Total synthesis: an enabling science

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Total synthesis is a topic strongly related to synthetic methodology developments and to natural product isolation or biosynthesis. Thus, thematic issues dealing with total synthesis in the *Beilstein Journal of Organic Chemistry* have naturally been published in these fields, such as "Transition-metal and organocatalysis in natural product synthesis" (edited by D. Chen and D. Ma) [1] or "Natural products in synthesis and biosynthesis" (edited twice by J. Dickschat) [2,3]. Previously, the early thematic issue "Indolizidines and quinolizidines: natural products and beyond" (edited by J. P. Michael) from 2007 [4] displayed some of the very first total syntheses ever published in the *Beilstein Journal of Organic Chemistry*, such as those of frog indolizidine alkaloids [5,6]. However, no thematic issue specifically related to total synthesis has been published before, and we thought it would be time to fill this gap. Although innovative developments are constantly needed to improve methods and strategy, keeping in mind the difficulty of performing transformations on highly functionalized compounds, the total synthesis of complex natural products is indeed mature in terms of efficiency, practicality, economy, and scalability. In short, it has become an enabling science.

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Total synthesis is the science of constructing molecules from simple starting materials. It often deals with complex molecular architectures that require a thorough retrosynthetic problem-solving analysis [7]. Total synthesis and the discovery of new synthetic methodologies have always been intimately related. Specific methodologies have often been developed to synthesize valuable compounds, while total synthesis has often been a pretext to demonstrate the value of a new synthetic reaction [8,9]. Old and recent achievements show that connections to other disciplines are important to the success of total synthesis and can be a source of new discoveries. Indeed, as a science allowing the preparation of useful functional compounds, it is strongly connected to biological and medicinal studies, while the development of natural-product-based tools for chemical biology often requires the construction of complex molecules [10,11]. Incidentally, the term "total synthesis" is not limited to natural products but also, sometimes, targets complex drugs [12,13]. Furthermore, it is possible to test biosynthetic hypotheses concerning natural products through synthetic approaches (biomimetic synthesis) [14]. In addition, total syntheses have also been achieved with enzymes, strengthening the links to biology [15].

Total synthesis is not limited to academic laboratories but rather also pursued in industry, where a particular efficiency and economy of tasks is of paramount importance [12], as illus-
trated in this thematic issue with the synthesis of pheromones [16]. This requires permanent technological progress. Thus, the recent boom of artificial intelligence, machine learning, and computational chemistry for retrosynthetic analyses and beyond foreshadows a renewed interest in harvesting increasingly complex synthetic strategies for industrial processes. Although it can be useful in operating routine processes, AI will not replace human creativity [17]. In terms of discoveries in organic chemistry, total synthesis is a fruitful feed, and serendipity has well been exploited. Even dead ends, yet always heartbreaking for synthetic chemists, still provide a wealth of useful information for the chemical community [18]. Finally, this is not to forget that organic chemistry, which is above all an experimental science, is performed daily by researchers in the laboratory, and some of these lives can be truly inspiring to current and future generations.

It was the aim of this thematic issue to cover any of the previous remarks. Thanks to the contributions of talented and enthusiastic authors, we were able to gather articles on total synthesis (Figure 1), not only illustrating the utility but also the vitality of this field.

I warmly thank all the authors of this thematic issue for their beautiful contributions. I also thank the Editorial Team of the Beilstein Journal of Organic Chemistry for their significant efforts in checking, formatting, and finally subtilizing all these articles.

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References

Figure 1: A summary of compounds targeted in this thematic issue.


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Synthesis of tryptophan-dehydrobutyrine diketopiperazine and biological activity of hangtaimycin and its co-metabolites

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Abstract

An improved synthesis for tryptophan-dehydrobutyrine diketopiperazine (TDD), a co-metabolite of the hybrid polyketide/non-ribosomal peptide hangtaimycin, starting from l-tryptophan is presented. Comparison to TDD isolated from the hangtaimycin producer Streptomyces spectabilis confirmed its S configuration. The X-ray structure of the racemate shows an interesting dimerisation through hydrogen bridges. The results from bioactivity testings of hangtaimycin, TDD and the hangtaimycin degradation product HTM222 are given.

Introduction

Hangtaimycin (1, Scheme 1) was first isolated from Streptomyces spectabilis and shown to possess weak antimicrobial activity against Bacillus subtilis [1]. Together with a structural revision from 29Z to 29E configuration and further biological evaluation of its hepatoprotective properties, its biosynthetic gene cluster was recently identified [2]. The biosynthetic machinery is composed of a hybrid trans-acyltransferase (trans-AT, [3,4]) polyketide synthase (PKS) and non-ribosomal peptide synthase (NRPS) [2] with a dehydrating bimodule [5,6] involved in the installation of the remaining Z-configured double bond within the polyketide backbone [7]. Furthermore, a cytochrome P450 monoxygenase was recently shown to be responsible for the oxidation of deoxyhangtaimycin (3), a compound with antiviral activity, to 1 [8]. The thereby installed
hemiaminal function is also the breaking point for 1 into a larger lactone-polyene peptide fragment and a smaller fragment HTM\textsubscript{222} (2, named after its molecular mass of 222 Da) [2]. Another hangtaimycin co-metabolite in S. spectabilis [9] is tryptophan-dehydrobutyryl diketopiperazine (TDD, 4) that was already isolated several decades before the discovery of 1, and likewise reported to have no antibacterial activity [9]. The initially published structure was that of (E)-4 [9], but later revised as that of (Z)-4. The same compound is also observed in S. olivaceus [10] and was reported to function as a competitive inhibitor of glutathione S-transferase [11], which may be a result of a thiol addition of glutathione to the Michael acceptor in 4. While the relative and absolute configuration of hangtaimycin have not yet firmly been established, 2 is known to be S-configured and is derived from an \textalpha-\text{-}alanine unit [2]. TDD (4) was recently suggested to be R-configured, containing a \textalpha-tryptophan unit, based on a comparison of the optical rotation of the isolated compound ([\alpha]_{D}^{24.5} = +10.0, c 1.1, 95\% EtOH [9]), in contrast to the later reported negative value mentioned above [1]. In order to resolve the confusion, we have reisolated 4 from S. spectabilis and report on an improved synthesis. Furthermore, the results from bioactivity tests with 1, 2 and 4 are discussed.

Results and Discussion
Synthesis of TDD
The first synthetic route towards 4 started from \textalpha-\text{-}tryptophan (5) that was converted through a standard transformation into the methyl ester 6 and then through sequential reductive aminations with benzaldehyde and paraformaldehyde into 7 (Scheme 2) [13]. Cleavage of the benzyl group by catalytic hydrogenation afforded 8 that was coupled with tert-butylxycarbonyl (Boc)-protected threonine using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) [14,15] and Hünig’s base to give 9. Cleavage of the Boc group with 5\% TFA followed by
basic treatment resulted in the cyclisation to the dioxopiperazine 10. Acetylation and subsequent treatment with LiClO₄ and DBU is a common strategy for the dehydration of serine and threonine units in peptides [16], but unfortunately the acetylation of 10 failed. Interestingly, the direct treatment of 10 with LiClO₄ and DBU under prolonged reaction times (3 days) resulted in the elimination of water. This reaction proceeded with a high diastereoselectivity (Z/E = 8:1), giving access to 4 in a satisfactory yield of 29% over 6 steps. However, the optical rotation of the obtained material showed only a small positive value ([α]D²⁵ = +1.9, c 0.27, EtOH), suggesting that 4 had undergone racemisation during the prolonged basic treatment with DBU in the last step. This was confirmed by HPLC analysis on a chiral stationary phase, showing that the obtained target compound 4 was nearly racemic (Figure 1A).

Because of the configurational instability of 4 under base treatment, we aimed at an approach for the final elimination step.
using milder conditions (Scheme 3). The newly developed synthesis started from 7 that was Boc-protected at the indole to yield 11. Removal of the benzyl group by catalytic hydrogenation to 12 was followed by coupling with benzylxycarbonyl (Cbz) and methoxymethyl (MOM)-protected threonine to give 13. Removal of the Cbz group by catalytic hydrogenation proceeded with spontaneous cyclisation to 14. With this material, the elimination of the MOM group smoothly proceeded by treatment with KH and 18-crown-6 in THF at 25 °C to 15, that upon removal of the Boc group with TFA and 1,3-dimethoxybenzene [17] gave (Z)-4 as a single diastereomer through anti elimination. Overall, TDD was obtained from l-tryptophan in a high yield of 37% over eight linear steps. HPLC analysis on a chiral stationary phase showed that 4 obtained through this second route was enantiomerically enriched (80% ee by peak integration, Figure 1B). Further improvement of the enantiomeric excess of 4 (90% ee, Figure 1C) was possible by performing the elimination reaction with 14 and KH and 18-crown-6 under ice cooling. This helped to suppress basic racemisation of 4, but required prolonged reaction times and gave a slightly diminished yield for 15 (70%), lowering the overall yield of TDD to 33% over eight steps. The major enantiomer of 4 obtained from this second route was identical to natural TDD (Figure 1D) which is thus S-configured, i.e., derived from l-tryptophan. Moreover, the olefinic double bond in 4 is Z-configured as indicated by a strong NOESY correlation between the amide NH and the neighbouring methyl group.

**The structure of TDD**

These findings not only challenge the originally assigned structure of (E)-4 [9] and confirm the structural revision of (Z)-4 [1], but also question the suggested structural revision that placed the N-methyl group at the other nitrogen of the dioxopiperazine moiety [12]. Moreover, the confusing situation about the absolute configuration and optical rotation are resolved through this work, clearly showing S-configuration for 4 that exhibits a negative optical rotation ([α]D25 = −15.5, c 0.102, MeOH). The reason for the varying melting points for 4 in the literature is unclear, but we noticed a pronounced difference in the crystallisation behaviour of racemic and enantiomerically pure 4. While (rac)-4 readily formed crystals (mp 134–136 °C), several attempts to crystallise (S)-4, a material that was obtained as a viscous oil, failed. The X-ray crystallographic analysis of (rac)-4 showed an interesting dimer interaction of its enantiomers through hydrogen bridges between the amide (NH-CO) groups (Figure 2, for crystallographic parameters cf. Supporting Information File 1, Table S1), that may support its easy crystallisation in comparison to enantiomerically enriched 4.

![Scheme 3: Second synthetic route towards TDD (Z)-4.](image-url)
Bioactivity testing

Previous reports have mentioned that TDD (4) exhibits no antibacterial activity, without providing information about the test organisms used [9]. For this reason, and because of the above-mentioned confusions about the true nature of 4 in the previous literature, the bioactivity of natural (enantiomerically pure) 4 isolated from S. spectabilis was reinvestigated. For comparison, synthetic (rac)-(Z)-4 and its stereoisomer (rac)-(E)-4 (Scheme 2) were included in the bioactivity testing, as well as the previously synthesised HTM222 (2) and 1 isolated from S. spectabilis. Neither 2 nor any of the stereoisomers of 4 showed antibacterial effects against a panel of Gram-positive and Gram-negative organisms (Supporting Information File 1, Table S2). Only 1 exhibited concentration-dependent growth retardation of the Gram-positive species Bacillus subtilis 168 and Acinetobacter baumannii 09987 (Figure 3A and B). However, growth inhibition was not strong enough to yield a clear MIC value, as the determination of a MIC requires complete

Figure 3: Bioactivity testing with hangtaimycin (1). A) Growth retardation of model species B. subtilis 168 and of B) nosocomial pathogen A. baumannii 09987 monitored by recording the turbidity increase of growing culture aliquots exposed to a concentration series of 1 every 10 min over 24 h. An increase in the optical density at 600 nm (OD\textsubscript{600}) reflects biomass production. At concentrations of ≥64 µg/mL 1 precipitated, leading to elevated OD\textsubscript{600} values at the beginning of the experiment that were unrelated to growth. The curves reflect the mean values of three separate cultures and standard deviations are depicted by black bars. C) MIC assay against E. coli. The MIC is defined as the lowest concentration of an antibacterial agent inhibiting visible bacterial growth (no turbidity detected by the naked eye) after overnight incubation. Only when the outer membrane was permeabilised by polymyxin B nonapeptide (PMBN), 1 inhibited growth of E. coli sufficiently to yield a clear MIC. GC, growth control (no inhibitor), SC, sterile control (no bacteria), DMSO, culture medium supplemented with 1% DMSO, reflecting the DMSO concentrations in the hangtaimycin-containing samples.
inhibition of visible bacterial growth and residual growth occurred up to the highest concentration tested (256 µg/mL). In the Gram-negative Escherichia coli, the outer membrane protects the cells from the impact of I. When the integrity of the outer membrane was compromised by adding the outer-membrane permeabilizing polymyxin B nonapeptide (PMBN, 10 µg/mL), a MIC of 128 µg/mL was achieved (Figure 3C).

We also investigated whether the reported inhibition of glutathione S-transferase [11] is a result of a Michael addition of glutathione to TDD. However, no reaction occurred between glutathione and TDD in DMF/H2O (1:1) under prolonged stirring at room temperature. Also the addition of base (NEt3) did not promote the reaction. Therefore, the mode of action of TDD towards glutathione S-transferase needs further investigation.

**Conclusion**

We have established an efficient synthesis of TDD that makes this compound available from L-tryptophan with a high yield of 33% (90% ee) over eight linear steps, establishing S configuration for the natural product from S. spectabilis that is likely reflected in the corresponding portion of hantaimycin. A key step in the synthesis is the elimination of a MOM group using KH and 18-crown-6 that must be carried out with care, because TDD easily undergoes racemisation under basic conditions. The X-ray analysis showed an interesting dimer interaction of the enantiomers in racemic TDD through hydrogen bridges, that may support its much easier crystallisation in comparison to enantiomerically pure or enriched TDD. In fact, the obtained viscous oils did not crystallise, suggesting that the previously reported melting point of 121–123 °C [9] that is close to our measured point for (rac)-4 (134–136 °C) may have been measured for isolated material after it had undergone (partial) racemisation. The reported inactivity of 4 against bacteria was confirmed in this study, and also 2 is an inactive metabolite of S. spectabilis, while for I moderate growth retardation against A. baumannii and B. subtilis, and growth inhibition against PMBN-treated E. coli was observed. However, the low activity of I in these assays suggests that the natural function of this structurally remarkable compound awaits future clarification.

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**Supporting Information**

Supporting Information File 1

Experimental, analytical and X-ray data as well as copies of NMR spectra.

[https://www.beilstein-journals.org/bjoc/content/supporting/1860-5397-18-120-S1.pdf]

**References**


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Abstract

This review summarizes examples for the application of vicinal ketoesters such as α-ketoesters, mesoxalic esters, and α,β-diketoesters as key intermediates in the total synthesis of natural products utilizing their electrophilic keto group as reactive site. Suitable key reactions are, e.g., aldol additions, carbonyl ene reactions, Mannich reactions, and additions of organometallic reagents. The vicinal arrangement of carbonyl groups allows the stabilization of reactive conformations by chelation or dipole control.

Introduction

Vicinal ketoesters contain a carbonyl group adjacent to an ester group. One keto group results in α-ketoesters 1 and two vicinal keto groups lead to α,β-diketo esters 2 (Scheme 1). On the other hand, two carboxylic acid functionalities adjacent to a keto group result in mesoxalic diesters 3, or mesoxalic ester amides 4. The increased electrophilicity of the keto group and the high density of these complex functional groups make such structures attractive as key intermediates for the total synthesis of natural products [1]. Thus, the high electrophilicity of the central carbonyl group in α,β-diketoesters 2 allows the formation of stable hydrates 5. In case of an enolizable position enolization (2 → 6) is facilitated.

The chemistry of vicinal polycarbonyl compounds such as vic-diketoesters has been investigated in depth by Wasserman, Parr [2] and Gleiter, Rubin [3]. Important contributions for the use of α,β-diketoesters in stereoselective transformations came from Doyle’s group [4,5]. One remarkable example is the diastereoselective intramolecular aldol addition of ketones such as 7 (Scheme 2) [5]. Brønsted-acid catalysis leads via a transition state 8 to the aldol 9, while the use of chelating Lewis acids results via 10 in the epimeric aldol 11.

This review is a collection of total syntheses of natural products where vicinal keto esters were used as key intermediates.
Scheme 1: Structures of vicinal ketoesters and examples for their typical reactivity.

2. **Mesoxalic diester and ester amides** as key intermediates: (+)-awajanomycin, (−)-aplaminal, cladoniamide G.
3. **α,β-Diketoesters** as key intermediates: preussochromones E and F.

**Review**

1. **α-Ketoesters** as key intermediates: (+)-Euphorikanin A

In the final step of the synthesis of (+)-euphorikanin A (16), an ingenane-derived diterpenoid with a 5/6/7/3-fused tetracyclic carbon skeleton, Carreira et al. used an intramolecular nucleophilic addition of an alkenyl metal species to the α-ketoester 15 (Scheme 3) [6]. The ketoester 15 was synthesized by a chiral pool approach starting from (+)-3-carene derived cycloheptenone 13 [7,8] and aldehyde 12 (accessible from (R)-Roche ester [9]) via the γ-lactone 14. The ketoester moiety was established by an enolate hydroxylation with Davis’ oxaziridine and subsequent oxidation using Dess–Martin periodinane. Initial attempts for the key step (15 → 16) like a Nozaki–Hiyama–Kishi reaction failed, but lithium–halogen exchange using t-BuLi at low temperatures gave the desired vinyllithium intermediate I which successfully added to the desired α-carbonyl group.

(−)-**Preussochromone A**

In 2020, the Koert group disclosed the synthesis of (−)-preussochromone A (24), a fungal metabolite with a highly substituted tetrahydrothiopyran core annulated to a chromene [10]. The tetrahydrothiopyran ring was closed by a Lewis-acid-promoted cycloisomerization of the α-ketoester 22, which can be described as a Friedel–Crafts-type reaction or an aldol reaction of an S,O-ketene acetal (Scheme 4). The re-
Scheme 3: Synthesis of euphorikanin A (16) by intramolecular, nucleophilic addition [6].

Required ketoester 22 was synthesized from sulfonylchromenone 20, accessible from dihydroxyacetophenone 19 and thiol 18 derived from known alcohol 17 [11,12]. DMP oxidation of α-hydroxyester 21 and subsequent cycloisomerization led to the desired cyclization product 23 via transition state II in a dr of 5:1. Final deprotection gave preussochromone A (24).
Scheme 5: Diastereoselective, intramolecular aldol reaction of an α-ketoester 28 in the synthesis of (−)-preussochromone D (30) [13,14].

(--)-Preussochromone D
A similar approach was chosen in the synthesis of the structurally related natural product preussochromone D (30) reported by Koert et al. [13]. The synthesis commenced with the efficient production of alcohol 26 from 5-hydroxy-4H-chromen-4-one (25, Scheme 5) [14]. The ketoester moiety was build up via oxidation and nucleophilic addition of methyl diazoacetate, yielding alcohol 27. Subsequent oxidation gave α-ketoester 28 which was used in an intramolecular, Lewis acid-mediated aldol reaction, presumably via tridentate complex transition state III, to give diol 29 as a single diastereomer. Inversion of the secondary alcohol and deprotection gave preussochromone D (30).

(--)-Jiadifenoxolane A
The Illicium sesquiterpenes containing a seco-prezizaane carbon framework are highly oxidized, structurally complex natural products. Maimone et al. published a remarkable synthesis of the Illicium sesquiterpene (−)-jiadifenoxolane A (36), starting from the abundant sesquiterpene (+)-cedrol (31, Scheme 6) [15]. Through a series of finely tuned CH oxidations, cedrol (31) was converted to the lactone 32. In a single step, using Riley oxidation conditions, the methyl ketone moiety was transferred to the α-ketoester 33. Reduction, lactonization, and elimination gave the ketoesters-derived enol 34. Oxidation of the latter compound to the α-keto-β-hydroxy ester IV using DMDO and subsequent heating in PhCF₃ triggered an α-ketol rearrangement which led to ketol V. Diastereoselective reduction gave α,β-dihydroxyester 35 which was converted to (−)-jiadifenoxolane A (36) in five further steps.

Palau’amine
Palau’amine (45), a dimeric pyrrole-imidazole-bisguanidine alkaloid, was first isolated from the marine sponge Stylotella aurantium in 1993 [16,17]. It received considerable attention from the synthetic community because of its broad range of biological activities and complex structure. In an early endeavour of L. Overman et al. in 1997 [18] towards the originally proposed structure of palau’amine (44), a [3 + 2]-dipolar cycloadition of α-ketoester 41 and the thiosemicarbazide 42-derived azomethine imine VI to the triazacyclopenta[cd]pentalene 43 was utilized as a key step (Scheme 7) [18-21].

The α-ketoester 41 was accessible from amide 38, which in turn was obtained from allylic alcohol 37. Oxidation and Horner–Wadsworth–Emmons reaction with phosphonate 39 delivered the silyl enol ether 40, which was deprotected and
Scheme 6: Synthesis of an α-ketoester through Riley oxidation and its use in an α-ketol rearrangement in the synthesis of (+)-jiadifenoxolane A (36) [15].

(-)-Hopeanol

In the synthesis of the polyphenolic natural product (-)-hopeanol (59), Nicolaou et al. used an α-ketoester moiety as a precursor for an intramolecular Friedel–Crafts cyclization (Scheme 9) [24]. Therefore, phenylacetaldehyde 52 was converted to the alcohol 53, which was esterified with the α-ketoacid 54 to give ketoester 55. Grignard addition to the keto carbonyl and subsequent TBS deprotection delivered the tertiary alcohol 56, which was dehydroxylated to the diastereomeric cations VIII and IX. Friedel–Crafts reaction gave diastereomeric lactones 57 and 58. The major diastereomer 58 could be converted to the complex polyphenol (-)-hopeanol (59) in seven further steps.

(+)-Camptothecin

In the formal synthesis of the pentacyclic, antiproliferative quinoline alkaloid camptothecin (65), Peters et al. used an α-ketoester moiety in an auxiliary controlled approach towards the only stereogenic center present in the natural product (Scheme 10) [25]. First, the ketoacid 60 was esterified with 8-phenylmenthol (61) to yield the α-ketoester 62, followed by nucleophilic addition of isopropenylmagnesium bromide to give α-hydroxyester 63 in excellent yield and diastereoselectivity. Eight additional steps gave the bicyclic compound 64 which was already known from previous camptothecin syntheses.
Isoretronecanol
The α-ketoester moiety can also be used in photochemical reactions, as shown by Gramain et al. in the synthesis of the pyrrolizidine alkaloid (rac)-isoretronecanol (69, Scheme 11) [26]. A Claisen condensation of the lithium enolate of N-acetyl-pyrrolidine (66) with diethyl oxalate gave the ketoester 67. Irradiation of compound 67 with a medium pressure mercury lamp in Pyrex® glassware triggered a 1,6-HAT leading to biradical X which combined to the racemic pyrrolizidine 68 as a 1:1 mixture of diastereomers. Three more steps gave the target compound 69 in 31% overall yield.

Corynoxine
Hiemstra et al. used the α-ketoester moiety for different purposes in the syntheses of a range of oxindole alkaloids. The start of the synthesis of (rac)-corynoxine (76) was the conversion of tryptamine (70) to oxindole 71, which was used in a chemoselective Mannich reaction with aldehyde 72, introducing the α-ketoester moiety (Scheme 12) [27]. The major trans-isomer 73 was further converted to the natural products corynoxine and rychnophylline. The minor cis-isomer 74 was used in an intramolecular Tsuji–Trost reaction, where the ketoester served as a nucleophile, which build up the piperidine ring and selectively set the desired cis-substitution. Subsequent transesterification gave the α-ketoester 75, which was used in a Wittig reaction. The undesired Z-configured double bond was isomerized to the E-alkene and final hydrogenation delivered corynoxine (76).

(+)-Gracilamine
The Mannich reaction was also used by Nagasawa et al. as a key step in the synthesis of (+)-gracilamine (83), a penta-
Scheme 8: Intramolecular diastereoselective carbonyl-ene reaction of an α-ketoester in the synthesis of jatropane diterpenoids [22].

Scheme 9: Grignard addition to an α-ketoester and subsequent Friedel–Crafts cyclization in the synthesis of (-)-hopeanol (59) [24].
cyclic alkaloid isolated from the plant *Galanthus gracilis*, (Scheme 13) [28]. The synthesis started from readily available sesamol (79) and imine 78 which gave the advanced intermediate 80 in ten steps. An intramolecular Mannich reaction of compound 80 with α-ketoester 81 furnished compound 82 with the last ring of the target (+)-gracilamine (83), which was accessible after two further steps.

(−)-Irofulven
Irofulven (87) is a highly cytotoxic, semisynthetic drug obtained from the illudin sesquiterpene family. In a de novo synthesis towards (−)-irofulven (87), Movassaghi et al. used a CuII-catalyzed asymmetric aldol reaction of O-silyl ketene S, O-acetal 84 with methyl pyruvate (85) to enantioselectively install the crucial tertiary TMS-protected alcohol in ester 86 (Scheme 14) [29]. Eleven further steps gave (−)-irofulven (87).

2. Mesoxalic diesters and ester amides as key intermediates
(+)-Awajanomycin
Diethyl mesoxalate (90a) is a valuable building block due to the high density of carbon atoms in high oxidation states. As a victricarbonyl compound, its central keto group is an especially potent electrophile. The Koert group used this reactivity in their synthesis of (+)-awajanomycin (92), a marine natural product with a γ-lactone-δ-lactam core structure (Scheme 15) [30,31]. Key step was an asymmetric allylboration of diethyl mesoxalate (90a) with boronate 89, which was easily accessible through a Matteson homologation of dichloromethyl boronate 88. The reaction of (Z)-alkenyl boronate 89 with mesoxalate 90a delivered product 91 through the six-membered transition state XI. Eight further steps accomplished the total synthesis of (+)-awajanomycin (92).
Scheme 12: α-Ketoester as nucleophile in a Tsuji–Trost reaction in the synthesis of (rac)-corynoxine (76) [27].

Scheme 13: Mannich reaction of an α-ketoester in the synthesis of (+)-gracilamine (83) [28].

(--)-Aplaminal

Dimethyl mesoxalate (90b) was used by Smith and Liu in the synthesis of the cytotoxic metabolite (--)-aplaminal (96), which was isolated from the sea hare Aplysia kurodai [32]. The natural product is characterized by a triazabicyclo[3.2.1]octane, where each bridge possesses a nitrogen atom. The synthesis commenced with N-Boc-serine (93) which was converted to secondary aniline 94 in three steps (Scheme 16). Subsequent deprotection and condensation with dimethyl mesoxalate (90b) gave imidazolidine 95. With compound 95 at hands, five further steps gave (--)-aplaminal (96) in a good overall yield of 19%.

Cladoniamide G

The unsymmetrical mesoxalic acid amide 102 was used by Koert et al. in the racemic synthesis of the bisindole alkaloid (rac)-cladoniamide G (103, Scheme 17) [33]. The synthesis
Scheme 14: Enantioselective aldol reaction using an α-ketoester in the synthesis of (-)-irofulven (87) [29].

Scheme 15: Allylboration of a mesoxalic acid ester in the synthesis of (+)-awajanomycin (92) [30,31].

Scheme 16: Condensation of a diamine with mesoxolate in the synthesis of (-)-aplaminal (96) [32].
Scheme 17: Synthesis of mesoxalic ester amide 102 and its use in the synthesis of (rac)-cladoniamide G (103) [33].

started with benzaldehyde 97 and indole 99 which were converted to the indole building blocks 98 and 100, respectively. These were connected to bisindole 101, which reacted with mesoxalic ester amide 102 in a Friedel–Crafts reaction followed by a spontaneous lactamization to give (rac)-cladoniamide G (103). The mesoxalic ester amide 102 was synthesized from malonyl chloride 104 through amidation and Regitz diazotransfer, yielding diazo compound 105. Subsequent oxidation and dehydration of the resulting hydrate through short-path distillation gave the desired vic-tricarbonyl compound 102.

3. α,β-Diketoesters as key intermediates

Preussochromone E and F

In a short and enantioselective total synthesis of preussochromone E (110) and F (109), Koert et al. used the complex vic-tricarbonyl compound 108 to set two stereogenic centers and correct one via an intramolecular aldol addition (108 → 109; Scheme 18) [34]. The vic-tricarbonyl compound 108 was synthesized via DMDO oxidation from α-diazo-β-ketoester 107, which was easily accessible from 5-methoxy-4H-chromen-4-one (106). The thermodynamically controlled basic intramolecular aldol addition of compound 108 using the bulky amine base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) led to epimerization of the methyl group and cyclization, giving preussochromone F (109) as single isolable diastereomer probably via transition state XII. The subsequent reduction of compound 109 gave preussochromone E (110).

Conclusion

The variety of examples prove that vicinal ketoesters are valuable synthetic intermediates for the synthesis of complex target structures such as natural products. α-Ketoesters, mesoxalic esters, and α,β-diketoesters can be used bearing an electrophilic keto group as reactive site. The vicinal arrangement of carbonyl groups allows the stabilization of reactive conformations by chelation or dipole control. Suitable key reactions are e.g., aldol additions, carbonyl ene reactions, Mannich reactions, and addi-
Scheme 18: The thermodynamically controlled, intramolecular aldol addition of a vic-tricarbonyl compound in the synthesis of preussochromones E (110) and F (109) [34].

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Enantioselective total synthesis of putative dihydrorosefuran, a monoterpen with an unique 2,5-dihydrofuran structure

Irene Torres-García, Josefa L. López-Martínez, Rocío López-Domene, Manuel Muñoz-Dorado, Ignacio Rodríguez-García and Miriam Álvarez-Corral*

Abstract
An original synthesis of the structure of dihydrorosefuran, a compound allegedly identified in *Artemisia pallens* and *Tagetes mendocina*, has been developed. The key steps in the five-step 36% overall yield synthesis are a CpTiCl₃ mediated Barbier-type allenylation of a linear aldehyde and the formation of a 2,5-dihydrofuran scaffold through a Ag(I)-mediated cyclization. Neither of the reported spectral data for dihydrorosefuran match those of the synthetic product, suggesting that the isolated compound from *Tagetes mendocina* is in fact the natural product rosiridol, while the real structure of the product from *Artemisia pallens* remains unknown.

Introduction
*Artemisia pallens* is an aromatic plant from southern India whose essential oil, known as Davana oil, has shown increasing interest mainly for its use in some beverages, cakes, pastries, etc., as well as in the perfumery industry [1]. In addition, *A. pallens* has been used in Indian traditional medicine (Ayurveda) for the treatment of measles, cough, cold, depression, diabetes, and high blood pressure [2]. More recently other biological activities have been reported, such as the blood glucose lowering effect of *A. pallens* [3,4], and its anti-asthmatic potential [5].

A component responsible for the fresh and floral odor of the essential oil was isolated from Davana oil and was assigned as a 2,5-dihydrofuranic monoterpenoid (compound 1 in Scheme 1) and named dihydrorosefuran [6-8]. Furthermore, the same structure was attributed to an isolated substance from the Argentinean herb *Tagetes mendocina* [9], although not all of its spectroscopic features did match point by point with those previously reported. This made us think that this could be a case of misassigned natural product [10], hence we decided to perform its total synthesis.
Results and Discussion

Our synthetic strategy is based on two metal-mediated steps (Scheme 1). In this way, we thought that the 2,5-dihydrofuran structural motif that is found in the target molecule 1 could be prepared through a Ag(I)-induced intramolecular addition of the hydroxy group to the terminal double bond of the allene in compound 3. Another key step is the Ti(III)-mediated straightforward synthesis of this α-hydroxyallene, which could be achieved through a regioselective Barbier-type coupling of a propargylic halide (1-bromo-2-butyne) with the aldehyde 4 mediated by the organometallic half-sandwich complex [CpTiIIICl2] [11,12].

Following this retrosynthetic proposal, our route starts from ethyl 4-oxobutanoate (4) [13] which was prepared by ozonolysis of commercially available ethyl pent-4-enoate (Scheme 2). Coupling of the aldehyde 4 with 1-bromobut-2-yn (in the presence of CpTiIIICl2 (generated in situ by reduction of CpTiCl3 with Mn) afforded α-hydroxyallene 3. We have recently described that this Barbier-type reaction affords α-hydroxyallenes as major products, mixed with smaller amounts of homopropargylic alcohols, either if the reaction is performed with stoichiometric amounts of CpTiCl3 or if catalytic amounts are used [12]. However, using the particular substrates in this approach, the allenic compound 3 was exclusively formed, in a satisfactory 81% yield [14]. It is also important to control the pH during the reaction workup, as some contamination of the product with lactone 5 can arise at low pH values, which goes in detriment of the yield. The 2,5-dihydrofuran ring in target compound 1 was obtained through a Ag(I)-mediated intramolecular addition of the hydroxy to the allene group, a process that transformed allene 3 into compound 2. The isopropenyl residue of the target compound 1 was assembled through a two-step sequence. The first one was the addition of an excess of methylmagnesium bromide to the ester 2, that completed the carbon skeleton. The second step was the pH-controlled regioselective dehydration of the tertiary alcohol 6 with amberlyst-15® leading to the monoterpene 1. Other systems tested for the elimination of the hydroxy group in 6 were pyridinium p-toluenesulfonate (PPTS) and camphorsulfonic acid (CSA), that gave poorer results, failing to afford a single product. On the other hand, lactone 5 could also be transformed into alcohol 6 through a simple change in the order of the reactions: addition of methylmagnesium bromide to 5 afforded 7, which was then transformed into 6 by the Ag(I)-mediated cyclization (Scheme 2).

Once we had synthesized racemic compound 1, we designed a chiral version using a stereoselective kinetic resolution of allenol 3 via lipase AK-catalyzed acetylation [15]. In this way, unaltered, (−)-hydroxyallene 3 could be separated from (+)-acetyl derivative 9 through standard column chromatography.
phy (Scheme 3). Enantiomeric excesses of (−)-3 and (+)-9 were determined by chiral HPLC analyses. Analysis of the NMR data of the Mosher’s derivatives of 8 suggested (S) configuration for the alcohol (−)-3 [16].

On the other hand, enantiopure acetate (+)-(R)-9 was transformed into diol (+)-(R)-7 by the addition of an excess of MeMgBr. Finally, these enantiopure compounds, α-hydroxyallene (−)-(S)-3 and diol (+)-(R)-7, can be used to prepare both enantiomers of compound 1 following the procedures shown in Scheme 2.

Unfortunately, once the racemic synthesis was successfully completed and the chiral design was fulfilled, it was found that the spectroscopic data of compound 1 did not match neither with those published for the allegedly dihydrorosefuran isolated from Artemisia pallens nor with those reported for the compound from Tagetes mendocina (see Table 1 and Table 2). The $^{13}$C NMR data of compound 1 are quite similar to those of the natural product isolated from T. mendocina, except for the signals of the oxygenated carbons (C2 and C5). The same behavior pattern can be observed in the $^1$H NMR data. This made us think that the natural product of T. mendocina could have an acyclic skeleton instead of a dihydrofuran one. For this reason, we propose this compound should be the diol called rosiridol (Table 1), a substance that has been isolated from other natural sources [18,19], whose structure was also confirmed by total synthesis some years ago [20]. Comparison of NMR data (Table 1) confirmed the initial suspicion. We are still intrigued about the real structure of the natural product isolated from A. pallens. However, it must be considered that this product was elucidated using low frequency NMR machines, which suggests that further research on the chemical composition of this oil is needed.

![Scheme 3: Racemic resolution of alleno 3 and synthesis of derivatives.](image)

**Table 1: $^1$H NMR data of isolated and synthetic products.**

<table>
<thead>
<tr>
<th>compounds of dihydrorosefuran</th>
<th>1</th>
<th>rosiridol$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. pallens$^a,c$ [7,8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. mendocina$^d$ [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>this work synthesis$^a$</td>
<td></td>
<td></td>
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<tr>
<td>literature synthesis$^d$ [20]</td>
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<th></th>
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<th>H4</th>
<th>H5</th>
<th>H1'</th>
<th>H2'</th>
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<th>H5'</th>
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<td>4.04</td>
<td>5.07</td>
<td>4.55</td>
<td>2.30</td>
<td>5.32</td>
<td>1.67</td>
<td>1.60</td>
<td>2.05</td>
</tr>
<tr>
<td>(td, J = 8.0, 1.0 Hz)</td>
<td>(td, J = 8.0 Hz)</td>
<td>(td, J = 8.0 Hz)</td>
<td>(d, J = 7.0 Hz)</td>
<td>(m)</td>
<td>(l, J = 7.0 Hz)</td>
<td>(s)</td>
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<td>(s)</td>
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<tr>
<td></td>
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<td>5.66</td>
<td>4.21</td>
<td>2.24</td>
<td>5.13</td>
<td>1.75</td>
<td>1.66</td>
<td>1.69</td>
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<tr>
<td>(l, J = 8 Hz)</td>
<td>(l, J = 8 Hz)</td>
<td>(dd)</td>
<td>(m)</td>
<td>(l, J = 7.0 Hz)</td>
<td>(s)</td>
<td>(s)</td>
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<td>2.41</td>
<td>5.21</td>
<td>1.74</td>
<td>1.66</td>
<td>1.72</td>
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<tr>
<td>(br s)</td>
<td>(br s)</td>
<td>(m)</td>
<td>(m)</td>
<td>(hept, J = 6.9, 1.5 Hz)</td>
<td>(s)</td>
<td>(s)</td>
<td>(s)</td>
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<tr>
<td></td>
<td>4.02–3.99</td>
<td>5.67–5.62</td>
<td>4.24–4.15</td>
<td>2.28–2.19</td>
<td>5.13–5.09</td>
<td>1.73 (d, J = 1.1 Hz)</td>
<td>1.64 (s)</td>
<td>1.67 (s)</td>
</tr>
</tbody>
</table>

$^a$CDCl$_3$ in all cases; $^b$arbitrary numbering for comparison purposes; $^c$80 MHz; $^d$400 MHz; $^*500$ MHz.
δJH NMR (300 MHz, CDCl₃ = 2.3, 3.2 Hz, 2H), 13C NMR (100 MHz; CDCl₃) δ 17.5, 21.5 (CH₂), 28.5 (CH₂), 42.1, 42.5 (CH), 60.7 (CH₂), 14.2 (CH₂), 14.5 (CH₂), 15.0 (CH₂); HRMS–ESI (Q-TOF, m/z): [M + H]+ calc for C₁₀H₁₄O₃, 185.1178; found, 185.1158. A lactone is formed as side product (0–10%) when the HCl solution used for the workup has a concentration higher than 3%. Compound 5: IR (ATR) ν (cm⁻¹): 2982, 2927, 1600, 1722, 1427, 1331, 1162, 974, 918, 855; ¹H NMR (300 MHz, CDCl₃) δ 4.89 (m, 1H), 4.86 (m, 2H), 2.55 (m, 2H), 2.30 (m, 2H), 1.79 (t, J = 3.1 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 204.8 (C), 174.0 (C), 101.6 (C), 77.0 (CH₂), 71.5 (CH), 60.5 (CH₂), 30.4 (CH₂), 30.0 (CH₂), 14.5 (CH₃), 14.2 (CH₃) ppm; HRMS–ESI (Q-TOF, m/z): [M + H]+ calc for C₆H₁₀O₂, 139.0759; found, 139.0782.

Conclusion
In summary, we have proved that the two-step sequence Ti(III) allenylation–Ag⁺ cyclization is a simple and efficient strategy for the preparation of the 2,5-dihydrofuran moiety present in many natural products. In fact, we have achieved the total synthesis of the 2,5-dihydrofuran structure 1. After systematic data analysis of our prepared compound and those in the literature, it can be concluded that the proposed structure of the product isolated from Artemisia pallens oil, dihydrorosefuran, is not correct. In addition, it is clear that the compound isolated from Tagetes mendocina is the acyclic diol named rosiridol.

Experimental
Ti-induced allenylation of ethyl 4-oxobutanoate (4)
Under an Ar atmosphere, dry THF (8 mL) that was deoxygenated prior to use was added to a mixture of CpTiCl₃ (329 mg, 1.50 mmol) and Mn dust (165 mg, 3.00 mmol) resulting in a green suspension. Then, a solution of ethyl 4-oxobutanoate (4, 196 mg, 1.50 mmol) and 1-bromobut-2-yne (0.27 mL, 3.00 mmol) in THF (2 mL) was dripped and the mixture was stirred for 2.5 hours. The mixture was filtered, diluted with EtOAc, washed with 3% HCl and brine, and dried (anhydrous MgSO₄), and the solvent was removed. The residue was purified by flash chromatography (n-hexane/EtOAc 8:2) to afford ethyl 4-hydroxy-5-methylhepta-5,6-dienoate (3, 225 mg, 81%) isolated as light yellow oil. IR (ATR) ν (cm⁻¹): 3434, 2972, 2928, 1958, 1723, 1436, 1374, 1172, 1028, 925, 853; ¹H NMR (300 MHz, CDCl₃) δ 4.77 (dq, J = 2.3, 3.2 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.05 (m, 1H), 2.42 (t, J = 7.2 Hz, 2H), 2.18 (s, 1H), 2.04–1.77 (m, 2H), 1.70 (td, J = 0.5, 3.2 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 204.8 (C), 174.0 (C), 101.6 (C), 77.0 (CH₂), 71.5 (CH), 60.5 (CH₂), 30.4 (CH₂), 30.0 (CH₂), 14.5 (CH₃), 14.2 (CH₃) ppm; HRMS–ESI (Q-TOF, m/z): [M + H]+ calc for C₁₀H₁₄O₃, 185.1178; found, 185.1158. A lactone is formed as side product (0–10%) when the HCl solution used for the workup has a concentration higher than 3%. Compound 5: IR (ATR) ν (cm⁻¹): 2982, 2927, 1600, 1722, 1427, 1331, 1162, 974, 918, 855; ¹H NMR (300 MHz, CDCl₃) δ 4.89 (m, 1H), 4.86 (m, 2H), 2.55 (m, 2H), 2.30 (m, 2H), 1.79 (t, J = 3.1 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 204.8 (C), 177.0 (C), 98.0 (C), 80.4 (CH), 77.5 (CH₂), 28.5 (CH₂), 26.1 (CH₂), 15.0 (CH₃) ppm; HRMS–ESI (Q-TOF, m/z): [M + H]+ calc for C₆H₁₀O₂, 139.0759; found, 139.0782.

Silver(I)-promoted cyclization of ethyl 4-hydroxy-5-methylhepta-5,6-dienoate (3)
A solution of the allenol (3, 65 mg, 0.35 mmol) in acetone (2 mL) was added to a suspension of AgNO₃ (120 mg, 0.70 mmol) in acetone (1.5 mL) in the absence of light, and the mixture was stirred at 40 °C overnight. Brine was added and the mixture was extracted with Et₂O. The organic phase was washed with 3% HCl and brine, and dried (anhydrous MgSO₄), and the solvent was removed. The residue was purified by silica gel flash chromatography (n-hexane/EtOAc 9:1) to afford ethyl 3-(3-methyl-2,5-dihydrofuran-2-yl)propanoate (2, 57 mg, 88%) isolated as colorless oil. IR (ATR) ν (cm⁻¹): 2969, 2927, 2849, 1731, 1442, 1376, 1251, 1160, 1092, 1026, 895, 734; ¹H NMR (300 MHz,
CDCl₃) δ 5.53 (m, 1H), 4.69 (br s, 1H), 4.56 (m, 2H), 4.15 (q, J = 7.1 Hz), 2.39 (m, 2H), 2.12–2.06 (m, 1H), 1.83–1.74 (m, 1H), 1.72 (br s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ¹³C(¹H) NMR (75 MHz, CDCl₃, DEPT) δ 173.9 (C), 137.2 (C), 121.3 (CH), 86.4 (CH), 74.7 (CH₂), 60.3 (CH₂), 29.4 (CH₂), 28.9 (CH₃), 14.2 (CH₃), 12.3 (CH₃) ppm; HRMS–ESI (Q-TOF, m/z): [M + H]⁺ calcd for C₁₀H₁₉O₃, 185.1172; found, 184.1162.

Synthesis of 2-methyl-4-(3-methyl-2,5-dihydrofuran-2-yl)butan-2-ol (6)

Under an N₂ atmosphere, methylmagnesium bromide (3 M in Et₂O, 0.075 mL, 0.23 mmol) was added dry Et₂O (1.5 mL). A solution of ethyl 3-(3-methyl-2,5-dihydrofuran-2-yl)propanoate (2, 16 mg, 0.087 mmol) in Et₂O (1 mL) was added dropwise and the reaction mixture was stirred for 3 hours at room temperature. The reaction was quenched with saturated NH₄Cl and extracted with EtOAc. The combined organic layer was washed with saturated NaHCO₃, brine, and dried over anhydrous MgSO₄. The solvent was evaporated in vacuum and the residue was purified by column chromatography (n-hexane/ EtOAc 7:3) to give 2-methyl-4-(3-methyl-2,5-dihydrofuran-2-yl)butan-2-ol (6, 169 mg, 90%) isolated as colorless oil. IR (ATR) ν (cm⁻¹): 3425, 2969, 2922, 2852, 1636, 1444, 1382, 1089, 1057, 1025; ¹H NMR (300 MHz, CDCl₃) δ 5.51 (br s, 1H), 4.68 (br s, 1H), 4.58 (m, 2H), 2.05 (br s, 1H), 1.82 (m, 1H), 1.72 (br s, 3H), 1.57 (m, 3H), 1.24 (s, 6H) ppm; ¹³C(¹H) NMR (75 MHz, CDCl₃, DEPT) δ 173.9 (C), 137.2 (C), 121.3 (CH), 86.4 (CH), 74.7 (CH₂), 60.3 (CH₂), 28.9 (CH₃), 14.2 (CH₃), 12.3 (CH₃) ppm; HRMS–ESI (Q-TOF, m/z): [M + H]⁺ calcd for C₁₀H₁₉O₂, 171.1385; found, 171.1368.

Synthesis of 3-methyl-2-(3-methylbut-2-en-1-yl)-2,5-dihydrofuran-1 (1)

The reaction of amberlyst®-15 (dry, 97 mg) and 2-methyl-4-(3-methyl-2,5-dihydrofuran-2-yl)butan-2-ol (6, 97 mg, 0.57 mmol), based on the previously reported literature procedure [21], afforded 3-methyl-2-(3-methylbut-2-en-1-yl)-2,5-dihydrofuran (1, 64 mg, 74%) isolated as colorless oil. IR (ATR) ν (cm⁻¹): 3066, 2965, 2918, 2843, 1648, 1445, 1377, 1080, 975, 778, 1H NMR (500 MHz, CDCl₃) δ 5.51 (br s, 1H, H₄), 5.21 (t, hept, J = 7.0, 1.5 Hz, 1H, H₂), 4.67 (br s, 1H, H₂), 4.62–4.53 (m, 2H, H₅), 2.41 (m, 1H, H₁a), 2.20 (ddd, J = 14.0, 7.0, 6.5 Hz, 1H, H₁b), 1.74 (d, J = 1.5 Hz, 3H, H₄⁺), 1.72 (m, 3H, H₁⁺), 1.66 (br s, 3H, H₅⁺) ppm; ¹³C(¹H) NMR (125 MHz, CDCl₃, DEPT) δ 138.1 (C, C₃), 133.6 (C, C₃'), 120.7 (CH, C₄), 119.7 (CH, C₂'), 87.5 (CH, C₂), 74.5 (CH₂, C₅), 32.9 (CH₂, C₁'), 25.9 (CH₃, C₄'), 18.0 (CH₃, C₅'), 12.5 (CH₃, C₁') ppm (*may be interchanged); HRMS–ESI (Q-TOF, m/z): [M + H]⁺ calcd for C₁₀H₁₉O, 153.1274; found, 153.1262.
14. Reaction performed with stoichiometric amounts of CpTiCl₂.
17. Under this standard esterification conditions, some lactonization leading to compound 5 is observed.

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Preparation of an advanced intermediate for the synthesis of leustroducsins and phoslactomycins by heterocycloaddition

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Full Research Paper

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Keywords:
cycloaddition; organolithium; stereoselective; total synthesis

Abstract
A convergent strategy for the synthesis of leustroducsins and phoslactomycins has been designed, relying on the synthesis and the coupling of three main fragments. The central fragment was synthesized via a regio-and stereoselective nitroso Diels–Alder reaction with an enol phosphate, followed by reductive cleavage of the phosphate to the ketone \(11b\). Coupling studies of this fragment with the lactone fragment was accomplished in a stereoselective fashion through a vinyllithium intermediate. An advanced synthetic intermediate was then obtained after functional group transformation.

Introduction

Leustroducsins \(1a-c\) and phoslactomycins \(2a-f\) are a family of closely related natural products extracted from \textit{Streptomyces platensis} (leustroducsins) or \textit{Streptomyces nigresens} (phoslactomycins) [1-4]. The main difference within this large family is the presence of an additional ester substituent on the terminal cyclohexane ring. Common structural motifs include a polyunsaturated acyclic chain with an unsaturated lactone ring and an amine-containing side chain (Figure 1).

These natural products have attracted much attention due to their original structure and to their activity as inhibitors of the serine/threonine phosphatase enzyme PP2A [5,6]. Therefore, phoslactomycins [7-12] and leustroducsins [13-17] have been subject of extensive synthetic studies.

In a project related to the synthesis of leustroducsins and phoslactomycins, we have designed a convergent synthetic strategy involving the preparation and the coupling of three main fragments (Figure 2): the lactone fragment \(3\), the central fragment \(4\) and the cyclohexane fragment \(5\). We have previously described the enantioselective synthesis of the lactone fragment \(3\) [18]; we now disclose the synthesis of the oxazi-
none 4 and attempts for coupling both fragments for the synthesis of an advanced intermediate.

The synthetic strategy for the synthesis of the central fragment takes advantage of the proximity between the terminal amino function and the hydroxy function at C9. It was anticipated that both functions could arise from the cleavage of a N–O bond from an 1,2-oxazine, itself obtained by a nitroso Diels–Alder reaction from a chiral nitroso derivative and a functionalized diene (Figure 3). The nitroso Diels–Alder cycloaddition reaction has been well studied and has been used as a powerful tool for synthesis [19-22].

We have reported extensive studies on the regio- and stereoselectivity of nitroso Diels–Alder reactions between various nitroso derivatives and functionalized dienes [23]. These studies led to the selection of enol phosphates as ketone precursors for the diene functionalization. Enol phosphates display several advantages over the related enol silyl ethers [24,25]: they are more stable towards acidic conditions, their electronic character contributes to high regioselectivity in cycloaddition reactions, and they can be converted to many other functions, including their hydrolysis to ketones [26]. In the other hand, we have shown that the Wightman reagent 6, a chiral chloronitroso derivative [27], led to a complete regio- and stereoselective reaction with functionalized dienes (Scheme 1). The chiral auxiliary contributes to both regioselectivity and stereoselectivity. After hydrolysis of the chiral auxiliary and Boc-protection of the nitrogen atom, cycloadduct 8 was obtained in 55% yield and 90% ee. Therefore, the combination of both these reagents
Results and Discussion

Asymmetric cycloaddition

Preliminary studies for the conversion of enol phosphate to the corresponding ketone were accomplished using an unprotected primary alcohol. However, it appeared that hydroxy group protection was necessary: control experiments made on the racemic cycloadduct 8 showed that basic hydrolysis of the enol phosphate led to the cyclic hemiacetal 9 in modest yield (Scheme 2).

Therefore, compound 8 was protected as silyl or benzyl ether using standard techniques. Unfortunately, no hydrolysis under several basic conditions provides the target ketone, no conversion and/or decomposition being observed (Scheme 3).

Enol phosphates can be hydrolysed under basic, acidic or reductive conditions [26]. Although acidic conditions could not be used due to the lability of the nitrogen Boc-protecting group, we found that the TIPS-protected cycloadduct 10b could be cleanly transformed into the ketone 11b with excess Red-Al [28], together with a small amount of the over reduced alcohol 12b,
which could be reoxidized to 11b (Scheme 4). Other substrates failed to deliver appreciable yields of the ketone under the same conditions.

These studies validate the role of TIPS ether as protecting group for the primary alcohol. At this stage we wondered whether it was possible to perform the whole synthetic sequence with this protecting group. Accordingly, the enol phosphate 13 was synthesized in five steps (26% overall yield) from 1,4-butanediol (Scheme 5). Since cycloaddition with the Wightman reagent 6 releases hydrogen chloride in the reaction medium, it was found necessary to add a small amount of calcium carbonate. Optically active cycloadduct 10b was obtained in 73% yield and 86% ee after nitrogen protection as its Boc-carbamate. Ketone

11b was obtained by Red-Al reduction in identical yield to the racemic equivalent.

We have therefore completed a quick, efficient and selective access to the central core of leustroducsins/phoslactomycins using an asymmetric nitroso Diels–Alder reaction. This fragment displays a ketone function that will be used for coupling with the lactone fragment 3 by generation of the tertiary alcohol.

Studies in fragment coupling

We have previously reported the synthesis of the lactone fragment by catalytic asymmetric [2 + 2] cycloaddition followed by ring extension [18]. The initial product was the TMS-acetylene 18 which could be easily desilylated to give 21. However, model studies for coupling revealed the incompatibility of the lactone function; therefore, it was reduced with DIBAL-H then transformed into 19 by a one pot acetalization–desilylation procedure (91:9 mixture of diastereomers) [17]. Hydrozirconation followed by treatment with iodine furnished the target vinyl iodide 20 (Scheme 6); iodination with NIS, as previously described [29], gave lower yields.

We first attempted the coupling with the terminal alkyne 19, anticipating the possibility of reducing the triple bond after coupling reaction. In agreement with literature precedents, we chose LiHMDS for deprotonation of 19 [30,31]. However, condensation of the corresponding lithium acetylide to the ketone 11b gave modest and non-reproducible yields of the desired product 22 (Scheme 7, Table 1). The configuration of the newly created stereogenic center was undetermined.

<table>
<thead>
<tr>
<th>entry</th>
<th>n₁</th>
<th>n₂</th>
<th>conditions</th>
<th>yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1,2</td>
<td>−78 °C, 15 min, then rt, 8 h</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1,2</td>
<td>−78 °C, 2 h, then rt, 16 h</td>
<td>16%</td>
</tr>
<tr>
<td>3</td>
<td>1,5</td>
<td>1,8</td>
<td>−78 °C, 2 h, then rt, 3 h</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>1,5</td>
<td>1,6</td>
<td>−78 °C, 2 h, then rt, 4 h</td>
<td>39%</td>
</tr>
</tbody>
</table>

These experiments showed the necessity to perform a fast reaction in order to avoid degradation. The optimal amount of base was found to be 1.6 equivalents (Table 1, entry 4). Higher

Scheme 6: Synthesis and derivatization of the lactone fragment.

Scheme 7: Coupling reaction between alkyne 19 and ketone 11b.
amounts lowered the yields (Table 1, entry 3), probably due to competitive enolization of the cyclic ketone. Excess alkyne was also necessary, as low yields were obtained when using equimolar amounts of both 19 and 11b (Table 1, entries 1 and 2).

These disappointing results with alkyne 19 prompted us to investigate the coupling with an organometallic reagent derived from vinyl iodide 20. This reagent was already synthesized and coupled with acyclic ketones in previous syntheses of leustroducins or phoslactomycins [7-17]. Thus, treatment of 20 with n-butyllithium in THF gave the organometallic intermediate which was condensed onto ketone 11b (Scheme 8, Table 2). Since no product was obtained under these standard conditions, we considered the use of additives in order to make the organolithium intermediate more nucleophilic. However, no reaction was observed when ZnMe₂ (which was used in the synthesis of leustroducsin B by Trost and co-workers [17]) was added; trimethylaluminum and cerium chloride also failed to promote the reaction. However, switching the solvent from THF to toluene afforded 21% of product 23 with CeCl₃ as additive. It appeared that the solvent had more influence on the course of the reaction than the metal. Indeed, reaction between vinyl iodide and ketone with n-BuLi in toluene [32] without any additive gave a reproducible 46% yield of 23. Optimal conditions were obtained using 1.8 equivalents of vinyl iodide and 1.7 equivalents of BuLi (Table 2, entry 6).

It was difficult at this stage to determine the stereoselectivity of the coupling reaction since the starting acetal in 20 was a mixture of diastereomers. Therefore, we decided to oxidize the acetal in 23 to the corresponding lactone (Scheme 9). The acetal was first hydrolyzed to the hemiacetal 24 in quantitative yield. Oxidation of 24 proved delicate due to the lability of the tertiary allylic alcohol, and the presence of acid-sensitive protecting groups. Several conditions were tested: silver oxide on celite [33] failed to give any conversion. PCC with sodium acetate [34] gave only traces of the target lactone 25. However, the use of the Jones’ reagent gave reproducible yields of 25, together with the deprotected alcohol 26. Under optimized conditions (1.15 equiv, 15 min) a combined 46% yield could be obtained. Higher equivalents of the oxidizing reagents or longer reaction time considerably lowered the yields.

NMR analysis of products 25 and 26 showed these compounds were obtained as single diastereomers, thus indicating the complete stereoselectivity of the coupling reaction. This validates the overall strategy for the synthesis of leustroducins or phoslactomycins by the synthesis of a central cyclic core and its coupling with the other fragments.

**Conclusion**

We have synthesized an advanced intermediate for the total synthesis of leustroducins and phoslactomycins using a highly regio- and stereoselective nitroso Diels–Alder reaction, and a coupling reaction between a ketone and a vinyllithium reagent. This strategy offered quick and stereoselective access to an advanced precursor to these natural products. Further studies concerning the completion of the total synthesis via the preparation and coupling of the fragment 5 is under study in our laboratory.
Experimental

Unless otherwise stated, all reactions were conducted in oven-dried glassware under an atmosphere of dry argon. Tetrahydrofuran was distilled over sodium/benzophenone ketyl under argon. Acetonitrile, dichloromethane, DMSO, DMF and toluene were distilled over calcium hydride under argon. All other reagents were used as received. Chromatographic purifications refer to flash chromatography on silica gel. 

1H NMR spectra were measured at 250, 300, 360 or 400 MHz using CDCl3 as solvent using residual chloroform (7.26 ppm) as an internal reference. 13C NMR spectra were measured at 62.5, 75 or 90 MHz using residual chloroform (77.1 ppm) as an internal reference. High-resolution mass spectrometry (HRMS) analyses were conducted with electro spray ionization (ESI).

6-Triisopropylsilyloxyhex-1-en-3-one (16): A solution of oxalyl chloride (0.49 mL, 5.75 mmol, 1.5 equiv) in dichloromethane (12 mL) was cooled to −78 °C and DMSO (0.82 mL, 11.49 mmol, 3 equiv) was added over 5 min. After 15 min, a solution of the alcohol 15 [35] (1.044 g, 3.83 mmol) in dichloromethane (5 mL) was added over 5 min. The reaction mixture was stirred for 30 min at −78 °C before addition of triethylamine (2.7 mL, 19.15 mmol, 5 equiv). The cooling bath was removed and the solution was allowed to warm to rt in 30 min. It was then poured into diethyl ether (50 mL) and the solution was successively washed with saturated aqueous CuSO4 solution (4 × 12.5 mL), saturated aqueous NH4Cl solution (3 × 12.5 mL), dried (MgSO4), filtered and concentrated under reduced pressure to give a brown oil (1.021 g, 99%). Rf: 0.59 (10% AcOEt/cyclohexane); 1H NMR (300 MHz, CDCl3) δ 6.32 (dd, J = 17.7, 10.2 Hz, 1H), 6.19 (dd, J = 17.7, 1.5 Hz, 1H), 5.78 (dd, J = 10.2, 1.5 Hz, 1H), 3.68 (t, J = 6 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 1.86–1.77 (m, 2H), 1.00 (m, 21H) ppm; 13C NMR (75 MHz, CDCl3) δ 200.8, 136.7, 127.9, 62.4, 35.9, 27.2, 18.0, 12.0 ppm; HRMS (m/z): [M + Na]+ calcd 293.1907; found, 293.1898.

(3Z)-3-Diethylphosphoryloxy-6-triisopropylsilyloxyhexa-1,3-dien (17): A 0.5 M solution of potassium hexamethyldisilazide in toluene (4.4 mL, 2.22 mmol, 1.2 equiv) was added to a cooled (−78 °C) solution of diethyl chlorophosphate (0.27 mL, 1.85 mmol) in anhydrous THF (7 mL). A solution of the enone 16 (500 mg, 1.85 mmol) in THF (6 mL) was then slowly added. The solution was stirred 30 min at −78 °C, then 1 h at 0 °C and then 1 h at rt, before being poured in diethyl ether (35 mL). The solution was washed with 5% aqueous ammonia solution (18 mL). The aqueous layer was extracted with diethyl ether (3 × 35 mL) and the combined organic layers were dried (MgSO4), filtered and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (25% AcOEt/cyclohexane) gave the enol phosphate 17 as a yellow oil (200 mg, 26%). Rf: 0.47 (30% AcOEt/cyclohexane); 1H NMR (360 MHz, CDCl3) δ 6.15 (dd, J = 17.3, 10.8 Hz, 1H), 5.47 (d, J = 17.3 Hz, 1H), 5.29 (dt, J = 7.2, 1.4 Hz, 1H), 5.08 (d, J = 10.8 Hz, 1H), 4.15–4.12 (m, 4H), 3.71 (t, J = 6.5 Hz, 2H), 2.48 (2dt, J = 7.2, 6.5 Hz, 2H), 1.31 (dt, J = 6.8, 1.1 Hz, 6H), 1.01 (m, 21H) ppm; 13C NMR (90 MHz, CDCl3) δ 146.2, 131.9, 118.0, 114.2, 64.4, 62.4, 30.0, 18.0, 16.2, 12.0 ppm; HRMS (m/z): [M + H]+ calcd 407.2377; found, 407.2359.

(6R)-tert-Butyl 5-(diethoxyphosphoryloxy)-6-(2-((triisopropylsilyl)oxy)ethyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (10b): A solution of the enol phosphate 17 (420 mg, 1.03 mmol) in chloroform (1.8 mL) was added to a solution of the Wightman reagent 6 (981 mg, 2.06 mmol, 2 equiv), calcium carbonate (206 mg, 2.06 mmol, 2 equiv) and water (40 µL,
2.06 mmol, 2 equiv) in isopropanol (1.8 mL). The mixture was stirred at rt for 30 h. Water (0.75 mL) was added and the solution was stirred for additional 1 h. The pH was adjusted to 8 by addition of saturated aqueous NaHCO₃ solution (1.6 mL), and a solution of Boc₂O (899 mg, 4.12 mmol, 4 equiv) in chloroform (0.8 mL) was added. The solution was stirred at rt for 64 h and poured into a mixture of water (37 mL) and dichloromethane (74 mL); the layers were separated and the aqueous layer extracted with dichloromethane (3 × 74 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (30% AcOEt/cyclohexane) gave the cyclodecaduct 10b as a yellow oil (404 mg, 73%). Rₑ 0.42 (30% AcOEt/cyclohexane); ¹H NMR (360 MHz, CDCl₃) δ 5.69 (m, 1H), 4.57 (broad d, J = 9.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 4H), 4.12–4.00 (m, 2H), 3.99–3.82 (m, 2H), 2.03–1.85 (m, 2H), 1.47 (s, 9H), 1.34 (t, J = 7.2 Hz, 6H), 1.05 (m, 2H) ppm; ¹³C NMR (90 MHz, CDCl₃) δ 154.8, 146.8, 105.1, 81.7, 75.2, 64.8, 59.3, 43.7, 33.7, 28.4, 18.1, 16.2, 12.1 ppm; HRMS (m/z): [M + Na]⁺ calcd 560.2779; found, 560.2775; [α]D: +5.8 (c 1.0, CH₂Cl₂); ee: 8% (Welck-O1, 1 mL/min, 95:5 hexane/EtOH, tR = 14.9 min, t₅ (S) = 16.2 min).

(6R)-tert-Butyl 5-oxo-6-((2-((triisopropylsilyloxy)ethyl)-1,2-oxazinane-2-carboxylate (11b): A solution of the cyclodecaduct 10b (404 mg, 0.751 mmol) in anhydrous THF (12 mL) was cooled to 0 °C and a 3 M solution of Red-Al in toluene (1 mL, 3 mmol, 4 equiv) was rapidly added. After stirring 30 min at 0 °C, the reaction was hydrolyzed by addition of an saturated aqueous NH₄Cl solution (4 mL). The solution was concentrated under reduced pressure, the residue taken up with dichloromethane (10 mL) and filtered, washing with dichloromethane (3 × 5 mL). The filtrate was concentrated under reduced pressure to give a yellow oil (300 mg) consisting in a mixture of the ketone 11b and the over-reduced alcohol. This mixture was carried into the next step without further purification.

DMSO (0.16 mL, 2.241 mmol, 3 equiv) was added dropwise to a cooled (−78 °C) solution of oxalyl chloride (0.1 mL, 1.121 mmol, 1.5 equiv) in dichloromethane (3.4 mL). After stirring 15 min at −78 °C, a solution of the crude product from reduction reaction (300 mg) in dichloromethane (2 mL) was added dropwise. After 30 min at −78 °C, triethylamine (0.52 mL, 3.735 mmol, 5 equiv) was added. The colling bath was removed and the solution stirred at rt for 40 min, before being poured into diethyl ether (45 mL). The solution was successively washed with saturated aqueous CuSO₄ solution (4 × 10 mL) and saturated aqueous NH₄Cl solution (3 × 10 mL) and dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by filtration through a short plug of silica gel, eluting with ethyl acetate. Concentration under reduced pressure gave the pure ketone 11b as an orange oil (255 mg, 84% over two steps). Rₑ 0.29 (10% AcOEt/cyclohexane); ¹H NMR (250 MHz, CDCl₃) δ 4.49 (dd, J = 8.3, 3.8 Hz, 1H), 4.18–4.08 (m, 1H), 3.94 (m, 4H), 2.67 (t, J = 7.0 Hz, 2H), 2.16–2.03 (m, 1H), 1.99–1.85 (m, 1H), 1.51 (s, 9H), 1.05 (m, 21H) ppm; ¹³C NMR (90 MHz, CDCl₃) δ 206.6, 154.9, 85.1, 82.3, 59.0, 45.0, 36.5, 32.2, 28.4, 18.1, 12.1 ppm; HRMS (m/z): [M + Na]⁺ calcd 424.2490; found, 424.2480; [α]D²⁰ +37.4 (c 0.5, CH₂Cl₂).

(5S,6R)-5-Ethyl-6-ethynyl-5,6-dihydro-2H-pyran-2-one (21): Caesium fluoride (290 mg, 1.91 mmol, 1.3 equiv) was added to a solution of the lactone 18 [6] (327 mg, 1.47 mmol) in anhydrous acetonitrile (15 mL). The solution was stirred at rt; after 2 h 20 min, additional CsF (112 mg, 0.74 mmol, 0.5 equiv) was added. After a total time of 3 h 30 min, the solution was partitioned between diethyl ether (70 mL) and water (35 mL). The layers were separated, the organic layer was washed with saturated aqueous NaCl solution (35 mL). The combined aqueous layers were extracted with diethyl ether (2 × 70 mL). The organic layers were combined, dried (MgSO₄), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (25% Et₂O/pentane) gave 21 as a yellow oil (171 mg, 77%). Rₑ 0.33 (30% Et₂O/pentane); ¹H NMR (250 MHz, CDCl₃) δ 6.82 (d, J = 9.8, 3.5 Hz, 1H), 6.05 (dd, J = 10.0, 2.0 Hz, 1H), 5.16 (dd, J = 4.8, 2.3 Hz, 1H), 2.68–2.59 (m, 1H), 2.56 (d, J = 2.0 Hz, 1H), 1.86–1.62 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H) ppm; ¹³C NMR (90 MHz, CDCl₃) δ 162.5, 148.8, 120.3, 77.4, 76.6, 70.7, 38.2, 22.6, 10.9 ppm; HRMS (m/z): [M + Na]⁺ calcd 173.0573; found, 173.0572; [α]D²⁰ +32.0 (c 1.0, CH₂Cl₂).

(2R,3S,6RS)-3-Ethyl-2-ethynyl-6-methoxy-3,6-dihydro-2H-pyran (19): This compound was prepared according to reference [18].

A solution of the lactone 18 (1.23 g, 5.53 mmol) in anhydrous dichloromethane (10 mL) was cooled to −78 °C and a solution of DIBAL-H in toluene (1.2 M, 6 mL, 7.19 mmol, 1.3 equiv) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min then poured into a NaHCO₃ solution (5 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue (1.3 g) was redissolved in anhydrous methanol (25 mL) and paratoluene sulfonic acid hydrate (53 mg, 0.277 mmol, 0.05 equiv) was added. After stirring 1 h at rt, solid K₂CO₃ (1.53 g, 11.06 mmol, 2 equiv) was added and the mixture stirred overnight at rt. Diethyl ether (50 mL) was added and the solution washed with water (2 × 50 mL). The organic layer was dried (MgSO₄), filtered and carefully concentrated under reduced pressure.
pressure. Purification by column chromatography (5% Et$_2$O/pentane), gave 19 as a colourless oil (866 mg, 94%, 91/9 mixture of stereoisomers). Analytical data were in agreement with literature data [18].

(2R,3S,6RS)-3-Ethyl-2-((E)-2-iodovinyl)-6-methoxy-3,6-dihydro-2H-pyran (20): This compound was prepared according to reference [18].

A solution of the alkyne 19 (300 mg, 1.80 mmol) in anhydrous dichloromethane (4.2 mL) was added dropwise to a suspension of Cp$_2$ZrHCl (696 mg, 2.70 mmol, 1.5 equiv) in anhydrous dichloromethane (9 mL). After stirring at rt for 15 min, a solution of iodine (777 mg, 3.06 mmol, 1.7 equiv) in anhydrous dichloromethane (9 mL) was added dropwise until a light brown solution was obtained. The reaction mixture was hydrolyzed by successive addition of a saturated aqueous Na$_2$S$_2$O$_3$ solution (25 mL) and water (9 mL). The layers were separated and the organic layer was washed with water (9 mL). The combined aqueous layers were back-extracted with diethyl ether (2 × 40 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (2.5% Et$_2$O/pentane) gave 20 as a yellowish oil (347 mg, 65%, 91/9 mixture of stereoisomers). Analytical data were in agreement with literature data [18].

Coupling reaction between vinyl iodide 20 and ketone 11b: A solution of the vinyl iodide 20 (283 mg, 0.962 mmol, 1.8 equiv) in anhydrous toluene (2 mL) was cooled to −78 °C, and a n-butyllithium solution (2.3 M in hexanes, 0.39 mL, 0.909 mmol, 1.7 equiv) was added dropwise. The solution was stirred for 30 min at −78 °C then a solution of ketone 11b (215 mg, 0.535 mmol, 1 equiv) in toluene (3.8 mL) was slowly added. The reaction was stirred at −78 °C for 45 h than slowly warmed to rt over 20 h. The reaction as quenched by addition of a saturated aqueous NH$_4$Cl solution (3.8 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 8 mL) and diethyl ether (2 × 8 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (20 to 30% AcOEt/cyclohexane) gave the coupling product 23 as an orange oil, which was carried into the next step (23 mg, 17%).

A solution of the crude lactol 23 as a sticky yellow oil (42 mg, 29% over two steps), further elution with 100% AcOEt gave the unprotected alcohol 26 (18 mg, 17%).

tert-Butyl (6R)-5-((E)-2-((2S,3S)-3-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)vinyl)-5-hydroxy-6-(2-((trisopropylsilyl)oxy)ethyl)-1,2-oxazinanine-2-carboxylate (25): Data for 25: Rf: 0.10 (30% AcOEt/cyclohexane); $^1$H NMR (360 MHz, CDCl$_3$) δ 6.97 (dd, J = 9.7, 5.5 Hz, 1H), 6.05 (dd, J = 9.7 Hz, 1H), 5.96 (dd, J = 15.5, 4.2 Hz, 1H), 5.82 (dd, J = 15.5, 1.4 Hz, 1H), 5.02 (dd, J = 4.2, 1.4 Hz, 1H), 3.99–3.90 (m, 3H), 3.76–3.69 (m, 1H), 3.55 (td, J = 13.1, 2.7 Hz, 1H), 2.44–2.37 (m, 1H), 1.90–1.70 (m, 2H), 1.67–1.57 (m, 3H), 1.49 (s, 9H), 1.45–1.39 (m, 1H), 1.05 (m, 21H), 0.93 (s, J = 7.5 Hz, 3H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 163.9, 155.1, 150.1, 135.5, 125.1, 121.0, 82.6, 81.8, 79.8, 70.8, 59.0, 42.3, 39.4, 35.9, 31.3, 28.4, 21.8, 18.1, 12.0, 11.1 ppm; HRMS (m/z): [M + Na]$^+$ calc 576.3327; found, 576.3330; [α]$_D^{20}$ +86.3 (c 1.1, CH$_2$Cl$_2$).

tert-Butyl (6R)-5-((E)-2-((2S,3S)-3-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)vinyl)-5-hydroxy-6-(2-hydroxyethyl)-1,2-oxazinanine-2-carboxylate (26): Data for 26: Rf: 0.38 (80% AcOEt/cyclohexane); $^1$H NMR (400 MHz, acetone-$_d_6$) δ 7.09 (dd, J = 10.0, 5.2 Hz, 1H), 6.02 (dd, J = 15.6, 5.5 Hz, 1H), 5.97 (dd, J = 10.0, 1.2 Hz, 1H), 5.85 (dd, J = 15.6, 1.2 Hz, 1H), 5.06 (dd, J = 5.5, 4.0, 1.2 Hz, 1H), 4.27 (s, exchangeable with D$_2$O, 1H), 3.96–3.91 (m, 2H), 3.74–3.66 (m, 2H), 3.63–3.59 (m, 1H), 2.61–2.53 (m, 1H), 1.95–1.83 (m, 2H), 1.73–1.67 (m, 1H), 1.67–1.55 (m, 2H), 1.49 (s, 9H), 1.47–1.38 (m, 1H), 0.94 (s, J = 7.6 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, acetone-$_d_6$) δ 163.83,
References


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Solid-phase total synthesis and structural confirmation of antimicrobial longicatenamide A

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Full Research Paper

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Keywords:
antimicrobial; longicatenamides; peptidic natural product; solid-phase synthesis; total synthesis

Abstract
Longicatenamides A–D are cyclic hexapeptides isolated from the combined culture of Streptomyces sp. KUSC_F05 and Tsukamurella pulmonis TP-B0596. Because these peptides are not detected in the monoculture broth of the actinomycete, they are key tools for understanding chemical communication in the microbial world. Herein, we report the solid-phase total synthesis and structural confirmation of longicatenamide A. First, commercially unavailable building blocks were chemically synthesized with stereocontrol. Second, the peptide chain was elongated via Fmoc-based solid-phase peptide synthesis. Third, the peptide chain was cyclized in the solution phase, followed by simultaneous cleavage of all protecting groups to afford longicatenamide A. Chromographic analysis corroborated the chemical structure of longicatenamide A. Furthermore, the antimicrobial activity of synthesized longicatenamide A was confirmed. The developed solid-phase synthesis is expected to facilitate the rapid synthesis of diverse synthetic analogues.

Introduction
Naturally occurring bioactive compounds can serve as both drug leads and research tools for chemical biology [1]. Because the rediscovery rate of these compounds has increased in the last few decades, new approaches to explore natural products are in demand [2]. To this end, the combined-culture strategy has been applied to discover new natural products. For example, the mycolic acid-containing bacterium Tsukamurella pulmonis TP-B0596 can influence the biosynthesis of cryptic natural products [3]. Additionally, we have developed several highly sensitive labeling reagents to detect and identify scarce and cryptic natural products [4]. Integrating the combined-culture strategy and new labeling reagents has led to the detection and structural determination of several unprecedented secondary metabolites [5-7].
Longicatenamides A–D (1–4, Figure 1) are cyclic hexapeptides isolated from the combined-culture of *Streptomyces* sp. KUSC_F05 and *T. pulmonis* TP-B0596 [8]. The planar structures were determined by analyzing two-dimensional (2D) nuclear magnetic resonance (NMR) spectra and mass spectrometry (MS) data, and the absolute configurations of their component amino acids were elucidated by using highly sensitive reagents that we recently developed [4]. Among the isolated longicatenamides, compound 1 exhibits weak but preferential antimicrobial activity against *Bacillus subtilis*. Because peptides 1–4 are not detected in the monoculture broth of *Streptomyces* sp. KUSC_F05, they are key tools for understanding chemical communication in the microbial world. To elucidate the role of compounds 1–4 in the microbial world, developing a strategy to synthesize compounds 1–4, including future derivatization to produce probe molecules, is required. Herein, we report the total synthesis of peptide 1 by Fmoc-based solid-phase peptide synthesis [9] and the evaluation of its antimicrobial activity. The present study confirmed our proposed structure of 1, which was determined by the use of our original labeling reagents [4].

**Results and Discussion**

Although the solution-phase total synthesis of an analogue of longicatenamycin A has been reported [10], a solid-phase strategy can facilitate the production of a wider variety of analogous compounds than solution-phase synthesis [11]. Consequently, in this study, compound 1 was synthesized using a solid-phase strategy for future derivatization to produce probe molecules for deciphering microbial chemical communication. The retrosynthesis of peptide 1 is displayed in Scheme 1. First, the cyclic peptide 1 was linearized by retrosynthesis, and acid-labile protecting groups were attached onto the reactive side chain. The biomimetic synthesis of cyclic peptides often enables efficient synthesis [12,13] and provides insights into the biosynthesis pathways of these peptides [14]. However, the biosynthetic gene clusters of compounds 1–4 remain unidentified. Therefore, the least stericly hindered amine, namely the amino group of glycine, was selected as a nucleophile of the cyclization reaction in this study. Second, to realize the solid-phase synthesis, the C-terminus of the linear peptide was connected to 2-chlorotrityl resin [15] to give resin-bound peptide 5. Peptide 5 was divided into six building blocks 6–11 by retrosynthesis.

At the beginning of the total synthesis, commercially unavailable building blocks 7 and 10 were chemically constructed from readily available starting materials. The synthesis of building block 10 commenced with the synthesis of compound 15 through Wittig reaction of Garner’s aldehyde (13) [16], which was readily obtained from tert-butylxocarbonyl (Boc)-protected ð-D-serine 12 (Scheme 2). Treatment of the olefin 15 with trifluoroacetic acid (TFA) cleaved the Boc protecting group and the acetonide to deliver unsaturated amino alcohol 16. The amino group in 16 was protected by the fluorenylmethyloxycarbonyl (Fmoc) protecting group for solid-phase peptide synthesis, and then hydrogenation of the double bond in 17 provided intermediate 18. Oxidation of the alcohol 18 to acid 10 was realized with the combination of Dess–Martin oxidation [17,18] and Pinnick oxidation [19].

Another unusual amino acid 7 was also synthesized from ð-serine (20, Scheme 3). The SnCl₂-catalyzed coupling reaction [20] between 21 and 22 afforded ß-keto ester 23, which
Scheme 1: Retrosynthesis of longicatenamycin A (1).

Scheme 2: Synthesis of building block 10.

was then reduced to the corresponding β-hydroxy ester 24 by K-Selectride (dr > 20:1), and subsequent acidic removal of the acetonide furnished diol 25. The stereochemistry of the newly generated hydroxy group was determined using the modified Mosher’s method [21]. Protection of diol 25 by tert-butyl(dimethyl)silyl (TBS) group followed by selective depro-
Scheme 3: Synthesis of building block 7.

tection of the primary alcohol led to 27. Finally, acid 7 was obtained from alcohol 27 through the same two-step oxidation used to obtain compound 10.

Having synthesized the necessary building blocks, we turned our attention to construct resin-bound peptide 5 (Scheme 4). The assembly of this hexapeptide started with the loading of Fmoc-\(\alpha\)-Trp(Boc)-OH (6) onto 2-chlorotrityl resin with iPr\(_2\)NEt, which was followed by piperidine treatment to liberate resin-bound amine 29. Then, five rounds of DIC/Oxyma-mediated amidation [22] and N\(^\alpha\)-deprotection with piperidine led to resin-bound peptide 5. Treatment of 5 with TFA/CH\(_2\)Cl\(_2\) 1:99 released 30 into the solution without unmasking the acid-labile protecting groups of the side chains. Subsequently, peptide 30 was cyclized by the action of PyBOP/HOAt [23,24] followed by treatment with TFA/iPr\(_3\)SiH/H\(_2\)O 95:2.5:2.5 to provide crude 1. After reversed-phase high-performance liquid chromatography (HPLC) purification, longicatanamide A (1) was obtained with 36% yield over 15 steps starting from 6.

The NMR spectra of synthesized compound 1 agreed with those of natural 1. At this stage the confirmation of the identity of natural and synthesized compounds by structural determination using NMR spectroscopy is often difficult because the NMR spectra of peptidic products vary depending on the conditions in the NMR tube [25-29], such as concentration, pH, and purity. Thus, analyses of the NMR spectra of peptides sometimes lead to incorrect structural determination even though total synthesis of the proposed structures is successful [30]. In this study, synthesized and natural 1 were compared by collecting LC–MS data. As displayed in Figure 2, the retention time of synthesized 1 was identical to that of natural 1. These results confirmed total synthesis of 1 and supported our proposed structure of isolated natural 1.

Total synthesis sometimes invalidates the reported biological activity of the isolated natural product, which could be due to the presence of uncharacterized impurities. To verify the bioactivity of 1, the antimicrobial activity of synthesized 1 was preliminary tested in this study following a previously reported
method [8], revealing that chemically synthesized \( \text{I} \) (minimum inhibitory concentration (MIC) = 50 \( \mu \text{M} \)) exhibited moderate but selective antimicrobial activity against \textit{Bacillus subtilis} similar to natural \( \text{I} \) (MIC = 100 \( \mu \text{M} \)).

**Conclusion**

We accomplished solid-phase total synthesis of longicatenamide A (1). Initially, commercially unavailable building blocks 7 and 10 were chemically synthesized with stereoccontrol. Then, the peptide chain was elongated by Fmoc-based solid-phase peptide synthesis. Finally, the cyclization of the peptide chain followed by simultaneous cleavage of all protecting groups in the solution phase afforded target compound 1. The comparison of the chromatograms of synthesized and natural 1 corroborated the chemical structure of 1. Further studies of the structure–activity relationship, identification of
biosynthetic gene clusters, and detailed investigations of the combined-culture production of longicatenamides are currently underway in our laboratory.

Supporting Information
Supporting Information File 1
Experimental procedures and compound characterization data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-166-S1.pdf]

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Abstract
The formal total synthesis of macarpine was accomplished by the construction of a naphthol intermediate in Ishikawa’s synthetic route with two different synthetic routes. The convergent synthetic strategies feature the utilization of Au(I)-catalyzed cycloisomerizations of a 1,5-enyne and alkynyl ketone substrates, which were prepared by Sonogashira coupling reactions.

Introduction
Benzo[c]phenanthridine alkaloids are an ancient and influential category of isoquinoline alkaloids, mainly found in Papaveraceae and Rutaceae (Scheme 1) [1,2]. According to their oxidation states, benzo[c]phenanthridine alkaloids can be divided into two types: partially hydrogenated base and fully aromatized base, in which natural fully aromatic alkaloids can be further classified into three subclasses: O4-base, O5-base, and O6-base [3].

Among these alkaloids, macarpine is the most oxidized tetracyclic alkaloid with many bioactivities, including anesthesia, anticancer, anti-inflammatory [4-8], insecticidal, fungicidal, etc [9]. In addition to the above-mentioned activities, macarpine was also used as a DNA probe for flow cytometry and fluorescence microscopy due to its fluorescent properties [10]. Despite some research on the activities of macarpine had been performed, a more in-depth evaluation of the biological activities was still limited due to the need of its isolation from natural sources. Inspired by the requirement of further biological evaluation, the chemical syntheses of macarpine have been developed rapidly in the last three decades.

The benzo[c]phenanthridine skeleton consists of a phenanthridine (rings A, B, C) and a benzene (ring D), and most of the
Scheme 1: Classification of benzo[c]phenanthridine alkaloids.

synthetic routes were completed in the last step by constructing ring B or ring C. Some representative examples and their key strategies are summarized in Scheme 2. In 1989, Hanaoka and co-workers developed the total synthesis of macarpine by Hofmann elimination from protoberberine by introducing rings B and C (Scheme 2a) [11]. In 1995, Ishikawa and co-workers accomplished the total synthesis via a Reformatsky reaction and aromatic nitrosation through the building of rings B and C (Scheme 2b) [12]. In 2010, Echavarren and co-worker completed the formal total synthesis via a Au(I)-catalyzed cyclization (Scheme 2c) [13]. In 2018, Pabbaraja and co-workers disclosed the synthesis of macarpine by constructing ring C through the domino Michael addition/SNAr reaction of nitromethane to an ynone precursor (Scheme 2d) [14].

Results and Discussion

The efforts on developing efficient synthetic strategies to access macarpine never ceased during the last decades, and we have joined this meaningful research. Herein, a strategy involving the synthesis of an intermediate reported by Ishikawa in 1995 in the total synthesis of macarpine [12] is proposed via a Au(I)-catalyzed cycloisomerization reaction.

Retrosynthetically, the target molecule macarpine (1) could be disconnected into naphthol 12 (Scheme 3), a key intermediate reported by Ishikawa in the total synthesis of macarpine. This intermediate could be synthesized from silyl enol ether compound 10 via the Au(I)-catalyzed cycloisomerization reaction developed by our group [15]. The compound 10 could be constructed by the Sonogashira coupling reaction from readily prepared iodoarene 8 [12,16] and ketone 5, which could be synthesized by using cheap 6-bromopiperonal (2) as the starting material.

To attempt the proposed synthetic strategy, ketone 5 and iodoarene 8 were prepared by following the synthetic route outlined in Scheme 4. Ketone 5 was prepared in a four-step procedure. Firstly, a Sonogashira coupling between 6-bromopiperonal (2) and trimethylsilylacetylene was performed to furnish aldehyde 3 [17,18] in 89% yield. A following nucleophilic addition reaction of aldehyde 3 by methylmagnesium bromide (MeMgBr) gave alcohol 4 in 99% yield, which was oxidized by pyridinium chlorochromate (PCC) leading to the formation of ketone compound and the deprotection of the silyl group was accomplished in the presence of potassium carbonate (K$_2$CO$_3$) and methanol to provide the terminal alkyne 5 in 96% yield in two steps. The iodoarene 8 [12,16] was facilely synthesized from sesamol (6) via methylation and iodination in an overall yield of 67%.

With the building blocks 5 and 8 in hand, ketone 9 was prepared via a palladium-catalyzed Sonogashira coupling reaction in a yield of 95%. The precursor 10 for the gold(I)-catalyzed [19-24] cycloisomerization was then synthesized by treating ketone 9 with sodium bis(trimethylsilyl)amide (NaHMDS) and tert-butylimethyleisyl chloride (TBSCI) (Scheme 5).
Scheme 2: Representative synthetic strategies for macarpine (1).

- **a) Hofmann elimination** (Hanaoka)
  - 4 steps, 13%
  - Follows the steps indicated in the diagram.

- **b) Reformatsky reaction** (Ishikawa)
  - 9 steps, 13%
  - Follows the steps indicated in the diagram.

- **c) Au(I)-catalyzed cyclization** (Echavarren)
  - 10 steps, 41%
  - Follows the steps indicated in the diagram.

- **d) Domino Michael addition/\(S_N\)Ar** (Pabbaraja)
  - 7 steps, 16%
  - Follows the steps indicated in the diagram.

Scheme 3: Retrosynthetic analysis of marcarpine precursor 12 for a partial synthesis.
To find the best cycloisomerization conditions, the 1,5-enyne substrate 10 was subjected to different reaction conditions as listed in Table 1. It was observed that [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) chloride (IPrAuCl) itself failed to catalyze the cycloisomerization (Table 1, entry 1). Evaluation of a number of silver salts illustrated that silver hexafluoroantimonate (AgSbF₆) was the optimal additive to activate the gold catalyst (Table 1, entries 2, 3, and 7).

Screening of the other ligands of Au(I) catalysts, including triphenylphosphane (Ph₃P), [1,1’-biphenyl]-2-yl-di-tert-butylphosphane (JohnPhos), dicyclohexyl(2’,4’-diisopropyl-3,6-dimethoxy-[1,1’-biphenyl]-2-yl)phosphane (BrettPhos) (Table 1, entries 4–6) revealed that 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) was still the best one (Table 1, entry 7). Neither decreasing nor increasing the loading of the catalyst gave better yields (Table 1, entries 8 and 9). Examination of the reaction time showed that 2 h was the shortest reaction time and that extending the reaction time did not help to increase the yield (Table 1, entries 10 and 11). Lowering or raising the reaction temperature resulted in lower yields (Table 1, entries 12 and 13). The solvent had less effect on the reaction, and combining various factors, DCM was used for the reaction (Table 1, entries 14 and 15). When AgSbF₆ was utilized as the sole catalyst, no product was generated indicating cationic Au(I) was the true catalyst (Table 1, entry 16). A control experiment using 2,6-di-tert-butylpyridine as a proton scavenger in the IPrAuCl/AgSbF₆ system provided the product in good yield, which excluded the influence of trace amounts of acids on the reaction (Table 1, entry 17).

The Au(I)-catalyzed cycloisomerization reaction of substrate 10 occurred under the catalysis of 5 mol % [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) chloride (IPrAuCl) and 5 mol % silver hexafluoroantimonate (AgSbF₆) [25,26] in anhydrous DCM at room temperature for 2 h forming a benzene ring smoothly, leading to the exclusive formation of biaryl intermediate 11 in a yield of 82%. It is worth noting that the methoxy substitution in the substrate played a crucial role in controlling the selectivity of the cycloisomerization according to our previous study [15]. It was rationalized that the methoxy substituent in the substrate played a crucial role in controlling the selectivity of the cycloisomerization according to our previous study [15]. It was rationalized that the electron-donating phenyl ring enabled the coordination of the alkyne with the Au⁺ complex in the α-position, which promoted the silyl ether to attack the β-position of the alkyne to promote a 6-endo-dig cyclization. Next, compound 11 was subjected to a
Table 1: Optimization of the Au(I)-catalyzed cycloisomerization conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>additive</th>
<th>T (°C)</th>
<th>yield (%)</th>
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<tr>
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<td>AgCO₂CF₃</td>
<td>23</td>
<td>23</td>
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<td>5</td>
<td>JohnPhosMeCNAuSbF₆</td>
<td>DCM</td>
<td>–</td>
<td>23</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>BrettPhosAuCl</td>
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<td>AgSbF₆</td>
<td>23</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
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<td>DCM</td>
<td>AgSbF₆</td>
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<td>82</td>
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<tr>
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<td>AgSbF₆</td>
<td>23</td>
<td>63</td>
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<tr>
<td>9</td>
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<tr>
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<td>AgSbF₆</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
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<td>DCM</td>
<td>AgSbF₆</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
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<td>toluene</td>
<td>–</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>16</td>
<td>–</td>
<td>DCM</td>
<td>–</td>
<td>23</td>
<td>80</td>
</tr>
<tr>
<td>17</td>
<td>IPrAuCl</td>
<td>THF</td>
<td>AgSbF₆</td>
<td>23</td>
<td>80</td>
</tr>
</tbody>
</table>

*3 mol % IPrAuCl and 3 mol % AgSbF₆ were used. ²10 mol % IPrAuCl and 10 mol % AgSbF₆ were used. ³The reaction was run for 1 h. ⁴The reaction was run for 3 h. ⁵5 mol % 2,6-di-tert-butylpyridine was added. IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]. JohnPhos = [1,1’-biphenyl]-2-yldi-tert-butylphosphane. BrettPhos = [dicyclohexyl(2’,4’-diisopropyl-3,6-dimethoxy-[1,1’-biphenyl]-2-yl)phosphane].

Scheme 6: Formal total synthesis of macarpine (1).
solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), resulting in the formation of naphthol 12 [12,13], a key intermediate in the previous total synthesis of macarpine (I) reported by Ishikawa (Scheme 6).

To simplify the synthetic procedure, a more straightforward strategy was proposed by using alkynyl ketone 9 [27–29] as the substrate for the gold-catalyzed cycloisomerization in the presence of protic acid. It was supposed that alkynyl ketone 9 would undergo enolization under the acidic conditions, followed by a gold-catalyzed cycloisomerization to provide the naphthol 12.

To test the idea, alkynyl ketone 9 was subjected to different reaction conditions as listed in Table 2. It was observed that both the acids and the temperatures had a great influence on the cycloisomerization. An attempt was also made by using only p-toluenesulfonic acid (TsOH) in the cycloisomerization step, but no corresponding product was obtained. Finally, the optimal conditions for the Au(I)-catalyzed cycloisomerization of alkynyl ketone 9 were determined as to stir the substrate under the catalysis of 5 mol % IPrAuCl/AgSbF₆ with 2 equiv of TsOH as the additive at 70 °C for 2 h (Table 2, entry 3). It is notable that our synthetic route to naphthol 9 is shorter and proceeds with higher yield (5 steps, 59% yield) than Ishikawa’s route (9 steps, 13% yield).

**Conclusion**

In summary, the formal total synthesis of the natural product macarpine was achieved through two synthetic routes by synthesizing Ishikawa’s naphthol intermediate via Au(I)-catalyzed cycloisomerizations. Compared to the route reported in the literature, these routes are more concise and easier to perform. This gold-catalyzed strategy provides a new approach to macarpine and related benzo[c]phenanthridine alkaloids and the application of this strategy to access benzo[c]phenanthridine derivatives and further assessments of their bioactivities are currently in progress in our laboratory.

### Supporting Information

**Supporting Information File 1**

Synthetic procedures and characterization data for compounds 3–5, 8–12, and their ¹H NMR and ¹³C NMR spectra.


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**Table 2: Reaction condition optimization of the cycloisomerization of alkynyl ketone 9.**

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>solvent</th>
<th>T (°C)</th>
<th>yield (%)</th>
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<tbody>
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<td>DCM</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TsOH</td>
<td>DCM</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>TsOH</td>
<td>DCE</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>DCE</td>
<td>70</td>
<td>50</td>
</tr>
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<td>DCE</td>
<td>70</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>PhCO₂H</td>
<td>DCE</td>
<td>70</td>
<td>39</td>
</tr>
</tbody>
</table>

---

References

Synthetic study toward the diterpenoid aberrarone

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Abstract

An approach to aberrarone, an antimalarial diterpenoid natural product with tetracyclic skeleton is reported. Key to the stereoselective preparation of the 6-5-5 tricyclic skeleton includes the mediation of Nagata reagent for constructing the C1 all-carbon quaternary centers and gold-catalyzed cyclopentenone synthesis through C–H insertion.

Introduction

Marine natural products have found myriad use in new drug development, exemplified by ET-743 and eribulin [1]. Back in 1990s, Rodriguez and co-workers isolated a rich array of terpenoid natural products from the Caribbean sea whip, Pseudopterogorgia elisabethae with unprecedented carbon skeleton, most of which showed antitumor, antituberculosis and antimalarial activities [2-6]. Among these structurally intriguing natural products, aberrarone (1) shows antimalarial activity against the chloroquine-resistant strain of Plasmodium falciparum (IC50 = 10 μg/mL) [7]. Structurally, aberrarone possesses an unusual tetracyclic carbon skeleton yet-to-be found in Pseudopterogorgia elisabethae species, although related cyclohexane-angularly-fused triquinane systems have been found in waihoensene (3), conidiogenone (4), lycopodium alkaloids magellamine (5) and lycojaponicumin C (6) (Figure 1). Its seven stereogenic centers, including two all-carbon quaternary moieties collectively render aberrarone as an attractive but challenging synthetic target. Its congener elisabanolide (2) with a lactone in the D ring shows their potential biosynthetic relationship [2].

These natural products have been popular synthetic targets mainly due to their intriguing structural features. For example, several total syntheses of 3-6 have been reported [8-29]. Previously, two synthetic studies of aberrarone were reported [30,31] and more recently, Carreira and co-workers reported [32] the first total synthesis of aberrarone through an impres-
sive cascade reaction including a gold-catalyzed Nazarov cyclization, a cyclopropanation followed by intramolecular aldol reaction to forge the A, B and D rings. Impressed by the structural features and biological profiles, our group embarked a project on the total synthesis of this natural product. Herein, we report our stereoselective synthesis of its 6-5-5 tricyclic skeleton.

![Selected representative natural products with 6-5-5 tricyclic skeleton.](image)

Our retrosynthetic analysis is shown in Scheme 1. For the formation of the D ring with one quaternary carbon stereocenter and 1,2-diketone moiety, Nazarov cyclization [33] of 7 was proposed for synthesizing this challenging moiety. The corresponding precursor cyclopentenone 8 may be prepared from alkynone 9 through a gold-catalyzed C–H insertion [34]. Alkynone 9 could be achieved through functional transformation from 10, which itself would be prepared through methylation and conjugate addition from Pauson-Khand adduct 11. This cyclopentenone could be readily accessed from 1,7-enzyme 12 which could be obtained through the reported procedure [35] from the commercially available 5-hexenoic acid.

**Results and Discussion**

Our synthetic route commenced from known compound 12 which is readily accessed from 5-hexenoic acid through a reported procedure [35]. In the mediation of Co$_2$(CO)$_8$, the 6-5 bicyclic skeleton [36] was constructed with the right configuration at C6, and the explanation of this stereoselectivity is possible through the conformation of 14 where the OTBS group is in pseudoequatorial position (Scheme 2). Therefore, the Pauson-Khand reaction proceeded to afford 11 containing an α-H at C6. From this intermediate, to our delight, the stereoselective attachment of the requisite methyl group through the corresponding lithium enolate occurred from the convex face of the bicyclic ring system [37]. After these two continuous stereocenters were successfully installed, the expected challenging all-carbon quaternary center at C1 was constructed utilizing the Nagata reagent (Et$_2$AlCN). By using this strategy, the stereogenic center at C1 was synthesized, along with a smooth attachment of the cyanate group served for further functional group transformation to construct the C ring through C–H insertion. The stereochemistry finding of this conjugate addition from the convex face of the 6-5 ring system was further confirmed through X-ray crystallographic analysis.

![Scheme 1: Retrosynthetic analysis of aberrarone (1).](image)
Scheme 2: Synthetic study toward aberrarone (1).

With the key intermediate 10 in hand, we were in a position to test the planned two-step transformation including the palladium-catalyzed reductive cross coupling with HCO₂H followed by Pd/C-catalyzed hydrogenation. To our surprise, the hydrogenation turned out to be a difficult transformation due to the steric hindered environment of the trisubstituted double bond, mainly caused by the bulky OTBS group. However, direct subjection of compound 16 to hydrogenation [38] afforded reduction of both triflate and double bond. The plausible pathway for this facile transformation might proceed with first hydrogenation followed by the substitution of the labile triflate ester (for details, see Supporting Information File 1). Moving forward, compound 17 was further converted into alkynone 9 through DIBAL-H reduction, nucleophilic addition and Dess–Martin oxidation. At this stage, the pivotal C–H insertion step was tried under the reported conditions [34], and cyclopentenone 8 was successfully obtained. Further study with cross coupling or halogen–magnesium exchange shows this moiety is inert for functional group transformation. The attempt for constructing the D ring is currently undergoing.

Conclusion

In summary, we have developed an approach to assemble the tricyclic skeleton of aberrarone through stereoselective methylation, conjugate addition and gold-catalyzed C–H insertion from the readily accessed cyclopentenone. Further work to access natural product aberrarone from the key intermediate cyclopentenone 8 is currently underway, and will be reported in due course.

Supporting Information

The crystallographic data of compound 10 (CCDC 2204711) has been deposited at the Cambridge Crystallographic Database Center (http://www.ccdc.cam.ac.uk).

Supporting Information File 1
Characterization data and ¹H NMR, ¹³C NMR, and HRMS spectra of the compounds. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-173-S1.pdf]

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References

Synthesis of (−)-halichonic acid and (−)-halichonic acid B

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Abstract

The first syntheses of the amino acids (−)-halichonic acid and (−)-halichonic acid B have been achieved in ten steps starting from commercially available (−)-α-bisabolol. The optimized synthetic route includes a new purification method for isolating (−)-7-amino-7,8-dihydrobisabolene in enantiomerically pure form via recrystallization of its benzamide derivative. The key intramolecular aza-Prins reaction forms the characteristic 3-azabicyclo[3.3.1]nonane ring system of halichonic acid along with the lactonized form of halichonic acid B in an 8:1 ratio. Optical rotation measurements confirmed that these synthetic compounds were in fact the enantiomers of the natural products, establishing both the relative and absolute configurations of the halichonic acids.

Introduction

Marine sponges produce a large number of structurally diverse natural products, including many that exhibit biological activity [1-3]. In 2019, Tsukamoto and co-workers isolated the amino-bisabolene sesquiterpenoid halichonic acid ((+)-1) from the sponge Halichondra sp. (Figure 1) [4]. This amino acid natural product features a rigid 3-azabicyclo[3.3.1]nonane ring system containing four stereogenic centers within the piperidine ring. In 2021, the same group re-isolated (+)-1 from the sponge Axinyssa sp. along with the structurally related compound halichonic acid B ((+)-2) [5]. Structurally, (+)-2 is a pipecolic acid derivative containing a cyclohexenyl ring as a substituent group. This compound also features four stereogenic centers (three of which are located within the piperidine ring) and a tertiary alcohol. The structures of compounds (+)-1 and (+)-2 were elucidated through a combination of HRMS and NMR spectroscopy, while the relative configuration of each compound was established through nuclear Overhauser effect (NOE) correlations. Additionally, the absolute configuration of each compound was determined based on calculated electronic circular dichroism (ECD) spectra that were compared to the experimental ECD spectra of (+)-1 and (+)-2. Although these natural products did not exhibit antimicrobial activity or cytotoxicity against HeLa cells, their biological activities in other assays have not yet been investigated.
Our group was particularly interested in the structure of halichonic acid ((+)-1), which shares the same bridged bicyclic ring system found in many of the Aristotelia alkaloids [6]. Since our lab recently reported a synthesis of the natural product aristolochine [7], we viewed the halichonic acids as ideal targets to extend the scope of our synthetic methodology. Given the structural similarity between compounds (+)-1 and (+)-2 (and the fact that they were co-isolated from the same sponge), Tsukamoto et al. proposed that these natural products could be derived from a common biosynthetic pathway starting from farnesyl pyrophosphate and glycine [5]. This prompted us to investigate a biomimetic synthesis in which the halichonic acids could be prepared from a common imine intermediate via divergent intramolecular aza-Prins cyclizations [8]. Herein, we report the first syntheses of the enantiomers of these natural products (i.e., (−)-1 and (−)-2), confirming the structural assignments of the halichonic acids and establishing their absolute configurations.

Results

Our synthetic route began with the readily available sesquiterpenoid (−)-α-bisabolol (3), as shown in Scheme 1. In 2013, Shenvi and co-workers reported an operationally simple and high-yielding method for converting tertiary alcohols (including 3) to the corresponding primary amines via the intermediary of an isonitrile [9]. This four-step procedure was conveniently carried out on a multigram scale, affording (−)-7-amino-7,8-dihydrobisabolene (4) and its C7-epimer as an 83:17 mixture of diastereomers in 87% overall yield. Unfortunately, these diastereomers were not separable by conventional column chromatography. Although this diastereomeric mixture could be converted into a variety of amine derivatives (e.g., hydrochloride salt, mandelic acid salt, phthalimide, ketopinic acid amide, salicylaldehyde imine, p-toluenesulfonylamine, acetamide, etc.), all attempts to separate the resulting isomers (which were oils) were similarly unsuccessful.

Seeking an alternative to column chromatography, we decided to prepare solid derivatives of 4 (and its C7-epimer) that could be purified by recrystallization. Although the α-bromoacet-
amide [10] and \( p \)-bromobenzamide derivatives of these amines are solids, no change in dr was observed upon recrystallization from a variety of solvents. Fortunately, we ultimately found success with the benzamide derivative 5, which could be prepared from the mixture of 4 and its C7-epimer in 93% yield upon treatment with benzyl chloride. Recrystallization of the resulting mixture of diastereomeric amides from cyclohexane improved the dr from 83:17 to 95:5 (as determined by \(^1\)H NMR based on integration of the C7-methyl signals). A second recrystallization from cyclohexane afforded 5 as a single stereoisomer (>99:1 dr) with 42% overall recovery of material (corresponding to 51% recovery of the major diastereomer 5).

Having finally separated the C7-diastereomers, we anticipated that the amide 5 could be hydrolyzed to give a single enantiomer of amine 4. However, we found that amide 5 was remarkably resistant to hydrolysis, even under forcing conditions. For example, no amide hydrolysis was observed in concentrated aqueous NaOH solution at reflux (with or without an organic co-solvent), and slow decomposition occurred under acidic conditions at elevated temperatures. Alternative methods to cleave the benzamide using sodium peroxide [11] or triethylxonium tetrafluoroborate [12] were also unsuccessful, giving either no reaction or significant decomposition, respectively. At this stage, we started to investigate alternative methods to cleave the amide via reduction. Achieving selective C-N-bond cleavage of amides under reductive conditions is still a largely unsolved problem since a C-O-bond cleavage is typically the preferred mode of reactivity, especially when using hydride reducing agents [13]. Nevertheless, specialized conditions for achieving C-N-bond cleavage of amides using SmI\(_2\) [13], \( \text{Ti}_x\text{O/} \text{Et}_y\text{SiH} \) [14], and stoichiometric Schwartz’s reagent [15] have been reported; however, none of these methods was successful in reducing amide 5 to the desired amine 4.

Although there is one literature example of directly reducing a benzamide with diisobutylaluminum hydride (DIBAL) to achieve C-N-bond cleavage [16], we observed exclusive over-reduction of compound 5 under these conditions to form the corresponding \( N \)-benzylamine, even at \(-78^\circ\text{C}\). We next investigated the reducing agent sodium bis[2-methoxyethoxy]aluminum hydride (Red-Al\(^{\oplus}\)), which is a convenient alternative to LiAlH\(_4\) that exhibits high solubility in organic solvents and is also known to reduce amides [17]. When a solution of amide 5 in toluene was treated with an excess of Red-Al\(^{\oplus}\) at \( 0^\circ\text{C} \), rapid gas evolution (likely \( \text{H}_2 \)) occurred. However, no reduction of the amide was observed, even after stirring at room temperature for 24 hours. In an effort to “salvage” the reaction by reducing the amide to the corresponding \( N \)-benzylamine (which could potentially be oxidized to the corresponding imine with IBX [18] and subsequently hydrolyzed to give 4), we added excess DIBAL and allowed the reaction mixture to stir at room temperature for an additional 24 hours. Upon quenching the reaction with a saturated aqueous solution of potassium sodium tartrate (Rochelle’s salt), we were astonished to observe the clean formation of imine 6. Presumably, the combination of Red-Al\(^{\oplus}\) and DIBAL reacts with amide 5 to form a stable tetrahedral intermediate that collapses to 6 upon aqueous workup. This type of direct amide semi-reduction using aluminum hydride reagents is, to the best of our knowledge, previously unknown within the chemical literature and is especially notable since it does not require cryogenic temperatures. Efforts to further investigate the scope of this unique transformation are currently underway in our laboratory and will be reported in due course.

Attempts to purify imine 6 by column chromatography on silica gel resulted in extensive decomposition. Therefore, the crude imine was immediately hydrolyzed using aqueous citric acid [14], affording \((-\text{-})\)-7-amino-7,8-dihydroisabolene (4) as a single stereoisomer in 90% yield over the two steps. The enantiomer of 4 is itself a natural product with cytotoxic, antifungal, and antimicrobial properties [10,19-22]. Notably, \((+)\)-4 was also co-isolated with compounds \((+)\)-1 and \((+)\)-2 in sponge extracts, suggesting that these compounds may share a common biosynthetic pathway [4,5]. Both enantiomers of 4 have been previously synthesized [9,23,24], and this compound has also been prepared in racemic form [25]. To supply the final two carbon atoms found in the halichonic acids, amine 4 was condensed with a solution of ethyl glyoxylate in toluene, giving imine 7 in 95% yield. We found that imine 7 could be purified by column chromatography on silica gel if the mobile phase contained approximately 2% triethylamine as a basic additive. However, it is also possible to use crude 7 in the subsequent cyclization step without significantly affecting isolated yields. \(^1\)H NMR analysis showed that 7 was formed as a single geometrical isomer; although the imine configuration was not rigorously established, we have assigned it as the \((E)\)-isomer, as is commonly observed in aldime formation.

The stage was now set for the key intramolecularaza-Prins reaction that would form the bicyclic structures of the halichonic acids (Scheme 2). When a solution of imine 7 in chloroform was treated with a large excess (85–100 equiv) of formic acid at room temperature, we were pleased to observe the formation of bicyclic compound 8 as the major product in 64% yield. Notably, 8 is the ethyl ester of \((-\text{-})\)-halichonic acid and features the characteristic 3-aza[bicyclo[3.3.1]nonane ring system found in this natural product. However, we were intrigued that a competing cyclization process also formed isomeric lactones 9 and 10 in 8% yield and 11% yield, respectively. \(^1\)H NMR analysis confirmed that compounds 9 and 10 were...
were both trans-fused 6/5 bicycles based on the magnitude of the vicinal coupling constant between the two methine hydrogens at the ring fusion ($^3J = 12.9 \text{ Hz}$). The rigid nature of the trans-fused 6/5 ring system results in distinct conformers for 9 and 10; fortunately, this allowed for the unambiguous assignment of the relative configurations of these diastereomers via NMR based on nuclear Overhauser effect (NOE) correlations (see the Supporting Information File 1 for additional details). This analysis showed that the minor product 9 corresponded to the lactone of ($\text{-}$)-halichonic acid B.

At this point, all that remained to complete the syntheses of the halichonic acids was hydrolysis of compounds 8 and 9 to form the corresponding amino acids. Thus, treating bicycle 8 with aqueous lithium hydroxide resulted in hydrolysis of the ethyl ester, and subsequent neutralization with pH 7 phosphate buffer afforded halichonic acid ($\text{-}$)-1 in 88% yield after purification by column chromatography. Similarly, hydrolysis of lactone 9 under analogous conditions afforded halichonic acid B ($\text{-}$)-2 in 76% yield. $^1\text{H}$ and $^{13}\text{C}$ NMR data for the synthetic compounds ($\text{-}$)-1 and ($\text{-}$)-2 were identical to those reported for the halichonic acids, confirming the proposed structures of these natural products. However, the observed optical rotations of these synthetic compounds were of opposite sign to those reported for the halichonic acids. Since we synthesized the enantiomers of these natural products, the absolute configurations of (+)-1 and (+)-2 assigned by Tsukamoto et al. have now been experimentally confirmed [4,5]. For the sake of comparison, the diastereomeric lactone 10 was also hydrolyzed under the same conditions to form the “unnatural” product 11 in 70% yield, which we have designated ($\text{-}$)-isohalichonic acid B. Although the NMR spectra of ($\text{-}$)-2 and 11 are quite similar, we did note a
Discussion

Rationalizing the outcome of the aza-Prins reaction leading to the formation of ethyl ester 8 and isomeric lactones 9 and 10 (Scheme 2) provides an interesting exercise in acyclic conformational analysis. Three divergent mechanistic pathways can be formulated by considering the different conformers of protonated imine 7, namely iminium ions 12a–c (Scheme 3). In each case, the chair-like transition state of the intramolecular aza-Prins reaction is controlled by the C7-stereogenic center, which bears a methyl group, the electrophilic site (the iminium ion), and two possible nucleophilic sites (a prenyl group and a trisubstituted alkene within a cyclohexene ring).

In conformer 12a, the prenyl group occupies a pseudo-axial position, the methyl group occupies a pseudo-equatorial position, and the trisubstituted alkene within the six-membered ring serves as the nucleophile. It is important to note that in this chair-like conformer, the ethyl ester group at C2 assumes a pseudo-equatorial position. Although an alternative boat-like conformer is also possible (which would ultimately lead to the C2-epimer of 8), the resulting transition state is presumably much higher in energy. In practice, the intramolecular aza-Prins reaction of 12a forms a new carbon–carbon bond to generate a rigid 3-azabicyclo[3.3.1]nonane ring system (13). Although

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**Scheme 3:** Proposed intermediates for the intramolecular aza-Prins reaction leading to the formation of ethyl ester 8 and isomeric lactones 9 and 10.
several different fates could be envisioned for this carbocation (e.g., a nucleophilic attack of formic acid to give a formate ester), only alkene formation was observed in this system. Interestingly, the deprotonation step is completely regioselective, giving the more highly substituted endocyclic trisubstituted alkene found in 8 as opposed to the isomeric exocyclic 1,1-disubstituted alkene [7,8]. Alternative mechanistic pathways involving (1) deprotonation to form a bridgehead alkene, or (2) intramolecular nucleophilic attack of the ethyl ester to form a lactone are not possible in this system due to the rigid geometric constraints of the 3-azabicyclo[3.3.1]nonane ring system. In any case, this aza-Prins reaction is by far the preferred mode of cyclization of iminium ion 12 based on the isolated yield of 8 (64%), ultimately leading to the carbon skeleton found in the natural product halichonic acid ((+)-1).

In conformer 12b, the cyclohexenyl ring system occupies a pseudo-axial position, the methyl group occupies a pseudo-equatorial position, and the trisubstituted alkene of the prenyl group serves as the nucleophile. The chair-like transition state of the intramolecular aza-Prins reaction allows both the ethyl ester and the resulting tertiary carbocation to occupy equatorial positions (14), establishing the observed trans-relationship between these groups while simultaneously setting two new stereogenic centers. As before, one can envision several different fates for the tertiary carbocation present in 14. Although elimination to form an alkene or intramolecular nucleophilic attack by formic acid (ultimately giving a formate ester) are reasonable mechanistically, only the intramolecular nucleophilic attack by the carbonyl group of the pendent ethyl ester was observed in this system to form the resonance-stabilized oxocarbenium ion 16. Subsequent loss of the ethyl group (either as ethyl formate upon solvolysis with the formic acid co-solvent or as ethanol upon aqueous workup) gives lactone 9, which features a strained trans-fused 6/5 ring system. Although this lactone survives aqueous workup at neutral pH, it is rapidly hydrolyzed under basic conditions (Scheme 2) to form the enantiomer of halichonic acid B ((−)-2). It is interesting to note that halichonic acid B exists exclusively as an open-chain 4-hydroxyxycarboxylic acid even though the corresponding γ-lactones typically form spontaneously. Indeed, no lactone formation was observed from (−)-2 even upon purification by column chromatography on silica gel, reflecting the highly strained nature of trans-fused lactone 9.

Finally, conformer 12c is similar to 12b in that the trisubstituted alkene of the prenyl group once again serves as the nucleophile; however, the methyl group now occupies a pseudo-axial position, and the cyclohexenyl ring system occupies a pseudo-equatorial position. In this case, the aza-Prins reaction forms trans-fused lactone 10 via an analogous intramolecular nucleophilic attack of the ethyl ester on the intermediate tertiary carbocation 15 to give oxocarboxylic acid even upon purification by column chromatography. Indeed, no lactone formation was observed even though the corresponding halichonic acid B exists exclusively as an open-chain 4-hydroxycarboxylic acid ((+)-2, 8, 9, 10, and 11). A tabular comparison between the NMR data reported for natural products (+)-1 and (−)-2 and that obtained for their synthetic enantiomers (+)-1 and (−)-2 is also provided.

Conclusion
In summary, we have synthesized the enantiomers of halichonic acid and halichonic acid B in 10 steps starting from commercially available (−)-α-bisabolol (3). An important intermediate in our route was (−)-7-amino-7,8-dihydrobisabolene (4), which was prepared in enantiomerically pure form following recrystallization of a diastereomeric mixture of the corresponding benzamides. A common imine intermediate (7) underwent two different intramolecular aza-Prins reactions in the presence of formic acid to give the ethyl ester of (−)-1 and the lactone of (−)-2 in 64% yield and 8% yield, respectively. Subsequent hydrolysis of these intermediates under basic conditions afforded (−)-halichonic acid and (−)-halichonic acid B, confirming the proposed structures of the natural products. Efforts to investigate the biological activities of compounds (−)-1 and (−)-2 and their synthetic analogs are currently underway in our laboratory.

Supporting Information
The supporting information file contains detailed experimental procedures, full characterization data and copies of 1H and 13C NMR spectra for all new compounds, and complete NMR spectral assignments for compound (−)-1, (−)-2, 8, 9, 10, and 11. A tabular comparison between the NMR data reported for natural products (+)-1 and (−)-2 and that obtained for their synthetic enantiomers (−)-1 and (−)-2 is also provided.

Supporting Information File 1
Experimental procedures, characterization data and copies of 1H and 13C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-174-S1.pdf]
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Total synthesis of grayanane natural products

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Abstract

Grayananes are a broad family of diterpenoids found in Ericaceae plants, comprising more than 160 natural products. Most of them exhibit interesting biological activities, often representative of Ericaceae use in traditional medicine. Over the last 50 years, various strategies were described for the total synthesis of these diterpenoids. In this review, we survey the literature for synthetic approaches to access grayanane natural products. We will focus mainly on completed total syntheses, but will also mention unfinished synthetic efforts. This work aims at providing a critical perspective on grayanane synthesis, highlighting the advantages and downsides of each strategy, as well as the challenges remaining to be tackled.

Introduction

The Ericaceae are a large plant family, with over 4250 known species all around the world [1]. While Ericaceae’s toxicity has been known since at least 400 BC, barks, leaves and flowers from these plants are still commonly used in traditional medicine in Asia, Europe and America, mainly for their anti-inflammatory and analgesic properties, but also to treat different conditions (e.g. arthritis, hypertension, diabetes, lung, liver and gastrointestinal disorders), and for crop protection [2].

Among natural products formed by Ericaceae, grayananes are a wide diterpenoid family whose biological activities are often representative of Ericaceae’s use in traditional medicine [3-5]. In particular, many grayananes were found to have analgesic [6], antifeedant [7-9], antituberculosis [10], cytotoxic [11] and antioxidant [12] properties. The grayanane family comprises more than 160 natural products, and new members are isolated every year. For instance, 13 new grayanane natural products were reported since 2020 [13-16].

Grayanane diterpenoids all share the same tetracyclic skeleton, with 5, 7, 6 and 5-membered carbocycles commonly named A, B, C and D (Figure 1). The diversity in this family arises from different oxidation states at positions 2, 3, 5, 6, 7, 10, 14, 15, 16, and 17 which can bear free, acylated or glycosylated alcohol, olefin, ketone or epoxide functionalities.

From a biosynthetic point of view, grayananes arise from an oxidative rearrangement of the ent-kaurane skeleton (Scheme 1).
The diversity is generated by cytochromes P450 (CYP) enzymatic oxidation of the grayanane skeleton [17].

The biological activities and low extraction yields have prompted various research groups to undertake the total synthesis of grayanane natural products. In this work, we will survey the literature for synthetic routes to grayanane diterpenoids, including uncompleted approaches. The review is chronologically organized, starting from the earliest synthetic efforts from 1971 to the latest in 2022. In a last part we will present unfinished syntheses.

Review
Early syntheses by Matsumoto and Shirahama

The first synthetic approach towards a grayanane natural product was reported by Matsumoto in the 70s, using a relay approach. The authors first reported in 1972 the synthesis of grayanotoxin II from a degradation product obtained in a few steps from grayanotoxin II itself (Scheme 2) [18]. Later on in 1976 [19], the same authors reported the synthesis of intermediate 1 from the known phenanthrene derivative 2 [20]. The tricyclic compound 2 was converted to 3 through a 6-step sequence involving reduction of the aromatic ring and oxidation of the enone to a dieneone. The resulting dieneone 3 underwent a key photoinduced santonin-like rearrangement in the presence of acetic acid, furnishing 4 in high yield. It should be noted that the group of Hiraoka had previously reported a similar rearrangement for the synthesis of a grayanane-type skeleton [21]. Further methylation and protecting group interconversions lead to an advanced tricyclic structure 5, which could be further elaborated into relay intermediate 1.

Although Matsumoto’s approach does not fit with the requisites of modern organic synthesis, as it requires over 40 steps to synthesize grayanotoxin II and was performed in racemic form (in the case of the formal synthesis), it represents an impressive piece of synthetic work. Achieving the synthesis of such a com-
plex structure represented a challenging puzzle at that time, and was brilliantly solved by Matsumoto and co-workers.

Almost 20 years later, in 1994, Shirahama’s group published the total synthesis of another member of the grayananes: grayanotoxin III [22]. One of the keys of their synthesis was the stereocontrolled 7-membered ring closure through a SmI$_2$-promoted pinacol coupling. This reaction had been previously described by the same group and proved to be highly effective [23]. For rings A, C and D, other SmI$_2$-promoted steps were employed, giving respectively the cyclopentane A ring moiety and the bicyclo[3.2.1]octane CD ring system with the correct configuration.

The synthesis started from commercially available (S)-2-((p-toluenesulfonyl)oxy)-1-propanol (6) which was converted to (R)-2-(benzyloxy)propionaldehyde (7) by a sequence involving formation of the a phenyl sulfide through an epoxide intermediate, protection of the secondary alcohol as a benzyl ether, oxidation of the sulfur and Pummerer rearrangement (Scheme 3). A
Wittig reaction gave compounds 8, as a 10:1 separable dia- stereomeric mixture. A diastereoselective Diels–Alder cycload- dition followed by oxidation of the resulting epimeric mixture gave substituted cyclohexanone 9, corresponding to the future C ring [24]. After deprotonation, the C3 position was stereoselec- tively alkylated using propargyl bromide, and the benzyl protecting group was cleaved with FeCl3, leading to spontaneous lactone closure. A Luche reduction stereoselectively con- verted enone 10 to the corresponding allylic alcohol, followed by an Au-catalyzed alkylene hydration, providing hemiketal 11. This intermediate was in equilibrium with hydroxy-ketone 12, which was suitable for a SmI2-promoted cyclization, affording intermediate 13 selectively, already bearing rings C and D. The selectivity was achieved by chelation of the Sm(III) interme- diate with hydroxy groups present on the structure. As the direct coupling with the A-ring precursor failed, a strategy to build this part was developed, starting with a sequence involving a protection of the alcohols as MOM ethers, lactone hydrolysis, esterification, and Jones oxidation, affording intermediate 14 with a good 79% yield over 4 steps. Next, the methyl ketone was converted to an enol triflate, and then coupled with Li2CuCN(CH2SPh)2. A reduction of the ester with DIBAL, fol- lowed by Dess–Martin oxidation and Wittig reaction lead to the formation of 15. This intermediate was coupled with an (R)- epoxide in presence of s-BuLi, and intermediate 16 with E con- figuration was then obtained by a (PhS)2-accelerated 1,3-sulfide shift. The A ring was then cyclized by a sequence consisting of protection of the alcohol, oxidative cleavage of the PMB protecting group, Dess–Martin oxidation, and SmI2-induced cyclization. This last step was highly selective, giving solely the intermediate 17. The synthesis was then pursued by the hydro- boration–oxidation of the monosubstituted alkene, followed by stereoselective epoxidation of the 1,1-disubstituted olefin and reductive epoxide ring-opening giving triol 18. After oxidation of the primary and the secondary alcohols with Dess–Martin periodinane, the remaining tertiary alcohol was protected as a MOM ether and the silyl ether protecting group was removed. The obtained intermediate 19 was then a suitable starting material for the SmI2-promoted pinacol coupling, directed by the free hydroxy group, affording a complete selectivity in the for- mation of the 7-membered ring B. The synthesis of grayan- otoxin III was then achieved by acetylation of the secondary alcohols, oxidative cleavage of the MOM protecting groups fol- lowed by hydrolysis of the acetyl protecting groups, affording the desired product with spectral data identical to reported natural samples.

Shirahama’s synthesis was an illustrative example that rings A, B and the bicycle CD of grayananes could all be obtained by SmI2-promoted steps, obtaining excellent selectivity in all cases. Alternatively, the same year, the authors published a vinyl radical cyclization occurring in presence of n-Bu3SnH, providing a stereoselective access to the bicyclo[3.2.1]octane unit corresponding to the CD rings [25].

Newhouse’s synthesis of principinol D

In 2019, Newhouse’s group published a total synthesis of prin- cinol D [26], a compound isolated from Rhododendron prin- cipis in 2014 [27,28]. Compared to grayanotoxin III, prin- cinol D displays an inverse configuration at C1 as well as an exo-olefin at C10–C20. The strategy developed by the group relied on the obtainment of two distinct fragments, a racemic bi- cyclo[3.2.1]octane unit 25 corresponding to rings C and D, and an enantioenriched cyclopentyl aldehyde derivative 29, corre- sponding to ring A. These fragments were successfully coupled under basic conditions, and the ring B was later reductively closed using SmI2.

The synthesis of fragment 25 began with commercially avail- able cyclohexenone (21), which underwent a copper-catalyzed vicinal difunctionalization with vinylmagnesium bromide and DMPO and trapping using methyl cyanoformate, leading to the formation of ketoester 22 (Scheme 4). This intermediate was then allylated, the ester group selectively reduced with Zn(TMP)2 and LiBH4,NMe2 and the resulting primary alcohol was protected as a TBS ether, providing intermediate 23 as a single diastereomer. This key intermediate 23 was then submitted to a Ni-catalyzed α-vinylation and direct TBS deprotection giving the bicyclo[3.2.1]octane subunit with a good yield of 74%. A sequence involving diastereoselective reduc- tion of ketone 24 with SmI2, Appel reaction to convert the pri- mary alcohol to the corresponding primary alkyl iodide fol- lowed by a MOM protection of the secondary alcohol afforded fragment 25 with 73% yield over 3 steps. On the other hand, the enantioenriched cyclopentyl aldehyde fragment 29 was ob- tained starting from commercially available 2,2-dimethylcyclo- pentane-1,3-dione (26). The dione was submitted to a se- quence involving a monoreduction, protection of the alcohol as a TBS ether, α,β-desaturation, dithiane addition, MOM protec- tion and dithiane deprotection.

The fragment 25 was then lithiated with t-BuLi and the fragment 29 was then added, forming the coupling product as a 5:5:1:1 separable mixture of diastereomers (Scheme 5). The desired diastereomer 30 was isolated with a yield of 26%. The secondary alcohol was protected as a MOM ether and the allylic silyl ether was converted to an enone. A selective oxidative cleavage, only affecting the monosubstituted alkene, led to the formation of 31, which underwent a key SmI2-promoted seven-membered ring closure, giving a single diastereomer. The stereochemistry and absolute configuration of the obtained tetracyclic structure 32 was confirmed by NOESY NMR and X-ray crystallography.
Scheme 4: Newhouse’s syntheses of fragments 25 and 29.

Some additional modifications were required on the structure to synthesize principinol D: oxidation of the secondary alcohol to the corresponding ketone was achieved using Dess–Martin periodinane with a pyridine buffer. Addition of Me$_3$SiCH$_2$Li efficiently afforded the Peterson adduct 33. The 1,1-disubstituted alkene was then submitted to Mukaiyama hydration to form the tertiary alcohol, in presence of Mn(dpm)$_3$, PhSiH$_3$ and O$_2$. Then, the ketone was selectively reduced in the presence of LiEt$_2$BH, while the Peterson adduct was eliminated concurrently, upon heating. Finally, treatment with H$_2$SO$_4$ allowed
total deprotection of the MOM ethers, leading to the formation of principinol D, in complete correspondence with reported spectral data.

Newhouse’s synthesis represents an efficient access to grayananes, relying on two accessible fragments. Remarkably, although the strategy is different from that of Shirahama as it involves different retrosynthetic disconnections, it makes use of similar tactics through the use of a SmI$_2$-promoted cyclization. This first total synthesis of principinol D, in 19 steps as the longest linear sequence, is asymmetric even though a separation of the mixture of diastereomers resulting from fragment coupling is necessary. The SmI$_2$-mediated reductive ring-closure of the 7-membered ring is among the most remarkable steps of the synthesis, along with the Ni-catalyzed formation of the bicyclo[3.2.1]octane unit. It should be noted that due to the SmI$_2$-mediated ring-closure’s stereochemical outcome, this synthesis can only be applied to compounds with an R-configured C$^1$ stereocenter, which are epimers of the vast majority of grayanane structures.

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Ding’s synthesis of rhodomolleins XX and XXII

Shortly after Newhouse’s synthesis, Ding’s group reported a synthetic strategy to access rhodomollein XX and XXII [29,30]. These natural products have the particularity of displaying an enone moiety on ring A. Ding’s approach involves the construction of a tetracyclic structure where rings A and B had the correct arrangement, while rings C and D form a bicyclo[2.2.2]octane structure [31]. The correct bicyclo[3.2.1]octane structure was obtained after a key reductive epoxide opening/Dowd–Beckwith rearrangement cascade.

The synthesis started from 3-hydroxy-2-methoxybenzaldehyde (34), which was converted into Grignard reagent 35 and added onto 3-methylbut-2-enal (Scheme 6). A sequence involving Claisen rearrangement, Roskamp homologation, diazo transfer and intramolecular cyclopropanation led to intermediate 37. The hydroxy group on C$^6$ was introduced after cyclopropane ring-opening, ketone protection, epoxidation and reductive ring-opening of the resulting epoxide. A one-pot β-keto phos-
phonic/Emmons reaction with formaldehyde afforded 38, a precursor for the key oxidative dearomatization-induced Diels–Alder cycloaddition. Treatment of 38 with TBAF followed by Phl(OAc)₂ led to the formation of 39, having the A and B ring correctly arranged. The product was obtained in 70% yield, along with 25% of an undesired diastereoisomer. The dimethoxy functionality was reduced in the presence of Kagan’s reagent and DMDO could induce an epoxidation on the strained olefin. From intermediate 40, the key reductive epoxide opening/Dowd–Beckwith rearrangement cascade could be performed in the presence of an in situ-generated Ti(III) catalyst. The main side-product of this reaction was due to a simple reductive opening of the epoxide (15%). From 41 having the correct tetracyclic skeleton, a transient protection followed by Petasis olefination, deprotection, selenide-mediated α,β-dehydrogenation and Mukaiyama oxidation afforded an advanced intermediate 42 bearing most of the target’s functionalities. A sequence of enol-ether formation/Grignard addition lead to intermediate 43, from which simple acidic treatment led to rhodomollein XXII, while α-oxidation in the presence of rhenium oxide followed by acidic work-up afforded rhodomollein XX.

Interestingly, Ding’s synthesis constitutes an efficient approach (22 and 23 steps) to access grayananes with a cyclopentenone moiety on the A ring. It should be noted that although this is a racemic synthesis, intermediate 37 was also synthesized in enantioenriched form using a chiral copper catalyst for the cyclopropanation and a chiral auxiliary on the ester moiety. Moreover, the same group reported a related approach for the synthesis of various diterpenoids including rhodomollanol, an abeo-grayanane natural product [32,33].

**Luo’s synthesis of grayanotoxin III, principinol E and rhodomollein XX**

In 2022, Luo et al. described an efficient and enantioselective synthetic route based on a convergent strategy to accomplish the synthesis of principinol E, grayanotoxin III and rhodomollein XX [34]. The key steps include i) a tandem reaction combining organocatalytic Mukaiyama aldol and intramolecular Hosomi–Sakurai reactions in a one-pot manner; ii) a 7-membered cyclization based on a bridgehead tertiary carbocation intermediate forging the B ring; iii) redox manipulations and a 1,2-migration as final steps. The synthesis started from (S)-ketone 44 which was prepared via asymmetric CBS reduction of diketone 26 (Scheme 7). Firstly, this (S)-ketone 44 was transformed into dimethylacetal 45 by Vilsmeier reaction followed by aldehyde protection in 54% yield over two steps. A Mukaiyama aldol reaction between trimethylsilyl enol ether 46 and dimethylacetal 45 followed by Sakurai cyclization provided an inseparable mixture of C⁹ epimers (dr = 2:1). A catalyst optimization showed that chiral squaramide 47 developed by Jacobsen’s group significantly accelerated the Mukaiyama reaction compared to TMSOTf or TiCl₄ thanks to chiral hydrogen bond-donor effect [35]. After Sakurai cyclization promoted by EtAlCl₂, the desired product 48 was obtained with the required diastereoselectivity in 58% on a 3 g scale. Subsequently, vinyl halide 48 was converted to diene 50 by Suzuki coupling with potassium vinyltrifluoroborate (49) in 90% yield (Scheme 8). The C⁷–C⁸ bond formation from a bridgehead carbocation was a real challenge to close the 7-membered ring. To achieve this, the secondary alcohol was oxidized by DMP, the tertiary alcohol was triflated, 4-phenylpyridine was added and the mixture was heated at 80 °C for 14 h. The intermediate carbocation was trapped by the terminal olefin, generating a dienone 51 after deprotonation at the relatively acidic position C². A singlet oxygen ene reaction involving the electron-rich olefin allowed the formation of an aldehyde, which was directly cleaved by an iridium-catalyzed deformylation, affording 52 in one-pot [36]. Deprotonation with KHMS allowed the formation of an electron-rich diene which could again react with singlet oxygen by diastereoselective cycloaddition followed by C¹⁵–C¹⁶ epoxidation with m-CPBA. Reductive cleavage of the O–O bond by Zn/AcOH treatment afforded epoxide 53 as a single diastereomer in two steps and 65% yield. The correct bicyclo[3.2.1]octane was obtained by Wagner–Meerwein epoxide rearrangement promoted by EtAlCl₂. Two separable alkene regioisomers 54 and 55 were
obtained in 19% and 50% yield, respectively. A metal-catalyzed hydrogen atom transfer (MHAT) allowed 54 to be partially converted to 55 via Shenvi’s isomerization [37]. Selective TBS protection on the bicyclo[3.2.1]octane moiety and ketone methylation gave access to 56. Directed C1–C5 vanadium-mediated epoxidation followed by DBU treatment and TBS deprotection afforded 57 in one pot. The tertiary alcohol 58 was obtained as a single diastereomer after hydration of position C18. Subsequent reduction with DIBAL-H gave the desired alcohol on the A ring in 75% yield. The C3 epimer was also obtained in 4% yield and confirmed by X-ray diffraction. Hydrogenation of the sterically hindered C1–C2 alkene was accomplished using a combination of Mn(dpm)3 and Ph(iPrO)SiH2, providing grayanotoxin III in 51% yield.

The authors also achieved the synthesis of principinol E and rhodomoline XX by slight modifications of the late-stage functional group transformations. The synthesis of principinol E was performed in 6 steps starting from 60, which was obtained by protection of 55 (Scheme 9). As before, directed epoxidation of C1–C5 in compound 60 was employed to form an α,β-epoxyketone intermediate which underwent SmI2 reduction at −78 °C, giving access to the desired syn diastereomer with good selectivity (dr = 8.5:1). The free alcohol was then protected with an ethoxymethyl ether (EOM). Finally, Peterson olefination, stereoselective carbonyl reduction and TBS deprotection afforded principinol E in 53% yield over 4 steps. For the synthesis of rhodomoline XX, an additional oxidation state at the C2 position was required. Luo’s team used Davis’ oxaziridine followed by treatment with K2CO3 to equilibrate the hydroxyketone, delivering an inseparable epimeric mixture (1:3) of 63 in 31% overall yield. An additional TBS protection allowed
Scheme 9: Synthesis of principinol E and rhodomollein XX.

separation of the epimers. After acidic treatment, pure rhodomollein XX and 3-epi-rhodomollein were obtained in 31% and 34% yield in two steps, respectively.

Luo’s synthetic work offers a powerful approach to synthesize grayanane natural products. The synthesis is both efficient (18 to 20 steps) and flexible, as demonstrated by the synthesis of 3 natural products, using pivotal intermediates 54 and 60.

Other synthetic efforts
In 2011, Williams and co-workers reported an efficient synthetic route detailing the central core construction of pierisformaside C, which is the first grayanane isolated displaying three central double bonds (Scheme 10) [38]. The team’s objective was to develop a synthetic pathway also giving access to several diterpene glycosides close to pierisformaside C in order to study the biological activity of this family. Their strategy was based on a common forward intermediate and a late construction of the central seven-membered ring.

In the beginning of the synthesis, the authors followed the strategy developed previously by Marinovi’s group to form the bicyclo[3.2.1]octane moiety [39]. The synthesis started from 64 with a one-pot Birch reduction/alkylation with vinyl bromide 65, affording 66 in 68% yield over two steps. Next the construction of the bicyclo[3.2.1]octane 67 was achieved by a radical cyclization using n-Bu3SnH in refluxing toluene. A sequence involving an ester reduction, Ley–Griffith oxidation and Seyferth–Gilbert homologation with Bestmann–Ohira reagent allowed to obtain the alkynyl bicyclo[3.2.1]octane 69. On the other hand, the five-membered trflate 71 was synthesized from diketone 26 in 5 steps and 37% overall yield. Both fragments were assembled by a Sonogashira cross-coupling, affording 72 in 72% yield. In a first attempt, TBS protection was considered on the bicyclo[3.2.1]octane. However, later in the strategy, the deprotection presented some difficulties, and the authors decided to investigate the use of a free ketone. The partial hydrogenation of alkyne 72 proved to be inefficient, due to a lack of chemoselectivity involving competitive olefin reduction on the bicyclo[3.2.1]octane. To overcome the over-oxidation, 72 was treated with m-CPBA, providing epoxide 73 as the main product in 71% yield (dr = 6:1). Lindlar hydrogenation of the alkyne and cyclization proceeded smoothly, and the tetracyclic skeleton 74 was obtained in moderate yield. However, the synthesis of pierisformaside C was never completed. The missing transformations include the removal of the ketone on the C ring, epoxide reductive opening, formation of the B ring exo-olefin, and glycosylation.
In 2021, Hong et al. presented a synthetic effort focused on the synthesis of rhodojaponin III B–C rings [40]. The authors employed a Mn(III)-mediated intramolecular radical cyclization of an alkynyl ketone as the key step. The synthesis started by a Cu-catalyzed conjugate addition of the vinyl Grignard reagent, followed by TMS α-propargylation under basic conditions, affording the TMS-alkynyl ketone 76 as the major diastereomer (Scheme 11). Originally a Au-catalyzed Conia-ene-type cyclization, classically considered as a reliable method for the construction of bridged bicyclic structures [41], was envisaged. However, using a gold(I) catalyst the desired 5-exo-dig cyclization failed and only a 6-endo-dig cyclization was observed. Thus, Hong et al. explored a Mn(III)-mediated radical cyclization, an approach which had been previously reported by Jia and co-workers during the synthesis of glaucocalyxin A [42]. After treatment with Mn(OAc)₃, the desired 5-exo-dig cyclization product 77 was obtained in 43% yield as an E/Z mixture. The TMS group was removed under acidic conditions. Then, a wide range of reducing agents was explored for the stereoselective ketone reduction. However, only the undesired diastereomer was obtained. Knowing that the correct diastereomer could be obtained in the presence of a primary alcohol instead of the ester moiety, as described by Newhouse previously [26], the authors performed a complete reduction of the carbonyl moieties using LiAlH₄ and TBS protection of the primary alcohol, affording intermediate 78 with the wrong configuration at the secondary alcohol stereocenter. After reoxidation and deprotection of the primary alcohol, SmI₂ reduction finally afforded the desired diastereomer 79. This synthetic work highlights again the challenge of the bicyclo[3.2.1]octane construction, especially regarding the diastereocontrol at the secondary alcohol moiety. To date, this approach towards rhodojaponin III was never concluded.

Conclusion

Over the past 50 years, the synthesis of grayanane natural products has attracted the interest of many synthetic chemists, leading to the development of five total synthesis approaches, as well as two unfinished syntheses [43]. Table 1 summarizes the completed total syntheses in terms of steps, yields, advantages and drawbacks. The clear superiority of recent syntheses beauti-
Table 1: Summary of previous syntheses.

<table>
<thead>
<tr>
<th>Synthesis</th>
<th>Number of steps</th>
<th>Overall yield</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto (1972–1976) [18,19]</td>
<td>&gt;40</td>
<td>&lt;0.0005%</td>
<td>–</td>
<td>many steps, racemic</td>
</tr>
<tr>
<td>Shirahama (1994) [22]</td>
<td>38</td>
<td>0.05%</td>
<td>enantioselective</td>
<td>many steps</td>
</tr>
<tr>
<td>Newhouse (2019) [26]</td>
<td>19</td>
<td>0.4%</td>
<td>convergent, few steps</td>
<td>limited to C₁ epimers of the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>general structure</td>
</tr>
<tr>
<td>Ding (2019) [31]</td>
<td>22–23</td>
<td>1.2–1.4%</td>
<td>few steps, highest</td>
<td>limited to C₁–C⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>yielding</td>
<td>dehydrogenated grayananes</td>
</tr>
<tr>
<td>Luo (2022) [34]</td>
<td>18–20</td>
<td>0.01–0.5%</td>
<td>few steps, flexible</td>
<td>lower yields</td>
</tr>
</tbody>
</table>

fully showcases the progresses in the field of organic synthesis over the last decades. Among the last three syntheses, Newhouse’s work has the huge advantage of being convergent, allowing a short synthesis (19 steps longest linear sequence). On the other hand, this strategy is limited to the synthesis of C₁ epimers of the grayanane general structure. Although linear and thus requiring a few more steps, Ding’s syntheses still provide higher yields than Luo’s and Newhouse’s. Still, this strategy is also limited in terms of accessible structures, as only C₁–C⁵ dehydrogenated natural products are obtained. It should be noted that despite this, a similar approach was applied by Ding’s group to the synthesis of various diterpenoids. Finally, Luo’s synthesis has the advantage of being more flexible, as it allows the synthesis of the general structure of grayananes. Nevertheless, this approach is somehow lower yielding than the previous ones. Regarding enantioselectivity, both Newhouse’s and Luo’s syntheses rely on an enantioenriched precursor obtained in 86% ee. On the other hand, while Ding’s syntheses were performed in racemic form, the authors showed that a key intermediate could be obtained enantioselectively (93% ee) by a combination of a chiral catalyst and chiral auxiliary, although requiring extra steps for auxiliary installation and cleavage.

Scheme 12 summarizes the last 3 synthetic strategies for grayanane synthesis. Each group proposes different disconnections. Newhouse identified a C¹–C¹⁰ disconnection for a radical cyclization and a C⁶–C⁷ for an organolithium addition, allowing a convergent approach with A ring and C–D rings as key fragments. In this case, the bicyclo[3.2.1]octane is obtained by a Ni-catalyzed enolate/alkenyl bromide coupling. While both Ding and Luo propose a 1,2-shift relying on epoxide ring-opening as key step, each group proposes a different disconnection. For Ding, the rearrangement forms bond C¹³–C¹⁶ through a Ti(III)-mediated reductive epoxide opening/Dowd–Beckwith rearrangement cascade. This allows to have a bicyclo[2.2.2]octane precursor, which can be obtained by a dearomatization/Diels–Alder cascade. For Luo, the 1,2-shift forms bond C¹²–C¹³ through a cationic Wagner–Meerwein-type rearrangement. The B ring is obtained by a key bridgehead carbocation trapping, while the skeleton arises from an A ring fragment and a C ring fragment, assembled by a diastereoselective aldol/Sakurai cascade.

In recent years, important advances have been made regarding the synthesis of grayanane natural products, paving the way for deeper biological activity evaluation. Nevertheless, important challenges still need to be tackled. A highly enantioselective synthesis is still desirable, as the only synthesis offering >90% ee relies on the combination of chiral ligands and chiral auxiliary. Moreover, to date only 6 natural products from the
grayanane family were synthesized, out of the more than 160 compounds known to date. Thus, we anticipate that in the future, organic chemists will keep focusing on highly enantioselective, efficient and flexible synthetic strategies towards grayanane natural products.

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References
Synthetic study toward tridachiapyrone B
Morgan Cormier, Florian Hernvann and Michaël De Paolis*

Abstract
A convergent approach to the skeleton of tridachiapyrone B is described taking advantage of the desymmetrization of \( \alpha,\alpha' \)-dimethoxy-\( \gamma \)-pyrone leading to \( \alpha \)-crotyl-\( \alpha' \)-methoxy-\( \gamma \)-pyrone in one step. To construct the quaternary carbon of the 2,5-cyclohexadienone of the target, a strategy based on the Robinson-type annulation of an aldehyde derived from \( \alpha \)-crotyl-\( \alpha' \)-methoxy-\( \gamma \)-pyrone was applied. The grafting of the simplified target’s side chain was demonstrated through an oxidative anionic oxy-Cope rearrangement of the tertiary alcohol arising from the 1,2-addition of a 1,3-dimethylallyl reagent to 2,5-cyclohexadienone connected to the \( \alpha' \)-methoxy-\( \gamma \)-pyrone motif.

Introduction
The \( \alpha' \)-methoxy-\( \gamma \)-pyrone motif is present in natural products and bioactive molecules [1-14]. Amidst these targets, a number contains a quaternary carbon vicinal to the scaffold, such as crispatene and photodeoxytridachione (Scheme 1a) [15]. These molecules feature a bicyclo[3.1.0]hexene core which photochemically arises from 1,3-cyclohexadiene precursors, tridachiapyrone A or 9,10-deoxytridachione, as demonstrated by Ireland [16,17]. In turn, the ring system arises from \( \alpha \)-tetraenyl-\( \alpha' \)-methoxy-\( \gamma \)-pyrone precursor 1a upon heating through \( 6 \pi \)-electrocyclization, as illustrated by Baldwin in the synthesis of 9,10-deoxytridachione [18]. In a further demonstration of the versatility of tetraenes connected to \( \alpha' \)-methoxy-\( \gamma \)-pyrone, the synthesis of both crispatene and photodeoxytridachione was accomplished by Trauner through the Lewis acid-catalyzed \( 6 \pi \)-disrotatory electrocyclization of compounds 1a and b [19-22]. Interestingly, Baldwin and Moses demonstrated the irradiation or sunlight-promoted cycloisomerization of a similar tetraenyl framework into the bicyclo[3.1.0]hexane core through a \( 6 \pi \)-conrotatory stereocontrol [23,24].

To date, the known strategies to install a quaternary carbon center connected to \( \alpha' \)-methoxy-\( \gamma \)-pyrone therefore rely exclusively on the electrocyclization of tetraenes. With recently demonstrated potent antitumoral [25] and anti-HIV properties [26], aureothin is a natural product featuring the \( \alpha' \)-methoxy-\( \gamma \)-pyrone motif connected to a chiral tetrahydrofuran...
Scheme 1: Routes to crispatene, photodeoxytridachione, aureothin, and tridachiapyrone B.

(Scheme 1b). To assemble the skeleton of the natural product, we developed a new strategy in which the \(\alpha,\alpha'-\text{dimethoxy-}\gamma\)-pyrone motif 2 was first desymmetrized by a sequence encompassing the conjugate addition of 2-lithio-1,3-dithiane, elimination of methoxide lithium, and deprotonation of 2-(\(\alpha'-\text{methoxy-}\gamma\)-pyrone)-1,3-dithiane. The resulting vinylogous enolate intermediate was trapped with the electrophile 3, amounting to the one-pot preparation of compound 4, having a masked carbonyl function connecting both key fragments [27,28].

Isolated and characterized by Schmitz [17], the metabolite tridachiapyrone B is related to tridachiapyrone A (Scheme 1c). As the 1,3-cyclohexadiene motif of the latest is oxidized into 2,5-cyclohexadienone, it is assumed that tridachiapyrone B arises from the ring opening of the epoxide (tridachiapyrone C) of tridachiapyrone A. To our knowledge, the synthesis of tridachiapyrone B was not investigated, even though it seems conceivable that the compound’s stability to light, air or cytochrome would be higher than its 1,3-cyclohexadiene counterpart. As the molecule combines electron acceptor functions such as \(\alpha'-\text{methoxy-}\gamma\)-pyrone and 2,5-cyclohexadienone, these considerations are advantageous with a view to evaluate the potential activity of tridachiapyrone B and analogues in biological electron transport processes.

With this context in mind, we sought to establish a straightforward access to the key 2,5-cyclohexadienone core connected to \(\alpha'-\text{methoxy-}\gamma\)-pyrone by desymmetrization of \(\alpha,\alpha'-\text{dimethoxy-}\gamma\)-pyrone 2 through the addition of hindered nucleophiles to construct the vicinal quaternary carbon. In a subsequent and potentially enantioselective desymmetrization step, compound 5 would be converted into trichiachiapyrone B by 1,4-addition of the side chain to the 2,5-cyclohexadienone scaffold. Avoiding heat and light sensitive tetraenes, the convergent plan would also give the opportunity to assess an enantioselective synthesis of the targets, noting that the \(\text{C}^{14}\) epimeric product, isotridachiapyrone B, has also been isolated by Schmitz.

Results and Discussion

At first glance, the structure of 2,5-cyclohexadienone 5 suggests a disconnection involving the dearomatic addition of 2,4,6-trimethylphenol to \(\alpha,\alpha'-\text{dimethoxy-}\gamma\)-pyrone 2 that we
eagerly sought to establish under basic activation of the nucleophile or by protonation of 2 (Scheme 2a). This ambitious coupling, however, met a dead-end and a less direct approach was explored. With a more reactive and less hindered nucleophile, we explored the coupling of lithiocyclopentadiene to compound 2. After conjugate addition and elimination of lithium methoxide, the resulting 6a would be deprotonated by lithiocyclopentadiene and the enolate intercepted with an alkylating reagent to build the quaternary carbon of 6b (Scheme 2b). This one-pot procedure was reminiscent of our previous study describing the addition of an allylic carbanion, generated from allylstannane with n-BuLi, to 2 which was followed by the addition of an aldehyde resulting in a regioselective aldolization [29]. Thereafter, we hypothesized converting cyclopentadiene 6b into 2,5-cyclohexadienone 5 by a sequence involving the oxidation into dialdehyde 7 and treatment with pentan-3-one to enable sequential steps of aldolization and crotonization. As an aromatic carbanion, it was unclear whether the addition of lithiocyclopentadiene to 2 would succeed [30].

Pleasingly, though, the coupling was successful and moreover simply implemented by reacting lithiocyclopentadiene (2 equiv) with pyrone 2 at room temperature, no reaction occurring at lower temperature in contrast with the nucleophile 2-lithio-1,3-dithiane, and with acetic acid as electrophile (Scheme 3). Among the possible isomers that can be expected, a single one 6a' was isolated in 49% yield after trituration, as it was found rather unstable on silica gel. While the addition of more reactive carbanions of 1,3-dithiane [27], allyl [27], and methyl-dienylbenzene groups [31] to compound 2 were demonstrated, this result amounts to the first grafting of an aromatic nucleophile to the motif.

The construction of the vicinal quaternary carbon of 6b was next investigated by methylation of the highly delocalized enolate intermediate 6a-Li. To that end, the addition of lithiocyclopentadiene to 2 was followed by the attendant quenching with a methylating reagent (MeI, Me2SO4, MeOTf) but a complex mixture of products was consistently obtained. To gather

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Scheme 2: Desymmetrization of 2.

Scheme 3: Addition of lithiocyclopentadiene to pyrone 2.
information on the reactivity of 6a·Li, the stabilized enolate was treated with 4-nitrobenzaldehyde to promote the aldolization reaction but the corresponding alcohol was not observed, which confirmed the reluctance of 6a·Li to react with other electrophiles than protons.

Unable to form the quaternary carbon of the target from this intermediate, the pathway to 2,5-cyclohexenedione 5 was accordingly updated and an approach to make use of the Robinson-type annulation was devised from aldehyde 9, prepared by oxidation of α-crotyl-α′-methoxy-γ-pyrone 8 (Scheme 4). While its synthesis was initially investigated by the coupling of tri(n-butyl)crotylstannane to 2 in the presence of n-BuLi, the direct transfer of the crotyl appendage failed, likely compromised by the steric hindrance of the nucleophile [31].

To alleviate this shortcoming, the crotyl appendage of 8 was assembled by methylation of the allylic pyrone counterpart (Scheme 5). Implemented by exposing 2 to the combination of reagents tri(n-butyl)allylstannane/n-BuLi (2 equiv) followed by the treatment with MeI, the crotyl derivative 8 was directly isolated in 55–60% yield (5 g scale) via the regioselective methylation of the intermediate vinylogous enolate 10·Li. The preparation of aldehyde 9 was carried out through a two-step sequence including dihydroxylation (K₂OsO₄·H₂O, 90% yield) of 8 and oxidative cleavage (NaIO₄, 91% yield) of the diol intermediate. Note that both ozonolysis and the one-pot Lemieux–Johnson oxidative cleavage process of 8 led instead to methyl ketone 11 in a significant amount (ca. 75% yield), probably by oxidation of the enol form of 9 [32]. The sensitive aldehyde was thus used without purification to investigate the Robinson-type annulation and a protocol was identified allowing the preparation of cyclohexenone 12 in 40% yield (2-step). Accordingly, the Michael addition of ethyl vinyl ketone (EVK), promoted by K₂CO₃ in a biphasic media (PhMe/H₂O), was followed by basic treatment (LiOH) of the keto aldehyde. Since compound 12
Scheme 6: Attempts to perform the conjugate addition.

bears the desired quaternary carbon of this family of natural products, it was pleasing to reach this milestone, keeping in mind that the fair yield of this two-step transformation may be the consequence of the aldehyde’s low stability.

Note that the Kotsuki method to perform the Robinson-type annulation of 9 with EVK, catalyzed by a combination of 1,2-cyclohexanediamine and 1,2-cyclohexanedicarboxylic acid, led to product 12 with higher yield but the scale-up of the reaction was less efficient [33]. It has to be underlined that all attempts, using either methods, to couple aldehyde 9 with 2-methylpent-1-en-3-one and directly produce 13 were unsuccessful. To achieve this goal a methylation step of 12 (LiN(iPr)2 (LDA); MeI) was thus necessary (70% yield, 2:1 dr).

The desaturation of the enone compound was next examined and while exposure of 13 to oxidant (o-iodoxybenzoic acid (IBX) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)) left the starting materials unchanged, treatment with NaH in the presence of oxygen to induce the aerobic oxidation caused instead the degradation of 13. An indirect approach was more rewarding as treatment of the enolate of 13 with PhSeBr led to 2,5-cyclohexadienone 5 in 51% yield after oxidation of the sele-noether intermediate with m-chloroperoxybenzoic acid (m-CPBA). An appreciable increase of the yield was actually noted with (PhSe)2 as electrophile, 5 being obtained in 62% yield, enabling thus an evaluation of the next desymmetrization step.

An overview of the scientific literature revealed that, while the asymmetric desymmetrization of prochiral 2,5-cyclohexadienones is a rich topic of investigation, it is mostly restricted to substrates bearing a tertiary alkoxy group [34]. Few examples of this intermolecular strategy actually involve substrates containing a quaternary carbon and the formation of a C–C bond [35,36]. Of note was the report of Takemoto and Iwata describing the 1,4-addition of AlMe3 to 4,4-dimethyl-2,5-cyclohexadienone 14, deprived of a methyl group, was prepared and tested but the reactivity was not significantly improved compared to 5. Both compounds appeared thus mostly reluctant to 1,4-addition and, when it was not the case, the process was poorly reproducible.

On the other hand, the 1,2-addition of Grignard reagents to 5 was observed, providing thus an alternative way of grafting a side chain. As summarized in Scheme 7a, this was envisaged through a sequence encompassing the 1,2-addition of the 1,3-dimethylallyl motif to 5 giving 17, followed by the anionic oxy-Cope rearrangement of the dienal into cyclohexenone 18. After desaturation, the resulting 2,5-cyclohexadienone 19 would provide a modular platform to construct the side chain of the target and analogues. Note that this updated route required the 1,2-addition of a rather hindered nucleophile to a carbonyl electrophile with low reactivity. Precedents were noted though, as Carreira used this strategy for the synthesis of indoxamycine B exploiting the reactivity of 1,3-dimethylallyltitanocene species [39]. The 1,2-addition of various allyltitanocene reagents to carbonyl compounds was described by Sato which were prepared from the corresponding allyl carbonates exposed to the combination of [Cp2TiCl2]/n-BuLi [40]. Pleasingly, conducting the coupling of carbonate 20 to 5 in conditions inspired from Carreira’s study (Scheme 7b) led to the desired 1,2-adduct 17 in 50% yield [41].

To perform the anionic oxy-Cope rearrangement, alcohol 17 was exposed to t-BuOK, in the presence of 18-crown-6 ether (−78 °C to rt) [42]. However, these conditions did not trigger the rearrangement and the starting material was recovered. On the other hand, treatment with KH in DMSO at room temperature caused the
degradation of 17. Scarcely examined for this purpose, hydroxide of quaternary ammonium salt was next evaluated to promote the anionic oxy-Cope rearrangement with the prospect that non-coordinating organic cations could facilitate the transformation by destabilizing the negative charge of the anion (Scheme 7c). Simply generated with Triton B (benzyltrimethylammonium hydroxide), the alcoholate of 17 smoothly (−20 °C to rt) underwent the [3,3]-sigmatropic rearrangement (75% conversion) directly affording 2,5-cyclohexadienone E-19 which was isolated in 41% yield [43] while cyclohexenone 18 was not observed in the crude reaction mixture (as analyzed by 1H NMR spectroscopy). Even though the mechanism was not investigated, the presence of oxygen during the rearrangement step was suspected to account for the oxidation of the enolate intermediate, enabling thus a practical one-pot preparation of 2,5-cyclohexadienone 19 from 17.

Conclusion
While the construction of the side chain’s target remains to be completed, we developed a convergent access to a highly substituted 2,5-cyclohexadienone motif bearing a quaternary carbon connected to α’-methoxy-γ-pyron, simplified analogues of tridachiapyrone B such as 19. Without requiring the construction of polyenes, the route is enabled by key transformations such as the formal crotylation of α,α’-dimethoxy-γ-pyron, the Robinson-type annulation of a sensitive aldehyde and 1,2-addition to 2,5-cyclohexadienone followed by an oxidative anionic oxy-Cope rearrangement promoted by hydroxide of
quaternary ammonium salt. Moreover, the coupling of lithiocyclopentadiene to \(\alpha,\alpha'-\text{dimethoxy}-\gamma\)-pyrone was demonstrated, enlarging the scope of nucleophiles grafted to the pharmaceutically relevant \(\alpha'-\text{methoxy}-\gamma\)-pyrone motif. Drawing from this work, future studies will be focused on an enantioselective access to the target.

Supporting Information

Supporting Information File 1
Experimental details, \(^{1}\text{H}\) and \(^{13}\text{C}\) spectra of new compounds.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-183-S1.pdf]

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41. Isolated as a single stereoisomer.
43. Isolated as a single stereoisomer. The dr of the reaction and the relative configuration of the product were not determined.

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Combining the best of both worlds: radical-based divergent total synthesis

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Review

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Abstract

A mature science, combining the art of the total synthesis of complex natural structures and the practicality of delivering highly diverged lead compounds for biological screening, is the constant aim of the organic chemistry community. Delivering natural lead compounds became easier during the last two decades, with the evolution of green chemistry and the concepts of atom economy and protecting-group-free synthesis dominating the field of total synthesis. In this new era, total synthesis is moving towards natural efficacy by utilizing both the biosynthetic knowledge of divergent synthesis and the latest developments in radical chemistry. This contemporary review highlights recent total syntheses that incorporate the best of both worlds.

Introduction

Societal needs push sciences into new directions, as the urge for new pharmaceutical leads grows, in order to counteract global health challenges. Following this trend, total synthesis has been remodeled from the purely academic quest and display of human abilities to synthetically achieve natural complexity [1] to a modern science addressing the need for the supply of natural products and congeners for biological screening.

The era of scalability [2] in total synthesis prompts researchers in this field to make use of more direct retrosynthetic disconnections with the aid of “radical” retrosynthetic analysis, as the advancement in the area now allows to harness one-electron power in a highly chemoselective manner [3]. The development of persistent radicals [4] as synthons in chemical synthesis, coupled with the advancements in generating and manipulating transient radicals [5] as cross-coupling partners in an array of chemical reactions, gives access to a wide variety of “new” retrosynthetic disconnections. As radical disconnections are gaining ground, more sophisticated retrosyntheses of natural products are unlocked, enriching thus their synthetic scalability.
A direct comparison of a classic vs a radical approach highlights the complementarity and, more often than not, the superiority of the latter, which is proven in the number of steps and the overall yield, hence establishing it as highly appealing for further development (Scheme 1).

In order to identify the new pharmaceutical leads of tomorrow, drug discovery relies on the available chemical space rising from existing chemical libraries. But how big should this chemical space be, so as to actually address our needs? A general consensus has emerged, supporting that “it is not actually the library size but rather the library diversity in terms of molecular structure and function which is fundamental for a successful drug discovery” [8]. And this is where divergent total synthesis might help. Divergent total synthesis is an old but yet underdeveloped strategy, utilizing the conceptual advantages of biosyn-

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**Scheme 1**: The power of radical retrosynthesis and the tactic of divergent total synthesis.
thetic routes that allow multi-target natural product synthesis through a unified synthetic plan [9,10]. Based on the logic of divergent synthesis, common synthetic scaffolds, which are regarded as the points of diversity of the synthetic plan, lie at the heart of retrosynthetic design. Radical disconnections on common scaffolds, in accordance to the trends of green chemistry [11] and the concepts of atom economy [12] and protecting-group-free synthesis [13], are gradually drawing more and more the interest of organic chemists as a sustainable way to deliver structurally diverse chemical libraries for biological screening. The current review is focusing on selected examples utilizing a radical-based divergent total synthesis approach, excluding electrochemical methods for generating radicals. An exhaustive review on radical total synthesis or divergent total synthesis lies beyond the scope of this review, and the readers are advised to refer to excellent reviews on these topics [6,10,14]. This review covers the years 2018–2022.

Review
Radical-based divergent synthesis

Commonly, the most successful divergent plans apply where the natural molecular complexity is rich. Not surprisingly, most of the divergent total syntheses carried out thus far are performed on terpenoid and alkaloid targets, utilizing common synthetic intermediates closely related to the biosynthetic origins of the family. On the other hand, radical retrosynthetic disconnections on common scaffolds are much less predictable and rarely similar due to the plethora of radical chemical transformations available nowadays.

Although radicals stopped being confronted as “scientific curiosities” in the late 1960s, when radical initiators and organomercury reagents were developed as reliable reaction partners (Giese reaction) [15], it was not until the mid-1980s, at which point they appeared as key reaction players in total synthesis (Figure 1). The change in the perception that radicals cannot be selectively used took place with the introduction of tin hydrides in organic synthesis. Apart from the lower toxicity compared to organomercury reagents, the stability and longevity of tin-centered radicals allowed better propagation of radical chain reactions [16]. Based on their reactivity, major contributions in carbon-centered radical formation followed, consequently unlocking highly predictable intramolecular reactions, deoxygenation protocols (Barton–McCombie reaction) [17], etc. Other reagents that majorly contributed were samarium diiodide for the generation of radicals from carbonyl reduction [18] but also manganese(III) acetate as a convenient one-electron oxidant [19]. The next twenty years, the field continued to flourish mainly by way of the decipherment of hydrogen atom transfer (HAT) mechanisms, which led to the establishment of several reactions of transition metal hydrides (Fe, Co, Mn, etc) with alkenes (e.g., Mukaiyama hydration) [20].

The last decade saw the development of milder methods for generating carbon-centered radicals as the advancement of their reactivity in cross-coupling reactions, the concept of photoredox catalysis [21], and electrochemistry [22] all refuelled the field, allowing for more practical radical disconnections for total synthesis.

Divergent synthesis of pyrone diterpenes

(Baran 2018) [23]: The modestly sized family of pyrone diterpenes exhibits a wide range of bioactivities, ranging from immunosuppressive to hypertensive properties [24-26] depending on the subtle substituents in the periphery of a

Scheme 2: Divergent total synthesis of α-pyrene-diterpenoids (Baran).

declain core (Scheme 2). In 2018, the Baran group reported the divergent total synthesis of several pyrone diterpene natural products, relying solely on one-electron-based retrosynthesis. The group recognized the disadvantages that stemmed from prior 2-electron disconnections, namely the complicated C–C bond formations and the necessity for excessive functional group manipulations but also the unavailability of a unified divergent plan for this class of diterpenoids. As an alternative, they proposed nickel-mediated decarboxylative Giese reactions and decarboxylative radical zinc-mediated cross-coupling reactions of redox-active esters, established from previous works of the group [27,28], for the key C–C bonds of the diverse congeners. To this end, a hypothetical intermediate 3 was envisioned for their synthesis (Scheme 2). The synthetic variant of 3 was designed as the common scaffold 16, bearing the appropriate substitution for sequential revelation of carboxylic acid moieties. The highly congested decalin core of common scaffold 16 was obtained by a modified electrochemical polycyclization of polyene 14 (prepared in two steps) in multigram quantities [23]. The reaction employed a divided cell with substoichiometric amounts of magnesium(II) acetate (0.5 equiv) and catalytic copper(II) 3,5-diisopropylsalicylate (0.02 equiv) to allow the redox radical cyclization of polyene in 42% yield. A Tsuji allylation using achiral H-PHOX followed to produce 16,
without being isolated. From this point of divergence, Baran’s group managed to reveal the requisite phthalimide carboxylates for each precursor of the diverse natural products and transformed it carrying out Giese reactions or nickel-catalyzed radical coupling to 13, 20, 25, and 28, few steps away from the total syntheses of sesquicillin A (18), subglutinols A and B (19 and 24) and higginsianin A (23, Scheme 2).

Merged chemoenzymatic and radical synthesis of oxidized pyrone meroterpenoids (Renata 2020) [29]: In 2020, a different approach was conceptualized by Renata’s group to access various oxidized members of pyrone meroterpenoids. The divergent plan of Renata’s group depended on the development of a highly chemoselective, chemoenzymatic 3-hydroxylation of sclareolide (29) and (−)-sclareol (43, Scheme 3 and Scheme 4). The group began by conducting a brief survey of several P450 BM3 mutants, deducing that the variant 1857 V328A (BM3-MERO1) was able to achieve high conversion of sclareolide (29) to the hydroxylated counterpart 30 in >95% yield. Based on this success, the group employed a radical disconnection approach of several 3-hydroxylated pyrone meroterpenoids on sclareolide (29). Key reaction of this strategy was the formal [3 + 3] cycloaddition, catalyzed by phosphoric acid 33, followed by addition of a pyrone residue 32 to sclareolide-derived aldehyde 31, which served as the common synthetic intermediate for the synthesis of 5-deoxyavruiactone C (42).
Scheme 4: Divergent synthesis of pyrone diterpenoids by merged chemoenzymatic and radical synthesis (part II, Renata).

(Scheme 3) [30]. HAT reductions of the C9–C11 alkene followed to deliver arisugacin F (35), phenylpyropene C (36), pyripyropene E (38), and phenylpyropene F (41). The steric bulk of the manganese catalyst employed suppressed the undesired reaction with tetrasubstituted alkenes and led to the exclusive reaction of the desired trisubstituted alkene due to stabilization of the incipient radical at C9. Furthermore, HAT reduction served to only deliver the thermodynamic product of the trans-decalin. Similarly, the C9–C11 alkene can serve as an ideal handle to C11-hydroxylated products, such as 42, through a Mukaiyama hydration [20] to furnish natural complexity.

A similar approach was devised for the synthesis of modified meroterpenoids chevalone A (52), taondiol (53), decaturin E (54), and styrodial (57, Scheme 4). For this purpose, tricycle 45 was prepared from compound 44 in gram-scale quantities by HAT–Giese coupling, followed by reductive cleavage of the lactone moiety with LiI. Enzymatic hydroxylation by the BM3 MERO1 variant worked equally well to provide the 3-hydroxylated product 46. Photochemical radical decarboxylation of the formed mercaptopyridine derivative and radical capture by iodoform led to common scaffolds 47 and diene 48 after subsequent elimination. Those molecules serve as templates for Ni-based radical-based sp³–sp² coupling and single-electron...
transfer (SET)-based [3 + 2] coupling, respectively (Scheme 4). Initial attempts to realize the [3 + 2] radical coupling with CAN led to competitive oxidation of the C3 alcohol to the respective ketone. Increasing the equivalents of pyrène led to 83% of 54. On the other hand, employment of the same conditions to phenol 55 resulted only in the oxidation of the phenol. A more controlled delivery of electrons was realized by applying an electrochemical method to provide the desired coupling towards 56 in 62% yield. Radical reduction by Mn(dpm)₃ afforded stypodiol (57) after BBr₃-mediated deprotection. Nickel-catalyzed coupling under a Weix procedure [31] was selected in order to elaborate the cores of taondiol (53) and chevalone A (52) as the radical cross-coupling employing redox-active esters of carboxylic acid 46 proved unsuccessful. The coupling was followed by an acid-catalyzed cyclization to yield the pyrone core of the natural products. The divergent plan described provided various meroterpenoids in 7–12 steps, comprising one of the most concise methods to attain this class of compounds, highlighting the power of merged biocatalytic and radical tactics [32].

(+)-Yahazunol (61) and related meroterpenoids

(Li 2018) [33]: In 2018, Li’s group reported a divergent plan for the synthesis of drimane-type hydroquinone meroterpenoids. This class of compounds possesses versatile bioactivities, ranging from anticancer and anti-HIV to antifungal properties, with minor modifications on the decoration of either the hydroquinone or the terpene part of the secondary metabolite [34]. The group applied a semisynthetic plan starting from (−)-sclareol (43) to access the common synthetic intermediate of (+)-yahazunol (61), inspired by prior work of Baran’s group on divergent synthesis of meroterpenoids utilizing bornosclareolide (Scheme 5) [35]. Li’s group instead utilized compound 58, readily available by the oxidative degradation of (−)-sclareol (43) [36] as the precursor to a photolabile Barton ester 59. When the latter was irradiated at 250 W in the presence of benzoquinone, a decarboxylated coupling occurred, yielding semiquinone 60, few steps away from the common scaffold 61. Following this protocol, researchers managed to synthesize more than 4 g of the natural product (+)-yahazunol (61). (+)-Yahazunol (61) can be readily transformed to several members of meroterpenoids of the class, either by Friedel–Crafts reactions or common oxidative manipulations.

Total synthesis of dysideanone B (75) and dysiherbol A (79)

(Lu 2021) [37]: Dysideanone B (75), isolated from the South China Sea sponge Dysidea avara, possesses an unprecedented 6/6/6/6-fused tetracycle with interesting anticancer properties against HeLa and HepG2 cancer cell lines (Scheme 6) [38]. The structurally similar dysiherbols 79 and 80, bearing a 6/6/5/6-fused tetracycle instead, were reported to possess NF-kB-inhibitory activity and anticancer activity against NCI H-929 cancer cell lines (Scheme 6) [39]. In 2021 Lu’s group reported the total synthesis of members of both meroterpenoid families based on a highly chemoselective α-alkylation in the thermodynamic position of a Wieland–Miescher ketone derivative 68 with benzyl bromide 69. Despite the challenging O- and C7-alkylations that required suppression, the desired C9-alkylation was achieved in 72% yield under thermodynamically controlled conditions (t-BuOK in THF at −40 °C). This coupled the terpene and the aromatic moieties present in these natural products and provided the common synthetic intermediate 70 (Scheme 6). The diverse tetracycles were accessed either via an intramolecular radical cyclization of the reduced congener 73 or through a Heck reaction of intermediate 71. Reaction of 73 with Bu₃SnH in the presence of AIBN as initiator provided the tetracyclic core of dysideanones. The late introduction of an ethoxy group completed the total synthesis of dysideanone B (75) and “dysideanone F” (76). Ring closure to the dysiherbol scaffold was a much more challenging task as the classic conditions of the Heck reaction to common scaffold 70 proved unsuccessful. Screening of several reaction conditions on different analogues led to the conclusion that reduction of the C8-carbonyl side and acetal deprotection to 71 are essential in order to create the 6/6/5/6-carbocycle in the presence of Pd₂(dba)₃, SPhos, and Et₃N in 86% yield. Reduction of the double bond with Pd/C followed by dual Stille coupling for the introduction of two methyl groups and Mukaiyama hydration utilizing Mn(dpm)₃ and PhSiH₃ furnished the misassigned structure for dysiherbol A (79). A revised structure was finally assigned after deprotection with BBr₃ to complete the first total synthesis of dysiherbol A (79).

Total syntheses of (+)-jungermatrobrunin A (89) and related congeners

(Lei 2019) [40]: The ent-kaurane diterpenoids constitute a highly diverse class of structurally complex natural products possessing promising biological profiles, including anticancer, antifungal, and antiviral activities [41]. The highly diverse nature of the family makes a divergent synthesis extremely challenging, even for closely related members. Biosynthetically, the jungermannenene natural products have been proposed to derive from ent-kaurane diterpenoids through carboxatic re-arrangements [42]. Jungermatrobrunin A (89) [43] bears a highly oxidized scaffold with a unique bicyclo[3.2.1]octene backbone and an unprecedented peroxide bridge (Scheme 7). Natural product (−)-1t,6a-diacetoxyjungemmannone C (88) [43] was projected by Lei’s group as the common scaffold for the divergent synthesis of this class. Finally, the closely related
Scheme 5: Divergent synthesis of drimane-type hydroquinone meroterpenoids (Li).

Congener 90 [43] was envisaged to originate by a radical rearrangement of the common scaffold 88.

Initially, Lei’s group unfolded the synthesis of 83 on a decagram scale, utilizing an asymmetric conjugate reaction of commercially available 81 and 82 using Fletcher’s protocol (94% ee) [44]. A subsequent intramolecular arylation in the α-position of the ketone of 83, catalyzed by a Pd(II)–NHC [45], followed by methylation, provided cis-decalin 84 (Scheme 7). Appropriate redox modifications allowed the delivery of trans-
Scheme 6: Divergent synthesis of natural products isolated from *Dysidea avara* (Lu).

Decalin 85 in a gram-scale quantity. Birch reduction of the electron-rich aromatic ring, followed by propargylic addition and functional group interconversion (FGI) provided dienyne 86. Compound 86, under the previously developed radical reductive cyclization for 1,6-dienyne cyclization (using Bu$_3$SnH and AIBN) [46], led to the construction of the key bicyclo[3.2.1]octene carbocyclic core of jungermatrobrunin, which was further elaborated to 87 in up to 61% yield, after alkene cleavage by OsO$_4$ and NaIO$_4$. The described reductive radical cyclization can be scaled up to 2 g without substantial decrease of the product yield. FGI, followed by methylation provided the common scaffold 88. Further elaboration of 88 to natural products 90 and 89 was accomplished by UV irradiation at 365 nm in MeOH and by utilizing singlet oxygen (using rose Bengal) in MeCN/pyridine, 40:1, respectively. Interestingly, irradiation at 365 nm even in the presence of photosensitizer and O$_2$ failed to furnish (+)-jungermatrobrunin A (89), and 90 was obtained as the sole product, albeit in low yield (14%). Attempts to optimize the yield always afforded recovered 88, hinting at a potential equilibrium between 88 and 90.

Total syntheses of magninoids and guignardones (Lou 2021) [47]: Magninoids and guignardones are two classes of biogenetically related meroterpenoids, bearing a highly substituted cyclopentane moiety and a 6-oxabicyclo[3.2.1]octane fragment [48,49]. These classes exhibit diverse biological properties, such as potent inhibition of 11-β-hydroxysteroid dehydrogenase type I and inhibition of *Candida albicans* [48]. Although earlier syntheses have been reported recently for magninoids [50,51], Lou’s group envisioned a divergent plan based on a late-stage bioinspired semipinacol rearrangement–cyclization of common synthetic intermediates 94 and 95 (Scheme 8). Compound 94 was obtained in three steps, with the key step being the Suzuki–Miyaura coupling of appropriately functionalized precursors 91 and 92 using Romo and co-worker’s protocol [52]. Reaction of 94 under PPTS acidic
conditions initiated a semipinacol rearrangement leading to 95, followed by subsequent cyclization to natural products guignardone A (96) and C (97). This process involved 1,2-allyl migration and C–O bond formation through a semipinacol rearrangement and a cyclodehydration cascade reaction (Scheme 8).

Following the same rationale, 94 was diverted to produce 100 after basic deprotection of the nonisolated 95. The radical oxidation of the former in the presence of dioxygen and sunlight or a catalytic amount of Mn(OAc)₃ led to the creation of the compounds 101 and 102. FGI, followed by the cleavage of the hydroperoxide bond and final dehydration by Burgess reagent provided the total syntheses of magninoids A (104) and C (103, Scheme 8).

Divergent total synthesis of crinipellins (Xie and Ding 2022) [53]: Crinipellins are highly congested tetraquinane natural products comprising 6–10 stereogenic centers, three of which are consecutive all-carbon quaternary carbon atoms [54-56]. Preliminary biological screening of this family revealed notable antibacterial and anticancer activities due to the α-methylene lactone moiety they bear [57]. Recently, in order to synthesize the common core present in crinipellins, Xie and Ding’s groups developed an approach using an unprecedented ring distortion. Their strategy consisted of a metal-catalyzed HAT to the exo-Δ-alkene of the 5/5/6/5 tetra-cycle 109, so as to subsequently favor a Dowd–Beckwith rearrangement [58] towards the tetraquinane skeleton of 112 (Scheme 9). The synthesis commenced with the generation of 107 from cyclopentenone 105 and aryl aldehyde 106 in a three-step sequence. An oxidative dearomatization induced a [5 + 2] cycloaddition–pinacol rearrangement of 107 to 109, according to previous studies of the same group (Scheme 9) [59-61]. The key HAT-mediated rearrangement was realized in an impressive yield of 95% to obtain 112 on a gram-scale, when cobalt complex C6 was used in the presence of PhSiH₃ and TBHP in isopropanol. Further modifications of 112 led to the common scaffold 113 in 47% yield, which could be readily transformed to several crinipellin natural products by chemoselective redox reactions.
Divergent total synthesis of Galbulimima alkaloids

(Shenvi 2022) [62]: Members of the Galbulimima alkaloids extracted from rainforest canopy trees were found to possess neuroactive properties, such as antagonistic activity at muscarinic receptors [63], psychotropic activity, and antiplasmodic activity [64]. Their structural diversity, consisting of different connectivities between piperidine and decalin domains, is especially difficult to be divergently accessed. Shenvi’s group recognized that an aromatic congener within this class could be traced back to aromatic common intermediate 9 (Scheme 10). Despite the simplicity, the most obvious disconnections, such as an anionic enone conjugated addition and a direct cationic Friedel–Crafts reaction failed. Highlighting the power of radical disconnection, the group thought of utilizing a β-keto carbon-centered radical to circumvent the unsuccessful Friedel–Crafts reaction. Prior reports implicated β-keto radical formation in the ring opening of siloxycyclopropanes with photoinduced electron transfer (PET) to 1,4-dicyanonaphthalene [65]. Inspired by reports on dual photoredox and Ni-catalytic cross-coupling platforms [66], the group considered a system in which a photoexcited catalyst oxidatively cleaves a siloxycyclopropane with endo selectivity [67], leading to aryl–nickel capture and reductive elimination. Thus, when substrates 121 and 122 were photoirradiated with blue LED light at 45 °C in the presence of lutidine base, 7 mol % organic photocatalyst 4CzIPN, 30 mol % NiBr₂, and 30 mol % bpy provided 57% of 9. Intramolecular Friedel–Crafts reaction by Et₂AlCl and HFIP complex led to 123, possessing the correct connectivity for the divergent synthesis of the family. Choreographically executed sequential reduction steps allowed the total synthesis of GB13 (8), himgaline (126), and GB22 (125) in only one third of the number of steps of prior syntheses (Scheme 10).

Concise syntheses of eburnane alkaloids

(Qin 2018) [68,69]: Eburnane indole alkaloids comprise a highly diverse class of natural products mainly distributed in Southeast Asia and China [70]. Compounds of this class are traditionally used for detoxification and as anti-inflammatory agents in Chinese medicine [71]. Qin and co-workers reported the asymmetric total syntheses of several eburnane alkaloids. Therein, they relied on one of their previous discoveries, namely a photoredox-catalytic nitrogen-centered radical cascade [72], which has resulted in the impressive collective total synthesis of 33 alkaloids of three different classes of indole natural products (please see the inset of Scheme 11 for concise representation). Specifically, this included (−)-eburnaminol (132), (+)-larutenine (133), (−)-terengganensine B (134), and

Scheme 8: Divergent synthesis of 6-oxabicyclo[3.2.1]octane meroterpenoids (Lou).
Scheme 9: Divergent synthesis of crinellins by radical-mediated Dowd–Backwith rearrangement (Xie and Ding).

(--)-strempeliopine (136), as well as the asymmetric formal total synthesis of (--)-terengganensine A (not shown, Scheme 11). The requisite common synthetic intermediate 129 for the cascade was accessed by an acid-promoted condensation of chiral aldehyde 127 and Boc-protected amine 128, followed by zinc reduction of the nitro group and subsequent protection of the amine by a tosyl group in 27% overall yield. Irradiating 129 with blue light at 30 W in the presence of 1 mol % of [Ir(dttbpy)(ppy)$_2$]PF$_6$ and 5 equiv of KHCO$_3$ in THF resulted in the radical formation of the tetracyclic core of 130 in 75%
yield as a mixture of two diastereoisomers (dr = 3:2) that were both used to access natural products. Impressively, the protocol allowed the installation of three rings and the stereoselective introduction of chiral centers at C2 and C21 for the final targets. With regard to the mechanism, it is hypothesized that it commences with the formation of a nitrogen-centered radical. The carbon radical is then formed after the aforementioned nitrogen radical attacks the enamide group. The α-amide positioning is theorized to improve drastically the radical stability, nucleophilicity, and selectivity of 139. Furnishing of the common scaffold can be carried out via an attack of intermediates of this type (e.g., 139) on Michael acceptors. Tosyl group deprotection of 130, followed by selenium anhydride oxidation and catalytic reduction of the amide using Wilkinson’s catalyst provided diastereoisomeric indole 131. Careful manipulation of the nitrile and alcohol side chains allowed selective cyclizations to the nitrogen atom of the indole core to conclude the total syntheses of 132–134. Samarium diiodide-mediated reductive cyclization of aldehyde 135, obtained also from 131, provided the pentacyclic core of (−)-strempeliopine (136) as a single diastereoisomer in 65% yield. Then, Barton’s radical deoxygenation resulted in the total synthesis of 136. Further, FGI of 136 led to (−)-enantiomer 147, which serves as the radical point of divergence of this plan. HAT-initiated transannular free-radical cyclization of (−)-enantiomer 147 according to Baran’s protocols provided the benzyl-protected (−)-pseudocopsinine 148 in 60% yield, when 147 was treated with PhSiH3 in the presence of Fe(acac)3. Notably, the reaction provided a diastereoselectivity of 3:1 for the formation of the C20-stereocenter and exclusive formation of the C3-center. Key to this success is the low level of Fe(III)–H generation, thus minimizing intermediate radical reduction. The observed diastereoselectivity can be rationalized by referring to earlier mechanistic studies. The same (−)-configured intermediate 147 was utilized in a HAT-initiated oxidation to access (−)-minovincinine (150) in 38% yield after deprotection (Scheme 12). Interestingly, the classic Mukaiyama conditions
Scheme 11: Divergent synthesis of eburnane alkaloids (Qin).

using Co(acac)$_2$ with PhSiH$_3$ provided compound 152 as the only isomer which, upon reduction, led to the exclusive formation of the compound epi-minovincinine (151). Replacement of Co(acac)$_2$ with Co complex A suppressed the formation of 152 and provided the desired 150 and the isomer as an almost 1:1 mixture.
Syntheses of (−)-FR901483 (160) and (+)-TAN1251C (162)

(Gaunt 2020) [80]: Nitrogen-spirocyclic natural products consist a common class of important pharmaceutical candidates. FR901483, which was isolated from the fermentation broth of Cladobotryum sp. No. 11231, exhibits impressively potent immunosuppressant activity. This has resulted in extensive synthetic efforts towards the compound, in order to meet the needs for the supply as a potential therapeutic for the treatment of arthritis, Crohn’s disease, and organ transplant rejection [81]. The TAN1251 natural products, on the other hand, show potent activity as muscarinic antagonists, with potential applications as antispasmodic and antiulcer agents [82]. Despite the synthetic efforts on these natural products [83-86], in 2020, Gaunt’s group recognized a novel common synthetic intermediate in the structure of spirolactam 157 to access the family (Scheme 13). To synthesize it, they conjectured that a tyrosine amino acid, a cyclohexadione derivative, and a nonracemic dehydroalanine derivative could be effectively combined to build the core structure, using an already known iridium-photocatalyzed radical reaction [87]. Indeed, when D-tyrosine methyl ester (154), 1,4-cyclohexanedione monoethylene acetal (155), and dehydroalanine derivative 156 were allowed to react in the presence of TFA, molecular sieves, 1 mol % of fac-Ir(ppy)3, and Hantzsch ester under blue LED irradiation at 40 W, this resulted in the formation of spirolactam 157 in 73% yield (Scheme 13). The reaction is estimated to take place initially with the one electron reduction to α-amino radical 164. This step is thought to be facilitated after TFA protonates the formed imine. Afterwards, radical addition of 164 to 156, generates an α-carbonyl species. A HAT from Hantzsch ester, which takes place diastereoselectively from the more accessible face, afforded the lactone 158. Spirolactam 157 can effortlessly be produced after the cyclization of the aforementioned lactone. Redox manipulations from this point on brought about the total synthesis of (−)-FR901483 (160) through an aldol reaction, and an intramolecular condensation resulted in the synthesis of (+)-TAN1251C (162, Scheme 13).

Divergent synthesis of bipolamine alkaloids

(Maimone 2022) [88]: Bipolamines were isolated from the fungi Curvularia sp. IFB Z10 and Bipolaris maydis in 2014 and were reported to possess antibacterial activity against a small panel of both gram-positive and -negative bacteria [89,90]. Interestingly, their chemical structure bears no resemblance to recognize antibiotics and their mechanism of action remains unknown. Based on the knowledge gained from the first total synthesis of (−)-curvulamine (171) [91], Maimone’s group leveraged their plan for accessing several members of this class (Scheme 14). The challenge this group had to address in this particular case was the high acid sensitivity and oxidative fragility of pyrrole intermediates. As common synthetic intermediate, the group utilized compound 170, readily available in gram-scale quantity, through a modified previously reported se-
Scheme 13: Photoredox based synthesis of \((-\text{FR901483})\) (160) and \((+\text{-TAN1251C})\) (162, Gaunt).

Flow-controlled divergent synthesis of aporphine and morphinandienone natural products
(Felpin 2022) [92]: Reticuline-type alkaloid oxidative coupling is a well-established biosynthetic pathway that produces important pharmaceutical structures [93], such as \((+\text{-corytuberine}), (-\text{-codeine}), (-\text{-morphine}), (+\text{-sebiferine})\) (181), etc., depending on the regioselectivity of the coupling (Scheme 15) [94]. During this process, two major families of natural compounds are formed, namely the aporphine and the morphinandienone alkaloids. Mimicking the selectivity of the natural process in laboratory setups commonly proves tricky, producing an irreproducible yield of isomers for both classes. Recently, Felpin’s group reported the flow-controlled divergent synthesis of aporphine and morphinandienone alkaloids based on biomimetic common scaffolds (e.g., 180) using hypervalent iodine(III) reagents. Capitalizing on previously reported mechanistic inves-
tations, they assumed that 180 can rearrange to glaucine (183) through the erythrinadienone intermediate 182. On contrary, common scaffold 180 should hydrolyze to sebiferine-type scaffolds in the presence of water. Taking these results into account, the group exploited the ability of HFIP to stabilize the radical cation formed by PIFA and BF$_3$·EtO$_2$ [95,96] to selectively produce aporphine natural products, while the use of PIDA or PIFA in the presence of BF$_3$·OEt or TMSOTf in wet CH$_3$CN allows to diverge the synthesis to morphinandienone natural products (e.g., 181, Scheme 15). The flow reaction was performed in a reaction coil at room temperature. Two reaction loops were used. The first one was loaded with the substrate and the second with PIFA and BF$_3$·EtO$_2$, while HFIP was used as the solvent. The two streams were mixed in a T-mixer, equipped with a 250 μL frit, to ensure efficient mixing. Under the optimized conditions, the method provided aporphine prod-

Scheme 14: Divergent synthesis of bipolamines (Maimone).

![Scheme 14](image-url)
products in good to moderate yield, depending on the substrates used. Altering the solvent to wet CH$_3$CN allowed the efficient delivery of morphindienone compounds.

**Pyrroloazocine natural products**

*(Echavarren 2018)* [97]: In 2018, Echavarren’s group reported the divergent synthesis of several pyrroloazocine alkaloids [98-100]. Preliminary biological screening indicates that members of this class are able to overcome multidrug resistance in vincristine resistant cells [98-100]. To access the common scaffold 188, the group relied on an intramolecular gold-photocatalyzed radical-mediated cyclization of an α-keto radical to the pendant indole core, reported earlier in the total synthesis of lundurines A–C (Scheme 16) [101]. The authors postulate that photoexcitation of [(dpmmAuCl)$_2$] with 365 nm light serves as initiator for radical generation in the brominated position of 186, prepared after following a 7-step sequence. The cyclization of the formed radical is 6-exo-trig and leads to the formation of a benzyl radical that is further oxidized to 188. From this common scaffold, the group managed to access several natural products of the class, majorly by utilizing the ability of conjugated alkenes to be further oxidized, and thus producing the respective benzylic cation. Intramolecular cyclization in the cationic position under participation of the methyl ester function provided the core for (+)-grandilodine C (191) and (+)-lapidilectine B (192), while allylation of the benzylic position allowed oxidative decomposition to the core of 194 and 195. FGI followed to complete targets 196–200 (Scheme 16).

**Pyrroloindoline natural products**

*(Knowles 2018)* [102]: In 2018, Knowles’ group demonstrated the ability of TEMPO to act as a trap for radical cations arising...
from the single-electron oxidation of protected tryptamine starting materials. The utilization of a chiral phosphate base is essential for the formation of a hydrogen bond between phosphate and tryptamines, allowing the decrease of the oxidation potential. This concept was used for the synthesis of pyrroloindoline natural products (Scheme 17). Thus, upon irradiation,
iridium polypyridyl photocatalyst allowed the oxidation of the phosphate complex 207 to radical cation 206, which can be readily trapped by TEMPO, and hence stabilizing the imine and allowing cyclization with the pendant amine to form the pyrroloindoline core 210 in 81% yield and 93% ee. The latter can serve as a common scaffold to access an array of pyrroloindoline natural products but also synthetic analogues (Scheme 17). Oxidation of 210 by a second iridium photocatalyst yields benzyl cation 213, which can undergo nucleophilic attack by tryptamine derivatives to allow the total synthesis of (+)-psychotriasine (202), (+)-calycanthidine (203), and (+)-chimonanthine (204).

Synthesis of structurally diverse lignans (Zhu, 2022) [103]: Lignans are structurally diverse natural compounds generated biosynthetically by the oxidative dimerization of phenylpropanoids [104]. Despite the wide oxidative diversity, classic lignans bearing a C8–C8’ bond can be biosynthetically traced back to coniferyl alcohol (Scheme 18). Commonly, lignans possess important pharmacological properties including antimicrobial, anti-inflammatory, immunosuppressive activities, etc. [105]. At the same time, some members have been recognized as potent topoisomerase inhibitors and have been used as anticancer drugs [106]. To access the rich diversity of this class, Zhu’s group recently applied a Fukuzumi salt ([Mes–Acr–Me]BF₄)-mediated photochemical oxidation of dicinnamyl ether derivative 225 in the presence of appropriate additives (Scheme 18). According to the postulated mechanism, the reaction is initiated by an SET of the dicinnamyl ether substrate to Fukuzumi’s salt 233, leading to radical cation 216. Earlier findings of the same group [107] revealed that substitution on the aryl groups is the determinant factor for either 8,8’-cis- or 8,8’-trans-cyclization to furan heterocycle cation 218, which serves as the hypothetical common scaffold of the plan. Diverting this mechanistic route to different lignans is possible by introducing nucleophilic additives (e.g., MeOH), oxidants (e.g., Cu(OTFA)₂), or quenchers (e.g., PhSSPh) to the reaction mixture. When monosubstitution of the aryl group is present,
the formed radical cation, the product of the photooxidation of the cinnamyl ether, readily cyclizes to cyclobutene radical cation 217. The latter cleaves the benzylic C–C bond to produce the 1,4-radical cation cis-218. On the other hand, when polysubstitution with methoxy groups is present, the cation in 216 is delocalized, inhibiting the production of cyclobutene 217. Thus,
radical cyclization according to the Beckwith-Houk model [108,109] via transition states TSI and TSII would take place, leading to the intermediate trans-218. In the presence of external nucleophiles (e.g., MeOH), the cation can be trapped, leading to substitution in the 7-position, while the radical is postulated to be oxidized to a cation, followed by a Friedel-Crafts reaction to the final product 222. When an excess of nucleophile is employed, radical 223 is favored, leading to either monosubstitution or dissubstitution with external nucleophiles, depending on the presence of oxidant or reductant in the reaction mixture. Based on this plan, Zhu’s group managed to synthesize a rich number of lignans and congeners, such as aglacin A (229), β-OH-aglacin E (227), α-OH-aglacin F (228), brassilignan (232), etc.

Diverse synthesis of highly oxidized dibenzocyclooctadiene (DBCOD)-type lignans

Lumb (2021) [110]: Extracts of Schisandraceae are rich sources of highly oxidized DBCOD lignans with interesting biological properties [111]. Designing their divergent plan on postulated biosynthetic steps, Lumb’s group managed to efficiently prepare DBCOD derivatives 238 bearing the appropriate handles for late-stage radical formation (Scheme 19). Their success relied on the strategic design of linear precursors.

**Scheme 19:** Divergent synthesis of DBCOD lignans (Lumb).
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References


Conclusion

The utility of radical retrosynthetic disconnections in natural product synthesis is highlighted in practice, day after day, when shorter and scalable syntheses are coming into light. Combining these advantages with the power of divergent synthesis provides a yet underdeveloped strategy to address the challenges that insufficient supply of pharmaceutical leads poses, enriching the chemical libraries with natural scaffolds for biological screening. The evidenced increase of divergent radical syntheses in the last few years indicates that this approach is here to change the way chemists will practice total synthesis in the future.

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Total synthesis of insect sex pheromones: recent improvements based on iron-mediated cross-coupling chemistry

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Abstract
In the current ecological context, use of insect sex pheromones as an alternative to conventional pesticides is in constant growth. In this report, we discuss the recent contributions brought by our groups in the field of iron-catalyzed cross-couplings applied to the synthesis of insect pheromones. The pivotal question of the development of sustainable synthetic procedures involving cheap, non-toxic and efficient additives is also discussed, as well as the mechanistic features guiding the reactivity of such catalytic systems.

Introduction
Public health issues related to environmental problems, particularly pollution and soil persistence, led in recent years to a decrease in the use of so-called conventional protection products for the protection of crops and plants. Some of these synthetic pesticides, such dimethoate (pesticides for the protection of cherry crops) or chlordecone (pesticides for the protection of banana crops) \cite{1}, have recently been forbidden in the EU. In this context, the development of eco-friendlier solutions for the protection of crops and plants is a major challenge. This is why biocntrol (that is: all plant protection methods that use natural mechanisms to help regulate/balance the populations of harmful species rather than eradicating them) based on the use of insect pheromones \cite{2-5} is an eco-friendly solution for the protection of a wide range of crops and plants against pests. Indeed, those chemical mediators, which are emitted by insects from a given species, trigger a specific reaction, such as sexual attraction, on an individual of the same species and represent very selective intraspecific means of communication. Used in crop protection,
synthetic pheromones can disturb communication between individuals in order to prevent their reproduction and then limit their proliferation, finally lowering the damages caused by pests to the crops. Moreover, those molecules are totally biodegradable, harmless to Humans and don’t interact with non-targeted insects [6].

However, at this time, few pathways for the synthesis of insect pheromones reported in the literature are applicable on an industrial scale, which slows the widespread application of this solution. As a matter of fact, the key step of the synthesis of such compounds, which is the introduction of C=C unsaturations, traditionally involves expensive, toxic and low atom economy methodologies. The synthesis of the sex pheromone of the horse-chestnut leaf miner (Cameraria ohridella), (8E,10Z)-tetradecadienal (1, Scheme 1) perfectly illustrates this issue: the main synthetic pathways reported in the literature until now (Svatoš, 1999 [7]; Francke, 2002 [8], Grodner, 2009 [9]) are linear syntheses involving a great number of steps and purifications as well as cryogenic temperatures. Moreover, the introduction of the C=C unsaturation is achieved via a Wittig reaction or a Pd-catalyzed Sonogashira cross-coupling followed by a reduction by a borane reagent, methods which lead to overall processes with a low atom economy, generating a significant amount of chemical waste, and which can be expensive when noble metals such as palladium salts are required (Scheme 1).

The high efficiency of transition-metal-catalyzed cross-coupling methods in C–C bond formation processes constitutes an extremely powerful tool in total synthesis. In order to reach sustainable and economically appealing conditions, the quest for the substitution of palladium by non-noble metals has been investigated for more than four decades. To address this issue, new eco-friendly synthetic routes relying on carbon–carbon iron-catalyzed cross coupling as a key step were developed, capitalizing on the low toxicity and the cheap cost of this abundant metal [10]. For instance, in 1971, Kochi developed an iron-catalyzed alkyl–alkenyl cross-coupling reaction between aliphatic Grignard reagents and vinyl bromides, using FeCl₃ as the catalyst, in order to obtain cross-coupling products with yields between 64 and 83% (Scheme 2a) [11]. Drawing his inspiration from Kochi, Cahiez reported that using N-methyl-2-pyrrolidone or NMP as a co-solvent drastically improved the efficiency of the iron-catalyzed alkyl–alkenyl cross coupling reaction developed by Kochi, leading to better yields, with no need to use an excess of one of the coupling partners (Scheme 2b) [12]. The yields obtained using this ligand-free method are comparable to those obtained in recent palladium-mediated alkyl–vinyl cross-couplings using exogenous N- or P-based ligands, highlighting the efficiency of iron as a credible alternative to noble metal catalysis in cross-coupling chemistry [13]. Cahiez’ pioneering work highlighted the potential of iron catalysis in organic chemistry and generated a new interest for the study of iron-catalyzed reactions, which witnessed considerable development in the last two decades [14], several cross-coupling methodologies involving soft nucleophiles, such as iron-mediated Suzuki–Miyaura cross-couplings, being reported [15].

The introduction of alkyl–alkenyl linkage by means of iron-catalyzed cross-coupling reactions thus appears as an appealing tool for the synthesis of insect pheromones, which often display linear chains involving C=C unsaturations with a well-defined stereoechemistry (Scheme 1). Therefore, we aimed at developing this strategy for the design of high-scale, eco-friendly and economic new synthetic procedures applied to obtain a variety of insect pheromones. The present report summarizes the recent progresses made in insect sex pheromone synthetic applications in our group, with a particular focus on the quest for non-toxic and sustainable catalytic platforms developed in the iron-catalyzed cross-coupling field.

Scheme 1: Structure of the (8E,10Z)-tetradecadienal (1, sex pheromone of the horse-chestnut leaf miner) and reported retrosynthetic pathways.
Discussion

The quest for non-toxic and efficient additives for iron-mediated cross-coupling reactions

Co-solvents used as NMP surrogates

In spite of the very good yields and soft conditions provided by Cahiez’ method (Scheme 2b), a major drawback of the latter is the requirement of NMP as a co-solvent. Indeed, NMP recently proved to be of very high concern due to its acute toxicity, since it was classified as a reprotoxic reagent [16,17]. In order to circumvent this matter and develop new non-toxic and sustainable iron-mediated coupling transformations, efforts were put in the quest for suitable additives as surrogates of NMP. Szostak and Bisz reported in 2019 that N-methyl-ε-caprolactame (NMCPL) could be used as an alternative solvent, and sp³–sp² cross-coupling reactions proceeding with good to excellent yields were reported. Alkyl Grignard reagents could thus be used in combination with a variety of alkenyl chlorides and (hetero)aryl chlorides [18].

Importance of the leaving groups: use of enol phosphates

In order to overcome the delicate choice of either NMP or one of its surrogates as a suitable co-solvent, it has also been demonstrated that amide-free catalytic procedures could afford satisfying coupling yields by a suitable variation of the nature of the leaving group. In 2008, Cahiez reported an iron-catalyzed alkenylation of organomagnesium reagents with enol phosphates as electrophiles, instead of alkenyl halides [19]. In this case, when reactive enol phosphates derived from aldehydes were used, excellent coupling yields were obtained in THF, with no need of NMP additive (Table 1, entries 1 and 2). However, less reactive α,β-disubstituted enol phosphates required the presence of NMP (Table 1, entry 3) or even N,N'-dimethylpropyleneurea (DMPU) (Table 1, entry 4) as a co-solvent. Nevertheless, capitalizing on these results, Cahiez further developed this iron-catalyzed cross coupling reaction with dienol phosphates as electrophiles, which are thermally more stable than dienyl halides [20]. It was found that when dienol phosphates were used as electrophiles, the presence of NMP is actually detrimental. Indeed, for the cross coupling reaction of octylmagnesium chloride with 1-butadienyl phosphate in THF at −20°C in the presence of 1% Fe(acac)₃ and 9 equivalents of NMP, the resulting 1,3-dodecadiene cross-coupling product was only obtained with a 54% yield, whereas when the reaction was performed in THF alone (at 20 °C), the yield improved significantly (92%, Scheme 3).

The efficient iron-mediated alkylation of dienyl phosphates, proceeding with an excellent retention of stereochemistry, was then successfully used in the introduction of the alkyl–alkenyl linkage of several insect pheromones. Cahiez paved the way of this strategy in 2008, showing that (E)-dodeca-9,11-dien-1-yl acetate (2), the sex pheromone of red bollworm moth (Diparopsis castanea), which contains a terminal diene, could be obtained at a laboratory scale (ca. 200 mg) by means of iron-mediated cross-coupling (77% yield for the coupling step, Scheme 4a) [20]. In this cross-coupling, an α,ω-difunctionalized Grignard reagent bearing a magnesium alkoxide moiety at the end of the aliphatic chain is used as a coupling partner. Following in those footsteps, similar syntheses of other insect pheromones involving a key alkyl–alkenyl linkage introduction by iron-catalyzed cross-coupling reactions of α,ω-difunctionalized alkyl Grignard reagents with stereochemically pure dienyl phosphates were successfully performed at higher scales, in order to be successfully implemented in industrial processes. (7E,9Z)-Dodeca-7,9-dien-1-yl acetate (3), the sex pheromone of European grapevine moth (Lobesia botrana), was thus obtained at a 14 g scale, with an overall 85% yield for the one-pot sequence involving the iron-catalyzed cross coupling followed by acetylation with Ac₂O (Scheme 4b) [21]. Illustrating the appli-
Table 1: Iron-catalyzed alkenylation of enol phosphates by Grignard reagents by Cahiez.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enol phosphate ((E:Z))</th>
<th>Product ((E:Z))</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Bu}O\text{PO}^{(86:14)})</td>
<td>((90:10))Bu</td>
<td>THF</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Ph}O\text{PO}^{(70:30)})</td>
<td>((85:15))Ph</td>
<td>THF</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Bu}O\text{PO}^{(68:32)})</td>
<td>((94:6))Bu</td>
<td>THF + NMP</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Pr}O\text{PO}^{(60:40)})</td>
<td>((92:8))Pr</td>
<td>THF + DMPU</td>
<td>70</td>
</tr>
</tbody>
</table>

Scheme 3: Iron-catalyzed cross-coupling of \(n\)-OctMgCl with a 1-butadienyl phosphate.

Cahiez of this process to large industrial scales, a synthesis of 50 kg of pheromone 3 was performed using this method [22,23]. Similarly, a 40 g batch of \((8E,10Z)\)-tetradeca-8,10-dienal (1), the sex pheromone of horse-chestnut leaf miner (Cameraria ohridella) was obtained following an analogous procedure (Scheme 4c) [24]. It is of note that a low 0.1 mol % catalytic loading could be used for the latter coupling, which is thus particularly appealing for high-scale applications. In this context, the procedure described in Scheme 4c is currently used for industrial medium-scale synthesis of 1 by the M2i Company.

Magnesium alkoxides used as additives

Although it can lead to efficient NMP-free cross-coupling procedures, the use of enol phosphates as coupling electrophiles also brings several issues for efficient and sustainable procedures meant to be carried out at large scales. First, dialkyl phosphates used as leaving groups lead to overall transformations which display a poor atom economy. Moreover, diethyl chlorophosphate (DCP), used as a classic starting material in the dienol phosphates synthesis, is also registered under REACH regulation, and its use brings several toxicity issues for living organisms [25,26]. Additionally, the classic stereoselective synthesis of dienol phosphates requires cryogenic temperatures \((-78 \, ^\circ\text{C})\) as well as NMP-based methodologies [27]. Therefore, motivated by those considerations, we sought a suitable efficient and non-toxic additive which would allow the use of alkenyl halides as cross-coupling partners in the absence of NMP.

A remarkable feature of the alkyl–dienyl cross-coupling reactions displayed in Scheme 4 is the implication of \(\alpha,\omega\)-difunctionalized Grignard reagents, bearing a magnesium alkoxide moiety at the end of the chain. Magnesium alkoxides exhibit
strong σ-donating properties, given the high nucleophility of the alkoxide moiety. Moreover, the beneficial effect of molecular σ-donating additives on the yields and selectivities of iron-mediated cross-coupling reactions had already been reported in the literature. Nakamura thus described an elegant aryl–aryl cross-coupling procedure suppressing the formation of Grignard homocoupling byproducts relying on the use of FeF₃ as catalyst, associated with strong N-heterocyclic carbenes (NHCs) and a source of fluoride anions [28]. A similar procedure involving sodium alkoxide additives and NHCs was also described by Duong for the aryl–aryl cross coupling [29]. Alkoxide salts appear as good alternatives to NMP or phosphate-based additives, since several classic alcohol sources display low toxicities and can also come from renewable resources [30].

In this context, Cahiez and Lefèvre developed an eco-friendlier, and easily scalable iron-catalyzed cross-coupling method between alkyl Grignard reagents and C₆H₅MgCl (alkenyl or aryl) organic halides [31]. By combining a catalytic charge of FeCl₃ with alkoxide magnesium salts such as EtOMgCl in THF, complete conversion of the alkenyl/aryl halides was observed and the cross-coupling products were afforded in good to excellent yields (Scheme 5). Moreover, this reaction can also be carried out at the gram scale (up to 50 mmol for alkyl–alkenyl coupling reactions, up to 10 mmol for alkyl–aryl couplings).

Scheme 4: Synthesis of several insect sex pheromones (a) red bollworm moth, (b) European grapevine moth, c) horse-chestnut leaf miner) involving a key alkyl–alkenyl iron-mediated cross-coupling between a dienol phosphate and an α,ω-difunctionalized Grignard reagent.

Alkoxide salts, such as EtOMgCl, are cheaper and much less toxic than NMP, making this method particularly eco-friendly. Moreover, this method also provides results equivalent to those obtained using NMP-based cross-coupling reactions. Again, no exogenous nor expensive ligands are required, leading to an overall economically viable process. Those results clearly demonstrate that magnesium alkoxide additives per se can play a beneficial role in alkyl–alkenyl iron-mediated cross-coupling reactions, similarly to the results observed when NMP is used as a co-solvent (Scheme 2b).

Therefore, targeting applications in pheromone synthesis, we aimed at combining the advantages brought by those additives with the atom-economy offered by the use of organic electrophiles bearing halide leaving groups (better than that obtained with phosphates leaving groups, Scheme 4). We thus investigated the development of pheromone synthesis involving cross-coupling methods using Grignard reagents bearing terminal alkoxide magnesium moieties and dienyl halides. This strategy is moreover particularly appealing since the magnesium alkoxide additive used in the cross-coupling is also a part of the final synthetic target. The oxygen atom of the -OMgX functionality indeed affords the terminal oxidized function of the pheromone molecule (alkoxy acetate in 2 or 3, Scheme 4a and 4b, or formyl group in 1, Scheme 4c).
As a representative target, we developed the total synthesis of the codling moth sex pheromone, (8E,10E)-dodecadien-1-ol (4), featuring the introduction of the C7–C8 linkage by a key iron-mediated cross-coupling sequence between the suitable α,ω-difunctionalized Grignard reagent and 1-bromopenta-1,3-diene as the electrophile (Scheme 6) [32].

A classic drawback of the use of dienyl halides as coupling partners is their intrinsic thermal instability. Dienyl halides indeed tend to polymerize at low temperatures, and drastic storage conditions must be applied. For example, chloroprene, a well-known precursor of isoprene polymers, must be transported under inert atmosphere below −10 °C, and an inhibitor must be added to prevent polymerization. Cross-coupling systems involving this reagent are thus particularly scarce, and few examples are reported, using for some of them Ni-based catalysts [33].

1-Bromopenta-1,3-diene used in the synthesis of 4 (Scheme 6) is not an exception. The expected (E,E) isomer was easily obtained from sorbic acid, a renewable C6 synthon, by a Hunsdiecker–Borodin bromodecarboxylation, adapting the recent micellar conditions developed by Rajanna for the synthesis of alkyl halides starting from α,β-unsaturated acids [34]. However, purification and concentration of 1-bromopenta-1,3-diene proved to only promote its degradation, likely by polymerization. To circumvent this matter, we developed a workup procedure allowing to directly obtain THF solutions of 1-bromopenta-1,3-diene in the 0.4–0.7 M concentration range, and no further purification was required. Those solutions can be directly used in a subsequent iron-mediated cross-coupling procedure. We demonstrated that the alkyl–dienyl cross coupling of those solutions of 1-bromopenta-1,3-diene with α,ω-difunctionalized Grignard reagents afforded the coupling product 4 with an excellent 94% yield and a total retention of stereochem-

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Scheme 5: Cross-coupling of alkyl Grignard reagents with a) alkenyl or b) aryl halides involving EtOMgCl as additive.

Scheme 6: Total synthesis of codling moth sex pheromone 4 using an iron-mediated cross-coupling between an α,ω-difunctionalized Grignard reagent and a dienyl bromide.
istry (Scheme 6). Overall, sex pheromone 4 can be obtained in a convergent total synthesis with a key iron-mediated cross coupling starting from sorbic acid and a commercially available α,ω-chloroalcohol in 4 steps, with an overall 38% yield.

This method can also be used for the alkylation of dienyl bromides by classic aliphatic or aromatic Grignard reagents which do not bear ω-magnesium alkoxide functionalities: in that case, EtOMgX can be used as an external additive to enhance the cross-coupling selectivity, in line with the alkyl–alkenyl and aryl–alkenyl cross-coupling methods discussed earlier (Scheme 5) [32].

The beneficial role of magnesium alkoxide salts in the outcome of iron-mediated alkyl–alkenyl cross-coupling reactions can thus display a double interest for the total synthesis of insect pheromones. Indeed, α,ω-difunctionalized Grignard reagents featuring a terminal magnesium alkoxide group can be used as both nucleophilic partners and as a magnesium alkoxide additive source, enabling the development of iron-mediated cross-coupling procedures with alkyl or dienyl halides, requiring neither heavy alkyl phosphate leaving groups nor toxic solvents such as NMP. Moreover, those procedures can be carried out at large industrial kilogram scales, leading to green, efficient and economically viable processes.

**Mechanistic considerations**

The improvements of the initial cross-coupling conditions developed by Kochi (Scheme 2a) discussed in this report have high potent synthetic applications since they do not require well-defined iron precursors stabilized by highly functionalized ligands, the high price of the latter often precluding their use in high-scale syntheses. On the other hand, the exact role played at a molecular level by the additives discussed herein (NMP or one of its surrogates, magnesium alkoxides, phosphate leaving groups, etc.) is still an unclear question, even if the latter species proved to have an unambiguous beneficial effect on the cross-coupling yields and selectivities. Several recent literature results which enlighten the role of those additives, either brought by external reagents or by in situ-formed intermediates, are gathered in Table 2.

The beneficial role of the NMP co-solvent on the alkyl–alkenyl cross-coupling yield reported by Cahiez (Scheme 2b) and considerably used ever since was explained at a molecular level by Neidig in 2018. It was demonstrated that NMP did not act as a ligand to the iron center in alkyl–alkenyl cross-coupling reactions featuring Grignard reagents, but was involved in the formation of the bulky dication \([\text{Mg}(\text{NMP})_6]^{2+}\), the presence of the latter contributing to the kinetic stabilization of the on-cycle active species \([\text{Me}_3\text{Fe}^{II}]^-\) (Table 2, entry 1) [35]. The exact nature of the interaction between the active \(\text{ate-ferrous complex}\) and the NMP-ligated magnesium cation is so far unknown. Although often neglected in the mechanistic analysis of a cross-coupling system, the importance of the coordination sphere of the main-group cation brought by the nucleophilic partner \(\text{R[M]}\) in a cross-coupling has been reported in the recent literature. It was indeed shown that some ligands (such as diphosphines) used in Fe-catalyzed Negishi cross-coupling reactions \((\text{R[M]} = \text{RZnX})\) were actually involved in the coordination of the Zn\(^{II}\) cation in a key on-cycle transmetallation step, and not in the coordination of the iron-containing intermediates [36,37].

![Table 2](image-url)
The use of magnesium alkoxide salts, either as an ω-functionalization of the nucleophilic partner (Scheme 4) or as an external molecular additive such as EtOMgCl (Scheme 5), also likely proceeds similarly to the NMP, as demonstrated by recent studies by Neidig and Lefèvre (Table 2, entry 2) [38]. No alteration of the structure of the active species [Me₃Fe]⁺ is observed in the presence of an excess of EtOMgCl, suggesting that the alkoxide additives solely bind to the magnesium cations. However, for very low RMgX:EtOMgX ratios, minor species possibly featuring alkoxide stabilized ferrous [FeII]-OEt intermediates were observed by paramagnetic ¹H NMR spectroscopy.

In line with this result, Fleischer and Lefèvre also recently demonstrated that the anionic thiolate leaving group EtS⁻ released in Fukuyama cross-coupling reactions between alkylmanganese nucleophiles AlkylMnX and thioesters RC(O)SeEt using Fe(acac)₃ as catalyst could act as a ligand to on-cycle organoiron(II) intermediates (Table 2, entry 3) [39]. This behaviour opens the door to interesting synthetic perspectives, since it suggests that leaving groups can act as stabilizing additives to on-cycle organometallic intermediates in cross-coupling procedures. Given that the quantity of free anionic leaving groups, released at each turnover cycle, increases upon completion of the coupling process, it means that the catalyst resting state strongly affects the usual decomposition of the iron catalyst, which tends to afford unreactive reduced aggregates at the end of the catalytic transformation, when the coupling kinetics is slowed down due to the drop of the concentration of coupling reagents.

The affinity of ferrous precatalysts for thiolate ligands had also been reported by Cahiez earlier in the cross-coupling of alkyl Grignard reagents with alkanyl halides, 2-naphthylthiolates being used as additives [40]. No in-depth mechanistic studies were so far reported regarding the reactivity of the enol phosphete electrophiles (Scheme 3 and Scheme 4, and Table 2, entry 4). Phosphate free anions released at each catalytic cycle could act either as NMP or alkoxides, that is, as ligands to the magnesium cations, or as thiolate leaving groups, and stabilize at a molecular level active FeⅡ species. In both cases, a beneficial effect should be observed at a molecular level on the stabilization and/or the reactivity of on-cycle species, given that phosphate electrophiles proved to afford satisfying coupling yields in the absence of other additives.

Conclusion
In conclusion, iron-mediated cross-coupling reactions between Grignard reagents and alkanyl organic electrophiles prove to be an efficient method for the introduction of the key alkyl-alkenyl linkages in insect sex pheromones total synthesis. This method has been applied to a variety of targets, and has witnessed important improvements since the seminal reports by Cahiez and Kochi. To date, alternatives to the use of reprotoxic additives such as NMP have been reported (involving, e.g., phosphate leaving groups, or magnesium alkoxide additives), and can be efficiently applied at large industrial scales.

Extension of such methods to more challenging hybridization patterns in cross-coupling chemistry applied to synthesis of other insect pheromones is currently investigated in our groups.

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15. Section 2.4.1. See for a complete review on Fe-catalyzed cross-couplings.

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Identification and determination of the absolute configuration of amorph-4-en-10β-ol, a cadinol-type sesquiterpene from the scent glands of the African reed frog

Hyperolius cinnamomeoventris

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Full Research Paper

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Keywords:
Anura; chiral gas chromatography; enantioselective synthesis; GC/MS; semiochemicals

Abstract

Hyperolid reed frogs are one of the few families of Anurans known to possess glands that emit volatile compounds used in chemical communication. *Hyperolius cinnamomeoventris*, a model species, possesses a gular gland on its vocal sac that emits chemicals, and sends visual and auditory signals during calling. Previous investigations have shown that the glandular compounds are typically macrocyclic lactones. However, in this work, we show that another major constituent of the male specific gland is (10R,1S,6R,7R,10R)-amorph-4-ene-10β-ol [(1R,4R,4aR,8aS)-4-isopropyl-1,6-dimethyl-1,2,3,4,4a,7,8,8a-octahydrodaphthalen-1-ol]. This compound was synthesized for the first time and has the opposite configuration to amorph-4-ene-10β-ol known from plants. A short synthesis using an organocatalytic approach through a tandem Mannich/intramolecular Diels–Alder reaction led to a mixture of cadinols, which was used for the assignment of the natural cadinol structures and their stereoisomers.

Introduction

*Hyperolius cinnamomeoventris* (Figure 1) is one of the largest species of reed frogs (Hyperoliidae), which are commonly found in Africa, south of the Sahara. Males of the Hyperoliidae possess a characteristic yellow gular patch on their vocal sac that also serves as a gland which emits volatile organic compounds during calling [1]. These courtship calls are trimodal, consisting of calls, yellow flashing signals, and volatile chemicals released from the gland [2]. The semiochemical signal, the glandular secretion, seems to be used for species recognition and mate choice. In the related frog family Mantellidae such
functions of volatiles from males have been demonstrated [3], but no behavioral experiments involving semiochemicals have been performed so far within the hyperolid family.

As biological material is scarce and the amount of analytes is low, GC–MS trace analytical methods are performed to investigate extracts from the glands of individual frogs to identify their constituents. The analysis of MS and GC–IR data as well as gas chromatographic retention indices and microderivatization of extracts finally lead to structural proposals that have to be verified by synthesis. On this way a large variety of hyperolid and mantellid frog gland constituents have been identified [3-9]. Herein, we report on the structural elucidation of sesquiterpene A, including spectral analysis and synthesis to determine its constitution and absolute configuration.

Results and Discussion
High-resolution mass spectrometry (HRMS) revealed both compounds A and C to be likely sesquiterpenes because of their molecular formula of C_{15}H_{26}O (m/z 222.1977, calcd for 222.1977) and C_{15}H_{22}O (m/z 216.1514, calcd for 216.1514), respectively, as well as the general appearance of their EI mass spectra. The mass spectrum of compound A (Figure 4) showed similarity to that of δ-cadinol (12) [10], but the linear gas chromatographic retention index [11] I = 1596 on an apolar DB-5 phase differed from the literature value of 1645 reported for compound 12 [12]. As no reference material was available, a problem hindering identification of sesquiterpenes in general, we planned to synthesize 12 and its seven diastereomers. Therefore, we adapted a synthesis of 12 originally developed by Taber and Gunn [13], using a Diels–Alder reaction as the key step, as it would allow access to several cadinol diastereomers, in line with a diversity-oriented synthetic plan.

The synthesis began with enamine formation of isovaleraldehyde (1) and piperidine (2) to give enamine 3 that was reacted in a Michael addition with methyl acrylate, affording aldehyde 4 (Scheme 1). Instead of the original Wittig reaction [13], a Horner–Wadsworth–Emmons reaction using diethyl (2-methylallyl)phosphonate and BuLi led to a higher yield and formation of the pure (E)-isomer 5. The required phosphonate was cleanly obtained in 75% yield from triethyl phosphate and 3-chloro-2-methylpropene by addition of NaI [14]. Subsequent reduction of

\[ \text{O} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{O} \]
Figure 4: Mass spectrum of sesquiterpene A (m/z = 1596) from the gular gland extract of male Hyperolius cinnamomeoventris, identified to be amorph-4-en-10β-ol (14).

Scheme 1: Racemic synthesis of cadinols modified from Taber and Gunn [13]. Conditions a) i) K₂CO₃ (0.35 equiv), 0 °C, 1 h, ii) rt, 2.5 h; b) i) methyl acrylate (1.3 equiv), MeCN, 90 °C, 42.5 h, ii) dest. H₂O, AcOH, reflux, 1 h; c) i) diethyl (2-methylallyl)phosphonate (1.3 equiv), n-BuLi (1.3 equiv), THF, −78 °C, 35 min, ii) 4 (1.0 equiv), THF, −78 °C, 1 h, iii) rt, 1.5 h; d) i) LiAlH₄ (1.2 equiv), Et₂O, 0 °C, 15 min ii) rt, 45 min; e) IBX (3.0 equiv), EtOAc, reflux, 3 h; f) i) CH₂=CHMgBr (1.5 equiv) Et₂O, 0 °C, ii) rt, 20 min; g) IBX (3.0 equiv), EtOAc, reflux, 6 h; h) i) MeMgBr (1.5 equiv) Et₂O, 0 °C, ii) rt, 30 min; j) NaOMe (25.0 equiv), MeOH, rt, 60 h.
the ester with LiAlH₄ and oxidation with IBX gave aldehyde 7 in 95% yield. Grignard addition of vinylmagnesium bromide afforded the alcohol 8, which comprised the desired triene system for an intramolecular Diels–Alder reaction. Oxidation of 8 with IBX changed the electronic properties of the system implementing an electron-deficient double bond suitable for a heat-induced intramolecular Diels–Alder reaction. The higher reaction temperature compared to the original synthesis by Taber that used dichromate as an oxidant [13] led to a less diastereoselective reaction furnishing the three ketones 9, 10, and 11 in a ratio of 36:2:5. The cis-conformation of the decalin backbone of 9 and 11 originates from the endo-selectivity of the Diels–Alder reaction and the boat conformation of the transition state. A chair transition state is less preferred because of inherent non-bonding interactions of some hydrogens. This has been discussed in detail in the original publication by Taber and Gunn, favoring 9 as the main diastereomer [13]. Our results confirm these data. To increase the ratio of the minor diastereomers, the ketone mixture was treated with NaOMe, resulting in epimerization of 9, arriving at a 3:3:1 mixture of 9, 10, and 11. Unfortunately, a moderate amount of material was lost due to competing aldol reactions of the ketones. While compound 9 was epimerized to a large extent into 10, the isomer 11 could not be converted into the respective trans-fused compound. This inseparable ketone mixture was then quantitatively converted into the target cadinols by addition of methyl magnesium bromide [15]. Major compounds were cedrelanol or τ-cadinol (13) and δ-cadinol (12) (for mass spectra see Supporting Information File 1). A minor diastereomer 14 was obtained in 9% yield after isolation by RP-HPLC using a LiChroPrep RP-18 phase because conventional column chromatography did not allow for good separation from the major products. Only one face of the carbonyl groups underwent nucleophilic attack, leading the formation of the three desired compounds.

The diastereomer 14 showed the same linear retention index \( I = 1596 \) and the same mass spectrum as A. After detailed NMR analysis, the relative configuration of the natural product could be determined. The most stable conformation was determined by calculation using force field methods (MMFF94 [16]) and is shown in Figure S2 of Supporting Information File 1. Key NOE couplings were observed between bridgehead H-8a, H-4a and H-4. The latter also couples with the methyl group at C-1, indicating a cis-decalin configuration with an equatorial isopropyl group and axial OH in compound 14. A more detailed description showing the relevant NOESY correlations is given in Supporting Information File 1.

Compound 14 proved to be identical to amorph-4-en-10β-ol, which is a rare natural product, known from the wood oil of *Cryptomeria japonica* [17], the essential oil from *Agaia odorata* [18], and from vetiver oil (*Vetiveria zizanioides*) [19]. Nevertheless, the absolute configuration of the natural compound remained unknown [18].

Having established the constitution and relative configuration of A, we then determined the absolute configuration. Controlling the stereogenic center C-4 of 4 would allow access to the respective enantiomers. Unfortunately, enantiomerically pure 4 is not easily available, in contrast to ketone 17. This compound can be obtained in high optical purity using Jørgensen’s organocatalyst 16 [20,21]. In addition, such a synthetic approach would shorten the synthesis from eight to four steps and allow access to both enantiomers of the compounds 12–14.

The synthesis started with an enantioselective Michael addition of aldehyde 1 to methyl vinyl ketone (15) catalyzed by (S)-Jørgensen’s organocatalyst S-16, to define the first stereogenic center at the isopropyl group, which becomes C-4 in the final products. Both S- and R-16 were used to obtain the respective products in high ee and high yields (\( R-17 = 87\%, 98\% \) ee, \( S-17 = 87\%, 99\% \) ee) (Scheme 2) [20].

As in the racemic synthesis (Scheme 1), a HWE reaction using diethyl (2-methylallyl)phosphonate gave diene ketone S-18 [13]. Here, we envisioned that a Mannich reaction would introduce the required \( \alpha,\beta \)-unsaturated carbonyl system needed for the following intramolecular Diels–Alder reaction, that likely would proceed directly under these conditions. This concept proved to be difficult to achieve, but by optimization of different parameters of this Domino reaction, the required enantiomerically almost pure ketones 9–11 were obtained (Table 1).

The Mannich reaction worked best using diisopropylammonium trifluoroacetate as the catalyst [22]. The isolation of S-19 was attempted (Table 1, entry 1) but proved not to be necessary as the intramolecular Diels–Alder reaction proceeded readily during the reaction. Other conditions using an excess of formaldehyde, paraformaldehyde, or gaseous formaldehyde (Table 1, entries 2–4) were unsuccessful, mostly due to slow reaction, but a 37% solution of formaldehyde in water/methanol proved to be successful (Table 1, entries 5–10). Nevertheless, two problems were encountered. First, the Diels–Alder products 9–11 proved to be also active Mannich acceptors, leading to the unwanted unsaturated ketone 20, a double Mannich product. To avoid this second addition, an excess or equimolar amounts of formaldehyde were avoided (Table 1, entries 6–10). The best result was achieved by adding only 0.4 equivalents formaldehyde to obtain products S-9–11 (Table 1, entries 9 and 10). The stereochemical descriptors \( S \) and \( R \) in compound numbers indicate the stereochemistry at C-4 in the cadinane system (Scheme 2) in the following discussion. Secondly, unreacted starting material 18 was not separable from
Scheme 2: Enantioselective synthesis with \((S)-Jørgensen's\) organocatalyst \(S-16\). Conditions: a) \(S-16\) (5 mol %), ethyl 3,4-dihydroxybenzoate (0.2 equiv), 4 °C, 36 h; b) i) diethyl (2-methylallyl)phosphonate (1.5 equiv), THF, −78 °C, 10 min, ii) \(n\)-BuLi (1.5 equiv), THF, −78 °C, 1 h, iii) \(S-17\) (1.0 equiv), −78 °C, 10 min, rt, 8 h; c) i) formaldehyde (0.4 equiv), disopropylamine (0.4 equiv), TFA (0.1 equiv), THF, reflux, 3 d, ii) maleic anhydride (1.2 equiv), reflux, 16 h; d) MeMgBr (3.0 equiv), THF, reflux, 4 h.

Table 1: Screening of different reaction conditions with the \((S)-Jørgensen's\) organocatalyst \(S-16\) for the key Domino reaction, consecutive Mannich and intramolecular Diels–Alder reactions. DIA TFA: disopropylammonium trifluoroacetate.

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent</th>
<th>base</th>
<th>solvent (reflux)</th>
<th>reaction time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>formaldehyde (11.8 equiv)</td>
<td>piperidine (0.13 equiv)</td>
<td>MeOH</td>
<td>1 d</td>
<td>S-8 23%</td>
</tr>
<tr>
<td>2(^b)</td>
<td>paraformaldehyde (2.0 equiv, cracked in reaction mixture)</td>
<td>DIA TFA (2.0 equiv)</td>
<td>THF</td>
<td>10 d</td>
<td>mixture</td>
</tr>
<tr>
<td>3(^b)</td>
<td>paraformaldehyde (1.0 equiv, cracked in reaction mixture)</td>
<td>DIA TFA (1.0 equiv)</td>
<td>THF</td>
<td>10 d</td>
<td>mixture</td>
</tr>
<tr>
<td>4(^b)</td>
<td>paraformaldehyde (1.0 equiv cracked in a separate flask)</td>
<td>DIA TFA (1.0 equiv)</td>
<td>toluene</td>
<td>1 d</td>
<td>S-12</td>
</tr>
<tr>
<td>5(^b)</td>
<td>formaldehyde (37%) (1.0 equiv)</td>
<td>DIA TFA (2.0 equiv)</td>
<td>toluene</td>
<td>12 h</td>
<td>S-12</td>
</tr>
<tr>
<td>6(^b)</td>
<td>formaldehyde (37%) (0.75 equiv)</td>
<td>DIA TFA (0.75 equiv)</td>
<td>toluene</td>
<td>8 h</td>
<td>S-12</td>
</tr>
<tr>
<td>7(^b)</td>
<td>formaldehyde (37%) (0.6 equiv)</td>
<td>DIA TFA (0.6 equiv)</td>
<td>toluene</td>
<td>8 h</td>
<td>S-12</td>
</tr>
<tr>
<td>8(^b)</td>
<td>formaldehyde (37%) (0.5 equiv)</td>
<td>DIA TFA (0.5 equiv)</td>
<td>toluene</td>
<td>8 h</td>
<td>S-12</td>
</tr>
<tr>
<td>9(^b)</td>
<td>formaldehyde (37%) (0.4 equiv)</td>
<td>DIA TFA (0.4 equiv)</td>
<td>toluene</td>
<td>3 d</td>
<td>S-9–S-11 21%</td>
</tr>
<tr>
<td>10(^b)</td>
<td>formaldehyde (37%) in methanol (0.4 equiv)</td>
<td>DIA TFA (0.4 equiv)</td>
<td>THF</td>
<td>3 d</td>
<td>S-9–S-11 21%</td>
</tr>
</tbody>
</table>

\(^a\)With AcOH (0.22 equiv) [23], \(^b\)with TFA (0.1 equiv) [22].
the products by column chromatography. Therefore, maleic anhydride was added at the end of the reaction to form a Diels–Alder adduct with 18 that was readily separable from the target ketones. Following the optimization of reaction conditions, a change of solvent to THF was shown to be as equally effective as toluene (Table 1, entry 10).

The ketones S-9, S-10, and S-11 were obtained in a ratio of 1:6.9:5.2, indicating a higher degree of epimerization at C-8a or a less selective Diels–Alder reaction compared to the racemic synthesis. Similar results were obtained within the R-series, starting with R-17. A final Grignard reaction using both ketone stereoisomeric mixtures with methylmagnesium bromide led to the R- and S-enantiomers of amorph-4-en-10β-ol (14), δ-cadinol (12), epí-α-muurolol or τ-muurolol (21), α-cadinol (22), and 10-epi-α-cadinol or τ-cadinol (13), respectively.

The isolation of product 14 proved unsuccessful due to the inseparability from the other cadinols. Nevertheless, with this material in hand, the absolute configuration of the sesquiterpene A was elucidated by enantioselective gas chromatography. The enantiomers of the alcohols could be separated on a Hydrodex β-6TBDM phase (Figure 5). This allowed to determine the absolute configuration of the sesquiterpene A. A coinjection of a gland extract with both the synthetic R- and S-samples would confirm the stereochemistry (Figure 6).

![Figure 5: TIC and gas chromatographic Kovats retention indices RI [24] values determined on a Hydrodex β-6TBDM phase. The compounds are color-coded with the respective mass spectra in Figure 7 of each cadinol-type. Orange: δ-cadinol; blue: τ-cadinol; red: amorph-4-en-10β-ol; violet: α-cadinol. Upper trace: (4S)-diastereomers; lower trace: (4R)-diastereomers. *Corresponding enantiomers.](image-url)
Figure 6: Coinjection of R-14 and S-14 with a gular gland extract of Hyperolius cinnamomeoventris performed with a Hydrodex β-6TBDM column. Compound B serves as relative standard to target compound A.

The coinjection of A with R-14 showed only one peak with increased intensity, while two peaks were observed with S-14. Therefore, the natural compound A is (1R,4R,4aR,8aS)-4-isopropyl-1,6-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (R-14) or, according to the nomenclature used initially [17,18], (10R,1S,6R,7R,10R)-amorph-4-ene-10β-ol (see Figure S3 in Supporting Information File 1 for a comparison of compound numbering). To the best of our knowledge, this is the first determination of the absolute configuration of amorph-4-ene-10β-ol (14) from a natural source. Alcohol 14 has been isolated before [17,18] or obtained by rearrangement from (+)-α-ylangene [25]. In the latter case the (4S)-stereoisomer of 14 was formed, as the isopropyl group is not affected by the rearrangement (see Figure S3 in the Supporting Information File 1). The same enantiomer was isolated from the wood oil of Cryptomeria japonica [17]. Therefore, the enantiomer R-14 from the frogs is different to the plant compound. This finding may point to a biosynthesis of 14 by the frogs themselves or by associated microorganisms, although uptake from the arthropod diet also may be possible, but less likely. The diet is varying. In addition, some arthropods can produce terpenes but they are not regarded as prolific producers of sesquiterpenes. The analysis of several H. cinnamomeoventris individuals from different locations showed a consistent composition of the gular gland blend, including always 14. Diet-dependent uptake of compounds by frogs usually results in individual differences in compound composition, as has been observed, e.g., for skin alkaloids of Madagascan poison frogs [26]. Finally, experiments with mantellines showed that at least scent gland macrolides can be biosynthesized by the frogs [7], although the macrolides are produced from the fatty acid biosynthetic pathway.

The gas chromatographic separation obtained with the chiral phase also allowed the determination of the identity of the minor diastereomers formed during the reaction. This was not possible on a conventional DB-5-MS GC phase, because of overlapping peaks. Next to the major diastereomers 12, 13 and 14, *epi*-α-muurolol or τ-muurolol (21), and α-cadinol (22) were identified by their mass spectra [10,27] (Figure 7). After publication of this article, mass spectra and I of 12 and 14, not present in the NIST 17 database will be made publically available in computer readable format through the open access mass spectra data base MACE [28].

**Conclusion**

In this work, we have characterized compound A to be (10R,1S,6R,7R,10R)-amorph-4-ene-10β-ol or (1R,4R,4aR,8aS)-4-isopropyl-1,6-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (R-14) as part of the semiochemical mixture released by gular glands of the African reed frog *Hyperolius cinnamomeoventris*. This establishes the importance of sesquiterpenes for reed frogs, alongside macrocyclic lactones [2]. The total synthesis and characterization showed that this compound is the opposite enantiomer of 14 known from plants. This may indicate biosynthesis in the frog, but more work has to be performed to establish this. Furthermore, a short diversity-oriented synthesis based on the work of Taber and Gunn [13] enabled mass spectrometric and gas chromatographic data to be
acquired, clarifying the identity and stereochemistry of several cadinols.

Supporting Information

Supporting Information File 1
Numbering scheme, experimental procedures, $^1$H, $^{13}$C and 2D NMR spectra, and mass spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-16-S1.pdf]

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References
Strategies to access the [5-8] bicyclic core encountered in the sesquiterpene, diterpene and sesterterpene series

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Abstract
Terpene compounds probably represent the most diversified class of secondary metabolites. Some classes of terpenes, mainly diterpenes (C20) and sesterterpenes (C25) and to a lesser extent sesquiterpenes (C15), share a common bicyclo[3.6.0]undecane core which is characterized by the presence of a cyclooctane ring fused to a cyclopentane ring, i.e., a [5-8] bicyclic ring system. This review focuses on the different strategies elaborated to construct this [5-8] bicyclic ring system and their application in the total synthesis of terpenes over the last two decades. The overall approaches involve the construction of the 8-membered ring from an appropriate cyclopentane precursor. The proposed strategies include metathesis, Nozaki–Hiyama–Kishi (NHK) cyclization, Pd-mediated cyclization, radical cyclization, Pauson–Khand reaction, Lewis acid-promoted cyclization, rearrangement, cycloadDITION and biocatalysis.

Introduction
Terpene compounds represent the largest and most diversified class of secondary metabolites. They are present in all organisms and their structure can vary from simple terpenes (C10 skeleton) to polymers (example of rubber) thanks to iterative addition of geranyl (C10) or farnesyl (C15) building blocks derived from isoprene as starting unit and further structure rearrangement and functionalization [1]. This ubiquitous distribution highlights their pivotal role in living systems such as cell wall structural agent or ecological mediator [2]. In several cases, terpenes possess a complex polycyclic framework which challenged the chemistry community over the years to develop efficient approaches and methodologies to access them. Indeed, some classes of terpenes, mainly diterpenes (C20) and sesterterpenes (C25) and to a lesser extent sesquiterpenes (C15), share a common bicyclo[3.6.0]undecane core which is characterized by the presence of a cyclooctane ring fused to a cyclopentane ring.
i.e., a [5-8] bicyclic ring system (Figure 1). In most cases, additional rings are present and original strategies have been considered to construct this bicyclic system.

This review focuses on the different strategies elaborated to build this [5-8] bicyclic ring system and their applications in the total synthesis of terpenes over the last two decades [3]. We are not providing here a comprehensive collection of the literature. When appropriate, the reader will be referred to specific reviews on a particular class of terpenes. Rather, we try to present the portfolio of available methods used nowadays to build this motif.

Accordingly, in most cases the overall approaches involve construction of the 8-membered ring from an appropriate cyclopentane precursor. The proposed strategies include metalation, Nozaki–Hiyama–Kishi (NHK) cyclization, Pd-mediated cyclization, radical cyclization (including SmI2), Pauson–Khand reaction, Lewis acid-promoted cyclization, rearrangement, cycloaddition, and biocatalysis. In particular, the purpose will focus on the following criteria: position/stage of the key cyclooctane ring formation in the synthesis plan, the selectivity, and the opportunity for late-stage functionalization.

### Review

#### 1 Metathesis: ring-closing metathesis and related methods

The metathesis reaction, first discovered by serendipity in the 1950s, has turned into one of the most used and powerful reactions in organic synthesis, and allows the formation of functionalized double or triple bonds. Over the time, this reaction drew more and more scientists’ attention, with increasing numbers of publications on this topic [4-6]. Proof of this success, Chauvin, Schrock and Grubbs were awarded the Nobel Prize in 2005 for their improvements in metathesis reactions [5,6]. Key to success of the metathesis reaction arises from its broad spectrum of application, its functional groups tolerance, its versatility, and its mild reaction conditions [4-9].

Metathesis reactions take place by the means of a metallic catalyst. Firstly, olefin metathesis was achieved with an air-sensitive tungsten complex [8]. An important focus on air-stable catalyst design was undertaken and contributed to the popularization of the reaction. Thus, Grubbs catalysts of 1st and 2nd generation (G-I and G-II, respectively) as well as more recent Hoveyda–Grubbs 1st or 2nd generation (HG-I and HG-II, respectively) (Figure 2) are now commercially available.

![Figure 1: Examples of terpenes containing a bicyclo[3.6.0]undecane motif.](image-url)
the design of new efficient catalysts is at the heart of research [4-7,9-12].

The synthesis of five- and six-membered rings can be readily achieved through ring-closing metathesis (RCM), but the synthesis of eight-membered rings has been carried out later [13,14]. In this part, we will focus on the use of RCM to achieve total syntheses of natural products or to access the carbon skeleton of natural products, and more particularly to construct the cyclooctane ring that is part in these motifs.

1.1 Ring-closing metathesis (RCM)
Among all metathesis reactions available in the chemist’s toolbox, ring-closing metathesis (RCM) is nowadays one of the most popular and has been used several times as a key-step to synthesize the cyclooctanoid ring that is part of the sesterterpenoid family.

1.1.1 Syntheses of fusicocans and ophiobolins: Fusicocananes and ophiobolins represent an important class of natural diterpenes, whose principal members are fusicocin A (6) and ophiobolin A (8), respectively (Figure 1). Both families share the same core structure bearing a fused [5-8-5] tricyclic skeleton and they vary within their decorative functional groups.

Over the years, many different syntheses to access compounds from the fusicocan and ophiobolin family have been reported, with two strategies standing out. The first one (strategy 1, Figure 3) consists in the successive formation of the eight-membered ring B followed by construction of the five-membered ring C; i.e., the cyclooctene ring is built first from a suitably substituted cyclopentane substrate, which then serves as a precursor for the cyclopentane ring C formation. In the second strategy (strategy 2, Figure 3), both cyclopentane rings A and C are formed first, and the eight-membered ring B is introduced at a late stage.

1.1.1.1 Strategy 1: Successive introduction of rings B and C starting from cyclopentene via the [5-8] bicyclic structure to the final [5-8-5] tricyclic core:
The synthesis of the core bicyclic structure 12 of ophiobolin M (13) isolated from the fungus Cochliobolus heterostrophus and cycloaraneosene (14) firstly isolated in 1975 from the fungus Sordaria araneosa, was undertaken by Williams et al. in 2002 [15]. Compound 14 shares the common [5-8-5] tricyclic framework emblematic of the fusicocan series, albeit cycloaraneosene (14) does not have any heteroatom (Scheme 1) [16]. Focusing on the B–C bicyclic fragment, they used diene 10, readily available from cyclopentane-1,3-dione (9), as the precursor for installing the eight-membered ring by RCM (Scheme 1). Optimization of the reaction parameters (temperature, solvent, concentration, and catalyst amount) was carried out with G-I catalyst. Indeed, the authors noticed that high temperatures improved the reaction conversion, and dichloromethane seemed to furnish clean reaction and easy work-up. Thus, the final conditions were determined as 8–10 mol % of G-I catalyst loading in refluxing dichloromethane, albeit C5-C8 bicycle 11 was formed in modest yields and incomplete conver-
Scheme 1: Synthesis of bicyclic core structure 12 of ophiobolin M (13) and cycloaraneosene (14).

sion. Interestingly, use of G-II catalyst, known to give better results, did not improve the yield nor the bicycle-to-monocycle ratio.

In 2005, Michalak et al. examined the synthesis of the dicyclopenta[\(\alpha,\delta\)]cyclooctane structure present in ophiobolins and fusicoccanes by the means of a ring-closing metathesis reaction [17]. The metathesis substrate 17 was readily prepared in four steps from accessible methylcyclopentenone 16 (Scheme 2). The sequence included a Mukaiyama–Michael reaction with silyl enol 15 followed by a Tsuji alkylation. With diene 17 in hands, the RCM reaction was performed by addition of G-II

Scheme 2: Synthesis of the core structure 21 of ophiobolins and fusicoccanes.
catalyst and furnished the expected C5-C8 bicyclic framework 18 in 95% yield [17,18]. This key intermediate was then converted into ketone 19 in 11 steps leading to the desired dicyclopenta[α,d]cyclooctane structure 21 [19].

As explained by the authors, the RCM reaction was not as easy as expected and extensive work was necessary to accomplished the construction of this eight-membered ring. Indeed, in the initial strategy, thioester 22 was the first substrate subjected to the cyclization. In the presence of G-I catalyst, the reaction delivered the dimeric compound 23 whereas [5-7] bicycle 24 was formed in the presence of the G-II catalyst (Scheme 3). The formation of compound 24 was rationalized by an isomerization of the double bond prior to the cyclization step.

Isolated from the Ecuadorian liverwort *Anastrophyllum auritum* in 1994, *ent*-fusicoauritone (28) is a diterpene presenting a fusicoccan skeleton with a β-hydroxyketone on the A-ring and 5 stereogenic centers [20]. Its total synthesis was explored by Srikrishna and Nagaraju in 2012 using a linear strategy (Scheme 4) [20]. Thus, menthene 25 was converted in 16 steps into cyclopentane 26 presenting two unsaturated lateral chains. This compound was then treated with G-I catalyst to give the corresponding [5-8] cyclooctene 27 in very high yield. The final stages of the synthesis corresponded to the elaboration of the second cyclopentenone ring allowing access to *ent*-fusicoauritone (28) in 24 steps.

1.1.1.2 Strategy 2: Late-stage formation of the 8-membered ring:

Ophiobolins belong to the family of sesterterpenoids which displays around 50 members [21]. All these molecules share a similar [5-8-5] tricyclic structure (A-B-C ring system), with different decorating groups. The first congener to be isolated was ophiobolin A (8), which is present in the fungus *Ophiobolus miyabeanus* [22]. Other fungal species were found to produce ophiobolin A (8), and many other ophiobolin congeners such as ophiobolin B (29), ophiobolin C (30), and ophiobolin M (13) were also isolated (Figure 4) [23].

This natural products family is of high interest because of its broad spectrum of biological activities ranging from anti-infectious to anticancer properties [21,24,25]. Indeed, access to the ophiobolin structure is crucial to study their biological activities in detail. Many synthetic approaches have emerged for the synthesis of ophiobolins and total syntheses of some congeners have also been reported [21,24].

Nakada and co-workers reported in 2011 the first enantioselective total synthesis of (+)-ophiobolin A (8), involving a RCM approach to form the central eight-membered ring [24]. In this way, their total synthesis involved the enantioselective preparation of the C-D spiro bicyclic ring system 33 in 21 steps from diester 31 and oxazolidinone 32 (Scheme 5) [26]. Subsequently,
Figure 4: General structure of ophiobolins and congeners.

Scheme 5: Total synthesis of (+)-ophiobolin A (8).
compound 33 was converted in four steps into aldehyde 34 which was engaged in a coupling reaction with bromoketone 35 according to Utimoto conditions to furnish the A-C-D adduct 36 as a single stereoisomer in high yield. Of note, the Utimoto reaction has never been used in the synthesis of natural products before this report, and no β-elimination of the silyloxy group was observed, although this often occurs in such systems [26]. The installation of the two alkenes in 37 required 13 additional steps, and further protecting group manipulations were necessary to give compound 38 as a precursor for the late-stage RCM cyclization. This ring formation was very challenging and necessitated extended optimization. Indeed, during the course of the RCM a dramatic effect of the OH-protecting group on the cyclopentane unit was observed. The presence of a TBDPS substituent in compound 40 was assumed unfavorable, since this bulky residue generates a steric hindrance precluding the cyclization (Scheme 6, path A) [27]. Its replacement by a sterically less demanding benzyl protecting group (compound 44) allowed the reaction to occur (Scheme 6, path B). It also appeared that the RCM depended on the substrate core structure and the presence of a protected allylic alcohol prevented the cyclization to take place. Taking these observations into account, the tricyclic [5-8-5] ring system 45 was obtained using the HG-II catalyst in refluxing toluene. Further functionalization steps finally furnished (+)-ophiobolin A (8).

In the fusicoccane family, cotylenol (50), the aglycon of cotylenin A (131) (see section 3.1), is a fungal metabolite which displays various interesting biological activities [28]. For example, it expresses a moderate cytotoxicity against human myeloid leukemia cells, and stabilizes the 14-3-3 – TASK3 protein–protein interaction [29,30]. Sugita et al. investigated the synthesis of the core structure of cotylenol (50) first through an RCM approach on the advanced intermediate 47 (Scheme 7) [31]. Despite many attempts, the authors could not obtain the desired tricyclic compound possessing the required eight-membered ring, but instead they recovered the starting material 47, together with a dimeric product or an eleven-membered ring resulting from a RCM and a retro-aldol reaction. Assuming that the allylic alcohol may induce a steric hindrance, alcohol 47 was converted into triene 48 upon dehydration, and further engaged in the RCM reaction. In this case, the use of HG-II catalyst proved to be the best choice to achieve cyclooctene ring formation giving rise to intermediate 49, providing entries for further functionalization and access to cotylenin A aglycon 50.

Other examples of fusicoccane derivatives are represented by alterbrassicicene D (54) and 3(11)-epoxyhypoestenone (55), recently isolated from Hypoestes verticillaris [32]. Structurally, alterbrassicicene D (54) comprises an α,β-unsaturated ketone C-ring, and a single hydroxy group on the central eight-membered ring and 3(11)-epoxyhypoestenone (55) shows a surprising oxa-bridge between the A and C rings, an α,β-unsaturated ketone on ring C, and an endo-alkene into the cyclooctene ring. Recently, Chen et al. reported the synthesis of the tricyclic

![Scheme 6](image-url)
core structure of the fusicoccane skeleton 53 using a RCM approach (Scheme 8) [33]. The key RCM reaction was envisioned on precursor 52 corresponding to the A-C rings of the tricyclic backbone. In this case, G-II catalyst was used and the expected product 53 was obtained in high yields. Interestingly, the tricyclic intermediate 53 could be obtained in only 8 steps and at a large scale. Validation of this strategy allowed the authors to extend this approach to the total synthesis of alterbrassicene D (54) and 3(11)-epoxyhypoestenone (55).

1.1.2 Other chemical series possessing a [5-8] unit;
1.1.2.1 Early-stage introduction of the eight-membered ring:
(−)-Teubrevin G (59) is an example of a C5-C8 bicycle in which the C5 unit corresponds to a furan ring (Scheme 9) [34]. Indeed, this compound isolated from aerial parts of Teucrum brevifolium has a unique structure composed of a cyclooctane, fused with a furan ring, and bearing a spirolactone. As illustrated with the previous examples, access to the final cyclooctane ring was envisioned through a RCM reaction from an appropriate precursor. In a first attempt, compound 57, prepared from oxazole 56, was heated in the presence of G-I catalyst but yielded bicycle 58 only in modest amounts even after extensive reaction times (more than 3 days) and high catalyst loadings (30–35 mol %). After reaction optimization, use of G-II catalyst allowed formation of cyclooctane 58 in excellent 90% yield. This compound could ultimately be advanced to 59 in 8 steps.

Exhibiting a [5-8-5] tricyclic framework, the basmane family of terpenes differs from the fusicoccans by the arrangement of the
cycles, especially the position of the shared C–C bond between ring B and ring C (Scheme 10). In 2010, Ravi et al. investigated the synthesis of the core skeleton of this family [35]. Dihydrolimonene 25 was converted in 9 steps into compound 60 before subsequent RCM. As the authors knew G-I catalyst isomerizes β,γ-unsaturated ketones, G-II catalyst was chosen to produce bicyclic compound 61. Several additional steps were necessary to forge the last ring and obtain the core structure 63 of this series.

Schindilactone A (68) is a nortriterpenoid isolated from Schisandraceae plant family which displayed interesting biological activities in cancer and anti-infectious axis. However, access to this compound is limited because it possesses a very complex structure composed of a highly oxygenated backbone with 8 fused rings, a unique [7-8] bicyclic motif, an oxa-bridge over the cyclooctane ring, and the presence of 12 stereogenic centers [36].

The strategy proposed by the authors was to carry out a RCM reaction to elaborate the cyclooctene ring from functionalized intermediate 66, prepared as a diastereomeric mixture (α-position of the lactone, OTES) (Scheme 11) [36]. Interestingly, in this transformation the G-II-mediated ring formation was performed in the presence of MgBr₂, which acted as an epimerization agent at the lactol position yielding compound 67 as a single diastereomer in 65% yield. Of note, this compound entails the oxabicyclo[4.2.1]nonane core present in schindilactone A (68). The synthesis of schindilactone A (68) was achieved in 29 steps (0.11% overall yield).

1.1.2.2 Late-stage introduction of cyclooctene: The marine sesquiterpene dactylol (72), isolated from both sea hare Aplysia dactylomela and red seaweed Laurencia poitei, bears a rare rearranged trans-bicyclo[6.3.0]undecane isoprenoid skeleton. Its structure is – only – composed of a bicyclic ring with fused five- and eight-membered rings, with a hydroxy group at the
junction cycle [37,38]. In 1996, Fürstner and Langemann reported an efficient and short total synthesis of the natural product dactylol (72) (Scheme 12) [37]. The main originality of this work was the use of the Schrock molybdenum carbene catalyst 73 for the ring-closing metathesis reaction. The metathesis precursor 70 was obtained in 4 steps from commercial cyclopentenone 69. Protection of the alcohol function was mandatory prior to the cyclization as the free alcohol substrate failed to cyclize. As proposed by the authors, interaction between the free alcohol 70 and the molybdenum metal center may explain the reaction inhibition. Thus, after protection of the alcohol function as a silyl ether leading to diene 71, the RCM was performed in refluxing hexane and dactylol (72) was isolated in 17% overall yield after silyl ether removal [18,37].

Asteriscanolide (2), isolated in 1985 from the hexane extract of the plant Astericus aquaticus, is a sesquiterpene with a unique framework. Indeed, this natural compound has a rare [6.3.0] carbocyclic backbone with a bridging butyrolactone, and possesses five cis stereocenters [39,40]. This compound, in a racemic version, has been studied by Krafft, Cheung and Abboud (Scheme 13) [39]. The initial strategy relied on an intramolecular RCM reaction on compound 74 between the two terminal olefins, that could lead to the formation of a trisubstituted double bond (compound 75), and further access to the required α-methyl ketone. However, despite many attempts, no cyclization occurred. Indeed, the disubstituted methylene in compound 74 and the formation of a trisubstituted alkene in 75 were assumed to cause an important steric hindrance unfavor-
able for the cyclization process. As a solution, the RCM was envisaged on 76 which possesses two terminal double bonds and successfully produced cyclooctene 77 in 65–80% yield with G-I catalyst in dichloromethane at room temperature. Diene 78 was also designed, with the two alkene side chains closer in length, and the cyclization produced tricyclic 79 in higher yields (80–86%). Finally, diene 80 bearing a functionalized lateral chain was submitted to RCM conditions and delivered cyclooctene 81, an advanced intermediate in the synthesis of \((\pm\)-asteriscanolide \((2\).

Pleuromutilin \((1\) is the flagship representative of a recent class of antibiotics which displays a propellane-like structure (Scheme 14) [41-44]. Indeed, these compounds possess a compact tricyclic backbone resulting from the fusion of a five-, six- and eight-membered ring in which the three rings share a

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**Scheme 13**: Ring-closing metathesis for the total synthesis of \((\pm\)-asteriscanolide \((2\).

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**Scheme 14**: Synthesis of the simplified skeleton of pleuromutilin \((1\).
Nitidasin (93) is a pentacyclic sesterterpenoid bearing a [5-8-6-5] tetracyclic all-carbon system with 10 stereogenic centers (Scheme 15). This natural product was isolated from two Gentianella plant species, namely G. nitida and G. alborosea used in Peruvian traditional medicine. The first report of its synthesis was given in 2014 by Hog and co-workers [46,47]. In this work, the RCM was envisaged at a late stage on advanced intermediate 90 to forge the central eight-membered ring. The synthesis begins with known hydrindanone 86 (Scheme 15). This compound was converted in 12 steps into derivative 87, allowing introduction of a methylallyl lateral chain in α-position to the keto function. This terminal double bond prefigures the late RCM cyclization. trans-Hydrindanone 87 was isolated as a single diasteromer and possesses 5 out of the 10 stereogenic centers of nitidasin (93). In parallel, (−)-citronellene (88) was converted into derivative 89 possessing a terminal alkene and a vinyl iodide moiety in 9 steps. This compound can be considered as a difunctionalized compound. Indeed, the vinyl iodide function will be engaged first in a coupling reaction with hydrindanone 87 and the terminal alkene will be involved in the key RCM reaction to ensure formation of the central eight-membered ring. To achieve this goal, a model study was first conducted to define the best reaction conditions. Thus, coupling of the lithio-derivative of 89 to hydrindanone 87 proceeded smoothly to furnish the expected tertiary alcohol 90 with a high stereo- and diastereoselectivity. In a first attempt, the RCM reaction was envisioned prior to the epoxide formation. Unfortunately, no reaction occurred probably due to the presence of the tetrasubstituted olefin. Therefore, this olefin was converted into epoxide 91 and further RCM in the presence of G-II catalyst delivered the expected tetracyclic

Scheme 15: Total synthesis of (−)-nitidasin (93) using a ring-closing metathesis to construct the eight-membered ring.
cyclooctane-bearing product 92 in high yield (86%). Of note, this cyclization occurred on a highly functionalized substrate. All the carbons of the cyclooctene ring were stereogenic, except the two of the double bond, and the precursor possesses both a hydridane and a cyclopentane unit. The final steps of this synthesis involved alcohol deprotection, double bond hydrogenation and oxidation, and allowed the total synthesis of (+)-niti dasin (93) in 27 steps.

Naupliolide (97) was first isolated from the aerial parts of *Nauplius graveolens* in 2006. This tetracyclic natural product displays a similar backbone as asteriscanolide (2), with an α,β-unsaturated ketone on the eight-membered ring, fused with a γ-butyrolactone and a cyclopentane, onto which a cyclopropane is also grafted [48]. The total synthesis of (±)-naupliolide (97) reported by Ito et al. constituted another example of the usefulness of the RCM to construct a cyclooctane ring fused to a cyclopentane unit and presenting a trans-ring junction (Scheme 16) [48]. The synthesis started from compound 94 which was converted in 16 steps into derivative 95, the precursor of the RCM. The cyclization was performed in refluxing toluene in the presence of G-II catalyst and provided tetracyclic compound 96 with 50% yield. In this case, the RCM involved a terminal diene and a disubstituted diene. Further oxidation of the secondary alcohol furnished naupliolide (97).

1.2 Enyne ring-closing metathesis
The enyne ring-closing metathesis (EYRCM) reported by Katz in 1985, represents an attractive variant of the classical RCM with the replacement of one of the alkenes by an alkyne function. Thus, EYRCM is atom economic and provides a 1,3 diene, which constitutes an ideal partner for further functionalization, typically a Diels–Alder process [4, 8, 10].

In 2008, Patrick et al. investigated the access to bicyclic structure 100 mimicking the A-B ring system of the fusicocccane series (Scheme 17) [49]. Starting from lactone 98, enyne 99 was prepared in 23 steps. The EYRCM was planned at the final stage allowing an access to compound 100. Despite the relative simplicity of substrate 99, the reaction was running in the exclusive presence of G-II catalyst and necessitated a high catalyst loading (30 mol %) to eventually furnish modest yields. The presence of two major byproducts was also noticed, namely the cross metathesis adduct resulting from 2 equivalents of 99 and the cross metathesis adduct resulting from 99 and a styrene unit coming from the catalyst. In addition, the corresponding RCM on the alkene analogue of 99 did not proceed either with G-II or Schrock catalysts, showcasing the substrate sensitivity of this reaction.

1.3 Tandem ring-closing metathesis
The tandem ring-closing metathesis (TRCM) approach offers the opportunity to form two contiguous cycles in one step from a well-designed precursor. To this end, the starting substrate should integrate a dienyne moiety in its backbone. One of the olefins reacts first with the alkyne to form a carbocycle possessing a vinyl moiety, which in turn reacts with the second alkene, thus producing the expected bicyclic structure in a tandem process.
Ophiobolin A (8), one of the representatives of the ophiobolin family, contains a [5-8-5] tricyclic backbone with a side chain on the D-ring. It was isolated in 1958 from the fungus *Ophiobolus miyabeanus*, and displayed a remarkable cytotoxicity against several cancer cell lines [50]. Meanwhile, variecolin (3) was isolated from the fermentation broth of the fungus *Aspergillus variecolor* in 1991, and it appears to be a potent immunosuppressant. Structurally, variecolin (3) has a complex tetracyclic backbone with a fused [5-8-6-5] skeleton, with 8 stereocenters, 4 of them being contiguous and located on the C-ring [50]. The synthesis of the core structures of ophiobolin A (8) and variecolin (3) was undertaken by Gao and his group who used this strategy to construct both A and B rings (Scheme 18) [50]. 2-Methylcyclopentenone 16 was selected as a suitable A-ring starting material for the synthesis of ophiobolin A (8) (Scheme 18). Sequential modulations resulted in dienyne intermediates 102 and 103, the latter presenting a functionalized alkyne moiety prefiguring the aldehyde function of ophiobolin A (8). These two compounds were submitted to the EYRCM in the presence of G-II catalyst and furnished two different outcomes. Indeed, compound 102 gave the expected product 104 in 78% yield, whereas precursor 103, bearing hindered gem-dimethyl and benzyl protecting group, did not undergo the tandem process and furnished the monocyclized product 105.

To circumvent this monocyclization reaction, Gao and co-workers decided to simplify the gem-dimethyl group by a methyl residue and prepared the analogous compounds of 102 and 103, namely 106 and 107, respectively (Scheme 19). With these compounds in hand, terminal alkyne 106 provided the desired product 108 as previously observed with 102, while the protected alkyne 107 furnished a 1:1.7 mixture of monocyclized 109 and the expected product 110 in overall good yield. This study highlighted that a less-hindered olefin facilitated the second enyne metathesis of this tandem reaction.

The same strategy was applied for the synthesis of the variecolin [5-8-6-5] skeleton (Scheme 20). Dienynes 112 and 113 were first prepared from methyl ketone 111 and subsequently submitted to the metathesis conditions in the presence of G-II catalyst. Interestingly, in both cases the expected compounds resulting from the TRCM were obtained in good yields. Of particular interest, precursor 113 furnished 115 as the sole product.

1.4 Allylsilane ring-closing metathesis
As demonstrated above and in the literature [4-10], the RCM reaction constitutes a powerful tool to construct rings of various sizes. In 2009, Vanderwal and Dowling extended this process to the use of allylsilane derivatives which can be further submitted to an electrophilic desilylation reaction [51-54] giving an access to exo-methylene [38,55]. This concept was exemplified with the synthesis of poitediol (118) (Scheme 21), a bicyclopentacyclooctane compound isolated from the red seaweed *Laurencia poitei* in 1978. This sesquiterpene bearing a [5-8] bicyclic structure includes an exo-methylene moiety on the eight-membered ring [38,55]. Thus, allylsilane diene 116 prepared from cyclopentenone 69 as a 4:1 diastereomeric mixture was submitted to RCM conditions in the presence of G-II catalyst in...
Scheme 19: TRLCM on optimized substrates towards the synthesis of ophiobolin A (8).

Scheme 20: Tandem ring-closing metathesis for the synthesis of variecolin intermediates 114 and 115.

Scheme 21: Synthesis of poitediol (118) using the allylsilane ring-closing metathesis.
refluxing dichloromethane. The bicyclic product 117 was obtained in quantitative yield. Given the amount of electrophilic desilylation agents which can be used, a large diversity of compounds can be accessible through this method [51,52]. Oxidation followed by desilylation with fluoride source produces the natural product poitediol (118) in overall good yield.

2 Nozaki–Hiyama–Kishi (NHK) cyclization

The Nozaki–Hiyama–Kishi (NHK) reaction is an interesting coupling reaction involving the addition of a halogeno derivative (either bromide or iodide) to an aldehyde in the presence of nickel and chromium salts, typically NiCl₂/CrCl₂, generating an alcohol. In its original version, the stereochemistry of the adduct was not controlled, yielding a mixture of stereoisomers. Recent developments were undertaken to propose an asymmetric version [56,57].

In its intramolecular version, the NHK reaction was successfully applied by Kishi in 1989 to forge the cyclooctane ring of ophiobolin C (30) [5-8-5] framework, thus opening the door for further applications [58]. Indeed, several groups included this method at a late stage in their synthetic plan.

2.1 Synthesis of pleuromutilin

The purpose of Sorensen’s work was to design an efficient strategy allowing a rapid access to the pharmacophoric core of pleuromutilin, e.g., compound 122 for further derivatization and structure–activity relationship (SAR) studies [59]. In this case, an intramolecular NHK was carried out on compound 120 prepared from 3-allylcyclopent-2-enone (119) to give the tricyclic compound 121 possessing the eight-membered ring in 73% yield as the major compound. The diastereoselectivity was modest with a dr of 3:2. Esterification of the secondary alcohol followed by silyl removal gave access to the key scaffold 122 (Scheme 22).

2.2 Synthesis of aquatolide (4): Late-stage NHK medium-ring formation

Aquatolide (4) is a sesquiterpene lactone isolated from Asteriscus aquaticus (Asteraceae) which possesses a unique backbone featuring a cyclobutane moiety fused to a cyclopentane ring, a γ-lactone, and an eight-membered enone [60,61]. Zhang and Gu achieved its preparation through the use of a late-stage intramolecular NHK reaction (Scheme 23) [62]. Thus, when compound 123 was treated with CrCl₂ in the presence of a catalytic amount of NiCl₂ in DMSO and further oxidized under Swern conditions, aquatolide (4) was obtained in 43% yield over the two steps along with 50% recovery of the starting material 123.

Of note, the initial strategy involved an intramolecular hydroacylation on alkynyl compound 124 to construct the cyclooctanone unit. Despite several attempts, no cyclization occurred (Scheme 24).

3 Pd-mediated cyclization

3.1 Pd-promoted intramolecular alkenylation of methyl ketone: synthesis of cotylenin A (130)

Nakada exploited the usefulness of a Pd-promoted intramolecular alkenylation of methyl ketone to forge in the late-stage of
the synthesis the eight-membered ring of cotylenin A (130) [63]. To this end, the two cyclopentane units of the tricyclic core of cotylenin A were prepared separately and first assembled by an Utimoto coupling reaction to give after additional functionalization steps the key intermediate 128. This compound constituted the substrate for the Pd-promoted intramolecular cyclization. In this case, an enol triflate was used instead of an alkenyl halide which required the presence of an electron-rich phosphine, a lower temperature (50 °C instead of 100 °C) to avoid C-7 epimerization, and two equivalents of the Pd complex. The cycloadduct 129 was obtained in very high yield and could be converted to cotylenin A (130) in 5 steps. This work constituted an enantioselective total synthesis of cotylenin A (130) (Scheme 25).

3.2 Intramolecular Mizoroki–Heck reaction: construction of the [5-8] bicyclic ring system of brachialactone

A study of the versatility of the Mizoroki–Heck reaction in an intramolecular version was recently described by Nishikawa to elaborate the eight-membered ring of brachialactone (7) (fusicoconnic series) from an advanced cyclopentane intermediate accessed from (S)-limonene [64]. Several cyclopentane precursors were prepared to investigate the importance of the alkene functionalization on the cyclization. Thus, the reaction proceeded in the presence of silylated allylic alcohol 131, producing 132 albeit in low yield. The presence of a terminal methyl ketone function did not influence the reaction outcome as compound 133 produced cycloadduct 134 in the same low-moderate yield. Interestingly, the reaction was highly selective and only one single diastereomer was formed (Scheme 26). However, replacement of the allylic alcohol by a vinyl ketone (compound 135) or a butenolide (compound 137) moiety dramatically influenced the outcome of the reaction and no cycloadduct was observed in both cases (Scheme 27).

4 Radical cyclization (including SmI₂)

Introduced by Kagan more than four decades ago, samarium diiodide (SmI₂) has found multiple applications in natural product synthesis [65]. Employed in C–C bond-formation reactions, this single-electron reducing agent has been particularly useful for five- to eight-membered ring cyclizations [65]. Its tunable reactivity opens access to both radical and anionic processes, hence favoring reactivity with various types of substrates, ranging from halides to carbonyls and alkenes/alkynes. It is comprehensible that this reagent attracted early interest in natural product synthesis and more precisely on medium-sized ring formation.

4.1 SmI₂-mediated Barbier-type ring annulation towards variecolin synthesis

Following Kagan’s work, Molander’s group thoroughly investigated the potential of SmI₂-mediated intramolecular ring closure. Among the approaches they studied, the Barbier-type cyclization rapidly gained popularity for five-to-eight-membered ring formation. Based on a reductive addition of an alkyl halide to a carbonyl group, implementation of the Barbier-type ring closure relied thus on the preliminary introduction of both
Scheme 26: [5-8] Bicyclic structure of brachialactone (7) constructed by a Mizoroki–Heck reaction.

Scheme 27: Influence of the replacement of the allylic alcohol moiety.

aldehyde and alkyl halide functional groups on a suitable substrate. The mechanism was first thought to involve the coupling of an alkyl radical and a ketyl radical, but is now assumed to proceed through the formation of an organosamarium intermediate, resulting from two successive single-electron reductions [66]. This strategy was successfully applied to the construction of variecolin intermediate 140 possessing a [5-8] ring system in its backbone (Scheme 28). Interestingly, the reaction was carried out under UV irradiation and in the presence of catalytic nickel diiodide allowing formation of the expected compound in 63% yield [67].

4.2 SmI$_2$-mediated ketyl addition: discussion around pleuromutilin scaffold access

Despite the promising results of the SmI$_2$-mediated ketyl addition, one would have to wait almost two decades before employing it again in eight-membered ring closure. Among the diterpenes and sesterterpenes featuring a cyclooctane framework, (+)-pleuromutilin (1) was recently targeted by Reisman’s group through an elegant approach involving a SmI$_2$-mediated cyclization as a key step of the synthesis [68]. Indeed, this pivotal annulation step was conducted on aldehyde 142 pre-
pared from (+)-trans-dihydrocarvone (141) and yielded the expected complex tricyclic [5-8-6] alcohol 144 in 93% with a high diastereoselectivity (dr 23:1). Of note, the reaction conditions were subjected to extensive studies for optimization. The intermediate hydridane enal fragment 142, bearing both an aldehyde and an alkene function, was subjected to rigorously anaerobic conditions, in the presence of 3 equivalents of SmI$_2$, 6 equivalents of H$_2$O, and TMSCl as a quenching agent (Scheme 29).

In their discussion, the authors highlighted the differences with previously reported SmI$_2$-mediated eight-membered ring closure in pleuromutilin (1) synthesis. Indeed, in 2013, Procter’s group was actually the first to report a 34-step enantiospecific total synthesis of (+)-pleuromutilin (1), where the eight-membered ring was accessed through a SmI$_2$-mediated cyclization cascade reaction of a dialdehyde [69]. In this approach, an original way was proposed to form in a single step the tricyclic core of pleuromutilin (1) with a stereocontrol at the four contiguous stereocenters [69,70]. The dialdehyde was obtained from trans-dihydrocarvone (141) and treated early in the sequence (step 13/34) by SmI$_2$. The authors assumed that the cascade reaction was initiated with the left-hand aldehyde ketyl formation 146 which further attacked the alkene and oriented the anti-5-exo-trig-cyclization toward (Z)-Sm$^{III}$ enolate 147. The cyclooctane ring was then accessed through the (Z)-Sm$^{III}$ enolate aldol cyclization. The different organosamarium species generated during the cascade cyclization mechanism were hypothesized to drive the diastereoselectivity on each of the stereocenters created during the process (Scheme 30).

4.3 Nickel-catalyzed reductive cyclization: mutilin and pleuromutilin C12-epimers access

In view of maximizing the scope of accessible pleuromutilin epimers from one single synthetic pathway, Herzon’s group reported a modular and convergent route, where the eight-membered ring was built intramolecularly in a late-stage step (Scheme 31A) [71,72]. With this strategy, the authors intended to benefit from the pre-installed quarternary carbon centers or sp$^2$-hybridized carbons to limit the number of rotatable bonds and transannular syn-pentane-type interactions, hence to lower the entropic penalty associated to ring closure. To reach this goal, they first dedicated efforts in optimal syntheses of an electrophilic enimide 151 [73] and its conjunctive reagent, the neopentyl iodide 153. Both fragments were then engaged in a two-fold neopentylic fragment coupling, giving a bicyclic intermediate which after appropriate modification led to the alkynyl aldehyde cyclization precursor 154. The ring closure was performed under catalytic reductive conditions in the presence of Ni(cod)$_2$ and ligand 155 as the catalytic system, and triethylsilane as a reductant. The expected cycloadduct was obtained as a single diastereomer (dr > 20:1) in 60% yield [71]. This intermediate allowed then access to several members of the mutilin/pleuromutilin family: total syntheses of (+)-12-epi-mutilin,
(+)-11,12-di-epi-mutilin, (+)-12-epi-pleuromutilin, (+)-11,12-di-epi-pleuromutilin, and (+)-pleuromutilin (1) itself were there described in 17 to 20 steps [71,72]. The series was later extended via a revised and improved synthetic strategy toward the tricyclic [5-8-6]-pleuromutilin platform [74], allowing access to remarkable chemical diversity for pleuromutilin derivatives which were evaluated against a panel of Gram-positive and Gram-negative bacteria (Scheme 31B).

4.4 Photocatalyzed oxidative ring expansion: alternative radical chemistry for pleuromutilin scaffold construction

Following the advent of photoredox catalysis in ring-opening and ring-expansion chemistry [75], a new route was proposed by Foy and Pronin to access the cyclooctane unit of the pleuromutilin scaffold [76]. In this very recent paper, the authors implemented adequately chosen tactics allowing the completion of the 15-step and 16-step synthesis of mutilin and pleuromutilin (1), respectively. To access the terpenoid core, the synthetic pathway was articulated around a ring expansion of a fused cyclobutane/perhydroindanone fragment, leading to the cyclooctane motif. Interestingly, and unlike the previously reported strategies, the perhydroindanone precursor was prepared starting from achiral building blocks [157 and 158]. They were engaged in a selective exo Diels–Alder cycloaddition, which resulted in compound 159. The enol ether was oxidized by ceric ammonium nitrate (CAN) to deliver intermediate 160, which was further subjected to an iron-catalyzed hydrogen atom transfer generating tricyclic intermediate 161. Further functionalization permitted the formation of the fused cyclobutane acid 162 as the desired precursor for the cyclooctane formation. The ring expansion was achieved in the presence of an iridium catalyst and under blue LED irradiation, via the trapping by TEMPO or O$_2$ of the cyclobutyl radical resulting from decarboxylation, which allowed a Criegee- or a Grob-type fragmentation to generate cyclooctadione 163. Pleuromutilin (1) was then accessed in 4 additional steps (Scheme 32).

4.5 Reductive radical cascade cyclization: toward total synthesis of (−)-6-epi-ophiobolin N (168) and (+)-6-epi-ophiobolin A (173)

Despite indisputable success of the radical approach in the formation of the eight-membered ring of pleuromutilin (1), the chemistry was scarcely extended to other terpenoid molecules. Only ophiobolin synthetic strategy was implemented with an 8-endo/5-exo radical cascade cyclization by Maimone’s group [77]. Inspired by the cyclase-mediated polyterpene cyclization mechanism, they proposed a rapid 9-step strategy starting from abundant monoterpene farnesol (164), chemically converted into cyclopentanol 165 bearing a trichloroketone function that is a well-known radical precursor. The authors found that the correct stereochemistry of the stereogenic centers formed during the cascade cyclization was secured by the use of benzo-thiophene-based TADDOL thiol 166 as chiral catalyst. They obtained in one single step a 5.3:1 and 3.4:1 diastereomeric ratio for C14 and C15, respectively, while forming the desired...
trans [5-8] ring junction in C10-C11 (Scheme 33). (−)-6-epi-Ophiobolin N (168) was then accessible with four additional steps.

Following the extensive work they dedicated to (−)-6-epi-ophiobolin N (168), Maimone’s group reused one of the investigated cyclization conditions for the total synthesis of (−)-6-epi-ophiobolin A (173), which was then described in a 14-step strategy, starting from geraniol (169) [78]. Unlike compound 168, the installation of stereogenic centers at C14 and C15 was not sought at the 8-5 cyclization stage of the strategy, since formation of the tetrastituted alkene provided an adequate precursor towards the tetrahydrofuran-ring formation. The intramolecular atom-transfer radical cyclization was thus carried out with achiral di-tert-butylpyridine-ligated Cu1 171 to generate the [5-8-5] scaffold 172 in 55% yield, while securing the C10 stereocenter in the required configuration and providing a suitable alkene bond for further functionalization. (−)-6-epi-Ophiobolin A (173) was eventually accessed with 9 additional steps (Scheme 34).

4.6 Other radical approaches towards eight-membered ring closure
As seen above, radical-based pathways proved to be efficiently implemented in peculiar pleuromutilin tricyclic scaffold construction. Alternative reagents were thus explored to close the
Scheme 32: Photocatalyzed oxidative ring expansion in pleuromutilin (1) total synthesis.

Scheme 33: Reductive radical cascade cyclization route towards (−)-6-epi-ophiobolin N (168).
Scheme 34: Reductive radical cascade cyclization route towards (+)-6-epi-ophiobolin A (173).

eight-membered ring via initial radical genesis. For instance, Bacqué et al. reported the insertion in the cyclization precursors of functional groups prone to form radicals (Scheme 35). In their investigations toward pleuromutilin scaffold synthesis, they proposed to perform a radical 8-endo-trig-cyclization of a xanthate precursor. The xanthate group was quantitatively installed on an adequately functionalized hydrindanone starting moiety 175, obtained in 10 steps from ethyl m-toluate (174), which was then refluxed in the presence of a small amount of dilauroyl peroxide (DLP) as radical initiator. The eight-membered ring 176 was obtained in 60% yield as a single diastereomer [79].

5 Pauson–Khand reaction
Discovered in the seventies [80], the Pauson–Khand reaction has been widely used for the formation of cyclopentenone motifs, by reaction of an alkene, alkyne, and carbon monoxide. This is only recently, in April 2022, that this reaction was reported to allow the formation of an eight-membered ring [81]. Indeed, Li and co-workers employed the Pauson–Khand reaction in order to undertake the total synthesis of hypoestin A (177), albolic acid (178), and ceroplastol II (179) (Figure 5) bearing the same [5-8-5] tricyclic core structure.

Figure 5: Structural representations of hypoestin A (177), albolic acid (178), and ceroplastol II (179) bearing the same [5-8-5] core structure.
(177) presents a complex structure: it is composed of a [5-8-5-3] tetracyclic core skeleton, with five stereogenic centers, whose four of them are contiguous. Before their work, no asymmetric total synthesis of hypoestin A (177) has been reported. During this study, they also looked into the asymmetric total synthesis of albolic acid (178) and ceroplastol II (179). Only one paper reported their total synthesis, using a reductive coupling of aldehydes for the synthesis of the eight-membered ring with an excellent yield of 96% [82]. However, the total synthesis included 24 steps, with an overall yield of 5% and 4% for albolic acid (178) and ceroplastol II (179), respectively. To synthesize these 3 complex natural products, they used the same method to access the [5-8-5] tricyclic advanced intermediate 184. After that, different strategies allowed the functionalization for each natural product. Their general method consisted in using an intramolecular Pauson–Khand reaction catalyzed by a rhodium complex from an allene-yne substrate to build the eight-membered ring, which was quite challenging.

Starting from commercial (R)-limonene (51), Li and co-workers synthesized allene-yne intermediate 182 (Scheme 36) in 7 steps, with a 16% overall yield. To access the allene moiety 182, they first tried addition of propadienyllithium to aldehyde 180, but they obtained a complex mixture of allenic alcohol and homo-propargylic alcohol. Then, they were inspired by Corey’s work [83] and formed this key function through the addition of propargylborane 181 to aldehyde 180, with a good 80% yield. Protection of the obtained alcohol was also necessary. All these 7 first steps set the stereochemistry of the methyl group on the further eight-membered ring and the hydrogen atom at the junction of the five- and eight-membered rings.

The next step of the synthesis was the key formation of the eight-membered ring and several attempts were necessary in order to determine the optimal conditions. They first explored the nature of the catalyst among different rhodium-based catalysts and 5% of [Rh(CO)2Cl]2 were found to be the best catalyst loading (28% yield). The addition of a silver additive, to make the reaction quicker and to remove a CO ligand, appeared to be useless in this case, with no reaction, and the use of 50% dppp as ligand allowed the formation of the product but with lower yields (25%). The effect of the concentration was also important, since increasing or lowering the concentration from 0.01 M resulted in lower yields. The same trend was observed when the temperature was varied. Finally, the amount of catalyst was explored: increasing from 5 mol % to 10 mol % almost doubled the yield (respectively 38% and 60% yield), and no significant increase in the yield was found when using 20% of catalyst (62% yield). Thus, the use of 10 mol % of [Rh(CO)2Cl]2 catalyst in toluene at 110 °C and under CO atmosphere yielded the cyclized compound 183 in 56%, even at large scale (2 g). Having this tricyclic structure in hands, several more steps were needed to access advanced intermediate 184 for the synthesis of both natural products. Thus, they first selectively hydrogenated the double bond on the eight-membered ring, and ketone reduction allowed to install the cyclopropane ring thanks to the allylic alcohol. The latter was submitted to Ley oxidation, then deprotection and removal of the obtained alcohol gave the [5-8-5] advanced intermediate 184 (Scheme 36).

The stage was set for the further functionalization to synthesize hypoestin A (177), albolic acid (178), and ceroplastol II (179)
(Scheme 37). For the synthesis of hypoestin A (177), the side chain was introduced by selective deprotonation of 184, addition of acetaldehyde, dehydration and conjugated addition of Me₂CuLi. These three last steps provided the desired product 177 in 50% overall yield. For the synthesis of albolic acid (178) and ceroplastol II (179), the side chain was introduced by deprotonation and addition of the corresponding aldehyde. After dehydration of the subsequent alcohol and conjugated addition of Me₂CuLi, the regioselective reductive opening of cyclopropane 185 was performed with lithium in liquid ammonia in order to introduce the angular methyl group. In the same time, the ketone was reduced into an alcohol, which one was submitted to Barton deoxygenation. The alkene side chain underwent a metathesis reaction with methyl methacrylate to introduce an ester. Finally, this latter was hydrolyzed or reduced to respectively provide albolic acid (178) and ceroplastol II (179).

The scope of the reaction was also extended to various products containing the [X-8-5] tricyclic system (Figure 6). Several functionalized terminal alkynes succeeded in the Pauson–Khand cyclization (186), with moderate yields ranging from 40 to 61%. It was also possible to change the alcohol protecting group (187) without significant change in yields (45–62%). The addition of a methyl group on the eight-membered cycle (188) was also possible through the functionalization of the internal position of the allene (51%). In the same conditions, an excellent yield (86%) was obtained for the synthesis of a precursor of schindilactone A (189) containing a [5-7-8-5] ring structure.

6 Lewis-acid-promoted cyclization
Several Lewis acid-promoted intramolecular cyclization reactions of appropriate substrates were proposed to access the [5-8] bicyclic scaffold including the Nazarov cyclization, the Nicholas reaction or a Mukaiyama-type aldolization.

6.1 Synthesis of fusicoauritone: Nazarov cyclization
In the case of fusicoauritone (28), Williams envisaged a Nazarov cyclization to construct the bicyclo[3.6.0]undecane
ring system in one step from an advanced intermediate [84]. The strategy proposed here was inspired by biogenetic considerations. Indeed, intermediate 191 possessing an eleven-membered ring could be considered as an equivalent of 3,7-dolabelladiene, the key biogenetic precursor of fusicoaines, neodolabellanes as well as clavulanes. Following this hypothesis, exposure of compound 191, prepared in 11 steps from cyclopentenol 190, to BF$_3$·OEt$_2$ induced an intramolecular five-membered ring formation revealing the central cyclooctane ring of fusicoauritone (192) in 77% yield (Scheme 38).

This approach was further extended to compound 193 which was cyclized in the presence of $p$-toluenesulfonic acid to furnish the corresponding tricyclic compound 194 in 92% yield. The latter was finally converted to fusicoauritone (28) upon direct oxidative treatment with tert-butyl hypochlorite in 40% yield (Scheme 39).

6.2 Synthesis of epoxydictymene (5): Nicholas reaction
In the synthesis of (+)-epoxydictymene (5), Schreiber proposed an elegant sequence involving a Nicholas cyclization followed by a Pauson–Khand reaction to build the overall tetracyclic backbone [85,86]. The Nicholas reaction took place on allylsilane 196 prepared from (R)-pulegone (195). After complexation of the triple bond with dicobalt octacarbonyl, the resulting red organometallic cluster underwent a cyclization in the presence of Et$_2$AlCl to give the fused [5-8] ring system 197 in 82% yield over two steps and a high degree of stereoselectivity. Compound 197 was then engaged in a Pauson–Khand reaction to finalize the construction of the sesquiterpene core which ultimately lead to epoxydictymene (5) (Scheme 40).

6.3 Synthesis of aquatolide: Mukaiyama-type aldolisation
The synthetic plan reported by Hiemstra to synthesize aquatolide (4) takes advantage of their previous work on a photochemical [2 + 2]-cycloaddition to access the crucial bicyclo[2.2.1]hexane core and a late-stage intramolecular Mukaiyama-type aldol reaction to form the eight-membered ring [87]. To this end, ketone 201 was regioselectively converted to the enol silyl ether and directly subjected to cyclization upon exposure to BF$_3$·OEt$_2$ to give a mixture of stereoisomers. Final treatment with TsOH in refluxing toluene afforded aquatolide (4) as a crystalline product in 59% yield over the three step sequence (Scheme 41).

7 Rearrangement: synthesis of variecolin (3) with tandem Wolff/Cope rearrangement
Stoltz reported a stereoselective access to the bicyclo[3.6.0]undecane core through a tandem Wolff/Cope rearrangement approach [88]. The strategy was first designed in a racemic version and further developed in an asymmetric fashion. The prerequisite for the rearrangement was the presence of a diazocyclobutyl ketone as represented by compound 203. When this strained bicycle was heated under microwave irradiation, the tandem Wolff/Cope rearrangement occurred to furnish the corresponding fused [5-8] carbocycle 204 in very high yield (Scheme 42).
Scheme 40: (+)-Epoxydictymene (5) synthesis through a Nicholas cyclization followed by a Pauson–Khand reaction to build the overall tetracyclic backbone.

Scheme 41: Synthesis of aquatolide (4) by a Mukaiyama-type aldolisation.

Scheme 42: Tandem Wolff/Cope rearrangement furnishing the A-B bicyclic moiety 204 of variecolin.

Extension to the asymmetric version corresponding to the A-B ring of variecolin (3) demonstrated the importance of non-polar solvents for this tandem reaction. Thus, replacement of toluene by heptane improved the yield of the reaction in the presence of an additional methyl substituent (206, 26% to 42%) (Scheme 43).
8 Cycloaddition reactions

As exemplified above, access to fused bicycles with one cyclooctanoid ring suffers from major drawbacks including ring strains, disfavored enthalpy and entropy, and transannular hindrance. Among the available methods described in the literature, cycloaddition reactions constitute an efficient route that combines both one-pot cascade and good stereocontrol of the newly formed asymmetric centers. Three types of cycloadditions have recently been reported depending on the nature of the activation, thermal, metal-catalyzed, or photocatalyzed.

8.1 Cycloadditions under thermal activation

Recently, an efficient synthesis of [5-8] fused oxabridged cyclooctanoids was reported by Radhakrishnan et al. [89]. They described the first [6 + 3] cycloaddition reaction between 6,6-diarylfulvene and the betaine 3-oxidopyrylium to give intermediate that rearranged itself upon 1,5-hydrogen shift into (Scheme 44). The reaction turned out to be regioselective and ab initio calculations rationalized a stereoselective endo-approach between the diene and the dienophile leading to the formation of C2(fulvene)–C2(betaine) and C6(fulvene)–C6(betaine) bonds [90]. The scope of the reaction was successfully extended to diaryl, dialkyl (including cycloalkyl), and aryl alkyl fulvenes. In the last examples, the stereogenicity of the C6 center of the newly formed cyclooctanoid ring was not controlled. Interestingly the [5-8]-fused ring scaffold possessed functions like an oxabridge, an α,β-unsaturated ketone and cyclopentadiene that can be derivatized at will [91]. For example, the dipolar cycloaddition on the olefin part of the enone allowed the synthesis of a [5-8-5] system while reduction gave access to either allylic alcohol or ketone.

Ghosh also reported a rapid access to the [5-8-6] ring system of variecolin through an intramolecular Diels–Alder approach [92]. The key annulation step was achieved on compound which was prepared from the carbohydrate chiral pool. The cycloaddition proceeded upon heating in a sealed tube over two days to give tricycle in 60% yield (Scheme 45). The stereoselectivity of the reaction was controlled by the chiral pento-side unit. Interestingly, compound possesses suitable function for further derivatization into variecolin. This study highlighted once again the potency of the Diels–Alder reaction in synthesis with the formation of a fused [6-8] ring system.
8.2 Metal-catalyzed cycloadditions

The efficient use of transition-metal catalysis to perform the direct formation of a [5-8-5] tricyclic skeleton was described in the context of the ophiobolan core synthesis. Previous work highlighted the efficient cyclocarbopalladation of propargylic diol 217 in the presence of vinylstannane 218 followed by a 6π electrocyclization to give the unusual tricyclic system [93]. Using stannylated dienes 218, the same cascade involving 4-exo-dig cyclization followed by a Stille coupling provided tetracene intermediates 219 (Scheme 46) [94]. In this case the 6π electrocyclization was unfavored as the resulting spirocyclic diene 220 was too strained. Instead, an 8π electrocyclization occurred to lead to the corresponding tetracyclic triene 221 as a pure diastereomer. Overheating of the reaction media caused the 4π electrocyclic ring opening of 221a followed by a 1,5-hydrogen shift to provide ketoallylic alcohol 222. Interestingly, using six-membered ring diols allowed to efficiently access in one pot the stable [6-4-8-5]-tetracyclic system 221b.

Another metal-catalyzed cycloaddition was also reported in the course of the synthesis of the asteriscan family. The first total synthesis of the asteriscanolide (2) intricate natural product was described by Wender and co-workers in the late 90’s [95]. They employed a Ni(0)-catalyzed intramolecular [4 + 4] cycloaddition as the key step toward the tricyclic core. Later on, Yu et al. reported the one-pot rhodium(I)-catalyzed [(5 + 2) + 1] cycloaddition of a tethered ene-vinylcyclopropane in the presence of CO [96]. They argued that while reductive elimination (RE) of the rhodium intermediate 224 was unfavored, the introduction of a CO unit in the catalytic step followed by migratory reductive elimination (MRE) would be easier (Scheme 47). Indeed, the cycloaddition of the ene-vinyl cyclopropane 223 in the pres-
ence of [Rh(CO)$_2$Cl]$_2$ and 1 atm of CO gave cycloadduct 227 as a single diastereomer with more than 70% yield. Interestingly, this reaction was tolerant to geminal function as well as heteroatoms. Also, the geometry of the double bond in 223 influenced the cis–trans ratio of the final products.

This powerful strategy was then applied to the stereoselective total synthesis of (±)-asterisca-3(15),6-diene (230) and (+)-asteriscanolide (2). The simpler [5-6] bicycle was obtained from bicyclic cis-cyclooctenone 229 that arose from a previous [(5 + 2) + 1] cycloaddition of ene-vinylcyclopropane 228 (Scheme 48) [97]. A hydroxy group was then introduced thanks to a hydroboration reaction. Isomerization of position C7 was performed in acidic conditions to provide the targeted compound 230 with 14% overall yield over seven steps. The unusual [6.3.0] carbocyclic system bridged by a butyrolactone was the object of a more complex strategy. Selection of the appropriate ene-vinylcyclopropane substrate led to extensive work which ultimately allowed to consider enantiopure precursor 231 for the rhodium(I)-catalyzed cycloaddition [98]. Thus, exposure of 231 to [Rh(CO)$_2$Cl]$_2$ complex in toluene under controlled CO/N$_2$ atmosphere yielded cyclooctenone 232 in 70% yield and high diastereoselectivity (>95:5). The presence of the TBS protecting group was critical for the stereoselectivity and the use of toluene rather than dioxane as initially described allowed to improve the yield from 30% to 70%. Moreover, the cis ring junction was in accordance with the configuration of the natural product. Density functional theory calculations were also undertaken to support the observed diastereoselectivity (Scheme 48) [40]. Interestingly, none of the other envisaged ene-vinylcyclopropanes were able to cyclize, highlighting the fact that preexisting five-membered rings were
8.3 Photocyclizations

Historically, the first attempt to attain the fusicoccan ring thanks to photocyclization started from linked 2-pyridones 233 (Scheme 49). Under irradiation provided by a 450 W mercury lamp, smooth conversion to dicyclopenta[\(a,d\)]cyclooctane was observed [99]. The intramolecular [4 + 4] cycloaddition allowed to control the stereoselectivity of C11 under the influence of C3 and C12. As for C7, the possibility to form H-bonds with the solvent greatly influences its stereogenicity. In the absence of N-methyl groups, polar solvents where strong H-bond networks exist lead to the trans-diastereomer 235 mainly, while non-polar solvents (like benzene) exclusively gave the cis isomer 234 [100]. This last compound quickly underwent irreversible Cope rearrangement at room temperature. To avoid this side reaction and to provide the targeted cyclooctane ring, a subsequent epoxidation was performed to give the corresponding epoxide 237. Remarkably, such epoxidation reaction is both facial and site selective. Finally, selective reductive opening of one lactam ring was performed after activation as urea to provide the corresponding carbinol.

Another straightforward access to the [5-8-5]-fused tricycle of the humulane core (see aquatolide (4)) has been reported using light-assisted cycloaddition. The humulane core was synthesized according to different methods including Mukaiyama aldol reaction [87] or intramolecular NHK strategy [62]. Recently, an elegant transannular [2 + 2] “crossed” cycloaddition was described by the group of Takao to obtain selectively (+)-aquatolide (4) from the asteriscanolide-type precursor 245 (Scheme 50) [101]. This is one of the first examples of a biomimetic transannulation strategy. It relied on the pioneering work of Li and co-workers on the isomerization of eleven-membered ring humulanes under irradiation [102]. In the report from Takao et al., the [2 + 2] photocycloaddition was performed starting from the same humulane ring using a high pressure mercury lamp (100 W) with a wide range of wavelengths to give the [5-5-4-8] ring system with moderate yield. The eleven-membered ring precursor 241 was obtained thanks to a ring-opening/ring-closing/cross-metathesis (ROM/RCM/CM) cascade followed by intramolecular Nozaki–Kishi reaction starting from the cyclobutenecarboxylate 238. Remarkably, compound 241 was obtained as a single diastereomer owing to the fact that the pseudoequatorial hydroxy group is favored in the NHTK reaction [103]. Interestingly, the intermediate, humulene lactone 241, is common to related natural products. Success of the crucial [2 + 2] cycloaddition was obtained after masking of the double bond C7–C8 to prevent simple isomerization. Transformation into an epoxide lead to the alternative parallel cycloaddition to give the regioisomer of aquatolide.
but after masking the olefin as methyl ether the bicyclo[2.1.1]hexane 247 was obtained with 37% yield. Elimination of methanol under acidic conditions gave the corresponding aquatolide (4). It confirms the crucial role of the alcohol or thiol function at position C6 in the natural precursor to provide the aquatolide skeleton by the plant. Conformational analyses confirmed the preferred cross-path adopted by intermediate 246. It is in accordance with the fact that intramolecular [2 + 2] photocycloadditions prefer to form five-membered ring regioisomers [104].

9 Miscellaneous

9.1 Biocatalysis

Despite cutting-edge organic methods available nowadays for the production of fused bicycle cyclocatin, numerous drawbacks remain including lengthy synthetic pathways, adequate control of the stereochemistry and low yields. The diversity of enzymes involved in the biosynthetic pathway could constitute an alternative to a total synthesis approach. Significant advantages of such a process are the high selectivity of the enzyme towards the substrate and the clean conversion to one and only one product. Thus, it reduces drastically the number of steps involved, the amount of waste generated and the need for purification. As many enzymes work in aqueous media under mild conditions, often at room temperature, the fingerprint on the environment is low and the amount of energy used is minimal. Biosynthetic pathways toward terpene cyclization are now well documented [105,106] but only two terpene cyclases involved in the [5-8-5]-fused ring structure have been reported so far [107,108]. They both used geranylgeranyl diphosphate (GGDP 248; C20) as precursor. Recently, the group of Oikawa managed to rebuild the biosynthetic pathway of brassicicenes...
thanks to the heterologous expression of eight genes including a N-terminal terpene cyclase BscA [109]. Earlier on, Kuzuyama et al. deciphered the mechanism involved in the biosynthesis of cyclooctat-9-en-7-ol 255 thanks to the combination of theoretical calculations, in vivo studies using $^{13}$C-labeled glucose and in vitro reaction with deuterated GGDP [110,111]. They showed that the reaction cascade catalyzed by the cyclooctat-9-en-7-ol synthase CotB2, a class I terpene cyclase derived from Streptomyces, was divided in 3 parts (Scheme 51); i) the ring construction that involved the formation of carbonation and subsequent electrophilic cyclization to provide the bicyclic cationic intermediate 249. Hydride-shift cascade gave the core tricyclic [5-8-5] fused ring structure 250, ii) long-range cation transfer via multiple hydride migration to generate carbocation 252, and iii) carbon–carbon bond rearrangement through the formation of cyclopropylcarbinyl cations 253 and 254. Finally, attack of water on the cyclopropyl gave the targeted monounsaturated cyclooctenol 255.

Remarkably, conformation of the starting GGDP (248) within the catalytic pocket as well as the cyclization mechanism described succinctly above allowed the strict control of the 6 stereocenters of 255 starting from the achiral C$_20$ allylic diphosphate GGDP (248). This specificity for one single product was further diverted for the biocatalyzed synthesis of non-natural analogs of 255. Site-saturation mutagenesis of CotB2 allowed to identify two mutants that catalyzed the conversion of GGDP into hitherto unknown fusicoccane macrocycles 256 and 257 (Scheme 52) [112]. In both mutants, swapping the hydrophobic amino acids phenylalanine 149 and 107, involved in the catalytic pocket, with shorter leucine and alanine, respectively modified either the spatial constraints or the charge profile of the active pocket.

To conclude this part, biocatalysis using mutated versions of cyclooctanol synthase constitutes an elegant and efficient alternative to classical multistep synthesis. The cost associated to GGDP (248) is now lifted thanks to the development of alternative production systems and it therefore paves the way to an innovative eco-friendly synthesis of [5-8-5] fusicoccane scaffolds.

**Conclusion**

The [5-8] bicyclic motif encountered in the sesquiterpene, diterpene, and sesterterpene series has stimulated the chemistry
community to develop efficient and straightforward synthetic methods, the main challenge consisting in the construction of the eight-membered ring. The intramolecular ring-closing metathesis (RCM) has attracted considerable attention due to its versatility, functional group tolerance and mild reaction conditions and represents the method of choice to access this scaffold. Indeed, two strategies have been designed to construct the eight-membered ring: early- or late-stage cyclization. The Grubbs II (G-II) catalyst appears to be the most versatile catalyst for this transformation. However, Grubbs I (G-I) and Hoveyda–Grubbs II (HG-II) catalysts were also used in some situations. Of particular interest, the tandem ring closing metathesis, allowing the formation of the [5-8] motif in a single step, constitutes a very powerful method. Among the most recent approaches described, the intramolecular radical cyclization proves to be very attractive and several groups focused on this strategy. Interestingly, radical-promoted intramolecular eight-membered ring-closing methodologies were successfully applied on advanced intermediates, delivering the cyclic compounds in high yields and high stereoselectivity. Thus, elaboration of pleuromutilin (1) and several analogs constituted a representative example showcasing the usefulness of this strategy. Also, cycloaddition reactions, either under thermal activation, metal-promoted or under photoactivation have been explored. However, applications are mainly confined to the preparation of a [5-8] bicyclic model mimicking the natural product. Finally, exploration of the biogenetic pathways allowed to propose some elegant biocatalytic approaches which pave the way to innovative eco-friendly syntheses.

Appendix
Abbreviations used in text, figures and schemes are collected in Table 1.

Table 1: List of abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetate</td>
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<tr>
<td>acac</td>
<td>acetylacetone</td>
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<tr>
<td>aq</td>
<td>aqueous</td>
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<td>BEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>triethylborane</td>
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<td>Bn</td>
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<td>DFT</td>
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<td>iPr</td>
<td>isopropyl</td>
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Table 1: List of abbreviations. (continued)

<table>
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<tr>
<td>LED</td>
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<td>m-CPBA</td>
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<td>M</td>
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<td>Nozaki–Hiyama–Kishi</td>
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<td>RE</td>
<td>reductive elimination</td>
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<tr>
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<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SAR</td>
<td>structure–activity relationship</td>
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<tr>
<td>SE</td>
<td>electrophilic substitution</td>
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<tr>
<td>SEM</td>
<td>trimethylsilylthioethylmethyl</td>
</tr>
<tr>
<td>TADDOl</td>
<td>α,α',α''-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDBPS</td>
<td>tert-butylidiphenylsilyl</td>
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<tr>
<td>TBS</td>
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<tr>
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<td>t-BuOH</td>
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<td>t-BuLi</td>
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<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-oxyl-triethylsilyl</td>
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<tr>
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<td>triflate</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TIPS</td>
<td>triisopropylsilyl ether</td>
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<td>trimethylsilyl</td>
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<td>TMSCI</td>
<td>trimethylsilyl chloride</td>
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<tr>
<td>TRCM</td>
<td>tandem ring closing metathesis</td>
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<tr>
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<td>tosyl</td>
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<td>TsOH</td>
<td>p-toluenesulfonic acid</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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<td>W</td>
<td>Watt</td>
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References


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Asymmetric synthesis of a stereopentade fragment toward latrunculins

Benjamin Joyeux‡1, Antoine Gamet‡1, Nicolas Casaretto2 and Bastien Nay*1

Abstract
Latrunculins are marine toxins used in cell biology to block actin polymerization. The development of new synthetic strategies and methods for their synthesis is thus important in order to improve, modulate or control this biological value. The total syntheses found in the literature all target similar disconnections, especially an aldol strategy involving a recurrent 4-acetyl-1,3-thiazolidin-2-one ketone partner. Herein, we describe an alternative disconnection and subsequent stereoselective transformations to construct a stereopentade amenable to latrunculin and analogue synthesis, starting from (+)-β-citronellene. Key stereoselective transformations involve an asymmetric Krische allylation, an aldol reaction under 1,5-anti stereocontrol, and a Tishchenko–Evans reduction accompanied by a peculiar ester transposition, allowing to install key stereogenic centers of the natural products.

Introduction
Latrunculins constitute a class of marine polyketide natural products isolated from Sponges like Negombata (= Latrunculia) magnifica [1,2]. They are characterized by the presence of an unsaturated fourteen- or sixteen-membered macrolactone decorated by an L-cysteine-derived 2-oxo-1,3-thiazolidin-4-yl substituent, and the presence of five stereogenic centers forming a 1,2,4,6,9-stereopentade (Figure 1). In latrunculins A (1) and B (2) three of them are embedded in a lactol ring, while latrunculin C (3) lacks this ring due to the reduction of C-15. The biological activities of latrunculins A and B have early been reported [3]. These compounds induce important but reversible morphological changes on mouse neuroblastoma and fibroblast cells at low concentrations such as 50 ng/mL [2]. It was rapidly demonstrated that the toxins target the cytoskeleton and inhibit the actin polymerization by specifically sequestering the G-actin monomers with a high affinity [4], unlike cytochalasin D that targets the actin filament [5]. Structure–activity relationships have also been demonstrated thanks to the synthesis of an-
alogues, which hardly superseded the natural product properties, highlighting the importance of the macrocycle and of the lactol ring for this biological activity (3 is inactive) [6,7].

Considering the structural features of these toxins and their valuable biological properties (1 and 2 are nowadays commercially available as tools for cell biology), latrunculins have been appealing targets for synthetic studies. Several total syntheses of latrunculins were reported by Smith III [8-10], White [11], Fürstner [6,12] and Watson [13]. These syntheses involved similar disconnection strategies for the macrocycle or the lactol formation (Figure 2, left), and for the aldol reaction leading to 4, using a 4-acetyl-1,3-thiazolidin-2-one 5 as ketone partner (Figure 2, route A). Strikingly, this last disconnection was adopted in all previous syntheses to form the (15,16)- or the (13,14)-bond of 1 and 2, respectively. Conversely, we envisaged an alternative disconnection to form the (16,17)- or the (14,15)-bond of 1 and 2, through an aldol reaction of aldehyde 8 readily available from l-cysteine, leading to aldol adduct 7 (Figure 2, route B). The methyl ketone partner 9 could be formed by the oxidation of an allyl moiety introduced by the asymmetric alkylation of an aldehyde derived from (+)-β-citronellene. At this stage, we can speculate that the stereocontrol of this reaction could either follow a polar Felkin–Anh model [14-16] based on chiral aldehyde partner 8 [17], or a 1,5-anti induction of the aldol reaction [18-20] based on chiral alkoxy partner 9. Furthermore, it could be envisaged to reduce the resulting β-hydroxyketone 7 in a diastereoselective manner to obtain a 1,3-diol.

This synthetic strategy could thus bring new stereochemical opportunities to synthesize latrunculin analogues for chemical biology studies. In particular, our initial goal was to protect an inactive lactol-opened form of latrunculins, which could cyclize in vivo upon deprotection under a specific stimulus (light or enzyme, for instance) for biological applications. This challenge precluded the installation of the pyran ring – and the use of its well-known isomerization to set up important stereocenters.
Results and Discussion

Our synthesis started from commercially available (+)-β-citronellene (10). The ozonolysis of the trisubstituted double bond followed by a reductive treatment with NaBH₄ chemoselectively afforded primary alcohol 11 in 78% yield (Scheme 1).

Due to easier purification, this alcohol was preferred to the aldehyde in our synthetic route, allowing a key stereoselective Krische allylation [21,22] to be envisaged. Applying reported conditions for this allylation – in presence of allyl acetate (10 equiv), [Ir(COD)Cl]₂ (2.5 mol %), (S)-SEGPHOS (5 mol %), 3-nitrobenzoic acid (10 mol %), Cs₂CO₃ (20 mol %) in THF at 100 °C for 24 hours – we obtained homoallylic alcohol 12 in a good 86% yield, with a diastereomeric ratio (dr) of 93:7 deduced from the NMR analysis of the methyl substituent signals in CD₃OD (NMR spectra compared to those of a 50:50 mixture of diastereoisomers, obtained from the addition of allylmagnesium bromide onto the corresponding aldehyde).

The stereochemistry of the resulting secondary alcohol was expected to be (R) according to Krische’s studies involving (S)-SEGPHOS [22]. This result was secured by the NMR analysis of Mosher’s esters made from (R)-(+)- and (S)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (see Supporting Information File 1) [23-25], confirming the installation of the C-11 stereocenter of latrunculins.

The next steps consisted in the functionalization of 12, in view of its coupling to 8. We first relied on the chemoselective epoxidation of the homoallylic alcohol, done in presence of VO(OiPr)₃ (20 mol %) and t-BuOOH to afford epoxide 13, in 86% yield and a dr of 75:25 (measured by NMR, presumably resulting from the major diastereoisomer of 13; minor isomers were not identified), when the reaction was performed at room temperature during 6 hours. This vanadium catalyst superseded VO(acac)₂ in terms of yields [26,27]. Additional epoxidation attempts allowed to improve the dr to 82:18 (82% yield) when the reaction was left at −30 °C for 6 days. Unfortunately, it was not possible to set up an appropriate nucleophile through the umpolung of aldehyde 8 to react with this epoxide, which led us to envisage the following aldol strategy through ketone 15.

Attempts of Wacker reactions to produce 15 were unsuccessful on 12, presumably due to a competition between the two olefinic parts. After protection of the secondary alcohol as a para-methoxybenzyl (PMB) ether (78% yield of 14), the ketone (15) was installed in two steps from the epoxide (direct rearrangement attempts of the epoxide to form the ketone were unsuccessful). Thus, the epoxide was first reduced on its primary carbon in presence of LiAlH₄, and the resulting secondary alcohol was oxidized in presence of Dess–Martin periodinane (DMP), giving ketone 15 in 78% yield over the two steps. This six-step sequence to 15 was performed in a 35% overall yield from starting material 10.

The aldehyde partner (8) for the aldol reaction brings the thiazolidinone heterocycle of the natural product. It was synthesized in four steps from L-cysteine ester derivative 16, first reacting with carbonyldiimidazole (CDI) to afford thiazolidinone 17 in 85% yield (Scheme 2). The nitrogen atom was protected with a PMB group in 72% yield (18), after deprotonation with NaH and reaction with PMBBr. The ester moiety of 18 was then
chemoselectively reduced into alcohol 19 in 90% yield, in presence of LiBH₄ to avoid the reduction of the thiazolidinone part. Finally, the aldehyde (8) was generated in 78% yield by oxidation in presence of DMP.

The assembly of aldehyde 8 and methyl ketone 15 was envisaged through a stereoselective aldol reaction. After unsuccessful attempts of Mukaiyama aldol reactions with silyl enol ethers [28], we found that dicyclohexylboron enolate 20, made in situ from ketone 15 and Cy₂BCl in presence of DIPEA, performed well in the aldol reaction to furnish product 21 in 55% yield with a good dr of 91:9 (Scheme 3).

The stereocntrol of the reaction could be envisaged through two principal mechanisms. A remote stereocntrol by the nucleophile could first be expected [29], through a 1,5-anti-induction of the aldol stereocenter by β-alkoxy ketone 9, leading to an (S)-configuration [18-20]. This control is supposed to follow a boat transition state A stabilized by a formyl hydrogen bond [30]. It is known to be dependent on the nature of the β-alkoxy substituent, being particularly favoured by the PMB and other aromatic groups, while being disfavoured by silyl protecting groups. Alternatively, an (R)-configuration of C-15 could result from a polar Felkin–Anh model controlled by aldehyde 8 through chair-transition state B [14-16]. To determine the configuration of C-15, we initially relied on the comparative NMR analysis of Mosher's esters [23]. Despite clear ¹H NMR spectra, irregular values of Δδ₅₅S-R precluded the unambiguous determination of the C-15 stereocenter [24]. These difficulties were attributed to the hindered character of this secondary alcohol, substituted by the thiazolidinone ring, possibly leading to a strong conformational distortion of Mosher’s model. The questin of the resulting stereoselectivity was thus left open for later resolution.
To complete this study, the 1,3-anti-diestereoselective reduction of β-hydroxyketone 21 was undertaken through the Evans–Tishchenko method [31,32], in presence of SmI₂ and an aldehyde (Scheme 4). para-Nitrobenzaldehyde was used [33] to introduce a labile para-nitrobenzoate on the product, planning an easy deprotection of the alcohol. This would also pave the way to an orthogonal manipulation of protecting groups on the stereopentade, in view of designing molecular tools for biological purpose. The reduction took place in 76% yield with complete stereoselectivity. However, a mixture of two inseparable products was obtained, containing the expected but minor alcohol 22 (10%), and more surprisingly the major isomer 23 (66%). This compound results from the transposition of the para-nitrobenzoyl (PNBz) group onto the 13-OH, which could be favoured by the steric hindrance of C-15 and a possible π–π stacking with the OPMB group.

These PNBz esters were readily hydrolyzed to furnished diol 24 in 97% yield. The oxydation of the PMB group, in presence of DDQ under anhydrous conditions [18], gratifyingly afforded acetal 25 in 74% yield, whose stereochemical assignment by NOESY NMR experiment showed the syn stereochemistry of the acetal. By deduction, it was confirmed that the asymmetric boron aldol reaction between 8 and 15 proceeded through a 1,5-anti induction by the ketone to form 21. Most importantly, compounds 22–25 bear the (11R,13R) configuration of latrunculins (1 and 2).

Conclusion
A straightforward synthesis of a stereopentade intermediate towards latrunculins and lactol-opened analogues was achieved with high stereoselectivity. Starting from the chiral pool bringing the 8-methyl substituent, the secondary alcohol on C-11 was stereoselectively introduced by the Krische allylation of alcohol 11. The next key step consisted in an aldol reaction of ketone 15 onto aldehyde 8, which proceeded with a high stereocontrol resulting from a 1,5-anti induction by the nucleophile leading to product 21, and excluding a Felkin–Anh control by the aldehyde. This reaction validates a unique disconnection among latrunculin synthetic strategies and avoids the construction of a 4-acetyl-1,3-thiazolidin-2-one. Finally, this β-hydroxyketone was submitted to the SmI₂-mediated Evans–Tishchenko reduction, which was performed with full 1,3-anti-stereocontrol but surprisingly resulted in the ester transposition to predominantly form alcohol 23 in good yields. This last reduction allowed to install the key (11R,13R) configuration of latrunculins.

Supporting Information
Crystallographic data of compound 19 were deposited in the Cambridge Crystallographic Data Center under the CCDC number 2225628.

Supporting Information File 1
Experimental procedures, compound characterizations and spectra. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-32-S1.pdf]

Supporting Information File 2
Crystallographic Information File of compound 19. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-32-S2.cif]
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