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Total synthesis of the pseudopterosin aglycones

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REVIEW

Total synthesis of the pseudopterosin aglycones

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Christopher G. Newton and Michael S. Sherburn*

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The pseudopterosin natural products have been the focus of a substantial number of synthetic studies since the first members were isolated almost 30 years ago. Herein we review all total and formal syntheses of this family of glycosylated diterpenes, with an emphasis on the synthetic strategies employed.

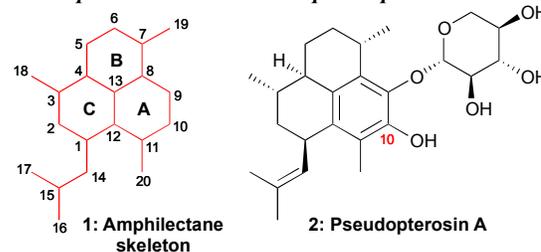
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1 The pseudopterosins

The pseudopterosins are a family of monoglycosylated amphilectanes produced by symbiotic single celled algae living inside the Caribbean sea whip *Pseudopteroorgia elisabethae* (the amphilectane skeleton (1), and a representative family member, pseudopterosin A (2), are shown in Fig. 1A).^{1,2} The first four members were isolated in 1986 by Fenical and co-workers.^{3,4} The family has since expanded to 31, and their isolation is described in a recent review by Kerr.⁵

All of the pseudopterosins are derived from one of three stereoisomeric aglycones (Fig. 1B). The remaining structural diversity arises from the position and identity of the sugar, and the extent of hydroxyl group acetylation. There exists some confusion in the literature regarding the naming of the pseudopterosins and their aglycones. In 2004, three research groups disclosed the isolation of new family members.^{6–8} Unfortunately, between the three publications the same name was assigned to different structures, and identical structures were assigned multiple names. Thus, the aglycone historical names remain in use, despite the identification of new pseudopterosins.

A. The amphilectane skeleton and pseudopterosin A



B. The pseudopterosin aglycones

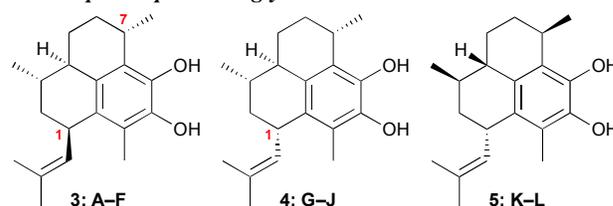


Fig. 1 (A) The amphilectane skeleton and pseudopterosin A and (B) the pseudopterosin aglycones.

Each of the pseudopterosin aglycones contain a fully substituted benzene ring (specifically a catechol) and four stereocentres distributed across the two non-aromatic rings. The

A–F (**3**) and G–J (**4**) aglycones are epimeric at C1 and the A–F and K–L (**5**) aglycones form an enantiomeric pair. The stereochemistry of the G–J aglycone was originally misassigned as the C7 epimer of the A–F aglycone,⁹ but was later corrected through total synthesis.¹⁰

The pseudopterosin family has been shown to exhibit various biological activities including anti-cancer,⁷ anti-malarial⁷ and anti-inflammatory properties.^{3,4} Methopterosin, the C10 methyl ether derivative of pseudopterosin A (**2**), has successfully completed Phase I and II clinical trials as a wound healing agent,^{5,11} and a *Pseudopteroorgia elisabethae* extract has been included in a cosmetic skin care product.¹²

2 Review scope and classification of syntheses

Although the pseudopterosins are not markedly complex natural products, the fused tricyclic framework, absence of neighbouring controlling functionality at each stereocentre, and the oxidative sensitivity of the catechol moiety make for challenging synthetic targets. These structural features, coupled with encouraging biological activity, have attracted the attention of many synthetic organic chemists.

To date, 15 total or formal syntheses of the pseudopterosin aglycones (or protected derivatives) have been completed. In this review, we have classified each based on an analysis of the synthetic strategies employed. We note, with one exception, that all pseudopterosin syntheses can be considered structure-goal based strategies¹³ (or a combination of structure-goal with another strategy). Specifically, a commercially available terpene or aromatic precursor that maps onto a section of a pseudopterosin has been selected as a starting material. In contrast, the most recently completed synthesis, conducted by the authors of this review and their coworkers,¹⁴ represents a transform-based strategy,¹³ in which a powerful sequence of reactions was used to access a pseudopterosin from an unusual precursor.

Our review focuses largely on the ring forming reactions of each synthesis (highlighted in red), and, where possible, metrics of each synthesis are presented. Some of the total syntheses reviewed herein commence with starting materials that are not

commercially available and authors cite earlier literature for their preparation. In an attempt to compare syntheses fairly, total step count – reported as longest linear sequence – and yields are measured from commercially available starting materials by incorporating details from these referenced literature procedures. We have elected not to include synthetic studies *towards* the pseudopterosins that have not yet achieved the final target,^{15–28} or the synthesis of simplified analogues^{29–32} (including biosynthetic precursors),^{33–37} or the synthesis of the originally proposed structure of the G–J aglycone.^{38,39}

We begin by presenting biosynthetic considerations, followed by an analysis of structure-goal based approaches (divided into terpene and aromatic starting materials), and we conclude with the recent transform-based strategy.

2 Biosynthetic origins

Many of the pseudopterosin syntheses employ reactions that, whether intentional or not, mimic aspects of the proposed pseudopterosin biosynthesis. For this reason, we present the biosynthetic proposal in order to place these works in context. The biosynthetic origins of the pseudopterosins were elucidated in a series of elegant isolation and biochemical studies conducted by the Kerr group (Fig. 2A).^{1,2,40–48} The first proposed intermediate, elisabethatriene (**11**), results from an enzyme-mediated cyclisation of geranylgeranyl pyrophosphate (**6**).^{41,44,47} A plausible mechanistic pathway for this cyclisation begins with the generation of tertiary allylic carbocation **7**, which cyclises to cyclohexene **8**. A sequence of two 1,2-hydride shifts produces allylic carbocation **9**, then a second cyclisation affords bicycle **10**. Two further 1,2-hydride shifts followed by loss of a proton with allylic transposition provides elisabethatriene, whose stereochemistry was recently revised by Fujimoto and co-workers.³³ Aromatisation and a sequence of two hydroxylations are next thought to occur, to generate catechol **12**.⁴⁶ Glycosylation (at either phenolic group) provides the family of *seco*-pseudopterosin natural products (**13**).⁴⁹ Dehydrogenation delivers a second family of natural products, the amphilectosins (**14**),⁴⁵ as a mixture of geometric isomers, which undergo the final cyclisation to provide the pseudopterosins (**15**).



Professor Michael Sherburn studied chemistry at the University of Nottingham, UK, and received his Ph.D. in 1991 with John A. Murphy. He then moved to Australia and worked as a post-doctoral fellow in the Research School of Chemistry, the Australian National University with Lewis N. Mander. He held academic positions at Massey University in New Zealand and the University of

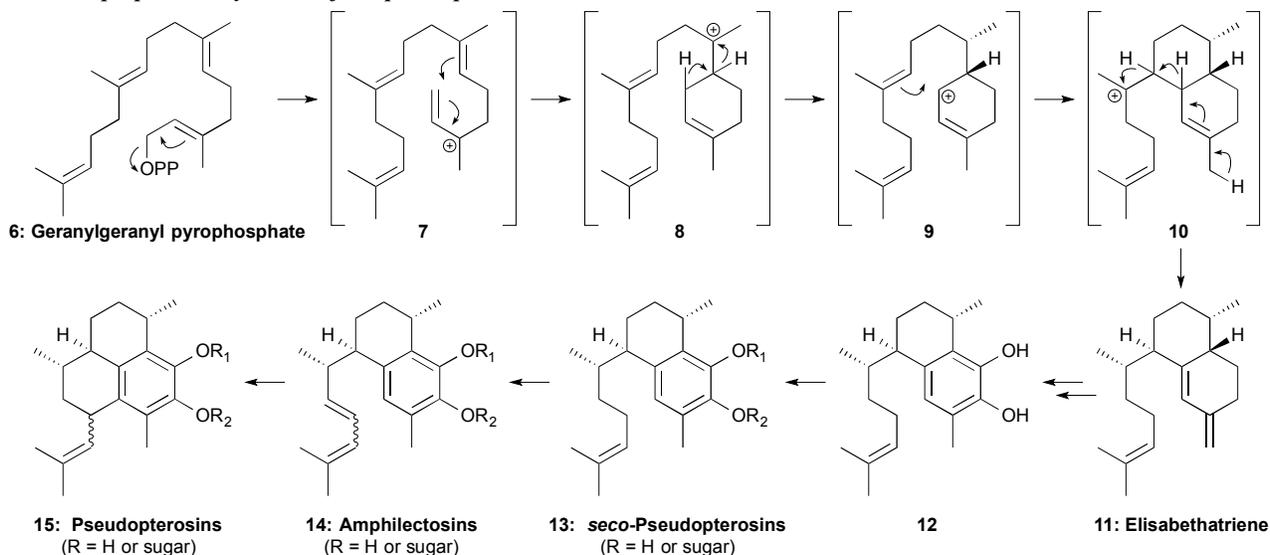
Sydney before being appointed at the Research School of Chemistry, ANU in 2002. His awards include the Le Fèvre Memorial Prize of the Australian Academy of Science (2006) and the A. J. Birch Medal of the RACI (2008).



Christopher Newton obtained a BSc majoring in chemistry (Honors, 1st class) in 2009, from Victoria University of Wellington, New Zealand. He commenced doctoral studies at the Australian National University in 2010, under the supervision of Professor Michael Sherburn, with his PhD conferred in 2014.

His research has focused on the synthesis of fundamental hydrocarbons and the application of the Diels–Alder reaction in target-oriented synthesis. In 2015 he will take up a postdoctoral position in the group of Professor Nicolai Cramer at the Ecole polytechnique fédérale de Lausanne, Switzerland.

A. Kerr's proposed biosynthesis of the pseudopterisins



B. Broka's 1988 total synthesis of pseudopterisins A

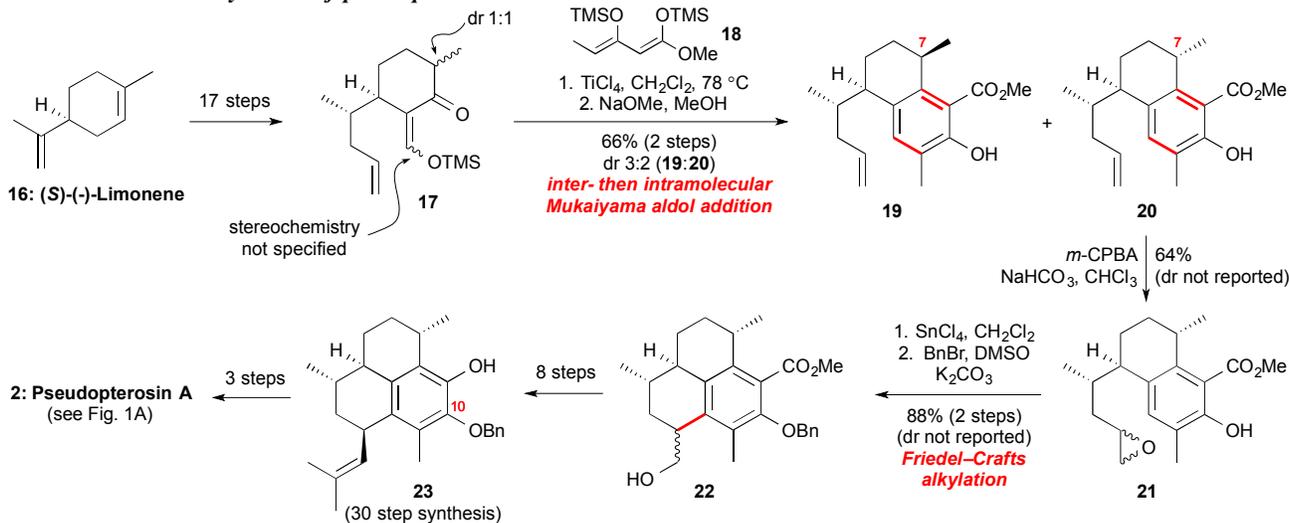


Fig. 2 (A) Kerr's proposed biosynthesis of the pseudopterisins and (B) Broka's 1988 total synthesis of pseudopterisins A.

4 Structure-goal approaches from terpenes

4.1 Pseudopterisins A, Broka, 1988

Broka and co-workers completed the first synthesis of a pseudopterisins in 1988 (Fig. 2B).⁵⁰ Their synthesis began with commercially available (S)-(-)-limonene (**16**), which was transformed into the precursor for the first annulation event, silyl enol ether **17**, in 17 steps.⁵¹ This compound, obtained as a diastereomeric mixture, was united with diene **18** in a one-pot [3+3] annulation, comprising an inter- followed by intramolecular Mukaiyama aldol reaction. Base-promoted aromatisation of the addition products provided the desired phenol **20** as the minor diastereoisomer (the major diastereoisomer was the C7 epimer, compound **19**). Following separation, bicycle **20** was transformed into diastereomeric epoxides **21**, and in a cyclisation reminiscent of the final step of

the pseudopterisins biosynthesis (and a strategy shared by many), epoxides **21** were subjected to a Friedel-Crafts alkylation facilitated by an excess of SnCl_4 . The resulting phenol was then protected as the corresponding benzyl ether to provide compound **22** in 88% yield over two steps. Conversion into the C10 *O*-benzyl protected A-F aglycone **23** (accessed in 30 steps total), followed by a glycosylation/deprotection sequence, delivered pseudopterisins A (**2**).

4.2 Pseudopterisins A and E, Corey, 1989

Only one year later, Corey and Carpino published a notably shorter total synthesis of the pseudopterisins A-F aglycone, requiring only 21 steps (Fig. 3).⁵² This would be the first of several pseudopterisins syntheses from the Corey group, and like Broka's inaugural synthesis, it utilises a terpene starting material, in this case (-)-neoisomenthol (**24**). The first cyclisation was achieved by way of an intramolecular aldol

reaction of diketone **26** (accessed in 4 steps from lactone **25**), yielding α,β -unsaturated ketone **27**. After conversion to alkyne **28** *via* a Mukaiyama aldol/oxidation sequence, the aromatic ring annulation to tricycle **29** was brought about by Michael addition. Although the mechanism of this step is not discussed, a closely related transformation reported by Deslongchamps⁵³ proposes addition of the enolate to the non-conjugated π -bond of the alkyne, thereby avoiding the highly strained allenic enolate intermediate that would arise from addition to the conjugated π -bond. Oxidation of phenol **29** to imine **30**, followed by hydrolysis to the *o*-quinone and reduction to the catechol completed the installation of the aromatic A ring. Interestingly, this approach and the most recent 2015 contribution¹⁴ are the only pseudopterosin syntheses that prepare the aromatic ring last. Such an approach is favourable since it avoids protecting the sensitive catechol functionality. Stereoselective introduction of the isobutenyl group was achieved in four steps utilising Wittig chemistry to provide the A–F aglycone (**3**), which could be chemoselectively tosylated at the C10 phenol group, thereby allowing subsequent elaboration into pseudopterosins A and E.

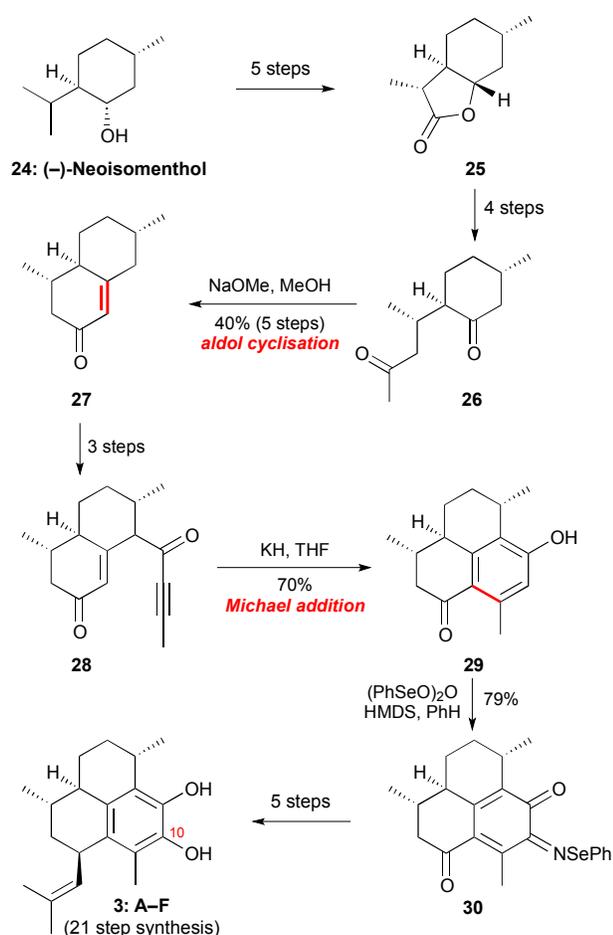


Fig. 3 Corey's 1989 total synthesis of pseudopterosin A and E.

4.3 Pseudopterosin A and E revisited, Corey, 1990

One year later, Corey published an improved synthesis of α,β -unsaturated ketone **27**, thus completing a formal synthesis of pseudopterosins A and E (Fig. 4).⁵⁴ Following a Knoevenagel condensation between (*S*)-citronellal (**31**) and dimethyl malonate, an FeCl₃-catalysed intramolecular ene reaction of diester **32** generated cyclohexane **33** in high yield and high diastereoselectivity. Chemoselective conversion into acyl chloride **34**, followed by Lewis acid-promoted cyclisation provided β -keto ester **35**. Ketone **27** was then intercepted after three additional steps, reducing the total step count from 10 to 8 steps, and increasing the overall yield from 9.7%^{52,55} to 28%.^{54,56}

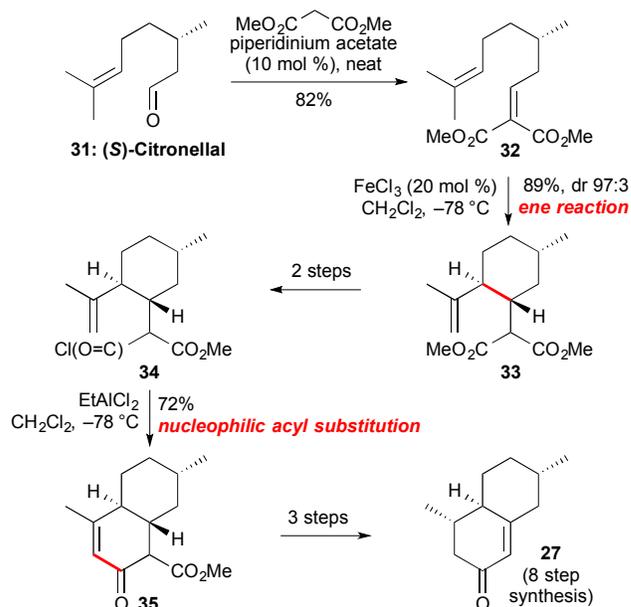


Fig. 4 Corey's 1990 formal synthesis of pseudopterosins A and E.

4.4 A–F Aglycone, Corey, 1998

In 1998, the Corey group published their third synthesis of the A–F aglycone, this time incorporating a new approach that enabled access to the target in an improved 16 steps.⁵⁷ Mono-*O*-benzylated-1,2-diketone **37** was synthesised *via* an intramolecular aldol condensation of diene **36**, which in turn was prepared through a seven-step sequence from (*S*)-limonene (Fig. 5A). Following silyl enol ether formation, aromatisation of the resultant 1,3-cyclohexadiene with MnO₂ delivered the protected amphilectosin **38**. A methanesulfonic acid-promoted intramolecular Friedel–Crafts alkylation generated the undesired diastereomer **39**. Parenthetically, the stereochemistry of structure **39** matches that of the pseudopterosin G–J aglycone, although this would not have been known at the time, as the G–J aglycone structure remained misassigned.⁹ Exchanging the silyl protecting group of precursor **38** for a mesylate altered the stereoselectivity of Friedel–Crafts cyclisation, giving the desired diastereomer **41**, which was globally deprotected over two steps to yield the A–F aglycone.

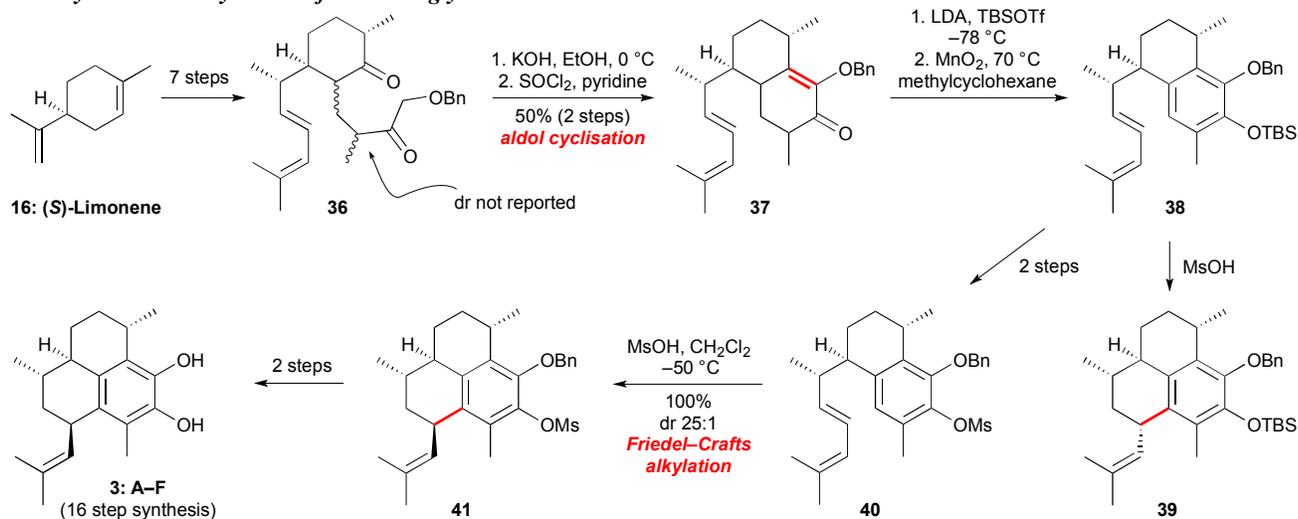
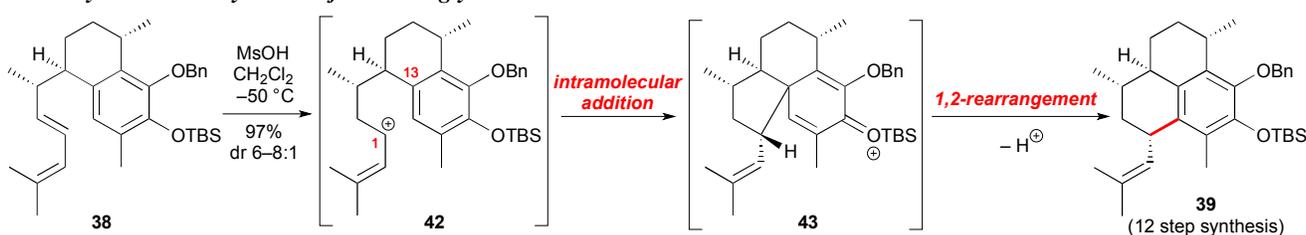
A. Corey's 1998 total synthesis of the A–F aglycone**B. Corey's 2000 total synthesis of the G–J aglycone**

Fig. 5 (A) Corey's 1998 total synthesis of the A–F aglycone, and (B) Corey's 2000 total synthesis of the G–J aglycone.

4.5 G–J Aglycone, Corey, 2000

Two years later, Corey published a follow up study in which the structure of the G–J aglycone was revised and its first total synthesis was described.¹⁰ ¹H NMR spectroscopic comparison of the natural product with intermediates in the Corey 1998 total synthesis (Fig. 5A) suggested that the stereochemistry of the G–J aglycone may match that of **39**, rather than – as originally proposed – the C7 epimer of the A–F aglycone. This was confirmed by the double deprotection of **39**, providing the G–J aglycone in a longest linear sequence of only 14 steps (Fig. 5B). The stereoselectivity observed in the cyclisation of silyl ether **38** is worthy of discussion. The reaction is believed to proceed firstly through protonation of diene **38** to form allyl cation **42**. Cyclisation then occurs between C1 and C13, to provide spiro-intermediate **43**, as a result of the stabilising electron donating effect of the silyl ether. A 1,2-rearrangement and proton loss provides the protected G–J aglycone in 97% yield and in a diastereomeric ratio in the 6:1–8:1 range. The ability to alter the diastereoselectivity of the cyclisation by tuning the electronic properties of the catechol represents a powerful approach to the pseudo-terpenes, and perhaps echoes the final stages of their biosynthesis.

4.6 A–F and K–L Aglycones, Kocienski, 2001

The most recent pseudo-terpenes aglycone syntheses utilising terpenes as starting materials were published in two back-to-back papers by the Kocienski group in 2001, and included a synthesis of the A–F aglycone, the putative G–J aglycone (not covered here), and the first synthesis of the K–L aglycone in enantioenriched form.^{39,58} The first annulation event of Kocienski's K–L aglycone synthesis incorporates a benzannulation procedure, initially developed in the labs of Dieter,⁵⁹ and Ila and Junjappa⁶⁰ (Fig. 6A). This reaction sequence begins with the nucleophilic addition of methylmagnesium chloride to (–)-isopulegol-derived ketone **45**, to yield a mixture of diastereomeric alcohols **46**. In the next step, addition of a large excess of $\text{BF}_3 \cdot \text{OEt}_2$ in MeOH resulted in cationic cyclisation, occurring with overall propane-1,3-dithiol expulsion and methanol addition (further discussion of the mechanism is provided by Kocienski⁵⁸). The aromatic annulation is accompanied by deprotection of the silyl ether. Implementation of their previously developed Friedel–Crafts approach¹⁹ to the final cyclisation proceeded by way of allyl sulfones **48**, and in good yield. Deprotection of methyl ether **49** intercepted an intermediate (in this case as a single enantiomer) from McCombie's 1990 synthesis^{61–63} (*vide infra*). The synthesis of the K–L aglycone was completed *via* slight modification to the oxidation procedure employed by

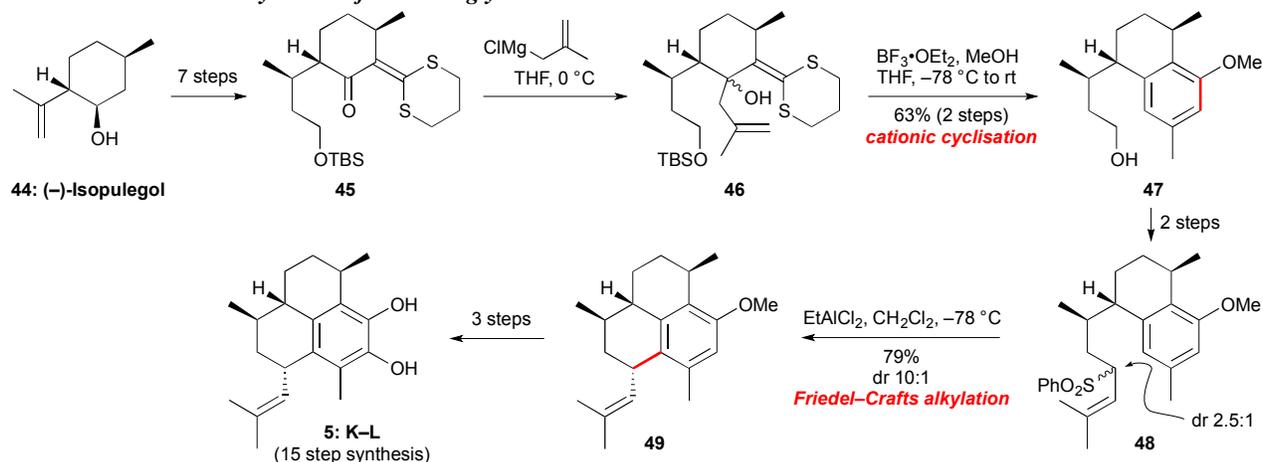
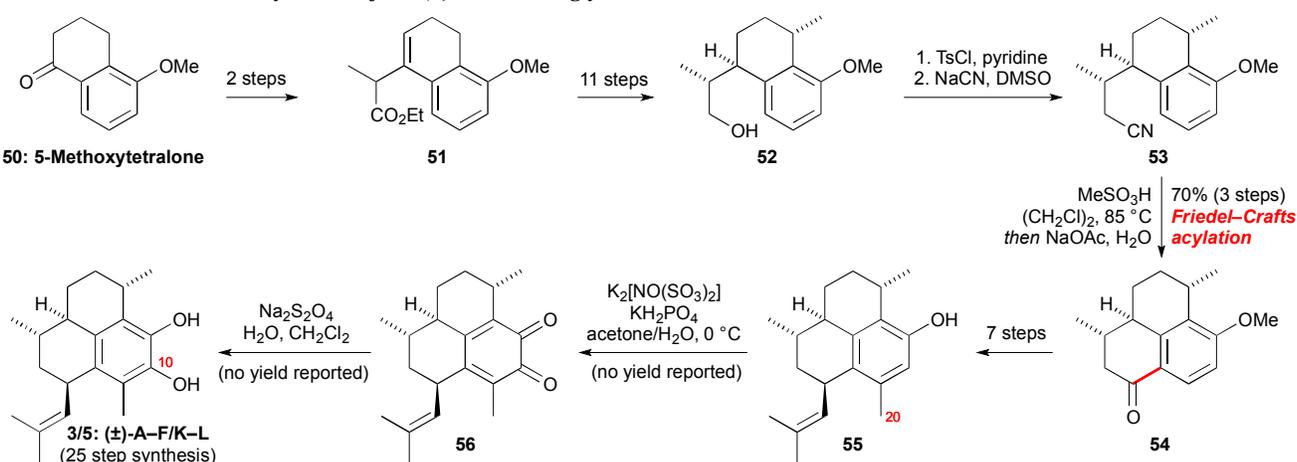
A. Kocienski's 2001 total synthesis of the K–L aglycone**B. McCombie's 1990 total synthesis of the (±)-A–F/K–L aglycones**

Fig. 6 (A) Kocienski's 2001 total synthesis of the K–L aglycone and (B) McCombie's 1990 total synthesis of the (±)-A–F/K–L aglycones.

McCombie, providing the target in a total of 15 steps. Kocienski's synthesis of the A–F aglycone (not shown) proceeded through the enantiomer of ketone **45**, which, due to the unavailability of (+)-isopulegol, required a different pathway to be devised (a general problem for many syntheses that begin with “chiral pool” starting materials). The annulation reactions, however, mirror those employed in the K–L aglycone synthesis.

5 Structure-goal approaches from aromatics

5.1 (±)-A–F/K–L Aglycones, McCombie, 1990

Moving away from terpenes as starting materials, McCombie's 1990 synthesis of the (±)-pseudopterosin A–F/K–L aglycones began from commercially available 5-methoxytetralone (**50**) (Fig. 6B).^{61–63} Ester **51** was accessed through a Reformatsky reaction/dehydration sequence, introducing the first stereocentre of the A–F/K–L aglycones. Following elaboration into tetralin **52** over 11 steps, nitrile **53** was then synthesised *via* one-carbon homologation, then annulation of the C ring was

achieved through an intramolecular Friedel–Crafts reaction. *In situ* hydrolysis of the imine led to ketone **54**. Seven more steps were required to introduce the isobutenyl group – stereoselectively – and the C20 methyl group, to access phenol **55**. Finally, introduction of the C10 phenolic group was achieved through a two-step sequence involving oxidation with Frémy's salt to give *o*-quinone **56** (*cf.* the oxidation sequence used by Corey in 1989, Fig. 3), followed by reduction to deliver a racemic mixture of the A–F/K–L aglycones.

5.2 A–F Aglycone, Buszek, 1995

Up until the most recent 2015 contribution (*vide infra*), Buszek's 1995 total synthesis of the pseudopterosin A–F aglycone⁶⁴ (Fig. 7A) was the only synthesis that employed a Diels–Alder reaction, which is surprising given its utility in efficiently generating six membered rings. The Diels–Alder reaction does, however, make an appearance in a number of studies *towards* the pseudopterosins,^{16,20,26,27} as well as in the synthesis of many natural products closely related to the pseudopterosins.^{65–74}

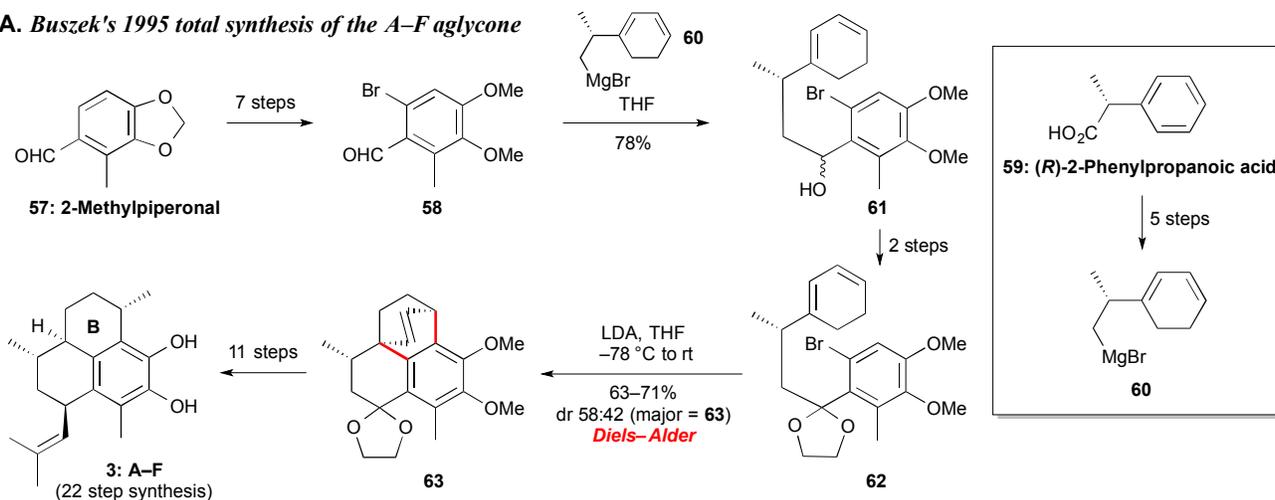
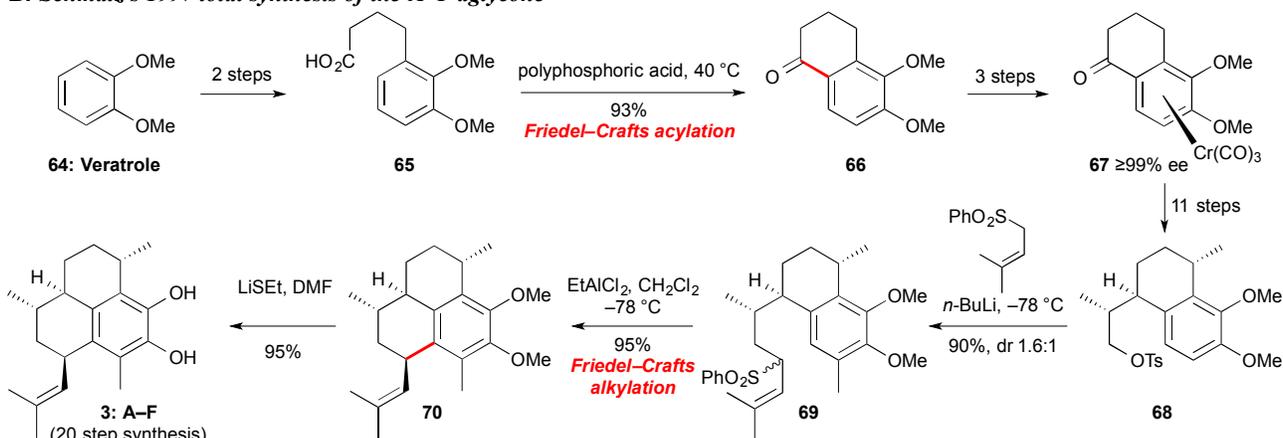
A. Buszek's 1995 total synthesis of the A–F aglycone**B. Schmalz's 1997 total synthesis of the A–F aglycone**

Fig. 7 (A) Buszek's 1995 total synthesis of the A–F aglycone, and (B) Schmalz's 1997 enantioselective total synthesis of the A–F aglycone.

In the Buszek group's synthesis, 2-methylpiperonal-derived aldehyde **57**⁷⁵ underwent nucleophilic addition with 1,3-cyclohexadiene-containing Grignard reagent **60**, synthesised in 5 steps from (*R*)-2-phenylpropanoic acid (**59**), furnishing diastereomeric alcohols **61**. Oxidation and protection yielded ketal **62**. Low temperature benzyne generation led to *in situ* intramolecular Diels–Alder reaction, which proceeded in good yield but with poor diastereoselectivity. Notably this represents one of the earliest examples of an intramolecular aryne Diels–Alder cycloaddition,⁷⁶ and moreover, is the first intramolecular example involving a non-aromatic partner. Despite accessing the pseudopterosin tricyclic framework relatively quickly (longest linear sequence of 11 steps), 11 additional steps were required to reach the A–F aglycone, the majority of which were focused on manipulation of the bridging –CH=CH– generated in the cycloaddition reaction.

5.3 A–F Aglycone, Schmalz, 1997

The first enantioselective synthesis of a pseudopterosin aglycone was completed in 20 steps by Schmalz and co-workers in 1997 (Fig. 7B).⁷⁷ Their synthesis began with

alkylation of veratrole (**64**). An intramolecular Friedel–Crafts acylation of acid **65** yielded ketone **66**,⁷⁸ which was subjected to a Corey–Bakshi–Shibata reduction, followed by Cr(CO)₃ complexation of the aromatic ring and reoxidation of the alcohol, to provide complexed dimethoxy tetralone **67** in $\geq 99\%$ ee. Exploiting the benzylic activation and π -facial discrimination imparted by the Cr(CO)₃ group, three of the four pseudopterosin aglycone stereocentres were introduced, followed by oxidative decomplexation of the Cr(CO)₃ group. Inspired by Kocienski's strategy in studies towards the pseudopterosins,¹⁹ tosylate **68** was alkylated with lithiated phenylprenylsulfone to provide the final cyclisation precursor **69**, as an inconsequential mixture of diastereomers. Lewis acid-promoted intramolecular Friedel–Crafts alkylation afforded dimethoxy catechol **70**, a deprotection away from the A–F aglycone.

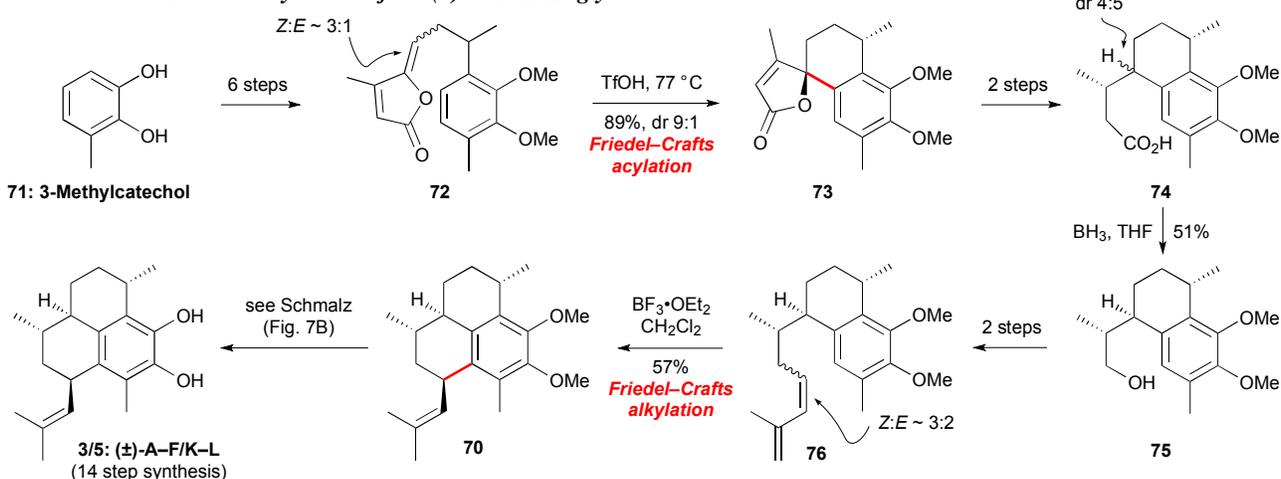
5.4 (±)-A–F/K–L Aglycones, Harrowven, 2004

In 2004, the Harrowven group synthesised a racemic mixture of the pseudopterosin A–F/K–L aglycones⁷⁹ in 14 steps from 3-methylcatechol (**71**)⁸⁰ (Fig. 8A). Lactones **72** were accessed in six steps as a mixture of geometrical isomers that, when

warmed in triflic acid, yielded spiro lactone **73** as the major diastereoisomer. Sequential stereoselective hydrogenation then benzylic C–O hydrogenolysis gave diastereomeric carboxylic

Conversion into the acid chloride set the scene for intramolecular Friedel–Crafts acylation, to yield ketone **81**. Elaboration into carboxylic acid **82** involved a second olefin

A. Harrowven's 2004 total synthesis of the (±)-A–F/K–L aglycones



B. RajanBabu's 2011 enantioselective total synthesis of the G–J aglycone

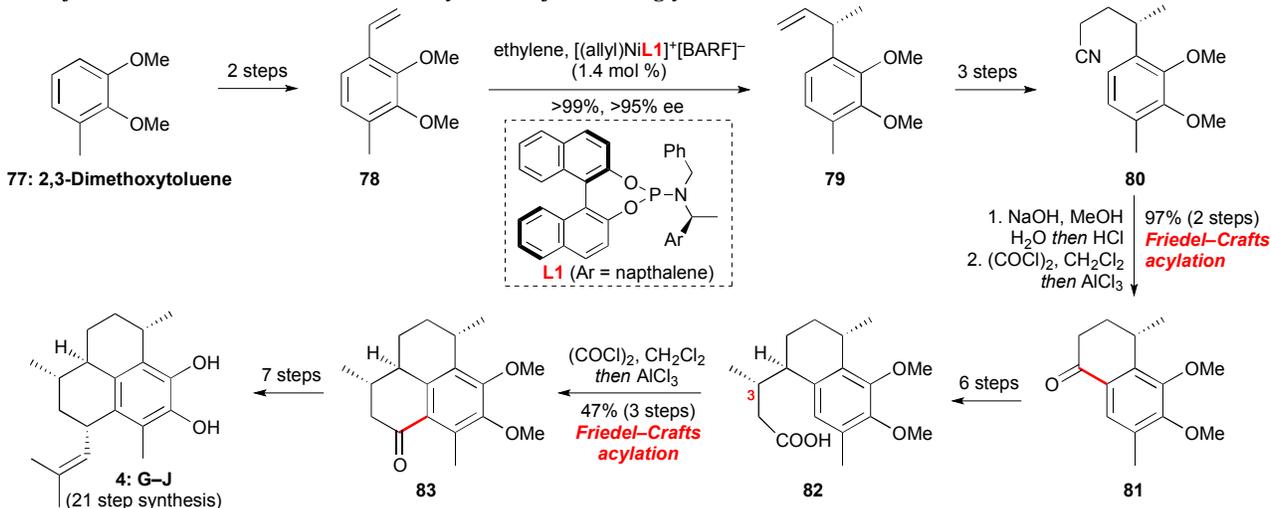


Fig. 8 (A) Harrowven's 2004 total synthesis of the (±)-A–F/K–L aglycones and (B) RajanBabu's 2011 enantioselective total synthesis of the G–J aglycone.

acids **74**, which could only be separated after borane reduction, providing primary alcohol **75** in 51% yield. Despite being an intermediate in Schmalz's 1997 synthesis (as a precursor to **68** in Fig. 7B), the Harrowven group developed a different approach to complete their synthesis, involving an oxidation/olefination/Friedel–Crafts cyclisation sequence.

5.5 A–F and G–J Aglycones, RajanBabu, 2011

The 2011 RajanBabu synthesis of the A–F and G–J aglycones is an enantioselective one, utilising a series of highly selective olefin hydrovinylation reactions (Fig. 8B).⁸¹ The synthesis began with the conversion of 2,3-dimethoxy toluene (**77**) into styrene analogue **78**, followed by a highly enantioselective nickel-catalysed hydrovinylation. Alkene **79** was then converted into one-carbon-homologated nitrile **80** over 3 steps.

hydrovinylation reaction, which also installed the stereocentre at C3. The final cyclisation was also brought about through an intramolecular Friedel–Crafts acylation of an acid chloride, to provide **83** (an intermediate from Buszek's 1995 synthesis of the A–F aglycone). RajanBabu went on to convert ketone **83** into the G–J aglycone *via* a six step sequence that incorporated a third hydrovinylation reaction. Although the synthesis of tricyclic ketone **83** constituted a formal synthesis of the A–F aglycone, RajanBabu developed a shorter – although less selective – three step route to the A–F aglycone.

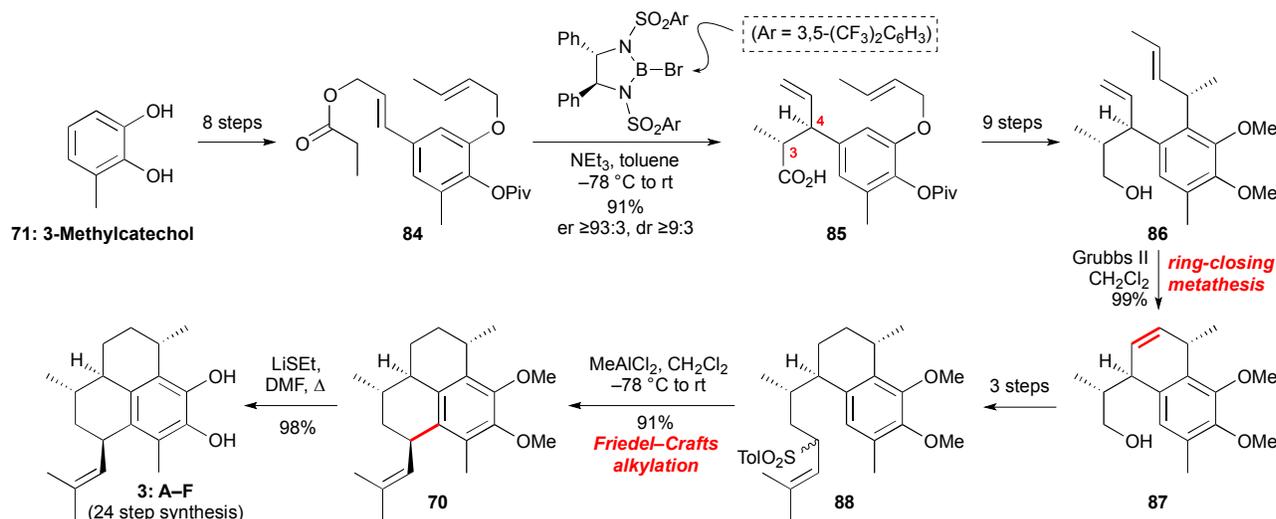
5.6 A–F Aglycone, Cooksey and Kocienski, 2012

The most recent structure-goal approach to a pseudopterosin natural product was published by Cooksey and Kocienski in 2012 (Fig. 9A).⁸² Ester **84**, accessed in 8 steps from 3-

methylcatechol (**71**), was subjected to an enantioselective variant of the Ireland–Claisen rearrangement originally developed by Corey,⁸³ installing both the C3 and C4

In 2015 the Sherburn group published a synthesis of the *ent*-G–J aglycone¹⁴ that, rather than employing a starting material which closely resembles a portion of the target, instead

A. Cooksey and Kocienski's 2012 total synthesis of the A–F aglycone



B. Sherburn's 2015 total synthesis of the *ent*-G–J aglycone

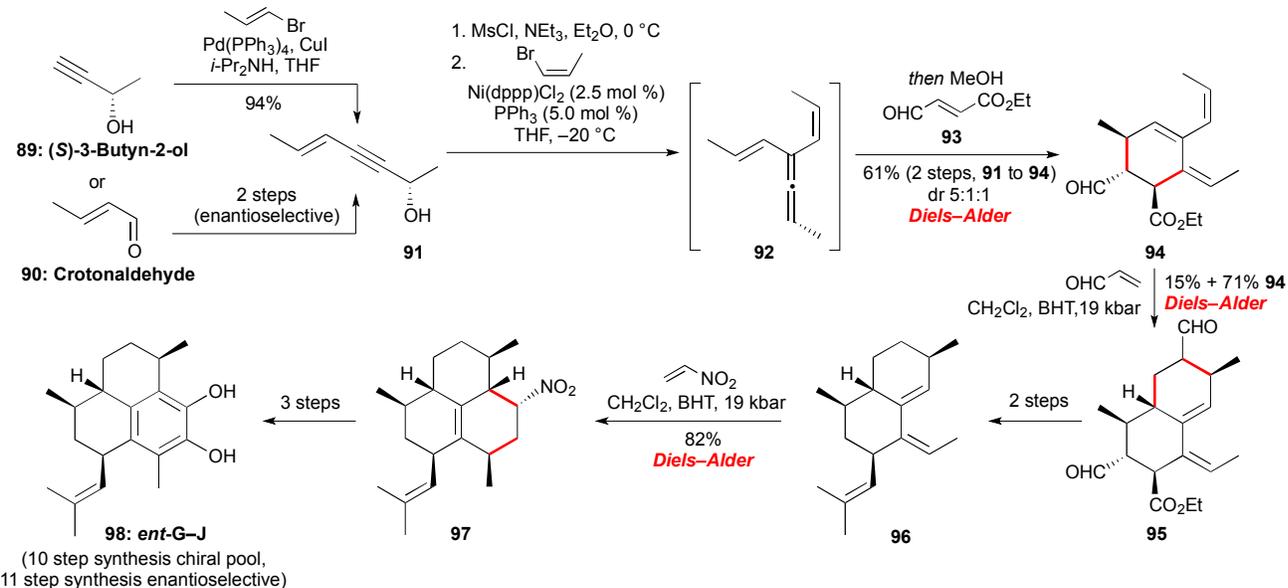


Fig. 9 (A) Cooksey and Kocienski's 2012 total synthesis of the A–F aglycone and (B) Sherburn's 2015 enantioselective total synthesis of the *ent*-G–J aglycone.

stereocentres. Acid **85** was then elaborated over nine steps into alcohol **86**, which was subjected to catalytic ring-closing metathesis to provide cyclohexene **87**. Hydrogenation intercepted an intermediate common to both Schmalz's 1997 (precursor to **68**, Fig. 7B) and Harrowven's 2004 (alcohol **75**, Fig. 8A) syntheses. As with Schmalz's work, the synthesis was completed using the alkylation strategy originally developed by Kocienski, in this case by way of tolylsulfonyl derivative **88**.

6 Transform based approach

6.1 *ent*-G–J Aglycone, Sherburn, 2015

employed a triple Diels–Alder sequence from a substituted 1,1-divinylallene⁸⁴ to quickly construct the tricyclic framework. Thus, enantioenriched propargylic alcohol **91** [accessed in one step from (*S*)-3-butyn-2-ol (**89**), or in a two step catalytic enantioselective route from crotonaldehyde (**90**)], was mesylated then engaged in a Ni(0)-catalysed cross-coupling with the Grignard reagent derived from (*Z*)-propenyl bromide. This generated the key, chiral cross-conjugated hydrocarbon intermediate **92** with retention of enantiopurity, which reacted *in situ* with commercially available dienophile **93** stereoselectively, and at the more reactive (*E*)-ene-allene site. This cycloaddition proceeds in a diene-transmissive sense,⁸⁵

generating a new semi-cyclic diene **94** for a subsequent Diels–Alder reaction, this time with acrolein as dienophile, which approaches from the diene face opposite to the allylic methyl

a direct consequence of the previous Diels–Alder reaction, thereby permitting a smooth synthetic journey.

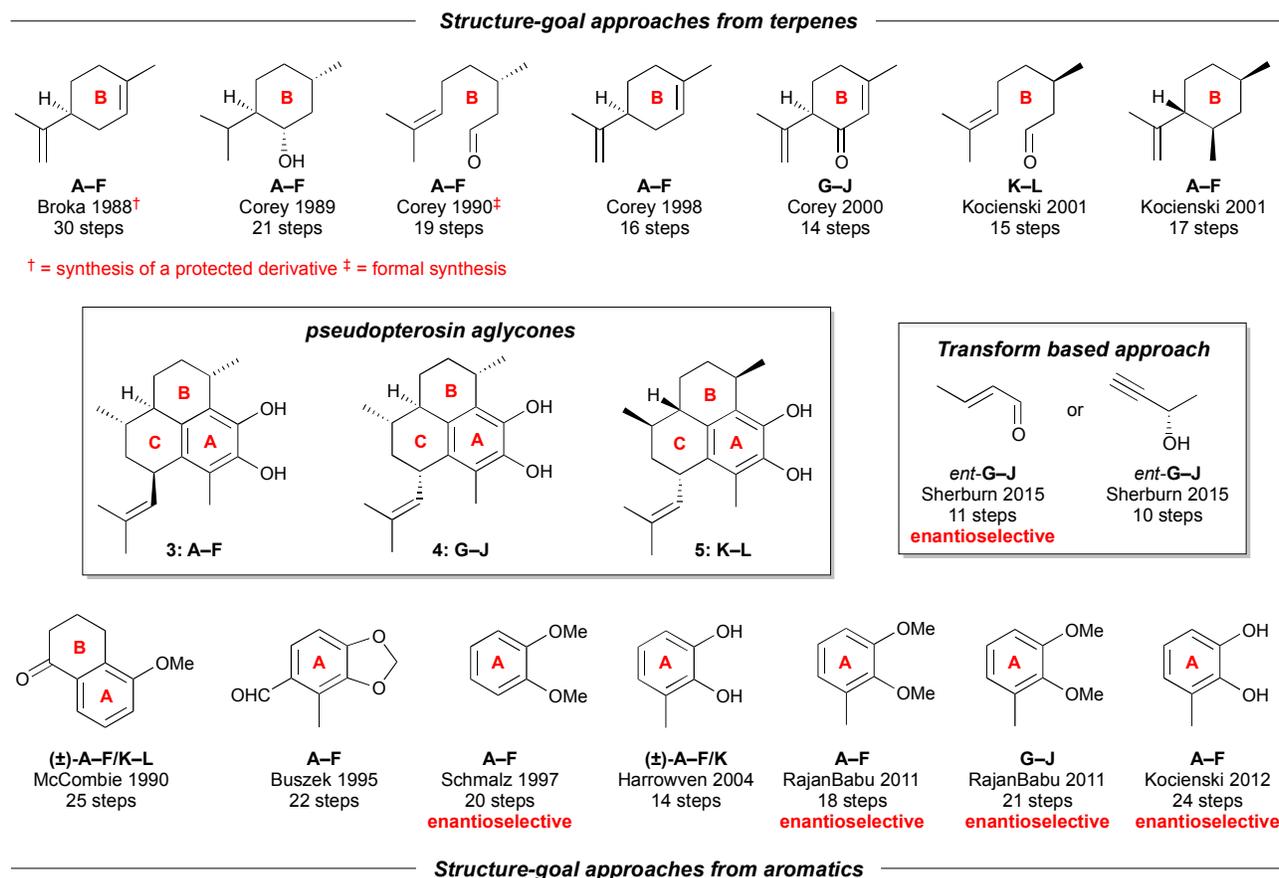


Fig. 10 Summary of the total and formal syntheses of the pseudopterosin aglycones.

group. Once again, the cycloaddition proceeds with diene transmission and a new diene **95** is generated. (The low conversion in this second cycloaddition was necessary to limit further reaction of **95** with acrolein.) Following deformylation and elaboration of the butenyl side chain, a third Diels–Alder reaction was performed on diene **96** with nitroethylene, which served as a ketene equivalent dienophile. Oxidation to the aromatic ring provided the *ent*-G–J aglycone (**98**) in 10 steps from chiral pool starting materials, or 11 steps *via* the catalytic enantioselective route from crotonaldehyde, representing the most step economic synthesis of a pseudopterosin aglycone to date.

This most recent, transform-based approach differs markedly from the previous syntheses. It involves the formation of more C–C bonds than all other routes, more rings than most other routes, employs smaller building blocks than most other syntheses and yet it exhibits the shortest step count. The concise nature of this approach is a consequence of the diene-transmissive cycloaddition behaviour *programmed into* the divinyl allene precursor. Thus, no additional steps are needed to set up a diene for subsequent cycloaddition: each is produced as

7 Conclusions

A summary of the 15 total and formal syntheses of the pseudopterosin aglycones is provided in Fig. 10, which identifies the group, year of publication, step count, starting material and class of approach. All but one deploy terpene or aromatic starting materials, which are elaborated into the natural product through successive annulation sequences. Intriguingly, all terpene-based approaches employ a starting material that maps onto the B ring of a pseudopterosin. Perhaps worthwhile opportunities remain for researchers who can map terpene-based starting materials onto the C ring of the pseudopterosins.

Analysis of the metrics listed in Fig. 10 reveal that enantioselective syntheses usually require more steps, terpene-based approaches are, generally speaking, more step economic than those commencing with aromatic starting materials, and later syntheses are often lower in step count than earlier ones.

This impressive body of work, from some of the very best exponents of the art of total synthesis over a period of more than 25 years, has elicited a much deeper understanding of

pseudopterosin biosynthesis and has stimulated the development of new reactions, synthetic strategies and tactics. We hope that this survey will serve to inspire the reader to develop even better pseudopterosin total syntheses.

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9 Notes and references

Research School of Chemistry, Australian National University, Canberra, ACT, 2601, Australia. E-mail: michael.sherburn@anu.edu.au

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