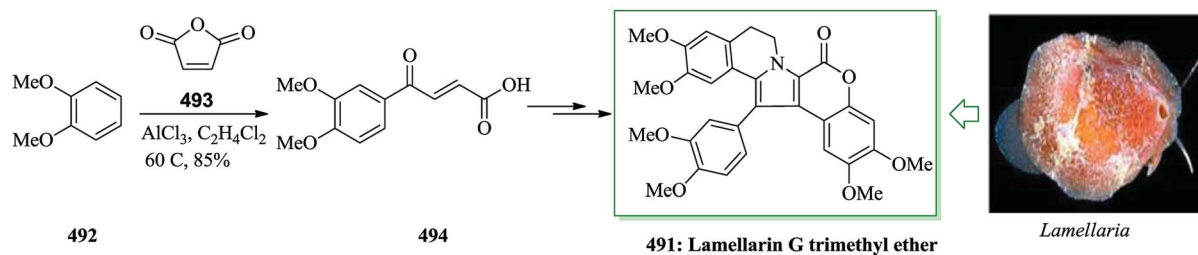
and **D 482d**, initially quinone **483**⁴⁷⁷ was converted into phenol **484** in several steps. At this point $TiCl_4$ was selected to perform regiocontrolled FC acylations. Actually, it was known that reaction of **484** in 1,2-dichloroethane with titanium tetrachloride and $AcCl$ under reflux introduced 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

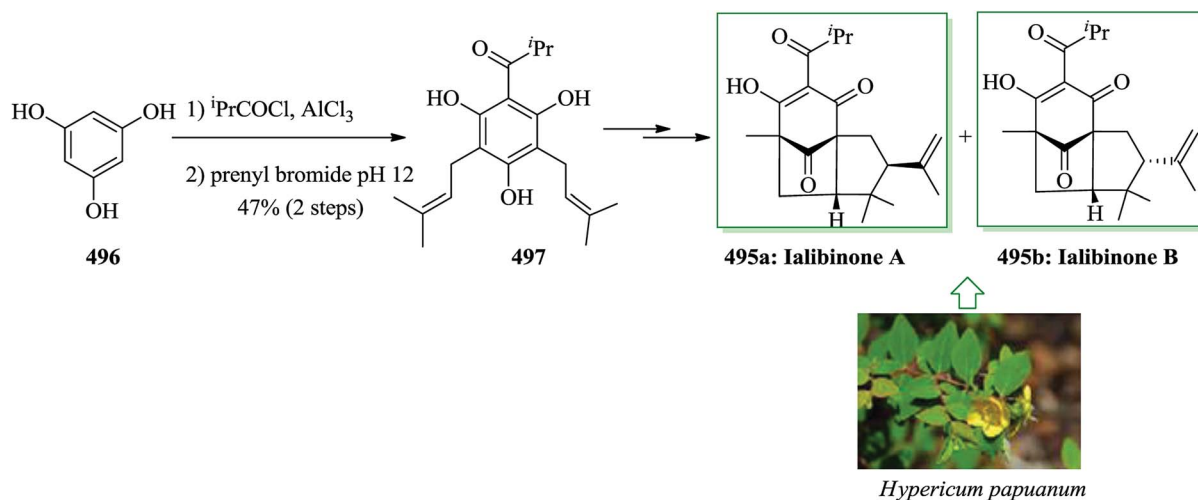
demonstrated the construction of deoxytylophorinine **486b** and antofine **486c**. Deoxytylophorinine **486b** and antofine **486c** were obtained in 44% and 46% overall yields, respectively, in six steps including a Perkin condensation reaction, intramolecular oxidative coupling reaction of acids, 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-6-baza 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





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

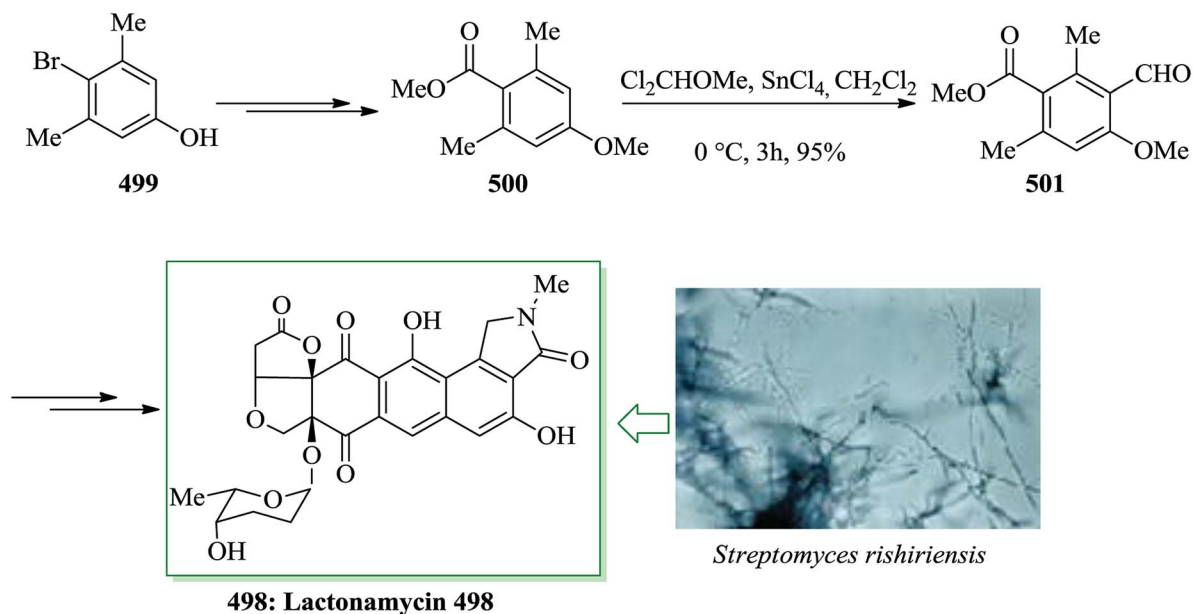
Lactonamycin **498**, extracted from a culture broth of *Streptomyces rishiriensis* MJ773-88K4, exhibited active antimicrobial properties against Gram-positive bacteria and vancomycin-resistant *Enterococcus* (VRE) as well as antitumor properties.^{496,497} Structurally, compound **498** contains a hexacyclic 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 reaction⁵⁰⁰ of **500**, gave aldehyde **501**. Upon several steps, compound **501** gave lactonamycin **498** (Scheme 107).⁴⁹⁸

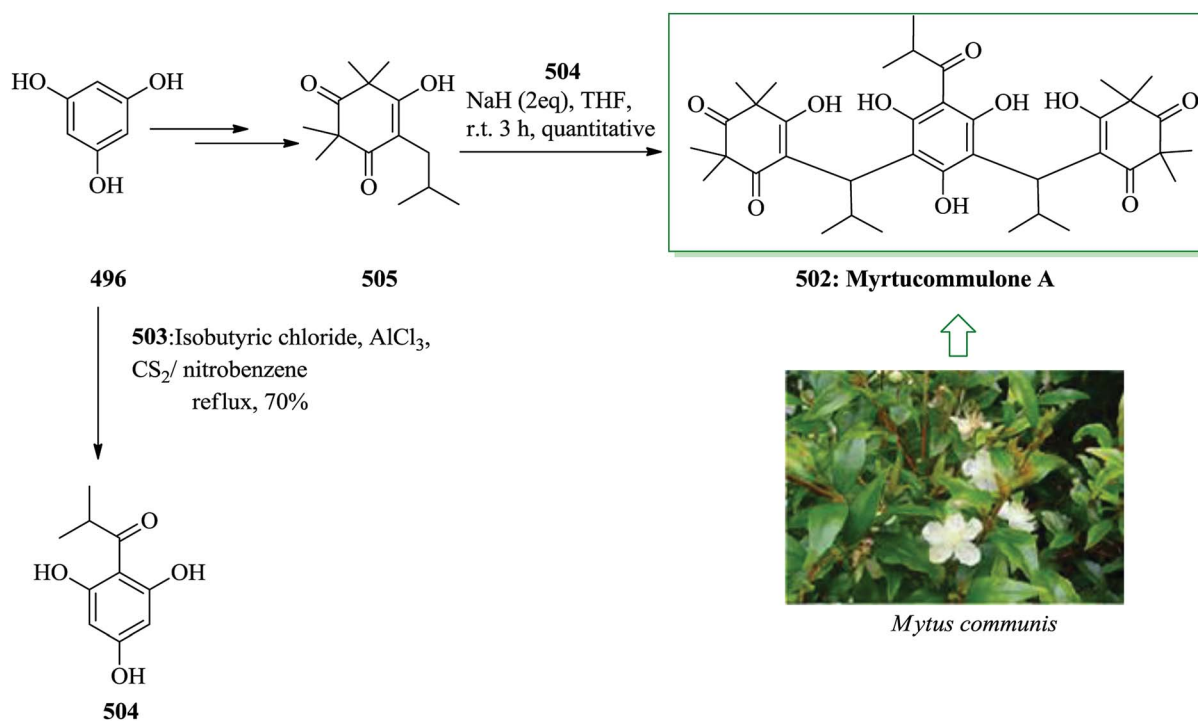
Myrtucommulone A **502** was developed in 1974 by Kashman *et al.* as a substance known in the common myrtle *Myrtus communis* L.⁵⁰¹ Jauch *et al.* in 2010 reported synthesis of myrtucommulone A **502** from isobutyryl phloroglucinol **504**, isobutyraldehyde, and syncarpic acid in one step. Isobutyryl 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,





Scheme 107 Total synthesis of lactonamycin 498.

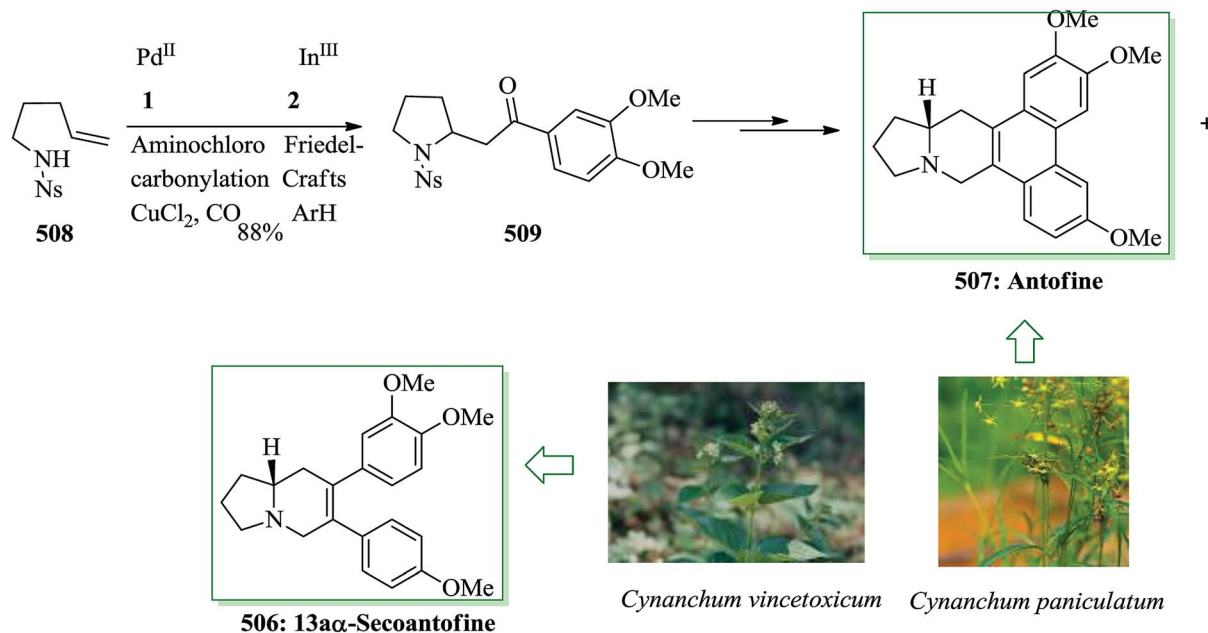
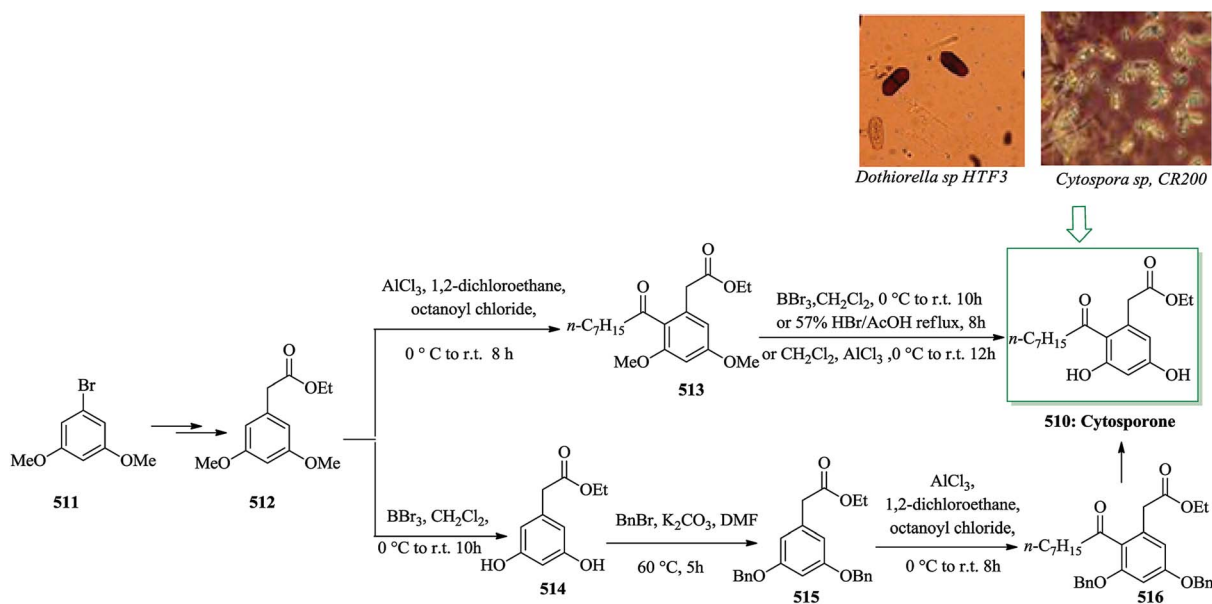


Scheme 108 Total synthesis of myrtucommulone A 502.

and anti-inflammatory properties.⁵⁰⁷ Antofine and 13 α -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 α -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 α -secoantofine and antofine in 19% and 48% overall yield, respectively (Scheme 109).⁵¹¹



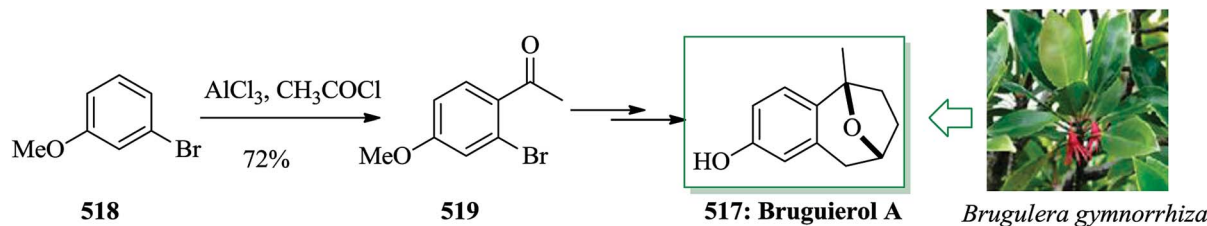
Scheme 109 Total synthesis of 13 α -secoantofine 506 and antofine 507.

Scheme 110 Total synthesis of cytosporone B 510.

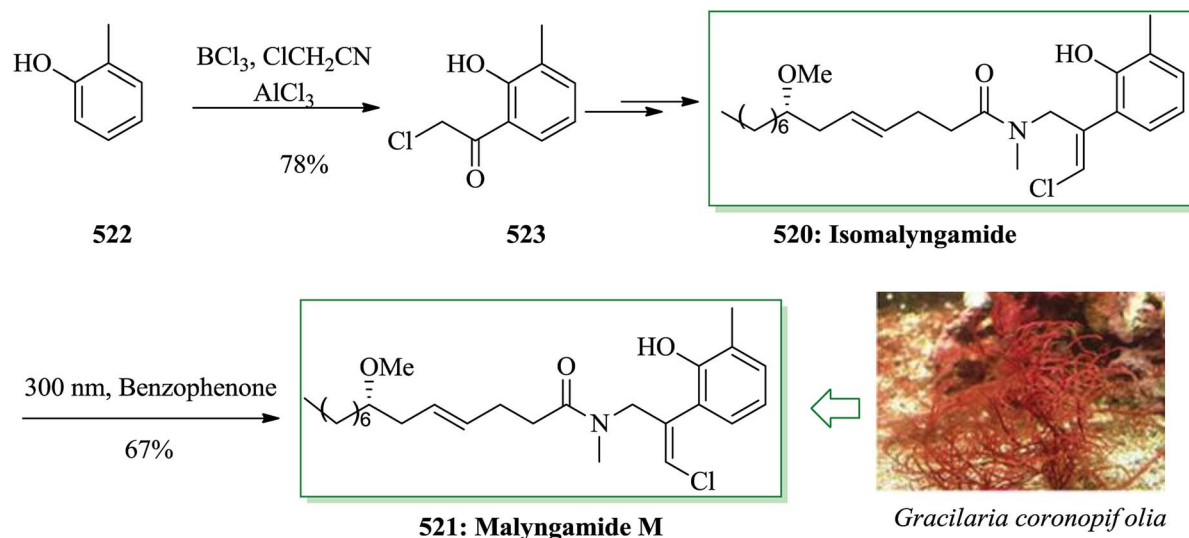
Cytosporone B **510**, extracted from *Cytospora sp.* CR200 and *Dothiorella sp.* HTF3,⁵¹² exhibits antibacterial activity.^{512–515} The total synthesis of cytosporone B was achieved from 1-bromo-3,5-dimethoxybenzene. The key steps are sequential Grignard reaction and Lemieux-van Rudloff oxidation followed 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%





Scheme 111 Total synthesis of bruguierol A 517.



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

yield. Finally, the debenzoylation 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

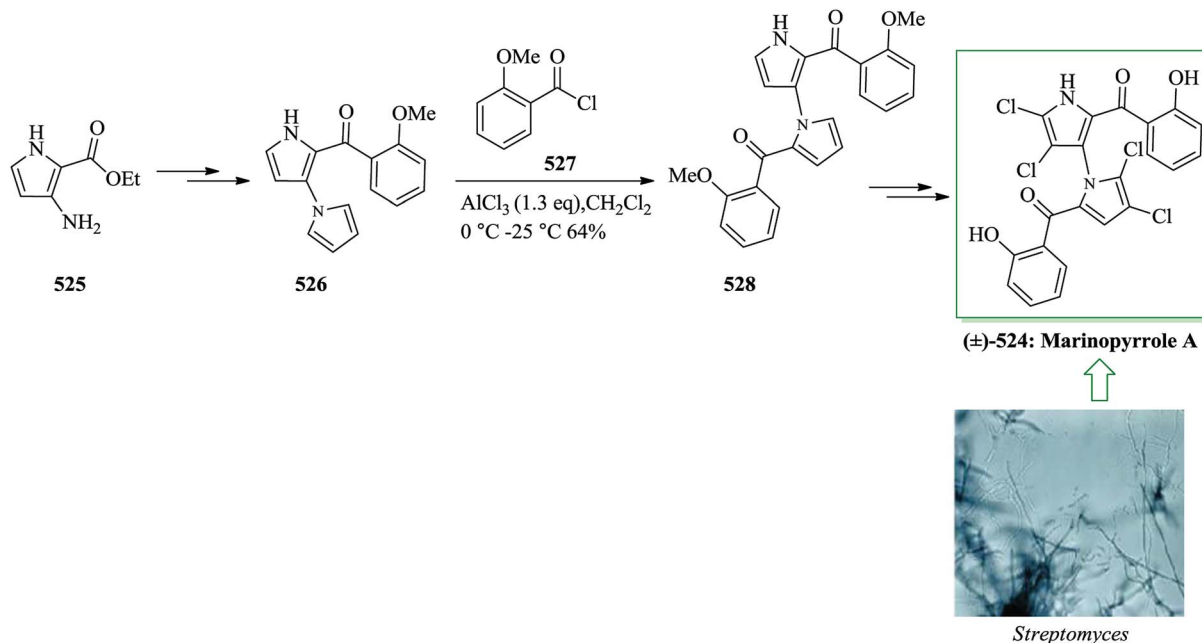
Bruguierol A **517** was extracted and identified by Sattler *et al.* from the stem of *Bruguiera gymnorrhiza* tree in 2005.⁶⁶ This natural product has a unique structure characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. Total synthesis of (\pm)-bruguierol A **517** was achieved in 10 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 $\text{Sc}(\text{OTf})_3$ -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, (\pm)-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

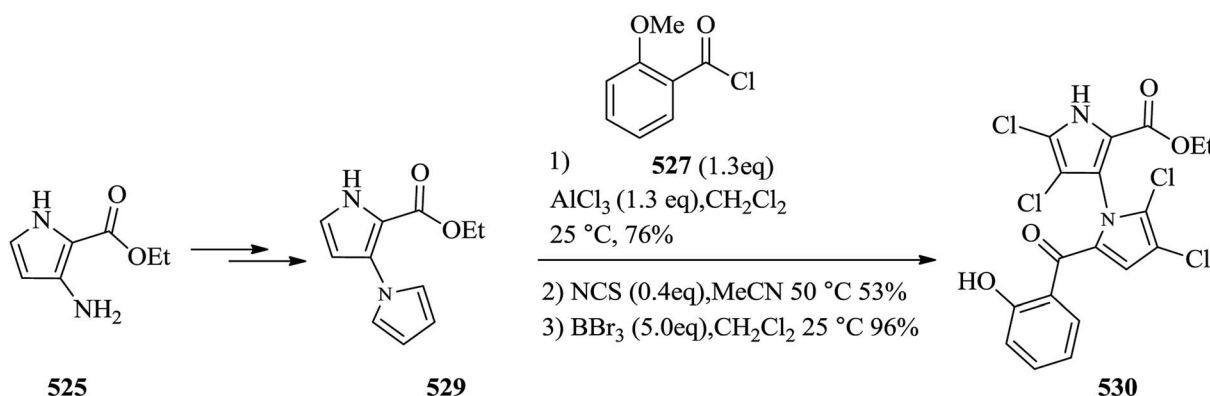
synthesis of malyngamide M **521** was achieved in nine steps from *o*-cresol in 12% overall yield. The key steps included the Wittig reaction, FC acetylation, amidation, and isomerization reaction. The isomalyngamide M **520** was also obtained in 2010 by Cao *et al.*⁵¹⁹ In this pathway, total synthesis of malyngamide M **521** was started from *o*-cresol **522**. FC acylation 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





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

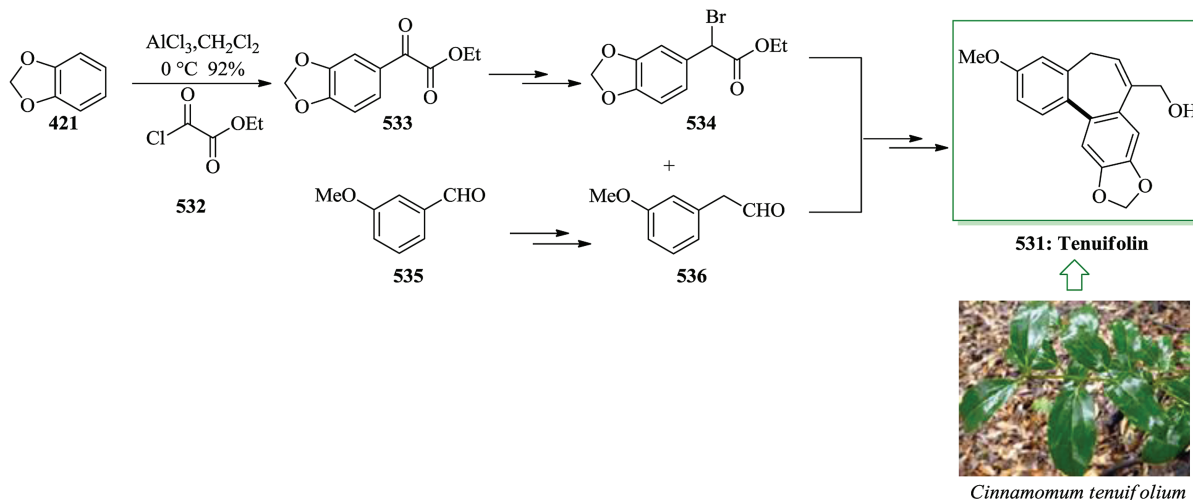
In a similar method, mono-arylated marinopyrrole **530** was synthesized from bis-pyrrole **529** (obtained from compound **525**), *via* a three-step sequence containing a FC C-arylation with acid chloride **527**, *tetra*-chlorination with NCS in acetonitrile, and demethylation with BBr₃ in dichloromethane 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





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 a para-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 reaction²⁶⁴ 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 dictyodendrin A **275** (Table 1, entry 2). It was found that silver triflate⁵³⁰ 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 ZnCl₂ 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: ZnCl₂ (10 equiv.), RX (2 equiv.), Et₂O, 0 °C.

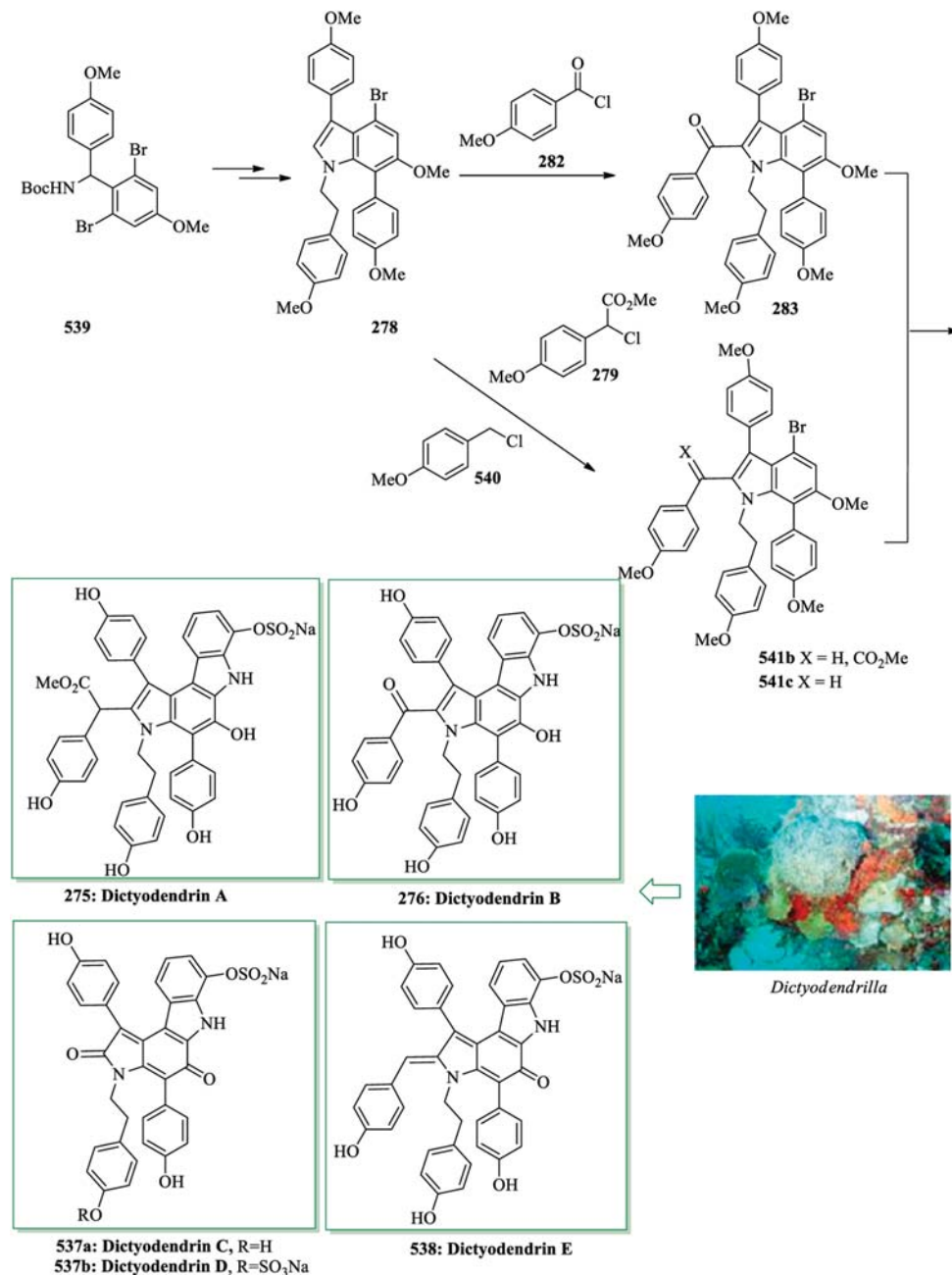
^b Reaction condition: AgOTf (4 equiv.), RX (3 equiv.), THF, -78 °C.

^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 allylacetly chloride in CH₂Cl₂ 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 2006⁵³⁵ and the isolation of lysidicins D–H was reported by the same group in 2007⁵³⁶ 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



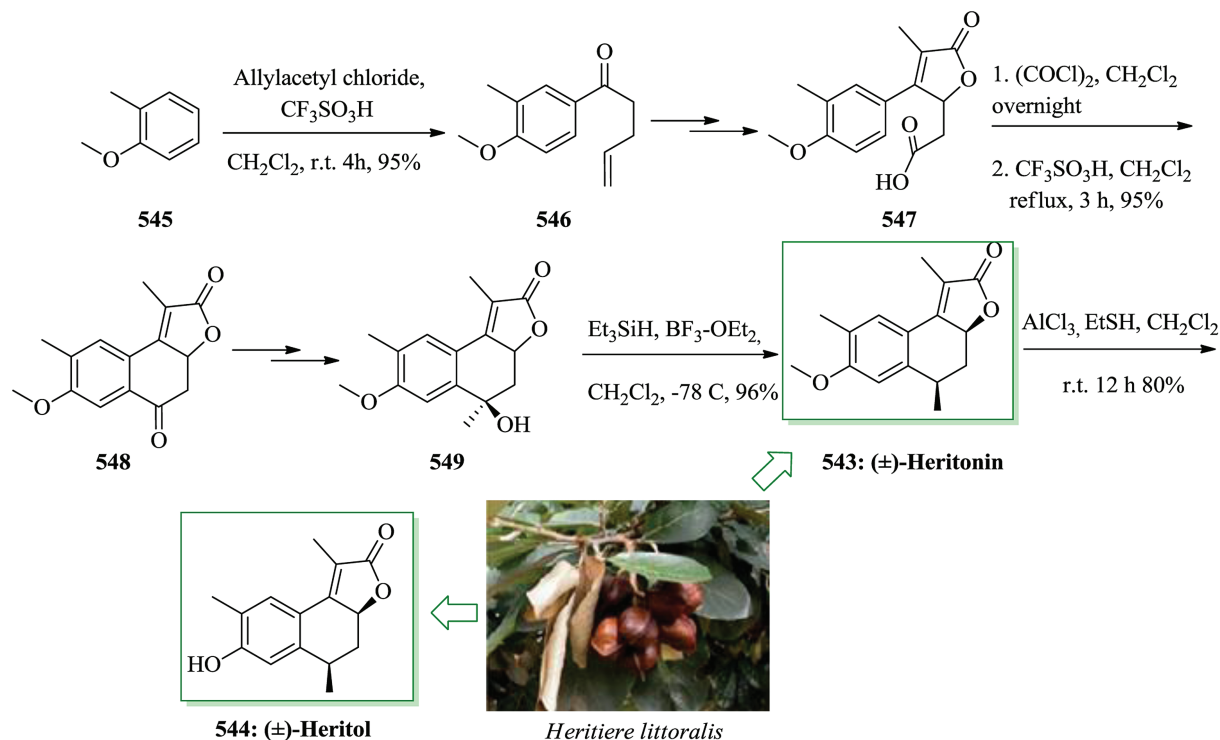


Scheme 116 Total synthesis of dictyodendrins A–E.

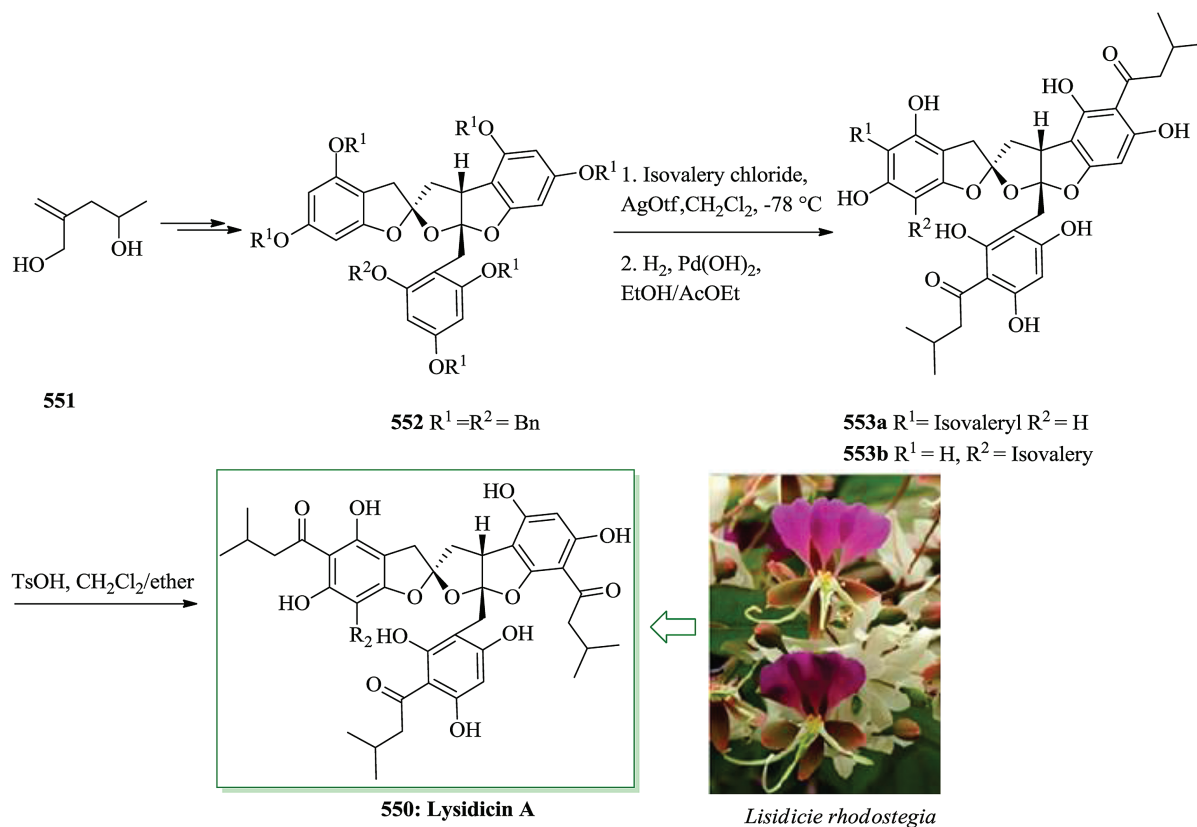
et al. in 2012 reported the initial total synthesis of (\pm)-lysidicin A significantly through single and cascade Claisen rearrangements and FC acylation reaction with AgOTf.⁵³⁸ In this method, the overall yield was 3.5% in 15 steps from diol **551**. The total synthesis was started from diol **551**, 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 (\pm)-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

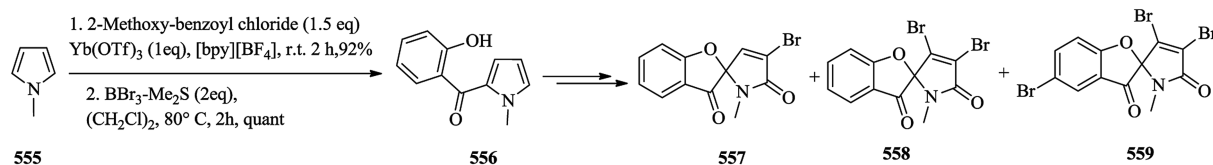




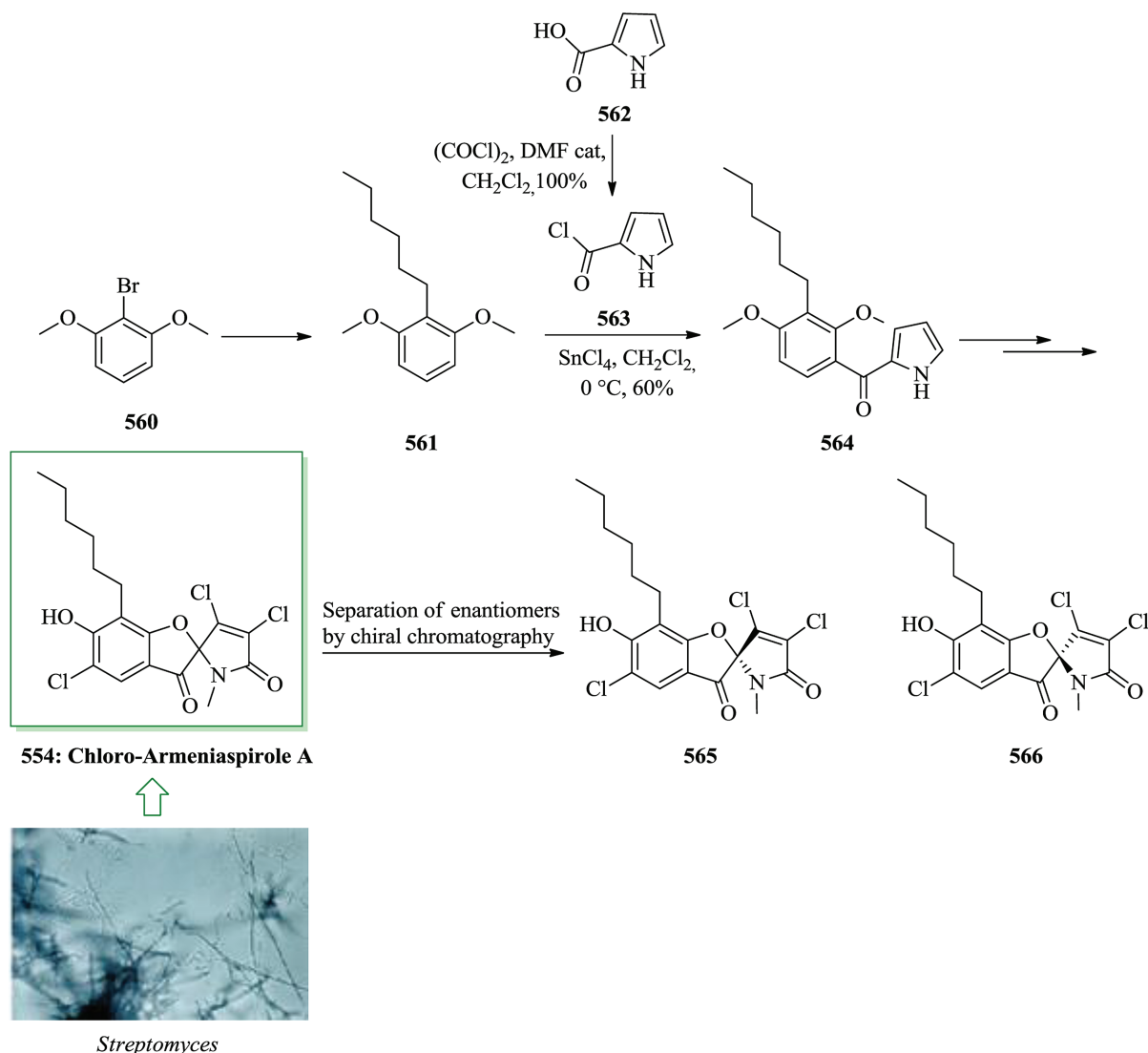
Scheme 117 Total synthesis of (±)-heritonin 543 and (±)-heritol 544.



Scheme 118 Total synthesis of lysidicin A 550.



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



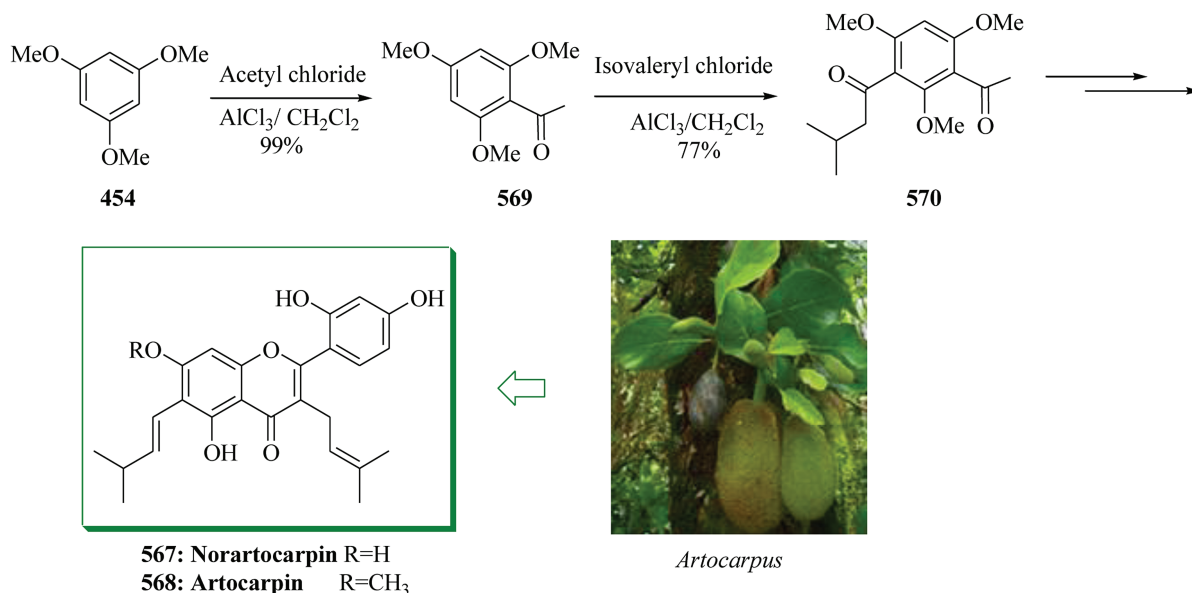
Scheme 120 Total synthesis of 5-chloro-armeniaspirole 554.

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

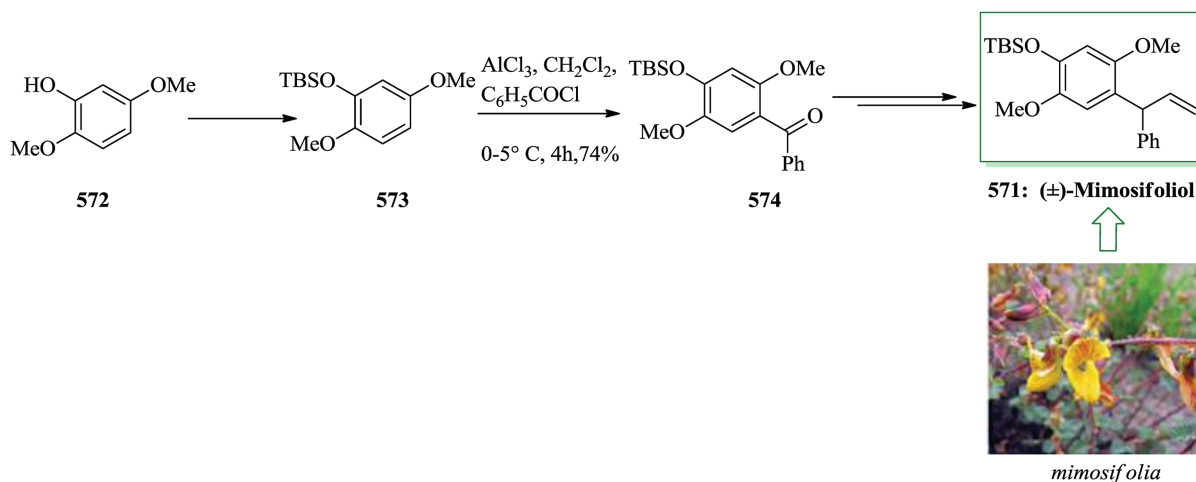
Norartocarpin **567** and artocarpin **568** are natural isoprenylated flavonoids isolated from the genus *Artocarpus*.^{541–543} They have a wide range of remarkable biological properties,

including inhibitor effects on melanin biosynthesis and 5 α -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 CH₂Cl₂ with aluminium





Scheme 121 Synthesis of norartocarpin 567 and artocarpin 568.



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

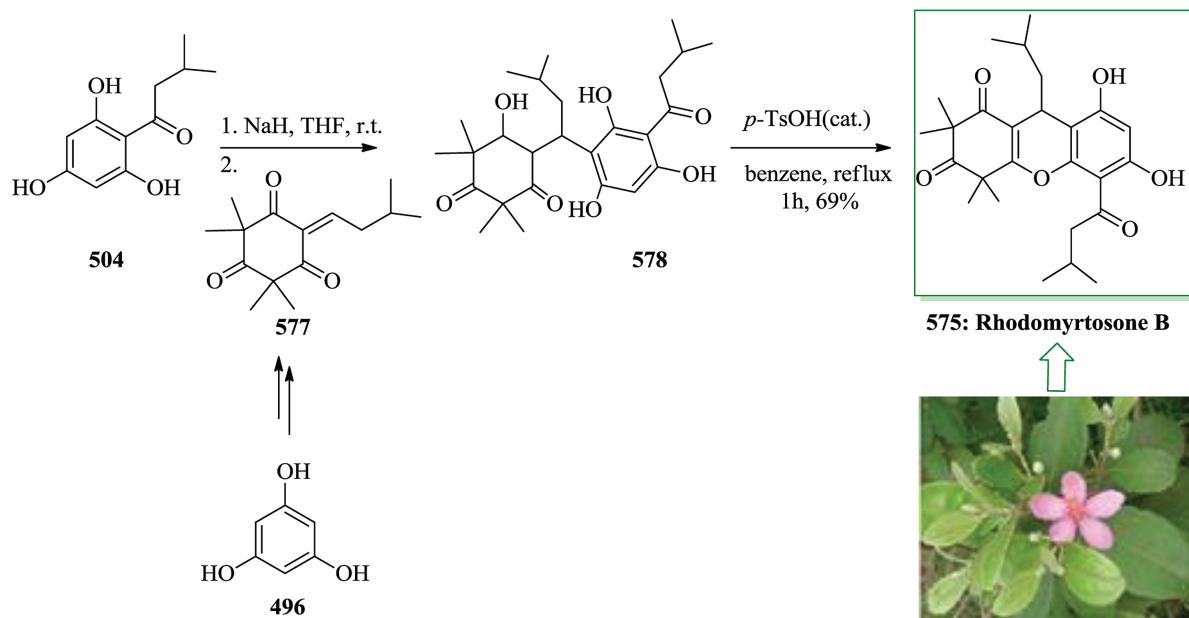
chloride using acetyl chloride and 3-methylbutanoyl chloride as the acylated reagents, respectively, gave the intermediate 570 in moderate yields (75% for two steps). In the course of FC acylation, the corresponding demethylation simultaneously happened, which may be related to the effect of two carbonyl 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

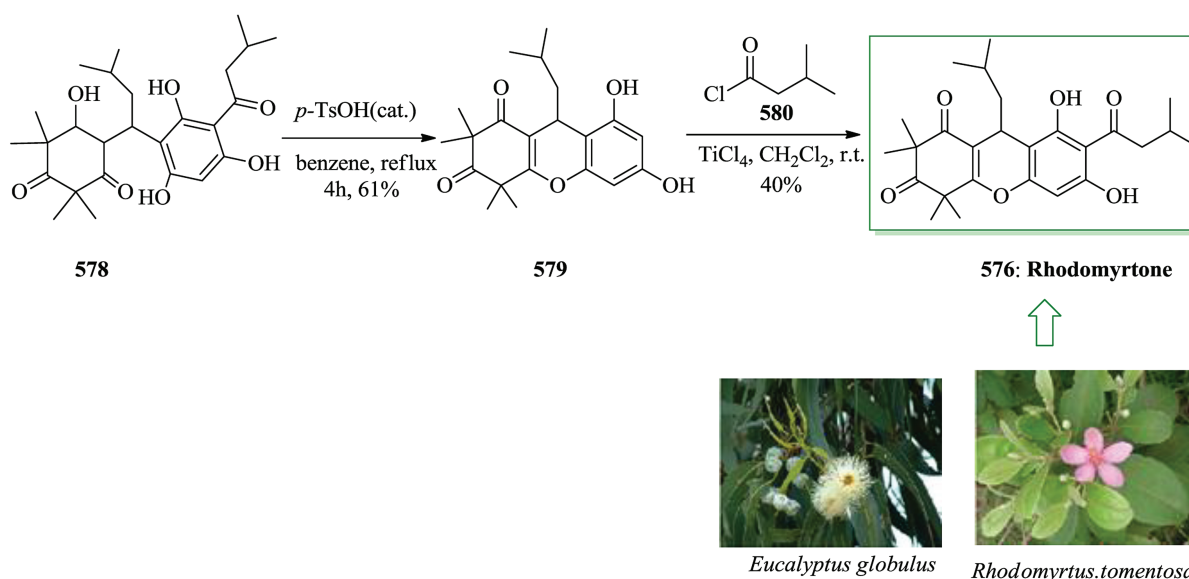
intermediate and subsequently (+)-mimosifoliol was obtained through cycloaddition of the same intermediate with a chiral enol ether.⁵⁴⁷ A two-step method was developed to vinylate the diarylmethanes at the bridging CH₂ with lateral lithiation and formylation followed by a Wittig reaction. This strategy 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





Scheme 123 Total synthesis of rhodomlyrtosone B 575.



Scheme 124 Synthesis of rhodomlyrtone 576.

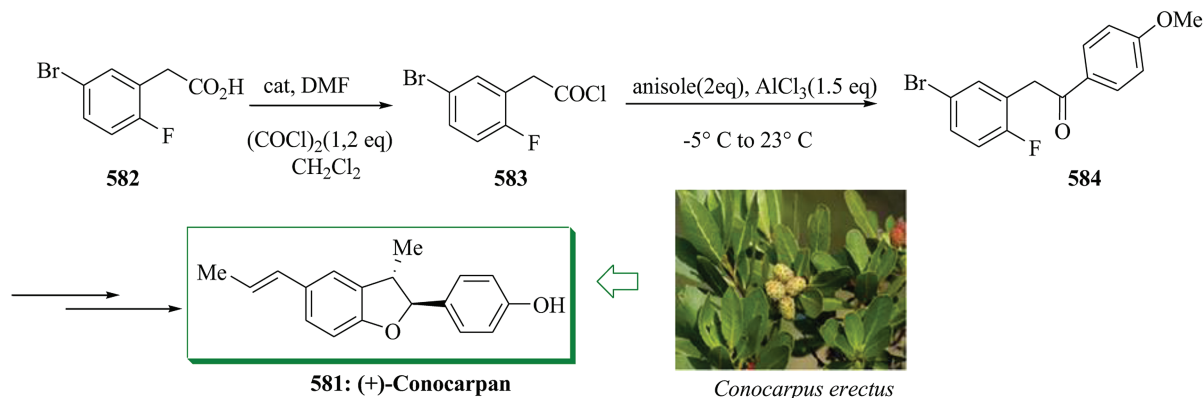
of ailments. Rhodomlyrtone **576** was isolated from the ethanol extract. The same compound was extracted from the bark of small twigs of *Eucalyptus globulus* Labill, which is a member of the *Myrtaceae* group.^{549,550} This acylphloroglucinol exhibits significant antibacterial activity. Additional acylphloroglucinols could be isolated from the leaves of *R. tomentosa*, which contain the isomer rhodomlyrtosone B **575**.⁵⁵¹ In 2013, Maier *et al.* developed a concise synthesis of the isomeric acylphloroglucinols rhodomlyrtosone B **575** and rhodomlyrtone **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 acylphloroglucinol **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 rhodomlyrtosone B **575** in 69% yield (Scheme 123).⁵⁵²

The other isomer, the antibiotic rhodomlyrtone **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





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 glycol 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

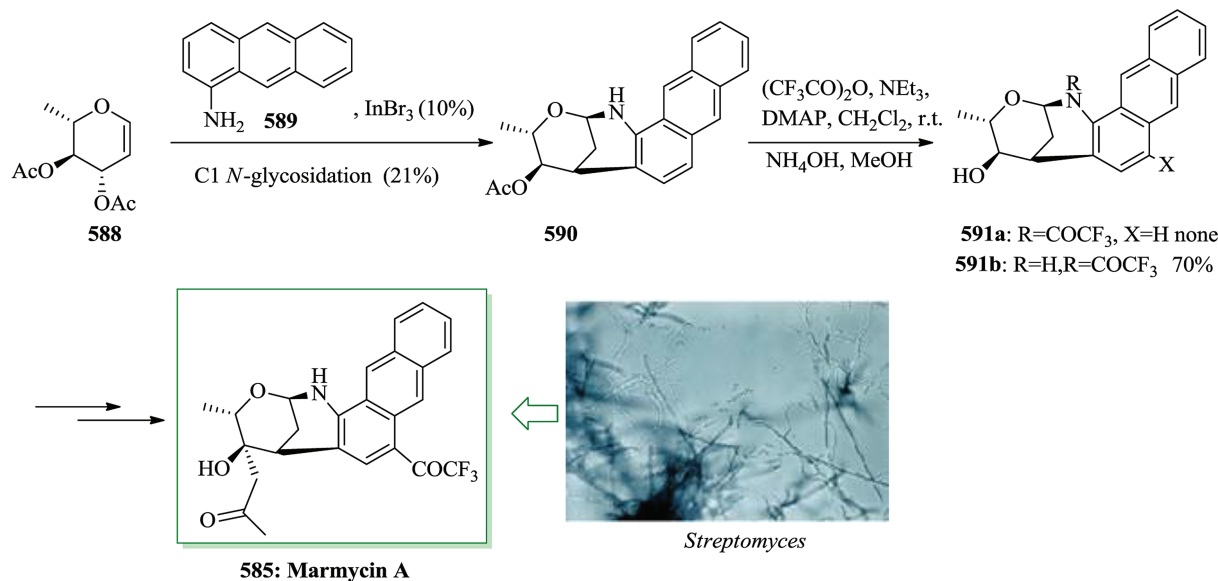
Marinamide 596 and its methyl ester 602 are two isoquinolinone alkaloids that were isolated from the metabolite of mixed fermentation of two mangrove endophytic fungi (strains no. 1924 and 3893) from the South China Sea. These two compounds were identified as 4-(2-pyrrolyl)-1-isoquinolone-3-carboxylic acid 596 and methyl 4-(2-pyrrolyl)-1-isoquinolone-3-

carboxylate 602, respectively. Compounds 596 and 602 exhibited significant antibacterial and⁵⁶² 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

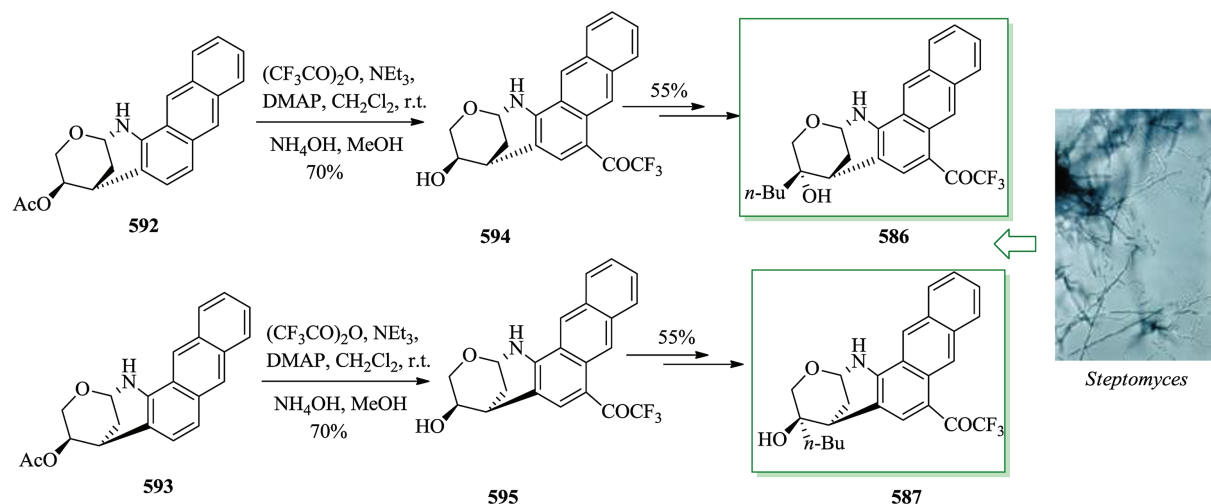
The naphtho[2,3-*c*]furanoidiones (isofuranonaphthoquinones), a relatively small group of secondary metabolites with various biological properties, have been isolated from fungal, botanical, bacterial and insect sources. Monosporascone 603 was isolated from the fungus *Gelasinospora pseudoreticulata*.⁵⁶⁶ 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 605⁵⁶⁸ 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 permethoxy 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





Scheme 126 Total synthesis of marmycin A 585.



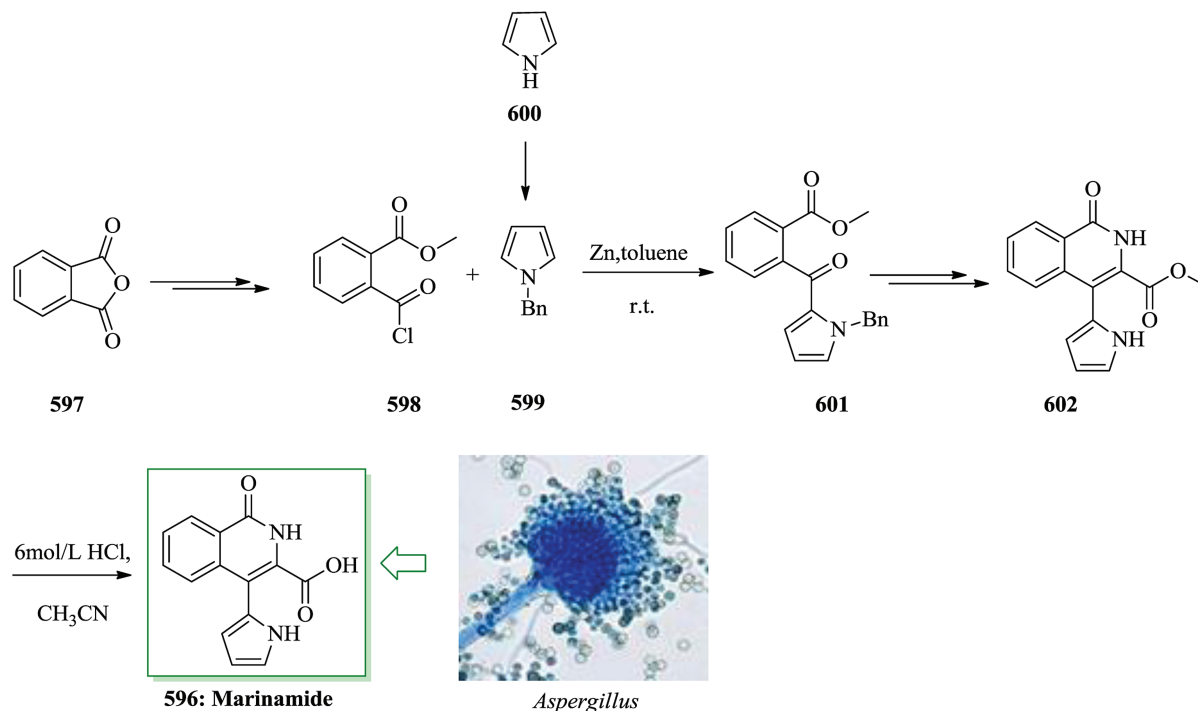
Scheme 127 The formation of quaternary alcohols 586 and 587.

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





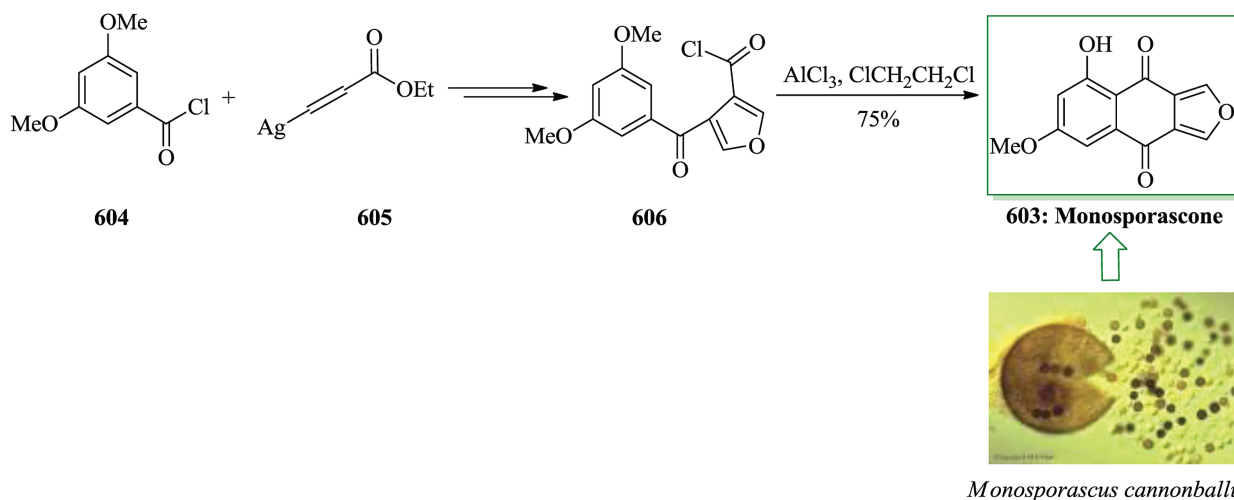
Scheme 128 Total synthesis of marinamide 596.

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-geranylacetophenone (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*.

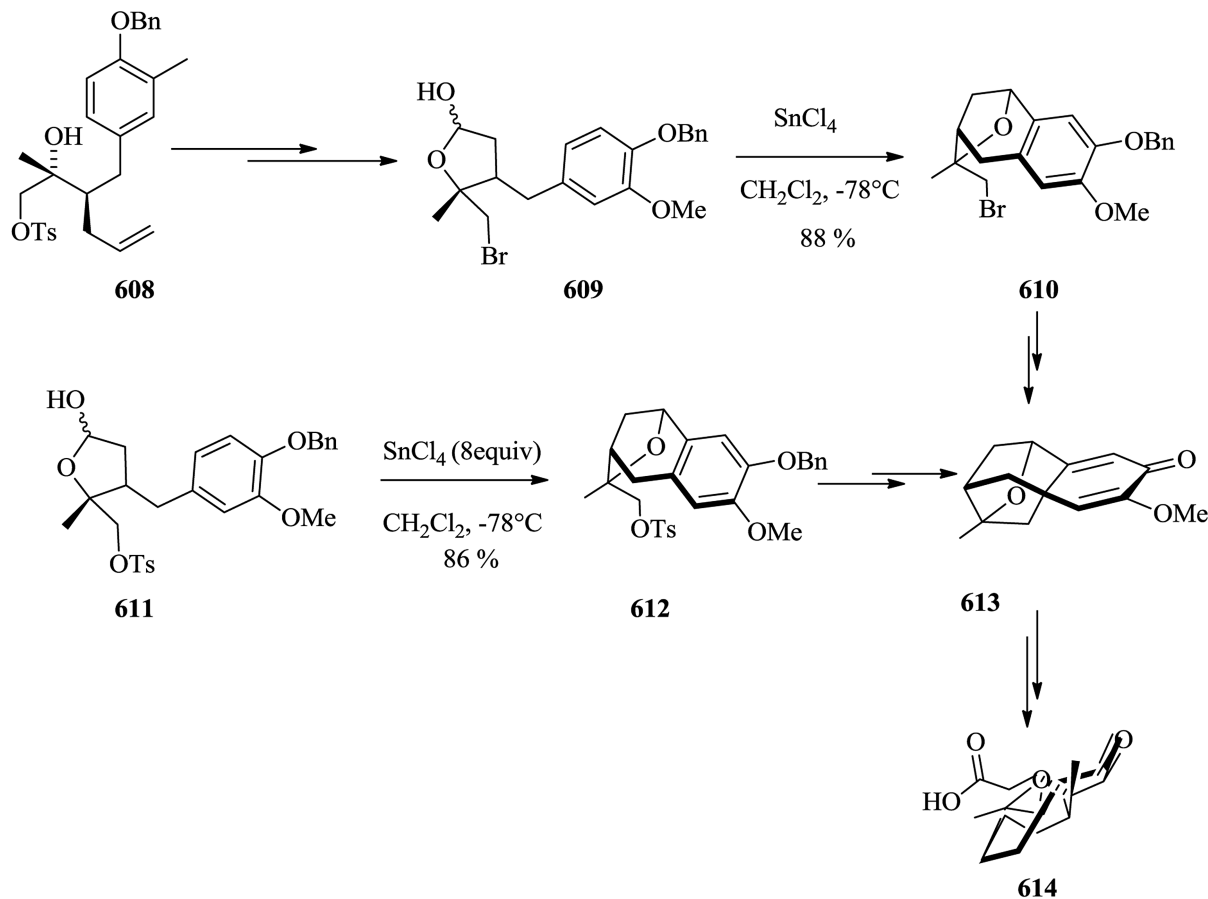
Direct FC acylation of phloroglucinol **496** was achieved with isobutyryl chloride as the acylating agent using anhydrous AlCl₃ to provide compound **619**.⁵⁷⁸ Subsequently, the geranyl scaffold was introduced through electrophilic substitution of geranyl bromide with anhydrous K₂CO₃ as the base in dry MeOH under reflux to afford the FC alkylated 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

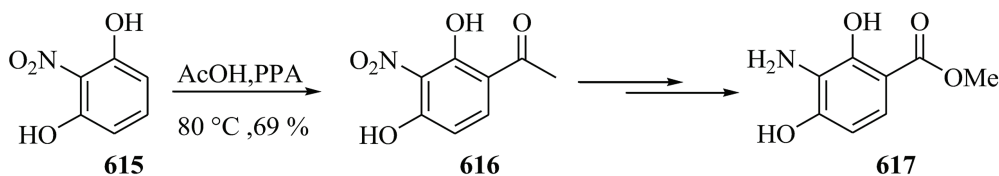


Scheme 129 Total synthesis of monosporascone 603.





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}

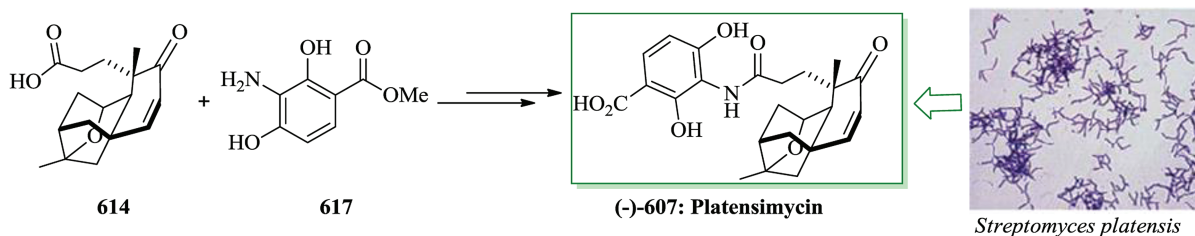
Total synthesis of merochlorin A was exhibited alongside the biosynthetic studies of George *et al.* in 2015.⁵⁸² Synthesis of merochlorin A 620 was started with a FC reaction of methyl 3,5-dimethoxyphenylacetate 621 and chloroacetyl chloride to afford ketone 623 in 56% yield. Finally, merochlorin A 620 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

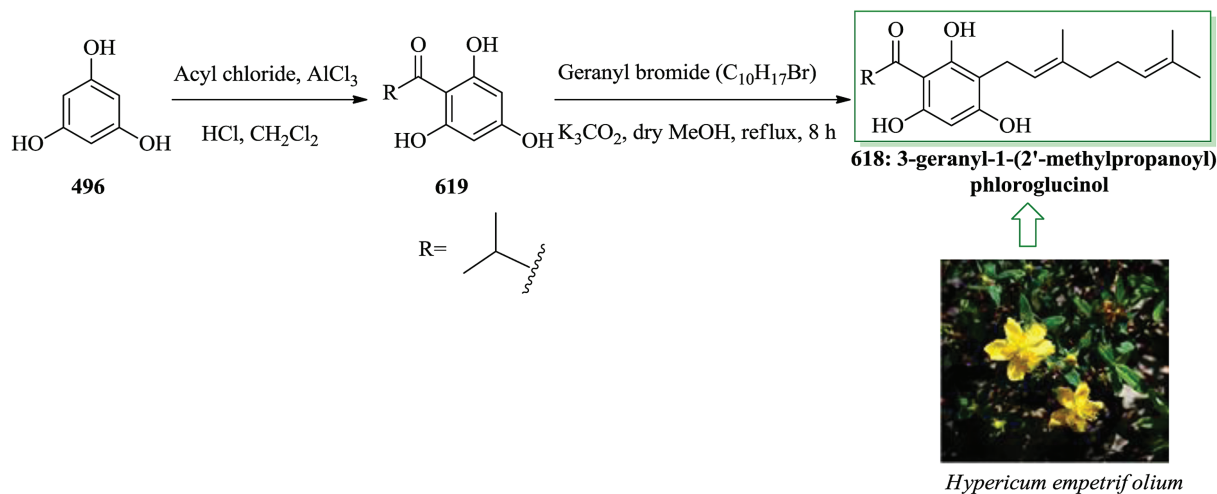
from 3,5-dihydroxybenzoic acid 625. Next, compound 625 afforded ester 626 upon several steps. The FC acylation reaction of ester 626 was performed with whole regioselectivity with a 2-chlorobenzyl protecting group to afford ketone 628 in 89% yields. Finally, ketone 628 afforded the target natural product 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 (\pm)-triumphalone was accomplished in 8 steps from phloroglucinol. Synthetic triumphalone was converted into (\pm)-isotriumphalone in one step. In this route, firstly phloroglucinol 496 was converted into 632 through the FC acylation reaction in 82% yield.⁵⁸⁸ Subsequently, (\pm)-triumphalone 629 was provided from compound 632 *via* several steps and also compound 629 was transformed to (\pm)-isotriumphalone 630 in one step. An spontaneous change of 629 to





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

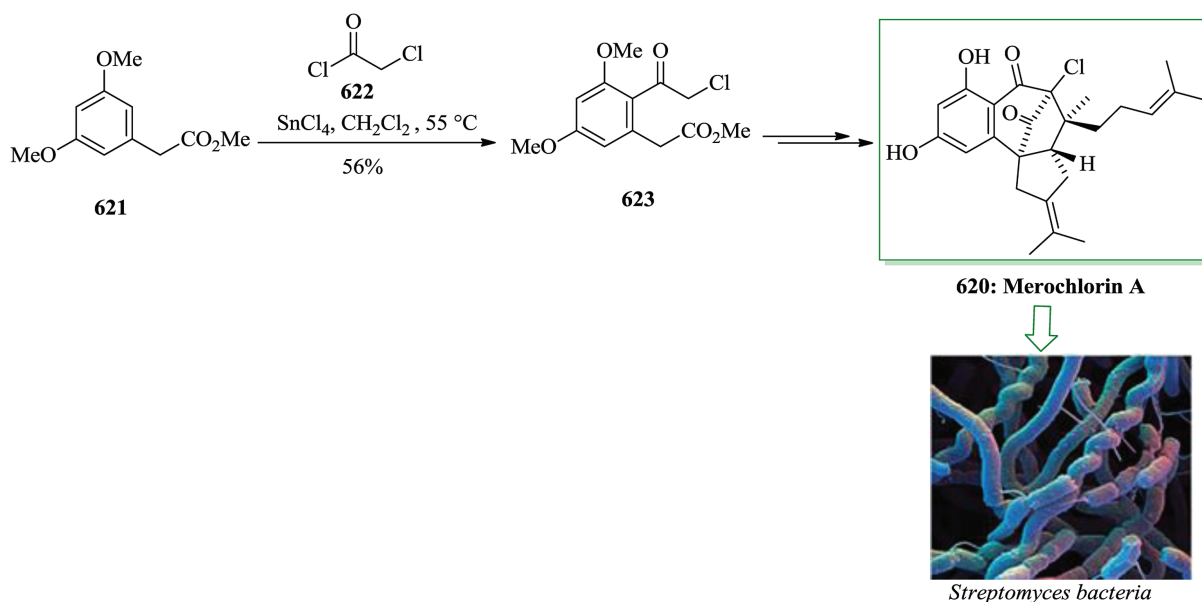


Scheme 133 Total synthesis of 3-geranyl-1-(2'-methylpropanoyl)phloroglucinol 618.

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

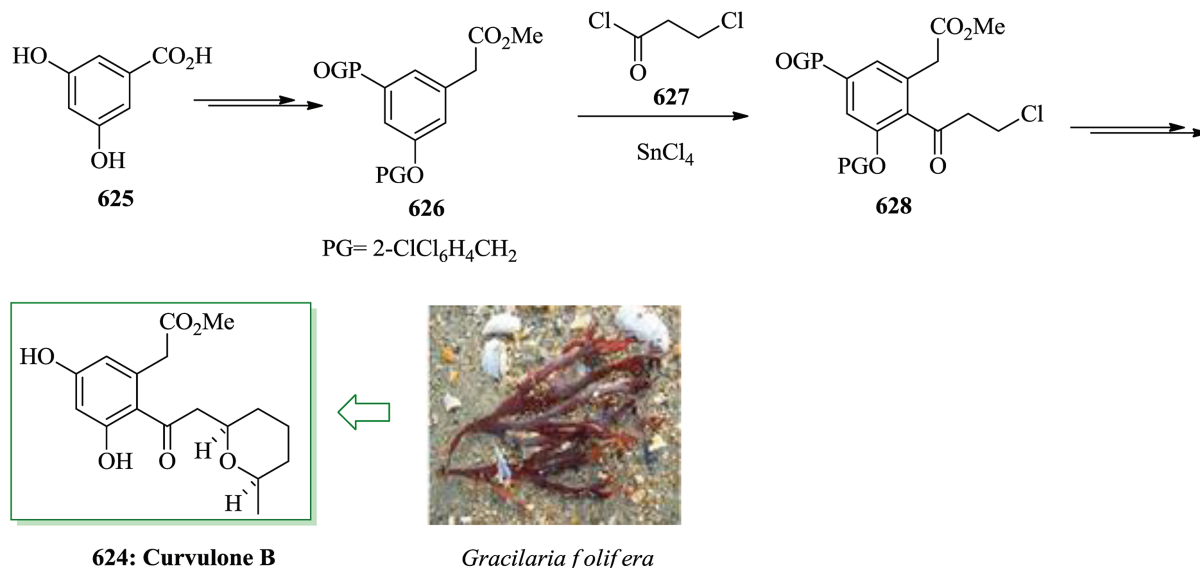
Flavonoids, a group of polyphenolic compounds that are abundant in plants,⁵⁹⁰ include dietary components of potential importance to health.⁵⁹¹ In addition, flavanoids are emerging as

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 anticancer⁵⁹⁷ and molluscidal⁵⁹⁸ properties.⁵⁹⁹ Peng *et al.* described the isolation and



Scheme 134 Total synthesis of merochlorin A 620.





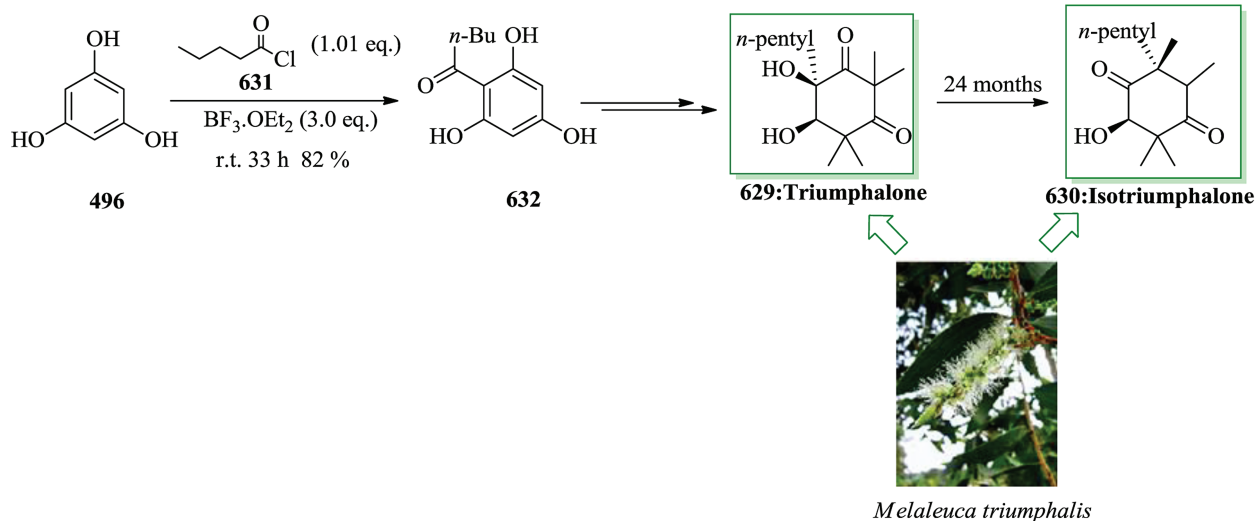
Scheme 135 Total synthesis of curvulone B 624.

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 C₇ 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

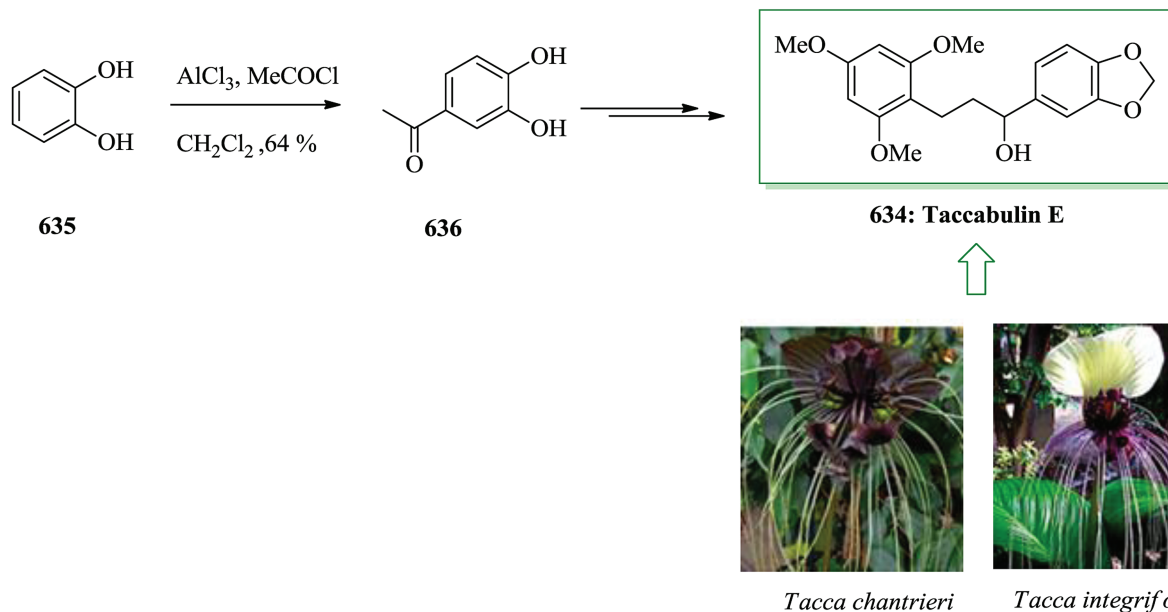
demonstrated to have satisfactory cytotoxicity against the IMR-32 human neuroblastoma cell line. Seçen *et al.* in 2015 reported a synthetic strategy for the formation of two natural diarylheptanoids, 2-benzyl-5-(2-phenylethyl)furan 637 and 2-methoxy-4-[[5-(2-phenylethyl)furan-2-yl]methyl]phenol 638.⁶¹⁰ 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

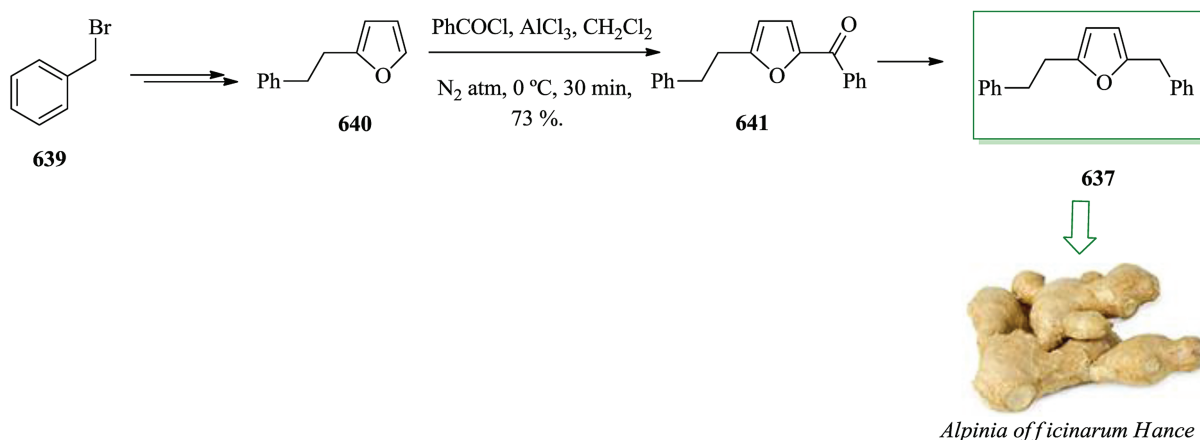


Scheme 136 Total synthesis of triumphalzone 629 and isotriumphalzone 630.





Scheme 137 Total synthesis of taccabulin E 633.



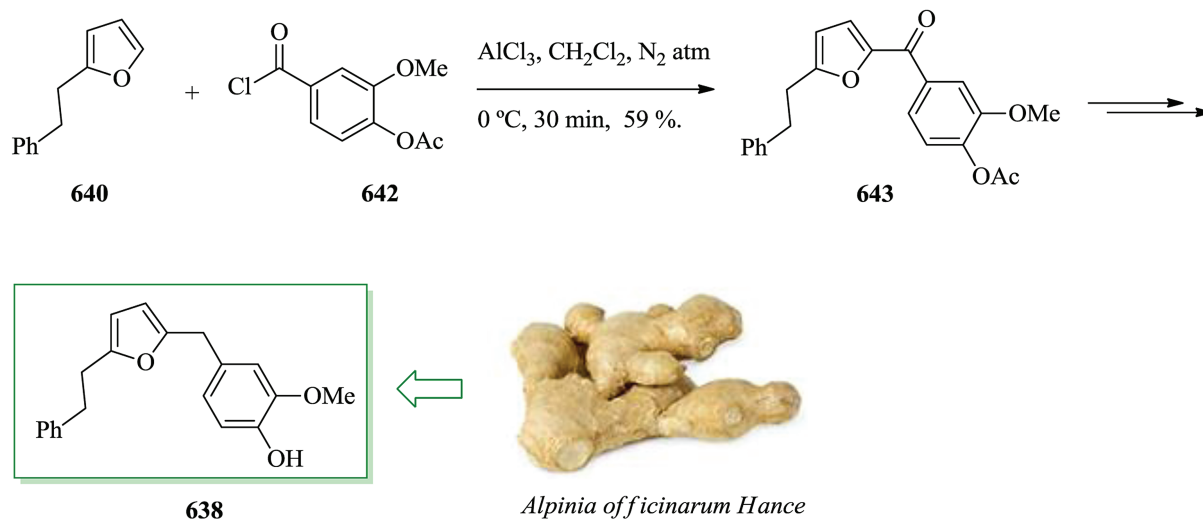
Scheme 138 Total synthesis of furan-cyclized diarylheptanoid 637.

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 *Amaryllidaceae* 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

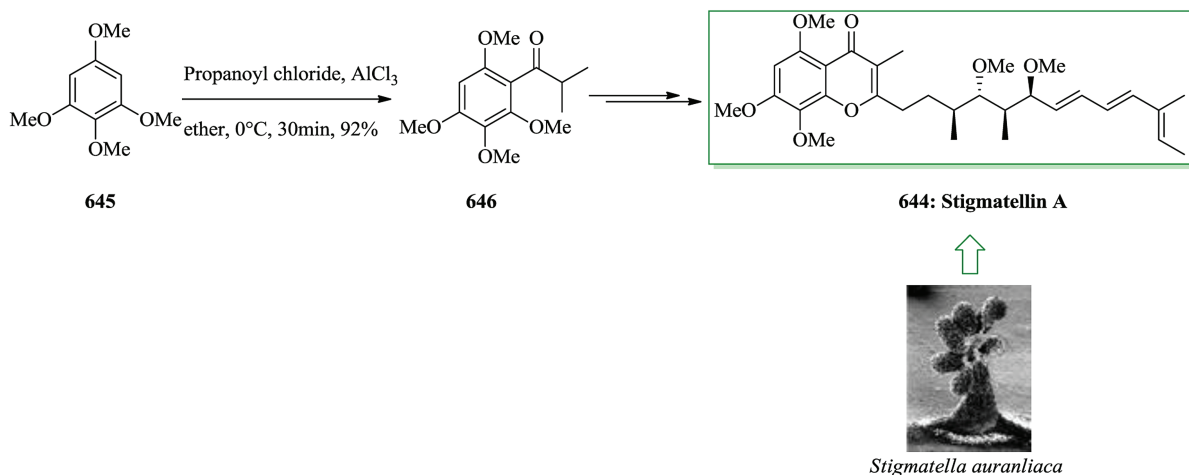


Scheme 139 Total synthesis of furan-cyclized diarylheptanoid **638**.

Calothrix A and B are unique indolo[3,2-*f*]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 $0\text{ }^{\circ}\text{C}$ 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, mameasins C and D (**656** and **657**), were isolated together with 20 other coumarins.⁶²³ Compounds **656** and **657** are rare coumarins, wherein a dioxaphenylene 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**.

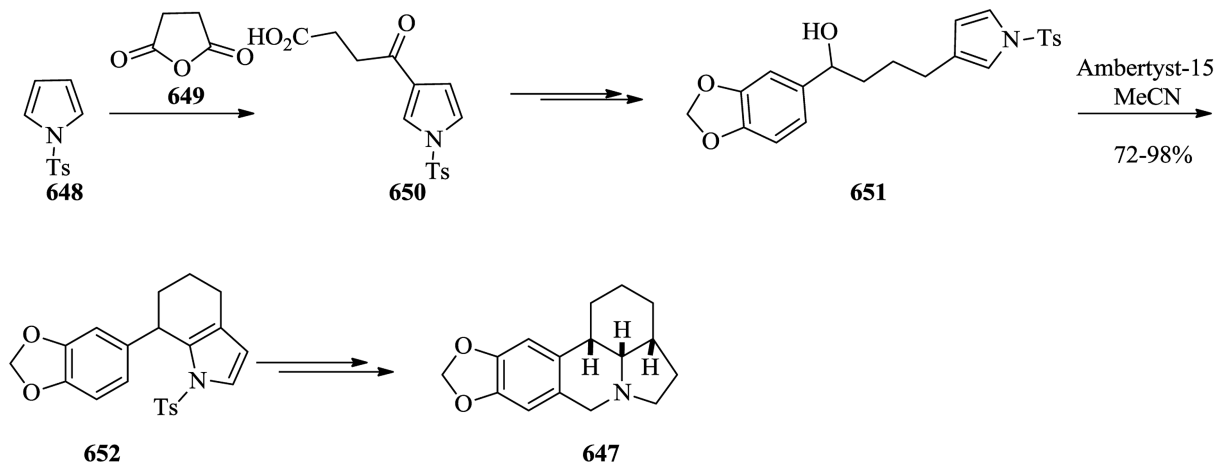
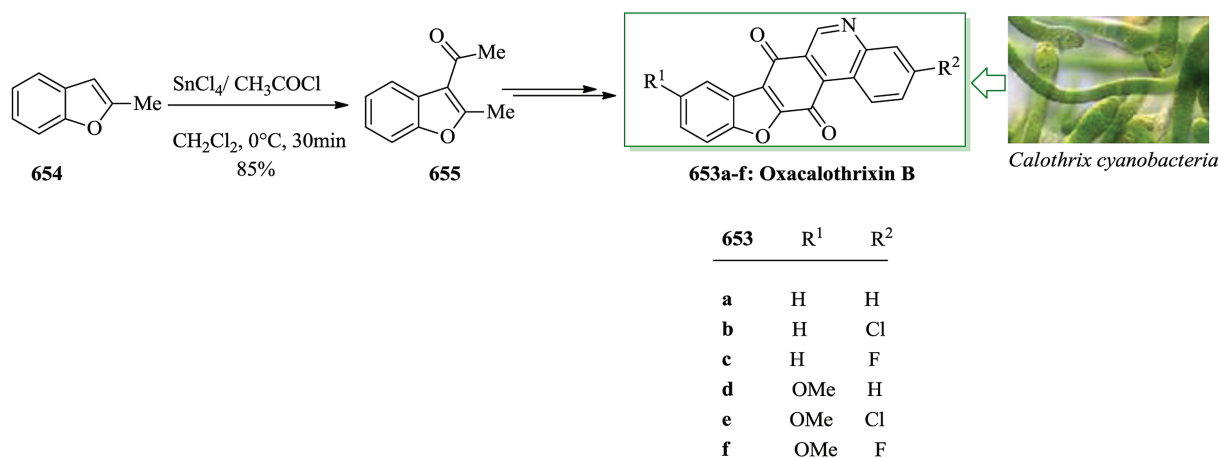
Scheme 141 Total synthesis of γ -lycorane **647**.Scheme 142 Total synthesis of oxcalothrixin B **653a–f**.

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

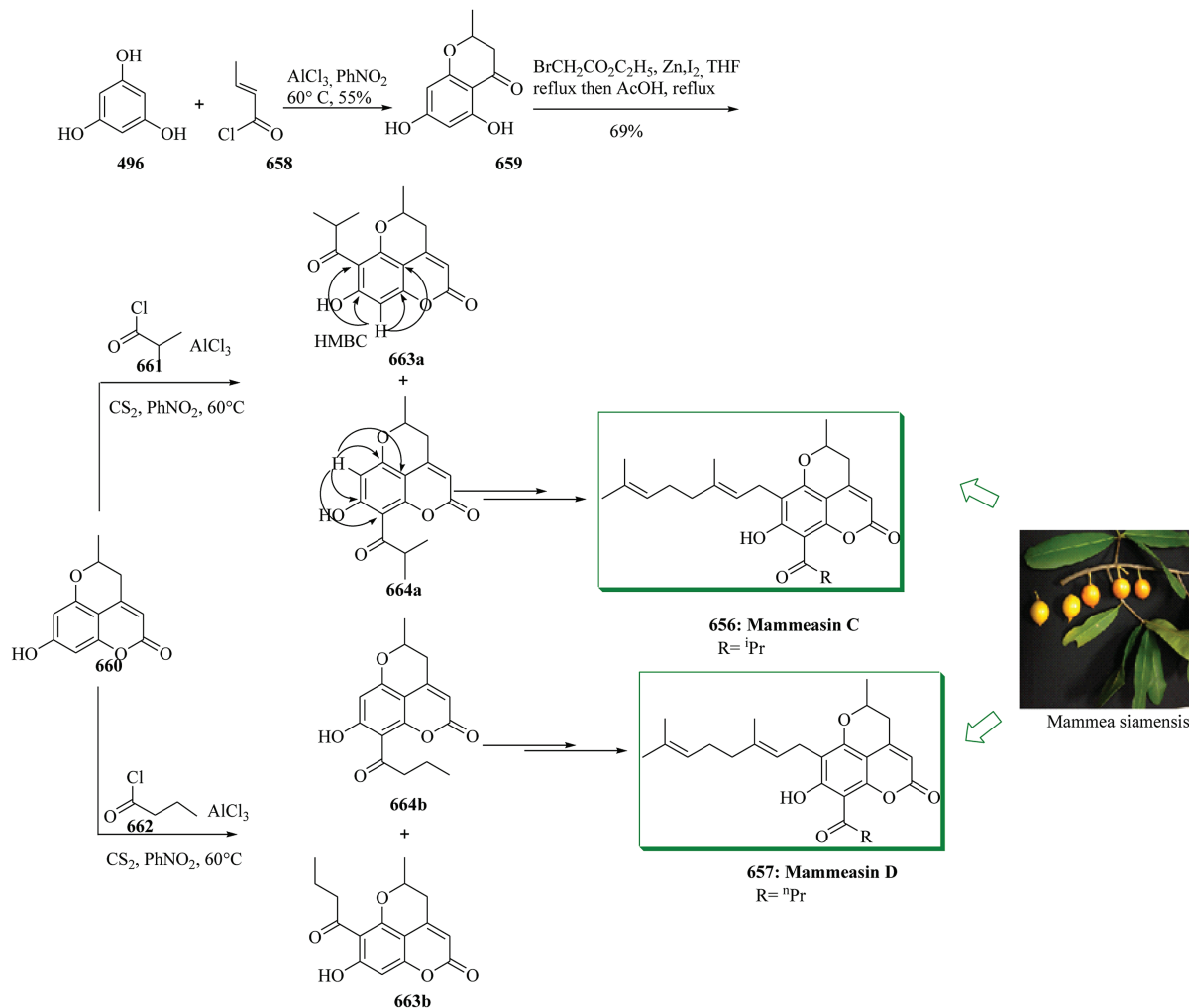
Isoflavone C-glycosides, in which the sugar scaffold is attached by a carbon–carbon bond directly to the isoflavone ring, are not simply hydrolyzed in acidic gastric juices, unlike O-glycosides and aglycone. These glycosides exhibit several biological properties, including radioprotective,⁶²⁵ anti-myocardial ischemic,⁶²⁶ mitogenic and colony-stimulating,⁶²⁷ and antidiabetic⁶²⁸ 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 AlCl₃ 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 cortical and 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





Scheme 143 Total synthesis of mammeasins C 656 and 657.

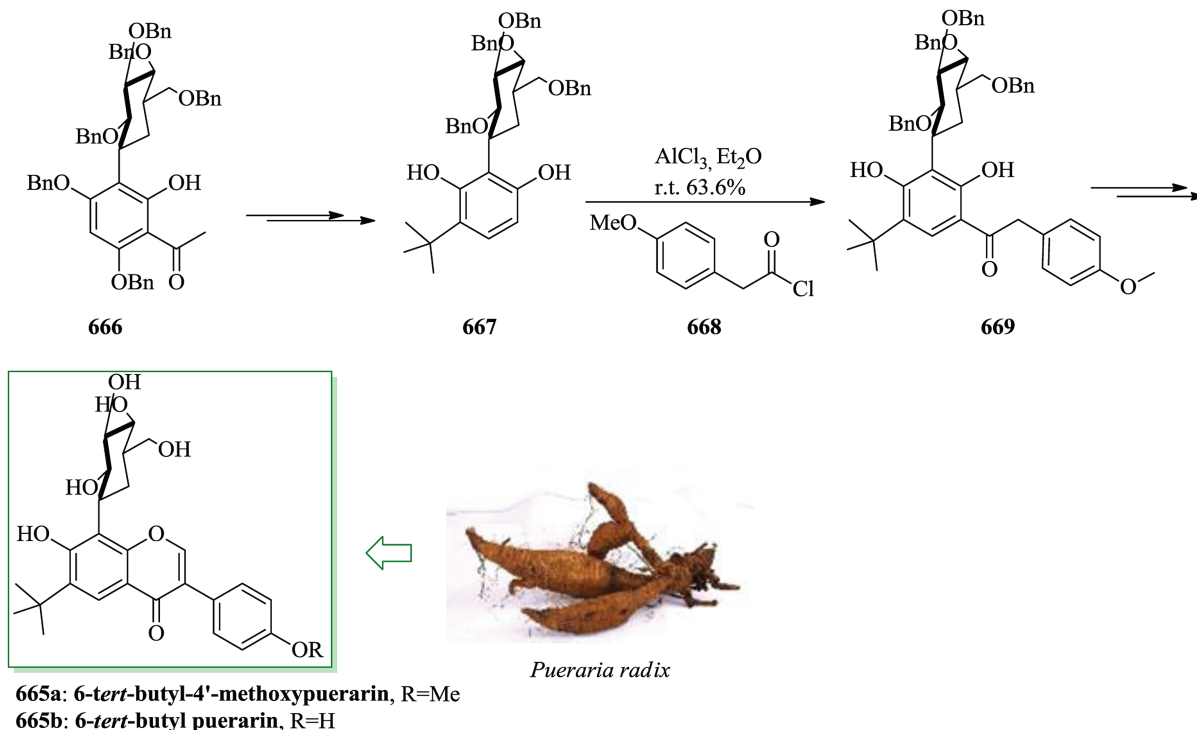
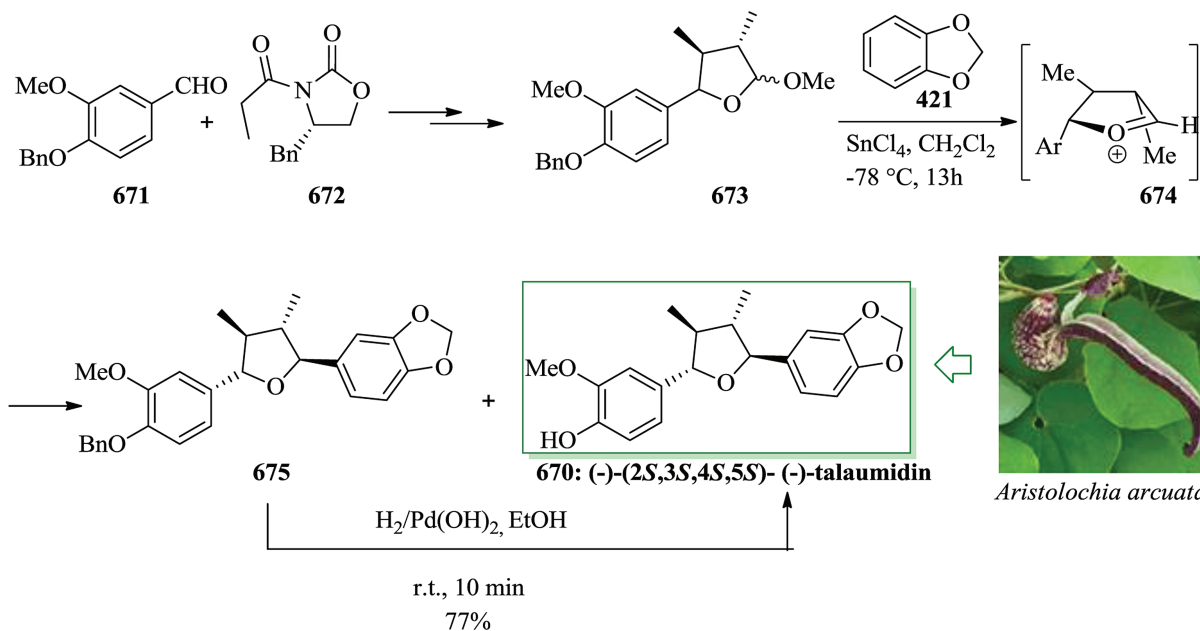
(-)-talaumidin **670** was started from the reaction between 4-benzyloxy-3-methoxybenzaldehyde **671** and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone **672** to provide five-membered acetal **673** via several steps. Then, FC-type arylation reaction of **673** with 1,2-methylenedioxybenzene **421** using tin(IV) chloride in dichloromethane afforded only the corresponding (5*S*)-**675** in 89% yield along with 2% of talaumidin **670**. Finally, debenylation 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*-methyljoubertamine, mesembrine, and its natural derivative the dihydro-*O*-methylsceletone, 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*-methyljoubertamine **681** are alkaloids present in *Scelletium tortuosum*. They were demonstrated to be very active serotonin reuptake inhibitors, potent at very low doses. The 4,5-dihydro-4'-*O*-methylsceletone **680b** is a simpler natural derivative of mesembrine

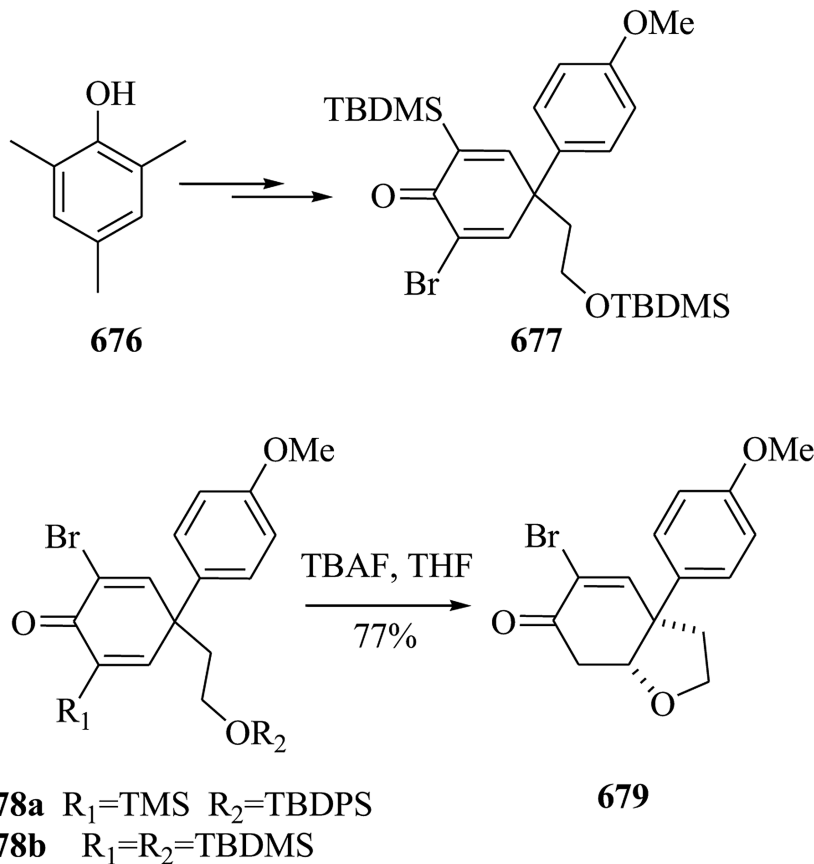


Scheme 144 Total synthesis of 6-*tert*-butyl-4'-methoxypuerarin **665a** and 6-*tert*-butyl puerarin **665b**.Scheme 145 Total synthesis of (-)-talaumidin **670**.

extracted from *Aptenia cordifolia*. Starting from 2-(4-hydroxyphenyl)ethanol **682**, total synthesis of mesembrine and 4,5-dihydro-4'-*O*-methylsclerenone was achieved *via* several steps in 86% yield. Furthermore, the transformation of 4,5-dihydro-4'-*O*-methylsclerenone, **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





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 acid 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

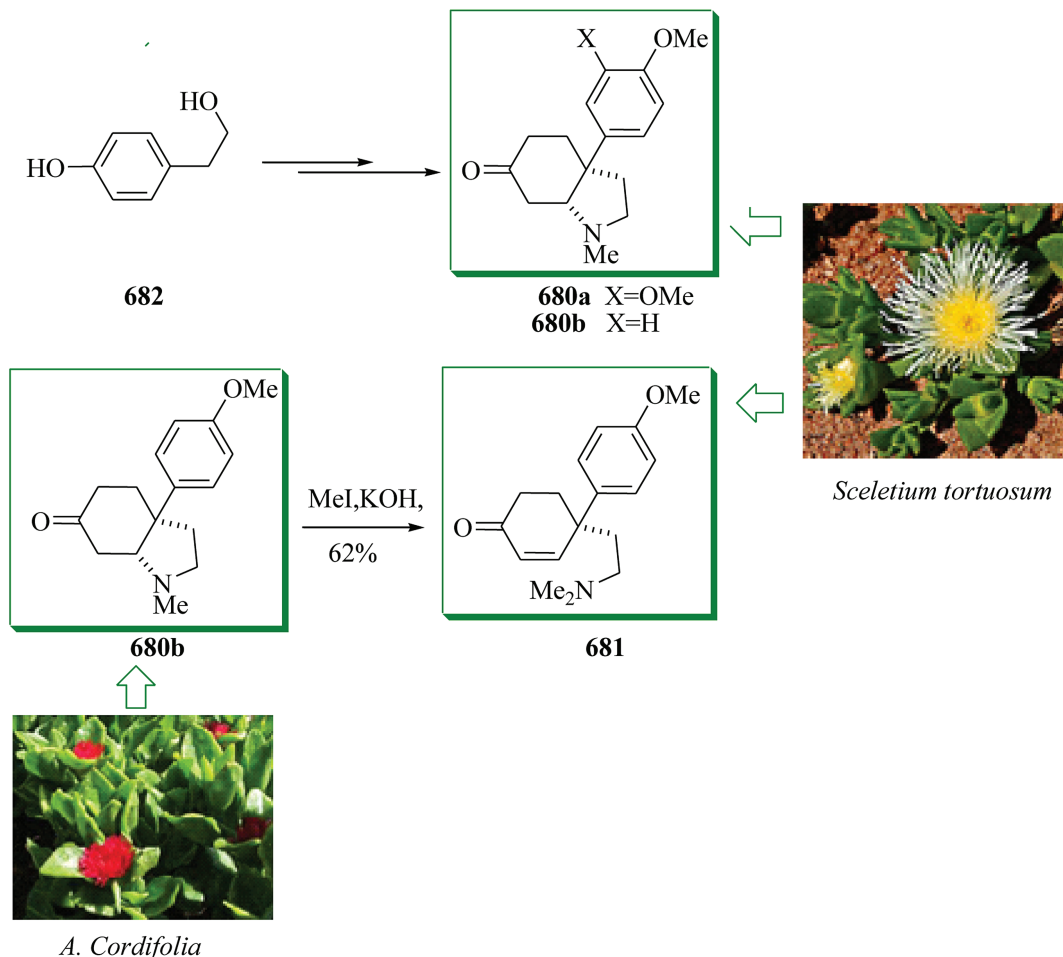
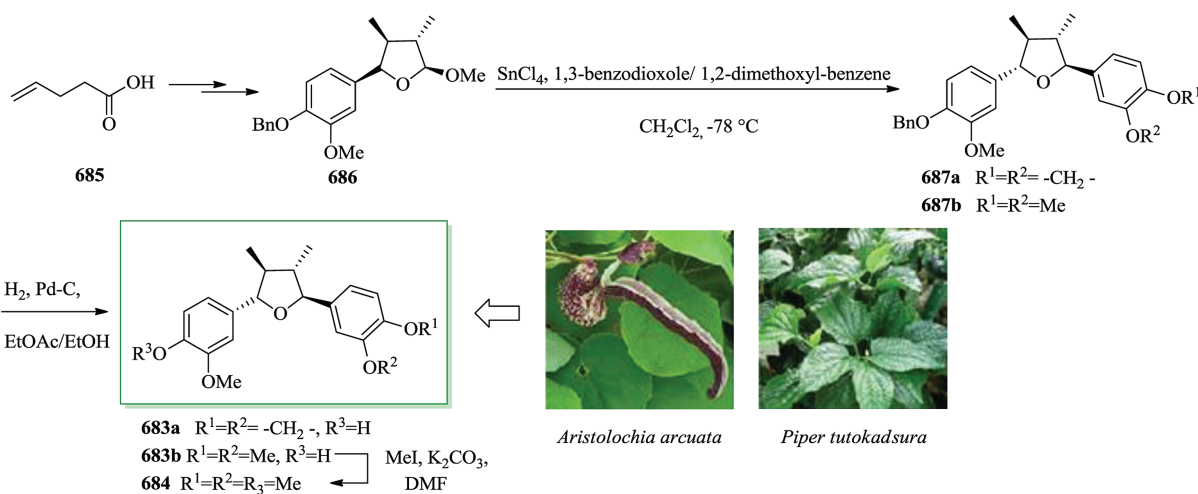
Extracts from the plants *Pycnanthus angolensis* and *Holostylis reniformis* were applied to treat malaria throughout Africa and Brazil, respectively.⁶⁴⁵ Extracted lignans from these and other plants,²⁵⁰ such as (–)-8'-*epi*-aristoligone **689**, have demonstrated promising antiplasmodial activity against 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*-aristoligone **698** and (–)-pycnanthulignene B **697**, were synthesized in 43% and 70% yield, respectively, from compound **700** via several steps (Scheme 150).⁶⁴⁶

Santalalin 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



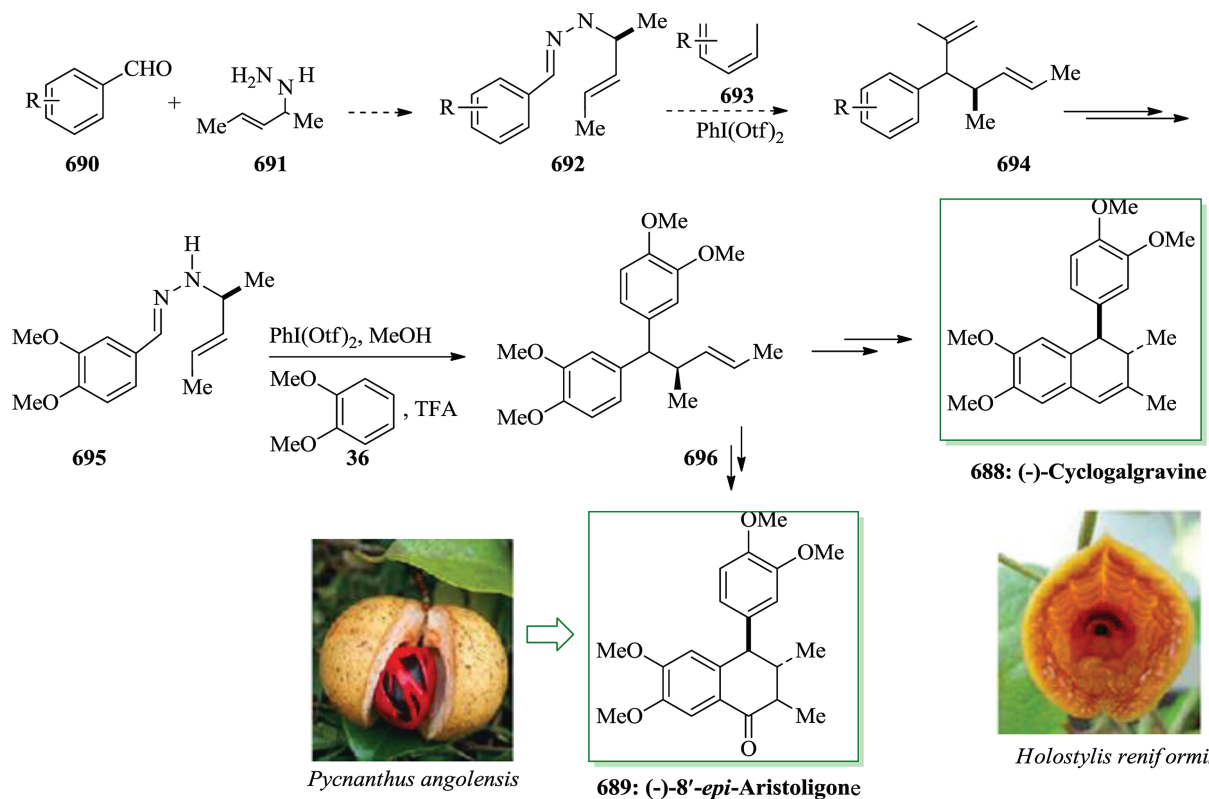
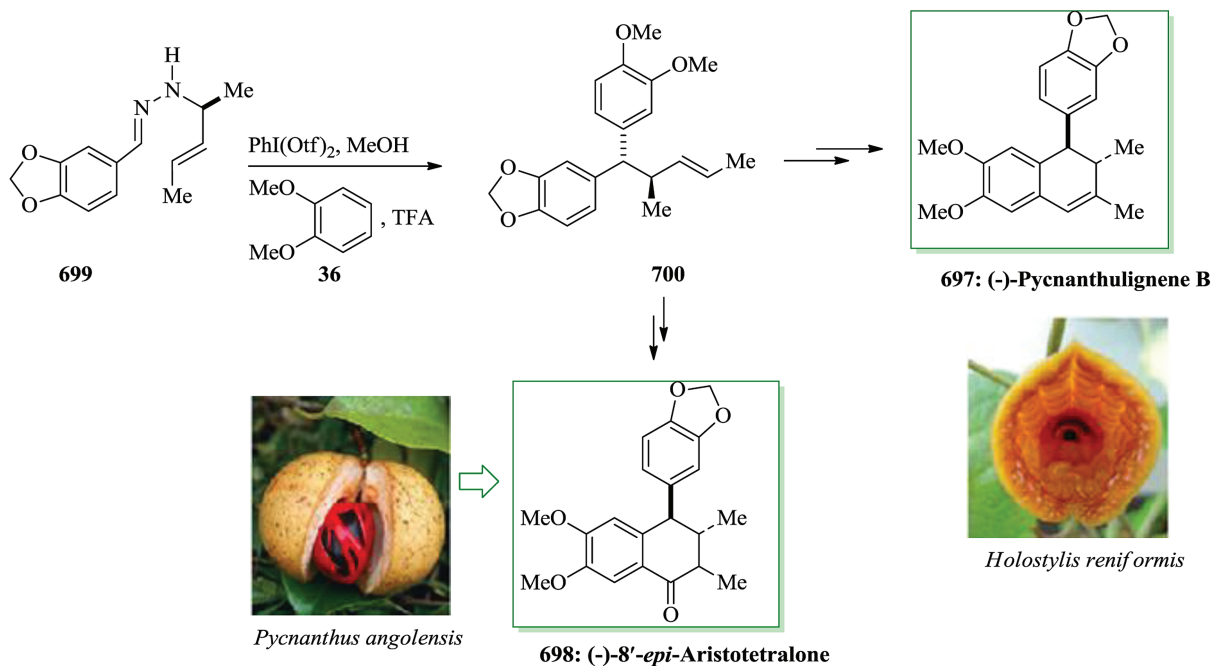
Scheme 147 The formation of 4,5-dihydro-4'-O-methylsceletenone **680b** into O-methyljoubertiamine **681**.Scheme 148 Total synthesis of (2)-talaumidin **683** and (2)-galbelgin **684**.

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 isoflavylum 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

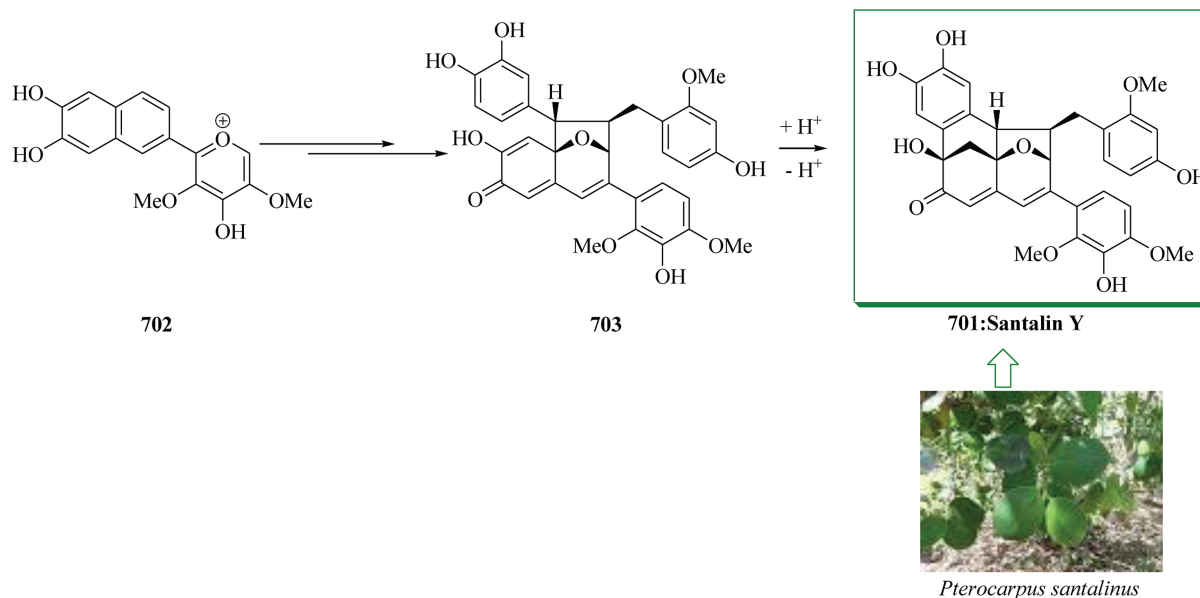


Scheme 149 Total synthesis of (-)-cyclogalgravin **688** and (-)-8'-epi-aristoligone **689**.Scheme 150 Total synthesis of (-)-pyncnanthulignene B **697** and (-)-8'-epi-aristotetralone **698**.

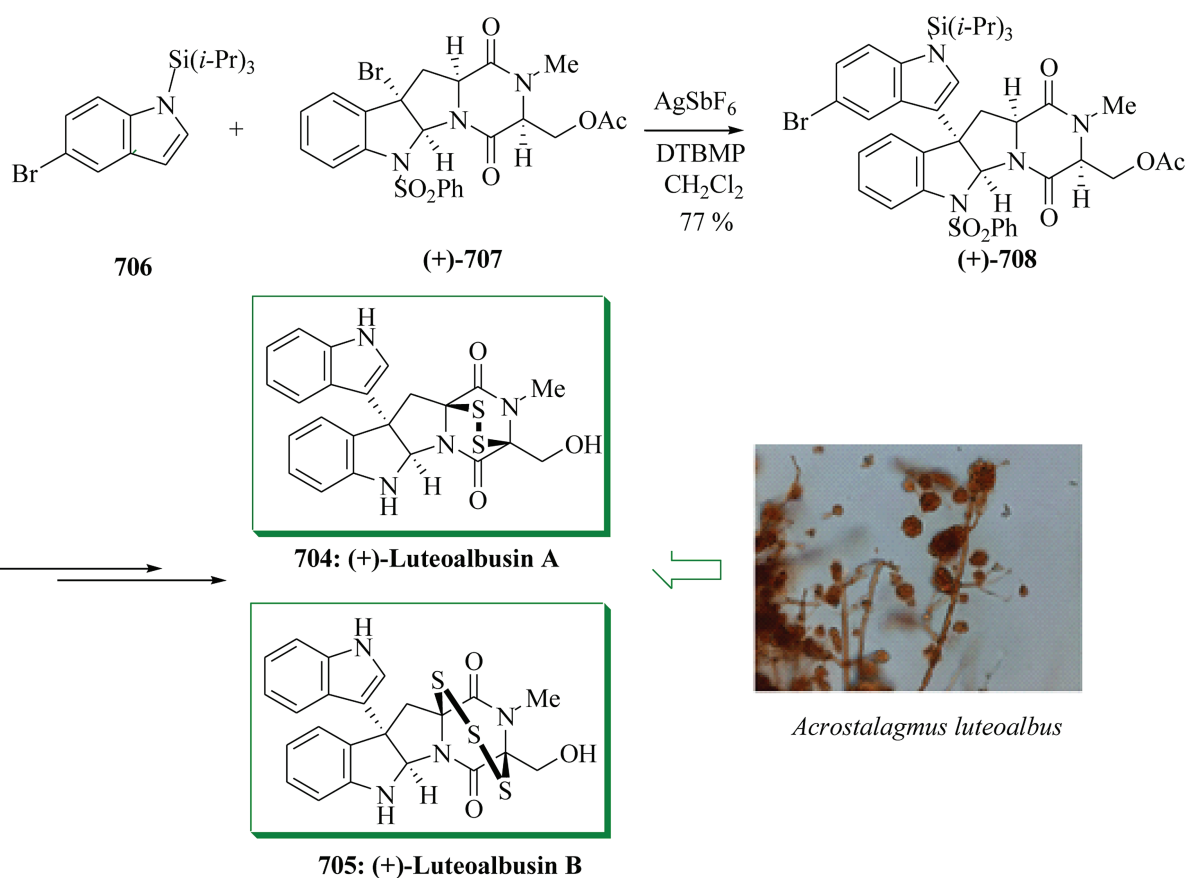
metabolites.^{162,268,649} Several members of this group of natural products share a cyclo-tryptophan unit and an eponymous epipolythiodiketopiperazine (ETP) substructure. Among them, (+)-luteoalbusin A **704** and (+)-luteoalbusin B **705** were isolated

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





Scheme 151 Total synthesis of santalin Y 701.

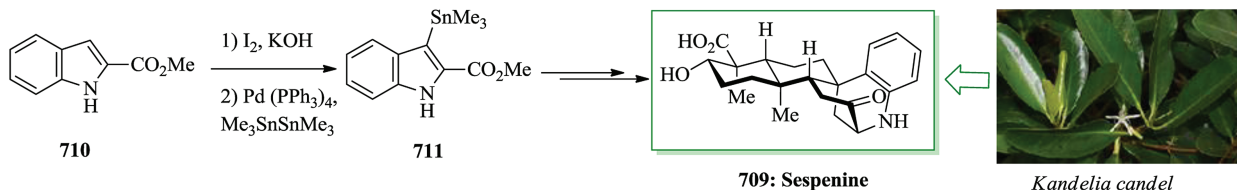


Scheme 152 Total synthesis of (+)-luteoalbusin A 704 and (+)-luteoalbusin B 705.

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





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(PPh₃)₄, Me₃SnSnMe₃]. 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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