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Strategies for the synthesis of C_2 symmetric natural products—a review

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1. Introduction

The existence of C_2 symmetry in a natural product is of great interest to the organic chemist as it opens up the possibility of the parallel synthesis of multiple parts of the molecule, thus increasing the convergence of retrosynthetic strategies. Interestingly, the number of targets found to possess such symmetry seems to exceed that expected to arise from pure chance. A literature survey, involving theoretical calculations and comparisons of the energy of monomers, dimers, trimers and tetramers has recently been published by Greer and co-workers.[1]

Our interest in this area first started during the preparation of the antipode of the C_2 symmetric natural product papuamine, where the symmetry of the target was exploited to provide a concise synthetic strategy.[2,3] Since that time, we have reviewed the literature for examples of other C_2 symmetric natural products and found them to be widespread. Of those that have been synthesized, a large number have implemented routes that take advantage of the symmetry elements of the target.

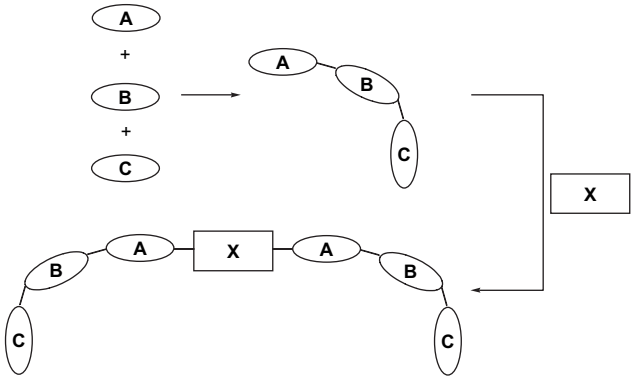
We present the current review of commonly employed strategies employed during the synthesis of C_2 symmetric natural products, which we have illustrated with selected examples. It should be noted that it is outside of the scope of this article to present a comprehensive review of the syntheses of all known C_2 symmetric natural products, and we have notably omitted the large families of carotenoids, polyamines, lignans and polypeptides. Finally, we have classified the syntheses into two broad categories: 'core expansion' and 'dimerization.' Our definitions of these strategies can be found at the beginning of each sub-section. In those cases where a compound has been synthesized, via more than one of these strategies, we have classified it with respect to the initial total synthesis published.

To aid distinction, in each section we have grouped the natural products by source, and thus present synthesis under the sub-headings of 'marine organisms', 'plants and fungi', and 'bacteria, algae and lichen'.

2. Core expansion strategies

The core expansion strategies are those that employ a central symmetrical core on which further assembly of the molecule is subsequently carried out by two-directional bond construction. There are three main sub-divisions within this class and these are described below.

(a) *Three-component coupling*: In this strategy, two units are synthesized and subsequently coupled to a central core entity (Scheme 1). The phrase 'three-component' refers to the two side chains and the central core. For the purpose of this review, we have stipulated that syntheses where deprotection or minor functional group

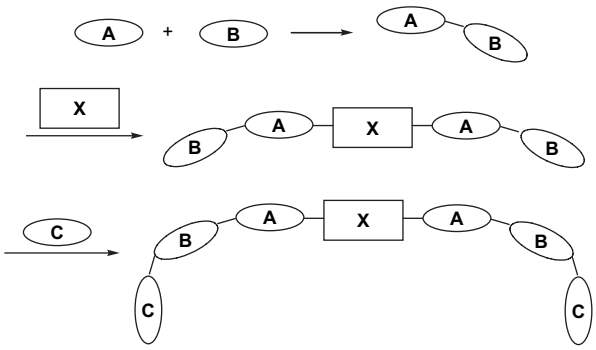


Scheme 1. Illustration of three-component coupling.

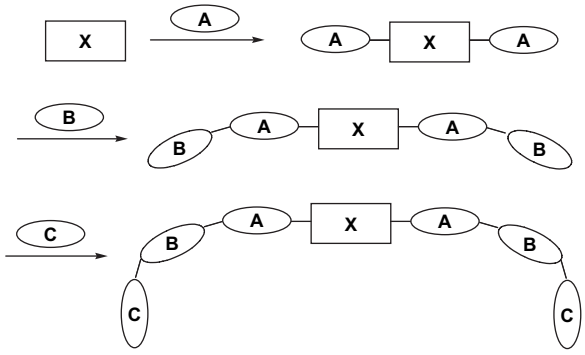
interconversions are carried out after the assembly of the interior are also classified as three-component coupling.

(b) *Three-component coupling followed by two-directional synthesis*: In this strategy, following a three-component coupling as described above, two-directional chain elongation and/or modification takes place (Scheme 2).

(c) *Two-directional synthesis*: In this strategy two-directional chain elongation and modification is applied to a central core in a stepwise manner (Scheme 3).



Scheme 2. Illustration of three-component coupling followed by two-directional synthesis.



Scheme 3. Illustration of two-directional synthesis.

2.1. Three-component coupling

2.1.1. Marine organisms.

2.1.1.1. Aerothionin and homoaerothionin. Both aerothionin (**1**, Fig. 1) and homoaerothionin (**2**, Fig. 1) have been isolated from the sponges *Aplysina aerophoba*, *Aplysina fistularis* and *Verongia thiona*[4–6] and the absolute stereochemistry of the former was determined by X-ray crystallographic analysis.[6] The combination of the unusual spiroisoxazoline moiety present in these natural products and their interesting biological activity has resulted in a number of racemic[7,8] and biomimetic syntheses.[9]

The first total synthesis, which was reported by Nishiyama and Yamamura in 1983,[7] involved the formation of spiroisoxazoline ester **8** via oxime **5**, followed by bis-amidation with 1,4-butanediamine (representing the central core) (Scheme 4). Similarly, homoaerothionin was prepared from **9** and 1,5-pentanediamine. In each case the racemic trans and the *meso* cis isomers were separated by chromatography on silica.

Intermediate **8** has also been accessed in an enantiomerically enriched form by utilizing a novel tertiary alcohol as a chiral auxiliary during the oxidative cyclization of oxime **10** to oxazoline **11**.[10] Cleavage of the auxiliary was performed under mild conditions to give **8**, which was further elaborated to give (+)-aerothionin as reported by Nishiyama and Yamamura (Scheme 5).[7] The enantiomeric excess observed for (−)-**8** was increased to 84% by recrystallization.

In a recent synthesis of aerothionin (**1**),[11] a strategy based on three-component coupling followed by two-directional synthesis was used. The key step involved the construction of diamide **19** using a cyano ylide-coupling methodology via ylide **17**, which was obtained from methyl (4-methoxyphenyl)acetate. Subsequent oxime formation, followed by deprotection and oxidative cyclization gave **20**. Highly stereoselective trans/trans reduction was achieved using sodium cyanoborohydride to complete the synthesis of (±)-aerothionin (**1**) (Scheme 6).

2.1.1.2. Ancepsenolide. Ancepsenolide (**21**, Fig. 2), which is closely related to dehydrohomoancepsenolide (**181**, Section 3.1.1.2), was isolated from *Pterogorgia anceps*,[12] *Pterogorgia guadalupensis*[13] and *Pterogorgia citrina*,[14] and its structure elucidated by chemical degradation studies.[13] The terminal butenolide functionality flanking a long aliphatic chain is typical of this class of biologically interesting natural products, termed annonaceous acetogenins.[15]

The first racemic synthesis of ancepsenolide (**21**) as a mixture of diastereoisomers, by Sneden and Podraza in 1985, was achieved through bis-alkylation of 2 equiv of lactone **24** with 1,12-dibromododecane followed by thermolysis (Scheme 7).[16] An additional non-stereochemically controlled synthesis was also described at a similar time.[17]

The absolute configuration of ancepsenolide (**21**) was established by Trost and co-workers starting from known

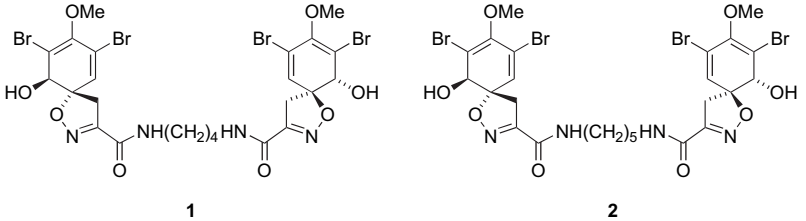
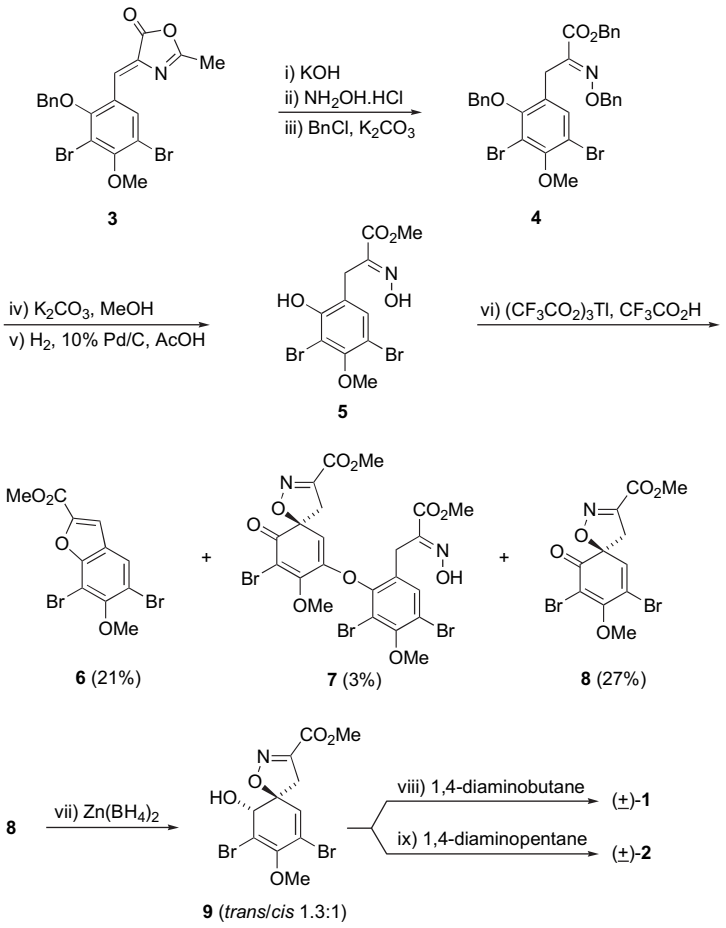
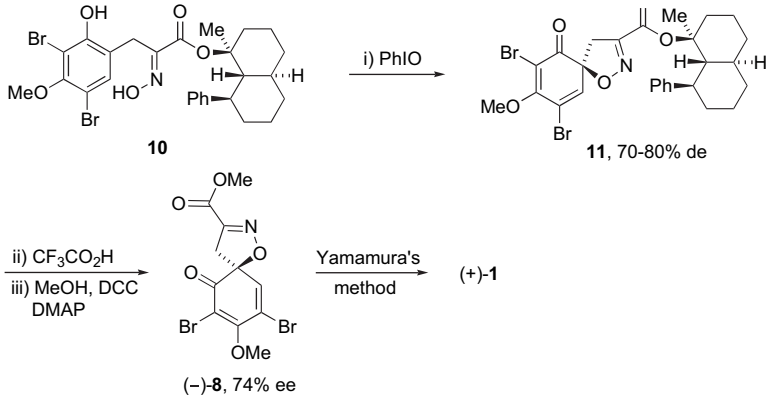


Figure 1. Structures of aerothionin (**1**) and homoaerothionin (**2**).



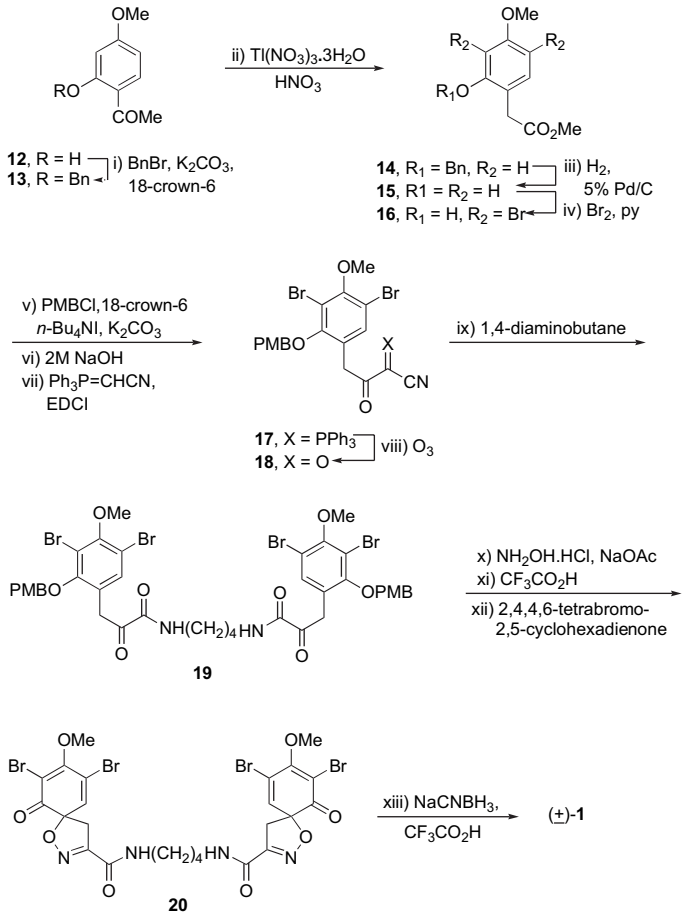
Scheme 4. Synthesis of aerothionin (**1**) by Yamamura and co-workers. Reagents and conditions:[†] (i) KOH, dioxane/H_2O 1:1, 100 °C; (ii) $HONH_3Cl$, dioxane/H_2O 1:1; (iii) BnCl, K_2CO_3, DMF (31% over three steps); (iv) K_2CO_3, MeOH/dioxane 1:1; (v) H_2, 10% Pd/C, AcOH/dioxane 1:1 (74% over two steps); (vi) $(CF_3CO_2)_3Tl$, CF_3CO_2H (27% of **8**); (vii) $Zn(BH_4)_2$, CH_2Cl_2/Et_2O 3:2 (40% of the trans isomer); (viii) 1,4-diaminobutane (18%); (ix) 1,4-diaminopentane (4%).



Scheme 5. Synthesis of (+)-aerothionin (**1**) by Murakata and co-workers. Reagents and conditions: (i) PhIO, 10-camphorsulfonic acid, CH_2Cl_2, −78–0 °C (83%); (ii) CF_3CO_2H, CH_2Cl_2, 0 °C; (iii) MeOH, DCC, DMAP, CH_2Cl_2 (71%).

lactaldehyde derivative **26**[18] and using a ruthenium-catalyzed Alder-ene reaction to construct the chain via acetylene **27**. Hydrogenation of diene **29** using Wilkinson's catalyst completed the synthesis of (+)-ancepsenolide (**21**) (Scheme 8).[19] Subsequent to the Trost publication, additional total syntheses of ancepsenolide (**21**) utilizing a three-component coupling strategy have been published.[20,21]

[†] In all schemes, all reactions were carried out at room temperature, unless otherwise specified.



Scheme 6. Synthesis of (±)-aerothionin (**1**) by Wasserman and co-workers. Reagents and conditions: (i) $PhCH_2Br$, K_2CO_3, 18-crown-6, Me_2CO, Δ (97%); (ii) $Tl(NO_3)_3 \cdot 3H_2O$, HNO_3, MeOH (76%); (iii) H_2, 5% Pd/C, MeOH (96%); (iv) pyridine·HBr_3, pyridine, 0–20 °C (90%); (v) 4-$MeOC_6H_4CH_2Cl$, K_2CO_3, *n*-Bu_4NI, 18-crown-6, Me_2CO, Δ (93%); (vi) 2 M NaOH, MeOH (94%); (vii) $Ph_3P{=}CHCN$, EDCI, CH_2Cl_2 (88%); (viii) O_3, CH_2Cl_2, −78 °C; (ix) 1,4-diaminobutane, CH_2Cl_2, −78–20 °C (64% over two steps); (x) $HONH_3Cl$, NaOAc, THF/EtOH 2:1, 50–60 °C (95%); (xi) CF_3CO_2H, CH_2Cl_2, 0–20 °C (92%); (xii) 2,4,4,6-tetrabromo-2,5-cyclohexadienone, MeCN, Δ to 20 °C (70%); (xiii) $NaBH_3(CN)$, CF_3CO_2H, CH_2Cl_2, 0 °C (25%).

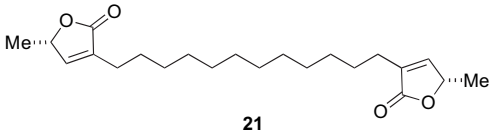
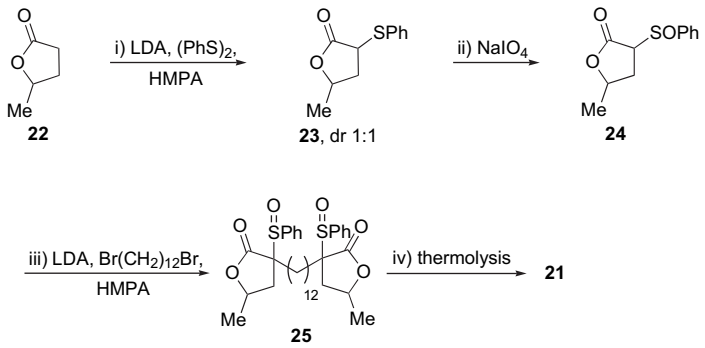
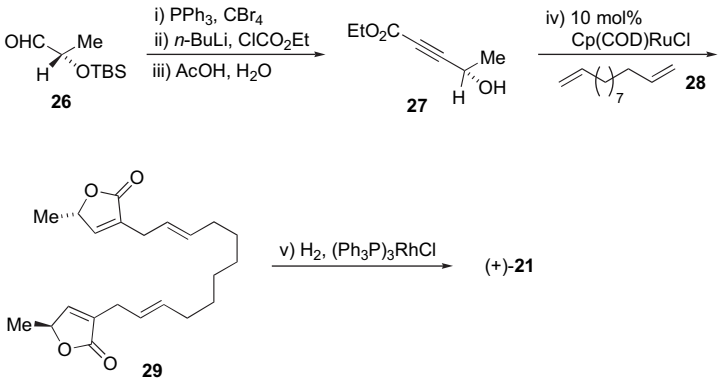


Figure 2. Structure of (+)-ancepsenolide.

2.1.1.3. Triophamine. Triophamine (**30**, Fig. 3) was isolated from the dorid nudibranch *Triopha catalinae* in 1982 by Gustafson and Andersen.[22] It was found to possess a unique diacylguanidine structure, and it was noted that this unusual carbon skeleton is unlikely to be formed by the 'standard' biosynthetic pathways.[22]



Scheme 7. Synthesis of (±)-ancepsenolide (**21**) by Podraza and co-workers. Reagents and conditions: (i) LDA, HMPA, diphenyl disulfide, −25 °C (52%); (ii) $NaIO_4$, MeOH, H_2O (100%), (iii) LDA, HMPA, $Br(CH_2)_{12}Br$, 0 °C, (iv) PhMe, 120 °C (40% over two steps).



Scheme 8. Synthesis of (+)-ancepsenolide (**21**) by Trost and co-workers. Reagents and conditions: (i) PPh_3, CBr_4, THF, −78 °C (77%); (ii) *n*-BuLi, THF, −78 °C; $ClCO_2Et$; (iii) AcOH, H_2O, THF (80% over two steps); (iv) 10 mol % Cp(COD)RuCl, **28**, MeOH, Δ (75%); (v) H_2 (2 atm), $(Ph_3P)_3RhCl$, PhH, EtOH (93%).

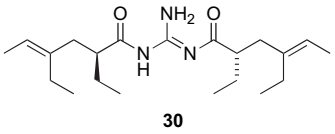


Figure 3. Structure of triophamine.

In 1984, Piers and co-workers reported a total synthesis of triophamine (**30**) using hydrostannylation and transmetallation chemistry (Scheme 9).[23]

Reaction of ethyl 2-pentynoate (**31**) with (tributylstannyl)-copper, followed by reduction afforded vinylstannane **34**. Transmetallation and conjugate addition followed by DIBAl-H reduction and PDC oxidation yielded carboxylic acid **37**. Subsequent conversion into the corresponding *o*-nitrophenyl ester and condensation with guanidine provided racemic triophamine (**30**) along with the separable *meso* isomer.

2.1.2. Plants and Fungi.

2.1.2.1. Homaline. Homaline (**39**, Fig. 4) is a member of a group of *Homalium* alkaloids isolated from the leaves of an African *Homalium* sp. and *Homalium pronyense* Guillaum (Flacourtiaceae), found in the forests of New Caledonia. Investigations by Pais and co-workers largely established its structure,[24–27] which has also been unequivocally determined by X-ray crystallography.[24–27]

The synthesis of homaline has been achieved in four accounts by bis-alkylation of the key intermediate **40** with central core **41**, and subsequent manipulation to yield homaline (**39**) (Scheme 10).

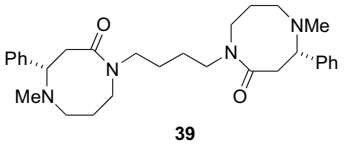
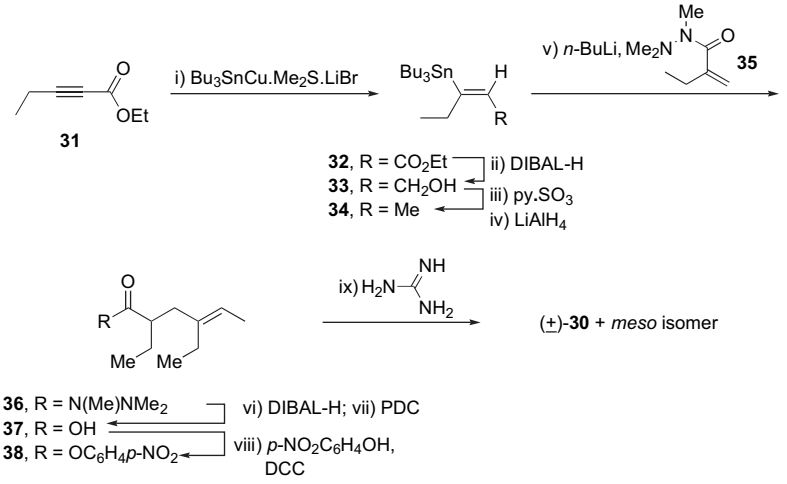
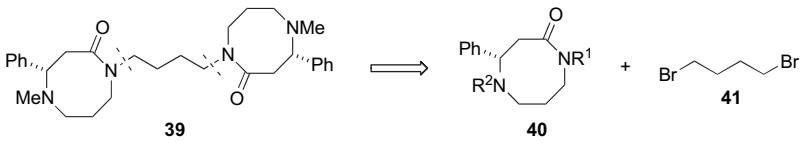


Figure 4. Structure of homaline.



Scheme 9. Synthesis of (±)-triophamine (**30**) by Piers and co-workers. Reagents and conditions: (i) $(n\text{-}Bu_3Sn)_2$, *n*-BuLi, THF, −20 to −78 °C; $CuBr{\cdot}Me_2S$; ethyl 2-pentynoate (**31**) (83%); (ii) DIBAl-H, Et_2O, −78 °C (94%); (iii) pyridine·SO_3, THF, 0 °C; (iv) $LiAlH_4$, 0–20 °C (83% over two steps); (v) *n*-BuLi, THF, −20 to −78 °C; **35** (41%); (vi) DIBAl-H, Et_2O, −78–0 °C; (vii) PDC, DMF (70% over two steps); (viii) 4-$NO_2C_6H_4OH$, DCC, MeCN (87%); (ix) guanidine, $CHCl_3$ (48%).



Scheme 10. Common retrosynthetic approach to homaline (**39**).

Matsuyama and co-workers[28] generated bis-lactam **45** by means of a diastereoselective conjugate addition and cyclization sequence involving pyrazolidine and vinyl sulfoxide **43**, followed by reduction of the chiral auxiliary and, finally, reductive cleavage of the N–N bond (Scheme 11).

An alternative approach, published by Crombie and co-workers,[29] involved the preparation of lactam **48** by means of a ring expansion of β-lactam **47** carried out in liquid ammonia (Scheme 12).

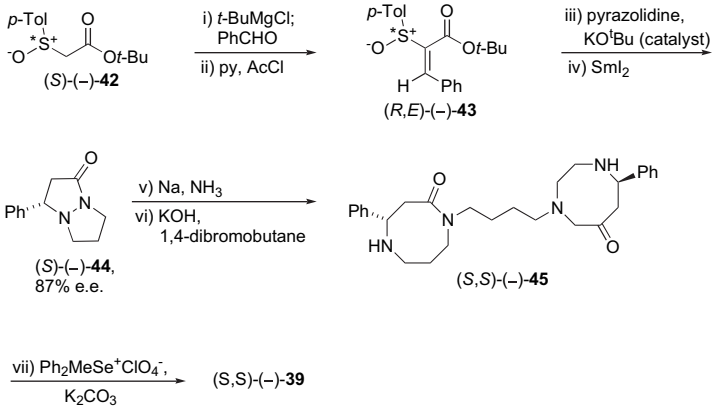
In an elegant approach, Wasserman and co-workers constructed bis-lactam **54** (as part of a strategy based on three-component coupling followed by two-directional synthesis), which underwent a trans-amidation step to generate bis-lactam **55**.[30,31] Methylation of the latter completed the synthesis (Scheme 13).

2.2. Three-component coupling followed by two-directional synthesis

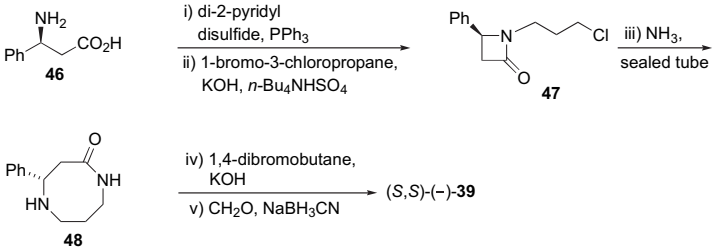
2.2.1. Marine organisms.

2.2.1.1. Adociacetylenes B and D. Adociacetylenes B (**56**, Fig. 5) and D (**57**, Fig. 5) were among a group of polyacetylenes isolated from an Okinawan marine sponge of the *Adocia* sp. by Kobayashi, Kitagawa and co-workers in 1996.[32] They were both found to be optically active, and adociacetylene D was found to inhibit neutrophil leukocyte adhesion to tumour necrosis factor-α (TNF-α)-stimulated endothelial cells.[32]

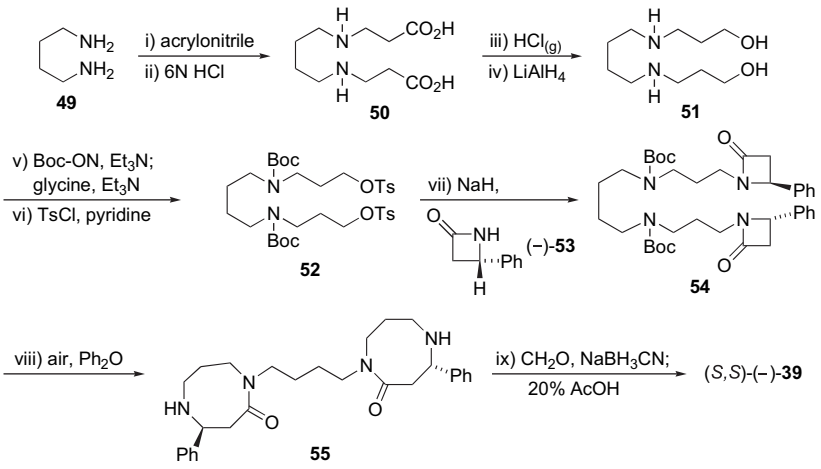
A concise synthesis of adociacetylene B (**56**) was published in 2001 by Gung and co-workers.[33] Their innovative approach avoided the use of protecting groups and employed a two-directional strategy (Scheme 14). Coupling of two



Scheme 11. Synthesis of (*S*,*S*)-(−)-homaline (**39**) by Matsuyama and co-workers. Reagents and conditions: (i) *t*-BuMgCl, THF, −78 °C; PhCHO (94%); (ii) pyridine, AcCl, Et_2O (61%); (iii) pyrazolidine, *t*-BuOK (cat.), THF; (iv) SmI_2, MeOH, THF, 0 °C (66% over two steps); (v) Na, NH_3, THF, −78 °C (99%); (vi) KOH, 1,4-dibromobutane, DMSO (68%); (vii) $Ph_2(Me)Se^+ \cdot ClO_4^-$, K_2CO_3 (43%).



Scheme 12. Synthesis of (*S*,*S*)-(−)-homaline (**39**) by Crombie and co-workers. Reagents and conditions: (i) dipyridyl disulfide, PPh_3, MeCN (53%); (ii) 1-bromo-3-chloropropane, KOH, *n*-Bu_4NHSO_4 (94%); (iii) NH_3, sealed tube (90%); (iv) 1,4-dibromobutane, KOH (75%); (v) CH_2O, $NaBH_3CN$ (90%).



Scheme 13. Synthesis of (*S*,*S*)-(−)-homaline (**39**) by Wasserman and co-workers. Reagents and conditions: (i) acrylonitrile, 0–20 °C (97%); (ii) 6 N HCl, Δ; (iii) $HCl_{(g)}$, EtOH, Δ (68% over two steps); (iv) $LiAlH_4$, Δ; 0 °C; 20 °C to Δ to 20 °C (36%); (v) Boc-ON, Et_3N, dioxane/H_2O 4:1; glycine, H_2O/Et_3N 10:1 (91%); (vi) TsCl, pyridine, 0–4 °C (41%); (vii) NaH, (−)-**53**, DMF, 90 °C (63%); (viii) air, Ph_2O, Δ (37%); (ix) CH_2O, $NaBH_3CN$; 20% AcOH (40%).

units of **59** with one of **58** was followed by chain elongation and isomer resolution using a suitable lipase from *Pseudomonas* sp. (lipase AK from Amano). In contrast, no synthesis of adociacetylene D (**57**) has yet been published.

2.2.1.2. Auriculol. The isolation of auriculol (**65**, Fig. 6) from the Japanese sea hare *Dolabella auricularia* was reported in 2001 by Kigoshi and co-workers alongside its synthesis, which confirmed the structure.[34] This oxygenated squalene derivative was found to be cytotoxic against HeLa S_3 cells. The total synthesis of auriculol **65** was based on the coupling of two equivalents of epoxide **66** and central core disulfide **67** followed by bromoetherification and epoxidation to yield **69** as a diastereoisomeric mixture (Scheme 15). Reduction of the latter gave the enantiomer of auriculol (**65**).

2.2.1.3. Papuamine. Papuamine (**73**, Fig. 7) is the major metabolite of *Haliclona* sp., a thin red encrusting sponge from Papua New Guinea, which overgrows and kills coral. Papuamine inhibits the growth of the fungus *Trichophyton mentagrophytes*,[35] and exists in nature as the dihydrochloride and is thought to be formally derived from a C_{22} unbranched hydrocarbon and 1,3-diaminopropane.

Papuamine has attracted attention amongst synthetic chemists due to its novel structure, which incorporates two identical trans-fused perhydroindane moieties connected by a 13-membered macrocyclic ring containing a conjugated *E*,*E*-1,3-diene and two basic nitrogens. In 1994, Barrett and co-workers established its absolute configuration by arbitrarily choosing to synthesize (+)-papuamine (**73**). Chance had it that the (+)-isomer turned out to be enantiomeric with the natural product.[2,3] Thus, optically active diol (+)-**74** was elaborated to afford intermediate **78** in a diastereoisomeric ratio of 4.5:1 (Scheme 16). The latter was subsequently coupled to 1,3-dibromopropane to give **79**. At this point, the benzyl ether side chains of the latter were suitably modified in order to undergo an intramolecular palladium(0)-catalyzed Stille coupling and install the core of (+)-papuamine (**73**). Further elaboration of **82** completed the total synthesis.

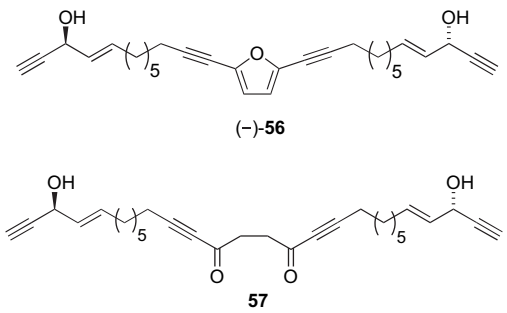
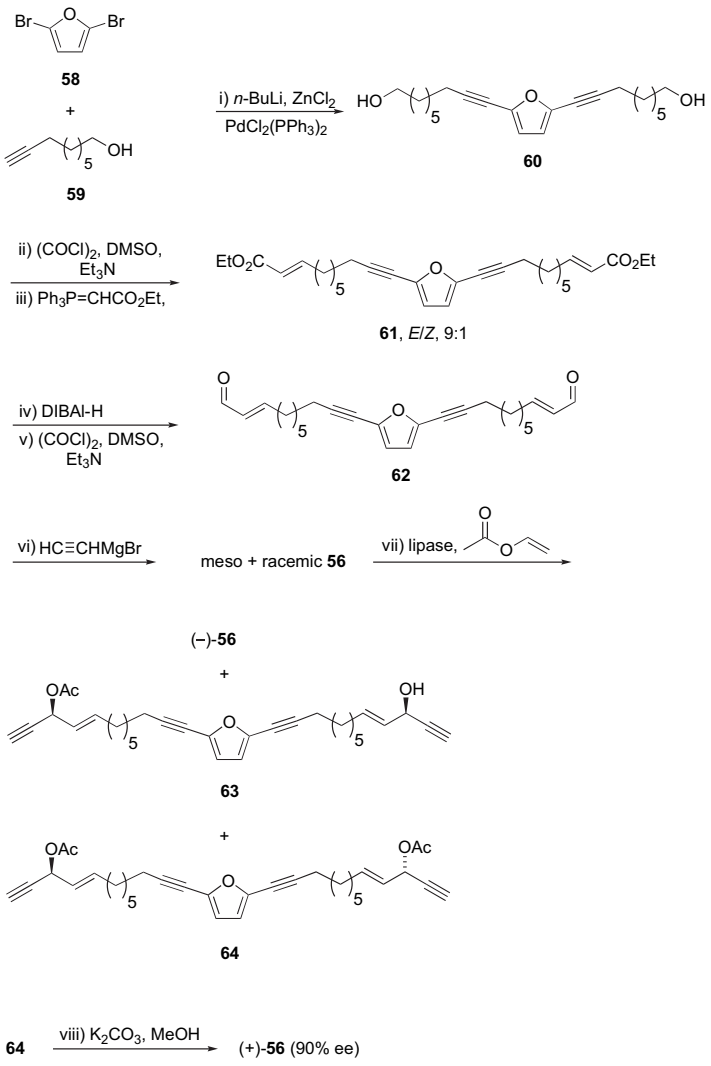


Figure 5. Structure of (+)-adociacetylene B (**56**) and adociacetylene D (**57**).

Not long after the publication by Barrett and co-workers, Weinreb and co-workers employed a novel imino-ene reaction as the key step towards the total synthesis of naturally occurring (−)-papuamine (**73**) (Scheme 17).[36–38] More specifically, *meso*-diester **84** was converted into allene **91**. Reaction of the aldehyde moiety of the latter with propane-1,3-diamine afforded transient intermediate **92**, which then underwent the double imino-ene reaction to yield **93**. Conversion of the latter into bis-(tributylstannyl)alkene **94**, followed by cyclization employing a suitable palladium(II) catalyst completed the synthesis of natural (−)-papuamine (**73**).

Naturally occurring (−)-papuamine (**73**) has also been independently synthesized by Heathcock and co-workers following a conceptually similar route to that reported by Barrett and co-workers for the unnatural antipode.[39] More recently, Saha and Bhattacharjya developed a novel intramolecular 1,3-cycloaddition between the nitrile oxide moiety of intermediate **100** and its alkene unit, which could potentially be applied to the synthesis of papuamine (Scheme 18).[40] Finally, a biomimetic route to the creation of the *trans*-1,2-disubstituted cyclohexyl ring of papuamine (**73**) **109**, involving an ene cyclization step, has been proposed by Baldwin and co-workers (Scheme 19).[41]



Scheme 14. Synthesis of (+)-adociacetylene B (**56**) by Gung and co-workers. Reagents and conditions: (i) *n*-BuLi, $ZnCl_2$, $PdCl_2(PPh_3)_2$ (66%); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (iii) $Ph_3P{=}CHCO_2Et$ (90% over two steps); (iv) DIBAl-H; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (75% over two steps); (vi) ethynylmagnesium bromide, THF (95%); (vii) *Pseudomonas* sp. Lipase, vinyl acetate, hexanes (22% of **56**, 50% of **63** and 19% of **64**); (viii) K_2CO_3, MeOH (93%).

2.2.2. Plants and fungi.

2.2.2.1. Calycanthine. Although calycanthine (**111**, Fig. 8) was first isolated from the seeds of *Calycanthus glaucus*, Willd., by Eccles in 1888,[42] its correct structure was independently elucidated by Woodward,[43] Robertson and co-workers in 1960.[44] Synthetic approaches to structurally related amauromine (**110**) will be discussed in Section 3.1.3.1, whereas a number of syntheses of racemic chimonanthine ((±)-**112**) have appeared in the literature.[45,46] Recently, both isomers of chimonanthine have been enantioselectively synthesized by Overman and co-workers en route to calycanthine (Scheme 20).[47]

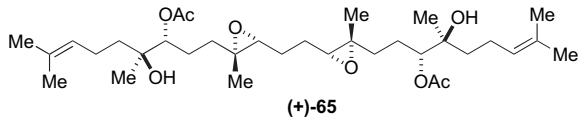


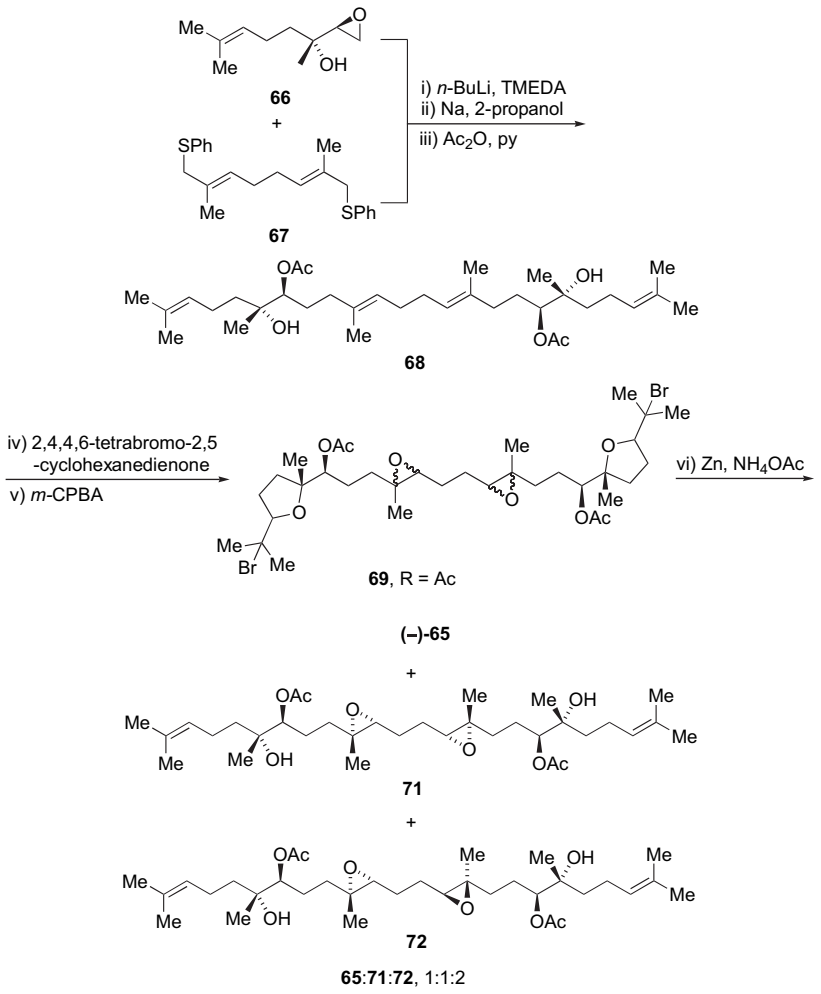
Figure 6. Structure of auriculol.

Synthetic approaches to racemic calycanthine (**111**) have been reported by Hendrickson,[48] Scott and co-workers,[49] and the (+)-isomer has also been synthesized stereoselectively by Overman and co-workers via an elegant double Heck cyclization of intermediate **118** to afford **119** (Scheme 20).[47] The latter was further elaborated to yield **123**, which upon heating in methanol, underwent a double-cyclization sequence to afford **124**. Reductive methylation of the two pyrrole units followed by deprotection of the benzyl groups, and an additional acid-mediated cyclization sequence completed the synthesis of calycanthine (**111**).

2.3. Two-directional synthesis

2.3.1. Plants and fungi.

2.3.1.1. Glabrescol. Glabrescol (**127**, Fig. 9) belongs to the diverse oxasqualenoid family and was isolated from the branches and wood of *Spathelia glabrescens*. Although presently, no biological data have been reported, it is suggested that glabrescol (**127**) should exhibit activities



Scheme 15. Synthesis of auriculol by Kigoshi and co-workers. Reagents and conditions: (i) *n*-BuLi, TMEDA, THF, −78 °C; (ii) Na, 2-propanol, Δ (56% over two steps); (iii) Ac_2O, pyridine (100%); (iv) 2,4,4,6-tetrabromo-2,5-cyclohexadienone, CH_2Cl_2, 0 °C (100%); (v) *m*-CPBA, CH_2Cl_2, 0 °C (87%); (vi) Zn, NH_4OAc, THF, H_2O, 50 °C (63%), **65**:**71**:**72**, 1:1:2.

associated with its ionophoric character via interaction with metal cations.[50]

Although the initial structure proposed for glabrescol (**127**) was the *meso* form, based on spectroscopic data,[51] the need for revision of the original assignment was soon highlighted by Xiong and Corey.[52] This prompted Morimoto and co-workers[53] to undertake and complete the first total synthesis of glabrescol (**127**), followed very closely by Xiong and Corey.[52] Additionally, a racemic synthesis employing a stereoselective cascade,[54] as well as second asymmetric synthesis by Morimoto and co-workers,[50] has also been reported. The original synthesis published by Morimoto and co-workers involved two sequential double *anti* oxidative cyclizations of tetraene **134**, which are directed by the hydroxyl functionality present and proceed via diene **135**.[53] The precursor **131** itself was obtained from diol **128** using the Sharpless asymmetric epoxidation (Scheme 21).

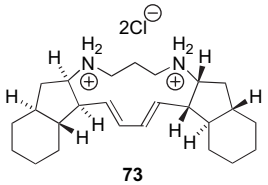
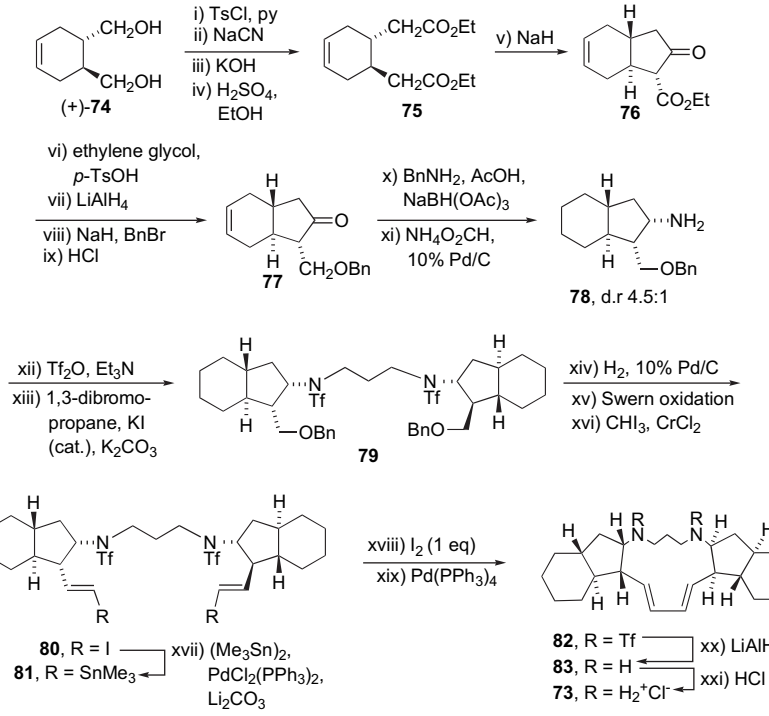


Figure 7. Structure of (−)-papuamine.

In contrast, Corey's synthesis started from the previously known (*R*)-2,3-dihydroxy-2,3-dihydrosqualene (**136**) using the Shi epoxidation. The latter proceeded with excellent enantiocontrol and good diastereoselectivity (dr 80:20) to afford **138**, which, upon treatment with camphorsulfonic acid, yielded glabrescol (**127**) (Scheme 22).[52]

2.3.1.2. Cuscohygrine. Cuscohygrine (**139**, Fig. 10) was isolated from the leaves of *Erythoxylon coca* in 1889 by Liebermann, who also conducted structural studies on this alkaloid.[55,56] Since its original isolation, it has also been reported as a minor component of a number of other Solanaceae alkaloids.[57] The structure proposed by Liebermann and co-workers was proven to be correct by the synthesis of cuscohygrine, reported by Jorgensen and Rapoport some 60 years later.[58] The natural product **139** readily epimerizes via a retro-Michael- and Michael-addition pathway and has, therefore, never been obtained as optically active material.



Scheme 16. Synthesis of (+)-papuamine (**73**) by Barrett and co-workers. Reagents and conditions: (i) TsCl, pyridine (83%); (ii) NaCN, EtOH (86%); (iii) KOH, H_2O, Δ (95%); (iv) H_2SO_4, EtOH (99%); (v) NaH, THF, Δ (95%); (vi) ethylene glycol, TsOH, PhH, 4 Å molecular sieves, Δ (100%); (vii) $LiAlH_4$, Et_2O (99%); (viii) NaH, BnBr, DMF (92%); (ix) 0.2 M HCl, THF, 25–60 °C (97%); (x) $BnNH_2$, AcOH, $NaBH(OAc)_3$, THF (85%); (xi) NH_4O_2CH, 10% Pd/C, MeOH, Δ (86%); (xii) Tf_2O, Et_3N, CH_2Cl_2, −78 °C (97%); (xiii) 1,3-dibromopropane, KI (cat.), K_2CO_3, MeCN, Δ (90%); (xiv) H_2, 10% Pd/C, EtOH (95%); (xv) $(COCl)_2$, DMSO, −60 °C; Et_3N, −60–20 °C; (xvi) CHI_3, $CrCl_2$, 1,4-dioxane/THF 6:1 (71% over two steps); (xvii) $(Me_3Sn)_2$, $PdCl_2(PPh_3)_2$, Li_2CO_3, THF, 60 °C (51%); (xviii) I_2 (1 equiv), Et_2O (44%); (xix) 30 mol % $Pd(PPh_3)_4$, PhMe, 100 °C (39%); (xx) $LiAlH_4$, Et_2O, Δ (42%); (xxi) HCl, MeOH, H_2O.

Cuscohygrine (**139**) has recently been synthesized by Stapper and Blechert via an elegant tandem ring-closing and -opening metathesis of the triene **145** (Scheme 23).[59] Double reduction of the ethyl carbamate to provide the tertiary amine **147**, followed by cleavage of the silyl protecting group and oxidation of the resulting alcohol under Jones oxidation conditions afforded cuscohygrine (**139**).

3. 'Dimerization' strategies

This category includes strategies that employ a dimerization or coupling of two similar components as the key way of installing the symmetry present in the final molecule. There are two main sub-divisions in this class, and these are described below.

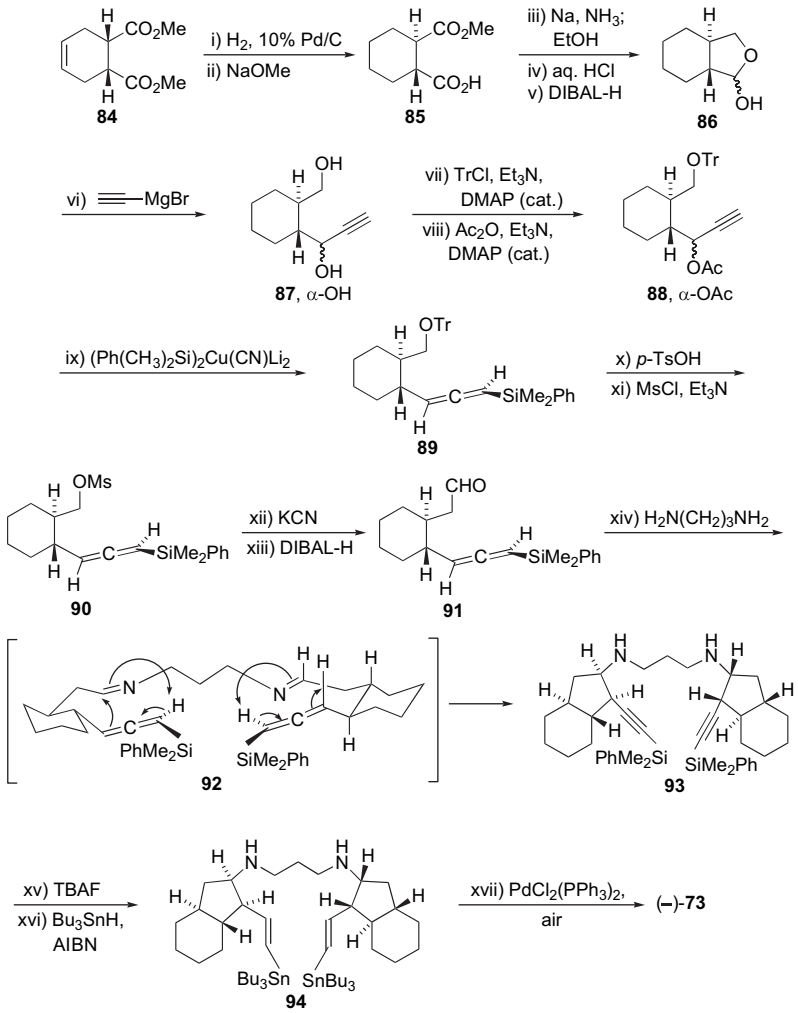
(a) *'Dimerization'*: In this approach, 'dimerization' or coupling of two similar components constitutes the final step in the synthesis (Scheme 24). For the purposes of this review syntheses where deprotection or single minor functional group interconversions were carried post-coupling are also classified here.
(b) *'Dimerization' followed by two-directional synthesis*: In this case, 'dimerization' or coupling of two similar components is followed by chain elongation or modification in a two-directional manner (Scheme 25).

3.1. 'Dimerization'

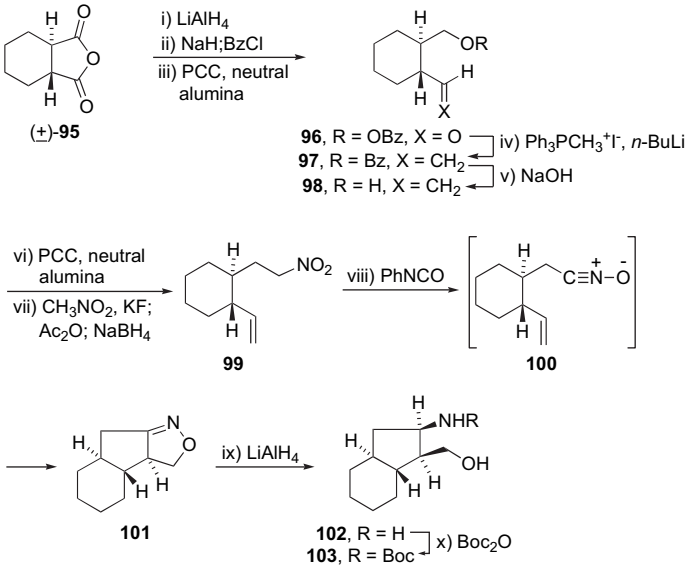
3.1.1. Marine organisms.

3.1.1.1. Cyclostellettamines A, C, and F. The cyclostellettamines (**148–150**, Fig. 11) are 3-alkylpyridine dimers isolated from the marine sponge *Stelletta maxima* by Fusetani and co-workers in 1994.[60] They inhibit binding of methyl quinuclidinyl benzylate to muscarinic acetylcholine receptors at concentrations between 0.026 and 0.15 (IC_{50}, μg/ml).[60] The latter plays an important role in various physiological functions, including learning and memory.[61] They are also known to be correlated with some disease states, and their agonists and antagonists may be potential drugs.[62] It has been proposed that, although they are structurally simple, they may be biogenetically related to a number of other more complex sponge metabolites, including the manzamine alkaloids.[63]

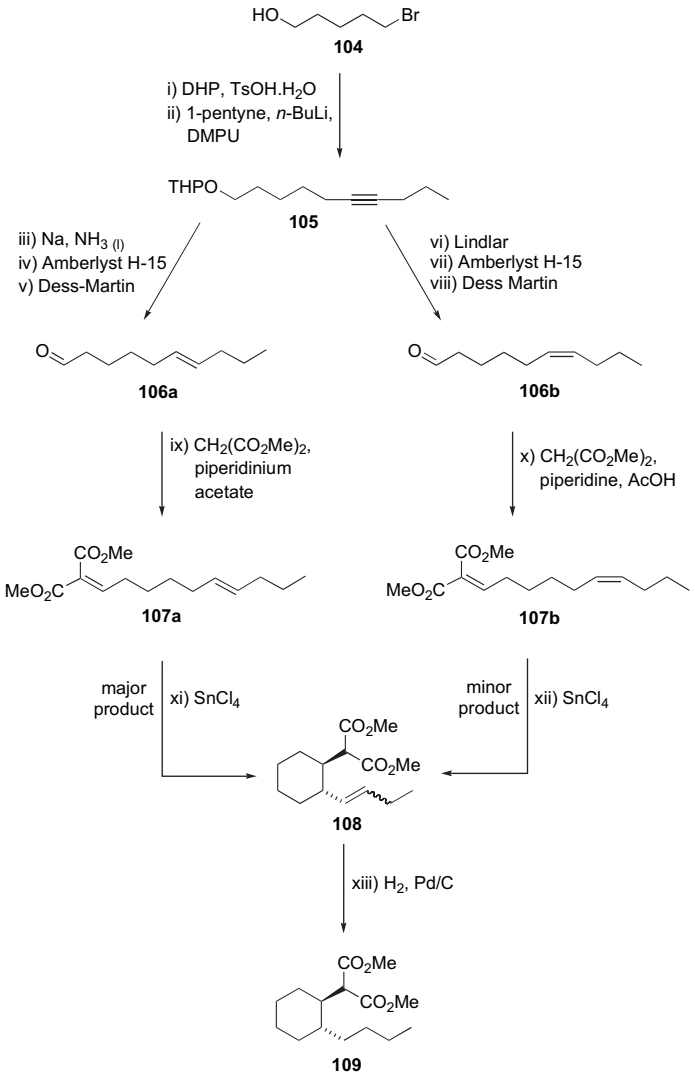
The cyclostellettamines (**148–149**) were first synthesized by Wanner and Koomen via a controlled 'dimerization' reaction of intermediates **158**, **159** and **160**, which bear increasingly elongated aliphatic chains, with **155**, **156** and **157**, respectively (Scheme 26).[64] Conversion of the terminal alcohol into the corresponding iodide followed by removal of the protecting group and cyclization afforded the cyclostellettamines (**148–150**). Soon after, Baldwin and co-workers reported a strategy based on the use of pyridine *N*-oxide as a protected form of pyridine (Scheme 27).[65] Thus, in the final stages of the total synthesis, the



Scheme 17. Synthesis of (−)-papuamine (**73**) by Weinreb and co-workers. Reagents and conditions: (i) H_2, 10% Pd/C, EtOH (100%); (ii) NaOMe, MeOH, 0 °C (96%); (iii) Na, NH_3, −50 °C; EtOH (70%); (iv) HCl, H_2O (pH 2) (70% over two steps); (v) DIBAl-H, PhMe, −78 °C (95%); (vi) ethynylmagnesium bromide, THF, 0–20 °C (95%); (vii) TrCl, Et_3N, DMAP (cat.), DMF (99%); (viii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 0–20 °C (99%); (ix) $PhMe_2SiLi$, CuCN, THF, 0 to −78 °C (88%); (x) TsOH, MeOH (99%); (xi) MsCl, Et_3N, CH_2Cl_2, 0–20 °C (99%); (xii) KCN, DMSO, 45 °C (77%); (xiii) DIBAl-H, PhMe, −78–0 °C (74%); (xiv) 1,3-diaminopropane, PhMe, 4 Å molecular sieves, Δ (70%); (xv) Bu_4NF, THF (74%); (xvi) Bu_3SnH, AIBN, PhMe, Δ (80%); (xvii) $PdCl_2(PPh_3)_2$, air, DMF (48%).



Scheme 18. Synthesis of key intermediate **103** by Bhattacharjya and co-workers. Reagents and conditions: (i) $LiAlH_4$, THF (90%); (ii) NaH; BnCl (82%); (iii) PCC, neutral alumina, CH_2Cl_2 (96%); (iv) Ph_3PMeI, *n*-BuLi (70%); (v) NaOH, MeOH, H_2O (96%); (vi) PCC, neutral alumina, CH_2Cl_2 (92%); (vii) $MeNO_2$, KF; Ac_2O; $NaBH_4$, EtOH (68%); (viii) PhNCO, PhH (72%); (ix) $LiAlH_4$, Et_2O (88%); (x) Boc_2O, EtOAc (90%).



Scheme 19. Biomimetic synthesis of key intermediate **109** by Baldwin and co-workers. Reagents and conditions: (i) DHP, TsOH·H_2O, CH_2Cl_2, 0–25 °C (78%); (ii) 1-pentyne, *n*-BuLi, DMPU, THF, −78–20 °C (78%); (iii) Na, $NH_{3(l)}$, Et_2O, −33 °C (90%); (iv) Amberlyst H-15®, MeOH, 45 °C (94%); (v) Dess-Martin periodinane, CH_2Cl_2, 0 °C (94%); (vi) H_2, Lindlar's catalyst, quinoline, CH_2Cl_2 (89%); (vii) Amberlyst H-15®, MeOH, 45 °C (90%); (viii) Dess–Martin periodinane, CH_2Cl_2, 0 °C (97%); (ix) $CH_2(CO_2Me)_2$, piperidinium acetate, CH_2Cl_2 (57%); (x) $CH_2(CO_2Me)_2$, piperidine, AcOH, CH_2Cl_2, 0–20 °C (40%); (xi) $SnCl_4$, CH_2Cl_2 (48% *E*/*Z* 7:1); (xii) $SnCl_4$, CH_2Cl_2 (10%, *E*/*Z* 10:1); (xiii) H_2, Pd/C, EtOAc (99% for both routes).

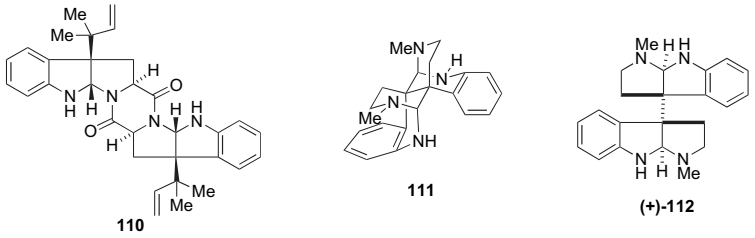
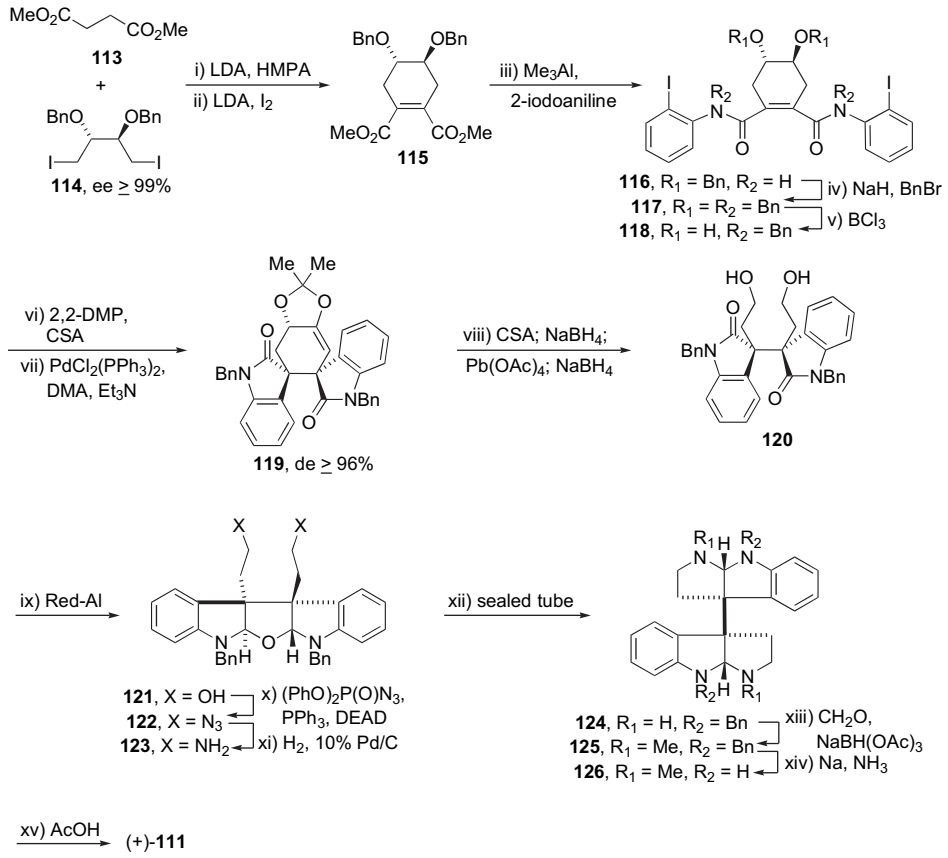


Figure 8. Structures of amauromine (**110**), (+)-calycanthine (**111**) and (+)-chimonanthine (**112**).

terminal iodide was introduced and the pyridine functionality unmasked. A dimerization–cyclization sequence completed the synthesis of the cyclostellettamines (**148**–**150**).

3.1.1.2. Dehydrohomoancepsenolide. Dehydrohomoancepsenolide (**177**, Fig. 12), which is closely related to ancepsenolide (**21**) (Section 2.1.1.2), was isolated from the gorgonian octocoral *P. citrina* and is hoped to have similar interesting biological properties to its related saturated congener.[14]

The synthesis of dehydrohomoancepsenolide (**177**) has recently been published by Fürstner and co-workers using



Scheme 20. Synthesis of (+)-calycanthine (**111**) by Overman and co-workers. Reagents and conditions: (i) LDA, HMPA, THF, −78 °C (46%); (ii) LDA, I_2, THF, −78 °C (72%); (iii) Me_3Al, 2-iodoaniline, PhMe (92%); (iv) NaH, BnBr, DMF (87%); (v) BCl_3, −78 °C (70%); (vi) 2,2-dimethoxypropane, 10-camphorsulfonic acid monohydrate (80%); (vii) 10 mol % $PdCl_2(PPh_3)_2$, DMA, Et_3N, 100 °C (90%); (viii) 10-camphorsulfonic acid, THF; $NaBH_4$, MeOH; $Pb(OAc)_4$, PhH, and finally $NaBH_4$, MeOH (88%); (ix) Red-Al, THF to Δ; (x) $(PhO)_2P(O)N_3$, PPh_3, DEAD, THF (92% over two steps); (xi) H_2, 10% Pd/C, EtOH (100%); (xii) sealed tube, MeOH, 110 °C; (xiii) CH_2O, $NaBH(OAc)_3$, MeOH (75% over two steps); (xiv) Na, NH_3, THF, 98%); (xv) AcOH, Δ (60%).

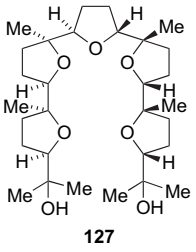


Figure 9. Structure of glabrescol.

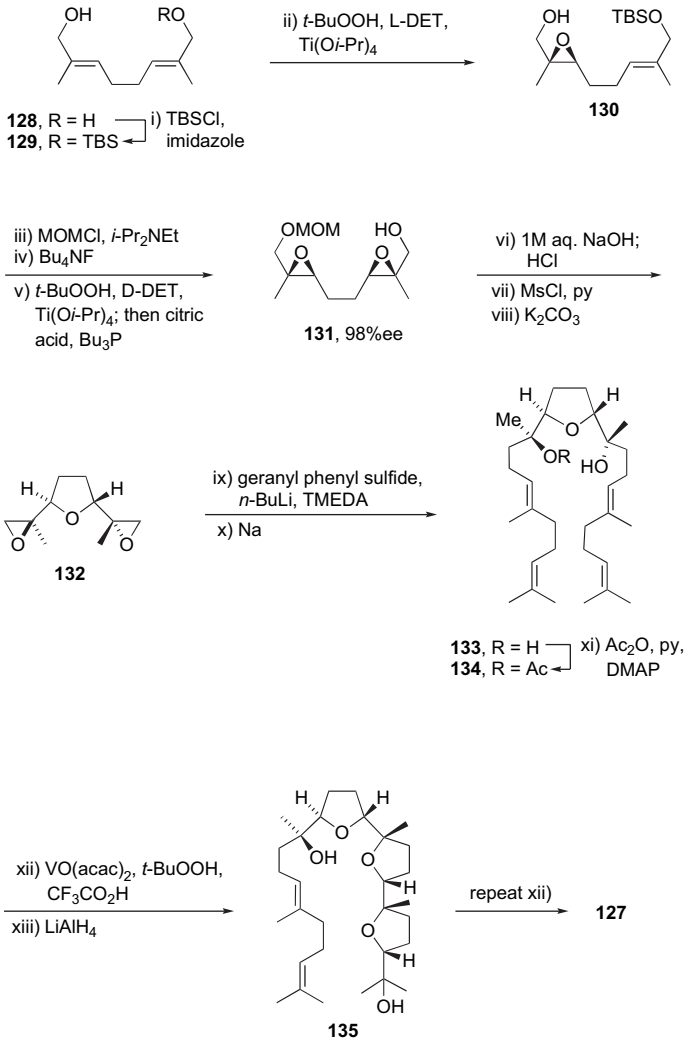
ring-closing metathesis of diene **181**, which was obtained via a zinc-mediated three-component coupling. Alkyne metathesis was then utilized for the dimerization of the resulting butenolide alkyne **182**, yielding bis-butenolide **183**, which underwent partial hydrogenation using Lindlar's catalyst to complete the synthesis (Scheme 28).[66]

3.1.1.3. Palythazine. Palythazine (**184**, Fig. 13) was isolated in 1979 from the zoanthid *Palythoa tuberculosa*[67] and the total synthesis by Jarglis and Lichtenthaler in 1982 established the absolute stereochemistry.[68] The synthesis followed a classic dimerization approach, but also took advantage of the chiral pool to introduce the required stereochemistry (Scheme 29).

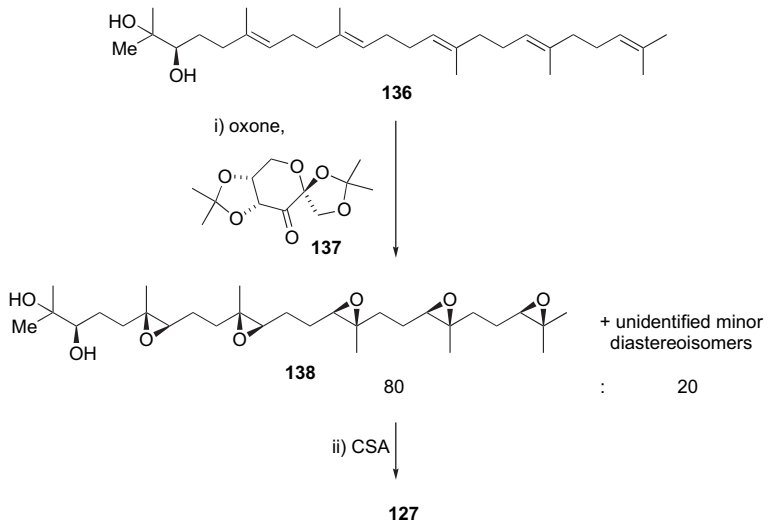
Thus, D-glucose derivative **185** was converted into the unsaturated ketone **186** via the corresponding oxime. Treatment of **186** with hydroxylamine and deprotection yielded the dione mono-oxime **187**. Reduction of the latter to the aminoketone **188** was followed by dimerization via self-condensation to form palythazine (**184**).[68]

3.1.1.4. Swinholide A. Swinholide A (**190**, Fig. 14) is a member of the swinholide family of complex macrodiolides, first isolated from the marine sponge *Theonella swinhoei*.[69] Following isolation from an additional sponge,[70] its initial monomeric assignment was revised to a dimer composed of two identical *seco* acids, based on mass spectrometric and X-ray crystallographic studies.[71–73]

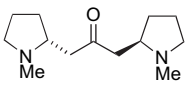
Swinholide A (**190**) exhibits antifungal activity and its high cytotoxicity against a variety of human carcinoma cell lines (L1210 cells and KB cells)[74,75] is attributed to its ability to disrupt the actin cytoskeleton.[76] The first total synthesis of swinholide A (**190**) was achieved by Paterson and coworkers in 1994.[77–81] The main strategies used in its synthesis are outlined in Schemes 30 and 31. Thus, advanced intermediate **193** was prepared via an aldol reaction between **191** and aldehyde **192**, which proceeded with excellent diastereoselectivity (dr 95:5). The former was subsequently converted into (−)-preswinholide A (which is the monomeric seco acid) derivative **194**. The latter was dimerized,



Scheme 21. Synthesis of glabrescol (**127**) by Morimoto and co-workers. Reagents and conditions: (i) *t*-BuMe$_2$SiCl, imidazole, CH_2Cl_2 (55%); (ii) *t*-BuOOH, Ti(O*i*-Pr)$_4$, L-DET, CH_2Cl_2, 4 Å molecular sieves, −20 °C (86%, 98% ee); (iii) $MeOCH_2Cl$, *i*-Pr$_2$NEt, CH_2Cl_2, 0–20 °C (96%); (iv) Bu_4NF, THF, 0 °C (98%); (v) *t*-BuOOH, Ti(O*i*-Pr)$_4$, L-DET, CH_2Cl_2, 4 Å molecular sieves, −25 °C; citric acid, Bu_3P (85%); (vi) 1 M NaOH in H_2O, 1,4-dioxane, Δ; HCl (pH 2), Δ (88%); (vii) MsCl, pyridine, CH_2Cl_2, 0–20 °C; (viii) K_2CO_3, MeOH (75% over two steps); (ix) geranyl phenyl sulphide, *n*-BuLi, TMEDA, THF, −78 °C; (x) Na, *i*-PrOH, THF, Δ (64% over two steps); (xi) Ac_2O, pyridine, DMAP, CH_2Cl_2 (62%); (xii) VO(acac)$_2$, *t*-BuOOH, CF_3CO_2H, CH_2Cl_2; (xiii) $LiAlH_4$, THF, 0 °C (26% over two steps); repeat (xii) (40%).



Scheme 22. Synthesis of glabrescol by Corey and co-workers. Reagents and conditions: (i) oxone, **137**, MeCN, $(MeO)_2CH_2$, H_2O (pH 10.5), 0 °C; (ii) 10-camphorsulfonic acid, PhMe, 0 °C (31% over two steps).



139

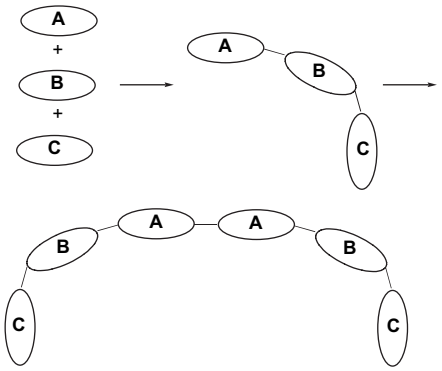
Figure 10. Structure of cuscohygrine.

and subsequently cyclized using the Yamaguchi esterification and macrolactonization protocols, respectively. Universal deprotection completed the total synthesis of swinholide A (**190**) in 0.4% overall yield.

A similar approach was envisaged by Nicolaou and co-workers, who chose to employ a coupling reaction between cyclic sulfate **202** and dithiane **203** as the key step towards the synthesis of (−)-preswinholide A derivative **209** (Scheme 32).[82–85] Swinholide A (**190**) was subsequently obtained from **209** in a similar fashion to that disclosed by Paterson and co-workers in 0.3% overall yield over 53 steps (Scheme 33).

Additional syntheses of preswinholide derivative including **209** have been accomplished by Nakata[86] and Mulzer groups,[87] as well as various synthetic studies on subunits of swinholide A (**190**). These include the stereoselective construction of the chiral tetrahydropyran[87,88] and dihydropyran[89] units, as well as the C_{13}–C_{25},[90] C_{19}–C_{35}[91] and the C_{11}–C_{23} segments.[86,92]

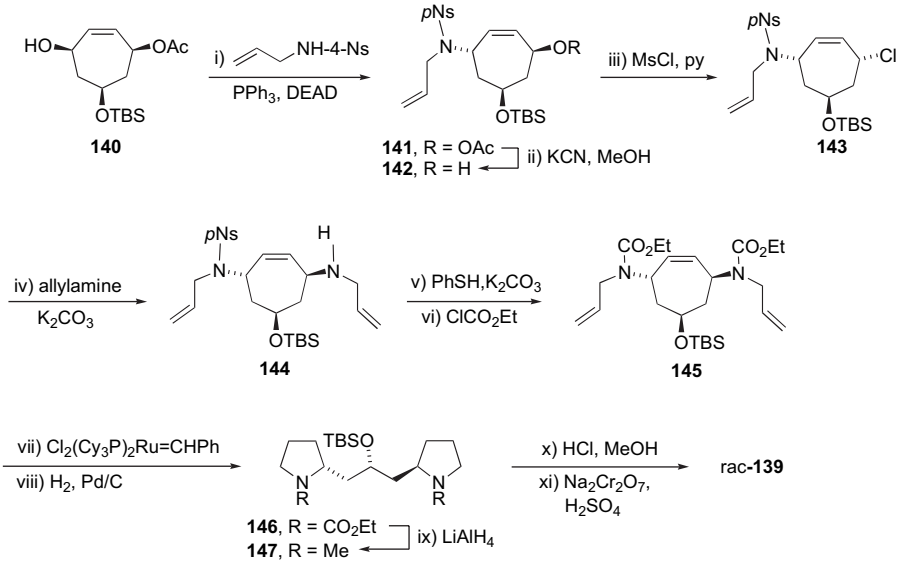
Another family of macrodiolides isolated from *Theonella* sp. includes the structurally similar bistheonellides.[93–96] Bistheonellide A, otherwise known as misakinolide A, is structurally very similar to swinholide A, but lacks an ethene portion in the monomeric unit. The structural similarities between the swinholides and bistheonellides initially led to the suggestion that they are metabolites of cyanobacteria



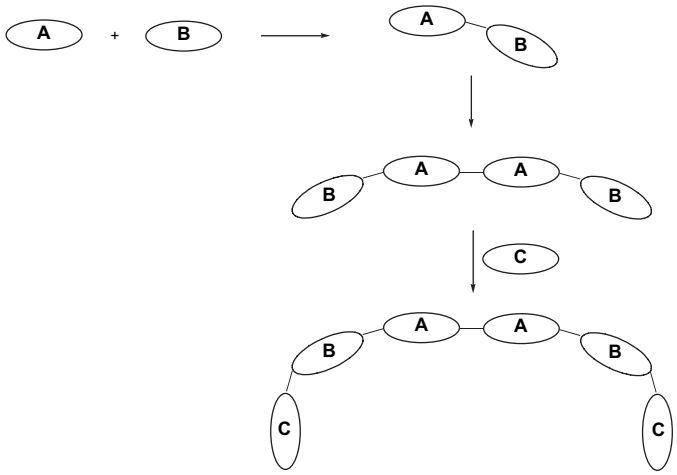
Scheme 24. Illustration of 'dimerization'.

associated with *Theonella* sp.,[97] but this is uncertain following the association of swinholide A (**190**) with unicellular heterotrophic bacteria.[98]

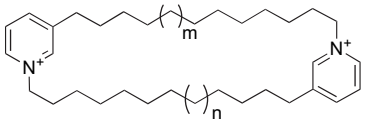
3.1.1.5. Testudinariol A. Testudinariol A (**213**, Fig. 15), which is structurally similar to limatulone (**411**, Section 3.2.1.2), was isolated along with its non-C_2 symmetric diastereoisomer testudinariol B from the skin and defensive mucus secretions of the *Notaspidea* mollusc *Pleurobranchus testudinarius* in 1997 by Spinella and co-workers.[99] Its structure was assigned and shown to be a dimer of a highly functionalized cyclopentanol framework with four adjoining stereocentres attached to a 3-alkylidene tetrahydropyran unit. This unusual triterpene alcohol has been found to be ichthyotoxic against *Gambusia affinis*, and is thought to be the main defensive allomone of *P. testudinarius*.[99] The general biosynthetic pathway for polycyclic tripterpenoid natural products via squalene 2,3-oxide cannot be responsible for these compounds as such a carbon skeleton would not be produced.[100]



Scheme 23. Synthesis of (±)-cuscohygrine (**139**) by Blechert and co-workers. Reagents and conditions: (i) 4-Ns-allylamine, PPh_3, DEAD, THF (92%); (ii) KCN, MeOH; (iii) MsCl, pyridine (78% over two steps); (iv) allylamine, K_2CO_3, MeCN (85%); (v) PhSH, K_2CO_3, DMF; (vi) $ClCO_2Et$ (82% over two steps); (vii) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2; (viii) H_2, Pd/C, EtOH (72% over two steps); (ix) $LiAlH_4$, Et_2O (92%); (x) HCl, MeOH (89%); (xi) $Na_2Cr_2O_7$, H_2SO_4, Me_2CO (73%).

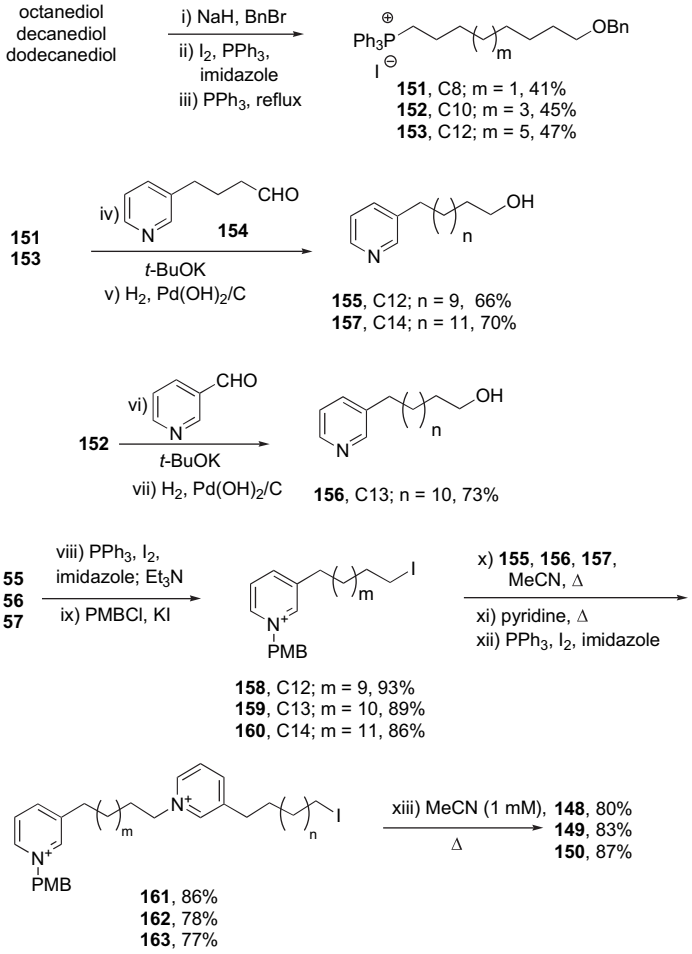


Scheme 25. Illustration of 'dimerization' followed by two-directional synthesis.

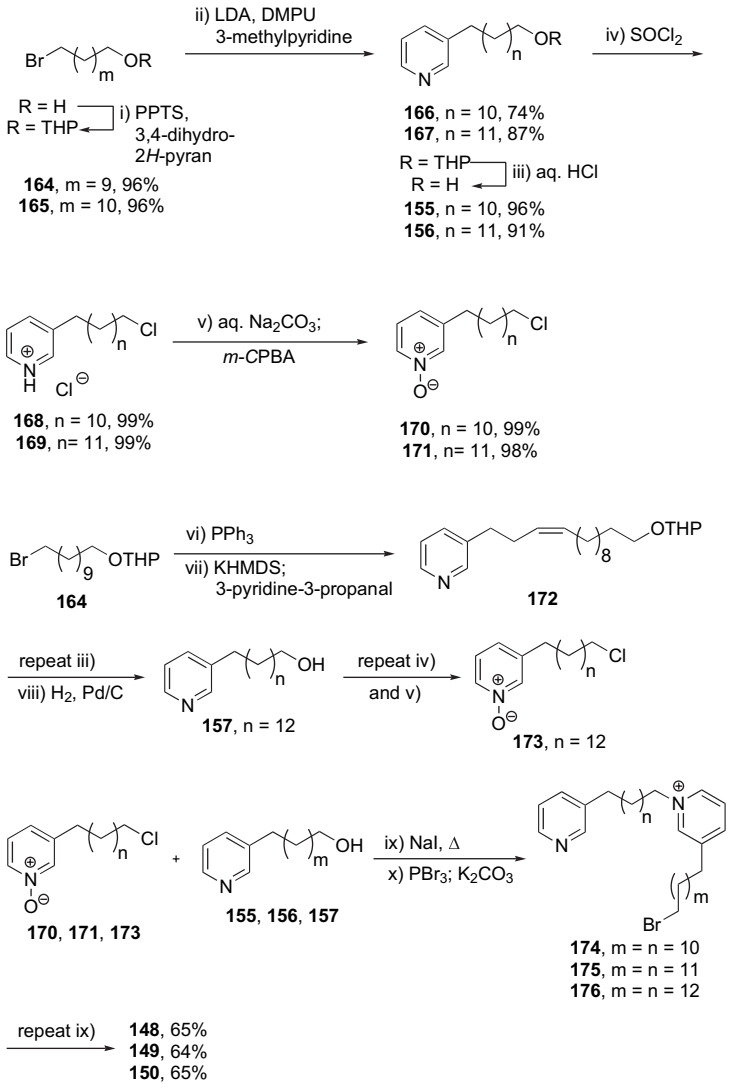


148: C12/C12 (m = 1, n = 1)
149: C13/C13 (m = 2, n = 2)
150: C14/C14 (m = 3, n = 3)

Figure 11. Structures of cyclostellettamines A (**148**), C (**149**) and F (**150**).



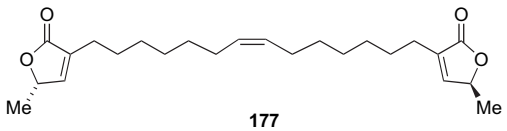
Scheme 26. Synthesis of cyclostellettamines **148**–**150** by Koomen and co-workers. Reagents and conditions: (i) NaH, BnBr, THF, 60–70 °C; (ii) I_2, PPh_3, imidazole, PhH; (iii) PPh_3, PhMe, Δ (**151**: 41%; **152**: 45%; **153**: 47% over three steps); (iv) **154**, *t*-BuOK, THF; (v) H_2, $Pd(OH)_2$/C, EtOH, 25% HCl in H_2O (**155**: 66%; **157**: 70% over two steps); (vi) nicotinaldehyde, *t*-BuOK; (vii) H_2, $Pd(OH)_2$/C, EtOH, 25% HCl in H_2O (73% over two steps); (viii) PPh_3, I_2, imidazole, PhH; Et_3N, CH_2Cl_2; (ix) 4-$MeOC_6H_4CH_2Cl$, KI, MeCN (**158**: 93%; **159**: 89%; **160**: 86% over two steps); (x) **156**, **157** or **157**, MeCN, Δ; (xi) pyridine, Δ; (xii) PPh_3, I_2, imidazole, PhMe/MeCN 2.4:1 (**161**: 86%; **162**: 78%; **163**: 77% over three steps); (xiii) MeCN, Δ (**148**: 80%; **149**: 83%; **150**: 87%).



Scheme 27. Synthesis of cyclostellettamines **148**–**149** by Baldwin and co-workers. Reagents and conditions: (i) PyHOTs, 3,4-dihydro-2*H*-pyran, CH_2Cl_2; (ii) LDA, DMPU, 3-methylpyridine; (iii) 3 M HCl in H_2O, MeOH; (iv) $SOCl_2$, 1,4-dioxane; (v) 2 M Na_2CO_3 in H_2O; *m*-CPBA, CH_2Cl_2; (vi) PPh_3, MeCN (91%); (vii) $KN(SiMe_3)_2$; 3-pyridin-3-propanal, THF (71%); viii) H_2, Pd/C, EtOH (99%); (ix) NaI, 2-butanone, Δ; (x) PBr_3, $CHCl_3$; K_2CO_3.

Synthetic studies have followed two paths: the dimerization of a monomer **216** constructed in its entirety prior to coupling,[100–102] and the coupling of the functionalized cyclopentanol framework **214** with a bridging diene chain **215** followed by cyclization to form the pyran (Scheme 34).[103]

The first published total synthesis by Mori and co-workers followed the former protocol (Schemes 35 and 36).[100,102] The previously reported diol **217** was converted to the highly functionalized protected cyclopentanol **225** via pyran **224**. Conversion into the bromide **230** and synthesis of the sulfone **231** was followed by 'dimerization', and desulfonylation, and deprotection yielded testudinariol A (**213**). While successful, Mori's synthesis relies on thermodynamic control and the separation of diastereoisomers of pyran **224** by silica flash column chromatography.[100,102] Kodama and co-workers followed a similar protocol, but synthesized the bromide **230** enantioselectively via chiral induction using bakers yeast.[104] Separation of the coupled isomers in this case was again unsuccessful.

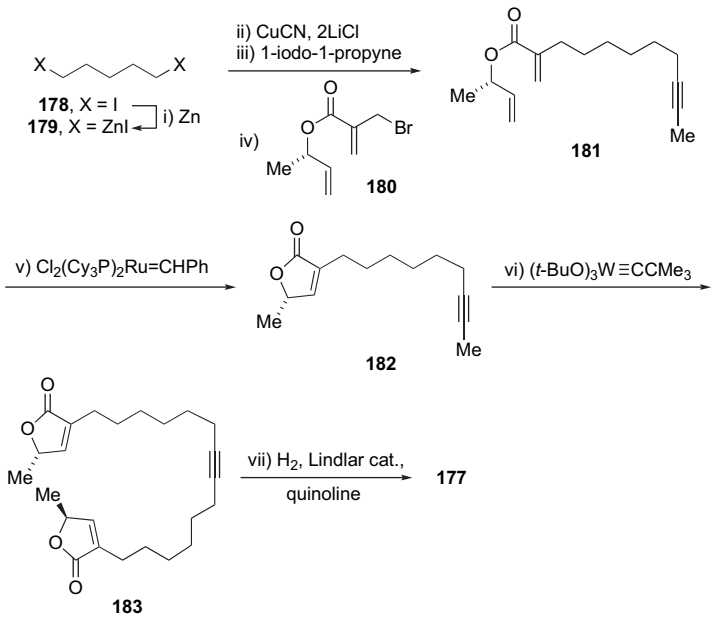


177

Figure 12. Structure of dehydrohomoancepsenolide.

Amarasinghe and Montgomery reported a second synthesis in 2002.[103] Their approach utilized a novel strategy for controlling the stereochemical features of these structurally intriguing natural products. The key step involved a novel nickel-catalyzed cyclization of allenyl aldehyde **235** to afford advanced intermediate **236**, which was further elaborated and coupled to dibromide **215** to complete the synthesis of testudinariol A (**213**) (Scheme 37).

3.1.1.6. Xestospongine A (araguspongine D). Xestospongine A (**240**, Fig. 16), which is closely related to



Scheme 28. Synthesis of dehydrohomoancepsenolide (**177**) by Fürstner and co-workers. Reagents and conditions: (i) Zn, THF, 40 °C; (ii) CuCN, 2LiCl, THF, 0 °C; (iii) 1-iodo-1-propyne, hexane, −60 to −35 °C; (iv) **180**, −78–20 °C (70% over four steps) (v) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, Δ (70%); (vi) $(t\text{-}BuO)_3W{\equiv}CCM_3$, PhMe, 100 °C (75%); (vii) H_2, Lindlar's catalyst, quinoline, hexane/EtOH 1:1 (96%).

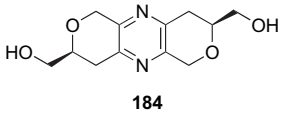


Figure 13. Structure of (*S*,*S*)-palythazine.

petrosin (**431**, Section 3.2.1.4), belongs to a family of vasodilative alkaloids isolated by Nakagawa and co-workers from the sponge *Xestospongia exiguai* in 1984.[105] Five years later, araguspongine D was isolated by Kitagawa and co-workers from *Xestospongia* sp. as a mixture of enantiomers (~70:30), the minor component of which was identical to (+)-xestospongine A.[106]

Xestospongine A (**240**) contains a pair of oxaquinolizidine moieties, with the parent oxaquinolizidine ring system able to access both *trans*- and *cis*-decalin-like conformations by bridgehead nitrogen atom inversion. Xestospongine A was originally synthesized by Hoye and co-workers (Schemes 38 and 39).[107,108] Interestingly, two years later, in a biomimetic synthesis of the title compound, Baldwin and co-workers demonstrated that the original stereochemical assignment

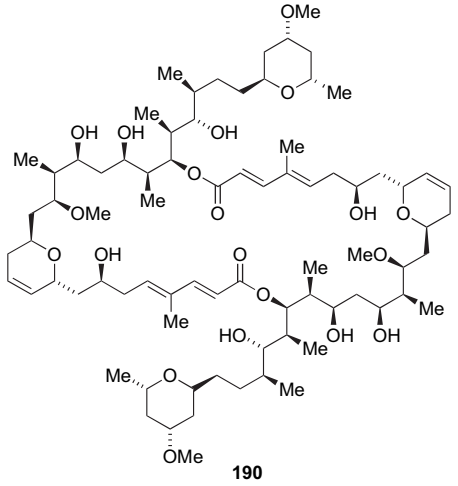
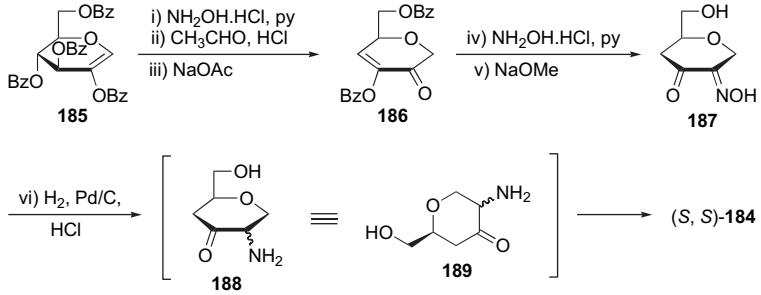
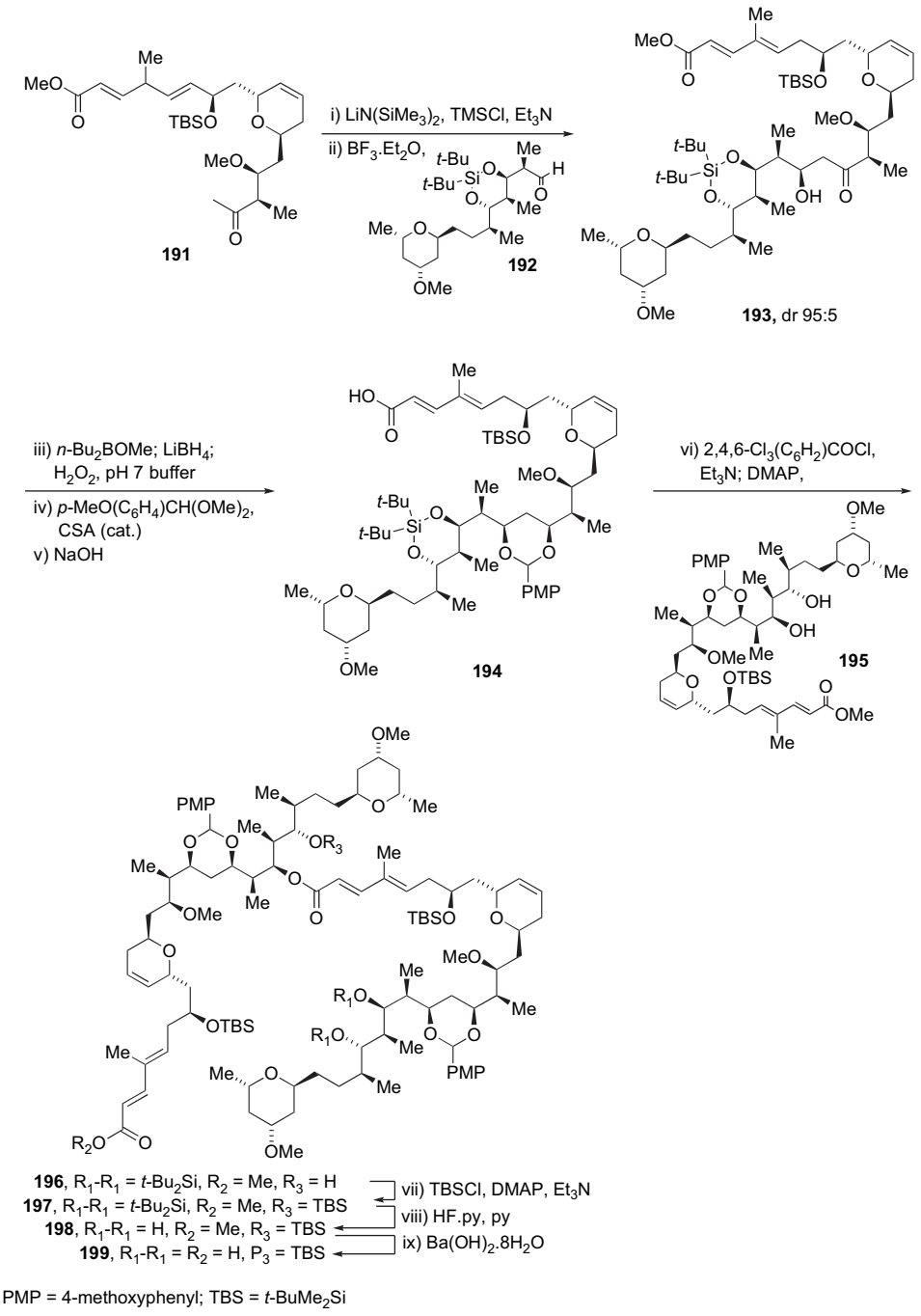


Figure 14. Structure of swinholide A.

by Kitagawa and co-workers[106] was flawed (Scheme 40).[109] Thus, the corrected configuration of (+)-xestospongine A (**240**) now stands as 2*R*,9*S*,9a*S*,2′*R*,9′*R*,9a′*S* (Fig. 16) instead of 2*S*,9*S*,9a*R*,2′*S*,9′*S*,9a′*R*. In the model studies carried out

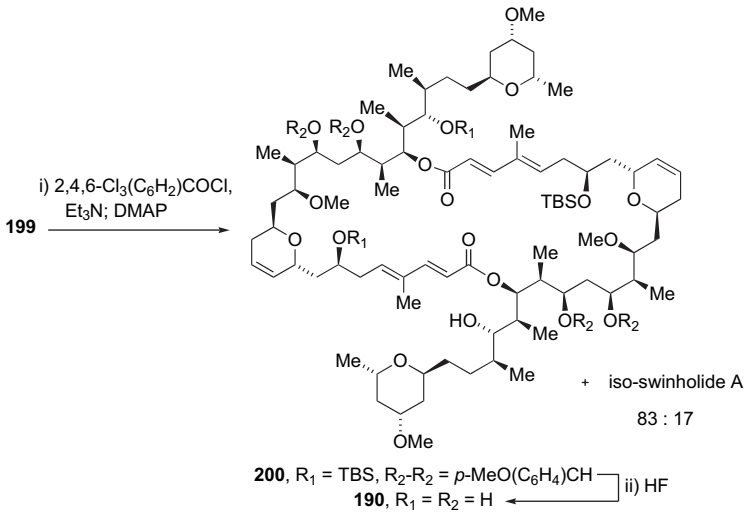


Scheme 29. Synthesis of palythazine (**188**) by Lichtenthaler and co-workers. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, pyridine, 70 °C (93%); (ii) MeCHO, HCl, MeCN (88%); (iii) NaOAc, Me_2CO (92%); (iv) $NH_2OH{\cdot}HCl$, pyridine, $CHCl_3$/EtOH 5:3 (96%); (v) NaOMe, MeOH, −10 °C (89%); (vi) H_2, Pd/C, HCl (57%).



Scheme 30. Synthesis of swinholide A (**190**) by Paterson and co-workers (Part A). Reagents and conditions: (i) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, −78 °C; (ii) **192**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C (91% over two steps); (iii) *n*-Bu_2BOMe, THF/MeOH 5:1 −78 °C; $LiBH_4$, −78 to −40 °C; H_2O_2, pH 7 buffer, MeOH (90%); (iv) 4-$MeO(C_6H_4)CH(OMe)_2$, 10-camphorsulfonic acid (cat.), CH_2Cl_2 (98%); (v) NaOH, MeOH, H_2O, 60 °C; (vi) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, PhMe; **195**, DMAP, PhMe (85% over two steps); (vii) *t*-$BuMe_2SiCl$, DMAP, Et_3N, DMF, 80 °C (80%); (viii) HF·pyridine, pyridine, THF (81%); (ix) $Ba(OH)_2{\cdot}8H_2O$, MeOH (100%).

by Hoye and co-workers, the key step for the preparation of the oxaquinolizidine moieties was a simple condensation of a 5-haloaldehyde, such as **241**, with a 1,3-aminoalcohol like **242** (Scheme 38). In the actual synthesis, key intermediate **255** was converted into 5-haloaldehyde **256** when treated with acid, whereas reduction of the nitrile group resulted in the synthesis of the 1,3-aminoalcohol condensation partner **257**. Following kinetic resolution with *Pseudomonas fluorescens*, alcohol (+)-**256** represents a pair of diastereoisomers epimeric at C-10, but of a single configuration at C3. The 'stereogenic purity' of the carbinol center was found to be ≥95% ee by ^1H and ^{19}F NMR analyses of the corresponding Mosher ester derivatives. Instead, Baldwin and coworkers chose pyridine derivative **266** as a precursor to one ring of the oxaquinolizine unit and introduced the second in a double-cyclization step upon treatment of intermediate **267** with diethyl azodicarboxylate (DEAD), which presumably proceeds via an iminium intermediate (Scheme 40).



Scheme 31. Synthesis of swinholide A (**190**) by Paterson and co-workers (Part B). Reagents and conditions: (i) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe; DMAP, PhMe, 80 °C (84%); (ii) HF, MeCN, 0 °C (43%).

3.1.2. Plants and fungi.

3.1.2.1. Amauromine. Amauromine (**110**, Fig. 8), a potent vasodilator structurally similar to calycanthine (**111**, Section 2.2.2.1), was isolated from the *Amauroascus* sp. 6237 by Takase and co-workers[110,111] and it belongs to a class of natural products termed the 'reverse prenyl' hexapyrrolo[2,3-*b*]indole alkaloids by Danishefsky et al., who also reported a stereoselective total synthesis of amauromine (Scheme 41).[112,113] Starting from L-tryptophan methyl ester (**271**), a heteroatom-mediated oxidation using *N*-phenylselenophthalimide gave the 3-selenenylated pyrroloindoles **272** and **273** in a 9:1 ratio. Further manipulation, separation of the diastereoisomeric mixture and 'dimerization' resulted in key intermediate **277**, which was easily converted into amauromine (**110**) upon cleavage of the protecting groups.

3.1.2.2. Biatractylolide and biepiasterolide. Biatractylolide (**278**, Fig. 17) and biepiasterolide (**279**, Fig. 17) have been isolated from the Chinese medicinal plant *Atractylodes macrocephala*[114,115] as well as from the resin of *Trattinickia rhoifolia*, Willd.,[116] and have been shown to possess sesquiterpenic lactone structures joined at the C_8–C_{8a} bridgehead position as determined by X-ray crystallographic analysis.[114–117] They have been shown to exhibit significant negative inotropic and chronotropic effects, thus showing potential for application in blood pressure lowering therapy.[118]

The biomimetic syntheses of biatractylolide **278** and biepiasterolide **279** have been reported by Baldwin and co-workers, utilizing radical dimerization of chloroatractylolide **287**.[119] Ketone **282** was obtained from **280** via a Birch reduction, Oppenauer oxidation and 1,4-cuprate addition sequence. Wittig olefination and further manipulation generated butenolide **285** (Scheme 42).

Initial treatment of butenolide **285** with di-*t*-butyl peroxide as the radical generator to provide any of the desired dimers **278** or **279** was unsuccessful and was attributed to the steric bulk of the monomer (Scheme 43).

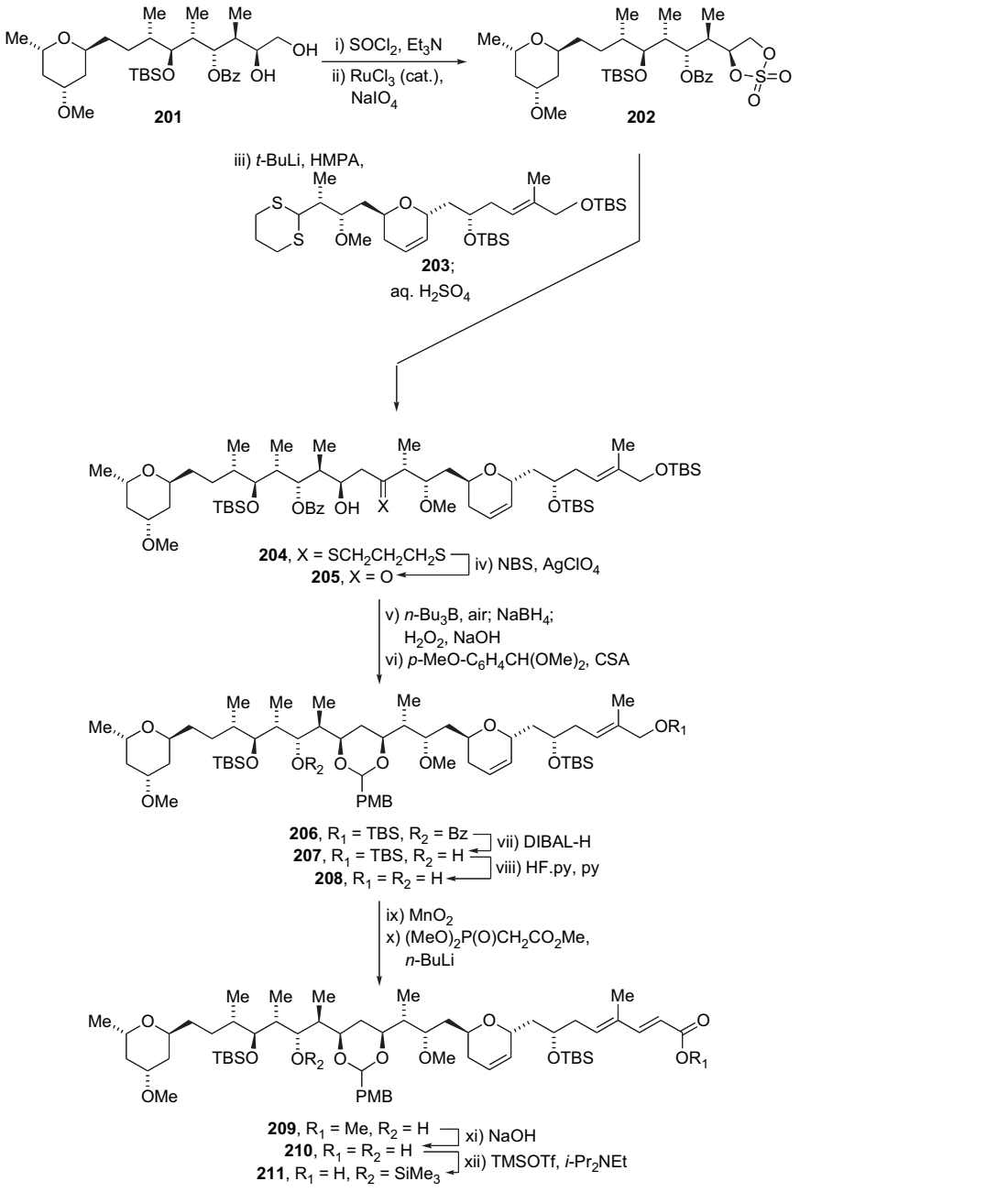
Butenolide **285** was subsequently converted into chloroatractylolide **287** via hydroxyatractylolide **286** and the dimerization step found to be successful using $Co(PPh_3)_3Cl$ (Scheme 44). Biatractylolide (**278**) and biepiasterolide (**279**) were isolated from the reaction mixture and characterized by X-ray crystallography.

3.1.2.3. Carpaine and azimine. Carpaine (**288**, Fig. 18) was isolated from the leaves of *Carica Papya* L. and its structure elucidated by means of chemical degradation and spectroscopy techniques.[120,121] It has been shown to possess antitumor activity in vitro against mouse lymphoid leukaemia and Ehrlich ascites tumour cells.[122] Interest in its unusual 26-membered ring and potential for host–guest interactions led to its recent characterization by an X-ray crystallographic study.[123]

The first synthesis of carpaine by Corey and co-workers utilized a double activation approach involving the 2-pyridinethiol ester of *N*-Cbz-carpamic acid **290** followed by deprotection of the resulting macrocycle by hydrogenolysis (Scheme 45).[124]

In a recent synthesis by Kibayashi, the carpamic acid monomer **290** was synthesized via a stereoselective intramolecular hetero-Diels–Alder reaction of acylnitroso intermediate **297**, obtained from Kirby oxidation of the hydroxamic acid **296** (Scheme 46).[125] The macrocyclic bis-lactonization of **290** was successfully carried out under Yamaguchi macrocyclization conditions (Scheme 47).

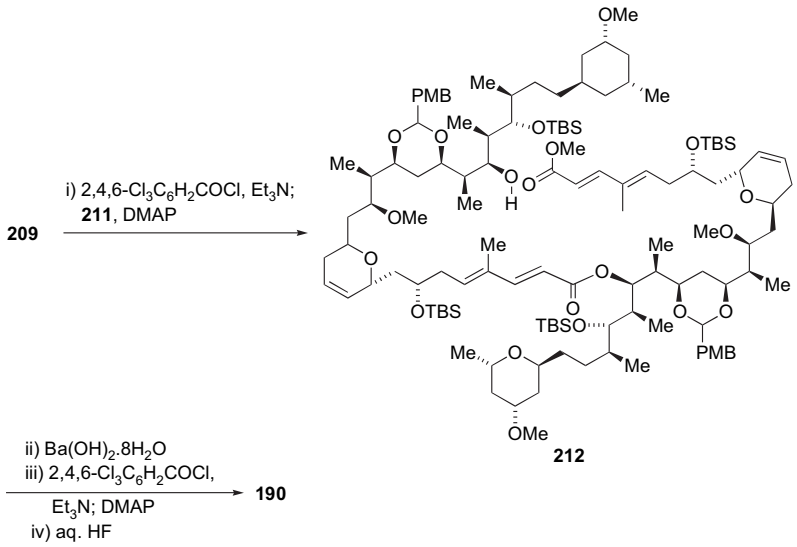
Various racemic syntheses of the carpamic acid (**288**) have been reported,[126–129] as well as two asymmetric syntheses.[130,131] The very similar alkaloid azimine (**289**, Fig. 18) was isolated from the leaves of *Azima tetracantha* and its structure determined by degradation studies.[132,133] A total synthesis has been recently achieved by Kibayashi and coworkers in an analogous fashion to that reported for carpaine (**288**).[125] In addition, various syntheses of the corresponding monomeric acid have been achieved.[127–130,134–140]



Scheme 32. Synthesis of swinholide (**190**) by Nicolaou and co-workers (Part A). Reagents and conditions: (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (ii) $RuCl_3$ (cat.), $NaIO_4$, CCl_4/MeCN/H_2O 2:2:3, 0 °C (95% over two steps); (iii) *t*-BuLi, HMPA, **203**, THF, −78 °C; 10% H_2SO_4 in H_2O, THF (72% over two steps); (iv) NBS, $AgClO_4$, 10% Me_2CO in H_2O, 0 °C (90%); (v) *n*-Bu_3B, air, THF; $NaBH_4$, −78 °C; 30% H_2O_2, 10% NaOH in H_2O, 0 °C (92%); (vi) 4-$MeOC_6H_4$-$CH(OMe)_2$, 10-camphorsulfonic acid, CH_2Cl_2, 0 °C (90%); (vii) DIBAl-H, CH_2Cl_2, −78 °C (95%); (viii) HF·pyridine, pyridine, CH_2Cl_2, 0 °C (90%); (ix) MnO_2, CH_2Cl_2 (99%); (x) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF, 0–25 °C (97%); (xi) NaOH, MeOH, THF, H_2O (92%); (xii) Me_3SiOTf, *i*-Pr_2NEt, CH_2Cl_2, 0–25 °C (89%).

3.1.2.4. Gossypol. Gossypol (**309**, Fig. 19) was isolated as the main coloring pigment of cotton seeds in 1886, but was not named until 1899.[141,142] Its structure and chemistry were elucidated some 50 years later in a large study on the pigment.[143–154] Optically active (*R*)-gossypol (**309**) has been reported to be an oral antifertility agent in men and male animals,[155,156] as well as showing activity for treatment of HIV infections and cancer,[157] whereas (*S*)-gossypol (**309**), which could be isolated from *Thespesia populnea*,[158] has been shown to be inactive as an antifertility agent.[159] Due to the restricted rotation about the internaphthyl 2,2′ bond, (*R*)- and (*S*)-gossypol (**309**) are chiral, with a C_2 axis of symmetry.

A formal synthesis of gossypol (**309**) was reported in 1957,[160] but an asymmetric synthesis of (*S*)-gossypol (**309**) was recently reported by Meyers, using an oxazoline-based approach.[161] Starting from 2,3,4-trimethoxybenzoic acid, bromooxazoline **318** was synthesized. The initial oxazoline was installed in order to mediate an *ortho*-Grignard coupling



Scheme 33. Synthesis of swinholide A (**190**) by Nicolaou and co-workers (Part B). Reagents and conditions: (i) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, PhMe; **211**, DMAP, PhMe, 105 °C (46% over two steps); (ii) $Ba(OH)_2 \cdot 8H_2O$, MeOH (83%); (iii) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, PhMe; DMAP, PhMe, 110 °C (38% over two steps based on 75% consumed acid); (iv) HF, H_2O MeCN, 0 °C (60%).

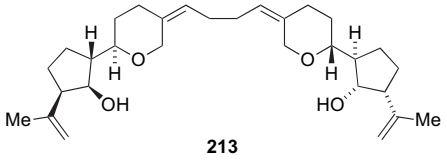


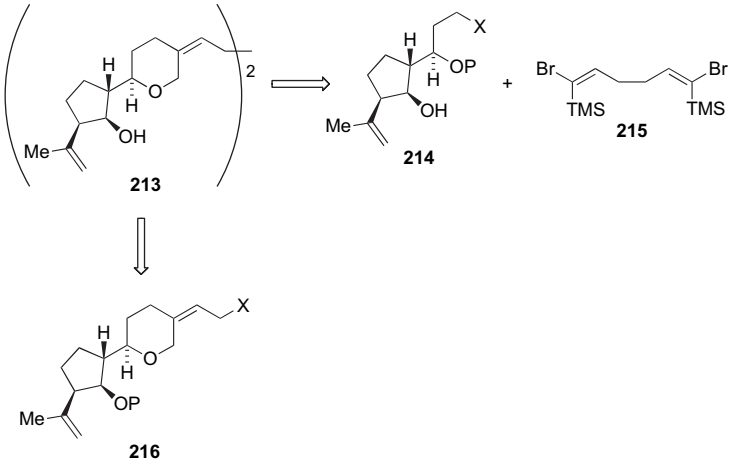
Figure 15. Structure of testudinariol A (**213**).

to generate **312**. Regioselective alkylation of the latter followed by oxazoline cleavage led to aldehyde **314**, which underwent a Stobbe condensation and ring-cyclization to afford naphthoic acid **315**. A second oxazoline formation followed by bromination afforded bromonaphthyloxazoline **318** (Scheme 48).

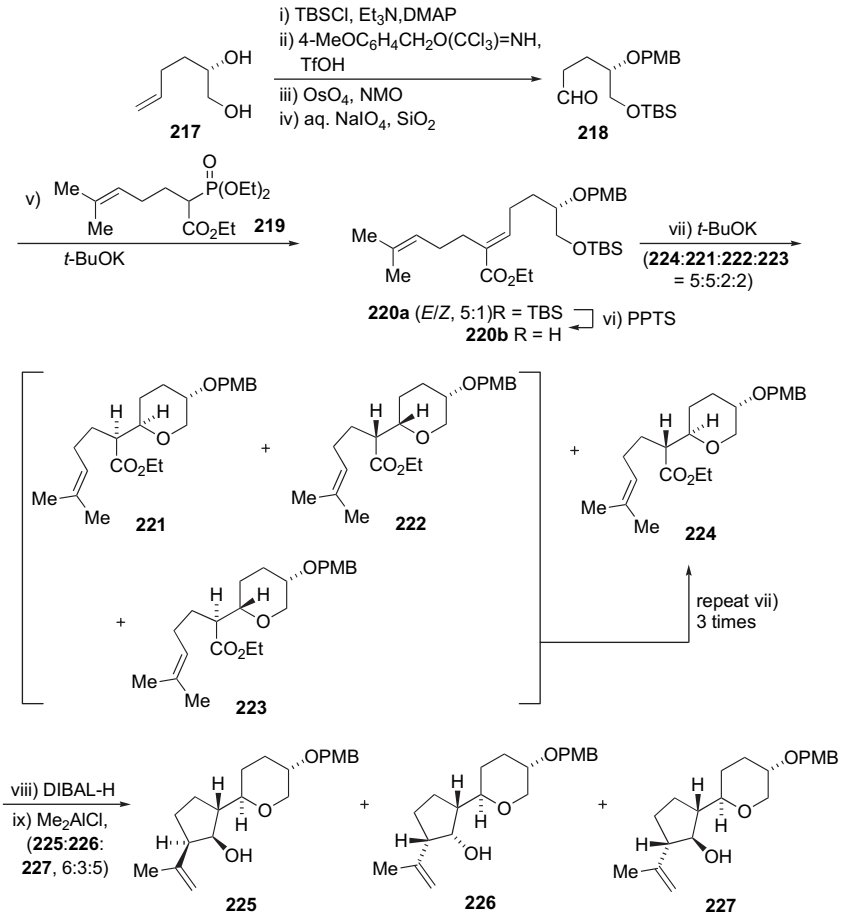
Ullman coupling of (*S*)-**318** proceeded in high yield and good stereospecificity (dr 17:1), to yield the coupled product **319**. The minor diastereoisomer could be removed by flash chromatography. Cleavage of the oxazoline group and global deprotection gave (*S*)-gossypol (**309**), which was isolated in high optical purity (Scheme 49).

3.1.2.5. Pyrenophorin. (−)-Pyrenophorin (**321**, Fig. 20), which is closely related to vermiculine (**345**, Section 3.1.3.7), is a metabolite of the plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum* and has been shown to have cytostatic properties and antifungal action.[162,163]

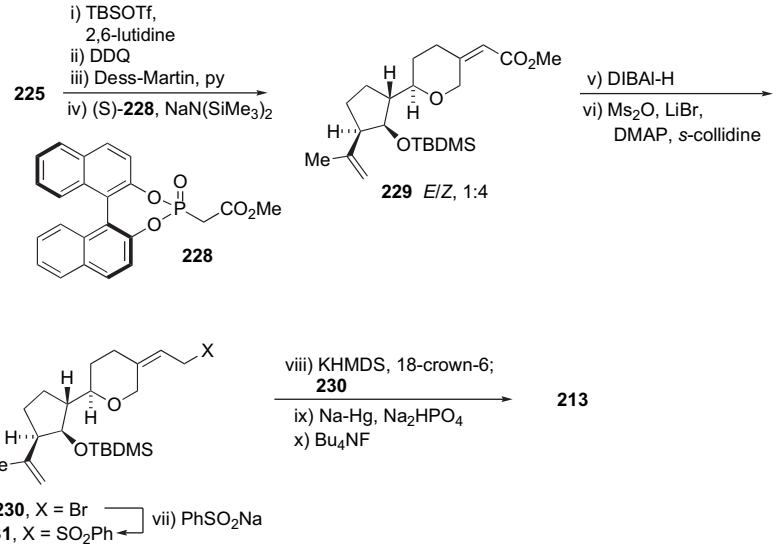
Significant levels of research have been devoted to the total synthesis of pyrenophorin (**321**) as both its racemic form[164–171] and diastereoisomerically pure (*R*,*R*)-(−)-isomer,[172–182] as well as a number of formal total syntheses.[183–205] The first total synthesis of racemic pyrenophorin (**321**) used a stepwise olefination and esterification approach for the formation of the macrocycle.[170,171] This work involved the introduction of 2-(4-tolylsulfonyl)ethyl ester as a carboxy-protecting group that would allow selective



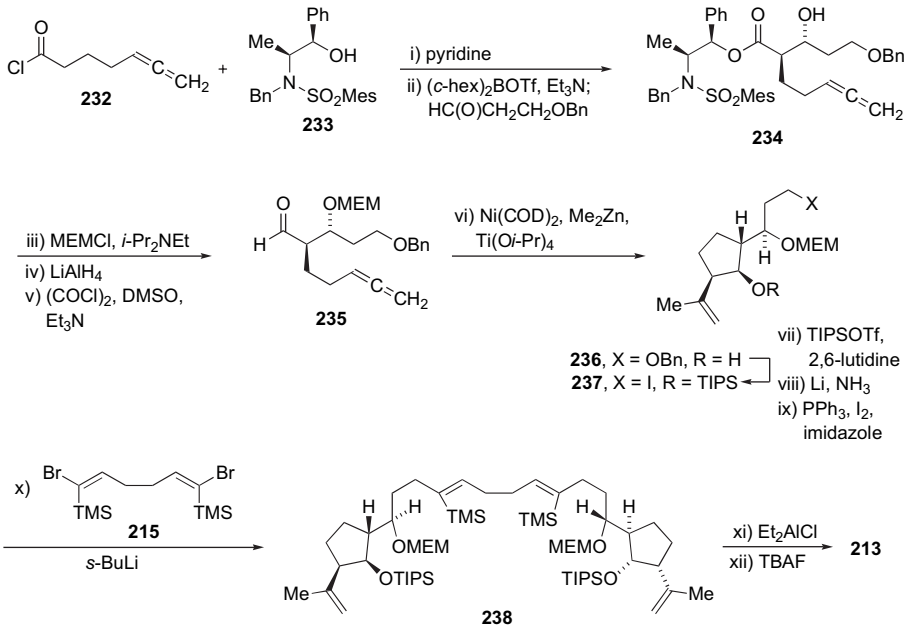
Scheme 34. Common retrosynthetic approaches to testudinariol A (**213**).



Scheme 35. Synthesis of testudinariol A (**213**) by Mori and co-workers (Part A). Reagents and conditions: (i) *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2 (85%); (ii) 4-$MeOC_6H_4CH_2OC(=NH)CCl_3$, TfOH, Et_2O (90%); (iii) OsO_4, NMO, *t*-BuOH, Me_2CO, H_2O (93%); (iv) $NaIO_4$, H_2O, SiO_2, CH_2Cl_2 (98%); (v) **219**, *t*-BuOK, PhMe, −20 °C (93%) (*E*/*Z* 5:1); (vi) PyHOTs, MeOH, (99%); (vii) *t*-BuOK, THF, −10–4 °C, (68% for **224**); (viii) DIBAl-H, PhMe, −78 °C (98%); (ix) Me_2AlCl, CH_2Cl_2, 0 °C (59%).



Scheme 36. Synthesis of testudinariol A (**213**) by Mori and co-workers (Part B). Reagents and conditions: (i) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2 (99%); (ii) DDQ, CH_2Cl_2, H_2O (97%); (ii) Dess-Martin periodinane, pyridine, CH_2Cl_2 (94%); (iv) (*S*)-**228**, $NaN(SiMe_3)_2$, THF, −78 to −20 °C (91%), *E*/*Z* 1:4; (v) DIBAl-H, CH_2Cl_2 (75%); (vi) Ms_2O, LiBr, DMAP, *s*-collidine, DMF (80%); (vii) $PhSO_2Na$, DMF (87%); (viii) $KN(SiMe_3)_2$, 18-crown-6, THF; **230** (84%); (ix) Na/Hg, Na_2HPO_4, MeOH; (x) Bu_4NF, THF (48% over two steps).



Scheme 37. Synthesis of testudinariol A (**213**) by Montgomery and co-workers. Reagents and conditions: (i) pyridine, CH_2Cl_2, 0–20 °C (99%); (ii) (*c*-hex)$_2$BOTf, Et_3N, CH_2Cl_2, −78 °C; $HC(O)CH_2CH_2OBn$, −78–0 °C (72%); (iii) $MeOCH_2CH_2OCH_2Cl$ (MEMCl), *i*-PrNEt, CH_2Cl_2, 0–20 °C (79%); (iv) $LiAlH_4$, THF, 0 °C (87%); (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (93%); (vi) $Ni(COD)_2$, Me_2Zn, Ti(*i*-PrO)$_4$, THF, 0 °C (62%); (vii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (95%); (viii) Li, NH_3, THF, −78 °C (87%); (ix) PPh_3, I_2, imidazole, THF, 0–20 °C (91%); (x) **215**, *s*-BuLi, THF, −78–20 °C; **237**, to 20 °C (38%); (xi) Et_2AlCl, CH_2Cl_2, −78–20 °C; (xii) Bu_4NF, THF (55% over two steps).

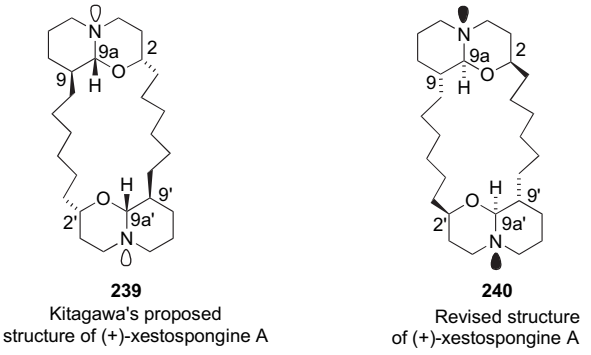
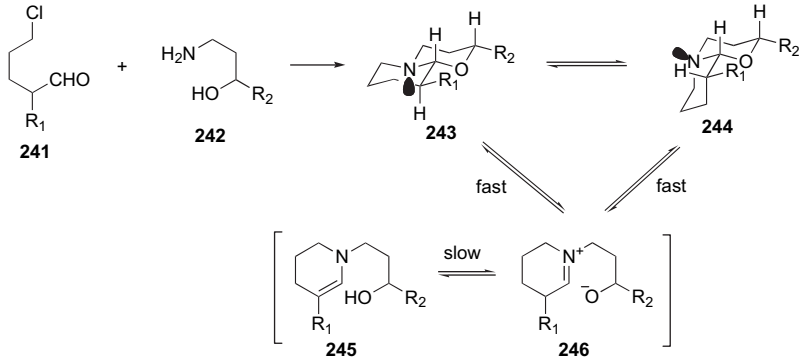


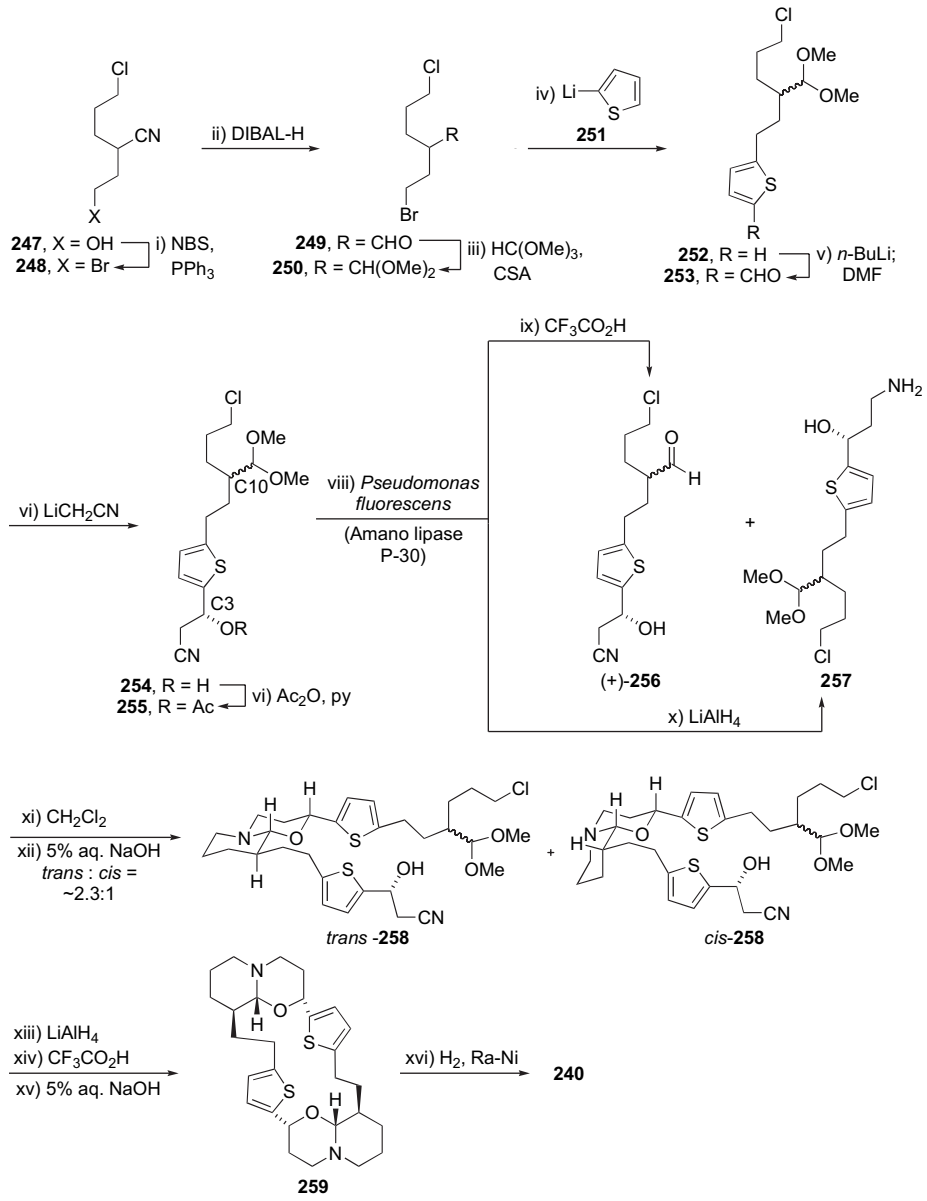
Figure 16. Initially proposed (**239**) and revised (**240**) structures of xestospongine A (araguspongine D).

deprotection in the presence of the initial ester functionality. Thus, an initial olefination reaction with the two coupling partners **323** and ylide **327**, obtained via olefination and 1,3-dithiane alkylation chemistry, afforded **328** as the (*E*,*E*)-diene product. Alcohol deprotection and selective cleavage of the 4-tolylsulfonylethyl ester yielded the hydroxy acid, which was coupled via the imidazolide to give the pyrenophorin precursor **332**. The synthesis was completed upon thioacetal removal to unmask (±)- and *meso*-pyrenophorin in a 1:1 ratio (Scheme 50).

The first total synthesis of pyrenophorin (**321**) as a single enantiomer and diastereoisomer was reported by Seebach and co-workers, who established the absolute configuration as being (*R*,*R*).[172,173] Their synthesis started with the optically active building block (*S*)-**333**, which was coupled by the dithiane method followed by a Wittig reaction to yield **334**. Acetal and ester hydrolysis yielded hydroxy acid **335**. Mitsunobu conditions were found to be the only conditions compatible with the sulfur-containing substrate, with the dimerization cyclization step proceeding in 60% yield. Hydrolysis with mercuric oxide and boron trifluoride yielded



Scheme 38. Synthesis of xestospongine A (**240**) by Hoye and co-workers (Part A).



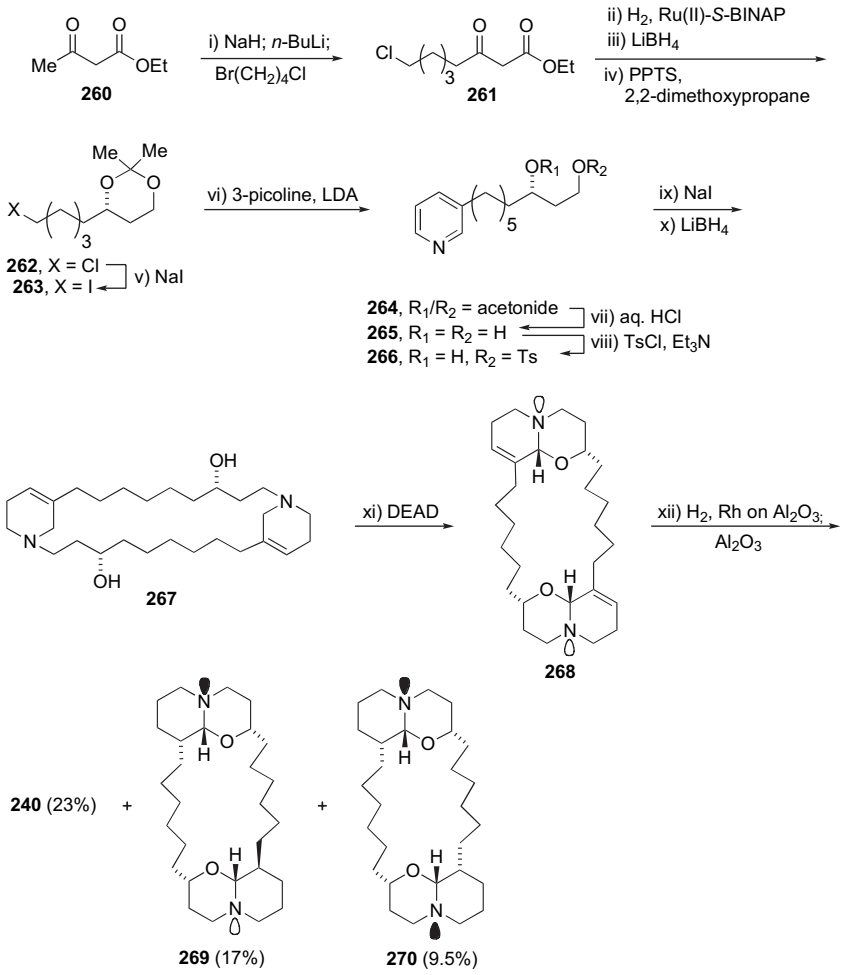
Scheme 39. Synthesis of xestospongine A (**240**) by Hoye and co-workers (Part B). Reagents and conditions: (i) NBS, PPh_3, CH_2Cl_2, −78–20 °C (77%); (ii) DIBAl-H, CH_2Cl_2, −78 °C (92%); (iii) $HC(OMe)_3$, 10-camphorsulfonic acid, MeOH (69%); (iv) **251**, THF, 0–20 °C (70%); (v) *n*-BuLi, THF, −78 °C; DMF, −78–20 °C (57%); (vi) $LiCH_2CN$, THF, −78 °C (87%); (vii) Ac_2O, pyridine (87%); (viii) *Pseudomonas fluorescens* (Amano lipase P-30), H_2O, Et_2O (38% for (+)-**254**); (ix) CF_3CO_2H, H_2O, DMSO, 65 °C (99%); (x) $LiAlH_4$, Et_2O, 0–20 °C (92%); (xi) CH_2Cl_2; (xii) 5% NaOH in H_2O, CH_2Cl_2 (42% for *trans*-**258** over two steps); (xiii) $LiAlH_4$, Et_2O, 0–20 °C (78%); (xiv) CF_3CO_2H, H_2O, DMSO, 80 °C; (xv) 5% NaOH in H_2O, CH_2Cl_2, pH>12 (70% over two steps); (xvi) H_2 (1 atm), Ra-Ni, EtOH (69%).

the natural product **321** as a single enantiomerically pure diastereoisomer (Scheme 51).

The most recent pyrenophorin (**321**) syntheses utilize the ring-closing olefin metathesis reaction. Both Fürstner[181] and Grubbs[182] published the dimerization of diene **338** (generated in two steps from (*R*)-methyloxirane (**337**) and 3-butenylmagnesium bromide), followed by chromium trioxide-mediated allylic oxidation to afford pyrenophorin (**321**) (Scheme 52).

3.1.2.6. Trichodimerol. Trichodimerol (**340**, Fig. 21) is a pentacyclic natural product isolated from *Trichoderma longibraciatum*,[206] *Penicillium chrysogenum*[207] and *Trichoderma* sp. USF-2690[208] and has been found to inhibit production of cytokine tumour necrosis factor-α (TNF-α), thus representing a potential lead for treatment of septic shock.[209]

The first synthesis of enantiomerically pure trichodimerol (**340**) was achieved by Barnes-Seeman and Corey.[210] Acetoxylation of the previously known sorbicillin **341** resulted in the formation of dienone **342** and its regioisomer **343**, which were separated by flash chromatography. Following resolution by chiral HPLC, (*S*)-**343** was dimerized via hydroxy dienone **344** to afford trichodimerol (**340**) in 10%



Scheme 40. Synthesis of xestospongine A (**240**) by Baldwin and co-workers. Reagents and conditions: (i) NaH, THF, *n*-BuLi, $Br(CH_2)_4Cl$ (78%); (ii) H_2, Ru(II)-*S*-BINAP, EtOH, 100 °C (96%); (iii) $LiBH_4$, Et_2O (84%); (iv) PyHOTs, 2,2-dimethoxypropane, Me_2CO (94%); (v) NaI, Me_2CO, Δ (98%); (vi) 3-picoline, LDA, THF, −78 to −10 °C (72%); (vii) HCl in H_2O, EtOH (94%); (viii) TsCl, Et_3N, CH_2Cl_2, 0 °C (88%); (ix) NaI, 2-butanone, Δ; (x) $LiBH_4$, MeOH, *i*-PrOH, 0 °C (34% over two steps); (xi) DEAD, CH_2Cl_2 (53%); (xii) H_2 (1 atm), Rh on Al_2O_3, MeOH; Al_2O_3, Δ.

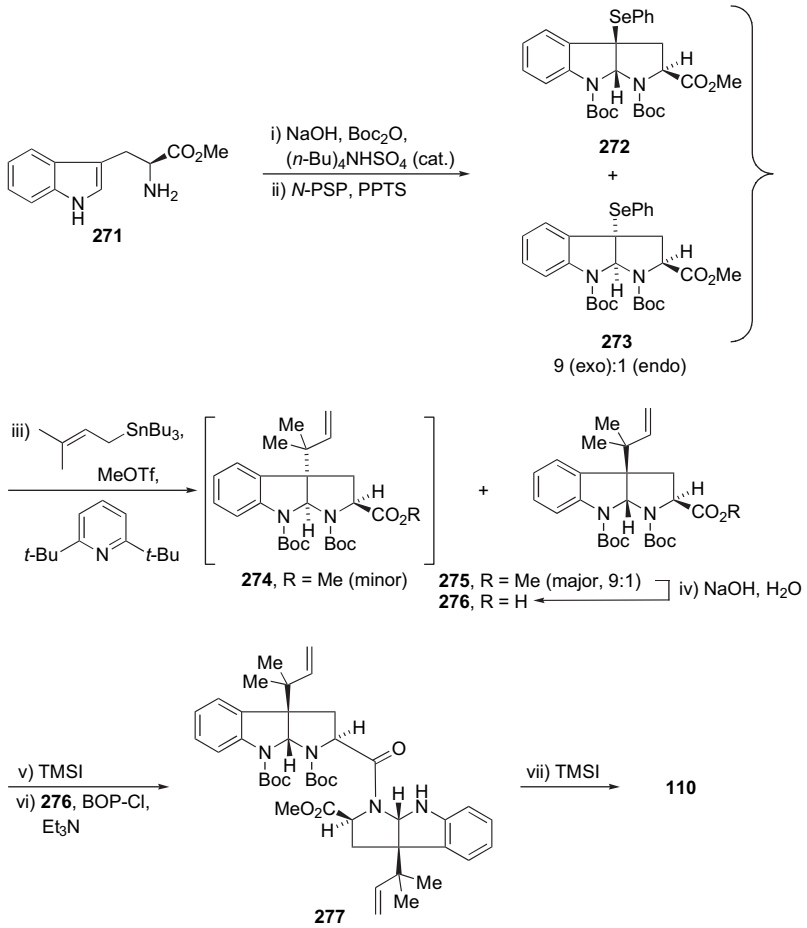
yield in addition to various other products.[210] The reaction was proposed to proceed via an intermolecular Michael addition followed by a second (intramolecular) Michael addition and a sequence of two hemiketal-forming ring closures (Scheme 53).

A mechanistic proposal for the biosynthesis of trichodimerol has been suggested by Nicolaou and co-workers involving an oxidation-Michael-ketalization cascade.[211] This was followed up by a synthesis involving dimerization of racemic **343** using cesium hydroxide in methanol.[212]

3.1.2.7. Vermiculine. Vermiculine (**345**, Fig. 22), which is structurally similar to (−)-pyrenophorin (**321**, Section 3.1.2.5), was isolated from *Penicillium vermiculatum*[213,214] and *Talaromyces wortmannii*,[215] and has been found to exhibit inhibitory effects on Gram-positive bacteria, cytotoxic effects against Ehrlich ascites carcinoma, lymphoadenoma and sarcoma cells,[216] and has been found to possess immunomodulatory properties.[217] The originally proposed structure[218] was revised after X-ray crystallography established its 16-membered diolide structure.[219]

Due to its similarity with pyrenophorin (**321**), analogous approaches have been used in the syntheses of vermiculine (**345**) as both its racemic[220–223] and diastereoisomerically pure forms,[172,173,224,225] as well as a number of formal total syntheses.[184,188] The first total synthesis of vermiculine (**345**) as a mixture of racemic diastereoisomers was published by Corey and co-workers in 1975 and was achieved by the dimerization of the activated ester **350**, formed through chain extension of the protected glutarate **346**.[124,223] Oxidation and deprotection of **351** gave the desired (±)-vermiculine (**345**) after separation from the *meso* isomer (Scheme 54).

At the same time as the pyrenophorin (**321**) synthesis, Seebach described the first synthesis of vermiculin (**345**) in its optically pure state, determining its absolute configuration as (*S*,*S*).[172,173] The starting material (*S*)-**353**, derived from malic acid, was used in three successive C–C bond-forming reactions in one pot, followed by ester hydrolysis to give the hydroxy acid **355**. Coupling of the latter under Mitsunobu conditions generated the bis-lactone **356**, which was deprotected to give the natural product **345** (Scheme 55).



Scheme 41. Synthesis of amauromine (**110**) by Danishefsky and co-workers. Reagents and conditions: (i) NaOH, Boc_2O, n-Bu_4NHSO_4 (cat.), CH_2Cl_2 (91%); (ii) *N*-phenylselenophthalimide, PyHOTs, CH_2Cl_2 (93%); (iii) MeOTf, 2,6-di-(*t*-butyl)pyridine, prenyl(*n*-butyl)stannane, CH_2Cl_2, −78 °C to Δ (60%); (iv) NaOH, THF, MeOH, H_2O, Δ (98%); (v) Me_3SiI, MeCN, 0 °C (83%); (vi) **276**, BOPCl, Et_3N, CH_2Cl_2 (58%); (vii) Me_3SiI, MeCN, 0 °C (58%).

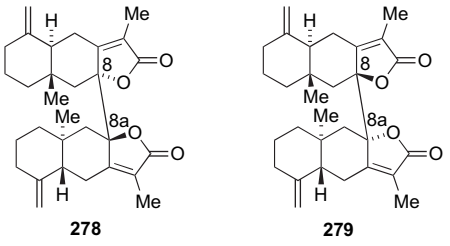


Figure 17. Structures of biatractylolide (**278**) and biepiasterolide (**279**).

3.1.3. Bacteria, algae and lichen.

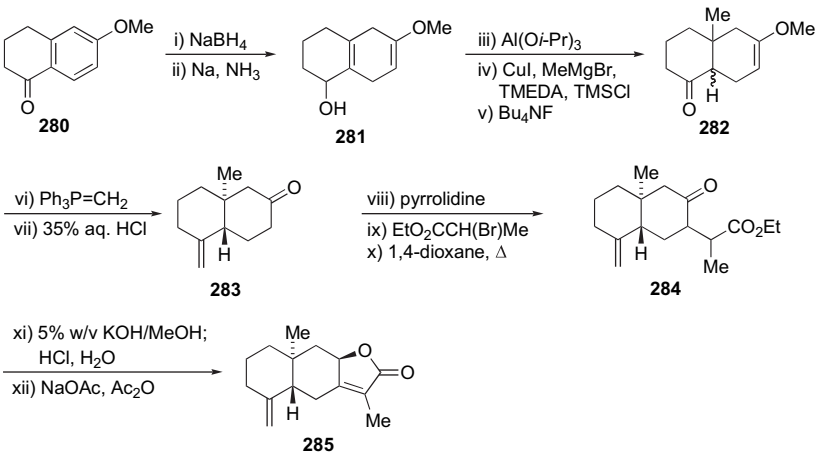
3.1.3.1. Aplasmomycin. Aplasmomycin (**357**, Fig. 23), which is closely related to tartrolon B (**485**, Section 3.2.3.2), was isolated from *Streptomyces griseus*[226] and its structure elucidated by X-ray crystallographic studies.[227] It is an ionophoric antibiotic and has been shown to inhibit Gram-positive bacteria and *Plasmodium berghei*.[226] Various studies have been performed on the biosynthesis of this unusual natural product.[228–232]

The first synthesis of aplasmomycin (**357**) was achieved by Corey and co-workers in 1982.[231,232] Starting from commercial (+)-pulegone, triol **361** was obtained via chain extension and Baeyer–Villiger oxidation, followed by dithiane chemistry. Subsequent ozonolysis and manipulation of the hydroxy groups yielded epoxide **364**. This was coupled with vinylstannane **365**[231] generating intermediate **366**, which underwent a chain extension to yield the monomeric unit as the α-keto ester **367** (Scheme 56). Stepwise BOP-chloride coupling yielded the masked intermediate **369**, which, upon reduction, desilylation, dithiane cleavage and boronation, afforded the diastereoisomerically pure aplasmomcycin (**357**) via thermodynamic equilibration at the C2 position (Scheme 57).[232]

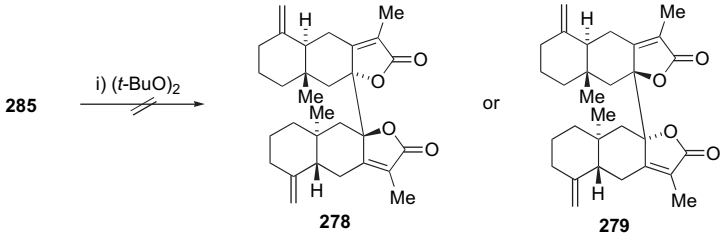
A second synthesis of (+)-aplasmomycin (**357**) by White and co-workers employed a Chan ring-contraction reaction of **383** to afford aplasmomycin (**357**) precursor **384**. The former was obtained by coupling of advanced intermediates **380** and **381** (Schemes 58 and 59).[233]

A number of formal syntheses of aplasmomycin have been reported,[234–236] as well as methodology towards the tetrahydrofuran moiety present in aplasmomycin (**357**).[237,238]

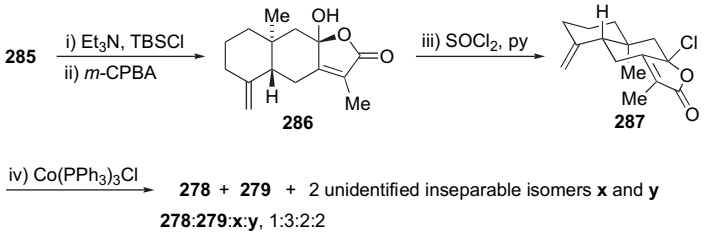
3.1.3.2. Hybocarpone. Hybocarpone (**385**, Fig. 24) is a napthazarin-derived pentacycle, isolated from a culture



Scheme 42. Synthesis of biatractylolide (**278**) and biepiasterolide (**279**) by Baldwin and co-workers (Part A). Reagents and conditions: (i) $NaBH_4$, MeOH; (ii) Na, NH_3, *t*-BuOH, −33 °C (90% over two steps); (iii) Al(O*i*-Pr)$_3$, PhMe, Me_2CO, 87 °C; (iv) CuI, MeMgBr, TMEDA, Me_3SiCl, THF; (v) Bu_4NF, THF (87% over three steps); (vi) $Ph_3P{=}CH_2$, DMSO, 55 °C; (vii) 35% HCl in H_2O (42% over two steps); (viii) pyrrolidine, PhH, Δ; (ix) ethyl 2-bromopropanoate, 1,4-dioxane, Δ; (x) 1,4-dioxane, H_2O, Δ; (xi) 5% w/v KOH/MeOH; HCl, H_2O; (xii) NaOAc, Ac_2O, Δ (57% over two steps).



Scheme 43. Synthesis of biatractylolide (**278**) and biepiasterolide (**279**) by Baldwin and co-workers (Part B). Reagents and conditions: (i) (*t*-BuO)$_2$, Me_2CO, 120–170 °C.



Scheme 44. Synthesis of biatractylolide (**278**) and biepiasterolide (**279**) by Baldwin and co-workers (Part C). Reagents and conditions: (i) Et_3N, *t*-$BuMe_2SiCl$, THF, 30 °C (90%); (ii) *m*-CPBA, CH_2Cl_2 (54%); (iii) $SOCl_2$, pyridine, THF, −60 °C; (iv) $Co(PPh_3)_3Cl$, PhH (26% over two steps).

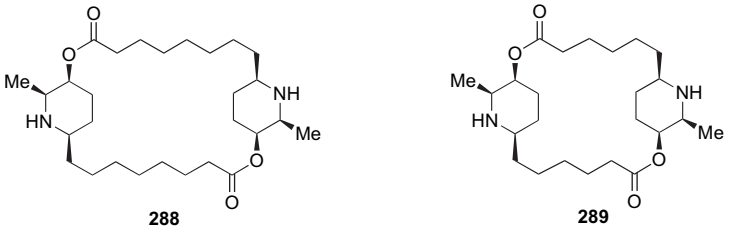
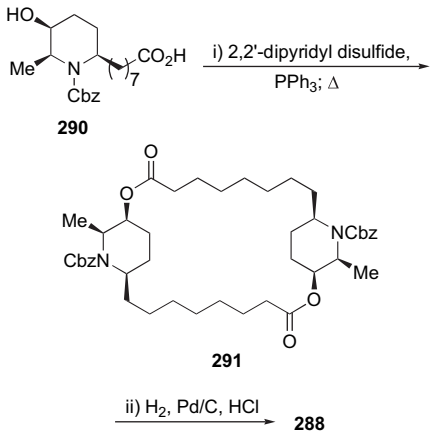


Figure 18. Structures of carpaine (**288**) and azimine (**289**).



Scheme 45. Synthesis of carpaine (**288**) by Corey and co-workers. Reagents and conditions: (i) 2,2′-dipyridyl disulfide, PPh_3, xylene; diluted with xylene and added to xylene at Δ (50%); (ii) H_2, Pd/C, HCl, EtOH (100%).

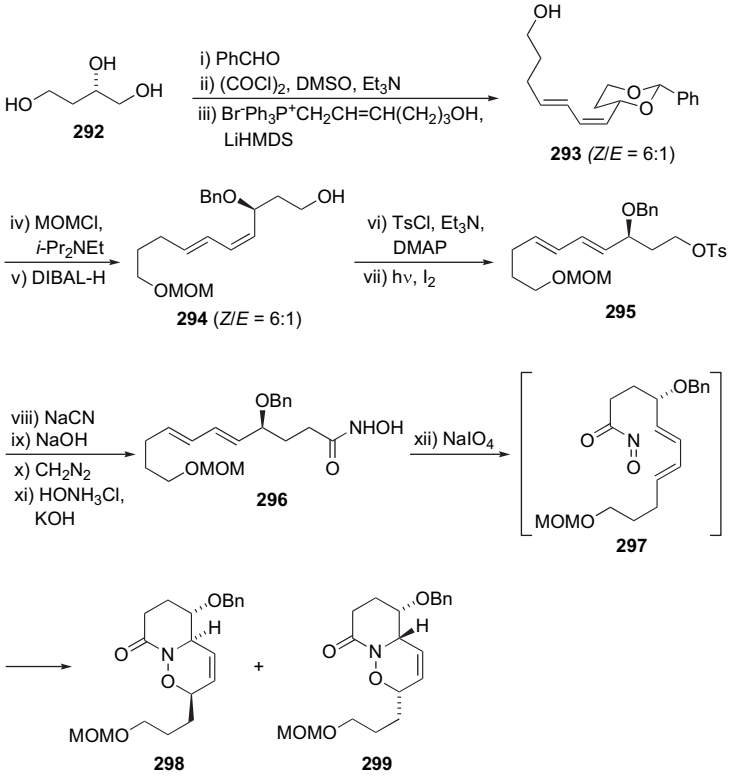
of the lichen mycobiont *Lecanora hybocarpa* (Tuck.) by Elix and co-workers in 1999.[239] It was found to exhibit potent cytotoxicity against the murine mastocytoma P815 cell line[239] and soon, after its disclosure, the total synthesis of hybocarpone was reported by Nicolaou and Gray (Scheme 60).[240] A cycloaddition reaction between methyl 2-ethylacrylate (**387**) and the photoenol resulting from the exposure of aromatic aldehyde **386** to light was employed to prepare key intermediate **389**. The latter was further elaborated to afford **391**, which dimerized upon treatment with cerium(IV) ammonium nitrate to give a diastereoisomeric mixture of **392** and **393** in a 1:1 ratio. The former was transformed to the more thermodynamically stable isomer **393** when exposed to acetic acid. Finally, removal of the protecting groups with aluminum tribromide completed the synthesis of hybocarpone (**385**).

3.2. Dimerization followed by two-directional synthesis

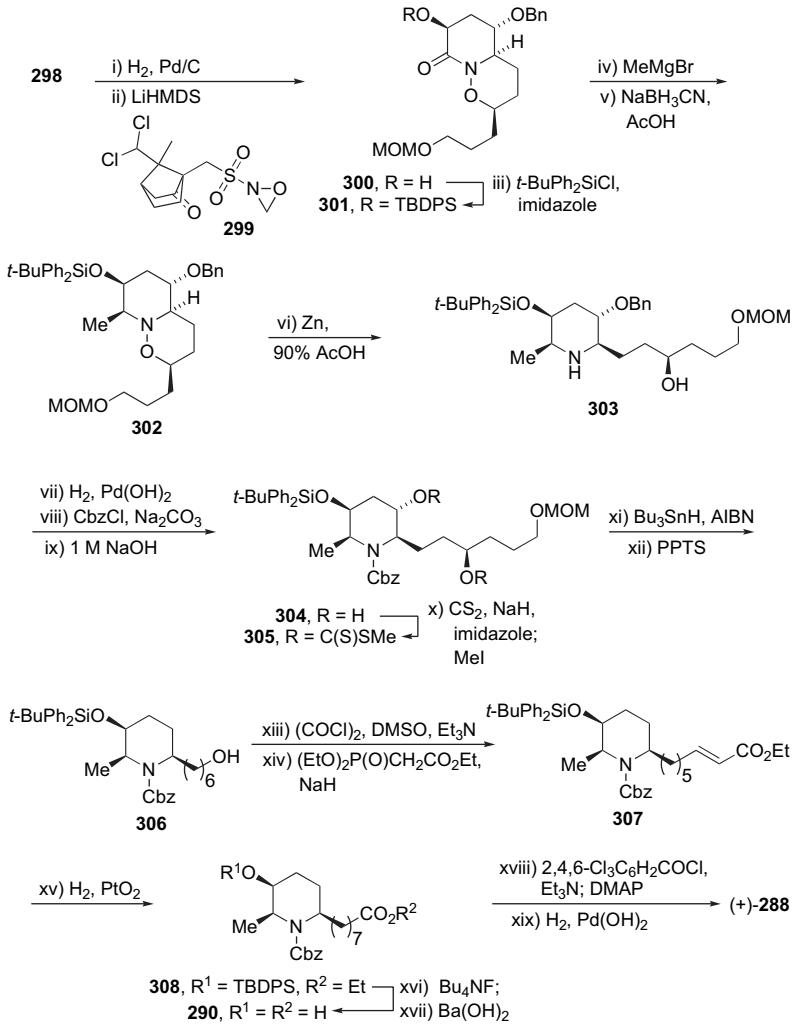
3.2.1. Marine organisms.

3.2.1.1. Duryne. Duryne (**394**, Fig. 25) was isolated in 1987 from the marine sponge *Cribrochalina dura* by Wright and co-workers.[241] It was found to inhibit the growth of several human tumour cell lines including P388 (murine leukaemia), HCT-8 (colon), A549 (lung), NUGC (gastric) and MCF7 (mammary).[241,242]

As yet, the geometry of the central C_{15}–$C_{15'}$ olefin and the absolute stereochemistry of the chiral centers have not been determined. However, two synthetic studies have been published. The first was focused on the reduction of alkyne **396** (Scheme 61). The second study by Sharma and Chattopadhyay utilized the protected diacetylene **405** to prepare (15*E*,*R*,*R*)-duryne (**394**) (Scheme 62).[243]



Scheme 46. Synthesis of carpaine (**288**) by Kibayashi and co-workers (Part A). Reagents and conditions: (i) PhCHO, TsOH, Δ; (ii) $(COCl)_2$, DMSO, Et_3N, −60–0 °C; (iii) $Br^- \cdot Ph_3P^+CH_2CH{=}CH(CH_2)_3OH$, $LiN(SiMe_3)_2$, THF/HMPA 2:1 (66% over three steps); (iv) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 60 °C (93%); (v) DIBAl-H, CH_2Cl_2, 0 °C (84%); (vi) TsCl, Et_3N, DMAP, CH_2Cl_2 (91%); (vii) hν, I_2, PhH (94%); (viii) NaCN, DMSO, 50 °C (95%); (ix) NaOH, MeOH, H_2O, Δ; (x) CH_2N_2, Et_2O, 0 °C (94% over two steps); (xi) $NH_2OH \cdot HCl$, KOH, MeOH, 0 °C (88%); (xii) $NaIO_4$, H_2O/DMF 50:1, 0 °C (69% of **298**).



Scheme 47. Synthesis of carpaine (**288**) by Kibayashi and co-workers (Part B). Reagents and conditions: (i) H_2, Pd/C, THF (97%); (ii) LiN($SiMe_3$)$_2$, (+)-((8,8-dichlorocamphoryl)sulfonyl)oxaziridine, THF, −78 °C (99%); (iii) *t*-$BuPh_2SiCl$, imidazole, DMF (73%); (iv) MeMgBr, THF, 0 °C; (v) $NaBH_3CN$, AcOH, THF, 0 °C (76% over two steps); (vi) Zn, 90% AcOH, 60 °C (93%); (vii) H_2, $Pd(OH)_2$, MeOH; (viii) CbzCl, Na_2CO_3; (ix) 1 M NaOH, MeOH (45% over three steps); (x) CS_2, NaH, imidazole, THF, Δ; MeI, Δ (93%); (xi) Bu_3SnH, AIBN, PhH, Δ (99%); (xii) PyHOTs, *t*-BuOH, Δ (73%); (xiii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78–0 °C; (xiv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −20 °C (91% over two steps); (xv) H_2, PtO_2, EtOAc (76%); (xvi) Bu_4NF, THF (97%); (xvii) $Ba(OH)_2\cdot 8H_2O$, MeOH (97%); (xviii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; DMAP, PhMe, Δ (71%); (xix) H_2, $Pd(OH)_2$, MeOH (87%).

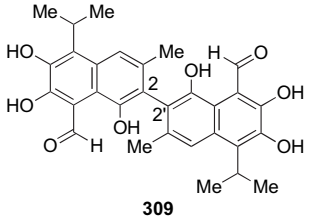


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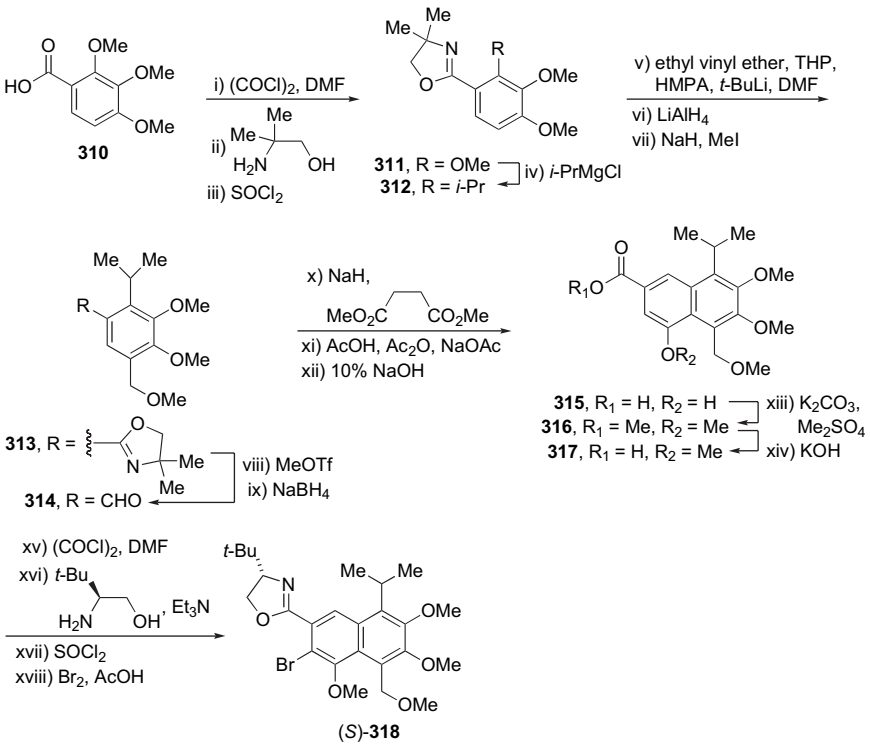
Figure 19. Structure of gossypol.

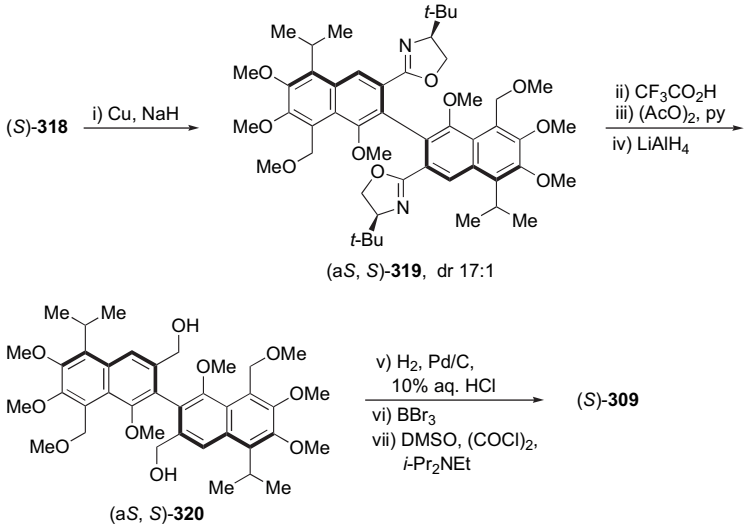
Unfortunately, neither of these synthetic studies has led to the determination of the absolute configuration of the natural duryne (**394**).[244]

3.2.1.2. Limatulone. Limatulone (**411**, Fig. 26), which is closely related to testudinariol A (**213**, Section 3.1.1.5), was isolated in 1985 by Faulkner and co-workers from an intertidal limpet, *Collisella limatula*.[245] It was noted to be a potent fish-feeding inhibitor and its structure determined as a C_2 symmetric triterpene containing a cyclohexenol. Interestingly, it exists in nature as a mixture of the racemic and *meso*-forms and, as such, is optically inactive. Limatulone (**411**) was identified as a structurally unique triterpene[246] and, unlike normal polycyclic triterpenes, is not derived biosynthetically from 2,3-epoxysqualene.[247] A total synthesis for both racemic limatulone (**411a**) and *meso*-limatulone (**411b**) was published by Mori and co-workers in 1993.[247] The strategy employed relied on a dimerization of the key intermediates **419** and **420**, and assumed that the *meso* and racemic products may be separated (Scheme 63).

The stereochemistry was controlled via the synthesis of the α,β-unsaturated lactone **415**, which was synthesized racemically and the two diastereoisomers separated by column chromatography and recrystallization. Subsequent synthesis of bromide **419** and sulfone **420** provided the coupling



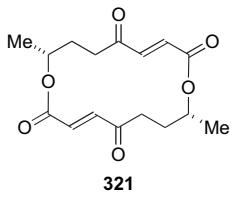
Scheme 48. Synthesis of (*S*)-gossypol (**309**) by Meyers and co-workers (Part A). Reagents and conditions: (i) oxalyl chloride, DMF, CH_2Cl_2; (ii) 2-amino-2-methyl-1-propanol, CH_2Cl_2; (iii) thionyl chloride, CH_2Cl_2 (96% over three steps); (iv) *i*-PrMgCl, Δ (96%); (v) ethyl vinyl ether, THP, HMPA, *t*-BuLi, DMF, −78 to −10 °C; (vi) $LiAlH_4$, THF, −10 °C; (vii) NaH, MeI, THF, 0 °C (72% over three steps); (viii) MeOTf, CH_2Cl_2; (ix) $NaBH_4$, THF/MeOH 4:1, 0 °C (89%); (x) NaH, dimethyl succinate, THF; (xi) AcOH, Ac_2O, NaOAc, Δ; (xii) 10% NaOH, MeOH, Δ (59% over three steps); (xiii) K_2CO_3, Me_2SO_4, Me_2CO (97%); (xiv) KOH, MeOH, Δ (98%); (xv) oxalyl chloride, DMF, CH_2Cl_2; (xvi) (*S*)-(+)-*t*-leucinol; (xvii) thionyl chloride, CH_2Cl_2 (87% over three steps); (xviii) Br_2, AcOH (74%).



Scheme 49. Synthesis of (*S*)-gossypol (**309**) by Meyers and co-workers (Part B). Reagents and conditions: (i) Cu, NaH, DMF, Δ (80%); (ii) CF_3CO_2H, $Na_2SO_4 \cdot 10H_2O$, THF, H_2O; (iii) Ac_2O, pyridine, CH_2Cl_2; (iv) $LiAlH_4$, THF, −10–20 °C (72% over three steps); (v) H_2 (40 psi), 10% Pd/C, 10% HCl in H_2O, EtOH; (vi) BBr_3, CH_2Cl_2, −78 °C; (vii) DMSO, $(COCl)_2$, *i*-Pr_2NEt, −78–20 °C (81% over three steps).

partners and, pleasingly, intermediates (±)-**422a** and *meso*-**422b** were also separable via chromatography (Scheme 63). Chain elongation of both intermediates gave racemic limatulone [(±)-**411a**] and *meso*-limatulone (**422b**) (Scheme 64).

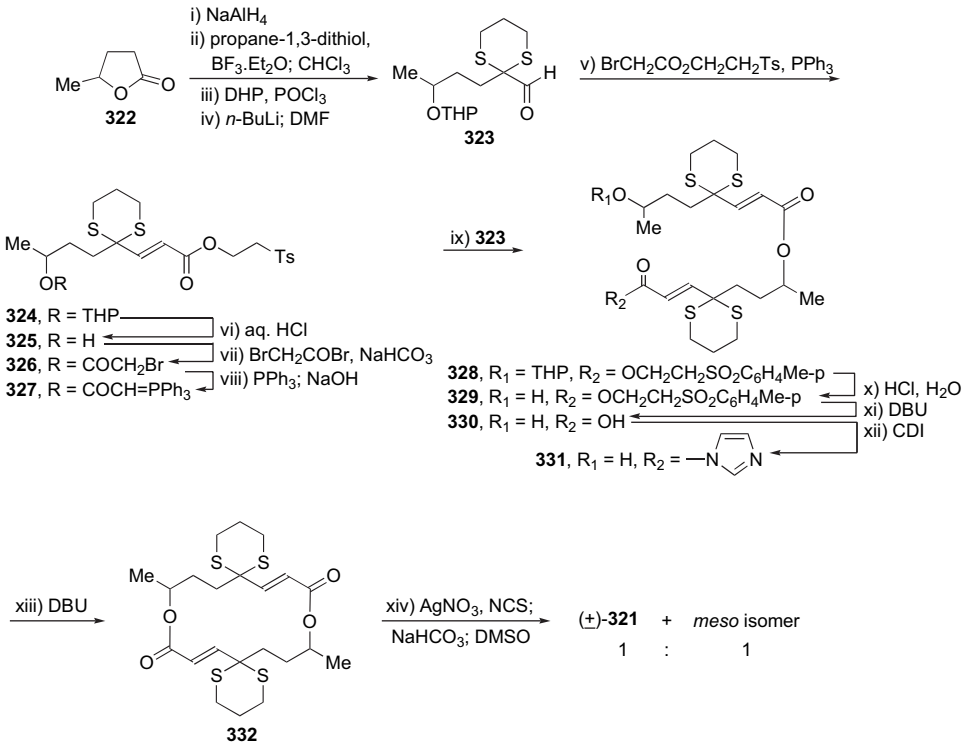
3.2.1.3. Ningalin A. The ningalins A–D were isolated in 1997 from an ascidian of the genus *Didemnum* by Kang and Fenical. Ningalin A (**425**, Fig. 27) is the simplest and only C_2 symmetric member of the family.[248]



321

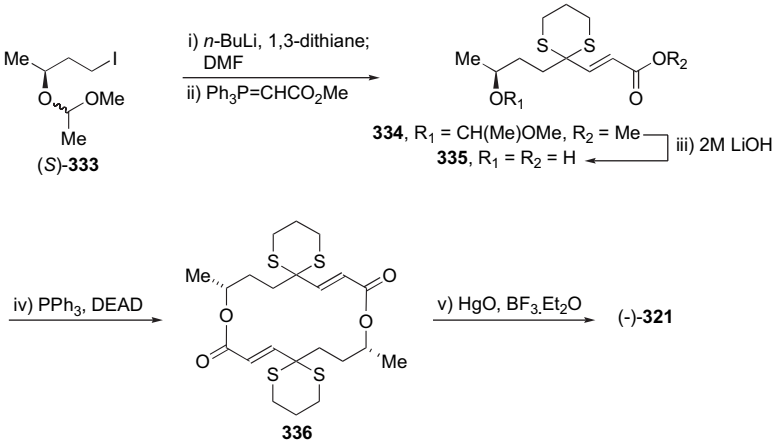
Figure 20. Structure of (*R*,*R*)-(−)-pyrenophorin.

In 1999, Boger and co-workers reported a highly unusual total synthesis of this compound utilizing a heteroaromatic azadiene Diels–Alder reaction (Scheme 65).[249] Double Stille coupling of bromide **426** with bis-(tributylstannyl)acetylene yielded the symmetrical arylacetylene **427**. The key Diels–Alder cyclization with the elimination of nitrogen then afforded the 1,2-diazine **429**, and subsequent ring contraction and deprotection afforded ningalin A (**425**).



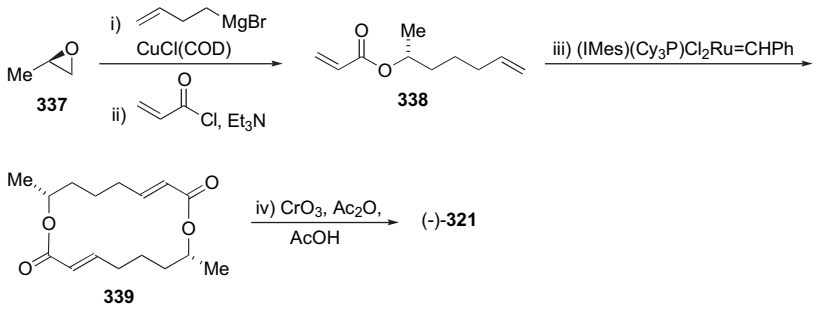
322 **323** **324**, R = THP **325**, R = H **326**, R = $COCH_2Br$ **327**, R = $COCH{=}PPh_3$ **328**, R_1 = THP, R_2 = $OCH_2CH_2SO_2C_6H_4Me$-p **329**, R_1 = H, R_2 = $OCH_2CH_2SO_2C_6H_4Me$-p **330**, R_1 = H, R_2 = OH **331**, R_1 = H, R_2 = imidazolyl **332**

Scheme 50. Synthesis of (±)-pyrenophorin (**321**) by Raphael and co-workers. Reagents and conditions: (i) $NaAlH_4$, THF, −78 to −20 °C (86%); (ii) propane-1,3-dithiol, $BF_3{\cdot}Et_2O$, 0 °C; $CHCl_3$; 5 M NaOH (40%); (iii) DHP, $P(O)Cl_3$, PhH (73%); (iv) *n*-BuLi, THF, −78 to −20 °C; DMF, −20 °C (68%); (v) 2-(4-tolylsulfonyl)ethanol, bromoacetyl bromide, $NaHCO_3$, 4 Å molecular sieves, PhH; PPh_3, PhH; 0.1 M NaOH (35%); (vi) HCl in H_2O, MeOH (96%); (vii) bromoacetyl bromide, $NaHCO_3$, 4 Å molecular sieves, PhH; (viii) PPh_3, PhH, Δ; 0.1 N NaOH; (ix) **323**, PhH, Δ (36% over three steps); (x) HCl in H_2O, EtOAc/MeOH 1:1 (93%); (xi) DBU, PhH (95%); (xii) CDI (carbonyl di-imidazole), THF; diluted with PhH and added DBU (61%); (xiii) $AgNO_3$, NCS, MeCN, H_2O, 0 °C; $NaHCO_3$; DMSO (13% of (±)-**321**).



(*S*)-**333** **334**, R_1 = CH(Me)OMe, R_2 = Me **335**, R_1 = R_2 = H **336**

Scheme 51. Synthesis of (*R*,*R*)-(−)-pyrenophorin (**321**) by Seebach and co-workers. Reagents and conditions: (i) *n*-BuLi, 1,3-dithiane, THF, −10 to −100 to −25 to −78 °C; DMF, −78 to −20 °C (92%); (ii) $Ph_3P{=}CHCO_2Me$, PhMe, 90 °C (92%); (iii) 2 M LiOH in H_2O (74%); (iv) PPh_3, DEAD, PhMe, −40 to −30 to −20 to −10 to −4 °C (84%); (v) HgO, $BF_3{\cdot}Et_2O$, THF, H_2O, 35 °C (56%).



Scheme 52. Synthesis of (*R*,*R*)-(−)-pyrenophorin (**321**) by Fürstner, Grubbs and co-workers. Reagents and conditions: (i) 3-butenylmagnesium bromide, CuCl(COD) (cat.), THF, −78–20 °C (75%); (ii) CH_2=CHCOCl, Et_3N, CH_2Cl_2 (82%); (iii) (IMes)(Cy_3P)Cl_2Ru=CHPh (5–10 mol %), CH_2Cl_2, Δ (37–46%), (iv) CrO_3, Ac_2O, AcOH, PhH, 0 °C (54%).

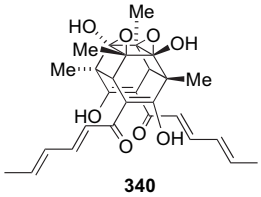


Figure 21. Structure of trichodimerol.

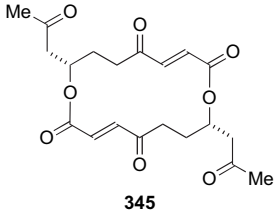
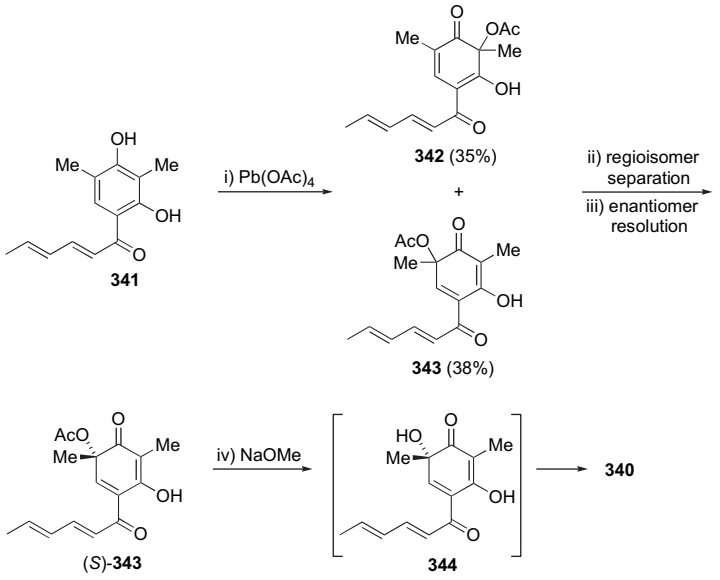


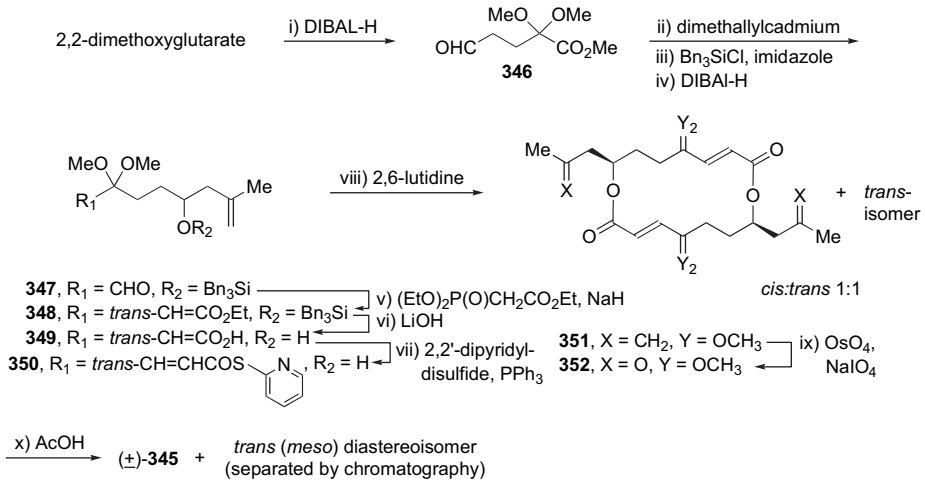
Figure 22. Structure of (*S*,*S*)-vermiculine.

3.2.1.4. Petrosin. Petrosin (**431**, Fig. 28), which is structurally similar to xestospongine A (**240**, Section 3.1.1.6), is one of three ichthyotoxic bis-quinolizidone alkaloids isolated from the sponge *Petrosia seriata* and structurally characterized by Braeckman and co-workers, between 1982 and 1988.[250,251] Petrosin (**431**) has only been isolated as a racemate and its relative stereochemistry was unequivocally established via X-ray crystallography.

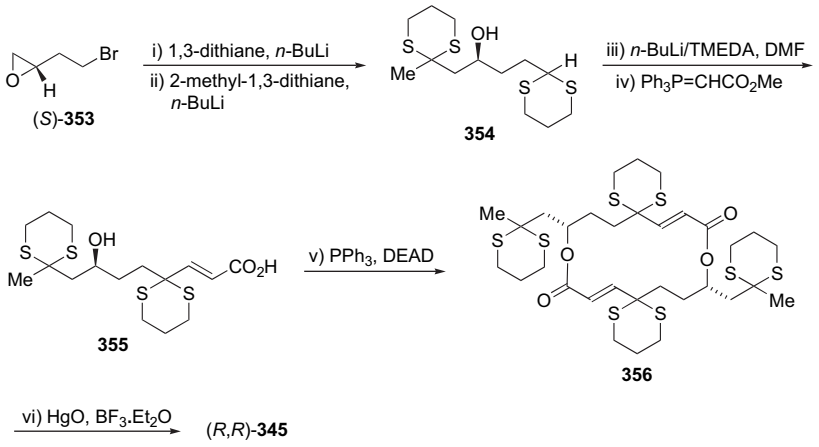
Petrosin (**431**) has recently been synthesized by Heathcock and co-workers (Scheme 66), as well as a C_2 symmetric diastereoisomer of the latter not found in nature, namely petrosin C (**432**, Fig. 28).[252,253] Thus, ozonolysis of methyl oleate (**433**) followed by further elaboration gave the amino ester **436**. The latter was 'dimerized' and subsequently cyclized via the stepwise formation of two amide bonds using dicyclohexyl carbodiimide. Oxidation of tetraol **440** with Dess–Martin periodinane followed by deprotection of the Boc groups and intramolecular Mannich condensation using acetic acid completed the synthesis of petrosin (**431**), which crystallized directly from the reaction mixture, along with other isomers.



Scheme 53. Synthesis of trichodimerol (**340**) by Corey and co-workers. Reagents and conditions: (i) $Pb(OAc)_4$, AcOH/CH_2Cl_2 5:1; (iv) NaOMe, MeOH (10%).



Scheme 54. Synthesis of (±)-vermiculine (**345**) by Corey and co-workers. Reagents and conditions: (i) DIBAl-H, CH_2Cl_2, −78 °C (50%); (ii) methallyl Grignard, CdBr, Et_2O, −78 °C; (iii) Bn_3SiCl, imidazole, DMF (70% over two steps); (iv) DIBAl-H, CH_2Cl_2, −78 °C; (v) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (94% over two steps); (vi) LiOH, MeOH/H_2O 2:1 (100%); (vii) 2,2′-dipyridyl disulfide, PPh_3, xylene, 0 °C (77%); (viii) 2,6-lutidine, xylene, Δ (30%); (ix) OsO_4, $NaIO_4$, 50% *t*-BuOH in H_2O (70%); (x) AcOH/H_2O/THF 3:1:1, 45 °C (100%).



Scheme 55. Synthesis of (*R*,*R*)-vermiculine (**345**) by Seebach and co-workers. Reagents and conditions: (i) 1,3-dithiane, *n*-BuLi, THF, −30 °C; **353**, −100 to −78 to −30 to 0 °C (84%); (ii) 2-methyl-1,3-dithiane, *n*-BuLi, THF, −30 °C; add to mixture −78 to −30 to 0 to 25 °C (89%); (iii) *n*-BuLi, TMEDA, −20 °C, then DMF, −70 to −10 °C; (iv) $Ph_3P{=}CHCO_2Me$, dioxane, Δ, (75%); (v) PPh_3, DEAD, PhMe, −25–12 °C (24%); (vi) HgO, $BF_3{\cdot}Et_2O$, THF, H_2O, 50 °C (72%).

3.2.2. Plants and fungi.

3.2.2.1. Biphyscion. In 1972, Steglich and co-workers reported the isolation of a 7,7′-linked bianthraquinone from the yellow pigment of fungi of the genus *dermocybe*.[254] It was not until 1999, however, that the first total synthesis of (±)-biphyscion (**441**, Fig. 29) was reported by Hauser and Gauuan.[255]

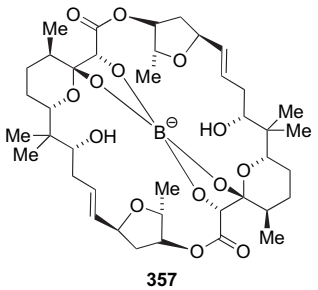
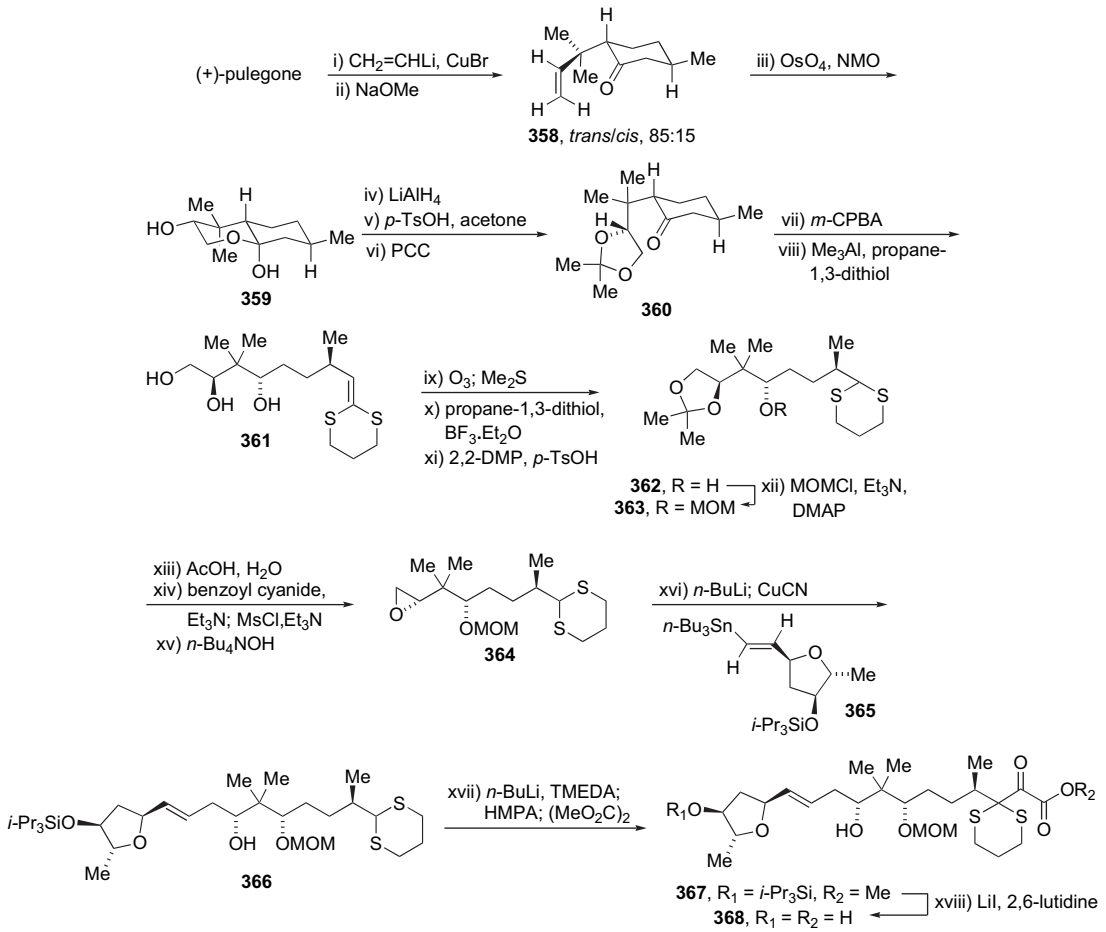


Figure 23. Structure of (+)-aplasmomycin.

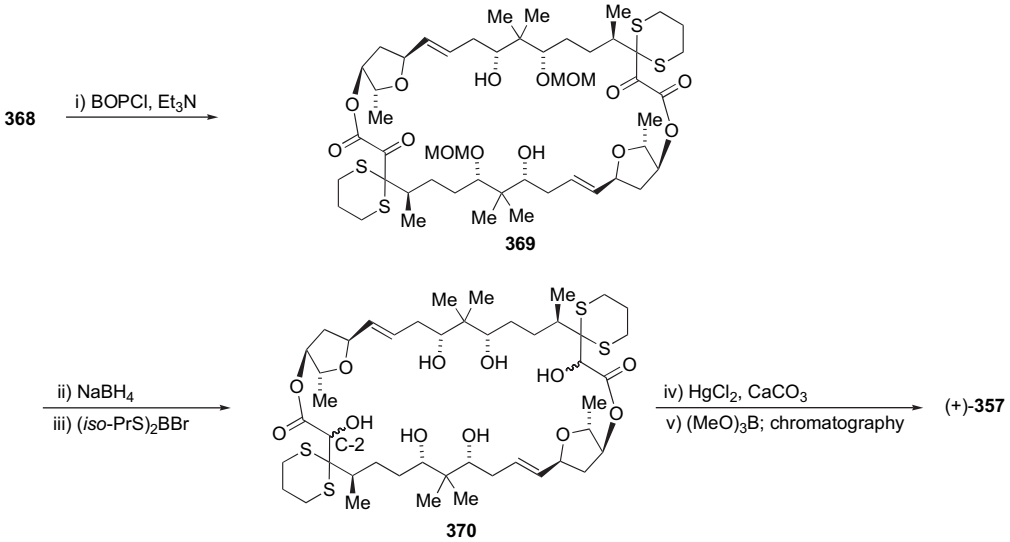
The central symmetrical biphenyl core **446** was prepared via Ullman coupling of iodoresorcinol **445**. The two-directional synthesis was effected through reaction of sulfone **448** in a one pot, double isobenzofuranone condensation with cyclohexenone **449** followed by oxidation and demethylation to afford (±)-biphyscion (**441**) (Scheme 67).[255]

3.2.3. Bacteria, algae and lichen.

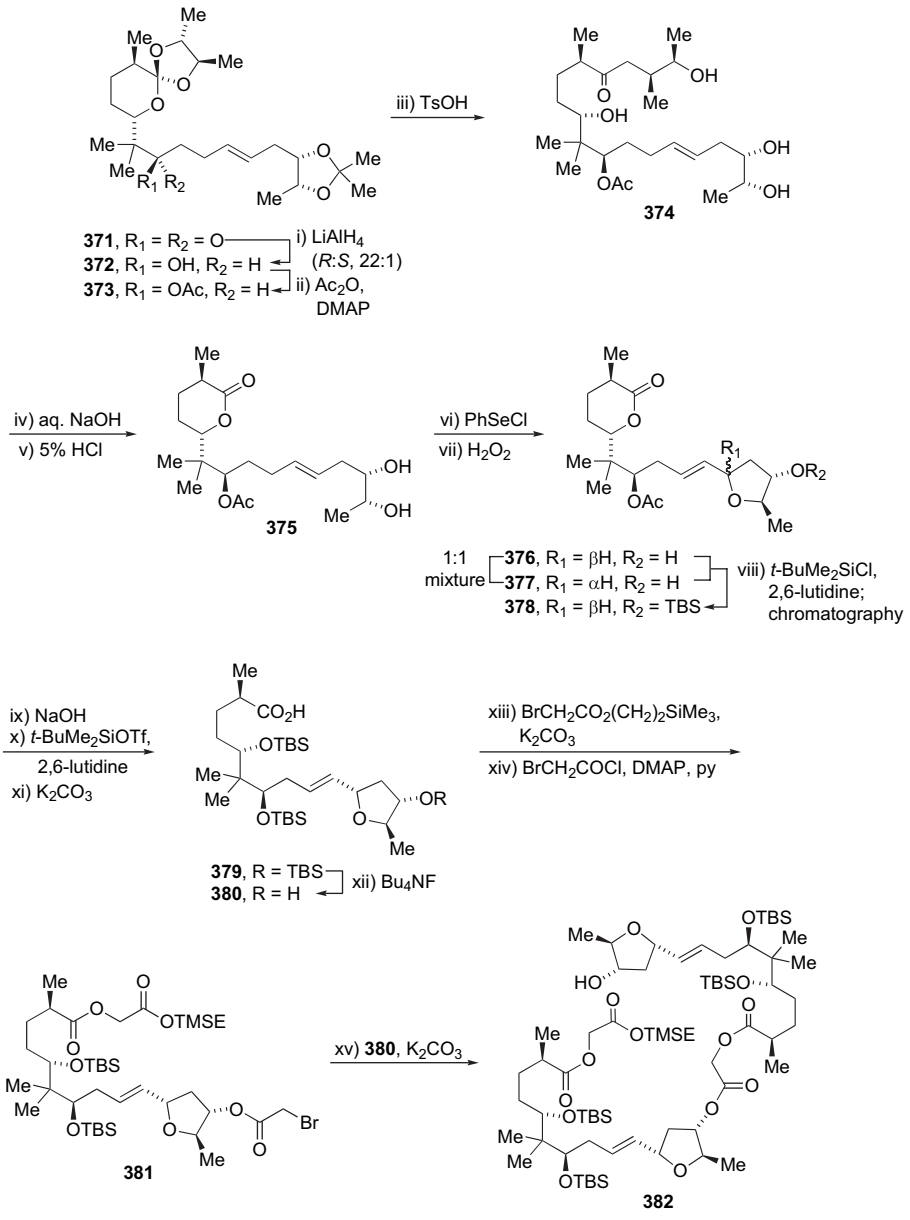
3.2.3.1. Cylindrocyclophanes A, D and F ([7.7]-paracyclophanes). The cylindrocyclophanes (**451**–**453**, Fig. 30) are [7.7]-paracyclophanes isolated by Bobzin and Moore in 1990–1992 from three strains of *Cylindrospermum lichenforme*: ATCC 29204 [cylindrocyclophane A (**451**)], ATCC 29412 [cylindrocyclophane D (**452**)] and UTEX 2014 [cylindrocyclophane F (**453**)]. Although they were found to



Scheme 56. Synthesis of (+)-aplasmomycin (**357**) by Corey and co-workers (Part A). Reagents and conditions: (i) vinylmagnesium bromide, CuBr, THF, −30 °C (88%); (ii) NaOMe, MeOH; (iii) OsO_4, NMO, Me_2CO/H_2O 2:1 (76% over two steps); (iv) $LiAlH_4$, THF, Δ; (v) TsOH (cat.), Me_2CO; (vi) PCC, CH_2Cl_2, 3 Å molecular sieves (70% over three steps); (vii) *m*-CPBA, PhH (83%); (viii) Me_3Al, propane-1,3-dithiol (87%); (ix) O_3, MeOH, −78 °C; Me_2S; (x) $BF_3\cdot Et_2O$, propane-1,3-dithiol, CH_2Cl_2 (72% over two steps); (xi) 2,2-dimethoxypropane, TsOH (80%); (xii) $MeOCH_2Cl$, Et_3N, DMAP, DMF, 60 °C (80%); (xiii) AcOH/H_2O 3:1, 50 °C; (xiv) PhCOCN, Et_3N, MeCN, −10 °C; MsCl, Et_3N, 0 °C; (xv) *n*-Bu_4NOH, MeOH, Et_2O (80% over three steps); (xvi) *n*-BuLi, THF, −78 °C; CuCN; **365**, −78 to −35 to −25 to −15 °C (75%); (xvii) *n*-BuLi, TMEDA, THF, −30 °C; HMPA, −78 °C; dimethyl oxalate, −78 to −50 to −30 to 0 °C (96%); (xviii) LiI, 2,6-lutidine, DMF, 75 °C (100%).



Scheme 57. Synthesis of (+)-aplasmomycin (**357**) by Corey and co-workers (Part B). Reagents and conditions: (i) BOPCl, Et_3N (25%); (ii) $NaBH_4$, MeOH, −20 °C; (iii) diisopropylthioboron bromide, CH_2Cl_2, −78 °C (80%); (iv) $HgCl_2$, $CaCO_3$, $MeCN/H_2O$ 4:1 (94%); (v) $(MeO)_3B$, MeOH, Δ.



Scheme 58. Synthesis of (+)-aplasmomycin (**357**) by White and co-workers (Part A). Reagents and conditions: (i) $LiAlH_4$, Et_2O, −110 °C; (ii) Ac_2O, DMAP (78% over two steps); (iii) TsOH, THF, H_2O; (iv) NaOH in H_2O; (v) 5% HCl in THF (74% over three steps); (vi) PhSeCl, CCl_4, 70 °C (94%); (vii) 30% H_2O_2, 0–25 °C (91%); (viii) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, −20 °C (90%); (ix) NaOH, MeOH, H_2O; (x) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, −20 °C; (xi) K_2CO_3, MeOH, THF, H_2O (92% over three steps); (xii) Bu_4NF, THF (90%); (xiii) $BrCH_2CO_2(CH_2)_2SiMe_3$, K_2CO_3, Me_2CO, Δ (93%); (xiv) $BrCH_2COCl$, DMAP, pyridine, CH_2Cl_2, 0 °C (92%); (xv) **380**, K_2CO_3, Me_2CO, Δ (88%).

be moderately cytotoxic (IC_{50}s 0.5–5 μg/ml), none showed any selective cytotoxicity in the Corbett assay against murine or human solid tumour cell lines.[256–258] The host–guest chemistry of [*m.n*]-paracyclophanes has also been reviewed.[259–262]

The biosynthesis of [7.7]-paracyclophanes from cyanobacteria (blue-green algae) has been reviewed by Moore and co-workers and a polyketide biosynthetic pathway to cylindrocyclophanes A (**451**), D (**452**) and F (**453**) has been proposed (Scheme 68).[258]

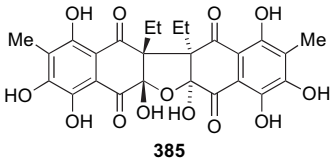


Figure 24. Structure of hybocarpone.

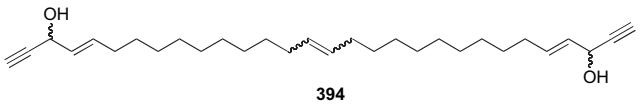
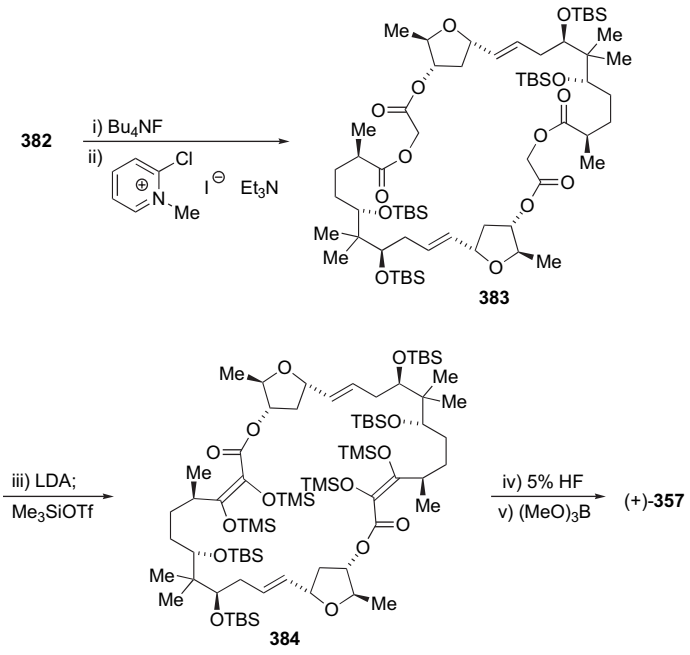
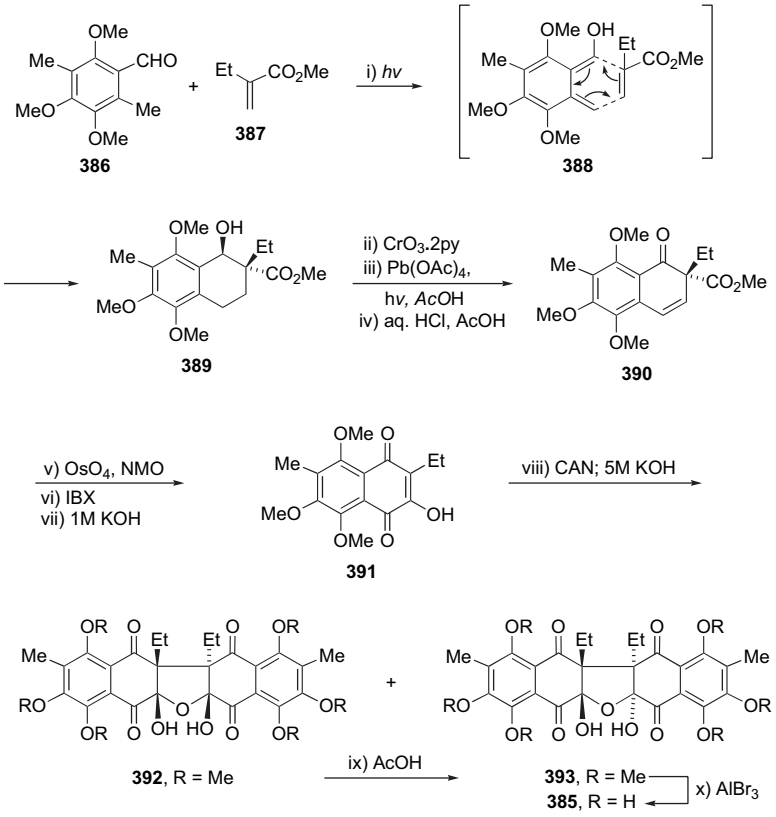


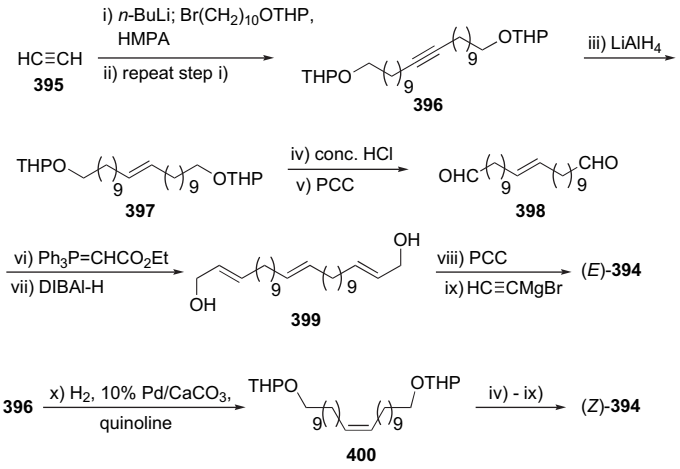
Figure 25. Structure of duryne.



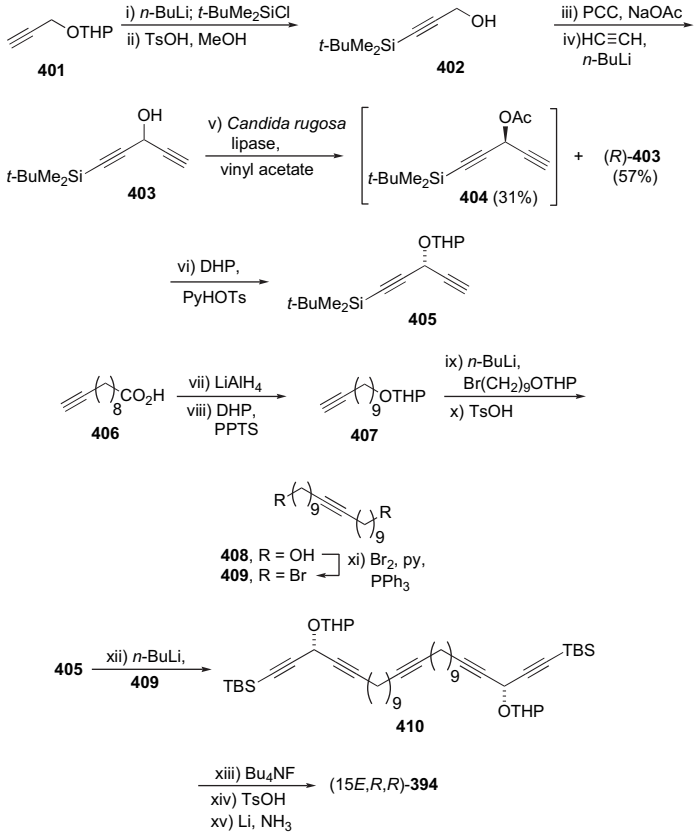
Scheme 59. Synthesis of (+)-aplasmomycin (**357**) by White and co-workers (Part B). Reagents and conditions: (i) Bu_4NF, THF, 0 °C; (ii) 2-chloropyridinium methiodide, Et_3N, CH_2Cl_2 (86% over two steps); (iii) LDA, THF, 0 °C; Me_3SiOTf, −78 °C; (iv) 5% HF in MeCN; (v) $(MeO)_3B$, MeOH, Δ.



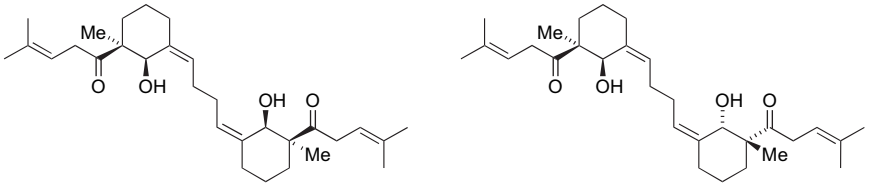
Scheme 60. Synthesis of hybocarpone (**385**) by Nicolaou and Gray. Reagents and conditions: (i) **387**, hν, PhMe (82%); (ii) $CrO_3 \cdot 2py$, CH_2Cl_2, 0–25 °C (86%); (iii) $Pb(OAc)_4$, hν, AcOH (71%); (iv) HCl, AcOH, H_2O (72%); (v) OsO_4, NMO, THF/*t*-BuOH/H_2O/pyridine 20:20:4:1 (92%); (vi) IBX, DMSO (92%); (vii) 1 M KOH, air, H_2O/THF 3:1 (87%); (viii) CAN, MeCN, −35–0 °C; 5 M KOH in H_2O, 0–25 °C (36% based on 60% recovered starting material) (dr **392**/**393** 1:1); (ix) AcOH (>95%); (x) $AlBr_3$, EtSH/CH_2Cl_2 1:1.5, 0 °C (60%).



Scheme 61. Synthesis of (*E*)- and (*Z*)-duryne (**394**) by Deshpande and co-workers. Reagents and conditions: (i) *n*-BuLi, THF, 0 °C; $Br(CH_2)_{10}OTHP$, HMPA (90% of the mono-alkylated derivative; (ii) repeat process (60%); (iii) $LiAlH_4$, diglyme, 140 °C (80%); (iv) concd HCl, MeOH (98%); (v) PCC, CH_2Cl_2 (60%); (vi) $Ph_3P{=}CHCO_2Et$, PhH, Δ (98%); (vii) DIBAl-H, PhMe, −78 °C (96%); (viii) PCC, CH_2Cl_2 (60%); (ix) HC≡CMgBr, THF (60%); (x) H_2, 10% $Pd/CaCO_3$, quinoline (cat.), *n*-hexane (95%).

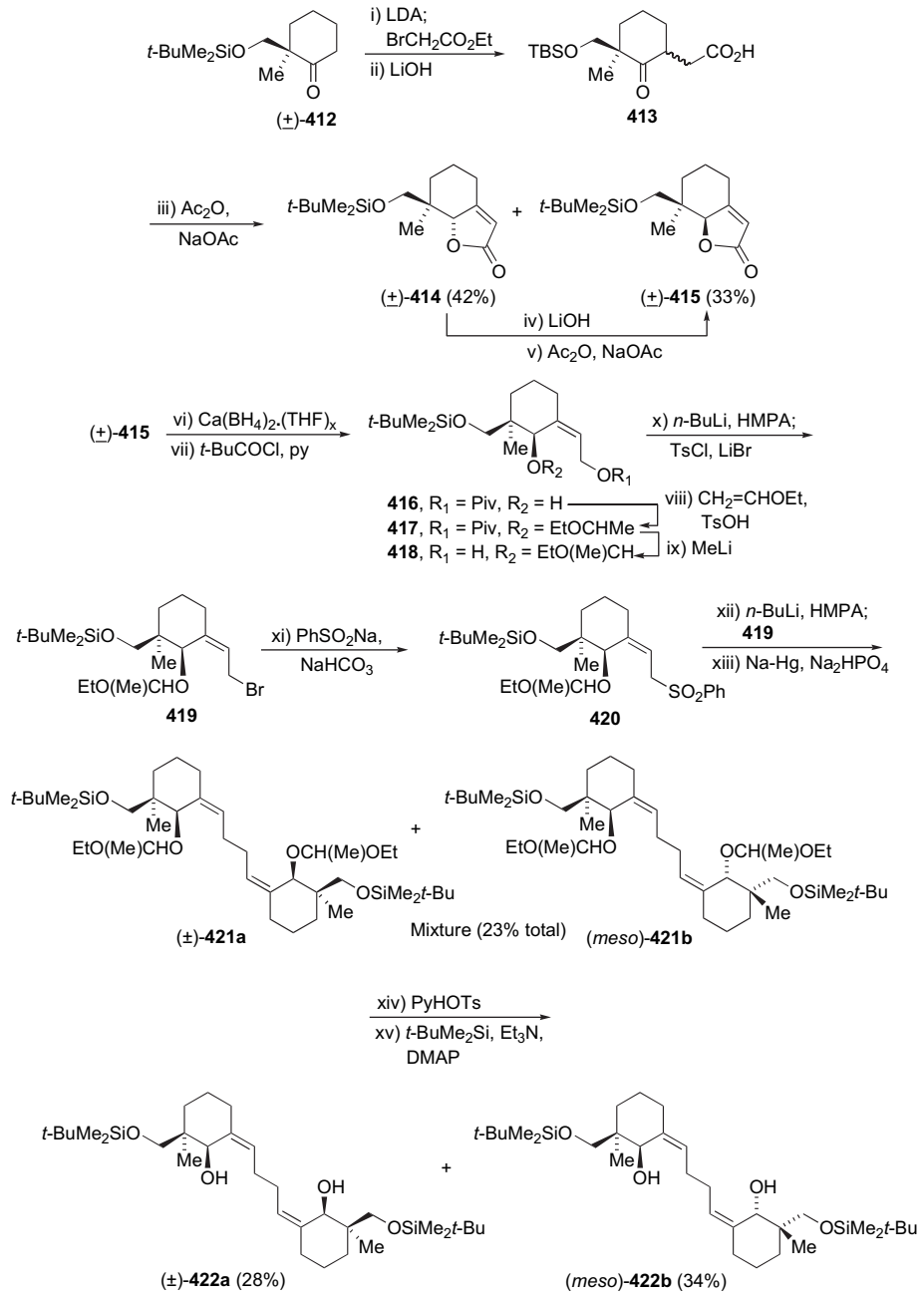


Scheme 62. Synthesis of (15*E*,*R*,*R*)-duryne (**394**) by Sharma and Chattopadhyay. Reagents and conditions: (i) *n*-BuLi, *t*-$BuMe_2SiCl$, THF, −30 to −78 °C (71%); (ii) TsOH, MeOH, Δ (92%); (iii) PCC, NaOAc, CH_2Cl_2, 0 °C (76%); (iv) ethylene, *n*-BuLi, THF, −40 to 20 °C (61%); (v) *Candida rugosa* lipase, vinyl acetate, *i*-Pr_2O; (vi) DHP, PyHOTs, CH_2Cl_2 (66%); (vii) $LiAlH_4$, Et_2O, Δ (84%); (viii) DHP, PyHOTs, CH_2Cl_2 (90%); (ix) *n*-BuLi, $Br(CH_2)_9OTHP$, HMPA, THF, −25–20 °C (68%); (x) TsOH, MeOH, Δ (88%); (xi) Br_2, PPh_3, pyridine, CH_2Cl_2, 0 °C (61%); (xii) *n*-BuLi, **409**, THF, HMPA, −25–20 °C (48%); (xiii) Bu_4NF, THF, −78 °C (100%); (xiv) TsOH, MeOH, Δ (68%); (xv) Li, NH_3, −78 °C (68%).

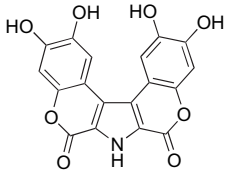


(±)-**411a** meso-**411b**

Figure 26. Structure of limatulone.

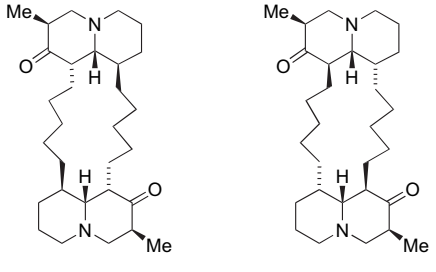


Scheme 63. Synthesis of limatulone (**411**) by Mori and co-workers (Part A). Reagents and conditions: (i) LDA, THF, −60 to −20 °C; $BrCH_2CO_2Et$, −60–20 °C (88%); (ii) LiOH, THF, MeOH, H_2O (100%); (iii) Ac_2O, NaOAC, Δ; (iv) LiOH, THF, MeOH, H_2O; (v) Ac_2O, NaOAc, Δ (23% over two steps); (vi) $Ca(BH_4)_2\cdot(THF)x$, *i*-PrOH (99%); (vii) *t*-BuCOCl, pyridine, 0 °C (96%); (viii) CH_2═CHOEt, TsOH, 0 °C (91%); (ix) MeLi, Et_2O, −15 °C (97%); (x) *n*-BuLi, HMPA, Et_2O, 0 °C; TsCl, LiBr (100%); (xi) $PhSO_2Na$, $NaHCO_3$, DMF (78%); (xii) *n*-BuLi, HMPA, THF, −78–0 °C; **419**; (xiii) Na-Hg, Na_2HPO_4, THF/MeOH 0 °C (23% over two steps); (xiv) PyHOTs, MeOH; (xv) *t*-$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2 (28% of (±)-**422**).



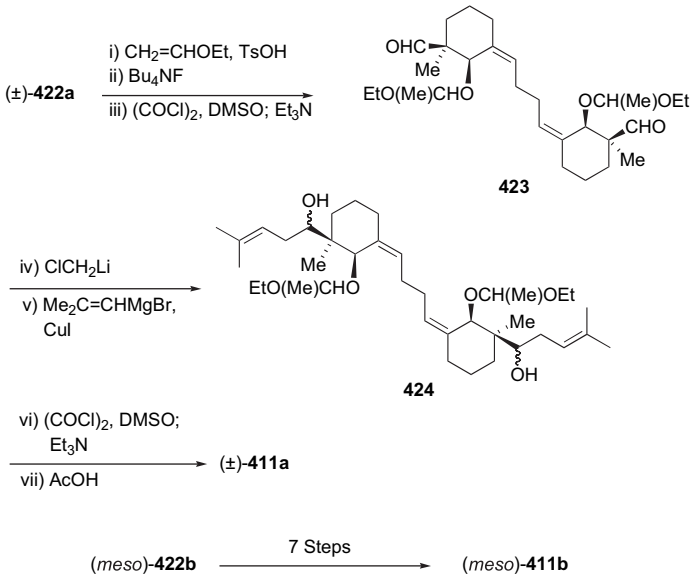
425

Figure 27. Structure of ningalin A.

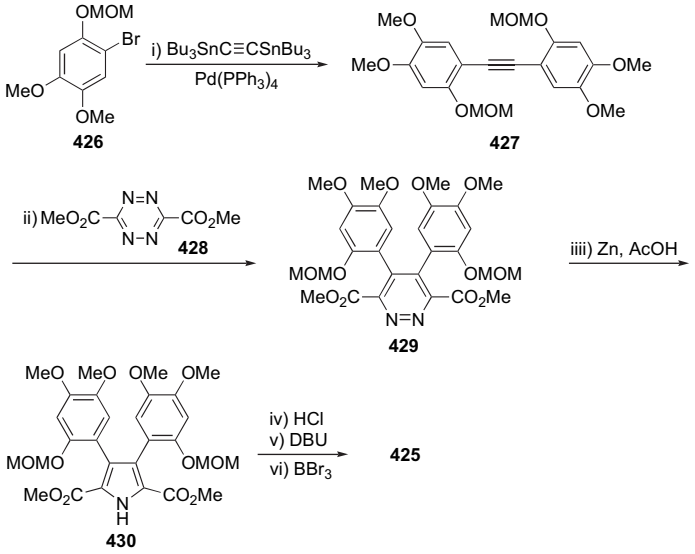


431 **432**

Figure 28. Structures of petrosin (**431**) and petrosin C (**432**).



Scheme 64. Synthesis of limatulone (**411**) by Mori and co-workers (Part B). Reagents and conditions: (i) CH_2=CHOEt, TsOH, 0 °C (90%); (ii) Bu_4NF, THF (98%); (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C; Et_3N, −70–0 °C (100%); (iv) *n*-BuLi, $ClCH_2I$, −78–20 °C (91%); (v) Me_2C=CHMgBr, CuI, THF, −70–20 °C (98%); (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C; Et_3N, −70–0 °C (90%); (vii) AcOH, MeOH, H_2O (43%).

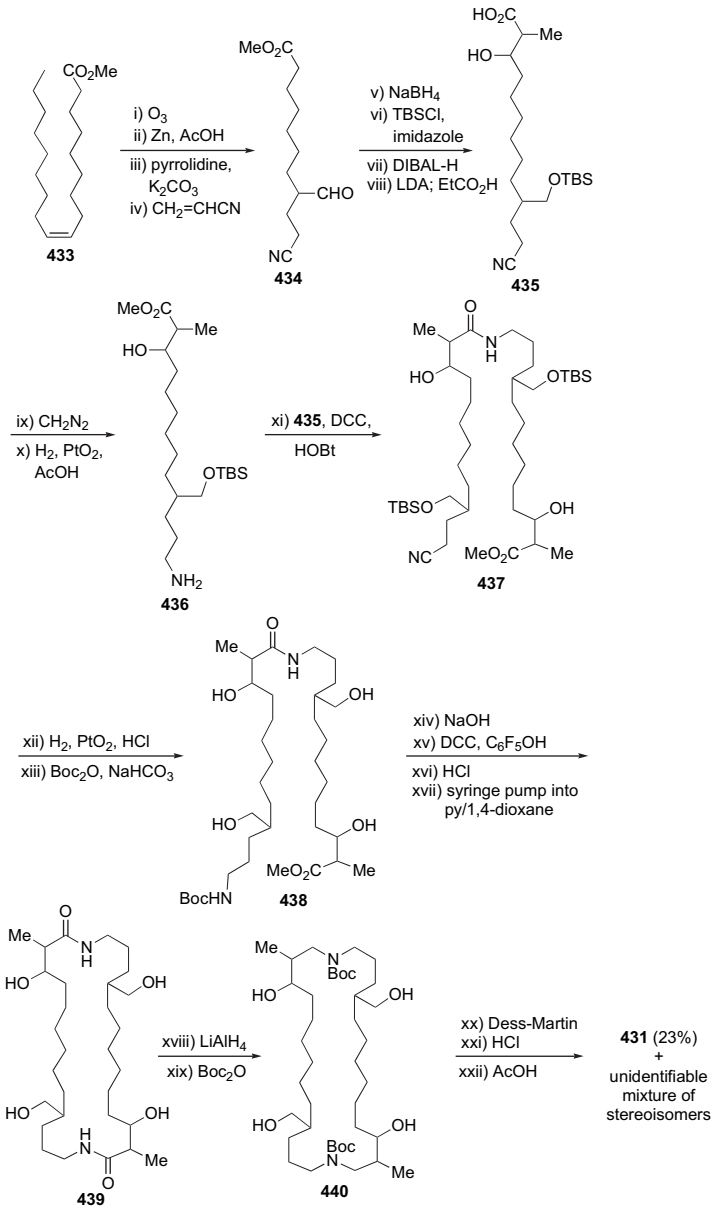


Scheme 65. Synthesis of ningalin (**425**) by Boger and co-workers. Reagents and conditions: (i) $Bu_3SnC{\equiv}CSnBu_3$, $Pd(PPh_3)_4$, PhMe, 100 °C (79%); (ii) **428**, PhMe, 105 °C (87%); (iii) Zn, AcOH (63%); (iv) 3 M HCl in EtOAc (94%); (v) DBU, PhMe, 105 °C (100%); (vi) BBr_3, CH_2Cl_2, −78–25 °C (96%).

(−)-Cylindrocyclophane F (**453**) was the first member of the family to be synthesized by Smith and co-workers using ring-closing metathesis (RCM) with the Schrock catalyst **463** as the key step.[263] Since that time, the Philadelphia group has also reported syntheses of both cylindrocyclophane A (**451**) and F (**453**), using a cross-metathesis dimerization strategy (Scheme 69).[264–266]

A synthetic approach to cylindrocyclophane A (**451**) has also been disclosed by Hoye and co-workers who employed a double Horner Emmons reaction as their key step (Scheme 70).[267]

3.2.3.2. Tartrolon B. Tartrolon B (**484**, Fig. 31), which is closely related to aplasmomycin (**357**, Section



Scheme 66. Synthesis of petrosin (**431**) by Heathcock and co-workers. Reagents and conditions: (i) O_3, MeOH/CH_2Cl_2 2:1, −78 °C; (ii) Zn, AcOH (96% over two steps); (iii) pyrrolidine, K_2CO_3, Et_2O, 0–20 °C; (iv) CH_2═CHCN, MeCN, 80 °C (73% over two steps); (v) $NaBH_4$, MeOH, 0 °C (100%); (vi) *t*-$BuMe_2SiCl$, imidazole, DMF (95%); (vii) DIBAl-H, CH_2Cl_2, −93 °C (86%); (viii) LDA, propionic acid, THF, 0–20 °C (77%); (ix) CH_2N_2, Et_2O (100%); (x) H_2 (53 psi), PtO_2, AcOH, EtOAc (97%); (xi) **435**, DCC, HOBt, THF, 0–20 °C (70%); (xii) H_2 (53 psi), PtO_2, 0.23 M HCl in EtOH, (xiii) Boc_2O, $NaHCO_3$, 1,4-dioxane, H_2O (72% over two steps); (xiv) 1 M NaOH in MeOH, THF; (xv) DCC, C_6F_5OH, THF, 0–20 °C; (xvi) 6 N HCl in 1,4-dioxane; (xvii) syringe pump into 1,4-dioxane/pyridine 5:1, 85–90 °C (78% over four steps); (xviii) $LiAlH_4$, THF, Δ; (xix) Boc_2O, dioxane, H_2O (90% over two steps); (xx) Dess-Martin, CH_2Cl_2; (xxi) 1 M HCl in EtOH/H_2O 5:1, Δ; (xxii) 0.2 M AcOH in EtOH, Δ (62% over three steps, including 23% of **431**).

3.1.3.1), was isolated from the myxobacterium *Sorangium cellulosum*[268] and was shown to be active against Gram-positive bacteria and mammalian cells.

A study into the biosynthesis of tartrolon B (**484**), as well as an X-ray structure analysis, have been performed to obtain the absolute configuration.[269] The only reported synthesis of tartrolon B (**484**) was completed by Mulzer and co-workers.[270–272] Starting from ester **485**, key intermediate **495** was prepared as a 1:1 epimeric mixture (Scheme 71). Lactonization using Yamaguchi conditions gave the macrolide **498**, which was further elaborated to complete the synthesis (Scheme 72).

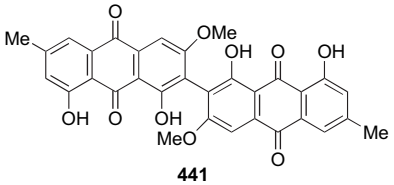
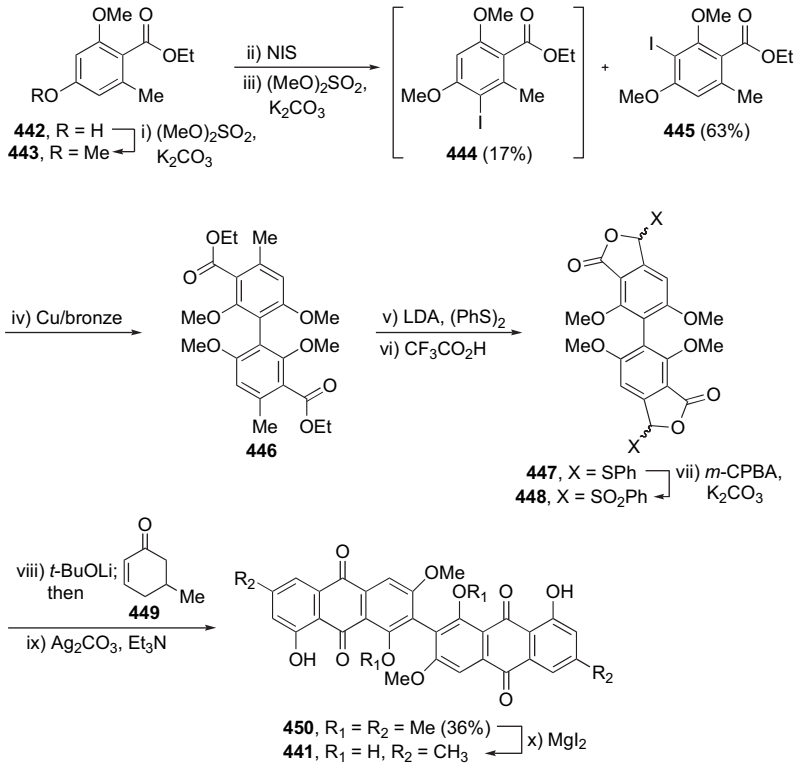


Figure 29. Structure of biphyscion.



Scheme 67. Synthesis of biphyscion (**441**) by Hauser and co-workers. Reagents and conditions: (i) $(MeO)_2SO_2$, K_2CO_3, CH_2Cl_2 (98%); (ii) NIS, CH_2Cl_2; (iii) $(MeO)_2SO_2$, K_2CO_3 (98% over two steps); (iv) Cu/bronze, 210–220 °C (72%); (v) LDA, $(PhS)_2$, −78 °C (55%); (vi) CF_3CO_2H, H_2O, Δ (100%); (vii) *m*-CPBA, K_2CO_3, CH_2Cl_2 (100%); (viii) *t*-BuOLi; **449**; (ix) Ag_2CO_3, Et_3N, CH_2Cl_2 (36% over two steps); (x) MgI_2, Et_2O (70%).

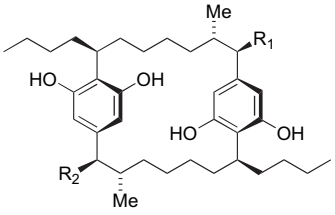


Figure 30. Structures of cylindrocyclophanes A (**451**), D (**452**) and F (**453**).

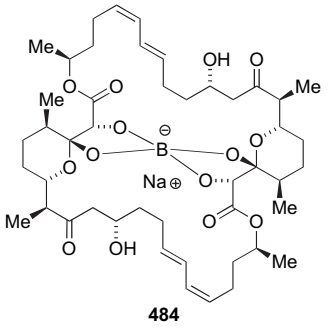
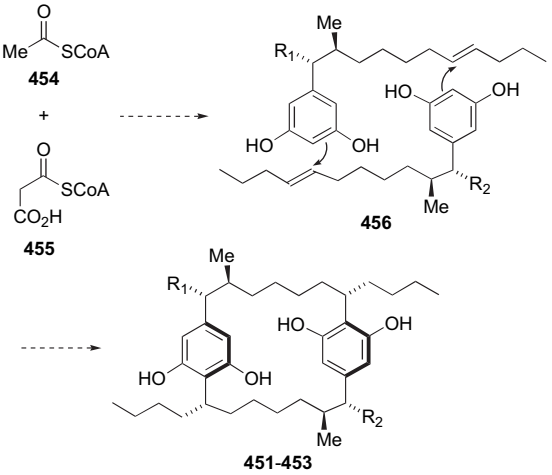


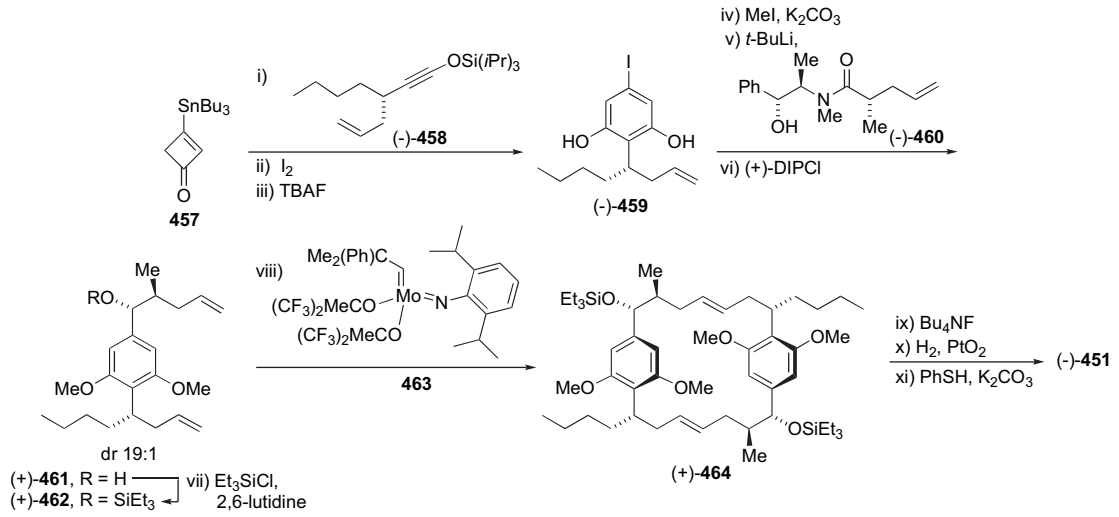
Figure 31. Structure of tatrolon B.



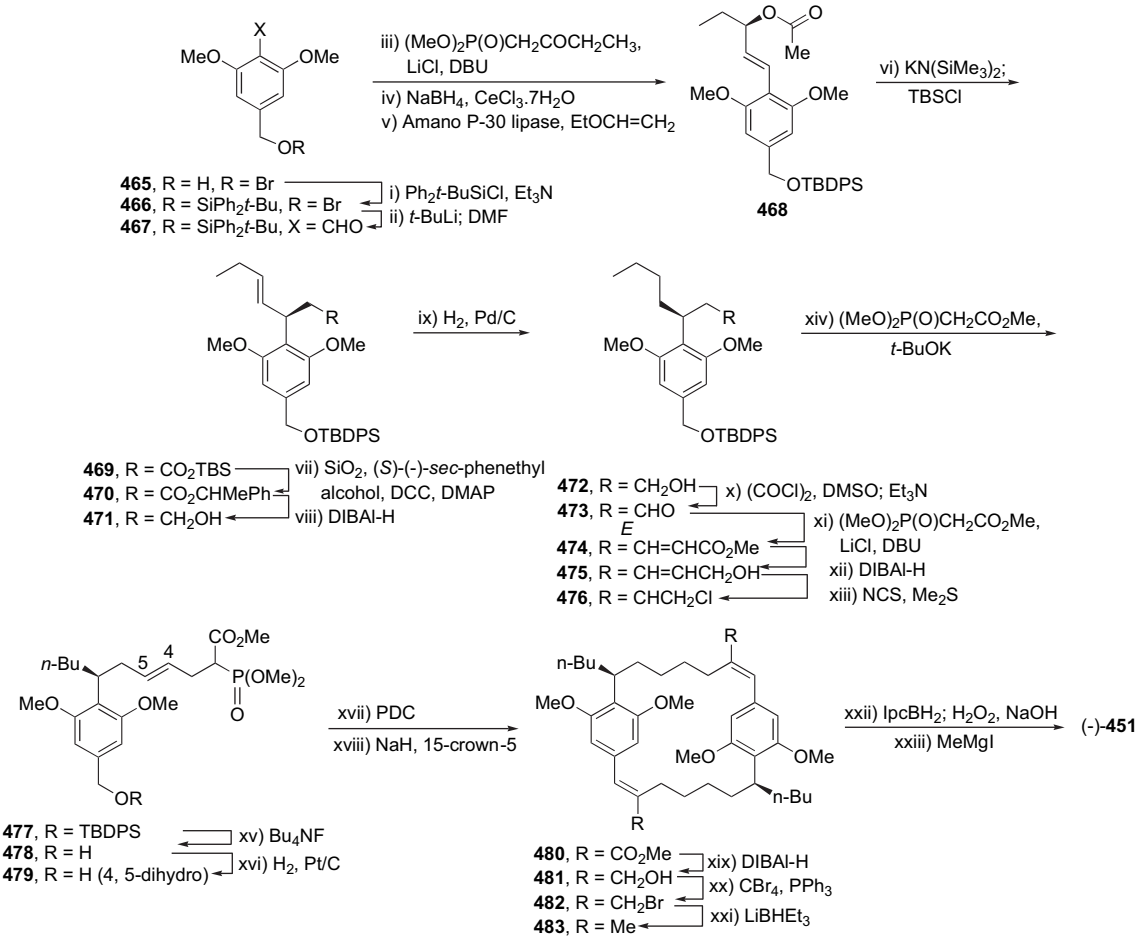
Scheme 68. Proposed biosynthetic pathway to cylindrocyclophanes A (**451**), D (**452**) and F (**453**) by Moore and co-workers.

4. Conclusion

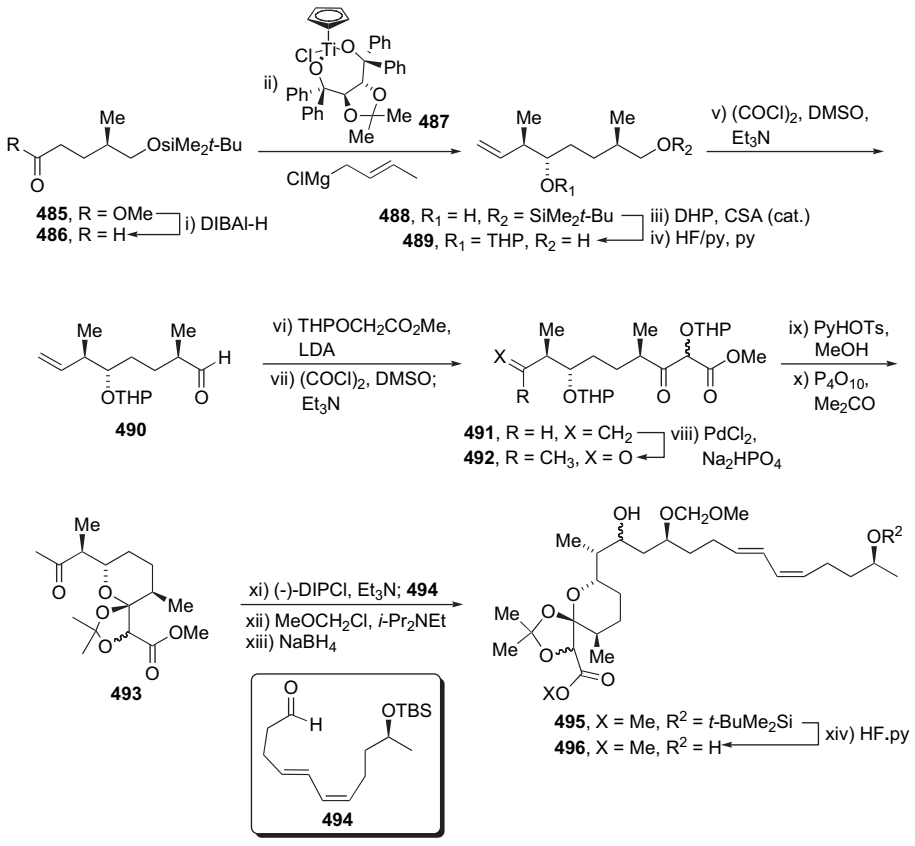
In summary, this review article has illustrated the application of three-component coupling reactions, core expansion and dimerization strategies that have greatly simplified the total synthesis of C_2 symmetric natural products. A variety of synthetic reactions have been employed in these key assembly steps including N- and O-acylation, alkylation and reductive amination, as well as organometallic transformations such as alkene and alkyne metathesis, palladium(0) coupling and the Ullman reaction. Since there are many naturally occurring C_2 symmetric molecules that are biologically active, the development of concise approaches for their total synthesis is of potential importance to pharmaceutical discovery and innovation.



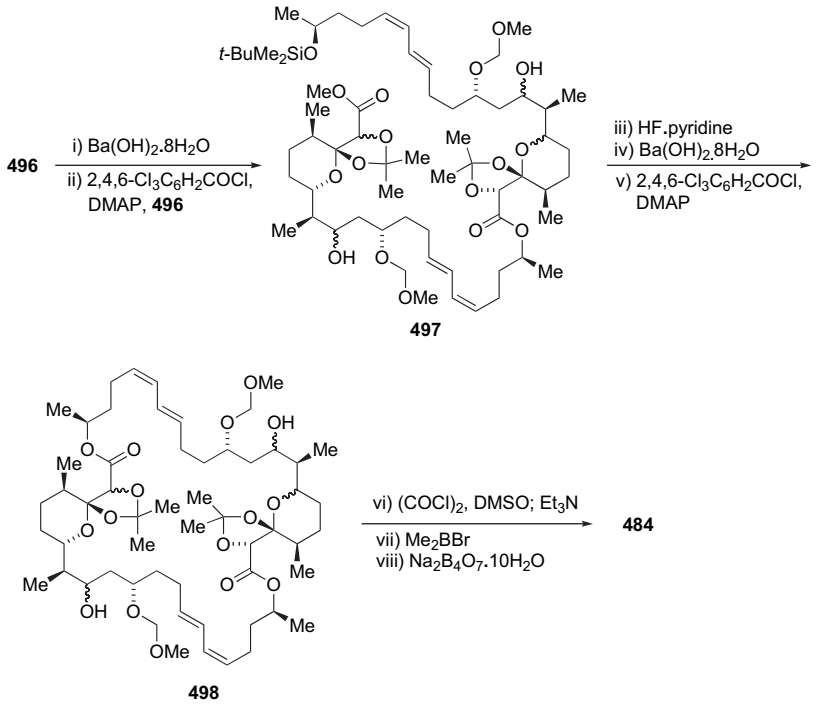
Scheme 69. Synthesis of (−)-cylindrocyclophanes A (**451**) by Smith and co-workers. Reagents and conditions: (i) (−)-**458**, PhMe, 100 °C; (ii) I_2, CH_2Cl_2 (79% over two steps); (iii) Bu_4NF, THF, 0 °C (88%); (iv) MeI, K_2CO_3, 2-butanone (89%); (v) *t*-BuLi, (−)-**460**, THF, −78–0 °C (68%); (vi) (+)-DIPCl, THF (55% over two steps); (vii) Et_3SiCl, 2,6-lutidine, CH_2Cl_2, 0 °C (92%); (viii) Schrock's catalyst (**463**) (34 mol %), PhH (77%); (ix) Bu_4NF, THF, 0 °C (71%); (x) H_2 (1 atm), PtO_2, EtOH (100%); (xi) PhSH, K_2CO_3, 1-methyl-2-pyrrolidinone, 215 °C (85%).



Scheme 70. Synthesis of (−)-cylindrocyclophane A (**451**) by Hoye and co-workers. Reagents and conditions: (i) *t*-$BuPh_2SiCl$, Et_3N, CH_2Cl_2, 0 °C (98%); (ii) *t*-BuLi, Et_2O, −78 °C; DMF, −78–20 °C (92%); (iii) $(MeO)_2P(O)CH_2COEt$, LiCl, DBU, MeCN (70%); (iv) $NaBH_4$, $CeCl_3\cdot 7H_2O$, EtOH, 0 °C (97%); (v) Amano P-30 lipase, vinyl acetate, hexanes, 4 Å molecular sieves (50% conversion, 94%); (vi) $KN(SiMe_3)_2$, THF, −78 °C; *t*-$BuMe_2SiCl$, −78–20 °C (80%); (vii) SiO_2, Et_2O, (*S*)-(−)-sec-phenethyl alcohol, DCC, DMAP, CH_2Cl_2 (62%); (viii) DIBAl-H, CH_2Cl_2, −78 °C (95%); (ix) H_2, Pd/C, EtOH (99%); (x) $(COCl)_2$, DMSO, −60 °C, CH_2Cl_2; Et_3N, −60–20 °C (90%); (xi) $(MeO)_2P(O)CH_2CO_2Me$, LiCl, DBU, MeCN (80%); (xii) DIBAl-H, CH_2Cl_2, −78 °C; (xiii) NCS, Me_2S, CH_2Cl_2, −30 °C (89% over two steps); (xiv) $(MeO)_2P(O)CH_2CO_2Me$, *t*-BuOK, DMSO (80%); (xv) Bu_4NF, THF, 0 °C (94%); (xvi) H_2, Pt/C, EtOAc (99%); (xvii) PDC, CH_2Cl_2 (96%); (xviii) NaH, 15-crown-5, PhH (55%); (xix) DIBAl-H, CH_2Cl_2 (100%); (xx) CBr_4, PPh_3, CH_2Cl_2; (xxi) $LiBHEt_3$, THF (91% over two steps); (xxii) $IpcBH_2$, THF, −20–20 °C; H_2O_2, NaOH (58%); (xxiii) MeMgI, neat, 160 °C (60%).



Scheme 71. Synthesis of tartrolon B (**484**) by Mulzer and co-workers (Part A). Reagents and conditions: (i) DIBAl-H, Et_2O, −90 °C (89%); (ii) crotylmagnesium chloride, **487**, Et_2O, −78 °C (81%); (iii) DHP, 10-camphorsulfonic acid (cat.), CH_2Cl_2 (96%); (iv) HF·pyridine, pyridine, THF (97%); (v) $(COCl)_2$, DMSO, −78 °C; Et_3N (97%); (vi) $THPOCH_2CO_2Me$, LDA, THF, −90 °C (83%); (vii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N (75%); (viii) $PdCl_2$, Na_2HPO_4 buffer, THF, DMF (84%); (ix) PyHOTs, MeOH, THF, 50 °C (96%); (x) P_2O_5, Me_2CO (69%); (xi) (−)-DIPCl, Et_3N, THF, −78 °C; **494** (72%, dr 4:1); (xii) $MeOCH_2Cl$, i-Pr_2NEt, CH_2Cl_2 (90%); (xiii) $NaBH_4$, MeOH, THF, −20–0 °C (89%); (xiv) HF·pyridine, THF (94%).



Scheme 72. Synthesis of tartrolon B (**484**) by Mulzer and co-workers (Part B). Reagents and conditions: (i) $Ba(OH)_2 \cdot 8H_2O$, MeOH; (ii) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N; DMAP, PhMe, **496** (74% over two steps); (iii) HF·pyridine, THF (96%); (iv) $Ba(OH)_2 \cdot 8H_2O$, MeOH; (v) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N; DMAP, PhMe, 35 °C (82% over two steps); (vi) $(COCl)_2$, DMSO, −78 °C; Et_3N (89%); (vii) Me_2BBr, CH_2Cl_2, −78 °C (65%); (viii) $Na_2B_4O_7 \cdot 10H_2O$, MeOH, 60 °C (41%).

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Biographical sketch

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Alice R. E. Brewer was born in St. Albans, UK (1978). Alice completed an MSc in Chemistry with Medicinal Chemistry at Imperial College London in 2000, during which time she studied under the supervision of Prof. A.G.M. Barrett working towards the total synthesis of a polycyclopropane natural product. In 2001 Alice began her PhD with Prof. Barrett where she worked towards the synthesis of two novel nitrophenyl pyrone natural products, and a novel terpenoid pyrrolobenzoxazine natural product. As a student, Alice spent time at Pfizer Global Research and British Biotech, and since receiving her doctorate in 2005 she has worked as a medicinal chemist at the Novartis Institute for BioMedical Research, Horsham.

Andrew A. Gray was born in Adelaide, Australia and raised in Scotland. In 2002 he obtained his Master of Chemistry with Industrial Experience from Edinburgh University, having carried out research for Prof. Nicholas J. Turner. Andrew then moved to London and began work on his doctoral thesis at Imperial College London, under the direction of Prof. A.G.M. Barrett. His graduate research focused on the synthesis of chiral sulfur-containing ligands and their application in organometallic catalysis. In 2006 Andrew received his PhD and is now currently employed as a consultant in the City of London.

Anthony G. M. Barrett started his academic career at Imperial College London (B.Sc. 1973; PhD 1975, with Derek H.R. Barton (Nobel Laureate); Lecturer, 1975; and Senior Lecturer, 1982). He was appointed a full professor of Chemistry at Northwestern University, Evanston, IL (1983), and at Colorado State University (1990). In 1993 he returned to his alma mater, IC, as Glaxo Professor of Chemistry, Sir Derek Barton Professor of Synthesis, Director of the Wolfson Centre for Organic Chemistry in Medical Science and Head of Synthesis. His research interests include the total synthesis of bioactive natural products, porphyrazine chemistry, the development of methods for organic synthesis including novel catalysis, enantioselective transformations, supported reagents and medicinal chemistry.