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Synthesis of propellane-containing natural products

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Keywords: Total synthesis; Natural products; Propellanes.

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1. Propellanes and their synthesis

The first propellanes were synthesized in the 1930s during investigations into the Diels–Alder reaction. However, the first 'propellane by design' was synthesized much later, in 1965. Bloomfield and Irelan reported a synthesis of [4.4.2]propellane (1) and used the term propellerane in this context, but the editors did not accept this nomenclature and the compound was reported as 9,10-dihydro-9,10-ethanonaphthalene. In the same year, Ginsburg and co-workers introduced the name propellane in a paper that reported the syntheses of a variety of different propellanes, without editorial dissent.

Webster’s Unabridged Dictionary defines a propeller as ‘a device having a revolving hub with radiating blades’ and, indeed, the structure of the molecules is in accordance with the name (see Fig. 1). The name propellane refers to a tricyclic system conjoined by a carbon–carbon single bond. The nomenclature, suggested by Ginsburg and co-workers, follows and simplifies that used for tricycloalkanes.

The first synthesis of a small-ring propellane, [3.2.1]propellane, was published in 1968. Theoretically, the most interesting propellane is [1.1.1]propellane (2) (Fig. 1). The reports of the first modeling studies concluded that 2 should be more stable than the corresponding diradical that lacks the conjoining bond. However, the researchers were uncertain that 2 could ever exist. A decade later, Wiberg and Walter reported the synthesis and isolation of a surprisingly stable molecule, [1.1.1]propellane. The nature of the central bond of the molecule has been the subject of many studies. The theoretical and experimental results of many different research groups agree on the special nature of the bond.

Ginsburg and Wiberg have reviewed the syntheses and structures of natural products possessing the propellane structure. Indeed, propellane structures are present in many different classes of natural products, for example, 3-5 (Fig. 2). Whereas theoretical studies have focused on small-ring propellanes containing more than one three- or four-membered ring, in the known natural products only one of the rings is small, the rest being five to eight-membered. The literature selected for this review describes the total syntheses of propellane-containing natural products. Particular emphasis is placed on propellanes having a three-membered ring in the ring system. The descriptions of the syntheses focus on the methods used for construction of the propellane ring systems of the molecules.

2. [m,n,1]Propellanes

There are quite a few natural products with the [m,n,1] propellane structure. However, only eight of them have been synthesized. Two of these contain a cyclopropane ring and, in six of them, the smallest ring is an epoxide. From a synthetic point of view this is a crucial difference, since constructing a cyclopropane ring is still considered a challenge, while many excellent methods exist for the formation of epoxides. The ring system of propellanes poses its own challenge for three-membered ring formation.

2.1. Cyclopropanes: marasmic acid and stereolide

Marasmic acid (3) and stereolide (4) can be described as [4.3.1]propellanes in which the smallest ring is a cyclopropane (see the highlighted parts in Fig. 2). The synthetic strategies that have been used to date for marasmic acid and...
stereopolide do not utilize a cyclopropanation reaction to install the challenging cyclopropane ring; instead, most of them have adapted variants of the method developed by Woodward, which accesses the cyclopropane ring by a Diels–Alder-enolate alkylation sequence (vide infra).

### 2.1.1. Marasmic acid

Marasmic acid (3) is an antibacterial agent isolated for the first time by Kavanagh et al. from Bacidiomycetes.\(^\text{35,36}\) To date, three different syntheses have been reported for this molecule. Retrosynthetic analysis of the syntheses (Scheme 1) reveals that two of the groups, those of Woodward\(^\text{37–39}\) and Boeckmann,\(^\text{40}\) have employed the Diels–Alder reaction as the key ring-forming step. While both of these used a similar enolate alkylation strategy to form the cyclopropane ring, the third synthesis by Tobe et al. used a 1-oxaspirohexane rearrangement to make the carbon framework of the molecule.\(^\text{41}\)

Woodward group’s synthesis of (±)-marasmic acid (Scheme 2)\(^\text{37–39}\) commences with a completely endo-selective Diels–Alder reaction of diene 9 and 2-(bromomethyl)maleic anhydride (8), yielding a mixture...
of tert-butyl esters 7a and 7b after treatment of the cycloaddition product with isobutylene under acidic conditions. Subjection of the esters to potassium tert-butoxide afforded a single cyclopropane 6 in 44% yield over the three steps. Having obtained the carbon framework of the molecule with the correct stereochemistry, the oxidation states of carbons C6 and C15 had to be adjusted. To that end, lactone 6 was subjected to a sequence of reductions and chloroformate formation with quinoline and phosgene to give dichloroformate 17. The dichloroformate 17 was then oxidized to dialdehyde 18, which gave (±)-marasmic acid (3) after de-esterification.

Boeckmann and co-workers chose to make the carbon skeleton of marasmic acid via an intramolecular Diels–Alder reaction (Scheme 3). While Woodward’s strategy provided essentially one diastereomer after the cyclopropane ring formation, Boeckmann’s group was unable to avoid a 1:1 mixture of two diastereomers 11 and 21 resulting from endo and exo transition states, respectively. They were able to transform both diastereomers into marasmic acid, however, thus enhancing the productivity of the synthesis. After isomerization of the double bond of 11 to give an α,β-unsaturated lactone (see 22), the acetate was transformed into a mesylate to set the stage for the remaining steps.

(±)-marasmic acid/Tobe* 1990

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cyclopropane ring formation. Exposure of mesylate 22 to DBU in refluxing THF provided cyclopropane 10 in excellent yield. Next, a sequence of phenylselenide formation, DIBAL-H reduction and m-CPBA oxidation yielded methyl marasmate (23). Finally, 23 was treated with BBr₃ to give (±)-marasmic acid (3).

Tobe and co-workers have reported a 1-oxaspirohexane rearrangement as an entry to the norcarane skeleton present in the marasmane-type natural products (Scheme 4). To utilize this rearrangement in the synthesis of marasmic acid, an entry to cyclobutyl epoxide 14 was required. Thus, enone 15 was irradiated in the presence of allene to yield the head-to-head photoadduct 26 as the major product. Sodium borohydride reduction of the remaining ketone and m-CPBA epoxidation of the exocyclic double bond provided the rearrangement precursor 14 in a highly stereoselective manner. Exposure of 14 to concentrated sulfuric acid in methylene chloride for 1 h gave cyclopropanolactone 13 in 80% yield, and <5% of the β-Me isomer of 13 was observed. Next, ketone 13 was reduced and eliminated and the lactone ring was opened to enable the oxidation at C14. Allylic oxidation of 28 followed by Swern oxidation gave methyl marasmate (23), completing a formal total synthesis (denoted with an asterisk in Scheme 4) of (±)-marasmic acid (3).

2.1.2. Stereapolide. Two different syntheses have been reported for the pentacyclic framework of stereapolide (4), a metabolite of the fungus Stereum purpureum (Scheme 5).
Trost and co-workers have reported a racemic \(^{46}\) and an asymmetric \(^{47}\) synthesis relying on a palladium-catalyzed cyclization and a Diels–Alder–cyclopropane formation sequence, very similar to that, which Woodward and co-workers used in their synthesis of marasmic acid (vide supra). Arai et al. have synthesized norsterepolide, which lacks the gem-dimethyl groups of sterepolide, utilizing a Diels–Alder–cyclopropane formation sequence and a Nazarov cyclization to form the ring system. \(^{48}\)

In 1985, Trost and Chung published a racemic synthesis of sterepolide. \(^{46}\) In 1989, they published a refined, enantioselective route to the molecule and assigned its absolute stereochemistry (Scheme 6). \(^{47}\) Thus, reduction of the acetylenic ketone \(^{31}\) with LiAlH\(_4\)/Darvon alcohol complex gave the protected alcohol \(^{37}\) in \(>98\%\) ee after PMB protection. The stage was now set for the palladium-catalyzed cyclization. In the presence of palladium acetate and ligand \(^{38}\), the Diels–Alder precursor \(^{30}\) formed smoothly in 81% yield. Heating diene \(^{30}\) and 2-(bromomethyl)maleic anhydride (8) in benzene followed by base treatment yielded cyclopropanoanhydride \(^{29}\) as a single diastereomer. Removal of the silyl protecting group then opened the anhydride and consequently closed the five-membered lactone ring. Reduction then closed the second lactone ring and deprotection followed by oxidation completed the total synthesis of \((-\)-sterepolide) \(^{4}\) and established its absolute stereochemistry as shown. On the basis of this stereochemical assignment, Trost has proposed that sterepolide and marasmic acid are biosynthetically derived from the same enantiomeric folding of farnesyl pyrophosphate (Fig. 3). \(^{36,45}\) Interestingly, the final step of the synthesis also destroys the stereocenter at C\(_1\) that has been employed as a stereochemical control element throughout the synthesis.

Arai and co-workers’ synthesis \(^{48}\) of norsterepolide (32) also commences with a Diels–Alder reaction of 2-(bromomethyl)maleic anhydride (8) and diene 35 (Scheme 7). The cycloaddition produced the \(endo\)-products 34a and 34b in a ratio of 4.5:1, which was inconsequential since, after esterification, the compound was treated with potassium tert-butoxide to close the cyclopropane ring in 90% yield. Next, the acetylenic side chain was introduced to prepare for the crucial Nazarov cyclization. Epoxidation, opening of the epoxide with hydrogen bromide, Jones oxidation and treatment with zinc to remove the bromide gave a ketone ready to be alkylated with 43. Alkylation of the ketone with the lithium acetylide of 43 followed by deprotection of THP in acidic conditions produced diol 33. Subjection of 33 to phosphorus pentoxide and methanesulfonic acid yielded the cyclopentenone 45 via a Rupe rearrangement followed by a Nazarov-type conrotatory electrocyclization. \(^{49}\) The final lactone ring was closed by protecting the enone as a ketal, reducing the lactone and treating the resulting hemiacetal with acid to close the lactone and release the enone to give \((\pm\)-norsterepolide) (32). Attempts were made to introduce the gem-dimethyl groups at C\(_{11}\), but they proved unsuccessful.

### 2.2. Epoxides: frenolicin B, dynemicin A, fusicogigantone A, SF 2315B, diepoxin \(\sigma\) and arthrinone

This rather heterogeneous group of molecules is unified by the fact that they all have an epoxide ring fused to two other rings in their ring system. Most of them, namely frenolicin B, dynemicin A, SF 2315B, and diepoxins, are \([4.4.1]\) propellanes, whereas fusicogigantone A is a \([6.3.1]\) propellane and arthrinone a \([4.3.1]\)propellane. The Diels–Alder reaction is a frequent feature of these syntheses; seven of the 10 routes described herein utilize the cycloaddition to

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**Figure 3.** Biogenetic origin of marasmic acid and sterepolide.

**Scheme 7.**

(a) PhH, rt, 72 h, 72%, \(^{34a,34b}\) 4:5:1; (b) CH\(_3\)N\(_2\), MeOH, Et\(_3\)O, quant.; (c) \(t\)-BuOK, \(t\)-BuOH, PhH, rt, 1 h, 90%; (d) \(m\)-CPBA, cat. bis-(3-tert-butyl-4-hydroxy-5-methylphenyl) sulfide, NaHCO\(_3\), CHCl\(_3\), reflux, 6 h, \(\alpha\):58%, \(\beta\):16%; (e) 48% HBr, CHCl\(_3\), 0 °C/rt, 1 h, \(\alpha\)-OH and \(\beta\)-Br: 80%; \(\alpha\)-Br and \(\beta\)-OH: 70%; (f) Jones reagent, acetone, rt, 6 h; (g) Zn, AcOH, rt, 15 h; (h) 43, BuLi, \(-70\rightarrow-30\) °C, 1 h, then sm, \(-78\) °C, 1 h; (i) \(\rho\)-TsOH, MeOH, rt, 48 h; 47% over two steps; (j) P\(_2\)O\(_5\), MsOH, rt, 2.5 h, 34%; (k) ethylene glycol, PPTS, PhH, reflux, 5 h, 93%; (l) DIBAL-H, THF, \(K\) 90 °C, 30 min, 84%; (m) \(\rho\)-TsOH, PhH, 55 °C, 7 h, 85%.
form the carbon backbone of the molecule. Once the rings are in place, the epoxidations generally proceed stereo-selectively and give good yields of the products.

2.2.1. Frenolicin B. Frenolicin B (46), a pyranonaphthoquinone antibiotic isolated from *Streptomyces fradiae* in 1960, has been synthesized only once, although six syntheses for deoxyfrenolicin (47) have been reported. Since those syntheses, by Naruta and co-workers, Semmelhack et al., Uno, Kraus et al., Moore and co-workers, Brimble and Lynds, as well as Xu et al., lack the formation of the epoxide, which makes the molecule a propellane, they will not be treated here. Scheme 8 shows Ichihara’s retrosynthetic approach to frenolicin (46). The key steps include a Lewis acid-catalyzed Diels–Alder cyclization and an alkylation followed by cyclization of the pyran ring.

Ichihara’s synthesis of racemic frenolicin starts with a highly selective boron trifluoride-catalyzed Diels–Alder reaction.
reaction of juglone (51) and acetoxybutadiene (50), which gives the tricyclic acetate 52 in excellent yield (Scheme 9). Selective reduction, ketal formation and reduction of the remaining ketone and acetate provided the allylic alcohol 49. Lemieux-Johnson oxidation of the double bond in 49 afforded an equilibrated mixture of aldehyde 48 and hemiacetal 53. This mixture was then treated with n-propylmagnesium bromide to give hemiacetal 54 stereoselectively in a chelation-controlled addition. Next, a Horner–Wadsworth–Emmons reaction added the needed two-carbon side chain, and a sequence of PCC- and DDQ-oxidations followed by basic hydrolysis provided naphthoquinone 47. Subjection of 47 to tert-butyl hydroperoxide in the presence of Triton B gave a 1:1 mixture of two unseparable epoxide diastereomers, which was methylated, separated and hydrolyzed to give (±)-frenolicin (46). The lack of selectivity in the epoxidation step can be explained by the fact that the two bulky substituents can reside either pseudo-equatorially/pseudo-axially or pseudo-axially/pseudo-equatorially (Fig. 4).

2.2.2. Dynemicin A. Dynemicin A (62), a potent antibacterial and anticancer agent isolated from Micromonospora chersina, has attracted wide synthetic interest due to its biological activity and intriguing molecular structure. So far, two elegant total syntheses of dynemicin A and one of di-O-methyl dynemicin A methyl ester have appeared in the literature (Schemes 10 and 11). Five different synthetic approaches to model compounds of the dynemicin A ring framework have also been published. The total syntheses by the groups of Schreiber, Myers, and Danishefsky will be treated here with more detail. The groups of Nicolaou, Isobe, Magnus, and Maier have reported their efforts towards dynemicin A model compounds. Of these, the Nicolaou and Takahashi models include a [4.4.1]propellane ring system, so the retrosynthetic analysis of these syntheses are shown in Scheme 15. The syntheses of Isobe, Magnus and Maier did not result in the formation of the propellane skeleton and are outside the scope of this review. Maier has published a review that details the investigations into different dynemicin A analogs.

Scheme 10. Retrosynthetic analysis of dynemicin A.
(±)-di-O-methyl dynemicin A methyl ester/Schreiber 1993

(+)-dynemicin A/Myers 1995

(±)-dynemicin A/Danishefsky 1995

Scheme 11. Retrosynthetic analysis of advanced intermediates of dynemicin A.

(±)-di-O-methyl dynemicin A methyl ester/Schreiber 1993

Scheme 12. (a) 73, Pd(PPh3)4, 85%; (b) 71, CICO2Me, THF; (c) TBAF, THF, 60% over two steps; (d) 72, Pd(PPh3)4, Cul, 20%; (e) LiOH, H2O, THF, 65%; (f) Bromo-tris-pyrrolidino-phosphonium hexafluoro-phosphate (PyBroP), Et3N, CH2Cl2, rt, 13 h, 51%; steps; (g) m-CPBA, pH 7 buffer, CH2Cl2, rt, 2.5 h, 73%; (h) 0.11 M DBU, MeOH, rt, 1 h; (i) CAN, aq MeCN, 0 °C, 45 min.
Retrosynthetic analyses of the dynemicin A syntheses are shown in Schemes 10 and 11. All of the groups have accessed the final compound via fairly similar ABC ring structures, although the Schreiber group installed the epoxide in the late stages of the synthesis. The Schreiber group also decided to use an intramolecular Diels–Alder reaction (IMDA) to form the A ring and close the enediyne bridge of the molecule, whereas the Danishefsky group utilized IMDA only to form the A ring. The Myers group joined the A and C rings with a Suzuki cross-coupling reaction and subsequently closed the B ring by lactam formation.

The synthesis of di-O-methyl dynemicin A methyl ester by Schreiber and co-workers begins with the assembly of the intramolecular Diels–Alder substrate (Scheme 12).66,68,69 Stille coupling of vinylstannane followed by a 1,2-addition of acetylide provided a diyne. Silyl deprotection gave an acetylide that was then coupled with vinyl bromide. After ester hydrolysis, the IMDA substrate was exposed to Yamaguchi macrolactonization conditions, effecting the macrocyclization, and, subsequently, the intramolecular Diels–Alder reaction to give lactone in 50% yield. Next, the stereochemistry at C4 and the oxidation state of carbons C3 and C8 were adjusted followed by functional group manipulation and construction of the anthraquinone fragment with a Diels–Alder reaction (see Scheme 10). Exposure of 59 to m-CPBA in pH 7 phosphate buffer gave epoxide stereoselectively after deprotection of the carbamate nitrogen with DBU. Finally, the secondary alcohol was oxidized with ceric ammonium nitrate to give (+)-di-O-methyl dynemicin A methyl ester (58).

The total synthesis of dynemicin A by Myers and co-workers starts with the construction of the A ring (Scheme 13).70,71 Condensation of menthyl acetoacetate and trans-ethyl crotonate provided a 36% yield of the correct b-methyl diastereomer after recrystallization. Stirring the 1,3-diketone in methanolic camphorsulfonic acid led to the formation of an enol ether, which was then subjected to sodium hydride and triflic anhydride to yield the coupling precursor. Suzuki cross-coupling of enol triflate with arylboronic acid afforded the AC ring structure in 90% yield. Next, heating the carbamate cleaved the nitrogen-protecting group and closed the B ring of the molecule. After a series of functional group manipulations as well as incorporation of the enediyne side chain, allylic alcohol was ready to be epoxidized. Initially, the Myers group tried to close the enediyne bridge with various
electrophiles at C7 before the epoxidation without succeeding. In the event, buffered m-CPBA effected the epoxidation in 88% yield. Then, removal of the silyl groups, reprotection of the phenol and oxidation at C7 provided the cyclization precursor. Indeed, deprotonation of the acetylene caused the enediyne bridge to attack the ketone at C7 and gave alcohol 65 in excellent yield. After adjusting the oxidation states of various carbons, the stage was set for the final Diels–Alder reaction to complete the anthraquinone part of the molecule. The Diels–Alder reaction between the quinone imine 67 and isobenzofuran 63 proceeded in 5 min to give the di-TMS-ether, which was immediately oxidized with manganese dioxide to provide (±)-dynemicin A (62) in 40% yield over two steps.

Danishefsky and co-workers also decided to begin the construction of dynemicin A ring system with an intramolecular Diels–Alder reaction (Scheme 14).72–77 A zinc chloride-catalyzed IMDA led selectively to the endo adduct 79 in 60% yield. Exposure of adduct 79 to ceric ammonium nitrate gave rise to quinone lactol 87 via oxidation of the aromatic ring and lactol formation between the unveiled alcohol and the aldehyde. Ammonium acetate followed by silylation then afforded 88 with both of its stereocenters arising from the Diels–Alder step. After installation of the acetylenic functions, olefin 78 was ready for the epoxidation step. Thus, epoxidation of olefin 78 with m-CPBA proceeded smoothly to give epoxide 89 in 87% yield. Next, the diacetylene 89 was transformed into a diiodide, which could then be treated with vinylbis(stannane) (90) and Pd(PPh3)4 to close the enediyne bridge, giving 68 in 81% yield. The enediyne bridge could not be closed without the presence of the epoxide (e.g., compound 78), and a similar observation was also made by the Myers group (Scheme 13 and discussion). Then, after adjusting the oxidation state of the C ring and adding a carboxyl group at C5, quinone imine 67 was ready to react with the anion of anhydride 66 to form the remaining rings of dynemicin A. The adduct was immediately oxidized with PhI(OCOCF3)2. Exposure of the product to air and daylight also oxidized ring D and the final step was to remove the MOM protecting groups. This was accomplished with magnesium bromide to provide (±)-dynemicin A (62) in 15% yield over the last four steps.

The synthesis of dynemicin A model compounds by Nicolaou and co-workers78–81 is based on functionalizing quinoline derivative 91 (Scheme 15).80,81 Takahashi and co-workers decided to form the A ring of their model compound 96 with a Diels–Alder reaction (Scheme 15).87,88 The diene part 99 is derived from a [2,3]-Wittig rearrangement. The enediyne bridge was closed with a palladium-catalyzed coupling.

2.2.3. Fusicogigantone A. Fusicogigantone A (103) and fusicogigantepoxide (112) were isolated from Pleurozia.
gigantea collected from East Malaysia in 1990. The only reported synthetic route to the fusicogigantones is from the group of Takeshita, the retrosynthetic analysis of which is shown in Scheme 16. The key ring-forming steps are a singlet oxygen oxidation and a titanium-mediated McMurry ring closure of a dialdehyde.

Optically active enal and allyl chloride were mixed with chromium dichloride to obtain alcohol in good yield (Scheme 17). Next, the double bond in was hydroborated, the benzyl group removed, the free secondary alcohol eliminated and the resulting double bond reduced with lithium and ethylamine. After a Swern oxidation of the diol, the resulting diadehyde was treated with titanium tetrachloride in the presence of zinc to obtain the cyclized a-cis-diol in 38% yield together with the b-cis-diol in 7% yield. The diol was removed by orthofromate formation and subsequent reductive elimination. The C8–9 double bond in was hydrogenated to give a mixture of C2–6 and C2–3 double-bond-containing compounds. This mixture was left to stand at room temperature for 10 h, and gradually turned into (+)-fusicogigantone A (103) and (+)-fusicogigantepoxide (112). Heating the mixture to 60 °C for 1 h gave two more products, (+)-fusicogigantone B (114) and 113, from the more stable endoperoxide 111b. The products were separated by column chromatography. The authors report that the attack of O2 had occurred exclusively from the a-side of the dienes in 104a and 104b.

2.2.4. SF 2315B. Sulikowski and co-workers have reported a synthetic route to the ring system of SF 2315B (120), an angucyclinone antibiotic isolated from a soil micro-organism of the Actinomycete strain Excellospora viridilutea. Their retrosynthetic analysis of the target is shown in Scheme 18. The key transformations in the synthesis are a highly selective Diels–Alder reaction to set up the carbon framework and an oxygenation to provide the correct oxidation pattern.

Sulikowski’s synthesis of epoxyquinol started with a highly regioselective Diels–Alder cycloaddition between 2-bromo-acetoxyjuglone (119) and diene (Scheme 19). The reaction produced cycloadduct 121, which was then dehydrobrominated with lithium hydroxide to give quinone 117. Exposure of 117 to molecular oxygen and tetra-butylammonium fluoride provided epoxyalcohols 116 and 122, which were separated by column chromatography.

Scheme 16. Retrosynthetic analysis of fusicogigantone A.
Then, a sequence of hydrogenation, acetylation of the phenol, TIPS deprotection, C-1-hydroxyl-directed reduction of the C-12-ketone and removal of the acetyl group gave epoxyquinol 115, which bears the complete array of stereogenic centers present in SF 2315B (120).

2.2.5. Diepoxin σ. Diepoxin σ (123) was isolated from fermentation broths of a nonsporulating fungus, LL-07F275, collected in Panama from a tree trunk in 1993.101 To date, one total synthesis of the molecule has appeared in the literature by Wipf and Jung (Scheme 20).102–104 The key steps in their synthesis include an Ullmann coupling followed by an oxidative spirocyclization to introduce the naphthalene ketal and a stereoselective epoxidation. Another notable feature is the use of a Diels–Alder-retro-Diels–Alder strategy to introduce chirality into the molecule as well as to protect the highly reactive naphthoquinone ring system.

The first task in the diepoxin σ synthesis by Wipf and Jung
Scheme 19. (a) Tol, reflux, 71%; (b) LiOH, THF/MeOH 1:1, 0 °C, 30 min, 70%; (c) TBAF, O₂, THF, −78 °C → rt, 116 33%, 117 16%, 118 20%; (d) H₂, PdO₂, EtOAc, 0 °C, 30 min, 76%; (e) Ac₂O, DMAP, pyr, CH₂Cl₂, rt, 30 min, 96%; (f) HF pyr, MeCN, 0 °C → rt, 2 h, quant.; (g) Me₄NB(OAc)₃, AcOH, MeCN/THF 1:1, −10 °C, 53% (+38% of recovered sm); (h) Bu₄NOH, THF, 0 °C, 80%.

Scheme 20. Retrosynthetic analysis of diepoxin σ.

Scheme 21. (a) 129, BH₃, THF, AcOH, THF, rt, 1 h, then cyclopentadiene, −78 °C, 2 h, 72%, 94% ee; (b) NaBH₄, THF, MeOH, −78 → 0 °C, 3 h, 88%; (c) 130, Cu₂O, pyr, reflux, 20 h, 70%; (d) Ph₂PH, n-BuLi, THF, rt, 7 days, 95%; (e) PhI(OAc)₂, 4 Å MS, 131, rt, 1 h, 61%; (f) TBSOTf, lutidine, CH₂Cl₂, −78 °C, 1 h, 91%; (g) PDC, DMF, rt, 24 h, 72%; (h) H₂O₂, K₂CO₃, THF, H₂O, 0 °C, 9 h, 88%; (i) PhOPh, reflux, 1 h; (j) HF, MeCN, H₂O, 0 °C → rt, 20 h, 73% over two steps.
(±)-arthrinone/Uchiyama 2000

![Scheme 21](image)

(Scheme 21) was the protection of the reactive double bond in 126 as a Diels–Alder adduct with cyclopentadiene.\textsuperscript{102–104} In their preliminary work, Wipf and Jung developed a racemic synthesis of the molecule, after which they successfully performed the cycloaddition in an enantioselective manner. In the strictest sense, the synthesis is thus a formal total synthesis of (±)-diepoxin \(\sigma\), but, because the same group performed the racemic synthesis, this is trivial. The Diels–Alder reaction of 126 and cyclopentadiene in the presence of borane and ligand 129 proceeded well to give 94% ee and 72% yield of the cycloadduct. Sodium borohydride reduction then gave the required precursor for the Ullmann ether coupling, which provided 128 after demethylation. The spiroketal ring was then closed with an oxidative cyclization in the presence of PhI(OAc)\(_2\) in hexafluoro-2-propanol (131) followed by TBS protection of the less hindered secondary alcohol and PDC oxidation of the remaining alcohol to yield dienone 125. Next, epoxidation of the two double bonds proceeded smoothly to give \(\text{syn}\)-diepoxide 124 in 88% yield as a single diastereomer. Now, the only remaining task was to cleave the protecting groups. Surprisingly, the enone double bond was unmasked with a retro-Diels–Alder reaction at 250 °C in boiling diphenyl ether without significant decomposition of the product. Then, treatment of the product with hydrogen fluoride gave (±)-diepoxin \(\sigma\) (123) in 73% yield over two steps.

2.2.6. Arthrinone. Arthrinone (132) is an antifungal metabolite, which was isolated from \textit{Artrinium} sp. FA 1744 in 1994.\textsuperscript{105} Its only total synthesis was reported in 2000 by Uchiyama and co-workers (Scheme 22).\textsuperscript{106} The key ring-forming steps in the synthesis include a Diels–Alder–cycloreversion reaction of a diene and an acetylene to form a highly substituted aromatic ring, as well as a Dieckmann condensation.

The synthesis of arthrinone by Uchiyama et al. is illustrated in Scheme 23.\textsuperscript{106} The Diels–Alder reaction between acetylene 136 and diene 137 proceeded smoothly and gave ester 135 in 81% yield after cycloreversion and TIPS protection. With all requisite carbon atoms in place,
NaHMDS effected a Dieckmann condensation to close the required cyclohexane ring. Because the cyclization product was not stable, it was immediately converted into phenyl sulfide 138 to create unsaturation for the subsequent epoxidation. After reduction of the ketone in 138, the sulfide was oxidized into two epimeric sulfoxides and eliminated to give the \(\alpha,\beta\)-unsaturated lactone 139. Attempts to insert the epoxide at this point in the synthesis, only resulted in aromatization of the cyclohexene ring. Thus, the lactone was reduced to diol 134 and the epoxidation took place to give epoxide 133 in 72% yield as a single diastereomer. The excellent selectivity obtained can be attributed to the directing effect of the allylic hydroxyl group. The tetrahydrofuran ring was then reconstructed using the following sequence: the less hindered primary alcohol was protected with a TBS group and the other with a TBDPS group, the TIPS and TBS groups were removed, the benzylic alcohol was oxidized with MnO\(_2\) and the free primary alcohol with TPAP and, finally, the two TBDPS groups were removed to give (±)-arthrinone (132).

3. Other propellanes with all-carbon quaternary stereocenters

3.1. Bukittinggine

Bukittinggine (140) was isolated in 1990 from the leaves and branches of *Sapium baccatum* near the town of Bukittinggi in West Sumatra, Indonesia\(^{107}\). The Heathcock group synthesized this unique heptacyclic alkaloid in 1992\(^{108}\). The main transformation in their synthesis, a tetracyclization reaction developed in the group, suggests diol 143 as a starting material (Scheme 24).

The tetracyclization process is effected by a Swern oxidation of diol 143 followed by gaseous ammonia (Scheme 25). Exposure of the product to acetic acid then triggers an inverse-electron-demand Diels–Alder reaction followed by an ene reaction to give the pentacycle 142. There has been some discussion as to whether the mechanism is stepwise or concerted\(^{109}\), but the Heathcock group has reported experimental evidence, which indicates

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**Scheme 24.** Retrosynthetic analysis of bukittinggine.

**Scheme 25.** (a) (COCl)\(_2\), DMSO, CH\(_2\)Cl\(_2\), –78 °C, 15 min, then Et\(_3\)N, –78 – 0 °C, 1 h, then NH\(_3\)(g), 0 °C – rt, 45 min; (b) NH\(_4\)OAc, AcOH, 30 min, rt, then 75 °C, 2 h; 76% from 143; (c) (CF\(_3\)CO\(_2\))\(_2\)Pd, PPh\(_3\), p-benzoquinone, MeCN, 24 h, rt, 70%; (d) BH\(_3\)·THF, THF, 0 °C – rt, 2 h, then NaBO\(_{3}\)·4H\(_2\)O, H\(_2\)O, 3 h, rt; (e) p-TsCl, DMAP, pyr, CHCl\(_3\), 0 °C – rt, 46 h; (f) LiEt\(_3\)BH, THF, 0 °C – rt, 4 h, then NaBO\(_{3}\)·4H\(_2\)O, H\(_2\)O, 0 °C – rt, 2.5 h; (g) Na, NH\(_3\), THF, –78 °C, 20 min; (h) Ag\(_2\)CO\(_3\) on Celite\(^{\circ}\), PhH, reflux, 5 h; 52% over five steps.
that the cyclization proceeds through a concerted, but asynchronous, Diels–Alder reaction.\textsuperscript{110,111} Next, the pentacyclic amine \textsuperscript{142} was treated with palladium triflate to cyclize the sixth ring of the molecule. The following sequence reduced the exocyclic double bond in \textsuperscript{141} stereoselectively (\textgreater 15:1): hydroboration and oxidation of the double bond and tosylation of the formed primary alcohol followed by reduction with lithium triethoxyborohydride. Removal of the benzyl protecting groups then gave diol \textsuperscript{144}, which was ready for the final cyclization. Finally, oxidation of the diol with Fetizon’s reagent provided (\textpm)-bukittinggine (\textsuperscript{140}) as the sole product.

3.2. Colombiasin A

Colombiasin A (\textsuperscript{145}), a diterpene isolated from the gorgonian octacoral \textit{Pseudopterogorgia elisabethae},\textsuperscript{112} has attracted the interest of the synthetic community with its novel and challenging molecular framework. To date, three total syntheses, from the Nicolaou,\textsuperscript{113,114} Rychnovsky,\textsuperscript{115} and Harrowven\textsuperscript{116,117} groups, have been published (Scheme 26). In addition, an approach to this complex ring system has appeared in the literature (Scheme 30).\textsuperscript{118}

Unsurprisingly, all of the total syntheses rely heavily on the Diels–Alder reaction in the final stages of the synthesis (Scheme 26). The main difference in the first two synthetic routes, by Nicolaou et al. and Rychnovsky et al., is the point at which the side chain, which later forms the B and C rings, is installed. In the Nicolaou group strategy, it is attached after the initial Diels–Alder reaction, whereas the Rychnovsky group decided to include part of the side chain, including the crucial C\textsubscript{7} methyl group, in their first Diels–Alder substrate. The Harrowven group relied on a Moore rearrangement to construct the A and D rings of colombiasin A in their recent synthesis. In this route, the methyl group stems from a hydroboration, where a separable 5:2 mixture of diastereomers is obtained.

The Nicolaou group synthesis commences with a catalytic asymmetric Diels–Alder reaction (Scheme 27).\textsuperscript{113,114} The reaction between diene \textsuperscript{148} and quinone \textsuperscript{149} in the presence of [(S)-BINOL-TiCl\textsubscript{2}] provided the Diels–Alder adduct \textsuperscript{147} after aromatization, methylation and desilylation in 94\% ee and 85:15 regioselectivity. The main regioisomer was thought to arise from a bidentate coordination of titanium, as shown in Scheme 27. The minor regioisomer would then originate from monodentate coordination of titanium to the more electron-rich vinylogous ester carbonyl oxygen at C\textsubscript{14} (colombiasin A)
numbering).† After further elaboration and attachment of the side chain, the sulfone-protected diene 146 was ready for the critical IMDA reaction. The reaction was performed at 180 °C in toluene in a sealed tube and provided tetracycle 157 in 89% yield as a single product. Deoxygenation at C₅ and demethylation at C₁₆ then gave (-)-colombiasin A (145).

Scheme 27. (a) [5]-BINOL-TiCl₂, toluene, 60 °C → 10 °C, 7 h, 85:15 regioselectivity, 94% ee; (b) K₂CO₃, MeI, acetone, reflux, 48 h; (c) TFA, CH₂Cl₂, rt, 2 h, 70% over three steps, 94% ee; (d) tol (sealed tube), 180 °C, 20 min, 89%, 100% selectivity; (e) NaH, THF/C₅H₅/MeI 4:1:1, 50 °C, 3 h, 95%; (f) AIBN, Bu₃SnH, toluene, 110 °C, 30 min, 77%; (g) BBr₃, cis-cyclooctene, CH₂Cl₂, −78 °C, 43% based on 70% conversion.

Scheme 28. (a) 5 M LiClO₄, Et₂O, rt, 24 h, 75%, 151/151’ 1.7:1; steps; (b) tol, 180 °C, 83%; (c) AlCl₃, PhMe₂, CH₂Cl₂, 0 °C→rt, 73%; (d) separation of diastereomers.

The Rychnovski group used a Lewis acid-catalyzed Diels–Alder reaction between diene 152 and quinone 149 to start the synthesis of the colombiasin A ring system (Scheme 28).†† The reaction gave a 1.7:1 mixture of 151 and 151’, that could only be separated in the last step of the synthesis, despite attempts to do so earlier. The use of chiral Lewis acids to catalyze the reaction was not successful. After

† Note that there is an error in the original paper in Scheme 9; the transition states TSₐ and TSₐ provide the enantiomers of compounds 8 and 8’. (Personal communication with Prof. G. Vassilikogiannakis.)
installing the C7-methyl and the diene required for the IMDA, compound \textit{150} was ready for cyclization. The final cyclization of diene \textit{150} (and \textit{150'}) was performed in a similar fashion to that used in the Nicolaou synthesis, followed by deprotection of the C16-methoxy group and separation of the diastereomers, providing (−)-colombiasin A (\textit{145}).

In the Harrowven group’s synthesis of colombiasin A (Scheme 29),\textsuperscript{116} the crucial intermediate \textit{154} for the Moore reaction\textsuperscript{119–121} was obtained from a Shapiro coupling between ketone \textit{155} and diketone \textit{156}. After some experimentation, it was found that an in situ formation of a trisylhydrazone from ketone \textit{155}, which could then be treated with \textit{n}-butyllithium and diketone \textit{156}, was the best way to obtain the Moore substrate \textit{154}. Heating \textit{154} to 110 °C in a microwave effected the formation of the Diels–Alder substrate \textit{153}. As the penultimate step, an intramolecular Diels–Alder reaction provided the tetracycle in a similar fashion to the Nicolaou (Scheme 27) and Rychnovski (Scheme 28) syntheses. Finally, trifluoro-borate-etherate deprotected the alcohol to give (−)-colombiasin A (\textit{145}).

The research group of Flynn\textsuperscript{118} has also published their efforts towards colombiasin A (Scheme 30). They used an enantioselective double Diels–Alder approach to construct the tetracyclic framework of colombiasin A. Their strategy is similar to Rychnovsky’s (Scheme 28), but differs in execution of the actual route. As a source of chirality, they use sulfoxide \textit{161}, which, after the first enantioselective Diels–Alder reaction, eliminates to give the substrate for the second intramolecular Diels–Alder reaction.

### 3.3. Modhephene

Modhephene (\textit{5}) was the first isolated natural product shown to possess the \([3.3.3]\)propellane skeleton. It was isolated for the first time in 1978 from \textit{Isocoma wrightii} by Zalkov et al.\textsuperscript{122,123} and has inspired a total of 19 syntheses, of which 13 are formal. The different approaches can be classified into five different key reaction types, namely acid-catalyzed rearrangements, thermal rearrangements, photochemical rearrangements, anionic cyclizations and radical cyclizations (Scheme 31). Because of the number of syntheses published, only the key ring-forming steps of each synthesis will be shown. The syntheses of modhephene until 1996 have appeared as a subsection in a review on polyquinane natural products.\textsuperscript{124} There have also been two accounts of approaches towards modhephene.\textsuperscript{125,126}
The stereoselective installation of the C₈-methyl group has been one of the greatest challenges in the synthesis of modhephene, further complicated by difficulties in the separation of diastereomers.

3.3.1. Acid-catalyzed rearrangement. Smith and Jerris published one of the first total syntheses of modhephene (5) (Scheme 32) in 1981 (others followed shortly; three different total syntheses were published in 1981 and another in 1980). They utilized Cargill's work on acid-catalyzed rearrangements of β,γ-unsaturated ketones to perform the key ring-forming step, namely 163 → 164. Ketone 163 was synthesized from enone 162 via a [2 + 2] photochemical cyclization, which, unfortunately, gave only a ca. 1.3:1 ratio of the C₈-methyl group with the major diastereomer being the desired isomer.

In 1984, Wilkening and Mundy published a formal total synthesis of modhephene (5) relying on a phosphorus pentoxide–methanesulfonic acid-catalyzed rearrangement (166 → 167). Catalytic hydrogenation was used to obtain

Scheme 32. (a) p-TsOH, PhH, reflux, 4 h, 64%, a-Me/β- Me 57:43; (b) MeLi, THF, rt, overnight, 80%; (c) MsOH, P₂O₅, 85 °C, 44 h, 22%; (d) allene, CH₂Cl₂, K₂C₂, 94%, 4.5:1 selectivity; (e) LiBr, HMPA, PhH, 60 °C, 86%, 10:1 selectivity. (f) p-TsOH, PhH, 70 °C, 20 min, 34%.

Scheme 31. Classification of different approaches towards modhephene by key reaction.
the correct stereochemistry at C₈ selectively. They also published a total synthesis of modhephene, but, later, the Curran group (see Scheme 36) found that there was a discrepancy with the assignment of a common intermediate (see Ref. 47 in the paper). Since Wilkening and Mundy only had mass spectral data of modhephene, this casts doubt over the identity of the products in the total synthesis.‡

The key step in the formal synthesis by the Tobe group is not an acid-catalyzed rearrangement, but a very efficient lithium bromide–HMPA-catalyzed epoxide–carbonyl rearrangement of epoxide 170. Since the rearrangement is chelation controlled, the less substituted carbon (C₆) migrates with good selectivity. The precursor to epoxide 170, olefin 169, is made from the readily available enone 168. It is interesting to note the similarity of this strategy to the Tobe group synthesis of marasmic acid in Scheme 4.

Fitjer et al. have published a short and original synthesis of modhephene via an acid-catalyzed cascade rearrangement of alcohol 173. The group has also studied the absolute configuration and optical rotation of modhephene by resolving an intermediate and preparing both (−)- and (+)-modhephene separately.144

3.3.2. Thermal rearrangement. Thermal rearrangement has been the strategy of choice for four different groups who have synthesized modhephene (Scheme 33). Karpf and Dreiding utilized an α-alkynone cyclization of alkyne 175 to construct the [3.3.3]propellane ring framework. While the reaction gives a good yield, it also gives two other products in a 2:1:1 ratio that can be separated later. They arrive at the same intermediate as Smith and Jerris (164, see Scheme 32), but, since the publications were received within 8 days by the editorial staff of the journals, the syntheses can be considered independent.

Schostarez and Paquette used an intramolecular ene reaction of acetylene 176 to form the modhephene ring system in good yield in their short synthesis of modhephene. Seven years later, Mash et al. published the first total synthesis of (−)-modhephene, where each chiral auxiliary-based strategy was used to synthesize enantio-merically enriched acetylene 176 (78% ee). From intermediate 176 onwards, they follow the footsteps of Schostarez and Paquette.

The Oppolzer group has published two different routes to 177 (see Scheme 32), a common intermediate to the Dreiding and Smith syntheses. Of these, the latter is significantly shorter. The key transformation in their synthesis was the ene reaction of 178, which produced propellane 179 selectively.

3.3.3. Photochemical rearrangement. A photochemical rearrangement has been the basis of three different syntheses of modhephene (Scheme 34), in the first of which, by Wender and Dreyer, indan (180) and vinyl acetate were
modhephene by photochemical rearrangement (= photo-RR)

(±)-modhephene/Wender 1982

\[
\begin{array}{c}
\text{arene} \xrightarrow{\text{a}} \text{acetate} \text{5: modhephene} \\
180 \quad 181
\end{array}
\]

(±)-modhephene/Mehta 1985

\[
\begin{array}{c}
\text{arene} \xrightarrow{\text{b}, \text{c}} \text{olefin} \xrightarrow{\text{d}} \text{photo-RR} \text{5: modhephene} \\
182 \quad 183 \quad 184
\end{array}
\]

(±)-modhephene/Uyehara* 1996

\[
\begin{array}{c}
\text{arene} \xrightarrow{\text{e}} \text{olefin} \xrightarrow{\text{f}} \text{radical} \xrightarrow{\text{g}} \text{5: modhephene} \\
314 \quad 186 \quad 187 \quad 188
\end{array}
\]

Scheme 34. (a) hr, Vycor, vinyl acetate, cyclohexane, 35 h, 21%; (b) 1-chloroacrylonitrile, tol, 80 °C, 16 h, 43%, 4:1 regioselectivity; (c) Na₂S·9H₂O, EtOH, 60 °C, 6 h, 58%; (d) hr, acetone, 45 min, 47%, 15:1 selectivity; (e) hr, acetone, rt, 1.5 h, 91%; (f) Bu₃SnH, AIBN, PhH, reflux, 2 h, 42%.

Irradiated with Vycor-filtered light to produce a complex mixture from which acetate 181 was isolated in 21% yield. This arene–olefin meta cycloaddition established the [3.3.3]propellane structure and the remaining steps were used to incorporate the required methyl groups into the molecule.

In their synthesis of modhephene, Mehta and Subrahmanyan relied on a Diels–Alder reaction (182 → 183) followed by an oxa-di-π-methane rearrangement (183 → 184).

The Uyehara group also chose an oxa-di-π-methane

modhephene by anionic cyclization (= AC)

(±)-modhephene/Cook 1983

\[
\begin{array}{c}
\text{arene} \xrightarrow{\text{a}} \text{oligonucleotide} \text{5: modhephene} \\
189 \quad 190 \quad 191
\end{array}
\]

(±)-modhephene/Kraus* 1991

\[
\begin{array}{c}
\text{arene} \xrightarrow{\text{b}, \text{c}} \text{olefin} \xrightarrow{\text{d}} \text{AC} \text{5: modhephene} \\
192 \quad 193 \quad 194
\end{array}
\]

(±)-modhephene/Suri* 1993

\[
\begin{array}{c}
\text{arene} \xrightarrow{\text{e}} \text{olefin} \xrightarrow{\text{f}} \text{AC} \xrightarrow{\text{g}} \text{5: modhephene} \\
195 \quad 196 \quad 197
\end{array}
\]

Scheme 35. (a) 190, pH 5 aqueous buffer, rt, several days, then H₂O -, heat; (b) (MeO)₂P(O)Me, n-BuLi, –78 °C, 15 min, then 192, –78 °C→rt, 1 h, 49%; (c) [Ir(COD)(PCy₃)(py)]PF₆, H₂, CH₂Cl₂, rt, 15 h; (d) KH, 18-crown-6, PhH, reflux, 6 h, 33% over two steps; (e) LDA, HMPA, THF, –70 °C, 79%.
rearrangement to construct the ring system of modhephene.\textsuperscript{158,159} Irradiation of bicycle 185 for 1.5 h provided the tricyclic ketone 186 in 91% yield. To form the third five-membered ring, ketone 186 was elaborated to bromide 187, which cyclized to give propellane 188 in the presence of tributyltin hydride and AIBN.

3.3.4. Anionic cyclization. An anionic cyclization has been employed by three research groups during their synthesis of modhephene (Scheme 35). Cook and co-workers\textsuperscript{160} decided to use the Weiss reaction,\textsuperscript{161,162} that is, the reaction between dimethyl 3-ketoglutarate (190) and diketone 189, to construct the [3.3.3]propellane system.

Kraus and Shi have published a formal total synthesis of modhephene utilizing a rearrangement of bridgehead bromide 192 with the anion of dimethyl methyl phosphonate followed by a potassium hydride-mediated cyclization of the resulting phosphonate 193.\textsuperscript{134,163}

Suri’s original, but lengthy, approach towards modhephene involved an intramolecular enolate alkylation of bromide 196 to provide the [3.3.3]propellane ring system.\textsuperscript{164}

3.3.5. Radical reaction. Radical cyclizations have been the most popular method to make the [3.3.3]propellane ring system in modhephene and have been the key reaction in six different total syntheses. In addition to the syntheses shown in Scheme 36, the Uyehara group has also utilized radical cyclization to build the third unsubstituted ring of modhephene (see Scheme 34, 187 $\rightarrow$ 188). The Curran group has published two different radical-based syntheses of modhephene. The first was a formal total synthesis with sequential radical cyclizations\textsuperscript{133} and the second used a tandem transannular radical cyclization.\textsuperscript{165} Because their first route was significantly shorter and more effective (11 steps and 16% overall yield vs 21 steps and 6% overall yield), it will be discussed here. Their strategy hinged on closing two of the three five-membered rings with a radical

\begin{equation}
\text{modhephene by radical reaction}
\end{equation}

\begin{equation}
(\pm)\text{-modhephene/Curran* 1990}
\end{equation}

\begin{equation}
\text{modhephene by radical reaction}
\end{equation}

\begin{equation}
(\pm)\text{-modhephene/Sha* 1990}
\end{equation}

\begin{equation}
\text{modhephene by radical reaction}
\end{equation}

\begin{equation}
(\pm)\text{-modhephene/Lee* 1996}
\end{equation}

\begin{equation}
\text{modhephene by radical reaction}
\end{equation}

\begin{equation}
(\pm)\text{-modhephene/Rawal* 1997}
\end{equation}

\begin{equation}
\text{modhephene by radical reaction}
\end{equation}

\begin{equation}
(\pm)\text{-modhephene/Pattenden* 1998}
\end{equation}

\begin{equation}
\text{Scheme 36. (a) Bu}_3\text{SnH, AIBN, PhH, reflux, 10 h, 90%; (b) Bu}_3\text{SnH, AIBN, DPPE, PhH, reflux, 7 h, 88%; (c) Bu}_3\text{SnH, AIBN, PhH, 85%, }\alpha: \beta 4:1; (d) Bu}_3\text{SnH, AIBN, PhH, 8 h, then SiO}_2, 74%, }\alpha: \beta 9:1; (e) Bu}_3\text{SnH, AIBN, PhH, }-78\degree\text{C, }\alpha: \beta 6:1; (f) 2-(o-IC}_6\text{H}_4)CH}_2CH}_2SH, DCC, DMAP, CH}_2Cl}_2, 85%; (g) Bu}_3\text{SnH, AIBN, PhH, reflux, 59%}.}
\end{equation}
reaction. Vinylstannane 198 cyclized smoothly to give the trans ester 199, which was further elaborated to give the vinyl iodide 200, which, in turn, provided the enone 164 in 88% yield.

In their formal total synthesis of modhephene, Sha et al. also used an intramolecular radical cyclization. 166 Their substrate, iodo-olefin 201, afforded a 4:1 selectivity of the desired α-C8 diastereomer when exposed to the standard tributyltin hydride/AIBN conditions.

Lee et al. have published a short and successful tandem radical cyclization approach towards modhephene. 167 Cyclization of N-aziridinyl imine 204 provided > 90% selectivity for the desired exocyclic olefin 205. Recently, they have published another tandem radical cyclization route to modhephene.168

Dvorak and Rawal synthesized their intramolecular radical cyclization substrate in an interesting manner.169 They used a Diels–Alder reaction followed by a Paterno-Büchi reaction to access oxetane 206. The hidden diquinane unit present in 206 was revealed by a direct fragmentation of 206 followed by oxidation of the remaining alcohol and selenation to give enone 207. Then, exposure of 207 to tributyltin hydride and AIBN provided propellane 167 in a 6:1 selectivity as the major product.

The latest synthesis of modhephene was published by De Boeck and Pattenden.170,171 Their approach called for the construction of an eight-membered ring that was then cyclized by virtue of an α-ketenyl radical intermediate into propellane 209.

4. Propellanes with lactones

4.1. Ginkgolide B

Ginkgolide B (210) is a complex polyoxygenated and polycyclic natural product isolated from the extracts of Ginkgo biloba.172–174 It is the most active platelet-activating factor (PAF) antagonist isolated from ginkgo extracts. This synthetically challenging molecule has been the target of two different total syntheses, by the groups of Corey175,176 and Crimmins (Scheme 37). 177–179 The key ring-forming transformation in the Corey group synthesis is an internal ketene–olefin cycloaddition, whereas the Crimmins group relied on a [2 + 2] photocycloaddition.

The first ring-forming step in the Corey group synthesis of ginkgolide B175,176 was an internal ketene–olefin cycloaddition (Scheme 38).181,182 Treatment of acid 217 with oxalyl chloride gave the corresponding acid chloride (213, see Scheme 37), which was then eliminated with tributylamine to form the ketene. The ketene immediately underwent cycloaddition followed by elimination of the anomeric methoxy group to give the tetracyclic ketone 212. Baeyer-Villiger oxidation by triphenylmethyl hydroperoxide then produced lactone 218, which was further elaborated into the more highly oxidized lactone 219. Treatment of 219 with acid then provided the ABCDE ring fragment of ginkgolide B (211), that also contains a [3.3.3]propellane structure. Ten further steps afforded (−)-ginkgolide B (210).

The first key ring-forming transformation in the Crimmins group’s synthesis of ginkgolide B (Scheme 39) was a [2 + 2] photocycloaddition of enoate 216, which proceeded with remarkable efficiency and stereoselectivity to give a single cycloadduct 220 in quantitative yield. The E ring of ginkgolide B was then closed via a sequence of silyl deprotection, mesylation and acid-catalyzed cyclization. Next, the cyclobutane ring was opened with a retroaldol fragmentation via a one-pot selenylation–elimination sequence followed by epoxidation of the C10–C11 double bond to furnish the dialdehyde hydrate 221. Several steps later, the dilactone 222 was ready for the closure of ring D. Treatment of dilactone 222 with camphorsulfonic acid gave the ABCDE ring fragment 223. Four more steps were required to deliver (±)-ginkgolide B (210).

§ The Corey group syntheses of ginkgolide A, B and bilobalide have been thoroughly analyzed in Professor Corey’s Robert Robinson lecture.180
**(-)-ginkgolide B/Corey 1988**

Scheme 38. (a) (COCl)$_2$, PhH, rt, 2 h, then (b) n-Bu$_3$N, toluene, reflux, 3 h, 71–89% over two steps; (c) Ph$_3$COOH, 8:1 acetone:1 N NaOH, −30 °C, 2 h, 86%; steps; (d) CSA, CH$_2$Cl$_2$, rt, 24 h (75% over two steps).

**(+)-ginkgolide B/Crimmins 1999**

Scheme 39. (a) hv, > 350 nm, hexanes, rt, 17 h, quant.; (b) 5% HF, MeCN, 0 °C→rt, 1 h; (c) MeCl, Et$_3$I, CH$_2$Cl$_2$, 0 °C, 45 min; (d) 4 Å MS, EtOH, reflux, 26 h, then H$_2$O, reflux, 8 h, then PPTS, PhH, reflux, 16 h, 63% from 220; (e) PhSeCl, HCl, EtOAc, rt, 1 h, then NaIO$_4$, H$_2$O, THF, 2 h, rt, 78%; (f) DMDO, acetone, H$_2$O, 8 h, rt, then p-TsOH, rt, 15 h, 94%; steps; (g) CSA, MeOH, reflux, 18 h, 88%; (h) PPTS, pyr, PhCl, reflux, 4 h, 85%; (i) VO(acac)$_2$, TBHP, 4 Å MS, CH$_2$Cl$_2$, rt, 4 days, then p-TsOH, rt, 2 h, 81%; (j) DMDO, acetone, H$_2$O, rt, 20 h; (k) Br$_2$, NaOAc, H$_2$O, AcOH, rt, 20 h, 52% over two steps.

**(±)-merrilactone A/ Danishefsky 2002**

**(+)-merrilactone A/ Inoue 2003**

Scheme 40. Retrosynthetic analysis of merrilactone A.
4.2. Merrilactone A

The pentacyclic sesquiterpene dilactone merrilactone A (224), isolated from *Illicium merrilianum* in 2000, has already been the target of two total syntheses, by the Danishefsky group in 2002, and by the Inoue group a year later (Scheme 40). The Danishefsky group had envisaged a radical cyclization to form the A ring and an allyl-lactonization to form the B ring. The CD ring fragment could be formed with a ring cleavage–reclosure sequence of the Diels–Alder adduct. The Inoue group strategy called for desymmetrization of meso-diketone through an intramolecular aldol reaction. Mehta and Singh recently published their approach to the ABCD ring system of merrilactone A.

The merrilactone A synthesis by Birman and Danishefsky commences with a Diels–Alder reaction of diene 228 and dimethylmaleic anhydride (Scheme 41). After reducing the C14-carbonyl (merrilactone A numbering) regioselectively, ozonolysis effected the opening of the six-membered ring. This was followed by an aldol condensation to close the five-membered ring to give enal. Reduction of the aldehyde paved the way for the Johnson ortho ester variant of the Claisen rearrangement, which provided a 1:1.8 mixture of esters, which was subsequently hydrolyzed. Iodolactonization and chromatographic separation then gave the pure minor iodide, which was allylated to prepare for the A ring cyclization. Selenylation at C10, bromoselenylation of the terminal vinyl group and oxidative deselenylation afforded the cyclization precursor.

The first step in the Inoue group’s synthesis towards merrilactone A (Scheme 42) was a [2+2] photocycloaddition between 1,2-dichloroethene and dimethylmaleic anhydride. The side chains of the symmetrical diol were installed so that a ring-closing metathesis could be performed. This was followed by opening of the four-membered ring to give diketone through an intramolecular aldol reaction. Mehta and Singh recently published their approach to the ABCD ring system of merrilactone A.

5. Indole alkaloids

Indole alkaloids are a large group of nitrogen-containing natural products. The scope of this review covers the

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5  The Danishefsky group has recently published an enantioselective approach to intermediate (Scheme 41).
Scheme 42. (a) hν, Benzophenone, acetone, rt, 3 h; steps; (b) i. (PCy3)2Cl2Ru[CHPh, CH2Cl2, reflux, 14 h, then ii. Pb(OAc)4, rt, 95%; (c) LHMDS, THF, −78 °C, 1 h, 64% 240a, 22% 240b; (d) m-CPBA, CH2Cl2, rt, 4 h, 81%; (e) DBU, CH2Cl2, −30 °C, 1 h, 81%; (f) IBX, DMSO, rt, 30 min, 94%; (g) Br2, ethyl vinyl ether, CH2Cl2, −78 °C, 15 min, then sm, N,N-dimethylaniline, →rt, 1 day, 62%, 4:1 selectivity; (h) Bu3SnH, BEt3/O2, tol, rt, 30 min, 57% 242a, 16% 242b.

Scheme 43. Retrosynthetic analyses of 1-acetoxyaspidoidalbidine and aspidophytine.
syntheses of four of them, namely 1-acetylaspidolalbine, aspidophytine, kopsanone and lapidilectine B, because these natural products can also be classified as propellanes. They have been further divided into two groups on the basis of the similarities in their structures (Schemes 43 and 48).

5.1. 1-Acetylaspidolalbine and aspidophytine

1-Acetylaspidolalbine (244) was isolated in 1963 from *Vallesia dichotoma* Ruiz Et Pav 189 and the structure was proposed originally by Walser and Djerassi in 1964. 190 Several syntheses of the molecule have been reported in the literature, by the groups of Ban 191–193 and Overman (Scheme 43). 194 The Ban group has considerable experience in this area and confirmed the structure of 1-acetylaspidolalbine by total synthesis in 1975. 193 The route described here is the latest of their total syntheses of this compound. The Overman group’s synthesis is based on a tandem aza-Cope-Mannich process with the disconnections shown in Scheme 43.

The structure of aspidophytine (250) differs from 1-acetylaspidolalbine (244) only in the degree of unsaturation at the C16-C17 bond and at C18 and in the substitution of the aromatic ring. Aspidophytine is actually a degradation product of haplophytine (243), which was isolated from *Haplophyton cimicidum* in Mexico. 195,196 Aspidophytine has inspired two total syntheses to date by the Corey 197 and Fukuyama 198,199 groups. The retrosynthetic analyses of these syntheses (Scheme 43) show the same basic disconnections, but the order of realization is different.

The key step in the 1-acetylaspidolalbine synthesis by the Ban group is the acid-catalyzed transannular cyclization of diol 245 to the pentacyclic alcohol 257, only three steps from the natural product itself (Scheme 44). 191–193 As the ultimate step, mercury(II) acetate effects the final cyclization to give the [4.4.3]propellane structure. 200

The key ring-forming transformation in the formal total synthesis of 1-acetylaspidolalbine by the Overman group 194 is the aza-Cope rearrangement-Mannich cyclization sequence that was developed in the group (Scheme 45). 109 The treatment of aminocacetaldehyde 247 with paraformaldehyde effects an imine formation, which is followed by an aza-Cope [3,3]-sigmatropic rearrangement–Mannich cyclization under acidic conditions to provide pentacycle 258. The five following steps then conclude the synthesis of (±)-1-acetylaspidolalbine (244).

The Corey group devised the concise and convergent synthesis of aspidophytine 250 shown in Scheme 46. 197 The key transformation was an acid-catalyzed cascade cyclization of the tryptamine derivative 252 and dialdehyde 253, which forms the pentacylic core of the molecule. Then, after having hydrolyzed the pivalate of 259, potassium...
Ferricyanide effected an oxidative lactonization to the [4.4.3]propellane 260. An oxidative cleavage of the exocyclic double bond in 260 followed by enol triflate formation and treatment with tributyltin hydride provided (−)-aspidophytine (250). A Sonogashira coupling between iodoindole 255 and acetylene 256 is the first step towards forming the propellane ring system of aspidophytine in the Fukuyama group’s synthesis (Scheme 47).198,199 The coupled product was Boc protected and the triple bond was reduced selectively to olefin 254. Changing the C5 substituent to a nosylate-activated nitrogen enabled the formation of the 11-membered ring (262) once the C3-alcohol was deprotected. Removing the nosylate and exposure of the product to trifluoroacetic acid furnished the pentacycle 263 in 56% yield over two steps. Conversion of the imine of 263 into the corresponding N-methylindole derivative followed by lactone formation to close the last remaining ring provided (−)-aspidophytine (250).

5.2. Kopsanone and lapidilectine B

The kopsane alkaloids have been known since 1890,201 but their structures remained unknown until the 1960s. Two total syntheses and one formal total synthesis have been

\[\text{(-)-aspidophytine/Fukuyama 2003}\]
published for kopsanone (264), a member of this group (Scheme 48). The syntheses of the Natsume202,203 and Kuehne204 groups use the same methods to install the [4.3.3]propellane ring system, so only the earlier synthesis from the Kuehne group is discussed here in detail (see Scheme 48). The Kerr group has also published an approach towards kopsane alkaloids.205 A key step in the first published synthesis of kopsanone by Magnus et al. is the intramolecular Diels–Alder reaction of 265.206,207 The Kuehne group synthesis is based on a Diels–Alder reaction between diene 267 and phenyl vinyl sulfone.204

Scheme 48. Retrosynthetic analyses of kopsanone and lapidilectine B.

(±)-kopsanone/Magnus 1984

Scheme 49. (a) Cl₃CCH₂OCOCl, i-Pr₂NEt, PhCl. 0 → 120 °C, 40 min, then 120 °C, 8 h, 50%; steps; (b) 95–100 °C, PhH, 4 h, 81%.
Lapidilectine B (270) was isolated from *Kopsia lapidilecta* in 1992 and was synthesized by the group of Pearson (Scheme 48). The main features of the synthesis of this polycyclic indole alkaloid include a Smalley azido-enolate cyclization to form the indoxy core of the molecule.

The synthesis of the propellane moiety of kopsanone by Magnus et al. began with the treatment of the vinyl chloride 266 with trichloroethyl chloroformate and gave tetracycle 273 in 50% yield (Scheme 49). After installing the diene portion and the allylic side chain, the stage was set for the intramolecular Diels–Alder reaction of 265, which provided the [4.3.3]propellane 274 in 81% yield. Six more steps were required to finish the first total synthesis of (+)-kopsanone (264).

### (-)-lapidilectine B/Pearson 2001

Scheme 50. (a) H$_2$BO$_3$, CH$_2$Cl$_2$, reflux, 12 h, 33%; (b) BnBr, NaH, DMF, rt, 30 min, 86%; (c) m-CPBA, CH$_2$Cl$_2$, −78 °C, 79%; (d) phenyl vinyl sulfone, PhH, 100 °C, 16 h, 57%; (e) Raney-Ni, EtOH, reflux, 3 h, 67%; (f) MeOH, 210 °C, 36 h, 88%.

### (-)-annotinine/Wiesner 1967

Scheme 52. (a) Acrylic acid, 135 °C, 2 h, 63%; (b) allene, hv, −70 °C, 20 h, 54%.
In the Kuehne group synthesis of kopsanone (Scheme 50), the key pentacyclic intermediate 276 came from an adaptation of a biomimetic secodine cyclization that they had investigated extensively. Benzoylation of the indole nitrogen and oxidative elimination of the selenyl group afforded N-oxide 267, which was ready for the Diels–Alder cyclization. Heating of diene 267 with phenyl vinyl sulfone effected the formation of hexacycle 277 after reduction of the double bond and the sulfone with Raney nickel. Finally, heating of ester 277 to 210 °C for 36 h provided (+)-kopsanone (264).

Treatment of azide 272 with potassium hydroxide is the first ring-forming step in the lapidilectine B synthesis by Pearson et al. (Scheme 51). The Smalley cyclization provided an indole derivative that was then protected at the nitrogen and dihydroxylated to give diol 278 in a 6:1 selectivity. Allylation of the ketone followed by oxidative cleavage of the diol and treatment with camphorsulfonic acid furnished methyl acetal 279. After closing the pyrroline ring with a cycloaddition (see Scheme 48), mesylate 280 was ready for the final eight-membered ring closure. Removing the Teoc-group from the pyrroline nitrogen and treatment of the remaining salt with diisopropylethylamine provided (+)-lapidilectine B (270).

Scheme 53. (a) MeNH2, CaO, PhH, 100–110 °C, 7 days, 69%; (b) MVK, rt, 1 h, then AcOH, 40 → −78 °C, evacuated to 125 mmHg, −70 °C, 5 h, 20%; (c) MVK, NaOH, MeOH, reflux, 45 min; (d) Na, EtOH, reflux, 4 h, 50% over two steps; (e) Bu3SnH, AIBN, PhH, 80 °C, 10 h; (f) K2CO3, MeOH, THF, H2O, rt, overnight, 56% over two steps; (g) NaH, MOMCl, THF, reflux, 15 h, 99%; (h) NaOMe, Br2, MeOH, THF, −78 °C, 1 h, → reflux, 1 h, 93% over two steps; (i) LiAlH4, THF, reflux, 22 h, 99%; (k) (COCl)2, DMSO, CH2Cl2, −78 → 10 °C, 1 h, then Et3N, −10 °C → rt, 30 min, 85%; (l) KH, 18-crown-6, DMF, 0 °C → rt, 30 min, then MeI, rt, 15 h, 65%; (m) p-TsOH, acetone, H2O, 60 °C, 39 h, 97%.
6. Other alkaloids

Other than the indole alkaloids covered in Section 5, the syntheses of four additional alkaloids with the propellane ring structure have appeared in the literature. Two of these, namely cepharamine and metaphamine, share a common ring structure called the hasubanan skeleton and will be discussed together in Section 6.2. Three research groups have reported on their synthetic efforts towards the hasubanan skeleton and these will also be briefly discussed in the same Section.

6.1. Annotinine

The same research group that reported the total synthesis of the Lycopodium alkaloid annotinine (284) in 1967\textsuperscript{212–215} deduced the structure of the molecule during the years 1956–1957 (Scheme 52).\textsuperscript{216} Their synthesis starts with a condensation of acrylic acid and vinylogous amide \(281\) to provide the \([2\text{\,+\,2}]\) photochemical cycloaddition substrate \(282\). The cycloaddition of \(282\) with allene proceeded smoothly to give the ABCD ring system of annotinine \((283)\). Several more steps, including an optical resolution, were required to finish the synthesis of \((-)\)-annotinine \((284)\).

6.2. Cepharamine and the hasubanan skeleton

Three total syntheses of cepharamine \((290)\), an alkaloid isolated from \textit{Stephania cepharantha} Hayata in 1966, have been published (Scheme 53).\textsuperscript{217} The Ibuka group published the first total synthesis in 1969,\textsuperscript{218,219} then the Tahk group published in 1970\textsuperscript{220} and Schultz in 1998.\textsuperscript{221} Ibuka et al. have also published a synthesis of methaphanine \((285)\)\textsuperscript{222,223} and hasubanonine \((286)\)\textsuperscript{224,225} but, since these syntheses use the same methodology to form the \([4.3.3]\)propellane ring system as in their synthesis of cepharamine, they will not be discussed here in more detail.

In the Ibuka group synthesis of cepharamine \((290)\) (Scheme 53),\textsuperscript{218,219} the key ring-forming step was the formation of the CD ring system. Exposure of nitrile \(291\) to methyl vinyl ketone (MVK) followed by treatment with sodium ethoxide provided ketoamide \(292\) in 50\% yield.

In the formal total synthesis of cepharamine by the Tahk group (Scheme 53),\textsuperscript{220} the CD ring system was formed by treatment of cyclopropyl ketone \(287\) with methylamine to afford the ring expansion product \(288\). Annulation with methyl vinyl ketone then completed the ring system of cepharamine \((289)\).

The Schultz group strategy for the synthesis of cepharamine differs significantly from the previous syntheses (Scheme 53).\textsuperscript{221} The key step in their synthesis was a radical cyclization of \(293\) followed by hydrolysis of the formate ester to give the ABC ring fragment \(294\). After an MOM protection and a Hofmann-type rearrangement to transform the five-membered lactone into a six-membered lactam ring,

\[
\text{(\pm)-hasubanan skeleton/Evans 1972}
\]

\[
\begin{align*}
\text{296} & \quad \text{PhSO} \quad \text{a} \quad \text{297} & \quad \text{MeN} \quad \text{b} \quad \text{298} & \quad \text{299}
\end{align*}
\]

\[
\text{(\pm)-hasubanan skeleton/Bruderer et al. 1977}
\]

\[
\begin{align*}
\text{300} & \quad \text{EtO}_2\text{C} \quad \text{c, d} \quad \text{301} & \quad \text{H} \quad \text{CO}_2\text{Et} \quad \text{e} \quad \text{302} & \quad \text{HN} \quad \text{303}
\end{align*}
\]

\[
\text{(\pm)-hasubanan skeleton/Mulzer 1998}
\]

\[
\begin{align*}
\text{304} & \quad \text{f} \quad \text{305} & \quad \text{g} \quad \text{306}
\end{align*}
\]

Scheme 54. (a) MeCN, 70 °C, 24 h; (b) Na\textsubscript{2}S\textsubscript{9}H\textsubscript{2}O, MeOH, 65 °C, 8 h; (c) PCl\textsubscript{3}, pyr, reflux, 5 h; (d) NH\textsubscript{3}, Raney-Ni, H\textsubscript{2}, EtOH, 80 °C, 38% over two steps; (e) HCl, H\textsubscript{2}O, reflux, 1 h, 83%; (f) PhH, reflux, 1 h, 76%; (g) pyr, reflux, 5 h, 73\%.
treatment with lithium aluminium hydride provided alcohol 295. This alcohol was then transformed into (C)-cepharamine ((C)-290), the unnatural enantiomer of the molecule, in three steps.

The synthetic efforts towards the hasubanan skeleton are summarized in Scheme 54. The key transformation in the Evans group approach is a Diels–Alder reaction between tetrahydrobenzindole 296 and sulfoxide 297 to give tetracycle 298. Bruderer et al. used a dehydration to achieve the closure of the five-membered pyrroline ring (300/301). An acid-catalyzed cyclization then furnished tetracycle 302. The latest synthesis of the hasubanan skeleton by the Mulzer group features an intramolecular 1,3-dipolar cycloaddition of 304 followed by a subsequent elimination of N₂ to give aminoenone 306.

6.3. Bathrachotoxinin A

Bathrachotoxinin A (312) is a unique steroidal alkaloid that possesses several interesting structural features. It has been synthesized partially from steroid precursors by Wehrli and co-workers. A total synthesis was published by the Kishi group in 1998 (Scheme 55). The synthesis features an exo-selective intramolecular Diels–Alder reaction (step a) and an oxy-Michael addition (step d).

7. Summary

The syntheses of propellane-containing natural products have been reviewed with the emphasis being on natural products, which contain a three-membered ring as part of the propellane structure. Propellanes are a well-established structural motif that can be found in diverse natural products. This makes their total synthesis a challenging task, because no generally applicable method can be utilized in the syntheses. However, the Diels–Alder reaction arises as one of the more commonly applied ring-forming reactions among these syntheses.

For the cyclopropane ring-containing natural products described here, only two different methods for the formation of the cyclopropane ring have been applied. Potential new avenues for synthesizing [m,n,1]propellane-containing natural products could involve both inter- and intramolecular cyclopropanation reactions.

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References and notes

Biographical sketch

Ainoliisa J. Pihko was born in 1976 in Oulu, Finland. She graduated with M.Sc. in organic chemistry from University of Oulu in 1999 before moving to the Scripps Research Institute in La Jolla, California, to start her graduate studies with Professor Nicolaou. In 2001, she moved to Helsinki University of Technology, Finland, to continue her graduate studies under the supervision of Professor Ari Koskinen and received her PhD in May 2005. Her research focused on total synthesis of natural products, namely callipeltoside and the cneorins.

Professor Ari M. P. Koskinen was born in Hyvinkää, Finland in 1956. He received his Doctor of Technology in 1983. After postdoctoral studies at the University of California, Berkeley, he joined the University of Surrey, England, as a lecturer in 1989. He moved to the University of Oulu, Finland in 1992 as Professor of Chemistry, and transferred to his current position at the Helsinki University of Technology in August, 1999 as Professor of Organic Chemistry. Professor Koskinen is a member of the Finnish Academy of Sciences and Letters since 2003, and member of the Novartis Foundation International Scientific Advisory Panel since 2004.