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Syntesis of propellane-containing natural products

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Synthesis of propellane-containing natural products

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Keywords: Total synthesis; Natural products; Propellanes.

1. Propellanes and their synthesis

The first propellanes were synthesized in the 1930s during investigations into the Diels–Alder reaction.^{1–6} However, the first ‘propellane by design’ was synthesized much later, in 1965.^{7,8} Their nomenclature was introduced shortly thereafter. In 1966, Bloomfield and Irelan reported a synthesis of [4.4.2]propellane (**1**) and used the term propellerane in this context,⁹ but the editors did not accept this nomenclature¹⁰ 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.¹¹

Webster’s Unabridged Dictionary defines a propeller as ‘a device having a revolving hub with radiating blades’¹² 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 (Fig. 1).¹¹

The first synthesis of a small-ring propellane, [3.2.1]propellane, was published in 1968.¹³ 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.^{14,15} 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.¹⁶ 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.^{17–19} Some groups have questioned the existence of the central bond,^{14,15,17,20,21} but Wiberg, Bader, and Lau argue cogently that the bond definitely exists between the bridgehead carbons with a bond order of 0.73.^{22,23} The controversy regarding the central bond revolves around differing explanations of similar experimental facts and theoretical results of the nature of the bonding interaction. In addition to Wiberg’s results, other theories have also been suggested.^{18,24–27}

Ginsburg^{28–30} and Wiberg^{19,31,32} have reviewed the syntheses and the theoretical studies of propellanes extensively, Wiberg concentrating on the small-ring propellanes and Ginsburg on the medium-sized rings. In his book entitled ‘Propellanes’, Ginsburg even describes the

syntheses and structures of natural products possessing the propellane structure.³³

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.

Figure 2. Natural products, which contain a propellane ring system.

By far, one of the most popular avenues to synthesize any ring system has been the venerable Diels–Alder reaction.³⁴ This has also been the case with propellane ring structures. If the ~20 syntheses of modhephene (**5**), a [3.3.3]propellane, are disregarded because the molecule consists of five-membered rings (see Fig. 2), half of the syntheses analyzed here have utilized the Diels–Alder reaction as one of the key ring-forming transformations. The following sections describe the syntheses of natural products, which contain a propellane ring system. The literature until the beginning of 2005 is covered.

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 sterepolide

Marasmic acid (**3**) and sterepolide (**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

General structure of propellanes

Numbering of [4.3.1]propellane

[1.1.1]propellane (**2**)

Figure 1. Propellanes.

(±)-marasmic acid/Woodward 1976

(±)-marasmic acid/Boeckman 1980

(±)-marasmic acid/Tobe* 1990

Scheme 1. Retrosynthetic analysis of marasmic acid.

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*.^{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^{37–39} and Boeckmann,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.⁴¹

Woodward group's synthesis of (±)-marasmic acid (Scheme 2)^{37–39} commences with a completely *endo*-selective Diels–Alder reaction of diene 9 and 2-(bromomethyl)maleic anhydride (8), yielding a mixture

(±)-marasmic acid/Woodward 1976

Scheme 2. (a) 8, CH_2Cl_2 , rt, 36 h, 16a:16b 1:1; (b) isobutylene, *p*-TsOH, CH_2Cl_2 , rt, 4 days; (c) *t*-BuOK, *t*-BuOH, PhH, rt, 10 min, 44% over three steps; (d) DIBAL-H, tol, -78°C , 4 h; (e) NaBH_4 , MeOH, rt, 15 min, 65% over two steps; (f) phosgene, quinoline, Et_2O , $0^\circ\text{C} \rightarrow \text{rt}$, 30 min, 91%; (g) DMSO, 15°C , 25 min, then Et_3N , 15°C , 20 min, 25%; (h) TFA, PhH, rt, 30 min, 50%.

(±)-marasmic acid/Boeckman 1980

Scheme 3. (a) NaH, **20**, DMF, $-5 \rightarrow 0^\circ\text{C}$, 30 min; (b) toluene, 200°C , 30 min, 92%, **11**:**21** 1:1; (c) *t*-BuOK, Et₂O, 0°C , 30 min, quant.; (d) cat. *p*-TsOH, MeOH, 65°C , 12 h, quant.; (e) MsCl, Et₃N, CH₂Cl₂, -5°C , 30 min; (f) DBU, THF, 65°C , 8 h, >90% over two steps; (g) PhSeBr, MeOH, rt, 2 h, 92%; (h) DIBAL-H, toluene/THF 1:1, -78°C , 12 h; (i) *m*-CPBA, CH₂Cl₂, $-78^\circ\text{C} \rightarrow \text{rt}$, 4.5 h, 77% over two steps; (j) BBr₃, CH₂Cl₂, $-20 \rightarrow 0^\circ\text{C}$, 4.5 h, 50%; [(k) ³⁶ *p*-TsOH, isopropenyl acetate, reflux, 5 h; (l) ³⁶ AcOH, HCl, H₂O, 'cold', 24 h, reactions not performed].

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 oxidized⁴² 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).⁴⁰ 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

(±)-marasmic acid/Tobe* 1990

Scheme 4. (a) *hν*, allene, CH₂Cl₂, -78°C , 3 h, 73%, 91% selectivity; (b) NaBH₄, MeOH, rt, 4 h, 98%; (c) *m*-CPBA, Na₂HPO₄, CH₂Cl₂, 0°C , 89%; (d) H₂SO₄, CH₂Cl₂, 80%; (e) NaBH₄, THF/MeOH 1:2, rt, overnight, 9:1 selectivity; (f) MsCl, pyr, DMF, 80°C , 1 h, 87% over two steps; (g) NaOH, H₂O, MeOH, reflux, overnight, 92%; (h) TBHP, SeO₂, CH₂Cl₂, rt, overnight; (i) (COCl)₂, DMSO, CH₂Cl₂, -60°C , 10 min, then Et₃N, 15 min $\rightarrow$ rt, 19% over two steps; [(j) ⁴⁰ BBr₃, CH₂Cl₂, $-20 \rightarrow 0^\circ\text{C}$, 4.5 h, reaction not performed, formal total synthesis].

(-)-sterepolide/Trost 1985/1989

(±)-norsterepolide/Arai 1985

Scheme 5. Retrosynthetic analysis of sterepolide.

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 BBr_3 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).⁴³ To utilize this rearrangement in the synthesis of marasmic acid,⁴¹ 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 C_{14} . Allylic oxidation⁴⁴ 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. Sterepolide. Two different syntheses have been reported for the pentacyclic framework of sterepolide (**4**), a metabolite of the fungus *Stereum purpureum* (Scheme 5).⁴⁵

(-)-sterepolide/Trost 1985/1989

Scheme 6. (a) LiAlH_4 /Darvon alcohol complex, Et_2O , -100°C , quant., >98% ee; (b) NaH, PMBBBr, cat. Bu_4NI , THF, rt, 82%; (c) 5% $\text{Pd}(\text{OAc})_2$, 10% **38**, PhH, 70°C , 81%; (d) **8**, PhH, 80°C ; (e) DBU, PhH, rt, 81% over two steps; (f) TBAF, THF, rt; (g) disiamylborane, Et_2O , $0^\circ\text{C} \rightarrow \text{rt}$, 75%; (h) DDQ, CH_2Cl_2 , H_2O , then PDC, 3 Å MS, CH_2Cl_2 , 83%.

Trost and co-workers have reported a racemic⁴⁶ and an asymmetric⁴⁷ 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 LiAlH₄/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 C₁ that has been employed as a stereochemical control element throughout the synthesis.

Arai and co-workers' synthesis⁴⁸ 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 electrocyclic cyclization.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 (±)-norsterepolide (**32**). Attempts were made to introduce the *gem*-dimethyl groups at C₁₁, but they proved unsuccessful.

2.2. Epoxides: frenolicin B, dynemicin A, fusicogigantone A, SF 2315B, diepoxin σ 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 diepoxin σ, 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

Figure 3. Biogenetic origin of marasmic acid and sterepolide.

Scheme 7. (a) PhH, rt, 72 h, 72%, **34a:34b** 4.5:1; (b) CH₂N₂, MeOH, Et₂O, quant.; (c) *t*-BuOK, *t*-BuOH, PhH, rt, 1 h, 90%; (d) *m*-CPBA, cat. bis-(3-*t*-Bu-4-hydroxy-5-methylphenyl) sulfide, NaHCO₃, CHCl₃, reflux, 6 h, α:58%, β:16%; (e) 48% HBr, CHCl₃, 0 °C → rt, 1 h, α-OH and β-Br: 80%, α-Br and β-OH: 70%; (f) Jones reagent, acetone, rt, 6 h; (g) Zn, AcOH, rt, 15 h; (h) **43**, BuLi, –70 → –30 °C, 1 h, then sm, –78 °C, 1 h; (i) *p*-TsOH, MeOH, rt, 48 h; 47% over two steps; (j) P₂O₅, MsOH, rt, 2.5 h, 34%; (k) ethylene glycol, PPTS, PhH, reflux, 5 h, 93%; (l) DIBAL-H, THF, –90 °C, 30 min, 84%; (m) *p*-TsOH, PhH, 55 °C, 7 h, 85%.

(±)-frenolicin/Ichihara 1980

Scheme 8. Retrosynthetic analysis of frenolicin B.

form the carbon backbone of the molecule. Once the rings are in place, the epoxidations generally proceed stereoselectively and give good yields of the products.

2.2.1. Frenolicin B. Frenolicin B (46), a pyranonaphthoquinone antibiotic isolated from *Streptomyces fradiae* in 1960,^{50,51} has been synthesized⁵² only once, although six syntheses for deoxyfrenolicin (47) have been reported. Since those syntheses, by Naruta and co-workers,⁵³ Semmelhack et al.,^{54–56} Uno,⁵⁷ Kraus et al.,⁵⁸ Moore and

co-workers,^{59,60} Brimble and Lynds,⁶¹ as well as Xu et al.,⁶² 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

Scheme 9. (a) BF_3 , PhH or CHCl_3 , 55 °C, 97%; (b) NaBH_4 , THF, 5 °C, quant.; (c) 2,2-dimethoxypropane, acetone, $\text{BF}_3 \cdot \text{OEt}_2$, 70%; (d) LiAlH_4 , Et_2O , 97%; (e) OsO_4 , NaIO_4 , *t*-BuOH, H_2O ; (f) NaOAc , DABCO, 99% over two steps, (g) *n*-PrMgBr, Et_2O , 66%; (h) **55**, *n*-BuLi, DMSO, rt, 2 h, 61%; (i) PCC, CH_2Cl_2 , rt, 98%; (j) DDQ, TsOH, MeOH, reflux, 9 h, then dioxane, reflux, 12 h; (k) KOH, MeOH, H_2O ; (l) TBHP, triton B, dioxane, EtOH, rt, α : β 1:1; (m) CH_2N_2 , then separation of diastereomers; (n) KOH, MeOH, H_2O , rt.

reaction of juglone (**51**) and acetoxybutadiene (**50**), which gives the tricyclic acetate **52** in excellent yield (Scheme 9).⁶³ 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

Figure 4. Conformations of alkene **47**.

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 *Microspora chersina*,^{64,65} 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,^{66–69} Myers^{70,71} and Danishefsky^{72–77} will be treated here with more detail. The groups of Nicolaou,^{78–81} Isobe,^{82–84} Magnus,⁸⁵ Maier,⁸⁶ and Takahashi^{87,88} 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.⁸⁹

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

(+)-dynemicin A/Myers 1995

(±)-dynemicin A/Danishefsky 1995

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**, ClCO₂Me, THF; (c) TBAF, THF, 60% over two steps; (d) **72**, Pd(PPh₃)₄, CuI, 20%; (e) LiOH, H₂O, THF, 65%; (f) Bromo-tris-pyrrolidino-phosphonium hexafluoro-phosphate (PyBroP), Et₃N, CH₂Cl₂, rt, 13 h, 51%; (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.

(+)-dynamycin A/Myers 1995

Scheme 13. (a) *t*-BuOK, *t*-BuOH, reflux, 3.5 h, 36% after recryst, 1:1 diastereoselectivity; (b) CSA, MeOH, rt, 12 h, 71%, 4:1 regioselectivity; (c) NaH, Et₂O, rt, 5 h, then Tf₂O, $-78 \rightarrow 0^\circ\text{C}$, 30 min, 95%; (d) **76**, Pd(PPh₃)₄, NaCO₃, *p*-dioxane, reflux, 45 min, 90%; (e) 4-ClPhOH, 180 $^\circ\text{C}$, 30 min, 84%; *steps*; (f) *m*-CPBA, pH 7 buffer, CH₂Cl₂, 0 $^\circ\text{C}$, 19 h, 88%; (g) TBAF, THF, 0 $^\circ\text{C}$, 15 min, quant.; (h) TBSCl, imid., DMF, rt, 1 h, 96%; (i) (COCl)₂, DMSO, CH₂Cl₂, -40°C , 10 h, then Et₃N, $-78 \rightarrow 0^\circ\text{C}$, 30 min, 92%; (j) KHMDS, CeCl₃, THF, -78°C , 5 min, 94%; *steps*; (k) **63**, THF, $-20 \rightarrow 55^\circ\text{C}$, 5 min; (l) MnO₂, 3HF·Et₃N, THF, rt, 9 min, 40% over two steps.

Retrosynthetic analyses of the dynamycin A syntheses are shown in [Schemes 10 and 11](#). All of the groups have accessed the final compound via fairly similar ABC ring structures (**61**, **65**, and **68**), 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 dynamycin 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 **70** with vinylstannane **73** followed by a 1,2-addition of acetylide **71** to the resulting pyridinium salt provided a diyne. Silyl deprotection gave an acetylide that was then coupled with vinyl bromide **72**. After ester hydrolysis, the IMDA substrate **69** was exposed to Yamaguchi macrolactonization conditions, effecting the macrocyclization, and, subsequently, the intramolecular Diels–Alder reaction to give lactone **61** 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 **82** stereoselectively after deprotection of the carbamate nitrogen with DBU. Finally, the secondary alcohol was oxidized with ceric ammonium nitrate to give (±)-di-*O*-methyl dynamycin A methyl ester (**58**).

The total synthesis of dynamycin A by Myers and co-workers starts with the construction of the A ring ([Scheme 13](#)).^{70,71} Condensation of menthyl acetoacetate (**83**) and *trans*-ethyl crotonate (**84**) provided a 36% yield of the correct β-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 **77**. Suzuki cross-coupling of enol triflate **77** with arylboronic acid **76** in the presence of tetrakis(triphenylphosphine)palladium and sodium carbonate afforded the AC ring structure **85** in 90% yield. Next, heating the carbamate **85** in 4-chlorophenol 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 **74** was ready to be epoxidized. Initially, the Myers group tried to close the enediyne bridge with various

(±)-dynamycin A/Danishefsky 1995

Scheme 14. (a) ZnCl_2 , CH_2Cl_2 , rt, 3 days, 60%, *endo:exo* 20:1; (b) CAN, MeCN, H_2O , 0 °C, 30 min, 90%; (c) NH_4OAc , AcOH, 100 °C, 1 h, 89%; (d) TBSCl, imid., CH_2Cl_2 , 0 °C, 2 h, 98%; steps; (e) *m*-CPBA, CH_2Cl_2 , rt, 8.5 h, 87%; (f) cat. AgNO_3 , NIS, THF, rt, 3.5 h, 91%; (g) **90**, $\text{Pd}(\text{PPh}_3)_4$, DMF, 75 °C, 1.2 h, 81%; steps; (h) LiHMDS, **66**, THF, 0 °C, 35 min, then **67**, 0 °C, 35 min; (i) $\text{PhI}(\text{OCOCF}_3)_2$, THF, 0 °C, 5 min; (j) air, daylight, THF, high concentration, 20 h; (k) MgBr_2 , Et_2O , 0 °C $\rightarrow$ rt, 12 h, 15% over four steps.

electrophiles at C_7 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 C_7 provided the cyclization precursor. Indeed, deprotonation of the acetylene caused the enediyne bridge to attack the ketone at C_7 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 **64** and isobenzofuran **63** proceeded in 5 min to give the di-TMS-ether, which was immediately oxidized with manganese dioxide to provide (+)-dynamycin A (**62**) in 40% yield over two steps.

Danishefsky and co-workers also decided to begin the construction of dynamycin 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 $\text{Pd}(\text{PPh}_3)_4$ 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 C_5 , quinone imine **67** was ready to react with the anion of anhydride **66** to form the remaining rings of dynamycin A. The adduct was immediately oxidized with $\text{PhI}(\text{OCOCF}_3)_2$. 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 (±)-dynamycin A (**62**) in 15% yield over the last four steps.

The synthesis of dynamycin A model compounds by Nicolaou and co-workers^{78–81} is based on functionalizing quinoline derivative **91** (Scheme 15).^{90,91} 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*

(±)-dynemicin A model/Nicolaou 1990

(±)-dynemicin A model/Takahashi 1995

Scheme 15. Retrosynthetic analyses of dynemicin A model compounds.

gigantea collected from East Malaysia in 1990.⁹² 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.^{93,94}

Optically active enal **106** and allyl chloride **107** were mixed with chromium dichloride to obtain alcohol **108** in good yield (Scheme 17). Next, the double bond in **108** 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 dialdehyde **105** was treated with titanium tetrachloride in the presence of zinc to obtain the cyclized α -cis-diol **109** in 38% yield together with the β -cis-diol in 7% yield. The diol was removed by orthoformate formation and subsequent reductive elimination.^{95,96} The C_{8–9} double bond in **110** was hydrogenated to give a mixture of C_{2–6} and C_{2–3} double-bond-containing compounds. This mixture was treated with singlet oxygen generated by means of Rose Bengal photosensitization, followed by reduction with triphenylphosphine and dehydration with silica gel to obtain a 2:3 mixture of **104a** and **104b**. Oxidation of this mixture with singlet oxygen generated with tetraphenylporphyrin at -78°C gave a mixture of **111a** and **111b** (observed by NMR), which were only stable below 0°C . This mixture

was left to stand at room temperature for 10 h, and **111a** 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 $^1\text{O}_2$ had occurred exclusively from the α -side of the dienes in **104a** and **104b**.

2.2.4. SF 2315B. Sulikowski and co-workers have reported a synthetic route^{97,98} to the ring system of SF 2315B (**120**), an angucyclinone antibiotic isolated from a soil micro-organism of the *Actinomycete* strain *Excelllospora viridilutea*.^{99,100} 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 **115** started with a highly regioselective Diels–Alder cycloaddition between 2-bromo-acetoxyjuglone (**119**) and diene **118** (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.

(+)-fusicogigantone A/Takeshita 1994

Scheme 16. Retrosynthetic analysis of fusicogigantone A.

(+)-fusicogigantone A and (+)-fusicogigantepoxide/Takeshita 1994

Scheme 17. (a) CrCl_2 , LiAlH_4 , DMF/THF 2:1, *i*-PrOH, 90%; (b) $\text{Me}_2\text{CHCMe}_2\text{BH}_2$, H_2O_2 , $^- \text{OH}$, 88%; (c) H_2 , Pd/C , 82%; (d) HCl , THF , 99%; (e) Li , EtNH_2 , 68%; (f) $(\text{COCl})_2$, DMSO , Et_3N , 74%; (g) TiCl_4 , Zn , PhH/THF 5:1, α -*cis* 38%, β -*cis* 7%; (h) $\text{CH}(\text{OMe})_3$, PPTS , CH_2Cl_2 , 93%; (i) Δ , Ac_2O , tol , 82%; (j) H_2 , Pd/C , EtOH , EtOAc , 99%; (k) $^1\text{O}_2$; (l) PPh_3 , silica , 90%, **104a:104b** 2:3; (m) $^1\text{O}_2$, tol , $-78^\circ\text{C} \rightarrow \text{rt}/60^\circ\text{C}$, **103** 23%, **112** 12%, **113** 8%, **114** 8%.

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

($\pm$)-SF 2315B ring system/Sulikowski 1995

Scheme 18. Retrosynthetic analysis of SF 2315B ring system.

(±)-SF 2315B ring system/Sulikowski 1995

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%, **122** 16%, **117** 20%; (d) H₂, PtO₂, 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%.

(+)-diepoxin σ /Wipf 1999/2000

Scheme 20. Retrosynthetic analysis of diepoxin σ .

(+)-diepoxin σ /Wipf 1999/2000

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 22. Retrosynthetic analysis of arthrinone.

(Scheme 21) was the protection of the reactive double bond in **126** as a Diels–Alder adduct with cyclopentadiene.^{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 σ , 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 $\text{PhI}(\text{OAc})_2$ 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 *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 σ (**123**) in 73% yield over two steps.

2.2.6. Arthrinone. Arthrinone (**132**) is an antifungal metabolite, which was isolated from *Artrinium* sp. FA 1744 in 1994.¹⁰⁵ Its only total synthesis was reported in 2000 by Uchiyama and co-workers (Scheme 22).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 23.¹⁰⁶ 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,

(±)-arthrinone/Uchiyama 2000

Scheme 23. (a) i. **137**, 160 °C, ii. THF, 5% HCl, rt, 81%; (b) TIPSCl, imid., DMF, rt, quant.; (c) NaHMDS, THF, −78 °C; (d) NaH, THF, 0 °C, then PhSCl, 87% over two steps; (e) $\text{Zn}(\text{BH}_4)_2$, CH_2Cl_2 , 0 °C, 83%; (f) *m*-CPBA, CH_2Cl_2 , 0 °C, 90%, 9:1 selectivity; (g) $\text{P}(\text{OMe})_3$, toluene, reflux, 89% from major sulfide, 76% from minor; (h) DIBAL-H, CH_2Cl_2 , −78 °C; (i) NaBH_4 , MeOH, 0 °C, 77% over two steps; (j) *m*-CPBA, CH_2Cl_2 , pH 7.9 phosphate buffer, 0 °C → rt, 72%; (k) TBSOTf, pyr, THF, −60 °C, 78%; (l) TBDPSCl, imid., DMF, rt, 91%; (m) 5% NaOH in EtOH, THF, rt, 61%; (n) MnO_2 , acetone, rt, 91%; (o) cat. TPAP, NMO, 4 Å MS, CH_2Cl_2 , rt; (p) TBAF, AcOH, THF, rt, 73% over two steps.

(±)-bukittinggine/Heathcock 1992

Scheme 24. Retrosynthetic analysis of bukittinggine.

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 α,β -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

(±)-bukittinggine/Heathcock 1992

Scheme 25. (a) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , 15 min, then Et_3N , $-78 \rightarrow 0^\circ\text{C}$, 1 h, then $\text{NH}_3(\text{g})$, $0^\circ\text{C} \rightarrow \text{rt}$, 45 min; (b) NH_4OAc , AcOH, 30 min, rt, then 75°C , 2 h, 76% from **143**; (c) $(\text{CF}_3\text{CO}_2)_2\text{Pd}$, PPh_3 , *p*-benzoquinone, MeCN, 24 h, rt, 70%; (d) $\text{BH}_3 \cdot \text{THF}$, THF, $0^\circ\text{C} \rightarrow \text{rt}$, 2 h, then $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$, H_2O , 3 h, rt; (e) *p*-TsCl, DMAP, pyr, CHCl_3 , $0^\circ\text{C} \rightarrow \text{rt}$, 46 h; (f) LiEt_3BH , THF, $0^\circ\text{C} \rightarrow \text{rt}$, 4 h, then $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$, H_2O , $0^\circ\text{C} \rightarrow \text{rt}$, 2.5 h; (g) Na, NH_3 , THF, -78°C , 20 min; (h) Ag_2CO_3 on Celite[®], PhH, reflux, 5 h; 52% over five steps.

that the cyclization proceeds through a concerted, but asynchronous, Diels–Alder reaction.^{110,111} Next, the pentacyclic amine **142** was treated with palladium triflate to cyclize the sixth ring of the molecule. The following sequence reduced the exocyclic double bond in **141** stereoselectively (>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 **144**, which was ready for the final cyclization. Finally, oxidation of the diol with Fetizon's reagent provided (±)-bukittinggine (**140**) as the sole product.

3.2. Colombiasin A

Colombiasin A (**145**), a diterpene isolated from the gorgonian octacoral *Pseudopterogorgia elisabethae*,¹¹² has attracted the interest of the synthetic community with its novel and challenging molecular framework. To date, three total syntheses, from the Nicolaou,^{113,114} Rychnovsky,¹¹⁵ and Harrowven^{116,117} groups, have been published (Scheme 26). In addition, an approach to this complex ring system has appeared in the literature (Scheme 30).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 C₇ 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).^{113,114} The reaction between diene **148** and quinone **149** in the presence of [(*S*)-BINOL-TiCl₂] provided the Diels–Alder adduct **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 C₁₄ (colombiasin A

Scheme 26. Retrosynthetic analysis of colombiasin A.

(-)-colombiasin A, Nicolaou 2001

Scheme 27. (a) [(*S*)-BINOL-TiCl₂], tol, -60 → -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; *steps*; (d) tol (sealed tube), 180 °C, 20 min, 89%, 100% selectivity; (e) NaH, THF/CS₂/MeI 4:1:1, 50 °C, 3 h, 95%; (f) AIBN, Bu₃SnH, tol, 110 °C, 30 min, 77%; (g) BBr₃, *cis*-cyclooctene, CH₂Cl₂, -78 °C, 43% based on 70% conversion.

(-)-colombiasin A, Rychnovsky 2003

Scheme 28. (a) 5 M LiClO₄, Et₂O, rt, 24 h, 75%, **151:151'** 1.7:1; *steps*; (b) tol, 180 °C, 83%; (c) AlCl₃, PhNMe₂, CH₂Cl₂, 0 °C → rt, 73%; (d) separation of diastereomers.

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**).

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).¹¹⁵ 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 paper¹¹⁴ in Scheme 9; the transition states TS_a and TS_b provide the enantiomers of compounds **8** and **8'**. (Personal communication with Prof. G. Vassilikogiannakis.).

(-)-colombiasin A, Harrowven 2005

Scheme 29. (a) Trisylhydrazine, **155**, THF, rt, 2 h, then *n*-BuLi, -78°C , then **156**, -20°C , 36%; (b) i. MW, THF, 110°C , then ii. air, rt, 80%; (c) tol, 150°C , 61%; (d) $\text{BF}_3 \cdot \text{OEt}_2$, 0°C , 78%.

installing the C₃-methyl and the diene required for the IMDA, compound **150** was ready for cyclization. The final cyclization of diene **150** (and **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 (**145**).

In the Harrowven group's synthesis of colombiasin A (Scheme 29),¹¹⁶ the crucial intermediate **154** for the Moore reaction^{119–121} was obtained from a Shapiro coupling between ketone **155** and diketone **156**. After some experimentation, it was found that an in situ formation of a trisylhydrazone from ketone **155**, which could then be treated with *n*-butyllithium and diketone **156**, was the best way to obtain the Moore substrate **154**. Heating **154** to 110°C in a microwave effected the formation of the Diels–Alder substrate **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, trifluoroborane-etherate deprotected the alcohol to give (–)-colombiasin A (**145**).

The research group of Flynn¹¹⁸ 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 **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 (**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 *Isocoma wrightii* by Zalkov et al.^{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.¹²⁴ There have also been two accounts of approaches towards modhephene.^{125,126}

(±)-colombiasin A model/Flynn 2003

Scheme 30. Retrosynthetic analysis of a colombiasin A model study.

* formal total synthesis, RR = rearrangement

Scheme 31. Classification of different approaches towards modhephene by key reaction.

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).^{127,128} They utilized Cargill's work on acid-catalyzed rearrangements of β,γ -unsaturated ketones¹²⁹ to perform the key ring-forming step, namely **163** $\rightarrow$ **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**)¹³⁰ relying on a phosphorus pentoxide–methanesulfonic acid-catalyzed rearrangement (**166** $\rightarrow$ **167**).¹³¹ Catalytic hydrogenation was used to obtain

modhephene by acid-catalyzed rearrangement (= ACRR)

($\pm$)-modhephene/Smith 1981

($\pm$)-modhephene/Mundy* 1984

($\pm$)-modhephene/Tobe* 1984

($\pm$)-modhephene/Fitjer 1988

Scheme 32. (a) *p*-TsOH, PhH, reflux, 4 h, 64%, α -Me: β -Me 57:43; (b) MeLi, THF, rt, overnight, 80%; (c) MsOH, P₂O₅, 85 °C, 44 h, 22%; (d) allene, CH₂Cl₂, –78 °C, 94%, 4.5:1 selectivity; (e) LiBr, HMPA, PhH, 60 °C, 86%, 10:1 selectivity. (f) *p*-TsOH, PhH, 70 °C, 20 min, 34%.

modhephene by thermal rearrangement (= *thermal RR*)

(±)-modhephene/Dreiding 1980

(±)-modhephene/Paquette 1981 and (-)-modhephene/Mash* 1988

(±)-modhephene/Oppolzer* 1981

Scheme 33. (a) 620 °C, 14 Torr, 1 h, 95%, 2:1:1 mixture of products; (b) decalin, 360 °C, 4 h, 85%; (c) toluene, 250 °C, 16 h, 76%; (d) H₂, Pd/C, EtOH, rt, 12 h, 98%.

the correct stereochemistry at C₈ selectively. They also published a total synthesis of modhephene,¹³² 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).¹³³ 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 group¹³⁵ is not an acid-catalyzed rearrangement, but a very efficient lithium bromide–HMPA-catalyzed¹³⁶ epoxide–carbonyl rearrangement^{137–140} 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 (**3**) in Scheme 4.

Fitjer et al. have published a short and original synthesis of modhephene via an acid-catalyzed cascade rearrangement of alcohol **173**.^{141–143} The group has also studied the absolute configuration and optical rotation of modhephene by resolving an intermediate and preparing both (–)- and (+)-modhephene separately.¹⁴⁴

[‡] The Curran group also reports¹³³ (see Ref. 70 in the paper) that there has been a misassignment of spectra of the two diastereomers of ketone **164** (Scheme 32) in the Smith paper.¹²⁸ Wilkening and Mundy used a sample provided by Smith to prove the identity of **164** and thus the product of their catalytic hydrogenation. Kraus and Shi¹³⁴ claim that the misassignment derives from the mix-up in Smith's data, but, in fact, the Mundy assignment was based on comparison with an authentic sample of **164** from Professor Smith. It remains unclear whether Professor Smith had sent the wrong diastereomer of **164** to Wilkening and Mundy or if there is a genuine error with the chemistry.

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.^{145,146} 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.^{147,148} Seven years later, Mash et al. published the first total synthesis of (–)-modhephene,^{149–151} where a chiral auxiliary-based strategy was used to synthesize enantiomerically 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.^{152,153} 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

(±)-modhephene/Mehta 1985

(±)-modhephene/Uyehara* 1996

Scheme 34. (a) $h\nu$, Vycor, vinyl acetate, cyclohexane, 35 h, 21%; (b) 1-chloroacrylonitrile, tol, 80 °C, 16 h, 43%, 4:1 regioselectivity; (c) $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$, EtOH, 60 °C, 6 h, 58%; (d) $h\nu$, acetone, 45 min, 47%, 15:1 selectivity; (e) $h\nu$, acetone, rt, 1.5 h, 91%; (f) Bu_3SnH , 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.¹⁵⁴ 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,^{155–157} Mehta and Subrahmanyam 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

(±)-modhephene/Kraus* 1991

(±)-modhephene/Suri* 1993

Scheme 35. (a) **190**, pH 5 aqueous buffer, rt, several days, then H_3O^+ , heat; (b) $(\text{MeO})_2\text{P}(\text{O})\text{Me}$, $n\text{-BuLi}$, –78 °C, 15 min, then **192**, –78 °C → rt, 1 h, 49%; (c) $[\text{Ir}(\text{COD})(\text{PCy}_3)_3]\text{PF}_6$, H_2 , CH_2Cl_2 , 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.^{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-workers¹⁶⁰ decided to use the Weiss reaction,^{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**.^{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.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** → **188**). The Curran group has published two different radical-based syntheses of modhephene. The first was a formal total synthesis with sequential radical cyclizations¹³³ and the second used a tandem transannular radical cyclization.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

modhephene by radical reaction

(±)-modhephene/Curran* 1990

(±)-modhephene/Shi* 1990

(±)-modhephene/Lee* 1996

(±)-modhephene/Rawal* 1997

(±)-modhephene/Pattenden* 1998

Scheme 36. (a) Bu₃SnH, AIBN, PhH, reflux, 10 h, 90%; (b) Bu₃SnH, AIBN, DPPE, PhH, reflux, 7 h, 88%; (c) Bu₃SnH, AIBN, PhH, 85%, α:β 4:1; (d) Bu₃SnH, AIBN, PhH, 8 h, then SiO₂, 74%, α:β > 9:1; (e) Bu₃SnH, AIBN, PhH, −78 °C, α:β 6:1; (f) 2-(*o*-IC₆H₄)CH₂CH₂SH, DCC, DMAP, CH₂Cl₂, 85%; (g) Bu₃SnH, AIBN, PhH, reflux, 59%.

(-)-ginkgolide B/Corey 1988

(±)-ginkgolide B/Crimmins 1999

Scheme 37. Retrosynthetic analysis of ginkgolide B.

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 Corey^{175,176} 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 B^{175,176} 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)^{177–179} 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) $(\text{COCl})_2$, PhH, rt, 2 h, then (b) $n\text{-Bu}_3\text{N}$, tol, reflux, 3 h, 71–89% over two steps; (c) Ph_3COOH , 8:1 acetone:1 N NaOH, -30°C , 2 h, 86%; steps; (d) CSA, CH_2Cl_2 , rt, 24 h (75% over two steps).

(±)-ginkgolide B/Crimmins 1999

Scheme 39. (a) $h\nu$, $>350\text{ nm}$, hexanes, rt, 17 h, quant.; (b) 5% HF, MeCN, $0^\circ\text{C} \rightarrow \text{rt}$, 1 h; (c) MsCl , Et_3N , CH_2Cl_2 , 0°C , 45 min; (d) 4 Å MS, EtOH, reflux, 26 h, then H_2O , reflux, 8 h, then PPTS, PhH, reflux, 16 h, 63% from **220**; (e) PhSeCl , HCl, EtOAc, rt, 1 h, then NaIO_4 , H_2O , THF, 2 h, rt; 78%; (f) DMDO, acetone, H_2O , 8 h, rt, then $p\text{-TsOH}$, rt, 15 h, 94%; steps; (g) CSA, MeOH, reflux, 18 h, 88%; (h) PPTS, pyr, PhCl, reflux, 4 h, 85%; (i) $\text{VO}(\text{acac})_2$, TBHP, 4 Å MS, CH_2Cl_2 , rt, 4 days, then $p\text{-TsOH}$, rt, 2 h, 81%; (j) DMDO, acetone, H_2O , rt, 20 h; (k) Br_2 , NaOAc, H_2O , AcOH, rt, 20 h, 52% over two steps.

(±)-merrillactone A/ Danishefsky 2002

(±)-merrillactone A/ Inoue 2003

Scheme 40. Retrosynthetic analysis of merrillactone A.

(±)-merrilactone A/ Danishefsky 2002

Scheme 41. (a) Symm-collidine, Methylene Blue, mesitylene, 165 °C, 2.5 days, 74%; (b) O₃, CH₂Cl₂, MeOH, −78 °C, then PPh₃, →rt; (c) Bn₂NH·TFA, PhH, 63 °C, 9 h, 94% over two steps; (d) NaBH₄, CH₂Cl₂, MeOH, −78 °C →rt, quant.; (e) MeC(OEt)₃, PivOH, mesitylene, 135 °C, 24 h, 92%, α:β 1:1.8; (f) LiOH, MeOH, H₂O, rt 12 h; (g) I₂, NaCHO₃, THF, rt, 12 h, then separation, 59% over two steps; (h) allylSnBu₃, AIBN, PhH, 85 °C, 4.5 h, 75%; (i) LHMDS, TMSCl, THF, −78 °C, 30 min, then PhSeCl, →rt, 1.5 h; (j) PhSeBr, MeCN, rt, 30 min; (k) O₃, CH₂Cl₂, −78 °C, then 1-hexene, then NEt₃, PhH, reflux, 30 min, 77% over three steps; (l) Bu₃SnH, AIBN, PhH, 85 °C, 1.5 h, 90%; (m) TsOH·H₂O, PhH, reflux, 3 h, 90%; (n) *m*-CPBA, CH₂Cl₂, rt, 2 days, α:β 3.5:1; (o) ¹⁸⁸TsOH·H₂O, CH₂Cl₂, rt, 1 day, 71% over two steps.

4.2. Merrilactone A

The pentacyclic sesquiterpene dilactone merrilactone A (**224**), isolated from *Illicim merrillianum* in 2000,¹⁸³ has already been the target of two total syntheses, by the Danishefsky group in 2002,¹⁸⁴ and by the Inoue group a year later (Scheme 40).¹⁸⁶ 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 **226** could be formed with a ring cleavage–reclosure sequence of the Diels–Alder adduct **227**. The Inoue group strategy called for desymmetrization of *meso*-diketone **231** through an intramolecular aldol reaction. Mehta and Singh recently published their approach to the ABCD ring system of merrilactone A.¹⁸⁷

The merrilactone A synthesis by Birman and Danishefsky commences with a Diels–Alder reaction of diene **228** and dimethylmaleic anhydride (**229**) (Scheme 41).¹⁸⁴ 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 **235**. 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 (**226**), which was subsequently hydrolyzed. Iodolactonization and chromatographic separation then gave the pure minor iodide **236**, 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 **225**. Exposure of the vinyl bromide **225** to tributyltin hydride and AIBN then effected the formation of the [3.3.3]propellane **237**. Isomerization of the exocyclic double bond, epoxidation and acid-catalyzed homo-Payne rearrangement according to the procedure of Fukuyama and co-workers¹⁸⁸ produced (±)-merrilactone A (**224**) in 71% yield over two steps.

The first step in the Inoue group's synthesis towards merrilactone A (Scheme 42) was a [2+2] photocycloaddition between 1,2-dichloroethene (**233**) and dimethylmaleic anhydride (**229**).¹⁸⁶ The side chains of the symmetrical diol **232** were installed so that a ring-closing metathesis could be performed. This was followed by opening of the four-membered ring to give diketone **231**. Exposure of **231** to LHMDS provided the AC ring fragment **240αα** together with the A ring diastereomer **240ββ** in a 3.1:1 ratio, respectively. A two-carbon side chain was attached to the C₄-hydroxyl of ring A (merrilactone A numbering) to allow the B-ring cyclization to be performed. With the enoate **241** in hand, cyclization with tributyltin hydride and triethylborane gave the ABC ring fragment **242** of merrilactone A. Another 13 steps were required to finish the synthesis of (±)-merrilactone A (**224**).

5. Indole alkaloids

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

[†] The Danishefsky group has recently published an enantioselective approach to intermediate **236** (Scheme 41).¹⁸⁵

(±)-merrilactone A/ Inoue 2003

Scheme 42. (a) $h\nu$, Benzophenone, acetone, rt, 3 h; *steps*; (b) i. $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$, CH_2Cl_2 , reflux, 14 h, then ii. $\text{Pb}(\text{OAc})_4$, rt, 95%; (c) LHMDS, THF, -78°C , 1 h, 64% **240αα**, 22% **240ββ**; (d) *m*-CPBA, CH_2Cl_2 , rt, 4 h, 81%; (e) DBU, CH_2Cl_2 , -30°C , 1 h, 81%; (f) IBX, DMSO, rt, 30 min, 94%; (g) Br_2 , ethyl vinyl ether, CH_2Cl_2 , -78°C , 15 min, then sm, *N,N*-dimethylaniline, $\rightarrow$ rt, 1 day, 62%, 4:1 selectivity; (h) Bu_3SnH , BEt_3/O_2 , tol, rt, 30 min, 57% **242β**, 16% **242α**.

(±)-1-acetylaspidalbidine

Ban 1987

Overman* 1991

(-)-aspidophytine

Corey 1999

Fukuyama 2003

Scheme 43. Retrosynthetic analyses of 1-acetoxyaspidalbidine and aspidophytine.

syntheses of four of them, namely 1-acetylaspidoalbidine, 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-Acetylaspidoalbidine and aspidophytine

1-Acetylaspidoalbidine (**244**) was isolated in 1963 from *Vallesia dichotoma* Ruiz Et Pav¹⁸⁹ 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-acetylaspidoalbidine 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-acetylaspidoalbidine (**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 cimidum* in Mexico.^{195,196} Aspidophytine has inspired two total syntheses to date by the Corey¹⁹⁷ 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.

243: haplophytine

The key step in the 1-acetylaspidoalbidine 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-acetylaspidoalbidine by the Overman group¹⁹⁴ is the aza-Cope rearrangement-Mannich cyclization sequence that was developed in the group (Scheme 45).¹⁰⁹ The treatment of aminoalcohol **247** with para-formaldehyde 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-acetylaspidoalbidine (**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 pentacyclic core of the molecule. Then, after having hydrolyzed the pivalate of **259**, potassium

(±)-1-acetylaspidoalbidine/Ban 1987

Scheme 44. (a) 10% HCl, THF, 0 °C, 30 min, 70%; (b) LiAlH₄; (c) acetylation; (d) Hg(OAc)₂, 5% AcOH, 65–70 °C, 7 h, 64%.

(±)-1-acetylaspidoalbidine/Overman* 1991

Scheme 45. (a) (CH₂O)_n, Na₂SO₄, toluene, rt, 24 h, quant.; (b) CSA, Na₂SO₄, PhH, reflux, 2.5 h; (c) LiAlH₄, THF, 0 °C, 2 h, 67% over two steps; (d) Na, NH₃, THF, –70 °C, quant.; (e) Pd/C, HCO₂NH₄, EtOH, reflux, 1 h, 98%; (f) Ac₂O; [(g)¹⁹³ Hg(OAc)₂, 5% AcOH, 65–70 °C, 7 h, 64%, reaction not performed, formal total synthesis].

(-)-aspidophytine/Corey 1999

Scheme 46. (a) MeCN, rt, 5 min, then TFAA, 0 °C, 2 h, then NaBH₃CN, 0 °C → rt, 30 min, 66%; (b) NaOH, EtOH, 75 °C, 20 h, 88%; (c) K₃Fe(CN)₆, NaHCO₃, *t*-BuOH/H₂O 1:2, rt, (fast), 92%; (d) OsO₄, DMAP, *t*-BuOH/H₂O 1:2, rt, 5–10 min, then Na₂SO₃; (e) Pb(OAc)₄, AcOH, CH₂Cl₂, –20 °C, 5–10 min, 71% over two steps; (f) KHMDS, THF, –78 °C, 30 min, then PhNTf₂, 54%; (g) Pd(PPh₃)₄, Bu₃SnH, THF, rt, 1 h, 86%.

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

(-)-aspidophytine/Fukuyama 2003

Scheme 47. (a) Pd(PPh₃)₄, CuI, Et₃N, 70 °C, 2 h, 78%; (b) Boc₂O, DMAP, CH₃CN, rt, 15 min, 94%; (c) Pd/C, H₂, EtOH, rt, 3.5 h, 97%; (d) K₂CO₃, H₂O, MeOH, rt, 1 h, 96%; (e) *o*-NsNH₂, PPh₃, PhH, DEAD, rt, 5 min, 93%; (f) TBAF, THF, rt, 1 h, 93%; (g) PPh₃, DEAD, PhH, rt, 5 min, 92%; (h) TMSBr, CH₂Cl₂, 70 °C, 15 min, then pH 7.0 buffer, 92%; (i) PhSH, Cs₂CO₃, MeCN, 55 °C, 20 min; (j) TFA, Me₂S, CH₂Cl₂, rt, 5 min, then pH 7.8 buffer, EtOAc, 5 °C, 30 min, 56% over two steps; (k) HCHO, pH 7.0 buffer, MeOH, H₂O, NaBH₃CN, –70 °C, 30 min, →rt, 2 h, 67%; (l) NaOH, EtOH, 70 °C, 2.5 h, then HCl, 5 °C, 52%; (m) K₃Fe(CN)₆, NaHCO₃, *t*-BuOH/H₂O 1:2, 5 °C →rt, 10 min, 56%.

(±)-kopsanone

Magnus 1984

264

265

266

Kuehne 1985 and Natsume 1987

264

267

Kuehne

268

Natsume

269

(±)-lapidilectine B

Pearson 2001

270

271

272

Scheme 48. Retrosynthetic analyses of kopsanone and lapidilectine B.

published for kopsanone (**264**), a member of this group (Scheme 48). The syntheses of the Natsume^{202,203} 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

(±)-kopsanone/Magnus 1984

264: kopsanone

274

Scheme 49. (a) $\text{Cl}_3\text{CCH}_2\text{OCOC1}$, $i\text{-Pr}_2\text{NEt}$, PhCl , $0 \rightarrow 120^\circ\text{C}$, 40 min, then 120°C , 8 h, 50%; steps; (b) $95\text{--}100^\circ\text{C}$, PhH , 4 h, 81%.

(±)-kopsanone/Kuehne 1985

Scheme 50. (a) **275**, H₃BO₃, CH₂Cl₂, reflux, 12 h, 33%; (b) BnBr, NaH, DMF, rt, 30 min, 86%; (c) *m*-CPBA, CH₂Cl₂, −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%.

Lapidilectine B (**270**) was isolated from *Kopsia lapidilecta* in 1992²⁰⁸ and was synthesized by the group of Pearson (Scheme 48).^{209,210} 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).^{206,207} 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 51. (a) KOH, *i*-PrOH, 15 °C, 1 h, (68% over two steps), 2.2:1 selectivity; (b) *t*-BuLi, ClCO₂Me, THF, −10 °C, 30 min, 89%; (c) OsO₄, NMO, acetone, rt, overnight, 82%, 6:1 selectivity; (d) allylMgBr, THF, −40 °C → rt, overnight, 90%; (e) NaIO₄, pH 7 buffer, THF, 0 °C → rt, overnight; (f) CSA, MeOH, 1 h, 59% over two steps; steps; (g) TFA, CH₂Cl₂, rt, 30 min; (h) *i*-Pr₂NEt, MeCN, rt, 2 h, then 60 °C, 10 h, 76% over two steps.

(-)-annotinine/Wiesner 1967

Scheme 52. (a) Acrylic acid, 135 °C, 2 h, 63%; (b) allene, *hν*, −70 °C, 20 h, 54%.

In the Kuehne group synthesis of kopsanone (Scheme 50),²⁰⁴ the key pentacyclic intermediate **276** came from an adaptation of a biomimetic secodine cyclization that they had investigated extensively.²¹¹ Benzylation 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).^{209,210} 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) NaNH₂, NH₃, THF, –30 °C → rt, 2 h; (i) NaOMe, Br₂, MeOH, THF, –78 °C, 1 h, → reflux, 1 h, 93% over two steps; (j) 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 metaphanine, 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^{212–215} deduced the structure of the molecule during the years 1956–1957 (Scheme 52).²¹⁶ Their synthesis starts with a condensation of acrylic acid and vinylogous amide **281** to provide the [2+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 *Stephania cepharantha* Hayata in 1966,

have been published (Scheme 53).²¹⁷ The Ibuka group published the first total synthesis in 1969,^{218,219} then the Tahk group published in 1970²²⁰ and Schultz in 1998.²²¹ Ibuka et al. have also published a synthesis of methaphanine (**285**)^{222,223} and hasubanonine (**286**),^{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),^{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),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).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,

(±)-hasubanan skeleton/Evans 1972

(±)-hasubanan skeleton/Bruderer *et al.* 1977

(±)-hasubanan skeleton/Mulzer 1998

Scheme 54. (a) MeCN, 70 °C, 24 h; (b) Na₂S·9H₂O, MeOH, 65 °C, 8 h; (c) POCl₃, pyr, reflux, 5 h; (d) NH₃, Raney-Ni, H₂, EtOH, 80 °C, 38% over two steps; (e) HCl, H₂O, reflux, 1 h, 83%; (f) PhH, reflux, 1 h, 76%; (g) pyr, reflux, 5 h, 73%.

(±)-bathrachotoxinin A/Kishi 1998

Scheme 55. (a) Mn_2O , CH_2Cl_2 , rt, 1 h; then filtration; then CH_2Cl_2 , rt, 12 h; (b) **308**, AcOH , 4 Å MS, PhH , rt, 3 h; then NaCNBH_3 , MeOH , 0 °C, 15 min; (c) Ac_2O , pyr, rt, overnight, 76% over three steps, > 25:1 selectivity; steps; (d) TASF, THF/DMF 10:1, 0 °C → rt, 1 h; then PhNTf_2 , Et_3N , 30 min, rt, 95%.

treatment with lithium aluminium hydride provided alcohol **295**. This alcohol was then transformed into (+)-cepharamine ((+)-**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**.^{226–228} 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**.²²⁹ 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 N_2 to give aminoenone **306**.²³⁰

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.^{231,232} A total synthesis was published by the Kishi group in 1998 (Scheme 55).²³³ 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.³⁴

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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