Structure, biosynthetic relationships and chemical synthesis of the icetexane diterpenoids

Eric M. Simmons and Richmond Sarpong*

Received 6th May 2009
First published as an Advance Article on the web 25th June 2009
DOI: 10.1039/b908984e

Covering: up to 2009

A detailed overview of the icetexane diterpenoid natural product family is presented. The structure, isolation and biological activity of these natural products is followed by an examination of their biosynthetic relationships and a comprehensive summary of the synthetic approaches to the icetexane family; 92 references are cited.

1 Introduction

The icetexanes are a family of diterpenoid natural products which have been isolated from a variety of terrestrial plant sources. The compounds in this family exhibit an array of interesting biological activities which, coupled with their unique structural features, has generated significant interest from the synthetic community. This review will begin by discussing the structure, isolation and biological activity of the icetexanes discovered to date. It will then examine their proposed biosynthetic relationships and conclude with a discussion of the current state of synthetic efforts toward these natural products.

The emphasis of this review is on the structure and chemistry of the icetexane natural products, with minimal focus on the phytochemical relationships between the plant sources of these compounds. In general, only simple diterpenes or their immediate biosynthetic derivatives have been included in this review. It should be noted, however, that a number of complex natural products that contain embedded icetexane skeletons have been reported,[1–6] which in turn have inspired several creative synthetic approaches.[7–9] Finally, although there have been no reviews published to date which focus exclusively on icetexane diterpenoids, a number of these compounds are discussed in several excellent articles which broadly cover diterpenoids isolated from various species in the *Salvia* genus.[10–13] These articles also provide an extensive analysis of the relationships among the plants from which these natural products have been isolated.

Department of Chemistry, University of California, Berkeley, CA, 94720, USA. E-mail: rsarpong@berkeley.edu; Tel: +1 510 643 6312

2 Structure, isolation and biological activity

Biosynthetically, the icetexane skeleton is believed to arise from a rearrangement of the more common abietane skeleton, giving rise to a 6-7-6 tricyclic framework that bears the systematic name 9(10→20)-*abeo*-abietane (Fig. 1). The details of this rearrangement are discussed in Section 3 (see Scheme 1).

The icetexane natural products that have been discovered to date vary widely in the degree of oxygenation and oxidation in each ring, leading to a diverse array of structures and biological activities. Although a formal classification scheme for the icetexanes does not currently exist, they can be logically divided into various subclasses based on the presence or absence of oxygenation at the C3, C11, C14 and C19 positions. We would like to propose the adoption of the classifications illustrated in Fig. 2. For pedagogical reasons, this review is organized according to these divisions.

The simplest subclass of icetexanes are the pisiferins (Fig. 3), which lack oxygenation at each of the C3, C11, C14 and C19 positions. The parent compound in this group, pisiferin, was first isolated from the leaves of *Chamaecyparis pisifera* in 1980.[14] The structure of pisiferin was originally proposed as **10**,[14] but was later revised to **1** following the re-isolation of pisiferin and the isolation of isopisiferin (**2**) from the seeds of *C. pisifera*.[15] Three additional members of this subclass, pisiferanol (**3**),

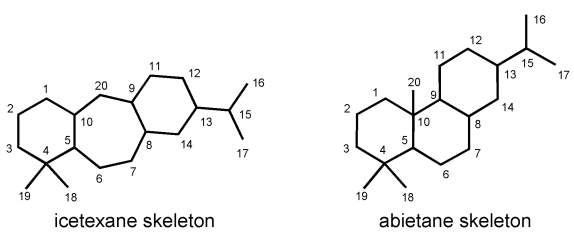


Fig. 1 Icetexane and abietane skeletons.

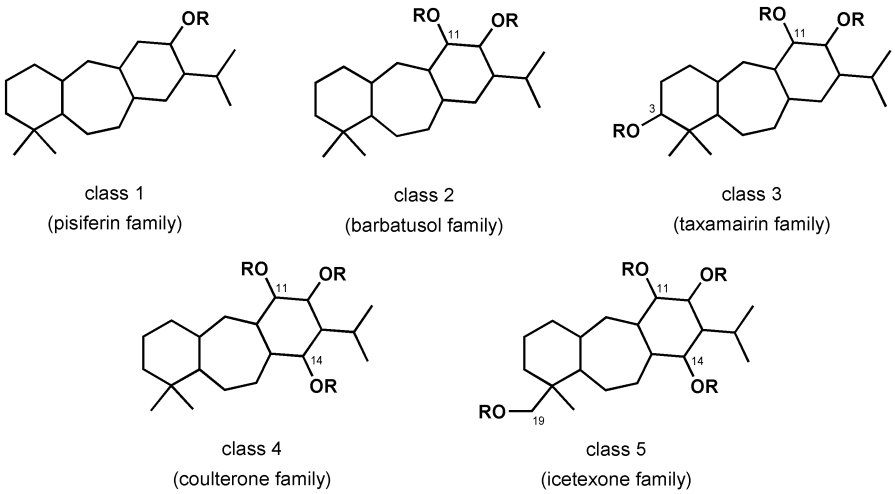


Fig. 2 Proposed classification scheme for the icetexanes.

12-deoxypisiferanol (**4**) and 1β-hydroxyisopisiferin (**5**), were also found in the seeds of *C. pisifera* in a subsequent study in 1985.[16] Some confusion arose when **3** was isolated from the roots of *Salvia lanigera* in 1995 and given the name lanigerol.[17] It was later realized[18] that this compound had already been isolated and named pisiferanol. However, the study of *S. lanigera* is the first reported isolation of a member of the pisiferin family outside of the *Chamaecyparis* genus. In addition, this study also identified, for the first time, that **3** possesses activity against the bacterial strains *Bacillus subtilis*, *Staphylococcus aureus* and *Mycobacterium luteus*.[17]

Compound **6** was independently isolated from the leaves[19,20] and seeds[16] of *C. pisifera* by two different groups and was alternatively named as pisiferdiol[19,20] and pisiferdinol.[16] The absolute configuration of **6** was determined by X-ray crystallographic analysis of a di-*p*-bromobenzoate derivative.[20] An extensive survey of the leaves of *Chamaecyparis formosensis* yielded the new compounds 12-*O*-methylpisiferanol (**7**) and 1β-hydroxypisiferanol (**8**) in 1999.[21] These compounds were the first new pisiferins to be found outside of the *C. pisifera* species. The *para*-quinol sawaradienone (**9**) was isolated from the leaves of *C. pisifera* in 2001, and was determined to be inactive against *S. aureus* and *B. subtilis*.[22] However, the same study found that pisiferdiol (**6**) possesses modest activity against both strains,[22] and also confirmed the previously observed antibacterial activity of pisiferanol (**3**).[17] It is interesting to note that although a number of abietane diterpenes isolated from *C. pisifera* have been extensively studied and identified as having antibacterial[23,24] and antifungal[25] activities, the biological activity of the pisiferins is less well explored.

The second subclass of icetexanes is exemplified by barbatusol (**11**, Fig. 4), which was isolated from the bark and heartwood of the Brazilian plant *Coleus barbatus* in 1983 and found to possess *in vivo* hypotensive activity in rats.[26] Barbatusol differs from pisiferin (**1**, Fig. 3) and congeners because it possesses an additional hydroxyl group at C11. This additional oxygenation is common to all of the members of the subclass illustrated in Fig. 4. The absolute configuration of barbatusol was determined by chemical correlation with carnosol, an abietane antioxidant of known configuration.[26] Also closely related to carnosol is rosmaridiphenol (**12**), which was identified in the leaves of *Rosmarinus officinalis* in 1984 and was found to possess antioxidant activity approaching that of

Eric M. Simmons

Eric M. Simmons was born in New Hampshire and grew up in Portland, ME. He received his B.A. in 2004 from Tufts University, where he conducted research in the laboratories of Marc d'Alarcao. He began his doctoral studies in the fall of 2004 at the University of California, Berkeley, working on the synthesis of icetexane and cortistatin natural products. In 2009, Eric will begin postdoctoral studies with John Hartwig at the University of Illinois.

Richmond Sarpong

Richmond Sarpong was born in Ghana, West Africa. He received his undergraduate degree from Macalester College in Saint Paul, MN. He received his Ph.D. from Princeton University (Princeton, NJ) working with Martin F. Semmelhack and conducted postdoctoral research with Brian Stoltz at Caltech (Pasadena, CA). Richmond is an assistant professor at UC Berkeley, where his group works in the area of natural products synthesis and organometallic methodology.

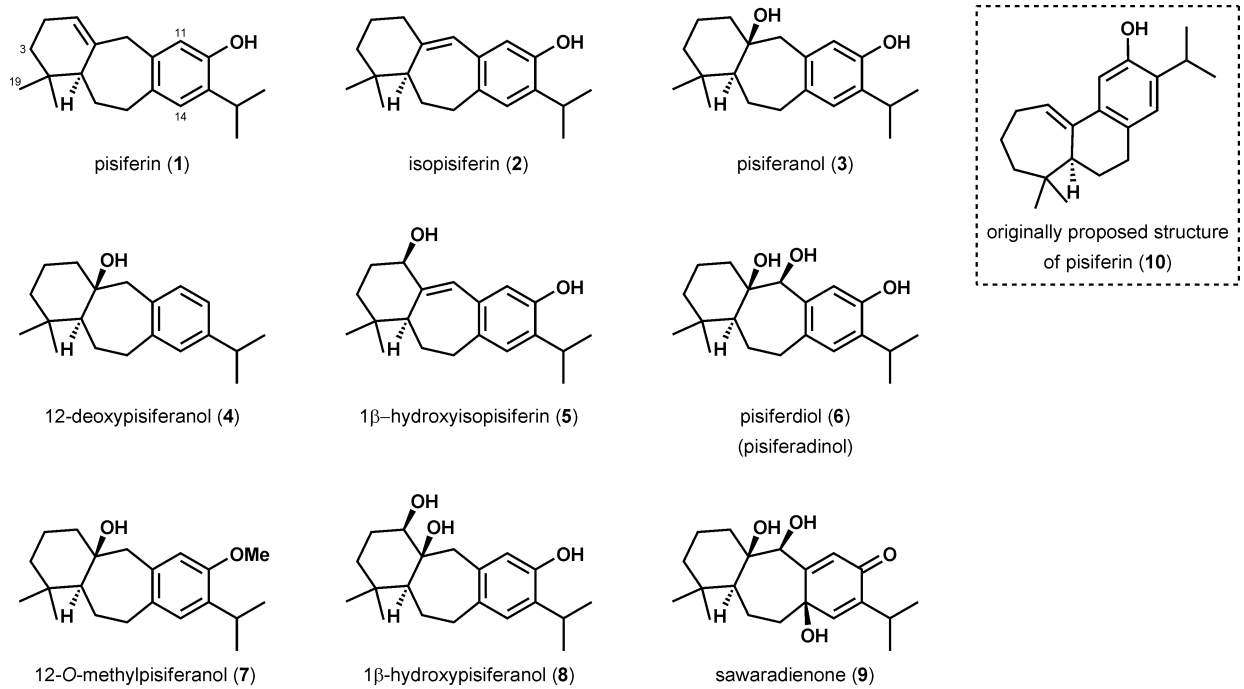


Fig. 3 Pisiferin and related compounds.

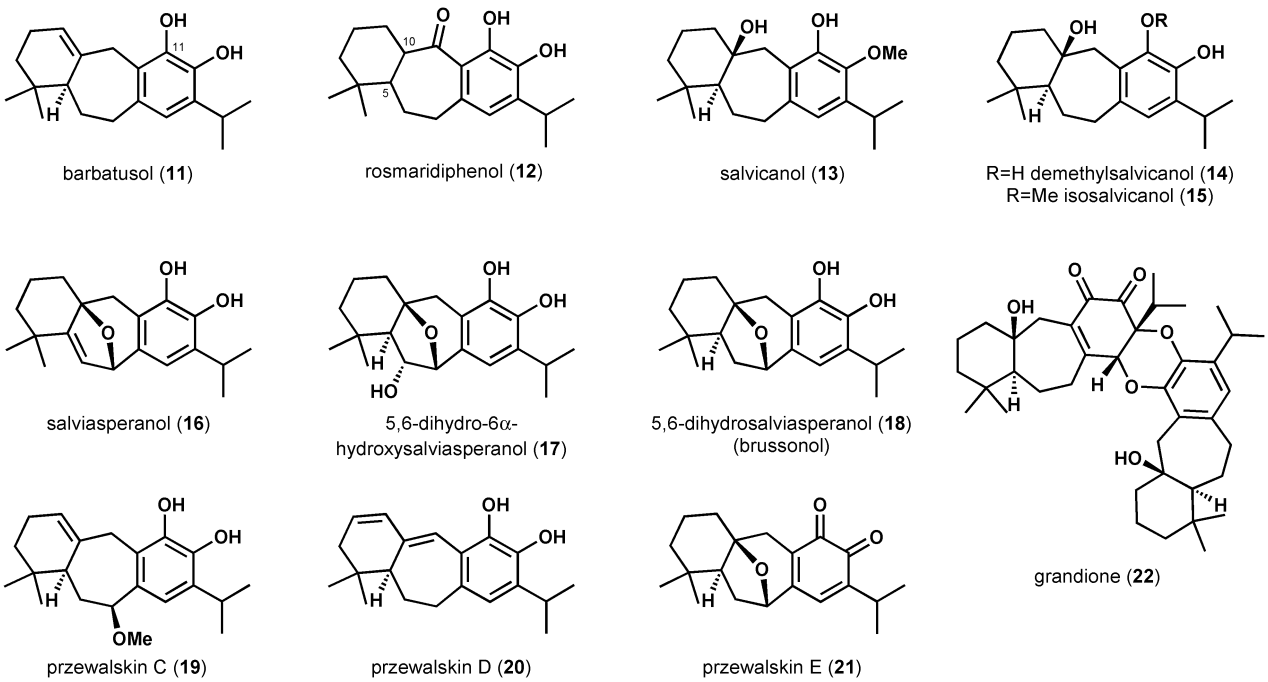


Fig. 4 Barbatusol and related compounds.

BHT.[27] Although the relative configuration of the C5 and C10 hydrogens was not determined, it is probable that they are *trans* given the thermodynamic preference for such a ring fusion and the likely facile epimerization of the C10 position. Salvicanol (**13**) was originally isolated from the roots of *Salvia canariensis*,[28] and was later found in the roots of *Salvia mellifera* in a study which also established the absolute configuration by X-ray crystallography.[29] The closely related compound demethylsalvicanol (**14**) was found in *C. barbatus*,[30] while isosalvicanol (**15**) was identified in the aerial parts of *Lepechinia meyeni*.[31] The unique icetexane dimer grandione was isolated from the wood of the coniferous evergreen tree *Torreya grandis* Fort.[32] The structure of grandione was initially proposed to be pseudo C2-symmetric, but was revised to **22** following its biomimetic synthesis from a sample of naturally-isolated demethylsalvicanol (**14**) and subsequent X-ray crystallographic analysis (see Section 3).[33]

Salviasperanol (**16**) and 5,6-dihydro-6α-hydroxysalviasperanol (**17**) were isolated from the roots of *Salvia aspera*.[34] Compound **18** was originally isolated from the roots of *Salvia mellifera*[35] and named 5,6-dihydrosalviasperanol, in accordance with its reported synthesis from salviasperanol.[34,36] However, following the independent isolation of **18** from a root culture of *Salvia broussonetii*[37] it was given the name brussonol, and this latter designation has been maintained in the literature. Brussonol and demethylsalvicanol (**14**) were both found to exhibit moderate cytotoxicity against insect Sf9 cells[37] and, along with grandione (**22**), against P388 murine leukemia cells.[33,38] Finally, przewalskins C (**19**) and D (**20**) were identified in extracts of the Chinese plant *Salvia przewalskii* Maxim in 2005,[39] while przewalskin E (**21**), the corresponding *ortho*-quinone of **18**, was isolated from *S. przewalskii* in 2009.[40]

The taxamairins are a subclass of highly unsaturated icetexanes which are oxygenated at both C11 and C3 (Fig. 5). Taxamairins A (**23**) and B (**24**) were the first members of this class to be discovered and were isolated in 1987 from *Taxus mairei*,[41,42] a Taiwanese plant which also produces the anticancer agent taxol. An initial survey of taxamairins A and B identified inhibitory activity against hepatoma (liver tumor) cells.[41] The isolation of taxamairins D–H (**25–29**) from the twigs of *T. mairei* was reported in 1998.[43] Two unnamed taxamairins (**30** and **31**) were discovered in callus cultures of *Taxus cuspidata* in 2005.[44] Compound **31** is the only icetexane identified to date which bears oxygenation at C2. The bark of *Taxus brevifolia* affords the unique diterpenolignan brevitaxin (**32**).[45] Brevitaxin is the Diels–Alder adduct of coniferyl alcohol and the *ortho*-quinone derivative of taxamairin A (**23**), and as might be expected, it was isolated as a racemate. Brevitaxin was screened against the NCI 60 panel and displayed selective, micromolar activity against prostate cancer cells.[45]

Coulterone (**33**, Fig. 6) was first isolated from the roots of *Salvia coulteri* in 1994,[46] and has subsequently been found in the roots of the Brazilian plant *Hyptis platanifolia*.[47] Although similar to the icetexanes in the barbatusol subclass (Fig. 4), coulterone bears additional oxygenation at C14. Its congeners cyclocoulterone (**34**) and komaroviquinone (**35**) were isolated from the Uzbekistani shrub *Dracocephalum komarovi*.[48] Both compounds showed trypanocidal activity against *Trypanosoma cruzi*, the causative agent of Chagas' disease (American trypanosomiasis).[49,50] Komaroviquinone was later identified in cultures of the seeds of *Hernandia ovigera* and was reported to inhibit the binding of MIP-1α to the G protein-coupled CCR5 receptor on Chinese hamster ovary (CHO) cell membranes.[51] As the CCR5 receptor has been implicated as a principal coreceptor in HIV-1 infection,[52] this intriguing finding suggests a potential role for komaroviquinone in the development of novel anti-HIV agents. The rearranged icetexane komarovispirone (**36**), similarly isolated from *D. komarovi*, also displays anti-Chagasic activity.[53] In an elegant study, it was demonstrated that komaroviquinone is readily converted to komarovispirone upon irradiation (see Section 3).[54] Abrotanone (**37**) was isolated from the aerial parts of the shrub *Perovskia abrotanoides*.[55] Originally assigned as the C5 epimer, its structure was revised following chemical synthesis.[36]

The anti-Chagasic activity of komaroviquinone has been studied in detail by Urade and co-workers.[56] They determined that the quinone moiety of **35** catalyzes a redox-cycling process which ultimately leads to oxidative stress in the parasite (Fig. 7). In the presence of the *Trypanosoma cruzi* old yellow enzyme (TcOYE), an NADPH-dependent, single-electron reduction of komaroviquinone yields semi-quinone radical anion **38**. This species can then undergo oxidation by molecular oxygen to regenerate **35** and produce superoxide ($O_2^{\bullet -}$). Interestingly, the original study of komaroviquinone determined an IC_{50} of 0.4 μM

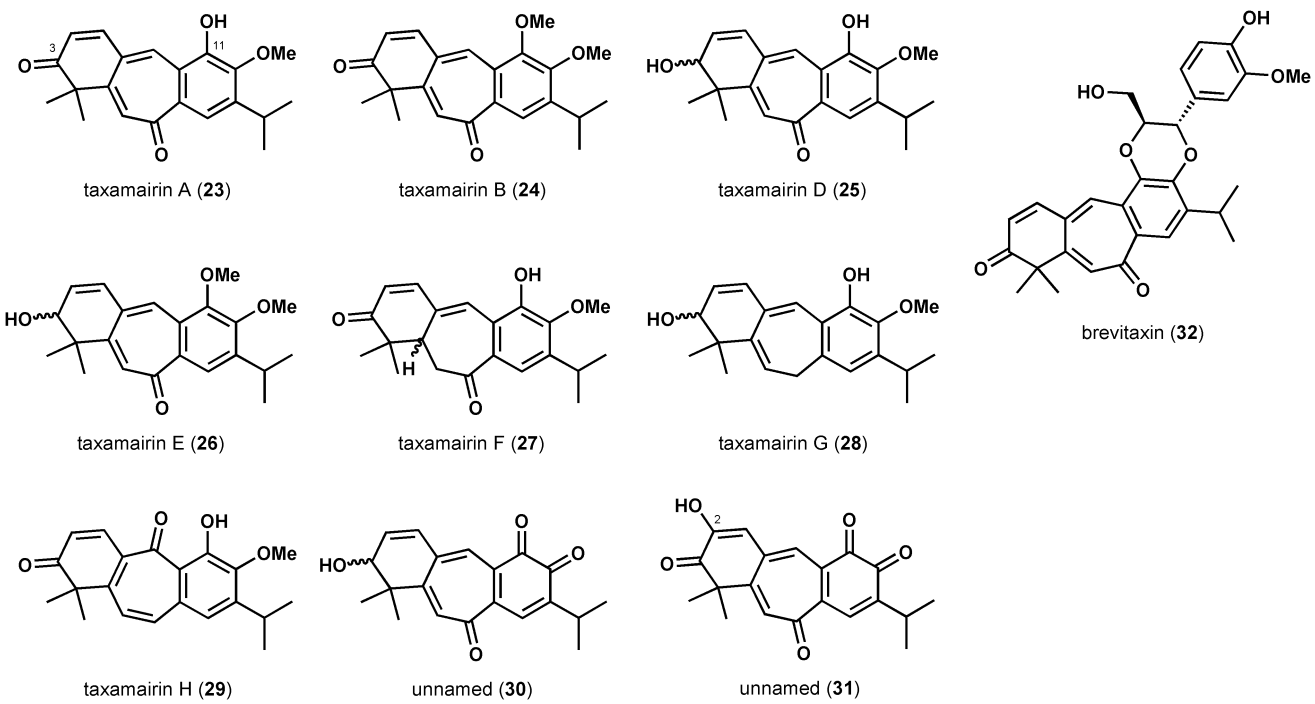


Fig. 5 The taxamairins.

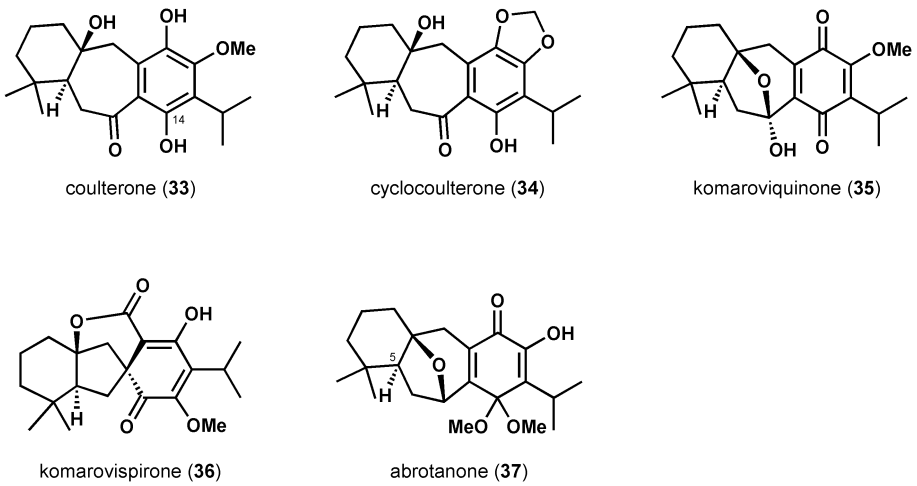


Fig. 6 Coulterone and related compounds.

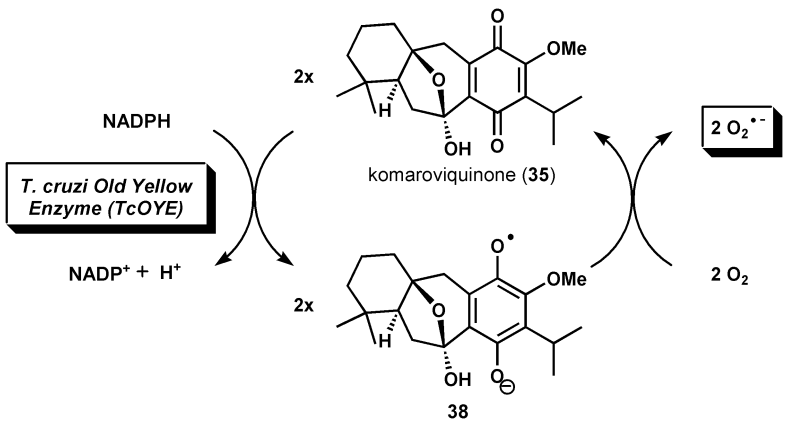


Fig. 7 Redox-cycling of komaroviquinone.[56]

against *T. cruzi* epimastigotes, the replicative form of the parasite.[48] However, the subsequent study by Urade *et al.* identified even more potent activity against *T. cruzi* trypomastigotes, the infective form of the parasite that circulates in the bloodstream, with an IC_{50} of 9 nM.[56]

Icetexone (**39**, Fig. 8) was the first 9(10→20)-*abeo*-abietane natural product to be isolated and structurally characterized. Accordingly, the icetexane family derives its name from this compound.[10,57] Icetexone is found in the aerial parts of the Mexican plant *Salvia ballotaeflora* Benth,[58,59] along with its *ortho*-quinone tautomer romulogarzone (**40**).[59] The structure of icetexone was assigned as **39** on the basis of X-ray crystallographic analysis.[60] The compounds in the icetexone subclass are characterized by oxygenation at C19 and the subsequent formation of a lactone or ether linkage between this position and either C10 or C6. Anastomosine (**41**) was isolated from the aerial parts of *Salvia anastomosans*.[57] The unnamed icetexanes **42** and **43** were found in extracts of the aerial parts of *Salvia candicans*.[61] It should be noted that compound **43** itself is not an actual metabolite, but was isolated following reductive acetylation of an unresolved mixture. The natural product precursor is likely the corresponding *para*-quinone or *para*-quinol derivative.

7,20-Dihydroanastomosine (**44**), 19-deoxyicetexone (**45**) and 19-deoxyisoicetexone (**46**) were isolated from the aerial parts of *Salvia ballotaeflora*.[62] 19(*R*)-Acetoxy-19-deoxoicetexone (**47**) was isolated from the aerial parts of *Salvia pubescens* and displayed moderate antibacterial activity against *Escherischia coli*.[63] 5-*epi*-Icetexone (**48**) was found in the aerial parts of *Salvia gilliessi* Benth.[64] In a subsequent study, 5-*epi*-icetexone was found to possess activity against *T. cruzi*.[65] Though its mode of action against *T. Cruzi* was not determined, it is likely that 5-*epi*-icetexone causes oxidative stress in the parasite by a mechanism similar to that outlined for komaroviquinone (**35**, Fig. 7).[56]

3 Biosynthetic relationships

The icetexane skeleton bears the formal name 9(10→20)-*abeo*-abietane, indicative of the fact that it is believed to arise in Nature from a rearrangement of the abietane skeleton (see Fig. 1).[10] In accordance with this hypothesis, the majority of icetexane natural products that have been discovered to date have been found in plant species which also produce abietane diterpenoids as secondary metabolites. A number of authors have speculated on the biosynthetic connections between various icetexane natural products, which have been compiled and summarized below.

The proposed biosynthetic relationships between barbatusol (**11**) and its related family members are illustrated in Scheme 1.

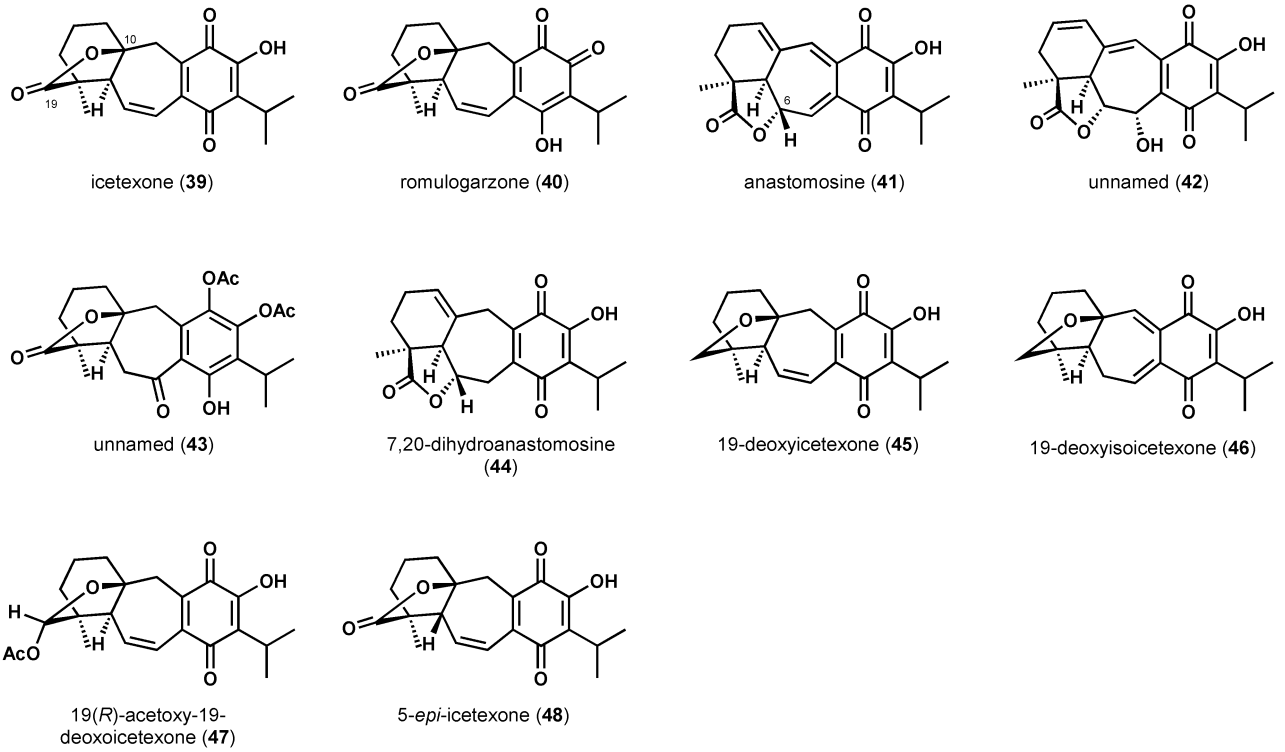
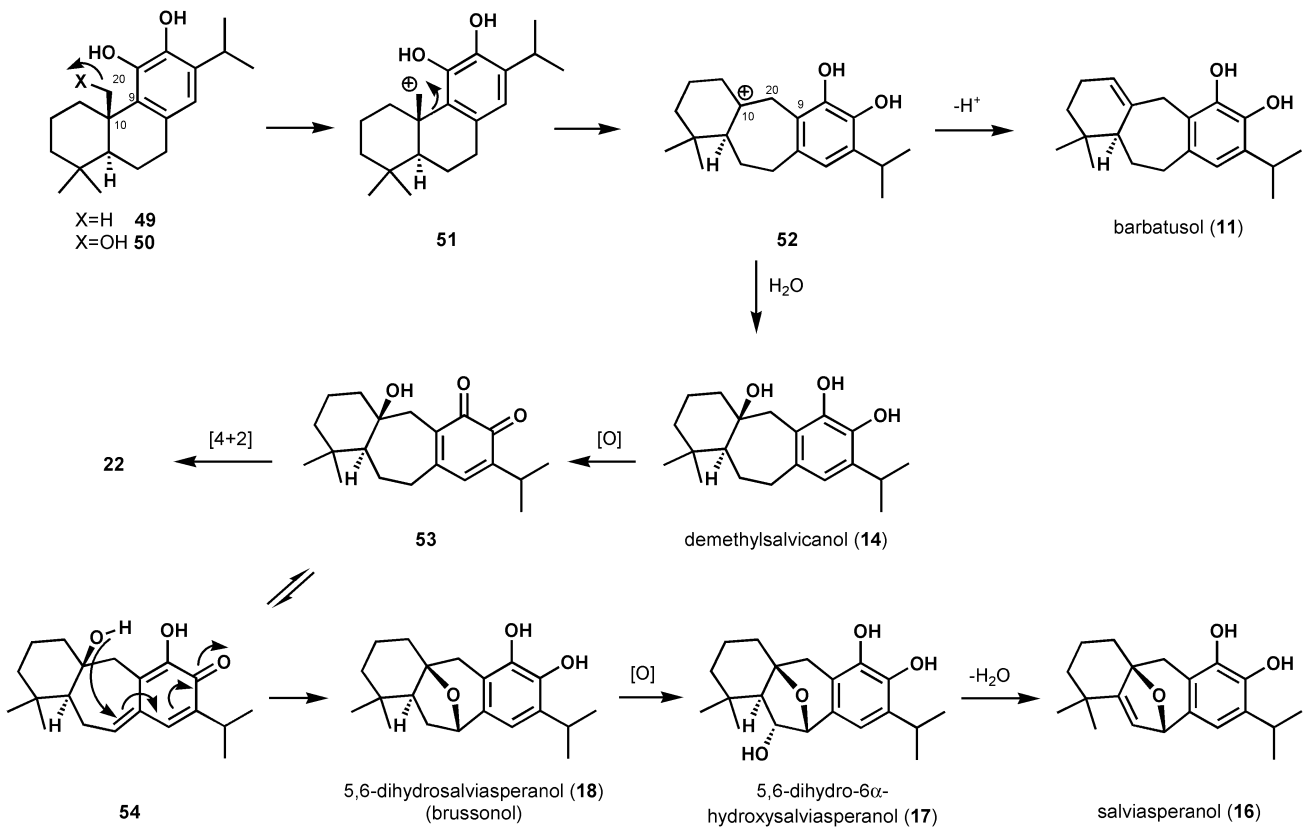


Fig. 8 Icetexone and related compounds.



Scheme 1 Biosynthetic relationships between barbatusol and related icetexanes.

Ionization of abietane **49** (*via* loss of a hydride) or **50** (*via* loss of hydroxide) would give primary carbocation **51**.[29,37] Migration of the C9–C20 bond then gives rise to the icetexane skeleton and yields tertiary carbocation **52**,[29,37] which upon deprotonation would give barbatusol (**11**). Notably, this rearrangement has been successfully demonstrated in the biomimetic synthesis of barbatusol.[26] Alternatively, trapping of carbocation **52** with water generates demethylsalvicanol (**14**). It has been noted that Drieding models indicate greater steric hindrance for the addition of water to the β-face of **52**,[29] and thus it is possible that this step is enzymatically guided given that only a *trans* 6,7-ring fusion has been observed.

Oxidation of demethylsalvicanol (**14**) would yield *ortho*-quinone **53**, which may either undergo dimerization *via* [4 + 2] cycloaddition to give grandione (**22**, Fig. 4)[33] or tautomerization to *ortho*-quinone methide **54** followed by nucleophilic addition of the C10 hydroxyl to give brussonol (**18**).[37] The formation of both grandione and brussonol from *ortho*-quinone **53**, itself obtained from demethylsalvicanol (**14**), has been successfully demonstrated in a laboratory setting.[33,38,66] Oxygenation of **18** would give rise to 5,6-dihydro-6α-hydroxysalviasperanol (**17**), which could then be dehydrated to yield salviasperanol (**16**).[37,67] Although not illustrated here, it should be noted that a series of rearrangements and intermediates analogous to those shown in Scheme 1 can be envisioned for the icetexanes in the pisiferin family (Fig. 3).

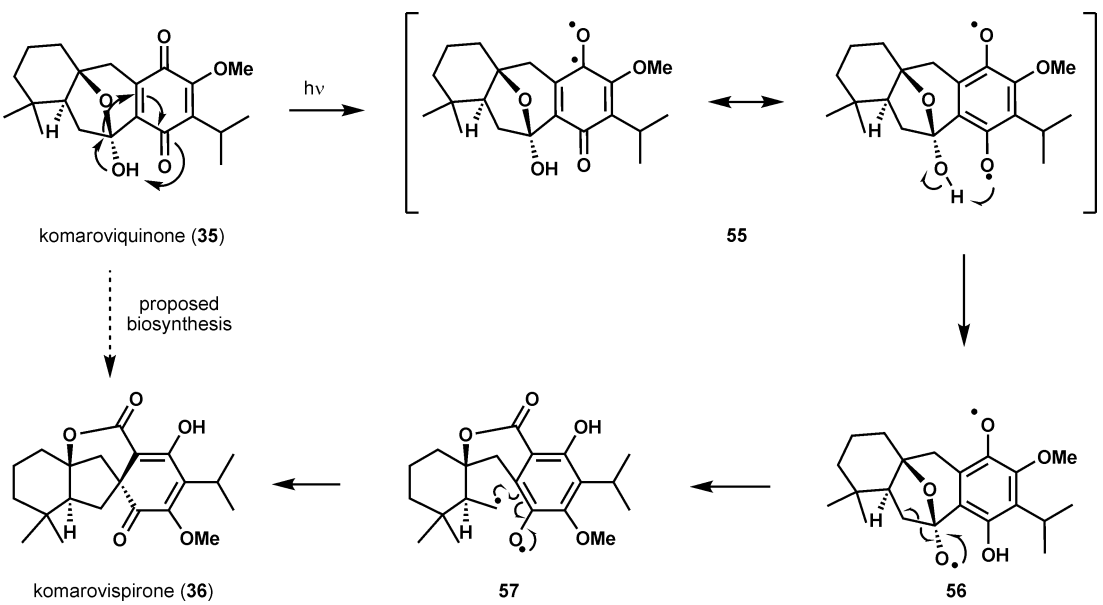
The formation of komarovispirone (**36**) from komaroviquinone (**35**) was originally proposed to occur *via* a concerted rearrangement (Scheme 2).[53] However, a study by Majetich and Yu found that a variety of acidic or basic conditions did not promote such a transformation.[54] These authors instead postulated that the rearrangement of komaroviquinone to komarovispirone might be promoted by light, a hypothesis that is supported by their discovery that irradiation of **35** with 254 nm light led to an impressive 90% yield of **36**.[54] It is speculated that an initial n → π* excitation of komaroviquinone (**35**) occurs to give the diradical species **55**, which can be represented by a number of different resonance structures (though only two are illustrated). Intramolecular hydrogen atom abstraction could then occur to yield **56**, which might then undergo C–C bond fragmentation to generate **57**. Recombination of this diradical then forms komarovispirone (**36**).

The fact that the rearrangement of **35** to **36** is promoted by light suggests the possibility that komarovispirone could be naturally produced by photoisomerization of komaroviquinone in the aerial parts of *Dracocephalum komarovi*. Alternatively, Majetich and Yu have posited that komarovispirone is simply an isolation artifact. In this scenario, it is argued that were the photoisomerization process to occur naturally within the shrub, then only komarovispirone should have been isolated given the rapid conversion of **35** to **36** in the presence of light.[54] However, it should be noted that both compounds were isolated from extracts of dried whole plants of *D. komarovi*,[48,53] and therefore until separate root and aerial extracts can be examined, both hypotheses would appear to be viable.

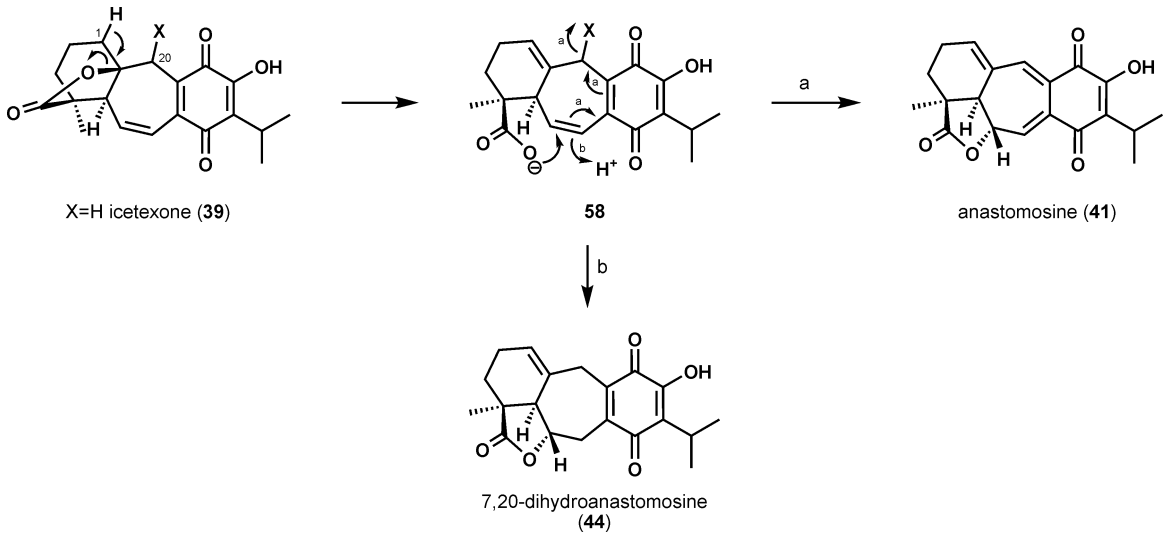
The proposed biosynthetic link between icetexone (**39**) and anastomosine (**41**) is illustrated as path A in Scheme 3.[10,57] Base-mediated fragmentation of the lactone moiety of an icetexone derivative *via* deprotonation at C1 would generate carboxylate **58**. Subsequent conjugate displacement of an appropriate leaving group at C20 would then yield anastomosine (**41**). The identification of both icetexone and anastomosine in a sample of *Salvia anastomosans* is consistent with this hypothesis.[57] Though not presented by the authors who isolated 7,20-dihydroanastomosine (**44**),[62] it is reasonable to assume that this compound could also be derived from **58** as shown in path B. In accord with this proposal, both 7,20-dihydroanastomosine (**44**) and anastomosine (**41**) were identified in the same sample of *Salvia ballotaeflora*.[62]

4 Synthetic approaches

Undoubtedly motivated by the unique structural features and intriguing biological activity of the icetexanes, a number of



Scheme 2 Conversion of komaroviquinone to komarovispirone.

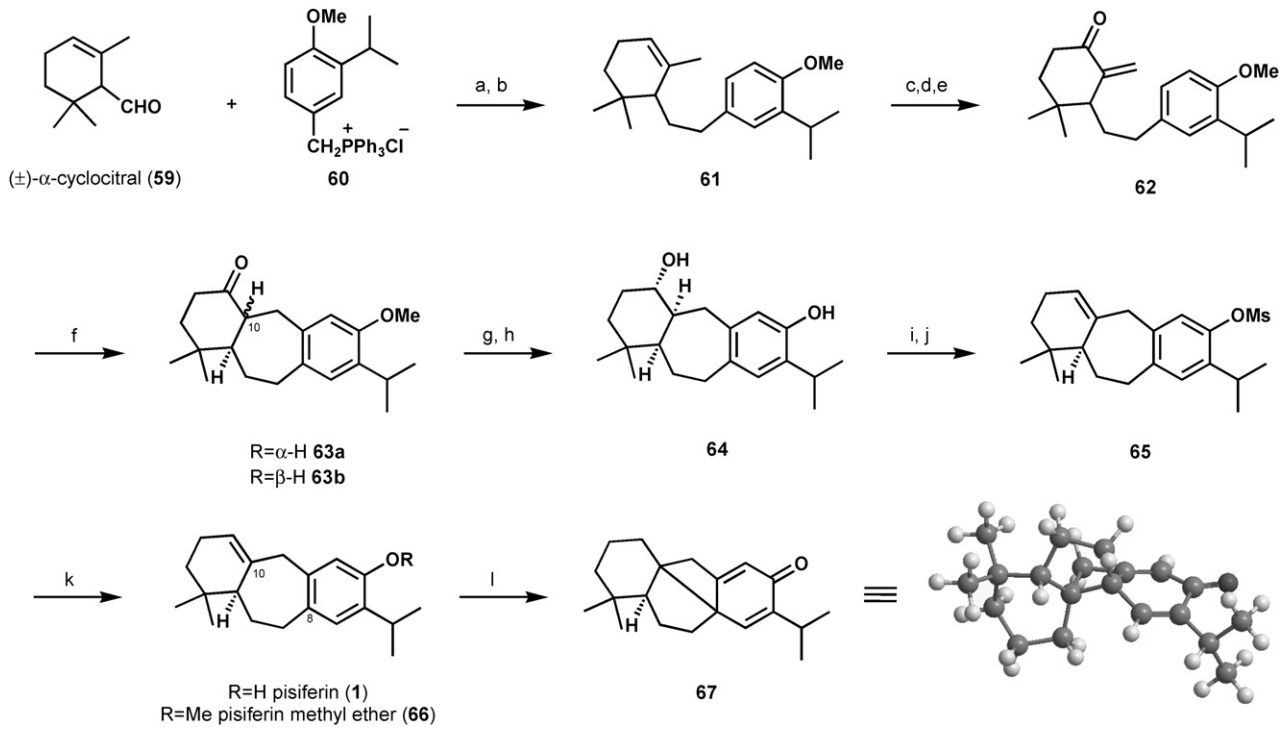


Scheme 3 Biosynthetic relationship between icetexone and the anastomosines.[10,57]

synthetic chemists have reported elegant approaches to the total synthesis of these natural products. These strategies are summarized below, and are grouped based on the subclass of the icetexane(s) targeted.

4.1 Approaches to pisiferin and related compounds

The first total synthesis of an icetexane diterpenoid to be disclosed was the total synthesis of (±)-pisiferin, which was reported by Matsumoto and co-workers in 1986 (Scheme 4).[68] Racemic α-cyclocitral (**59**) and phosphonium salt **60** were converted to alkene **61** by Wittig olefination and selective hydrogenation of the resulting styrenyl double bond. Epoxidation of **61** with *m*-CPBA, followed by epoxide opening with $LiNEt_2$ and oxidation of the resulting alcohol with PCC, provided enone **62**. Intramolecular cyclization of **62** was realized by heating with polyphosphoric acid (PPA) at 80–85 °C to give a separable mixture of the C10-epimeric ketones **63a-b**. Ketone **63a** was reduced with



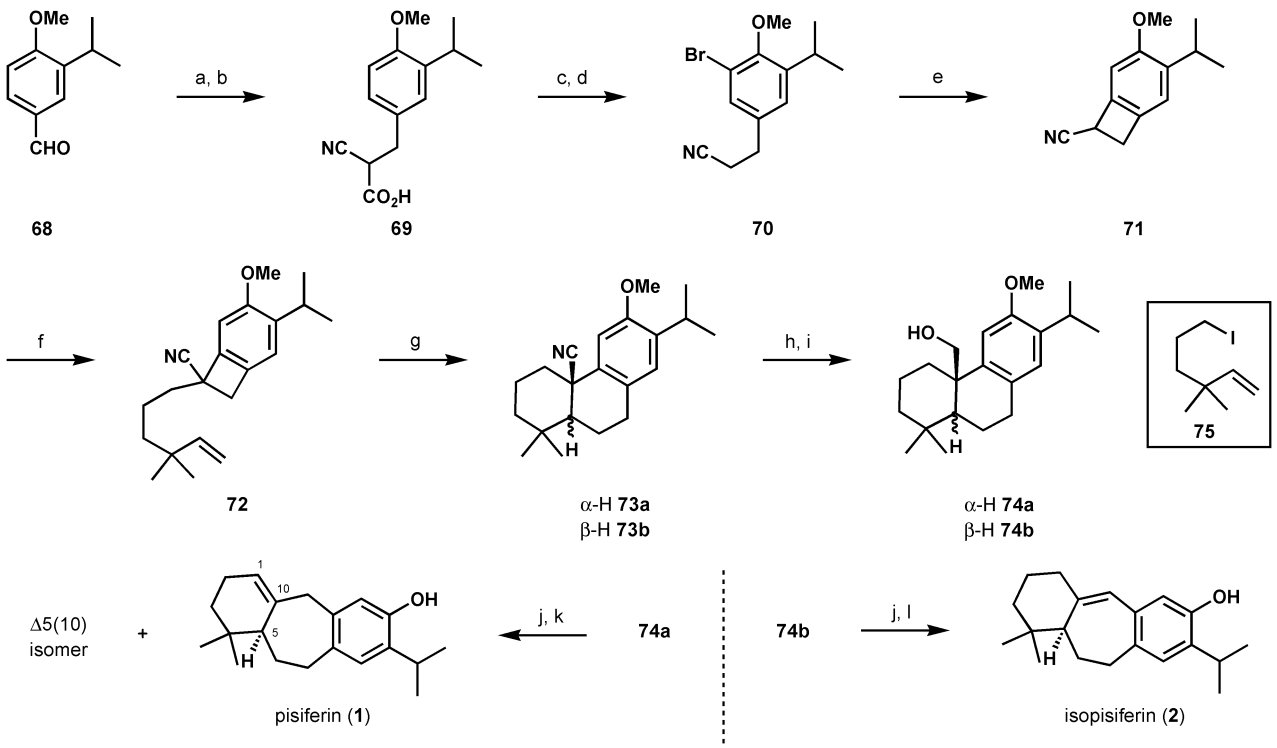
Scheme 4 Matsumoto's synthesis of (±)-pisiferin. *Reagents and conditions*: (a) **60**, *n*-BuLi, benzene, then **59**, 75%; (b) H_2 (1 equiv.), Pd/C, EtOH, 86%; (c) *m*-CPBA, CH_2Cl_2; (d) $LiNEt_2$, hexane, −50 °C → Δ, 61% (over 2 steps); (e) PCC, CH_2Cl_2, 89%; (f) PPA, 80–85 °C, 73% of **63a** + 17% of **63b**; (g) $LiAlH_4$, Et_2O, 0 °C → rt, 82% (from **63a**); (h) $AlCl_3$, EtSH, CH_2Cl_2, 89%; (i) MsCl, pyridine; (j) 2,4-lutidine, Δ, 72% (over 2 steps); (k) $LiAlH_4$, THF, Δ, 98% of **1**; (l) $AlCl_3$, EtSH, CH_2Cl_2, 93%.

$LiAlH_4$, and the methyl ether moiety of the resulting alcohol was cleaved with $AlCl_3$ and EtSH to yield diol **64**. Bismesylation and subsequent elimination of the secondary mesylate provided alkene **65**, which was readily converted to (±)-pisiferin (**1**) upon treatment with $LiAlH_4$. Interestingly, deprotection of pisiferin methyl ether (**66**) with $AlCl_3$ and EtSH did not allow for the isolation of **1**, but instead led to bond formation between the C8 and C10 positions to give dienone **67**. The presumed intermediacy of **1** in this transformation is supported by the fact that it was also converted to **67** in high yield under the same conditions. Similarly, the alcohol obtained from reduction of ketone **63b** was also converted to dienone **67** on treatment with $AlCl_3$ and EtSH due to rapid antiperiplanar elimination of water to generate **66** *in situ*.

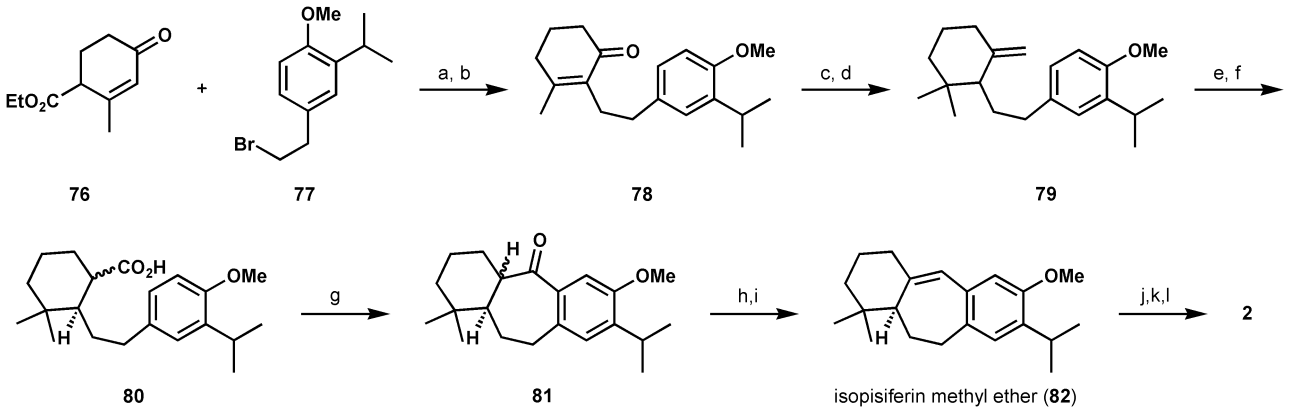
The second total synthesis of (±)-pisiferin and the first total synthesis of (±)-isopisiferin was reported by Honda and co-workers in 1990 (Scheme 5).[69] Benzaldehyde **68** underwent Knoevenagel condensation with cyanoacetic acid, which following reduction of the intermediate alkene yielded acid **69**. Decarboxylation and arene bromination provided bromide **70**, which was converted to benzocyclobutane **71** by benzyne formation and intramolecular addition. Alkylation of **71** with iodide **75** provided adduct **72**, which underwent a domino 4π-electrocyclic ring opening/intramolecular Diels–Alder (IMDA) cycloaddition to yield an inseparable 4:1 mixture of nitriles **73a-b**. A two-stage reduction of this mixture of diastereomers then yielded the separable alcohols **74a-b**. Biomimetic rearrangement of **74a** and **74b** was found to give the corresponding $\Delta^{1(10)}$ and $\Delta^{5(10)}$ ring-expanded products in varying ratios depending on the diastereomer employed. Thus, treatment of **74a** with TsCl and pyridine gave a 3:1 mixture of $\Delta^{1(10)}$ and $\Delta^{5(10)}$ alkenes. Cleavage of the methyl ether moieties of this mixture under nucleophilic conditions yielded (±)-pisiferin (**1**), along with its inseparable $\Delta^{5(10)}$ isomer, in a 3:1 ratio. Alternatively, ring expansion of **74b** led exclusively to the $\Delta^{5(10)}$ alkene, which upon tandem methyl ether cleavage/double bond isomerization under acidic conditions provided (±)-isopisiferin (**2**).

Very shortly after the publication by Honda *et al.*, a total synthesis of (±)-isopisiferin was reported by Ghatak and co-workers (Scheme 6).[70] Hagemann's ester (**76**) was alkylated with bromide **77**, and the resulting adduct was saponified and decarboxylated to give enone **78**. Cuprate addition to **78** and methylenation of the intermediate ketone provided alkene **79**, which was converted to a mixture of epimeric acids **80** by hydroboration and subsequent two-stage oxidation. Cyclization to a 4:1 *cis*:*trans* mixture of ketones **81** was achieved upon treatment of **80** with PPA at 80–85 °C. Reduction of **81**, followed by dehydration of the resulting alcohol yielded isopisiferin methyl ether (**82**). Cleavage of the methyl ether moiety of **82** with NaSEt then delivered crude (±)-isopisiferin (**2**), which was directly treated with Ac_2O and purified as its acetate derivative. The natural product was then unveiled by treating this acetate with $LiAlH_4$. In line with the related observations of Matsumoto *et al.*,[68] treatment of **82** with $AlCl_3$ and EtSH led to the formation of dienone **67** (see Scheme 4) instead of isopisiferin.

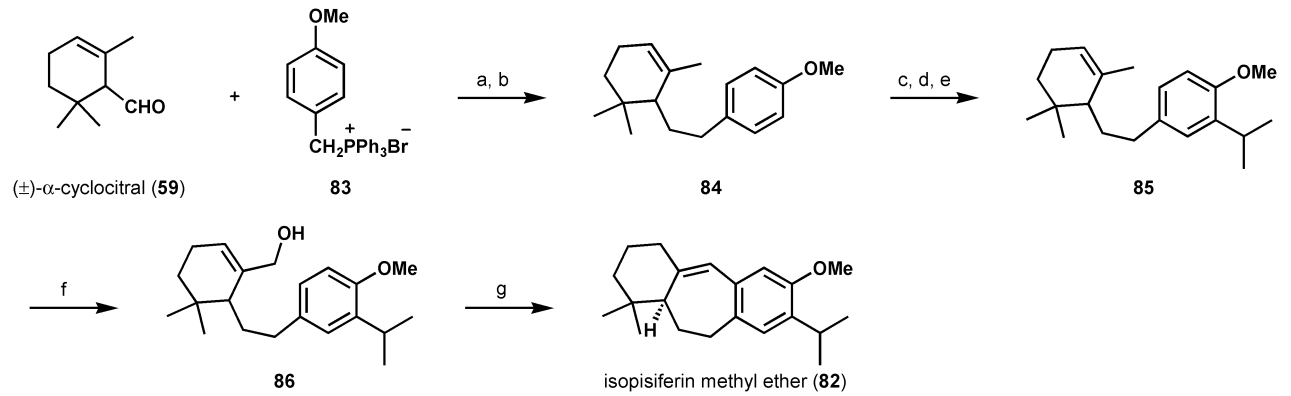
A concise synthesis of (±)-isopisiferin methyl ether was reported by Pan and co-workers in 1995 (Scheme 7).[71] Racemic α-cyclocitral (**59**) and phosphonium salt **83** (prepared in three steps from *para*-anisaldehyde) underwent Wittig olefination, and



Scheme 5 Honda's synthesis of (±)-pisiferin and (±)-isopisiferin. *Reagents and conditions*: (a) cyanoacetic acid, pyridine, NH_4OAc, benzene, Δ, 79%; (b) $NaBH_4$, MeOH/aq. $NaHCO_3$, 80%; (c) DMA, 150 °C, 95%; (d) Br_2, NaOAc, $CHCl_3$, 99%; (e) $NaNH_2$, THF, 68%; (f) NaH, **75**, DMF, 60 °C, 100%; (g) *o*-DCB, Δ, 80%; (h) DIBAl-H, toluene, −78 °C, 91%; (i) $NaBH_4$, MeOH/CH_2Cl_2, 0 °C, 14% of **74a** + 62% of **74b**; (j) TsCl, pyridine, 70 °C, 83% for **74a** or 90% for **74b**; (k) NaH, EtSH, DMF, Δ, 84%; (l) pyridine hydrochloride, 200–220 °C, 54%.



Scheme 6 Ghatak's synthesis of (±)-isopisiferin. *Reagents and conditions*: (a) KO*t*-Bu, *t*-BuOH, 83%; (b) KOH, EtOH, 65%; (c) MeLi, CuI, $BF_3 \cdot OEt_2$, −50 → 0 °C, 77%; (d) CH_3PPh_3I, sodium *t*-pentoxide, toluene, Δ, 91%; (e) BH_3, THF, 0 °C, then NaOH, H_2O_2, 96%, 1:3 dr; (f) Jones reagent, acetone, 50%; (g) PPA, 80–85 °C, 69%, 4:1 *cis:trans*; (h) $NaBH_4$, EtOH, 63%; (i) $KHSO_4$, 140 °C, 93%; (j) NaH, EtSH, DMF, Δ, 95%; (k) Ac_2O, pyridine, 95%; (l) $LiAlH_4$, Et_2O, 57%.

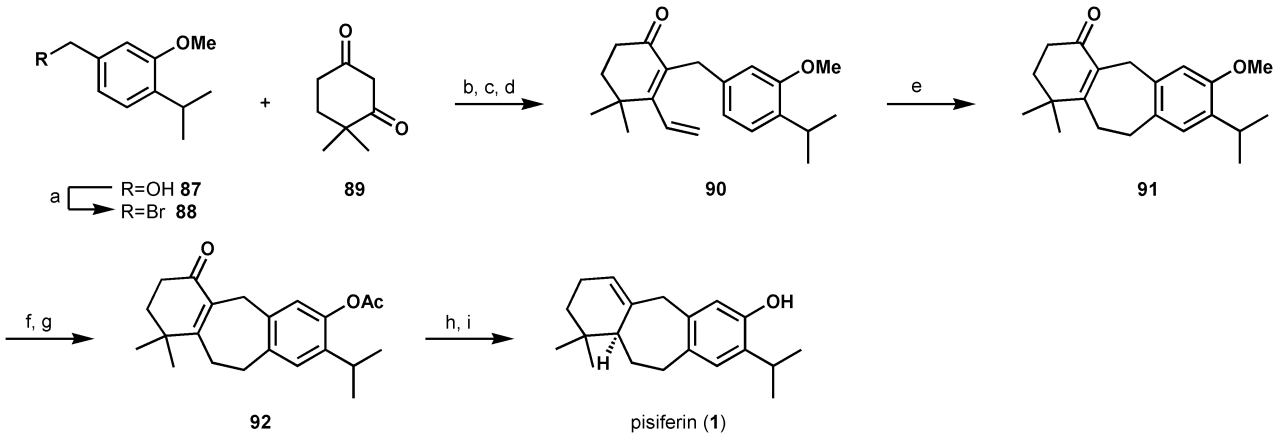


Scheme 7 Pan's synthesis of (±)-isopisiferin methyl ether. *Reagents and conditions*: (a) **83**, *n*-BuLi, benzene, then **59**, 0 °C → rt, 83%; (b) Li^0, NH_3, Et_2O, 88%; (c) *n*-BuLi, THF, rt, then acetone, −30 °C → rt, 87%; (d) TsOH, Ac_2O, 95%; (e) Li^0, NH_3, Et_2O, 87%; (f) SeO_2, *t*-BuOOH, CH_2Cl_2, then $NaBH_4$, 62%; (g) PPA, 85–90 °C, 83%.

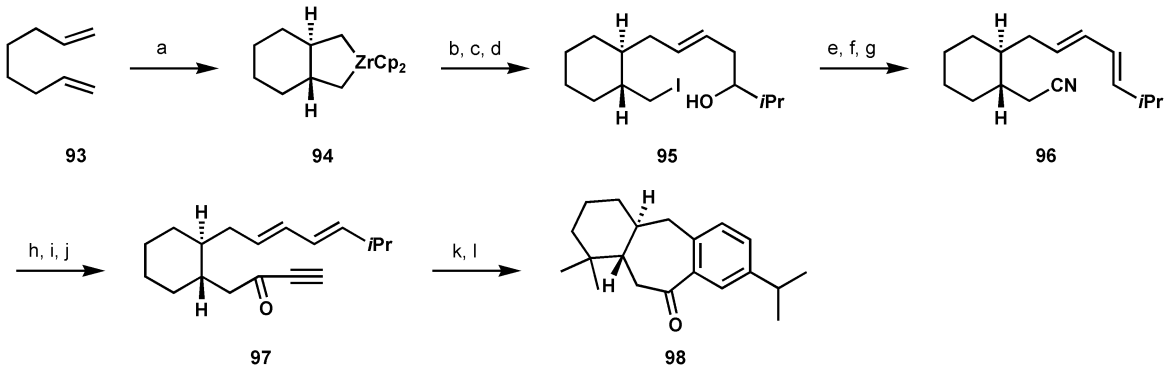
a selective reduction of the resulting styrenyl double bond with Li^0/NH_3 provided alkene **84**. Introduction of the isopropyl substituent was achieved by lithiation of **84** and quenching with acetone, which was followed by dehydration and selective reduction of the styrenyl double bond to give alkene **85**. Allylic oxidation of **85** with SeO_2 then yielded alcohol **86**. Intramolecular cyclization to forge the tricycle occurred upon treatment of **86** with PPA at 85–90 °C to directly yield (±)-isopisiferin methyl ether (**82**).

Majetich and co-workers used a cyclialkylation[72] reaction in their total synthesis of (±)-pisiferin in 1996 (Scheme 8).[73] This strategy was first employed in natural product synthesis by Majetich *et al.* in the total synthesis of (±)-barbatusol (*vide infra*, Scheme 11).[74] The synthesis of pisiferin began with 1,3-diketone **89**, which was alkylated with benzyl bromide **88** (prepared by treatment of alcohol **87** with PBr_3). The resulting adduct was *O*-methylated and then treated with vinylmagnesium bromide in the presence of $CeCl_3$ to give dienone **90**. Treatment of **90** with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at room temperature led to cyclialkylation to give tricycle **91**. Although a reductive transposition of enone **91** successfully delivered pisiferin methyl ether (**66**, Scheme 4), the methyl group could not be removed without partial isomerization of the trisubstituted double bond to the styrenyl position (*i.e.* isopisiferin, **2**). To circumvent this obstacle, cleavage of the methyl ether was performed first, and subsequent acylation of the resulting phenol gave acetate **92**. This compound was converted to (±)-pisiferin (**1**) by reductive transposition of the enone moiety with $TsNHNH_2$ and $NaBH_3CN$ and subsequent ester saponification.

In 1998, Whitby and co-workers reported an approach to the pisiferanol skeleton using an IMDA reaction (Scheme 9).[75] Zirconacycle **94** was prepared by cyclization of 1,7-octadiene (**93**) with the Zr(II) species generated from Cp_2ZrBu_2. Metallacycle **94** underwent sequential carbenoid and aldehyde insertion, and following iodinolysis gave iodide **95**. Displacement of the iodide with KCN was followed by dehydration of the secondary hydroxyl group *via* the corresponding mesylate. Reduction of the nitrile with DIBAl-H set the stage for addition of ethynyl magnesium bromide to the resulting aldehyde, and the intermediate propargylic alcohol was treated with PCC to provide ynone **97**. Heating **97** in toluene effected the IMDA cycloaddition, and the resulting adduct was oxidized with DDQ to give tricycle **98**.



Scheme 8 Majetich's synthesis of (±)-pisiferin. *Reagents and conditions*: (a) PBr_3, Et_2O, 0 °C → rt, 79%; (b) K_2CO_3. KI, H_2O, 75% (based on recovered **88**); (c) NaH, Me_2SO_4, DMF, 94%; (d) $H_2C{=}CHMgBr$, $CeCl_3$, THF, 78%; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 83%; (f) NaH, EtSH, DMF, Δ; (g) Ac_2O, pyridine, 80 °C, 80% (over 2 steps); (h) $TsNHNH_2$, EtOH, then $NaBH_3CN$, DMF/sulfolane, 100 °C, then HCl, 110 °C, 43%; (i) NaOH, EtOH, Δ, 92%.



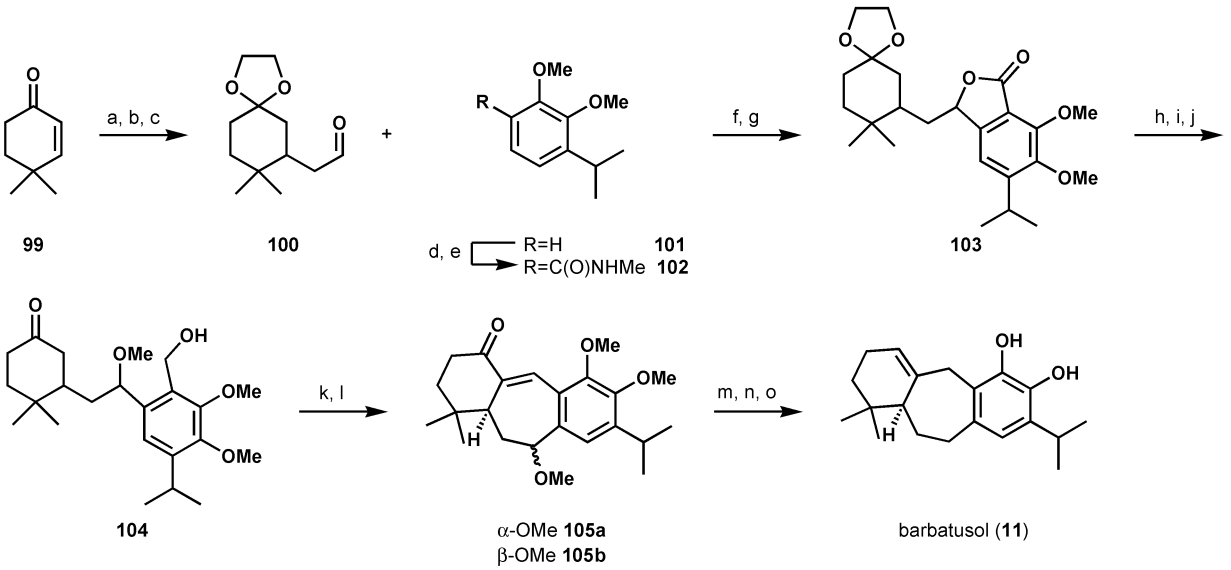
Scheme 9 Whitby's synthesis of the pisiferanol skeleton. *Reagents and conditions*: (a) Cp_2ZrBu_2, THF, −78 → °C; (b) $H_2C{=}CHCH_2Cl$, LiTMP, THF, −78 °C; (c) *i*PrCHO, $BF_3{\cdot}OEt_2$, −78 °C → rt; (d) I_2, −78 → 0 °C, then $NaHCO_3$, $Na_2S_2O_3$, 81% (over 3 steps); (e) KCN, DMSO, 40 °C, 88%; (f) MsCl, Et_3N, CH_2Cl_2, −20 °C; (g) KO*t*-Bu, THF, 68% (over 2 steps); (h) DIBAl-H, −78 °C → rt, 97%; (i) HC≡CMgBr, THF, rt; (j) PCC, CH_2Cl_2, 56% (over 2 steps); (k) toluene, 110 °C; (l) DDQ, 110 °C, 85% (over 2 steps).

4.2 Approaches to barbatusol and related compounds

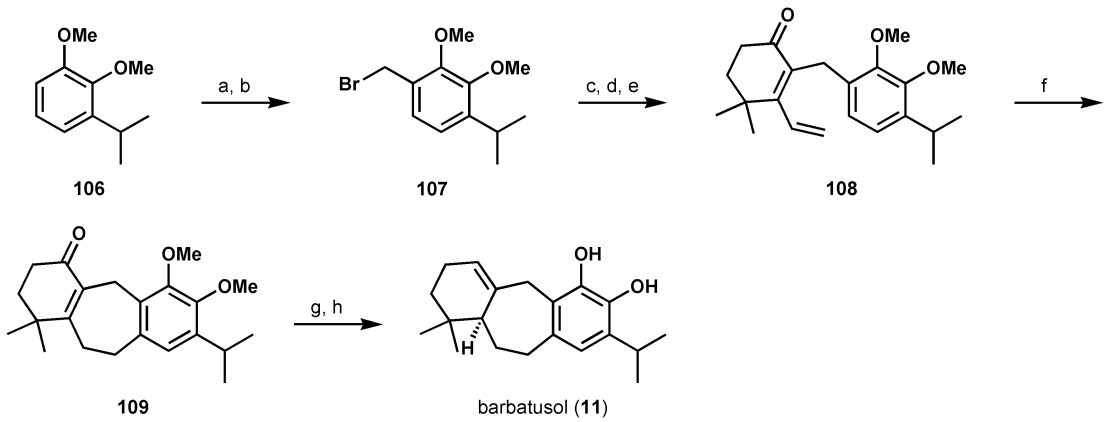
The first total synthesis of (±)-barbatusol was reported by Koft in 1987 (Scheme 10).[76] The synthesis began with enone **99**, which underwent a Sakurai addition of allyltrimethylsilane in the presence of $TiCl_4$. The resulting ketone was protected as the ketal and subjected to ozonolysis to give aldehyde **100**. Separately, amide **102** was prepared by lithiation of veratrole **101**, quenching with CO_2, and sequential treatment of the resulting acid with $SOCl_2$ and $MeNH_2$. Amide **102** was then metallated with *n*-BuLi, and the resulting dianion was treated with aldehyde **100**. Anhydrous acidic treatment of the crude adduct then provided lactone **103** as an inconsequential mixture of diastereomers. Lactone **103** was saponified with NaOH, and the intermediate hydroxy acid was methylated with MeI and treated with $LiAlH_4$ to yield alcohol **104**. Oxidation of **104** with PDC provided an aldehyde that underwent intramolecular aldol condensation upon treatment with NaOEt in EtOH to yield the diastereomeric enones **105a-b**. Ionic reduction of the benzylic methyl ether moieties of **105a-b** with $Et_3SiH/BF_3{\cdot}OEt_2$, followed by reductive transposition of the enone with $TsNHNH_2$ and $NaBH_3CN$ and nucleophilic demethylation of the phenolic methyl ethers with NaSEt then provided (±)-barbatusol (**11**).

Majetich and co-workers reported the second total synthesis of (±)-barbatusol in 1993 (Scheme 11).[73,74] Veratrole **106** was lithiated with *n*-BuLi, and the resulting anion was reacted with gaseous formaldehyde to give an intermediate benzyl alcohol. This alcohol was converted to the corresponding bromide (**107**) by the action of PBr_3. 1,3-Diketone **89** (Scheme 8) was then alkylated with **107**, and the resulting adduct was *O*-methylated and treated with vinylmagnesium bromide in the presence of $CeCl_3$ to provide dienone **108**. Treatment of **108** with $TiCl_4$ in CH_2Cl_2 at −78 °C effected a cyclialkylation reaction to generate tricycle **109**. Reductive transposition of the enone moiety of **109** with $TsNHNH_2$ and $NaBH_3CN$ followed by cleavage of the methyl ethers with NaSEt then delivered (±)-barbatusol (**11**).

Three years after Majetich's synthesis of barbatusol, Pan and co-workers reported the synthesis of (±)-barbatusol methyl ether (Scheme 12).[77] The strategy employed was similar to that used by the same group for the synthesis of (±)-isopisiferin methyl ether (see Scheme 7).[71] Thus, aldehyde **110** was reduced with $NaBH_4$, converted to the corresponding bromide with PBr_3 and treated with PPh_3 to generate phosphonium salt **111**. Lithiation with *n*-BuLi and addition to racemic α-cyclocitral (**59**) effected a Wittig olefination to give diene **112**. Selective reduction of the



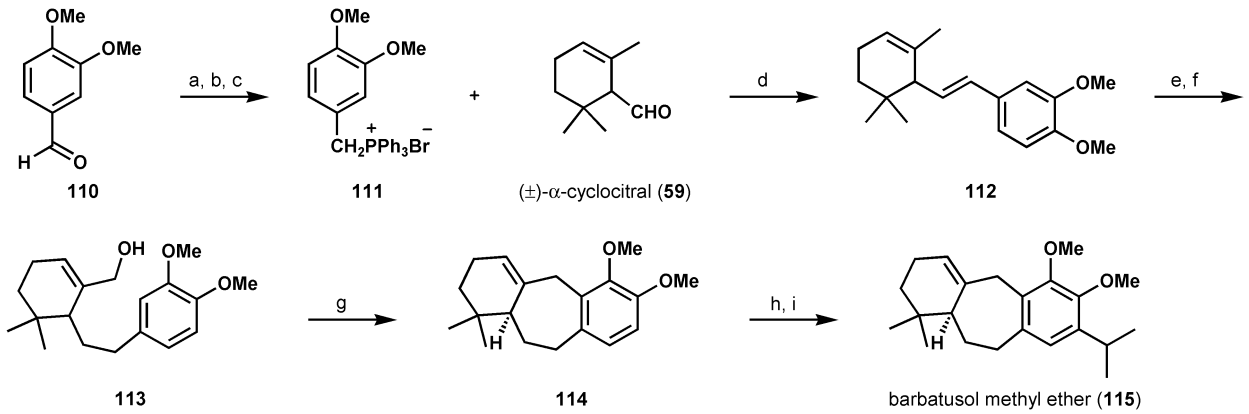
Scheme 10 Koft's synthesis of (±)-barbatusol. *Reagents and conditions*: (a) $TiCl_4$, $H_2C{=}CHCH_2TMS$, CH_2Cl_2; (b) TsOH, $(HOCH_2)_2$, benzene, Δ, 75% (over 2 steps); (c) O_3, −75 °C, then PPh_3, −75 °C → rt, 89%; (d) *n*-BuLi, TMEDA, Et_2O, rt, then CO_2, −60 °C → rt; (e) $SOCl_2$, CH_2Cl_2, then $MeNH_2$, THF, 64% (over 2 steps); (f) **102**, *n*-BuLi, THF, −10 °C, then **100**; (g) HCl (g), THF/$(HOCH_2)_2$, 64% (over 2 steps); (h) NaOH, MeOH, Δ; (i) NaH, MeI, THF, Δ, 75% (over 2 steps); (j) $LiAlH_4$, THF, 86%; (k) PDC, CH_2Cl_2, 94%; (l) NaOEt, EtOH, 72%; (m) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 0 °C, 61% + 28% recovered **105a**; (n) $TsNHNH_2$, EtOH, Δ, then $NaBH_3CN$, DMF/sulfolane, 110 °C, then HCl, 70%; (o) NaH, EtSH, DMF, 56%.



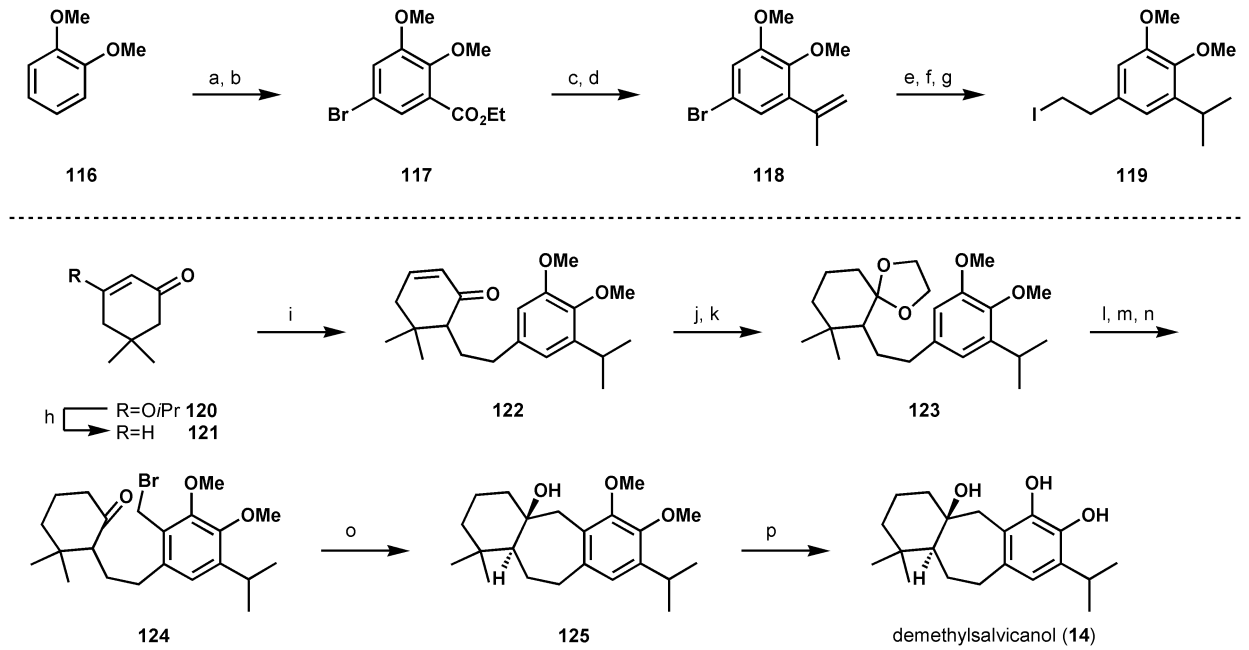
Scheme 11 Majetich's synthesis of (±)-barbatusol. *Reagents and conditions*: (a) *n*-BuLi, TMEDA, Et_2O, then CH_2O (g), 89%; (b) PBr_3, Et_2O, 0 °C → rt, 95%; (c) **89**, K_2CO_3. KI, H_2O, 65%; (d) NaH, Me_2SO_4, DMF, 98%; (e) $H_2C{=}CHMgBr$, $CeCl_3$, THF, 74%; (f) $TiCl_4$, CH_2Cl_2, −78 °C, 75%; (g) $TsNHNH_2$, EtOH, Δ, then $NaBH_3CN$, DMF/sulfolane, 100 °C, then HCl, 75%; (h) NaH, EtSH, DMF, Δ, 65%.

styrenyl double bond with Li^0/NH_3 and allylic oxidation of the resulting alkene with SeO_2 then yielded alcohol **113**. Intramolecular cyclization occurred upon treatment of **113** with PPA at room temperature to give tricycle **114**. Introduction of the isopropyl substituent was achieved by lithiation of **114** with *n*-BuLi and quenching the resulting anion with acetone to give an intermediate benzyl alcohol. Reduction of this species with $LiAlH_4/Cp_2TiCl_2$ delivered (±)-barbatusol methyl ether (**115**).

Pan and co-workers followed their synthesis of barbatusol methyl ether with the first total synthesis of (±)-demethylsalvicanol in 1996 by (Scheme 13).[78] The synthesis began with lithiation of veratrole (**116**) and trapping of the resulting anion with ethyl chloroformate to give an ester that was regioselectively brominated to yield bromide **117**. Addition of two equivalents of methylmagnesium bromide to **117** and dehydration of the intermediate tertiary alcohol provided alkene **118**. Lithium-halogen exchange of **118** and addition to ethylene oxide gave an alcohol that was converted to iodide **119** by hydrogenation and a subsequent Appel reaction. Cyclohexenone **121** (prepared by reduction of vinylogous ester **120**) was then alkylated with iodide **119** to give adduct **122**. Enone **122** was reduced with Li^0/NH_3 and the resulting ketone was protected as the corresponding ketal (**123**). Regioselective lithiation was achieved upon treatment of **123** with BuLi, and trapping of this anion with paraformaldehyde gave a benzyl alcohol that was converted to bromide **124** following reaction with PBr_3 and subsequent ketal cleavage. Intramolecular Barbier reaction of **124** with zinc metal in DMF formed the tricycle and provided tertiary alcohol **125**.



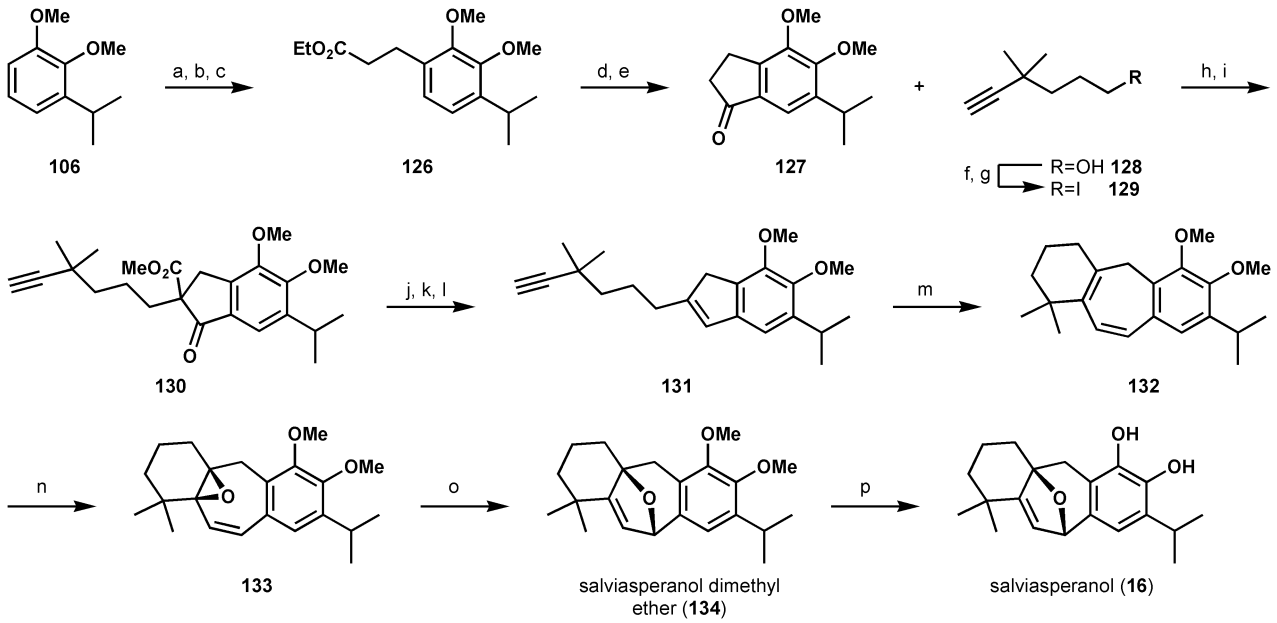
Scheme 12 Pan's synthesis of (±)-barbatusol methyl ether. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 95%; (b) PBr_3, petroleum ether, 93%; (c) PPh_3, benzene, Δ, 93%; (d) *n*-BuLi, benzene, 0 °C, then **59**, 0 °C → rt, 83%; (e) Li^0, NH_3, Et_2O, 88%; (f) SeO_2, *t*-BuOOH, CH_2Cl_2, then $NaBH_4$, MeOH, 0 °C, 64%; (g) PPA, 61%; (h) *n*-BuLi, THF, rt, then acetone, −30 °C → rt, 91%; (i) $LiAlH_4$, Cp_2TiCl_2, THF, Δ, 57%.



Scheme 13 Pan's synthesis of (±)-demethylsalvicanol. *Reagents and conditions*: (a) *n*-BuLi, THF, rt, then $ClCO_2Et$, −78 °C → rt, 79%; (b) Br_2, NaOAc, AcOH, 90%; (c) MeMgBr, Et_2O, Δ, 98%; (d) TsOH, benzene, Δ, 95%; (e) BuLi, THF, −78 °C → rt, then ethylene oxide, −78 °C → rt, 84%; (f) H_2, Pd/C, EtOH, 99%; (g) I_2, PPh_3, imid., MeCN/Et_2O, 0 °C, quant.; (h) $NaBH_4$, EtOH, 0 °C, then 10% aq. HCl, THF, Δ, 80%; (i) **121**, LDA, THF, −78 °C → rt, then **119**, −78 °C → rt, 54%; (j) Li^0, NH_3, Et_2O, 91%; (k) $BF_3 \cdot OEt_2$, $(HOCH_2)_2$, Et_2O, 84%; (l) BuLi, THF, rt, then $(CH_2O)_n$, −20 °C → rt, 86%; (m) PBr_3, CH_2Cl_2, 90%; (n) 10% aq. HCl, acetone/THF; (o) Zn^0, DMF, 73% (over 2 steps); (p) NaH, EtSH, DMF, Δ, 56%.

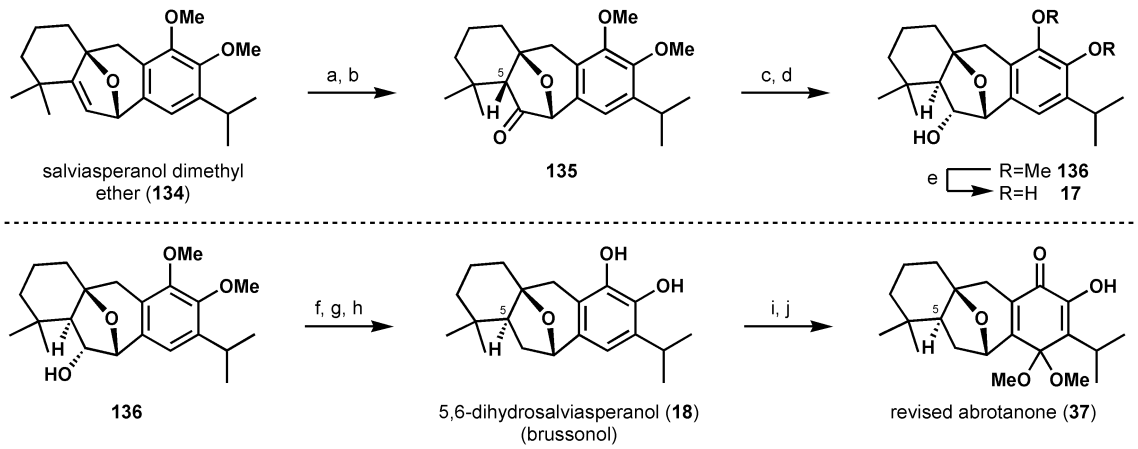
Cleavage of the methyl ether moieties of **125** with NaSEt then gave (±)-demethylsalvicanol (**14**).

In 2006, the first total synthesis of (±)-salviasperanol was reported by Simmons and Sarpong (Scheme 14).[79] Their synthesis employed veratrole **106**, which was lithiated and then reacted with DMF to give an intermediate benzaldehyde that underwent Wittig olefination and subsequent hydrogenation to yield ester **126**. Saponification of **126** with LiOH provided a carboxylic acid that was then cyclized to indanone **127** using a Friedel–Crafts acylation. After conversion of **127** to the corresponding β-keto ester using Mander's reagent, alkylation with iodide **129** (obtained in two steps from alcohol **128**) provided adduct **130**. Saponification of **130** was accompanied by decarboxylation to give an indanone that was subsequently reduced and dehydrated to deliver indene **131**. Treatment of **131** with catalytic $GaCl_3$ at 40 °C effected an enyne cycloisomerization to forge benzocycloheptadiene **132**. Chemoselective epoxidation of the tetrasubstituted double bond was achieved upon treatment of **132** with *m*-CPBA at 0 °C to yield epoxide **133**. Acid-catalyzed isomerization of the vinyl epoxide moiety of **133** to the corresponding dihydrofuran gave salviasperanol dimethyl ether (**134**). Cleavage of the methyl ether groups of **134** with NaSEt then delivered (±)-salviasperanol (**16**).



Scheme 14 Sarpong's synthesis of (±)-salviasperanol. *Reagents and conditions*: (a) *n*-BuLi, TMEDA, Et_2O, 0 °C → rt, then DMF, −78 °C → rt; (b) $EtO_2CHC{=}PPh_3$, CH_2Cl_2, Δ, 53% (over 2 steps); (c) H_2, PtO_2, MeOH, 98%; (d) LiOH, THF/H_2O, Δ, 96%; (e) $(COCl)_2$, CH_2Cl_2, 0 °C → rt, then $AlCl_3$, 0 °C, 84%; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt, 92%; (g) NaI, acetone, Δ, 92%; (h) **127**, LiTMP, THF, −78 °C, then TMEDA, MeO(CO)CN; (i) K_2CO_3, acetone, rt, then **129**, Δ, 49% (over 2 steps); (j) LiOH, THF/H_2O, Δ; (k) DIBAl-H, CH_2Cl_2, 0 °C; (l) Ms_2O, Et_3N, benzene, 64% (over 3 steps); (m) $GaCl_3$, 4 Å MS, benzene, 40 °C, 90%; (n) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C; (o) TFA, 4 Å MS, CH_2Cl_2, 0 °C, 73% (over 2 steps); (p) NaH, EtSH, DMF, Δ, 74%.

Sarpong and co-workers followed their report on the synthesis of salviasperanol with the first total synthesis of (±)-5,6-dihydro-6α-hydroxysalviasperanol, (±)-brussonol and (±)-abrotanone in 2007 (Scheme 15).[36] Salviasperanol dimethyl ether (**134**) was converted to ketone **135** by hydroboration with BH_3 and subsequent two-stage oxidation. Treatment of **135** with NaOMe led to epimerization at C5 to yield the more thermodynamically stable *trans*-fused tetracyclic ketone. Reduction of this intermediate with $NaBH_4$ gave alcohol **136**, which upon methyl ether cleavage yielded (±)-5,6-dihydro-6α-hydroxysalviasperanol (**17**). Alcohol **136** also served as a precursor to compound **18** by thiocarbonate formation, Barton deoxygenation and demethylation. Compound **18** has been previously isolated from two different sources and alternately given the name 5,6-dihydrosalviasperanol[35] and brussonol,[37] both of which were found to be identical with synthetic **18**. In addition, a recently isolated icetexane that was given the name abrotandiol[55] and originally proposed to be the C5 epimer of brussonol was also found to be identical to 5,6-dihydrosalviasperanol/brussonol (**18**). The structure of the related compound abrotanone[55] was revised, also at the C5 position, following the synthesis of **37** in two steps from **18** by oxidation with $Cu(NO_3)_2$ and subsequent treatment with NaOMe.



Scheme 15 Sarpong's synthesis of (±)-5,6-dihydro-6α-hydroxysalviasperanol, (±)-brussonol and (±)-abrotanone. *Reagents and conditions*: (a) BH_3, THF, rt, then NaOH, H_2O_2, 0 °C; (b) $SO_3{\cdot}$pyr, Et_3N, CH_2Cl_2/DMSO, 0 °C → rt, 60% (over 2 steps); (c) NaOMe, $MeOH/CH_2Cl_2$, 98%; (d) $NaBH_4$, *i*PrOH, quant.; (e) $Et_2NCH_2CH_2SH{\cdot}HCl$, NaO*t*-Bu, DMF, Δ, 60%; (f) NaH, THF, then CS_2, then MeI, 90%; (g) AIBN, Bu_3SnH, toluene, 80 °C, 74%; (h) NaH, EtSH, DMF, Δ, 83%; (i) $Cu(NO_3)_2$, morpholine, MeOH, air; (j) NaOMe, MeOH, 24% (over 2 steps).

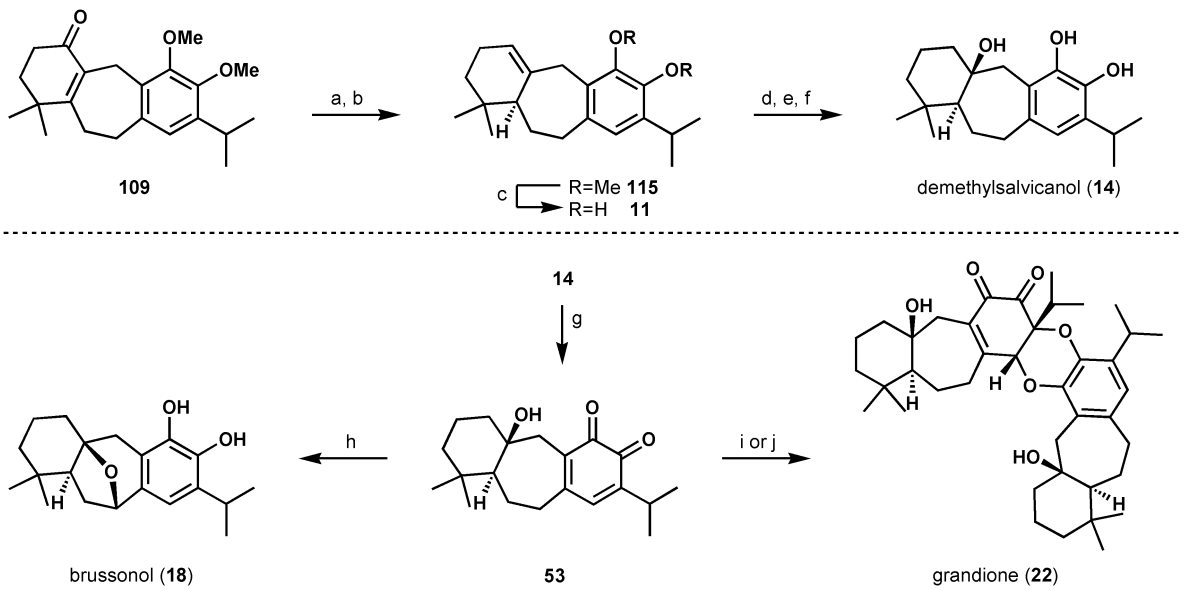
In late 2007, Majetich and Zou reported the first asymmetric total synthesis of (–)-barbatusol, (+)-demethylsalvicanol, (–)-brussonol and (+)-grandione (Scheme 16).[66] Enone **109**, a late-stage intermediate in the synthesis of (±)-barbatusol by Majetich *et al.* (see Scheme 11),[73,74] was converted to enantioenriched barbatusol methyl ether (**115**) by Corey-Bakshi-Shibata (CBS) reduction and subsequent Myers allylic transposition of the resulting allylic alcohol. Cleavage of the methyl ether moieties of **115** with NaSEt then delivered (–)-barbatusol (**11**). Compound **115** also served as a precursor to (+)-demethylsalvicanol (**14**). Following the pioneering work of Kelecom and Medeiros in their structure determination studies on **14**,[30] treatment of **115** with *m*-CPBA at 0 °C led to selective epoxidation from the β-face of the molecule. Regioselective opening of the intermediate epoxide was achieved with $LiAlH_4$, and methyl ether cleavage yielded (+)-demethylsalvicanol (**14**). Building upon related studies by Takeya and co-workers,[33,38] conditions were then examined for the selective biomimetic conversion of *ortho*-quinone **53** (obtained by oxidation of **14** with Ag_2CO_3) to either (–)-brussonol (**18**) or (+)-grandione (**22**) (see Scheme 1). After extensive studies, it was ultimately found that heating a concentrated (36 M) ethereal solution of **53** at 60 °C for 40 h gave a 70% yield of (–)-**18**. Alternatively, warming neat **53** at 50 °C for 60 h provided a 72% yield of (+)-**22**. The effects of light and water on the Diels–Alder dimerization of **53** were both independently examined. While exposure of **53** to sunlight at room temperature led to no reaction, heating **53** at 50 °C in the presence of a small amount of water gave a 61% combined yield of **22** and **18**, in a 6:1 ratio that was subsequently found to be dependent on concentration.

Majetich and co-workers also reported the first asymmetric total synthesis of (–)-salviasperanol in late 2007 (Scheme 17).[80] Vinylogous ester **137** was reacted with lithium acetylide, and treatment of the resulting adduct with aqueous HCl provided enynone **138**. Although a cyclialkylation of **138** to dienone **140** could be envisioned, Drieding models of this species indicated that the arene and alkyne moieties were not close enough to react, and in the event **138** could not be directly converted to **140**. However, exposure of the enynone to $BF_3 \cdot OEt_2$ and EtSH initially promoted thiol conjugate addition to generate vinyl sulfide **139**, which could be isolated and characterized. Alternatively, continued stirring of the reaction mixture effected cyclialkylation, and subsequent loss of EtSH then yielded dienone **140**. The dienone was reduced *via* the CBS protocol, and the resulting enantioenriched alcohol was then epoxidized with *m*-CPBA and acylated with thiocarbonyl diimidazole to give epoxide **141**. Acid-catalyzed isomerization of the vinyl epoxide moiety with TFA and Barton deoxygenation provided salviasperanol dimethyl ether (**134**, Scheme 14), and methyl ether cleavage with NaSEt then delivered (–)-salviasperanol (**16**).

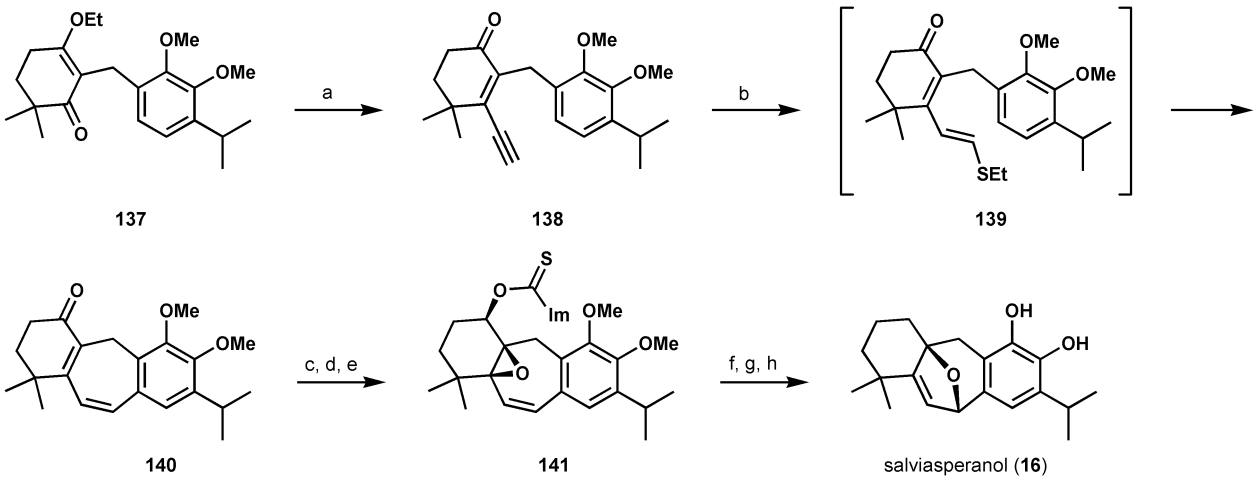
Martinez-Solorio and Jennings reported a formal synthesis of (±)-brussonol and (±)-abrotanone in late 2008 (Scheme 18).[81] Conjugate methyl addition to enone **142** in the presence of TMSCl provided a silyl enol ether that was then treated with *n*-BuLi and allyl iodide to yield ketone **143**. Veratrole derivative **144** (obtained in one step from **106**) was lithiated with *n*-BuLi, and addition of the resulting anion to ketone **143** yielded alcohol **145** as a single diastereomer. Ozonolysis of the allyl moiety of **145** in the presence of methanol generated methyl ketal **146**. Treatment of **146** with $BF_3 \cdot OEt_2$ effected a Marson-type cyclization to directly provide brussonol dimethyl ether (**147**), which was previously converted to (±)-brussonol (**18**) and subsequently to (±)-abrotanone (**37**) by Sarpong *et al.*[36]

4.3 Approaches to the taxamairins

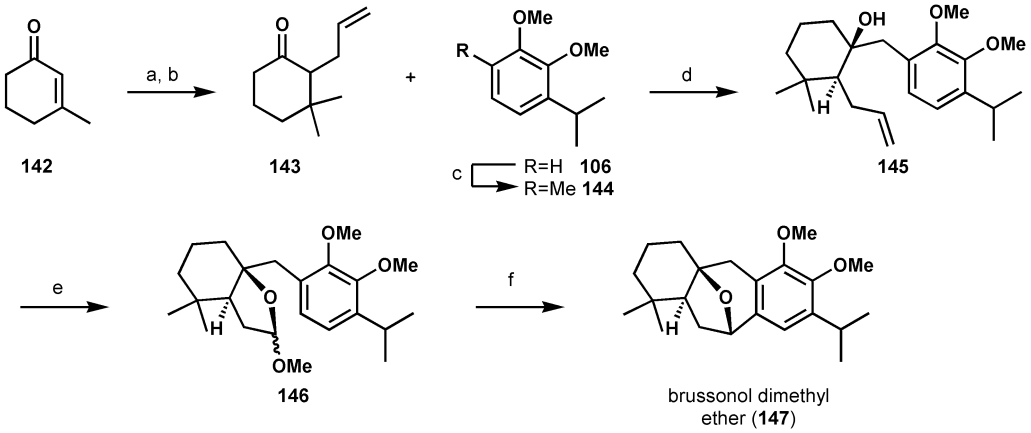
To date, the only taxamairin that has succumbed to total synthesis is taxamairin B. Pan and co-workers disclosed their



Scheme 16 Majetich's synthesis of (–)-barbatusol, (+)-demethylsalvicanol, (–)-brussonol and (+)-grandione. *Reagents and conditions*: (a) BH_3, (*S*)-MeCBS, THF, 90% (>96% ee); (b) DEAD, PPh_3, *N*-methyl morpholine/THF, −30 °C, then *o*-NBSH, −30 → 30 °C, 54%; (c) NaH, EtSH, DMF, Δ, 65%; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 95%; (e) $LiAlH_4$, THF, Δ, 92%; (f) NaH, EtSH, DMF, Δ, 70%; (g) Ag_2CO_3, Et_2O, 98%; (h) Et_2O, 60 °C, 70%; (i) neat, 50 °C, 72%; (j) H_2O, 50 °C, 52% of **22** + 9% of **18**.



Scheme 17 Majetich's synthesis of (–)-salviasperanol. *Reagents and conditions*: (a) LiC≡CH, THF, −78 → 0 °C, then HCl, 0 °C, 92%; (b) $BF_3 \cdot OEt_2$, EtSH, CH_2Cl_2, 0 °C → rt, 94%; (c) BH_3, (*S*)-MeCBS, THF, 91% (>95% ee); (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C; (e) 1,1-thiocarbonyldiimidazole, CH_2Cl_2, 53% (over 2 steps); (f) TFA, 4 Å MS, CH_2Cl_2, 0 °C → rt; (g) AIBN, Bu_3SnH, toluene, Δ, 76% (over 2 steps); (h) NaH, EtSH, 86%.



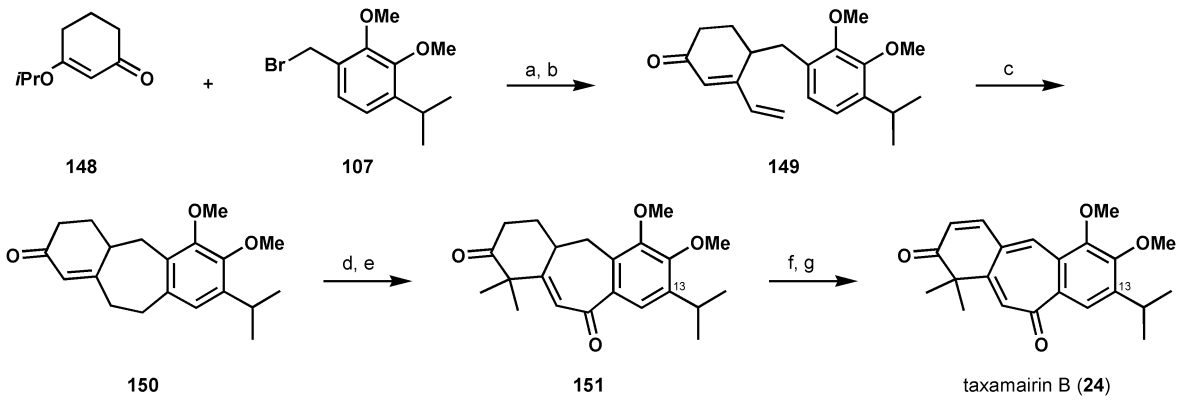
Scheme 18 Jennings' synthesis of (±)-brussonol dimethyl ether. *Reagents and conditions*: (a) LiCl, CuI, TMSCl, −40 °C, then MeMgCl, −40 °C, 91%; (b) *n*-BuLi, THF, rt, then HMPA, $H_2C{=}CHCH_2I$, −20 °C → rt, 77%; (c) *n*-BuLi, TMEDA, Et_2O, 0 °C → rt, then MeI, 0 °C → rt, 83%; (d) **144**, *n*-BuLi, TMEDA, Et_2O, −78 °C → rt, then **143**, −78 °C → rt, 42%; (e) O_3, MeOH, −78 °C, then PPh_3, −78 °C → rt, 89%; (f) $BF_3 \cdot OEt_2$, CH_2Cl_2, −20 °C, 91%.

original approach to taxamairin B (**24**) in 1995 (Scheme 19).[82] The synthesis commenced with the alkylation of vinylogous ester **148** with benzyl bromide **107**, a compound previously employed in the total synthesis of (±)-barbatusol by Majetich and co-workers (see Scheme 11).[73,74] Following addition of vinylmagnesium bromide to the resulting adduct, dienone **149** was then obtained. Cyclialkylation of **149** proceeded upon treatment with $BF_3 \cdot OEt_2$ in refluxing toluene to give tricycle **150**. Conversion of enone **150** to dione **151** was achieved by bis-alkylation with MeI under thermodynamically-controlled conditions, followed by allylic oxidation with catalytic CrO_3 and *t*-BuOOH. Oxidation of **151** with DDQ resulted in the undesired dehydrogenation of the C13 isopropyl group to yield an isopropenyl group. Accordingly, treatment of the intermediate alkene with one equivalent of H_2 in the presence of Pd/C delivered taxamairin B (**24**).

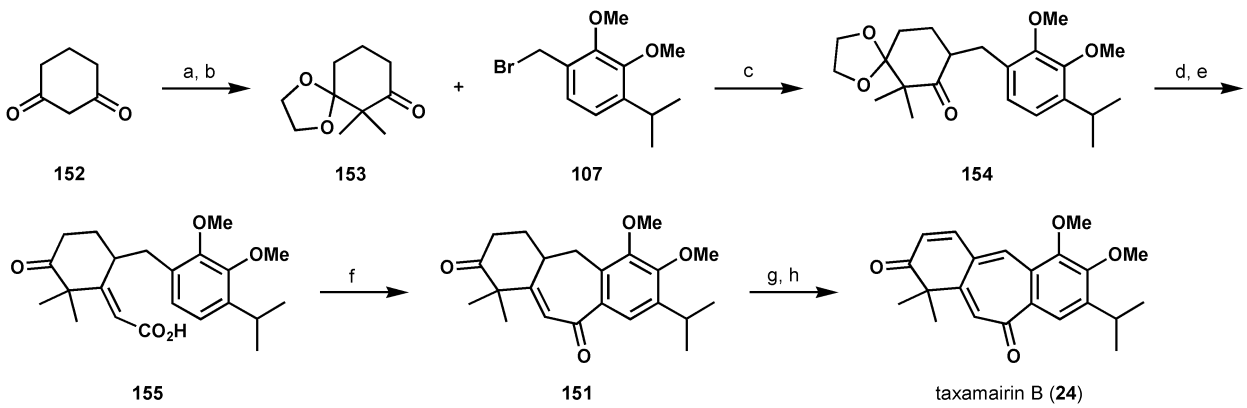
A second-generation total synthesis of taxamairin B was completed by Pan and co-workers in 1999 (Scheme 20).[83,84] 1,3-Cyclohexanedione (**152**) was converted to monoketal **153** by bis-alkylation with MeI and subsequent treatment with $BF_3 \cdot OEt_2$ and 1.05 equivalents of ethylene glycol. Alkylation of **153** with benzyl bromide **107** provided adduct **154**. Addition of vinylmagnesium bromide to **154** followed by treatment with acidic CrO_3 yielded acid **155**. Acid **155** underwent cyclization to dione **151** upon exposure to PPA at 80–90 °C. The final two-step conversion of **151** to taxamairin B (**24**) was identical to that reported previously by the same group (*i.e.*, DDQ, then H_2, Pd/C).[82]

4.4 Approaches to coulterone and related compounds

With oxygenation at the C11, C12 and C14 positions, the icetexanes in the coulterone subclass present a significant synthetic challenge in the form of a hexasubstituted benzene ring. The approaches to this group that have been reported to date all serve to highlight the limitations of current methods for the preparation of highly substituted arenes. Accordingly, some synthetic approaches to the coulterone subclass have been thwarted by the



Scheme 19 Pan's first-generation synthesis of taxamairin B. *Reagents and conditions*: (a) **148**, LDA, THF, −78 °C → rt, then **107**, −78 °C → rt, 84%; (b) $H_2C{=}CHMgBr$, THF, 0 °C → rt, 90%; (c) $BF_3{\cdot}OEt_2$, toluene, 80–90 °C, 73%; (d) NaH, DMSO, then concentrate, then THF, MeI, 48%; (e) CrO_3, *t*-BuOOH, CH_2Cl_2, 65%; (f) DDQ, benzene, Δ; (g) H_2 (1 equiv.), Pd/C, EtOH, 71% (over 2 steps).

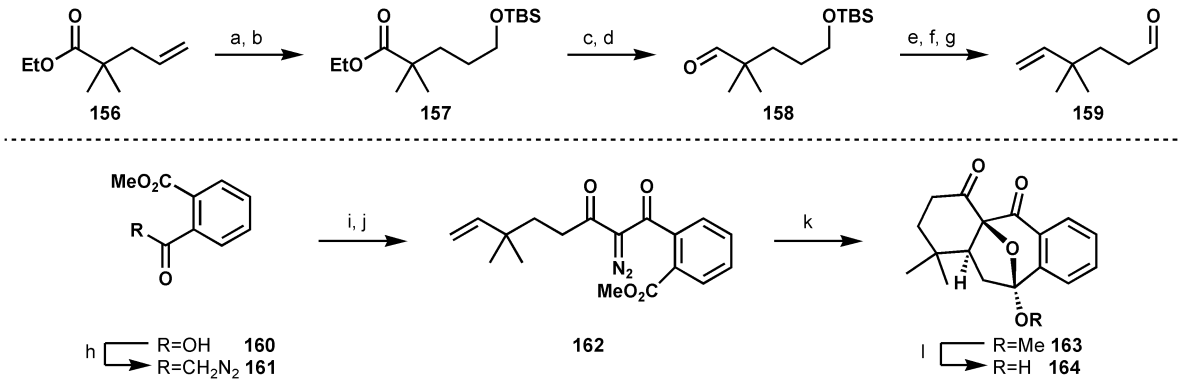


Scheme 20 Pan's second-generation synthesis of taxamairin B. *Reagents and conditions*: (a) K_2CO_3, MeI, acetone, Δ, 54%; (b) $BF_3{\cdot}OEt_2$, $(HOCH_2)_2$ (1.05 equiv.), Et_2O, 84%; (c) **153**, KH, THF, then **107**, 86%; (d) $H_2C{=}CHMgBr$, THF; (e) CrO_3, 5% aq. H_2SO_4, Et_2O, 5 °C, 62% (over 2 steps); (f) PPA, 80–90 °C, 79%; (g) DDQ, benzene, Δ; (h) H_2 (1 equiv.), Pd/C, EtOH, 71% (over 2 steps).

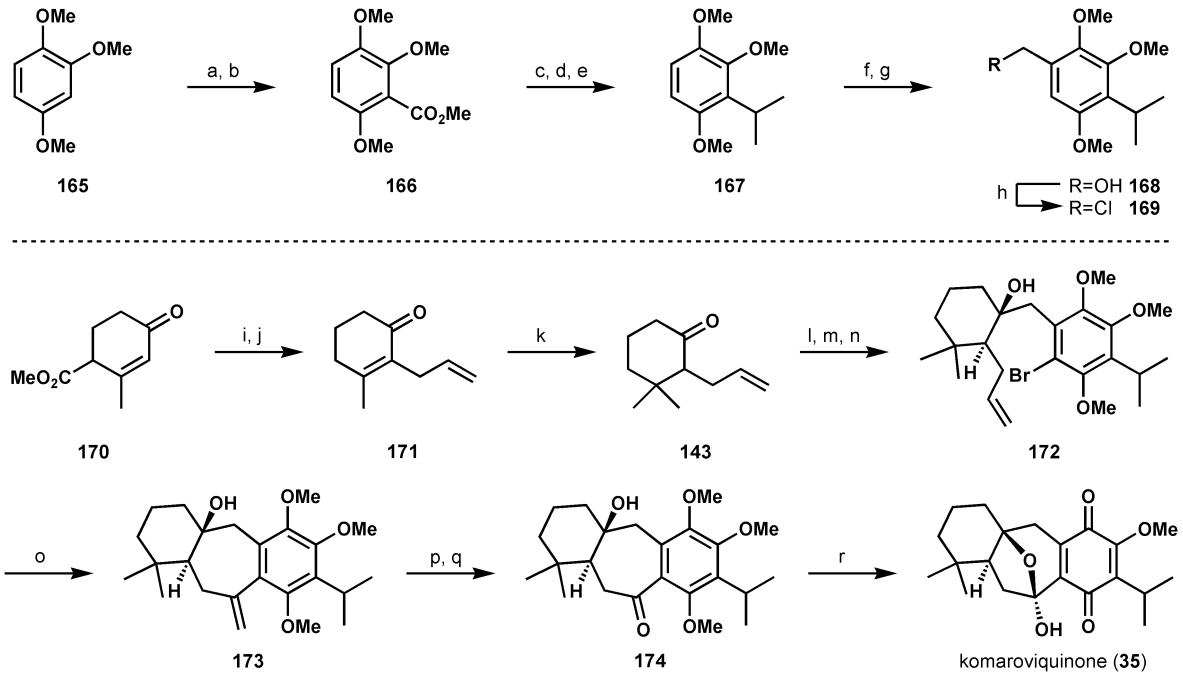
obstacle of obtaining the appropriate aromatic precursor. In those cases where a total synthesis was achieved, the overall sequence necessarily requires a rather lengthy series of steps to prepare the arene portion of the molecule.

Padwa and co-workers were the first to report an approach to komaroviquinone in 2005, which centered around a dipolar cycloaddition reaction to construct the tetracyclic framework (Scheme 21).[85] Alkene **156** underwent a hydroboration-oxidation sequence to provide an alcohol that was protected as its TBS ether (**157**). Reduction of the ester moiety of **157** with $LiAlH_4$ and oxidation of the intermediate alcohol with PCC delivered aldehyde **158**. A Wittig olefination of **158** was followed by silyl ether cleavage and subsequent alcohol oxidation to generate aldehyde **159**. $SnCl_2$-catalyzed addition of diazo ketone **161**, prepared in one step from phthalic acid monomethyl ester (**160**), to aldehyde **159** provided an intermediate 1,3-diketone that was converted to diazo ester **162** with *p*-nitrobenzenesulfonyl azide. Rh(II)-catalyzed decomposition of diazo ester **162** led to an intermediate carbonyl ylide that underwent intramolecular dipolar cycloaddition to generate tetracycle **163**. It was later reported in subsequent studies that the requisite diazo species containing an appropriately functionalized arene moiety necessary to complete the total synthesis of komaroviquinone proved to be elusive.[86]

The first total synthesis of (±)-komaroviquinone was reported by Banerjee and co-workers in 2005 (Scheme 22).[87] The synthesis began with the preparation of known benzyl alcohol **168**[7] *via* an alternate route. Thus, 1,2,4-trimethoxybenzene (**165**) was regioselectively lithiated with *n*-BuLi, and the resulting anion was allowed to react with CO_2 to give an intermediate acid that was methylated with Me_2SO_4 to yield ester **166**. Addition of two equivalents of MeMgI, followed by dehydration of the thus obtained tertiary alcohol with AcOH and hydrogenation of the resulting alkene delivered arene **167**. Lithiation of **167** with *n*-BuLi and subsequent treatment with DMF provided an aldehyde that was reduced with $NaBH_4$ to give **168**. Alcohol **168** was then converted to the corresponding chloride (**169**) by the action of PPh_3 and CCl_4. Separately, Hagemann's ester derivative **170** was transformed to enone **171** by allylation and Krapcho decarboxylation. Methyl conjugate addition to **171** yielded ketone **143**, which in turn underwent Barbier addition of benzyl chloride **169** in the presence of lithium metal in THF. Bromination of the resulting alcohol with NBS was accompanied by undesired bromoetherification of the allyl moiety by the tertiary



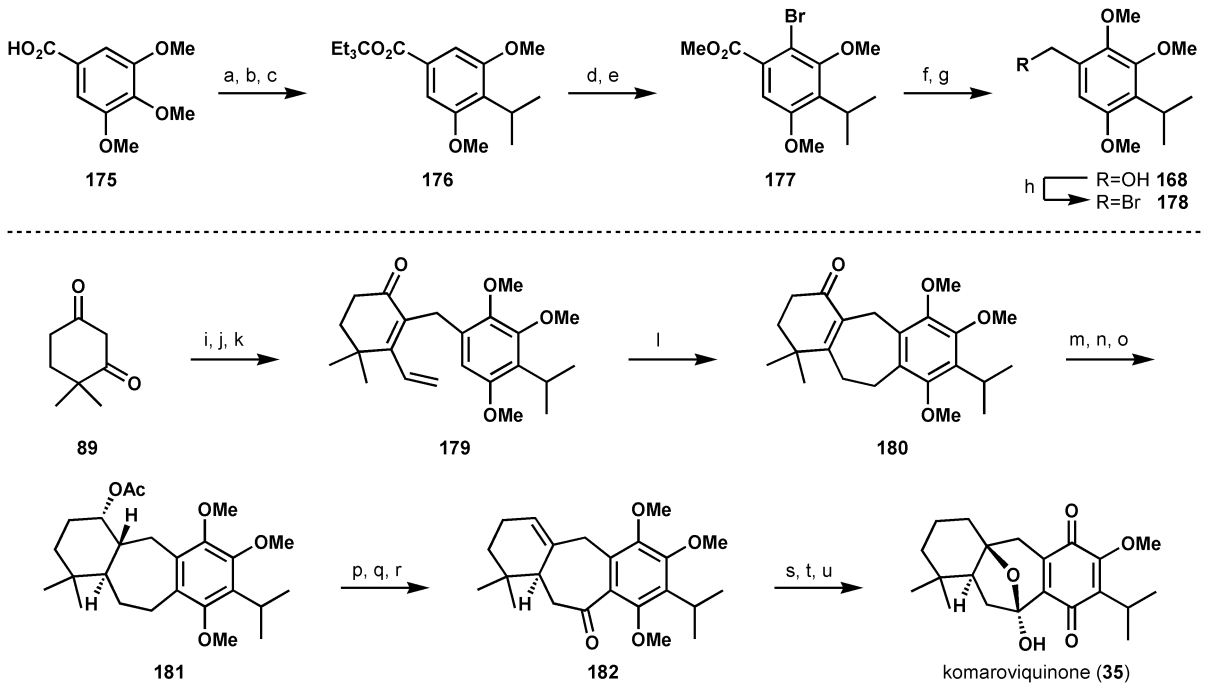
Scheme 21 Padwa's synthesis of the komaroviquinone skeleton. *Reagents and conditions*: (a) 9-BBN, THF, then NaOH, H_2O_2, 50 °C, 55%; (b) TBSCl, DMAP, imid., DMF, 0 °C, 95%; (c) $LiAlH_4$, Et_2O, 0 °C; (d) PCC, CH_2Cl_2, 70% (over 2 steps); (e) H_3CPPh_3I, *n*-BuLi, THF, 0 °C → rt, then **158**, 0 °C → rt, 80%; (f) TBAF, THF, 0 °C; (g) PCC, CH_2Cl_2, 80% (over 2 steps); (h) $SOCl_2$, then CH_2N_2, Et_2O, 0 °C → rt, 99%; (i) $SnCl_2$, CH_2Cl_2, then **159**, 20%; (j) *p*-$NO_2C_6H_4SO_2N_3$, Et_3N, MeCN, 0 °C, 38%; (k) $Rh_2(OAc)_4$, benzene, Δ, 92%; (l) aq. acid.



Scheme 22 Banerjee's synthesis of (±)-komaroviquinone. *Reagents and conditions*: (a) *n*-BuLi, Et_2O, 0 °C → rt, then CO_2 (g), −60 °C → rt, 75%; (b) LiOH, THF, then Me_2SO_4, Δ, 94%; (c) MeMgI, Et_2O, 0 °C → Δ; (d) AcOH, Δ; (e) H_2, Pd/C, EtOH, 72% (over 3 steps); (f) *n*-BuLi, THF, −78 → 0 °C, then DMF, −78 → 0 °C, 75%; (g) $NaBH_4$, MeOH, −20 °C, 94%; (h) CCl_4, PPh_3, MeCN, 0 °C → rt, 79%; (i) KO*t*-Bu, *t*-BuOH, 0 °C → rt, then $H_2C{=}CHCH_2Br$, 91%; (j) LiCl, H_2O, DMSO, 180–190 °C, 69%; (k) CuI, MeLi, Et_2O, −25 °C, then $BF_3{\cdot}OEt_2$, −50 °C, then **171**, −30 °C → −10 °C, 90%; (l) Li^0, **169**, THF, −10 → 0 °C, 52%; (m) NBS, MeCN, −20 °C → rt, 85%; (n) Zn^0, MeOH/AcOH, 84%; (o) $Pd(OAc)_2$, PPh_3, *i*Pr_2NEt, MeCN, rt → 90 °C, 68% (93% borsm); (p) OsO_4, NMO, *t*-BuOH/acetone/H_2O, 0 °C → rt; (q) $NaIO_4$, MeOH/H_2O, 0 °C → rt, 42% (over 2 steps, 77% borsm); (r) AgO, 6 N HNO_3, dioxane, 5 °C, 69%.

hydroxyl group; following treatment of this intermediate with activated zinc, monobromide **172** was obtained. Intramolecular Heck cyclization of **172** gave exocyclic alkene **173**, which was sequentially treated with OsO_4 and $NaIO_4$ to effect an oxidative cleavage and yield hydroxyketone **174**. Conversion to (±)-komaroviquinone (**35**) was achieved upon treatment of **174** with AgO and HNO_3.

In 2007, Majetich and co-workers reported the second total synthesis of (±)-komaroviquinone (Scheme 23).[88] Like Banerjee's earlier effort (see Scheme 22), the synthesis began with an alternative preparation of benzyl alcohol **168**, which was originally synthesized by Majetich and Zhang in their elegant total synthesis[7] of the icetexane-derived triterpene perovskone.[2] The new sequence began with gallic acid trimethyl ether (**175**), which was initially converted to its triethylcarbinyl ester derivative. An S_NAr addition of isopropylmagnesium chloride to this intermediate then provided ester **176**. Although the bulk of the triethylcarbinyl group was essential in preventing Grignard addition to the carbonyl moiety, **176** was first transesterified to the corresponding methyl ester in order for arene bromination to occur readily to yield

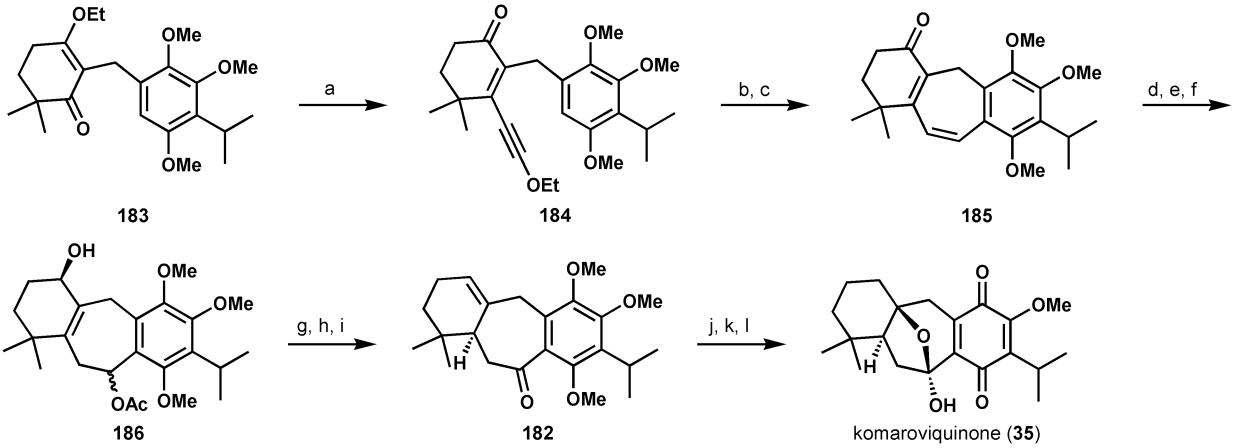


Scheme 23 Majetich's synthesis of (±)-komaroviquinone. *Reagents and conditions*: (a) $SOCl_2$; (b) Et_3COH; (c) *i*-PrMgCl, 70% (over 3 steps); (d) 10% HCl, MeOH, 97%; (e) NBS, 97%; (f) CuCl, NaOMe, 90%; (g) $LiAlH_4$, 95%; (h) PBr_3, 98%; (i) NaH, **178**; (j) NaH, Me_2SO_4, 85% (over 2 steps); (k) $H_2C{=}CHLi$, then H_3O^+, 95%; (l) $TiCl_4$, 95%; (m) H_2, Pd/C, KOEt, EtOH, 91%; (n) L-Selectride, −78 °C, 98%; (o) Ac_2O, 94%; (p) $CuSO_4$, $K_2S_2O_8$, then Jones reagent, 61%; (q) KOH, EtOH, Δ, 97%; (r) $SOCl_2$, pyridine, 0 °C, 82%; (s) NBS, acetone/H_2O, 83%; (t) AIBN, Bu_3SnH, 100%; (u) AgO, 7 N HNO_3, 54%.

bromide **177**. Treatment of **177** with CuCl and NaOMe transformed the aryl bromide into an aryl methyl ether, and subsequent $LiAlH_4$ reduction of the ester moiety delivered alcohol **168**. Following PBr_3-mediated conversion of **168** to bromide **178**, 1,3-diketone **89** was alkylated with this species and the resulting adduct was sequentially *O*-methylated and treated with vinyllithium to give dienone **179**. Cyclialkylation proceeded upon treatment of **179** with $TiCl_4$ to deliver enone **180**, itself also a key intermediate in Majetich's synthesis of perovskone.[7] Hydrogenation of the enone moiety of **180** in the presence of KOEt allowed for *in situ* epimerization of the initially formed *cis*-fused tricycle to the thermodynamically-preferred *trans* ring fusion. Reduction of the intermediate ketone with L-Selectride and acylation of the resulting alcohol then delivered acetate **181**. Benzylic oxidation of **181** proved to be quite challenging, and a number of reagents surveyed led to no reaction or to decomposition. However, treatment of **181** with $CuSO_4$ and $K_2S_2O_8$, followed by further oxidation with the Jones reagent, successfully installed the benzylic carbonyl functionality. Saponification of this intermediate and dehydration of the resulting secondary hydroxyl group with $SOCl_2$/pyridine then yielded ketone **182**. Conversion of **182** to (±)-komaroviquinone (**35**) was achieved by diastereoselective bromohydrin formation, radical dehalogenation and oxidative cleavage of the hydroquinone methyl ether moiety.

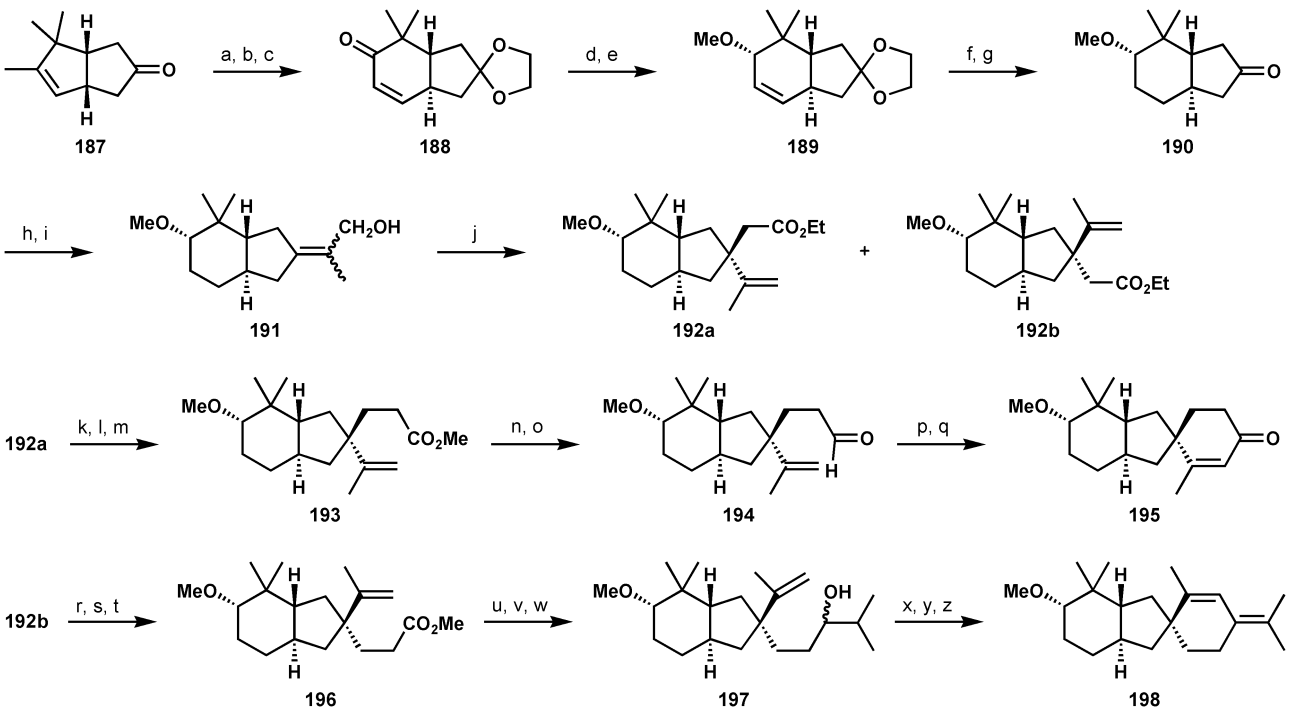
In a back-to-back publication immediately following their racemic synthesis of komaroviquinone,[88] Majetich and co-workers described the first asymmetric total synthesis of (+)-komaroviquinone (Scheme 24).[89] Vinylogous ester **183** was converted to enynone **184** by treatment with Aren's reagent and subsequent acidic workup. As noted for the related enynone employed in the total synthesis of salviasperanol by Majetich *et al.* (see Scheme 17),[80] direct cyclialkylation of **184** is not achievable due to the lack of proximity of the arene and alkyne moieties. However, Lindlar hydrogenation of **184** provided an intermediate dienone that was readily transformed to tricyclic dienone **185** on treatment with $TiCl_4$ or $BF_3{\cdot}OEt_2$. Bromination of **185** with NBS in acetic acid, followed by radical dehalogenation and CBS reduction of the enone moiety, yielded alcohol **186** as a 1:1 mixture of diastereomers. A Myers allylic transposition of **186** and subsequent acetate cleavage and alcohol oxidation provided ketone **182**, which in turn was converted to (+)-komaroviquinone (**35**) as previously described.[88] The successful synthesis of (+)-komaroviquinone by Majetich and co-workers set the stage for their investigation of the conversion of komaroviquinone (**35**) to komarovispirone (**36**, Scheme 2),[54] as discussed in Section 3.

A *de novo* approach to the komarovispirone skeleton was disclosed by Srikrishna and Beeraiah in 2007 (Scheme 25).[90] The synthesis commenced with bicycle **187**, which was previously prepared in the Srikrishna laboratory in enantiopure form. Ketal protection of the carbonyl group of **187** was followed by ozonolysis and intramolecular aldol condensation to generate ring-expanded bicyclic enone **188**. Reduction of the carbonyl group followed by methylation of the resulting alcohol delivered allylic ether **189**. Alkene hydrogenation and ketal cleavage yielded ketone **190**, which was subjected to Horner–Wadsworth–Emmons olefination and subsequent ester reduction to give tetrasubstituted alkene **191** as a mixture of diastereomers. A Johnson *ortho*-ester Claisen rearrangement of **191** then provided the chromatographically separable alkenes **192a-b** in a 2:3 ratio.

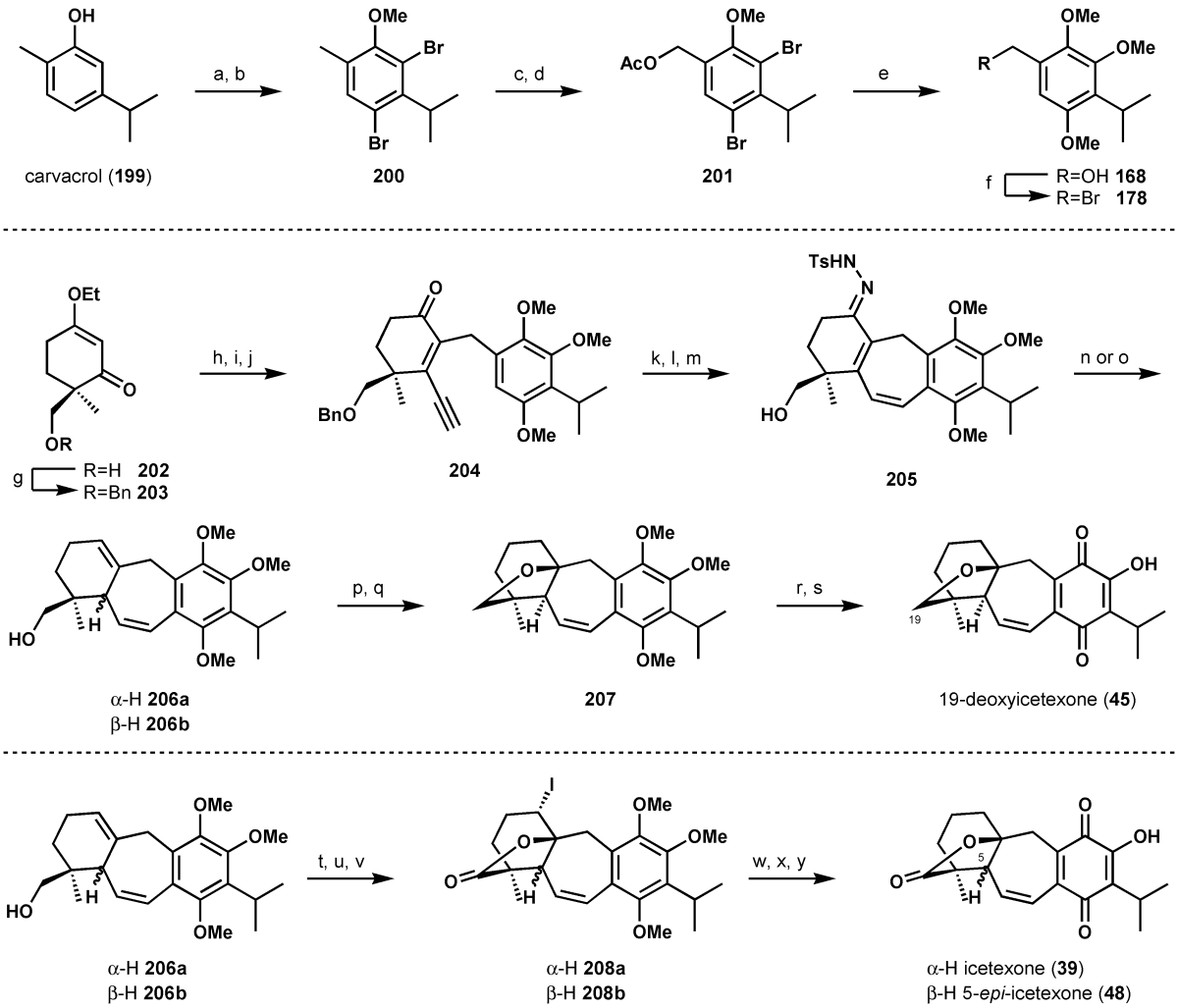


Scheme 24 Majetich's synthesis of (+)-komaroviquinone. *Reagents and conditions*: (a) LiC≡COEt, then H_3O^+, 79%; (b) H_2, 5% $Pd/BaSO_4$, 98%; (c) $TiCl_4$ or $BF_3{\cdot}OEt_2$, 66%; (d) NBS, AcOH; (e) AIBN, Bu_3SnH, 90% (over 2 steps); (f) CBS reduction, 88%; (g) DEAD, PPh_3, *o*-NBSH, 88%; (h) $LiAlH_4$; (i) Jones reagent, 85% (over 2 steps); (j) NBS, acetone/H_2O, 83%; (k) AIBN, Bu_3SnH, 100%; (l) AgO, 7 N HNO_3.

Each of these diastereomers was subsequently advanced to the tricyclic komarovispirone skeleton *via* a different strategy. In one approach, alkene **192a** was homologated to ester **193** by a standard Arndt–Eistert sequence. Oxidation state adjustment to aldehyde **194** set the stage for a Lewis acid-mediated intramolecular ene cyclization, which following oxidation of the intermediate alcohol and *in situ* olefin isomerization gave tricyclic enone **195**. Alkene **192b** was similarly advanced in five steps (*via* ester **196**) to an aldehyde intermediate that underwent addition of isopropylmagnesium bromide to provide alcohol **197**. Oxidation of **197** was followed by addition of vinylmagnesium bromide to deliver a diene that was converted to tricyclic diene **198** by ring-closing metathesis with Grubbs' second-generation catalyst in refluxing benzene and subsequent dehydration.



Scheme 25 Srikrishna's synthesis of the komarovispirone skeleton. *Reagents and conditions*: (a) TsOH, $(HOCH_2)_2$, benzene, Δ, 86%; (b) O_3, CH_2Cl_2/MeOH, −70 °C, then Me_2S, rt, 87%; (c) AcOH, piperidine, benzene, Δ, 83%; (d) $LiAlH_4$, Et_2O, −70 °C, 98%; (e) NaH, MeI, TBAI, THF, 0 °C → Δ, 93%; (f) H_2, Pd/C, hexane, 100%; (g) 3 N HCl, THF, 100%; (h) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, 0 °C → Δ, 89%; (i) $LiAlH_4$, Et_2O, −70 °C, 95%; (j) $CH_3C(OEt)_3$, $EtCO_2H$, 180 °C, 34% of **192a** + 50% of **192b**; (k) NaOH, MeOH/H_2O, Δ, 93%; (l) $(COCl)_2$, benzene, rt, then CH_2N_2, Et_2O, 0 °C, 85%; (m) hν, MeOH, 91%; (n) $LiAlH_4$, Et_2O, 0 °C, 95%; (o) PDC, CH_2Cl_2, 93%; (p) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 80%; (q) PCC, SiO_2, CH_2Cl_2, 86%; (r) NaOH, MeOH/H_2O, Δ; (s) $(COCl)_2$, benzene, rt, then CH_2N_2, Et_2O, 0 °C; (t) hν, MeOH, 73% (over 3 steps); (u) $LiAlH_4$, Et_2O, 0 °C; (v) PDC, CH_2Cl_2, 95% (over 2 steps); (w) *i*-PrMgBr, THF, 0 °C, 94%; (x) PCC, NaOAc, CH_2Cl_2, 0 °C → rt, 96%; (y) $H_2C{=}CHMgBr$, THF, 0 °C → rt, 94%; (z) Grubbs' II, benzene, Δ, 71%.



Scheme 26 Majetich's synthesis of (+)-19-deoxyicetexone, (–)-icetexone and (+)-5-*epi*-icetexone. *Reagents and conditions*: (a) Br_2, AcOH, rt; (b) KOH, MeI, THF, rt, 94% (over 2 steps); (c) NBS, cyclohexane, 80 °C; (d) NaOAc, DMF, 100 °C, 70% (over 2 steps); (e) NaOMe, CuI, MeOH/DMF, 110 °C, 70%; (f) PBr_3, 96%; (g) NaH, BnBr; (h) LDA, DMPU, **178**, 76%; (i) TMSC≡CH, *n*-BuLi, THF, 0 °C, then 6 M HCl; (j) TBAF, THF, rt, 83% (over 2 steps); (k) $BF_3{\cdot}OEt_2$, EtSH, CH_2Cl_2, rt, 85%; (l) BBr_3, 94%; (m) H_2NNHTs, EtOH, rt; (n) catecholborane, 14% of **206a** + 56% of **206b**; (o) NaB-H$(OAc)_3$, 42% of **206a** + 42% of **206b**; (p) I_2, K_2CO_3, MeCN, rt, 91% (from **206a**); (q) AIBN, Bu_3SnH, benzene, 80 °C, 94%; (r) NaSEt, DMF, 120 °C; (s) CAN, Et_2O/H_2O, 66% (over 2 steps); (t) DMP, CH_2Cl_2, rt, 91% (α) or 95% (β); (u) $NaClO_2$, NaH_2PO_4, acetone/H_2O, rt, 92% (α) or 90% (β); (v) I_2, K_2CO_3, MeCN, rt, 92% (α) or I_2, K_2CO_3, benzene, rt, 89% (β); (w) AIBN, Bu_3SnH, benzene, 80 °C, 90% (α) or Bu_3SnH, toluene, 110 °C, 95% (β); (x) BBr_3, CH_2Cl_2, −20 °C; (y) CAN, Et_2O/H_2O, rt.

4.5 Approaches to icetexone and related compounds

To date, there have been no published details of the total synthesis or synthetic studies toward members of the icetexone family. However, studies toward icetexone (**39**) and anastomosine (**41**) have been presented by Grove and Majetich.[91,92] In addition, the total syntheses of icetexone, 5-*epi*-icetexone (**48**) and 19-deoxyicetexone (**45**) were recently presented by Grove and Majetich.[93]

5 Conclusions

It has been over 30 years since the first member of the icetexane family was isolated from *Salvia ballotaeflora* Benth. Since that time, an additional forty-five icetexanes have been isolated from a variety of plant species, and there is nothing to indicate that the discovery of additional icetexanes will cease. The fascinating molecular architecture of the members of this natural product family has stimulated the interest of numerous synthetic chemists which has led to a number of creative synthetic approaches and beautiful total syntheses. The recent flurry of activity in this arena hints at even more innovative syntheses to come.

Note added in proof

Subsequent to the submission of this review, we became aware of a manuscript under review by Majetich and Grove detailing the total syntheses of (+)-19-deoxyicetexone, (–)-icetexone and (+)-5-*epi*-icetexone (Scheme 26),[94] which was recently published online as an ASAP article.[95] These efforts commenced with a novel, five-step preparation of benzyl alcohol **168**[7,88] from carvacrol (**199**). Dibromination of **199** in AcOH followed by

methylation of the resulting phenol yielded dibromide **200**. Radical bromination of the methyl group of **200** and displacement of the bromide with NaOAc gave acetate **201**, which underwent a one-pot Ullmann-type coupling and acetate cleavage with CuOMe to generate alcohol **168**. Concurrently, known primary alcohol **202**, obtained *via* enzymatic resolution of the racemate, was protected as the corresponding benzyl ether (**203**). Selective α-alkylation was achieved upon treatment of **203** with LDA, DMPU and bromide **178** to yield an intermediate adduct that underwent addition of (trimethylsilyl)ethynyl lithium and subsequent silyl cleavage to provide enynone **204**. Similar to the strategy utilized by Majetich *et al.* in the synthesis of (–)-salviasperanol (see Scheme 17),[80] treatment of **204** with $BF_3 \cdot OEt_2$ and EtSH effected a cyclialkylation to afford an intermediate dienone. Benzyl ether cleavage and treatment with H_2NNHTs then yielded hydrazone **205**. It was anticipated that the primary hydroxyl group might allow for a diastereoselective reductive transposition of **205** by complexation of an appropriate reducing agent, which would subsequently either block the β-face (to generate **206a**) or promote intramolecular hydride delivery (to generate **206b**). In the event, treatment of **205** with catecholborane provided a 70% yield of **206a-b** in a 1:4 ratio, whereas sodium triacetoxyborohydride gave an 84% yield of **206a-b** in a 1:1 ratio. Diene **206a** underwent iodoetherification on treatment with I_2 and K_2CO_3, and radical dehalogenation delivered ether **207**. Methyl ether cleavage with NaSEt and oxidation with CAN then yielded (+)-19-deoxyicetexone (**45**). Alternatively, two-stage oxidation of **206a** yielded a carboxylic acid that underwent iodolactonization to give iodide **208a**, and a similar dehalogenation/methyl ether cleavage/oxidation sequence provided **39**. An identical sequence beginning with **206b** provided **48**. The structures of **39** and **48** were both confirmed by X-ray analysis. However, the spectral and physical data for **39** were found to be consistent with those reported for 5-*epi*-icetexone,[64] while the data for **48** were consistent with those reported for icetexone,[58,59] indicating that the reported structural assignments for these two species should be swapped.

6 Acknowledgements

We would like to thank the ACS Division of Medicinal Chemistry and Eli Lilly for a predoctoral fellowship to E.M.S. (2007–2008). R.S. is a 2009 Alfred P. Sloan Fellow and a Camille Dreyfus Teacher-Scholar. We are grateful to Laura Miller and Brian Pujanauski for providing critical readings of this manuscript.

7 References and notes

1 T. Miyase, P. Ruedi and C. H. Eugster, *Helv. Chim. Acta*, 1977, **60**, 2789–2803.
2 A. Parvez, M. I. Choudhary, F. Akhter, M. Noorwala, F. V. Mohammad, N. M. Hasan, T. Zamir and V. U. Ahmad, *J. Org. Chem.*, 1992, **57**, 4339–4340.
3 V. U. Ahmed, A. Parvez and N. M. Hassan, *Tetrahedron Lett.*, 1993, **34**, 5337.
4 V. U. Ahamad, M. Zahid, M. S. Ali, Z. Ali, N. Alam, R. B. Tareen and M. Z. Iqbal, *Z. Naturforsch., B: Chem. Sci.*, 1999, **54**, 415–418.
5 V. U. Ahmad, M. Zahid, M. S. Ali, M. I. Choudhary, F. Akhtar, Z. Ali and M. Z. Iqbal, *Tetrahedron Lett.*, 1999, **40**, 7561–7564.
6 V. U. Ahmad, M. Zahid, M. S. Ali, Z. Ali, A. R. Jassbi, M. Abbas, J. Clardy, E. Lobkovsky, R. B. Tareen and M. Z. Iqbal, *J. Org. Chem.*, 1999, **64**, 8465–8467.
7 G. Majetich and Y. Zhang, *J. Am. Chem. Soc.*, 1994, **116**, 4979–4980.
8 G. Majetich, Y. Wang, Y. Li, J. K. Vohs and G. H. Robinson, *Org. Lett.*, 2003, **5**, 3847–3850.
9 M. E. Maier and A. Bayer, *Eur. J. Org. Chem.*, 2006, 4034–4043.
10 L. Rodiguez-Hahn, B. Esquivel, A. Adela Sanchez, C. Sanchez, J. Cardenas and T. P. Ramamoorthy, *Rev. Latinoamer. Quim.*, 1989, **20**, 105–110.
11 B. Esquivel, J. S. Calderon, A. A. Sanchez, T. P. Ramamoorthy, E. A. Flores and R. M. Dominguez, *Rev. Latinoamer. Quim.*, 1996, **24**, 44–64.
12 B. Esquivel, J. S. Calderon, M. G. Arano, P. M. Hernandez and A. A. Sanchez, *Rev. Latinoamer. Quim.*, 2005, **33**, 82–89.
13 B. Esquivel, *Nat. Prod. Commun.*, 2008, **3**, 989–1002.
14 M. Yatagai and T. Takahashi, *Phytochemistry*, 1980, **19**, 1149–1151.
15 S. Hasegawa, Y. Hirose, M. Yatagai and T. Takahashi, *Chem. Lett.*, 1984, 1837–1838.
16 S. Hasegawa, T. Kojima and Y. Hirose, *Phytochemistry*, 1985, **24**, 1545–1551.
17 A. M. El-Lakany, M. S. Abdel-Kader, N. N. Sabri and F. R. Stermitz, *Planta Med.*, 1995, **61**, 559–560.
18 A. M. ElLakany, *Planta Med.*, 1996, **62**, 288–288.
19 J. W. Ahn, K. Wada and S. Marumo, *Agric. Biol. Chem.*, 1984, **48**, 3177–3179.
20 J. W. Ahn, K. Wada and S. Marumo, *Tetrahedron*, 1986, **42**, 529–535.
21 T.-C. Lin, J.-M. Fang and Y.-S. Cheng, *Phytochemistry*, 1999, **51**, 793–801.
22 D. Xiao, M. Kuroyanagi, T. Itani, H. Matsuura, M. Udayama, M. Murakami, K. Umehara and N. Kawahara, *Chem. Pharm. Bull.*, 2001, **49**, 1479–1481.
23 K. Kobayashi and C. Nishino, *Agric. Biol. Chem.*, 1986, **50**, 2405–2407.
24 K. Kobayashi, C. Nishino, M. Fukushima, Y. Shiobara and M. Kodama, *Agric. Biol. Chem.*, 1988, **52**, 77–83.
25 K. Kobayashi, C. Nishino, H. Tomita and M. Fukushima, *Phytochemistry*, 1987, **26**, 3175–3179.
26 A. Kelecom, *Tetrahedron*, 1983, **39**, 3603–3608.
27 C. M. Houlihan, C. T. Ho and S. S. Chang, *J. Am. Oil Chem. Soc.*, 1984, **61**, 1036–1039.
28 B. M. Fraga, A. G. Gonzalez, J. R. Herrera, J. G. Luis and A. G. Ravelo, *Phytochemistry*, 1985, **25**, 269.
29 A. G. Gonzalez, L. S. Andres, J. G. Luis, I. Brito and M. L. Rodriguez, *Phytochemistry*, 1991, **30**, 4067.
30 A. Kelecom and W. L. B. Medeiros, *Bull. Soc. Chim. Belg.*, 1989, **98**, 413–414.
31 M. Bruno, G. Savona, F. Piozzi, M. C. De la Torre, B. Rodriguez and M. Marlier, *Phytochemistry*, 1991, **30**, 2339–2343.
32 B. Galli, F. Gasparrini, V. Lanzotti, D. Misiti, R. Riccio, C. Villani, H. Guan-Fu, M. Zhong-Wu and Y. Wan-Fen, *Tetrahedron*, 1999, **55**, 11385–11394.
33 Y. Aoyagi, Y. Takahashi, Y. Satake, H. Fukaya, K. Takeya, R. Aiyama, T. Matsuzaki, S. Hashimoto, T. Shiina and T. Kurihara, *Tetrahedron Lett.*, 2005, **46**, 7885–7887.
34 B. Esquivel, M. Flores, S. Hernandez-Ortega, R. A. Toscano and T. P. Ramamoorthy, *Phytochemistry*, 1995, **39**, 139–143.
35 J. G. Luis and L. S. Andres, *Nat. Prod. Lett.*, 1999, **14**, 25–30.
36 E. M. Simmons, J. R. Yen and R. Sarpong, *Org. Lett.*, 2007, **9**, 2705–2708.
37 B. M. Fraga, C. E. Diaz, A. Guadano and A. Gonzalez-Coloma, *J. Agric. Food Chem.*, 2005, **53**, 5200–5206.
38 Y. Aoyagi, Y. Takahashi, H. Fukaya, K. Takeya, R. Aiyama, T. Matsuzaki, S. Hashimoto and T. Kurihara, *Chem. Pharm. Bull.*, 2006, **54**, 1602–1604.
39 G. Xu, L.-Y. Peng, Y. Zhao, X.-L. Li, L. Tu, Q.-S. Zhao and H.-D. Sun, *Chem. Pharm. Bull.*, 2005, **53**, 1575–1576.
40 G. Xu, L.-Y. Peng, L. Tu, X.-L. Li, Y. Zhao, P.-T. Zhang and Q.-S. Zhao, *Helv. Chim. Acta*, 2009, **92**, 409–413.
41 J. Liang, Z. Min, M. Iinuma, T. Tanaka and M. Mizuno, *Chem. Pharm. Bull.*, 1987, **35**, 2613–2614.
42 J. Liang, Z. Min, T. Tanaka, M. Mizuno and M. Ilnuma, *Huaxue Xuebao*, 1988, **46**, 21–25.
43 S.-J. Yang, J.-M. Fang and Y.-S. Cheng, *Phytochemistry*, 1998, **49**, 2037–2043.

44 J. Bai, N. Ito, J. Sakai, M. Kitabatake, H. Fujisawa, L. Bai, J. Dai, S. Zhang, K. Hirose, A. Tomida, T. Tsuruo and M. Ando, *J. Nat. Prod.*, 2005, **68**, 497–501.
45 R. L. Arslanian, D. T. Bailey, M. C. Kent, S. L. Richheimer, K. R. Thornburg, D. W. Timmons and Q. Y. Zheng, *J. Nat. Prod.*, 1995, **58**, 583–585.
46 B. Frontana, J. Cardenas and L. Rodriguez-Hahn, *Phytochemistry*, 1994, **36**, 739–741.
47 E. C. C. Araujo, M. A. S. Lima, E. P. Nunes and E. R. Silveira, *J. Braz. Chem. Soc.*, 2005, **16**, 1336–1341.
48 N. Uchiyama, F. Kiuchi, M. Ito, G. Honda, Y. Takeda, O. K. Khodzhimatov and O. A. Ashurmetov, *J. Nat. Prod.*, 2003, **66**, 128–131.
49 J. W. Bastien, *The Kiss of Death: Chagas' Disease in the Americas*, The University of Utah Press, Salt Lake City, 1998.
50 N. Uchiyama, *J. Health Sci.*, 2009, **55**, 31–39.
51 Application: CA Pat., 2005–2522632 2522632, 2007.
52 E. A. Berger, P. M. Murphy and J. M. Farber, *Annu. Rev. Immunol.*, 1999, **17**, 657–700.
53 N. Uchiyama, M. Ito, F. Kiuchi, G. Honda, Y. Takeda, O. K. Khodzhimatov and O. A. Ashurmetov, *Tetrahedron Lett.*, 2004, **45**, 531–533.
54 G. Majetich and J. Yu, *Org. Lett.*, 2008, **10**, 89–91.
55 S. Khaliq, F.-J. Volk and A. W. Frahm, *Planta Med.*, 2007, **73**, 77–83.
56 N. Uchiyama, Z. Kabututu, B. K. Kubata, F. Kiuchi, M. Ito, J. Nakajima-Shimada, T. Aoki, K. Ohkubo, S. Fukuzumi, S. K. Martin, G. Honda and Y. Urade, *Antimicrob. Agents Chemother.*, 2005, **49**, 5123–5126.
57 C. Sanchez, J. Cardenas, L. Rodriguez-Hahn and T. P. Ramamoorthy, *Phytochemistry*, 1989, **28**, 1681–1684.
58 W. H. Watson, Z. Taira, X. A. Dominguez, H. Gonzales, M. Guiterrez and R. Aragon, *Tetrahedron Lett.*, 1976, **17**, 2501–2502.
59 X. A. Dominguez, F. H. Gonzalez, R. Aragon, M. Gutierrez, J. S. Marroquin and W. Watson, *Planta Med.*, 1976, **30**, 237.
60 Z. Taira, W. H. Watson and X. A. Dominguez, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1728–1730.
61 J. Cardenas and L. Rodriguez-Hahn, *Phytochemistry*, 1995, **38**, 199–204.
62 B. Esquivel, J. S. Calderon, E. Flores, A.-A. Sanchez and R. R. Rivera, *Phytochemistry*, 1997, **46**, 531–534.
63 B. Esquivel, J. S. Calderon, E. Flores, C. Chavez and M. Juarez, *Nat. Prod. Lett.*, 1997, **10**, 87–93.
64 M. Nieto, E. E. Garcia, O. S. Giordano and C. E. Tonn, *Phytochemistry*, 2000, **53**, 911–915.
65 A. M. Sanchez, V. Jimenez-Ortiz, T. Sartor, C. E. Tonn, E. E. Garcia, M. Nieto, M. H. Burgos and M. A. Sosa, *Acta Trop.*, 2006, **98**, 118–124.
66 G. Majetich and G. Zou, *Org. Lett.*, 2008, **10**, 81–83.
67 A referee proposed an alternative pathway to **17** and **16** from *ortho*-quinone methide **54**, which is illustrated below. Tautomerization of **54** would give rise to alkene **a**, which could undergo diastereoselective epoxidation to yield epoxide **b**. Opening of this epoxide by attack of the tertiary hydroxyl at the benzylic position would then deliver **17**.
68 T. Matsumoto, S. Imai, T. Yoshinari and S. Matsuno, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3103–3108.
69 T. Kametani, H. Kondoh, M. Tsubuki and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1990, 5–10.
70 S. Deb, G. Bhattacharjee and U. R. Ghatak, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1453–1458.
71 X. Wang, Y. Cui, X. Pan and Y. Chen, *Bull. Soc. Chim. Belg.*, 1995, **104**, 563–565.
72 The term "cyclialkylation" was introduced in the literature prior to the IUPAC introduction of "cyclo" as the preferred prefix for processes involving cyclization. Although technically outdated, "cyclialkylation" is used throughout this review for historical reasons..
73 G. Majetich, R. Hicks, Y. Zhang, X. Tian, T. L. Feltman, J. Fang and S. Duncan, Jr., *J. Org. Chem.*, 1996, **61**, 8169–8185.
74 G. Majetich, Y. Zhang, T. L. Feltman and S. Duncan, Jr., *Tetrahedron Lett.*, 1993, **34**, 445–448.
75 M. W. Tuckett, W. J. Watkins and R. J. Whitby, *Tetrahedron Lett.*, 1998, **39**, 123–126.
76 E. R. Koft, *Tetrahedron*, 1987, **43**, 5775–5780.
77 X. Wang, Y. Cui, X. Pan and Y. Chen, *J. Indian Chem. Soc.*, 1996, **73**, 217–219.
78 X. Wang, X. Pan, Y. Cui and Y. Chen, *Tetrahedron*, 1996, **52**, 10659–10666.
79 E. M. Simmons and R. Sarpong, *Org. Lett.*, 2006, **8**, 2883–2886.
80 G. Majetich, G. Zou and J. Grove, *Org. Lett.*, 2008, **10**, 85–87.
81 D. Martinez-Solorio and M. P. Jennings, *Org. Lett.*, 2009, **11**, 189–192.
82 X. Wang, X. Pan, C. Zhang and Y. Chen, *Synth. Commun.*, 1995, **25**, 3413–3419.
83 X. C. Wang and X. F. Pan, *J. Indian Chem. Soc.*, 1996, **73**, 497–498.
84 C. Ning, X.-C. Wang and X.-F. Pan, *Synth. Commun.*, 1999, **29**, 2115–2122.
85 A. Padwa, J. Boonsombat, P. Rashatasakhon and J. Willis, *Org. Lett.*, 2005, **7**, 3725–3727.
86 A. Padwa, M. J. Chughtai, J. Boonsombat and P. Rashatasakhon, *Tetrahedron*, 2008, **64**, 4758.
87 S. Sengupta, M. G. B. Drew, R. Mukhopadhyay, B. Achari and A. K. Banerjee, *J. Org. Chem.*, 2005, **70**, 7694–7700.
88 G. Majetich, Y. Li and G. Zou, *Heterocycles*, 2007, **73**, 217–225.
89 G. Majetich, J. Yu and Y. Li, *Heterocycles*, 2007, **73**, 227–235.
90 A. Srikrishna and B. Beeraiah, *Tetrahedron: Asymmetry*, 2007, **18**, 2587–2597.
91 J. L. Grove and G. Majetich, *Abstracts, 58th Southeast Regional Meeting of the American Chemical Society*, Augusta, GA, United States, November 1–4, 2006, SRM06–669.
92 J. L. Grove and G. F. Majetich, *Abstracts of Papers, 233rd ACS National Meeting*, Chicago, IL, United States, March 25–29, 2007, ORGN-375.
93 J. L. Grove and G. F. Majetich, *Abstracts of Papers, 236th ACS National Meeting*, Philadelphia, PA, United States, August 17–21, 2008, ORGN-515.
94 G. Majetich, *Personal communication*.
95 G. Majetich and J. L. Grove, *Org. Lett.*, DOI: 10.1021/ol9009128.