Natural Product Reports

REVIEW

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Cite this: *Nat. Prod. Rep.*, 2019, **36**, 289

2-Formylpyrrole natural products: origin, structural diversity, bioactivity and synthesis

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Covering: up to April 2018

2-Formylpyrroles are ubiquitous in nature, arising from the non-enzymatic Maillard reactions of amines and sugars. Often confused for secondary metabolites, these Maillard products display interesting biological activities including hepatoprotective, immunostimulatory, antiproliferative and antioxidant effects. This review presents all 2-formylpyrrole natural products reported to date and identifies structural sub-classes for their categorisation. The origin, biological activity and chemical syntheses of these natural products are discussed herein.

Received 13th June 2018

DOI: 10.1039/c8np00051d

rsc.li/npr

1. Introduction

5-Hydroxymethylpyrrole-2-carbaldehydes (Fig. 1), sometimes referred to as 2-formylpyrroles or pyrralines, have been isolated from a large array of natural sources,[1,2] as well as traditional medicine preparations[3] and cooked foods.[4,5] Their presence in various thermally-processed products reveals their likely origin — the non-enzymatic Maillard reaction — and to date no enzymatic biosynthesis has been proposed for these compounds. Regardless of their non-metabolic origin, these compounds exhibit a range of valuable bioactivities including hepatoprotective,[6] immunostimulatory,[7] antiproliferative[8] and antioxidant effects.[1,9,10] Furthermore, certain members of this compound family possess highly unique and complex structures, providing attractive targets for total synthesis and the development of novel synthetic methodologies.

This review aims to highlight the interesting biological properties of 2-formylpyrroles and the synthetic methods

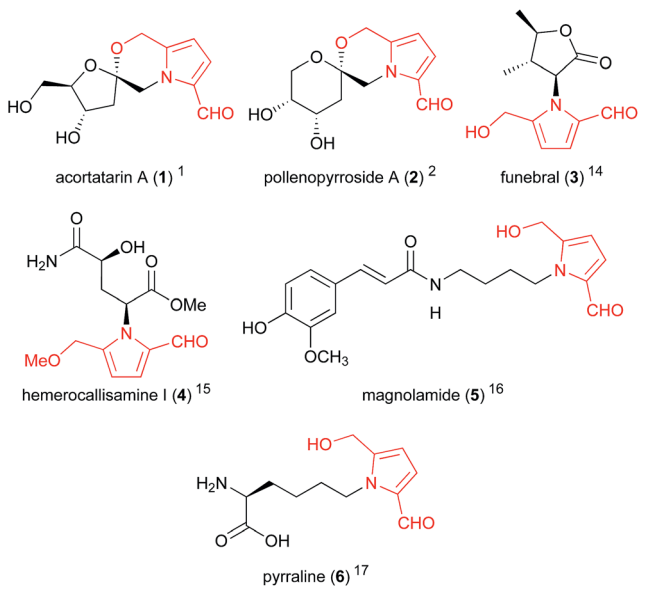

Fig. 1 Representative 2-formylpyrroles (5-hydroxymethylpyrrole-2-carbaldehyde system highlighted in red).

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developed to access them. One particular 2-formylpyrrole, the advanced glycation end-product pyrraline (**6**), will not be discussed here as it has been reviewed recently.[11] Acortatarin A (**1**) was reviewed previously by Butler and Aponick,[12] while a recent review by Shahzad and co-workers[13] provides a detailed account of the synthetic approaches to acortatarin A (**1**) and related pyrrolomorpholine spiroketals. These compounds will be discussed herein within the wider context of 2-formylpyrrole natural products.

2. Non-enzymatic origin

It has been established that 2-formylpyrroles form in biological systems,[18] yet no enzymatic biosynthesis has been proposed for the 5-hydroxymethylpyrrole-2-carbaldehyde ring system. Rather, it is accepted that these compounds arise from the condensation of amines with sugars in what are commonly referred to as Maillard or browning reactions.[19,20] This hypothesis stems from the first reports of 2-formylpyrroles in which these compounds were isolated directly from reaction mixtures of reducing sugars and amines in 1970.[21,22] Kato and Fujimaki characterised pyrroles **13–15** as the reaction products of D-glucose (**7**) and methylamine (**10**), ethylamine (**11**) or butylamine (**12**) respectively (Scheme 1).[21] This reaction was reproducible with hexoses D-galactose (**8**) and D-fructose (**9**), albeit with reduced yields.

It is widely proposed that 2-formylpyrroles **26** arise from the condensation of amines with 3-deoxy-D-glucosone (3-DG) (**19**) (Scheme 2).[23] 3-DG (**19**) is an intermediate in many Maillard reaction pathways and is a degradation product of Amadori compounds, which in turn form by condensation of glucose (**7**) with amines.[20,24,25] A number of plausible mechanisms exist for the formation of 2-formylpyrroles **26** from 3-DG (**19**). It has been suggested that this process is initiated by further dehydration of 3-DG (**19**) to enone **20** (Scheme 2).[23] Keto–enol tautomerisation, followed by conjugate addition of an amine affords hemiaminal **22**, which undergoes elimination of water. 5-*exo*-Trig cyclisation gives rise to another hemiaminal species **25**, which undergoes elimination of water to form the aromatic pyrrole ring system.[26]

This non-enzymatic synthesis from sugars is quite distinct from most characterised biosynthetic pathways leading to pyrroles, which involve amino acid (glycine, proline, serine, threonine, and tryptophan) and dicarboxylic acid (malonate, oxaloacetate, and succinate) precursors.[27] It should however be noted that a unique pyrrole biosynthesis from fructose-6-phosphate (**27**) was identified by Lautru and co-workers in 2012, operative in *Streptomyces ambofaciens* (Scheme 3).[28] 4-Acetamidopyrrole-2-carboxylate (**36**) was established as a biosynthetic precursor to congocidine (**37**), a DNA minor groove binder of the pyrrolamide family of natural products. The proposed biosynthetic pathway for 4-acetamidopyrrole-2-

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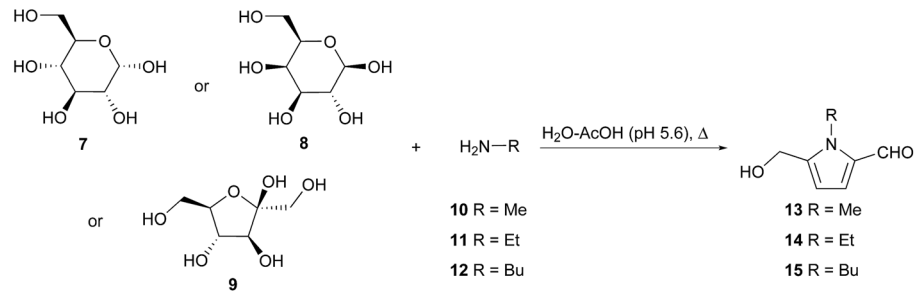
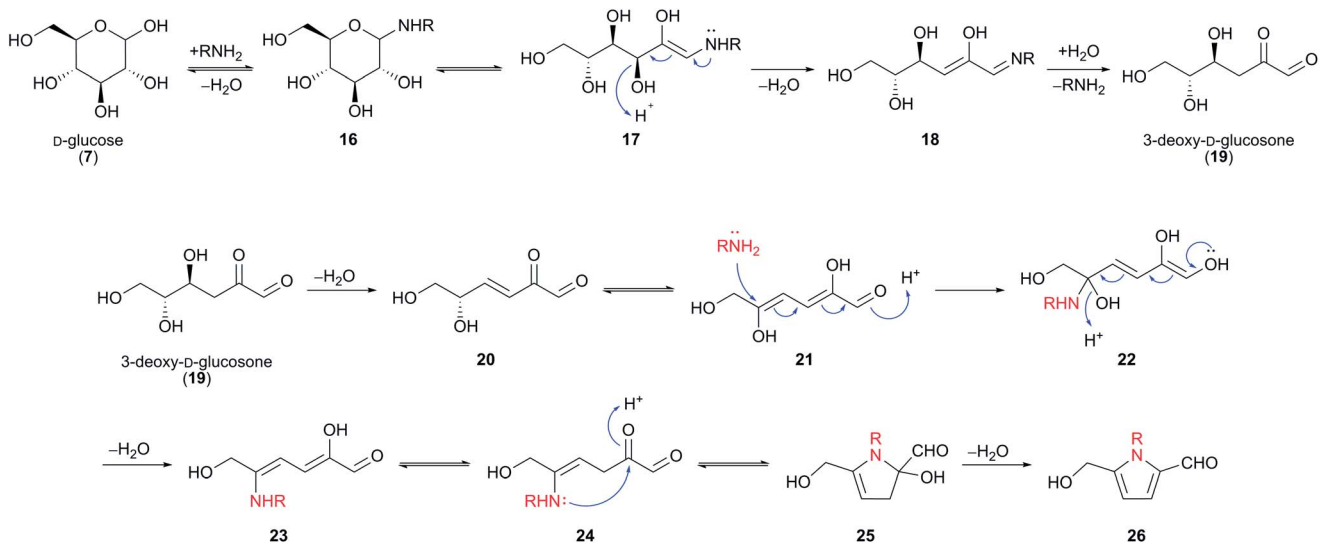
Daniel Furkert is a Senior Research Fellow at The University of Auckland, leading Professor Brimble's natural product synthesis and medicinal chemistry group in the School of Chemical Sciences. After obtaining his undergraduate and doctoral degrees at The University of Auckland, he carried out postdoctoral fellowships in the total synthesis of azaspiracid at Oregon State University (USA), and medicinal chemistry of novel opioid receptor ligands at the University of Bath (UK). He returned to New Zealand take up his current role in 2010, where his current interests include asymmetric synthesis and medicinal chemistry applications of natural products, novel chemical reactivity and drug discovery.

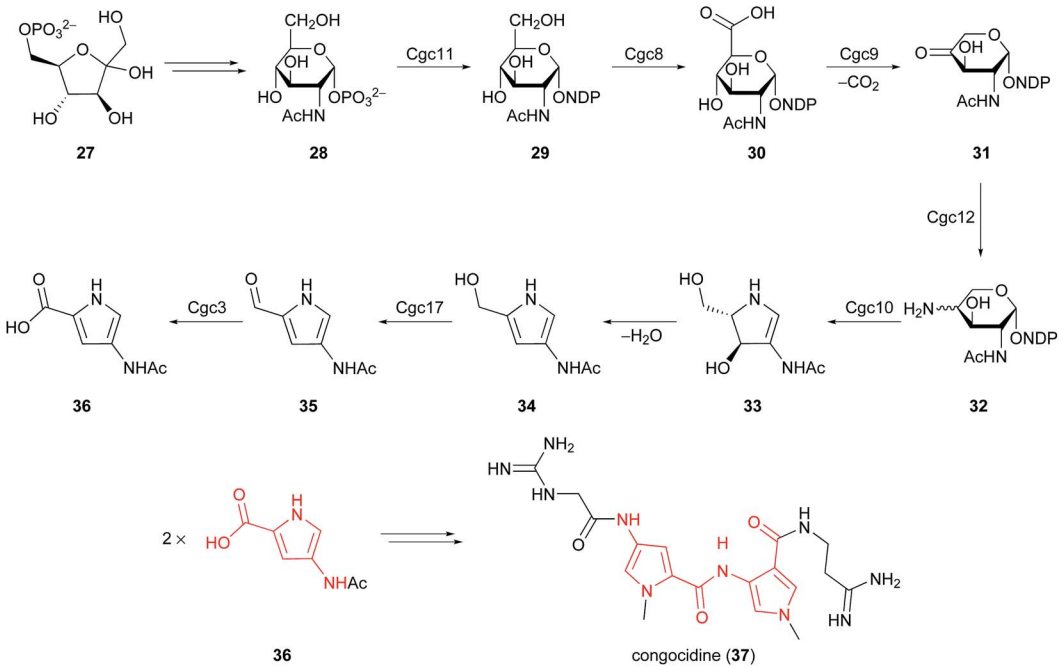
Margaret Brimble is a Fellow of the Royal Society (London) and a Distinguished Professor at the University of Auckland where her research program focuses on the synthesis of bioactive natural products and peptides. She has published >460 papers, 65 reviews, holds 30 patents, won the 2018 RSC Sosnovsky Award, 2016 Marsden Medal, 2012 Rutherford Medal (NZ top science award), the 2010 RSC Natural Products Award, named an IUPAC Distinguished Women in Chemistry (2015) and L'Oreal-UNESCO Women in Science laureate for Asia-Pacific, and conferred the Queen's Honour CNZM. She is Past-President of IUPAC Organic and Biomolecular Division III, co-Founder of cancer vaccine company SapVax, Associate Editor for Organic and Biomolecular Chemistry, and Past-President of the International Society of Heterocyclic Chemistry.



Scheme 1 Synthesis of 2-formylpyrroles from amine and hexose reducing sugar mixtures by Kato and Fujimaki.



Scheme 2 Proposed mechanism for the formation of 2-formylpyrroles **26** from amines and D-glucose (**7**), *via* 3-deoxy-D-glucosone (**19**).



Scheme 3 Proposed biosynthesis of 4-acetamidopyrrole-2-carboxylate (**36**) from fructose-6-phosphate (**27**) in *Streptomyces ambofaciens*.

carboxylate (**36**) involves enzymes and precursors from carbohydrate metabolism. The conversion of 4-aminopentose **32** into pyrroline **33** was attributed to Cgc10, an enzyme that resembles a glycosyltransferase. Spontaneous dehydration and subsequent oxidation by a putative alcohol dehydrogenase, Cgc17, delivers 2-formylpyrrole metabolite **35** *en route* to 4-acetamidopyrrole-2-carboxylate (**36**). This biosynthetic pathway was later extended to the pyrrolamides distamycin and disgocidine in *Streptomyces netropsis* DSM40846.[29] It is therefore evident that biosynthetic pathways exist for the conversion of carbohydrates into 2-formyl and 2-carboxylpyrroles, and it remains to be seen whether similar biosynthetic pathways will be characterised for 5-hydroxymethylpyrrole-2-carbaldehydes.

3. Structural diversity and bioactivity

2-Formylpyrroles appear frequently in the natural products isolation literature. The sources from which these compounds have been isolated are of limited significance, as no evidence exists for a biosynthetic pathway for these compounds. As such, details of isolation will be minimal, primarily serving to illustrate the ubiquity of 2-formylpyrroles in nature. This section instead highlights compounds with interesting biological activities and provides an overview of the structural diversity across this compound family. Compounds have been organised into three broad categories according to the type of amine from which they arise: amino acid, biogenic amine or amino sugar.

3.1. 2-Formylpyrroles derived from amino acids

Compounds which incorporate proteinogenic amino acids represent a major sub-class of 2-formylpyrroles (Fig. 2). Their prevalence reflects the ubiquity of the amino acids from which they arise. As an example of this prevalence, phenylalanine-derived lactone **38** has been isolated from flue-cured tobacco,[30,31] fruit (*Celastrus orbiculatus* Thunb. (Celastraceae),[32] *Morus alba*[33]), fungi (*Xylaria nigripes*[34]) and actinobacteria

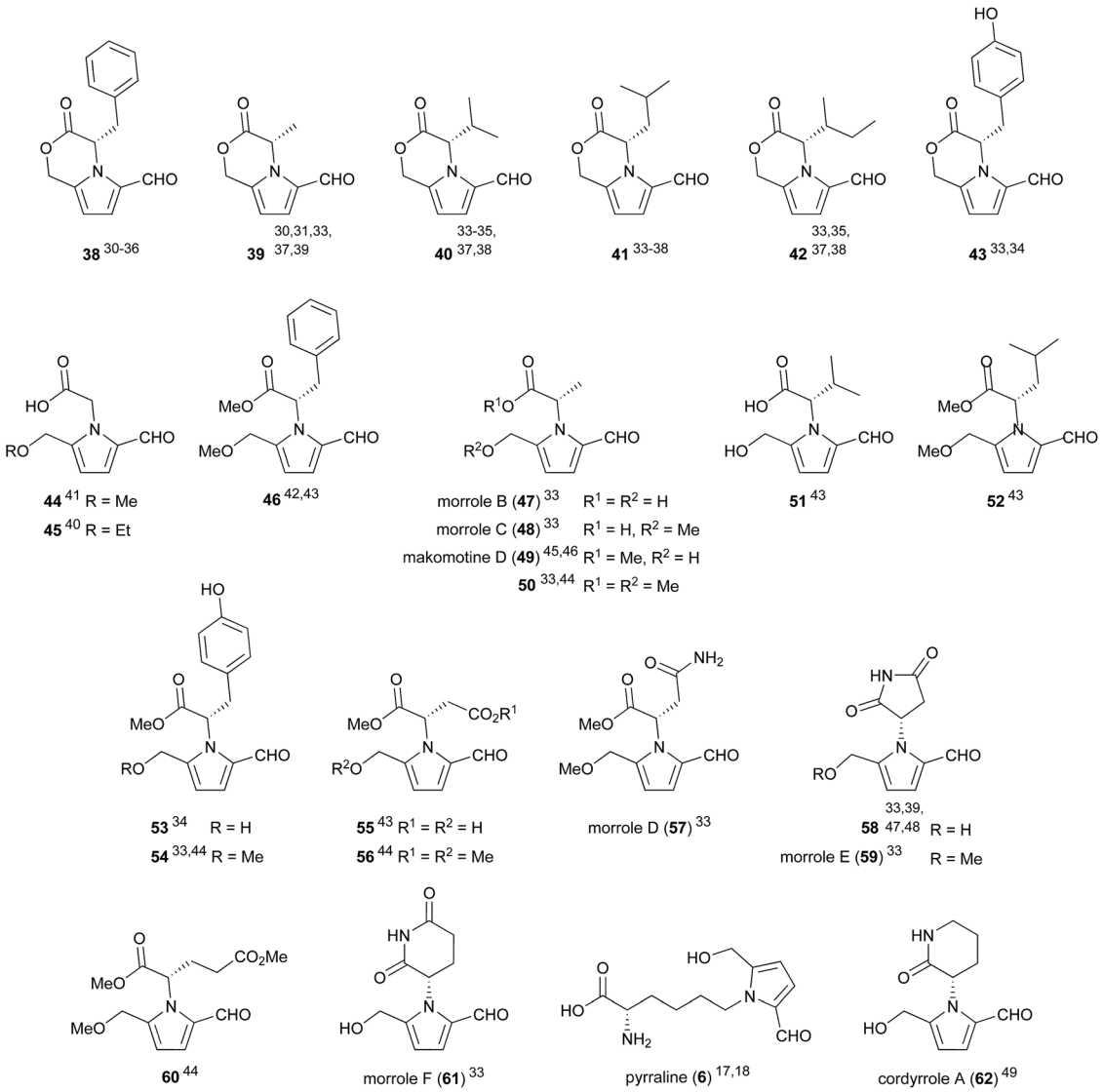


Fig. 2 2-Formylpyrroles derived from proteinogenic amino acids.

(*Jishengella endophytica* 161111,[35] *Streptomyces albospinus* RLe7 (ref. 36)).

Some notable compounds within this 2-formylpyrrole subclass are tyrosine derivative **43** and alanine derivative **50** which inhibit porcine pancreatic lipase by 70% and 40% respectively at 100 μM.[33] In a separate report, cordyrrole A (**62**) was also shown to inhibit porcine pancreatic lipase at 100 μM.[49] Pancreatic lipase is a target of interest for the development of anti-obesity treatments. Makomotine D (**49**) has been shown to induce quinone reductase (QR) activity thus enhancing carcinogen detoxification, with a concentration of 43.1 μM required to double QR activity.[46] In the same report, makomotine D (**49**) was shown to possess hydroxyl radical scavenging ability with an ED_{50} (concentration for hydroxyl radical scavenging by 50%) of 16.7 μM.

A small number of 2-formylpyrroles comprising unnatural amino acids have also been reported (Fig. 3). Funebral (**3**) and its Schiff base funebrine (**63**) were isolated from *Quararibea funebris*, a flowering tree native to Mexico.[14,50] The plant is used in traditional medicine as a cough remedy, antipyretic, and to control menstrual disorders and psychopathic fears,[51] although the bioactivity of funebral (**3**) and funebrine (**63**) has yet to be evaluated. γ-Hydroxyisoleucine, the amino acid incorporated in these two compounds, was isolated alongside funebrine (**63**).[50]

Homoserine lactone derivative **64** was isolated from 10 day-old *Pisum sativum* seedlings in 1987.[52] The absolute configuration of lactone **64**, which corresponds to D-homoserine lactone, was confirmed by total synthesis. The unusual D-homoserine moiety was proposed to arise from opine biosynthetic pathways. Pyrrole **64** was found to inhibit trigonelline-induced cell cycle arrest in G_2 phase with an ED_{50} of 0.5 μM, signifying the first chemically characterised substance to override hormonally induced cellular arrest in complex tissues. Notably, the synthesised (*S*)-enantiomer of pyrrole **64** was shown to be inactive.

Hemerocallisamine I (**4**) was isolated from *Hemerocallis fulva* var. *kwanso*, *H. flava*, and *H. minor* (daylily flowers) by Matsuda and co-workers in 2014 and again in 2016.[15,53] Originally assigned as (2*R*,4*R*)-**4** by X-ray crystal structure, the structure of hemerocallisamine I was later revised to the enantiomer (2*S*,4*S*)-**4** by total synthesis,[54] suggesting hemerocallisamine I (**4**) arises from L-γ-hydroxyglutamine metabolites in *Hemerocallis*. A variety of L-glutamine-based metabolites have been isolated from *Hemerocallis*,[55,56] some of which inhibit αβ42 aggregation and accelerate neurite outgrowth in PC12 cells, signifying their potential as novel therapies for Alzheimer's disease.[53] Hemerocallisamine I (**4**), however, was shown to lack any such neurological activity.

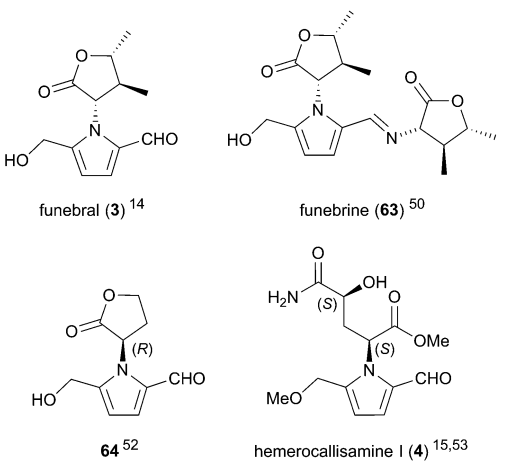


Fig. 3 2-Formylpyrroles derived from non-proteinogenic amino acids.

3.2. 2-Formylpyrroles derived from biogenic amines

Amino acid decarboxylation products, commonly referred to as biogenic amines, can arise from both the enzymatic decarboxylation of amino acids, as well as the Strecker degradation of amino acids with reducing sugars.[20,57] The most commonly encountered 2-formylpyrroles within this sub-class are those arising from γ-aminobutyric acid (GABA), the decarboxylation product of glutamic acid (pyrroles **65–75**, Fig. 4). 4-(2-Formyl-5-(hydroxymethyl)-1*H*-pyrrol-1-yl)butanoic acid (PBA) (**65**) was first isolated from kako-bushi-matsu, a thermally processed *Aconitum japonicum* root product used in oriental medicine for its analgesic, diuretic and cardiac effects.[58] PBA (**65**) has been isolated no fewer than eleven times,[4–7,34,41,58–62] and its methyl ether **66** no fewer than eight,[6–8,34,38,46,63,64] from both plant and fungal sources. The yield of PBA (**65**) from kako-bushi-matsu, which is prepared by autoclaving *Aconitum* roots at 110 °C, was determined to be 10-fold greater than the yield of PBA (**65**) from *Aconitum* roots dried at 50–55 °C.[58] This observation is consistent with the proposal that PBA is the product of Maillard-type reactions.[5]

PBA (**65**) and its derivatives possess an impressive array of biological activities. A 50 μg dose of PBA (**65**) caused a significant increase in the peripheral blood flow (90.3 ± 18.2 mL/30 min/100 g) of mice.[58] Free acids PBA (**65**) and methyl ether **66** were both shown to exhibit hepatoprotective effects at 0.1 μM (64.4 ± 3.9% and 65.8 ± 5.6% cell viability respectively).[6] The methyl esters **67** and **68** also exhibited hepatoprotective effects to a lesser degree, suggesting the importance of the free acid for high hepatoprotective activity. In another report, PBA (**65**) and methyl ether **66** were shown to possess immunostimulatory activity.[7] Incubation of RAW 264.7 macrophage cells with PBA (**65**) resulted in a significant increase in phagocytotic activity, while methyl ether **66** caused a smaller increase in activity and morrole A (**70**) had no effect. It was supposed that the 5-hydroxymethyl moiety was important for macrophage stimulatory activity as increasingly large substitution at this position corresponded with decreased activity.

PBA methyl ether **66** was found to inhibit rat lens aldose reductase with an IC_{50} of 39.71 ± 1.77 μM.[63] Aldose reductase is the first enzyme in the polyol pathway of glucose metabolism. Increased flux through this pathway can cause diabetic complications including retinopathy, neuropathy, nephropathy and cataracts. Methyl ether **66** also exhibits moderate antiproliferative activity, inhibiting four different human tumour cell lines; A459, SK-OV-3, SK-MEL-2 and HCT-15, with an IC_{50} range of 21.52 ± 1.82 μM to 40.74 ± 2.41 μM.[8] The cancer

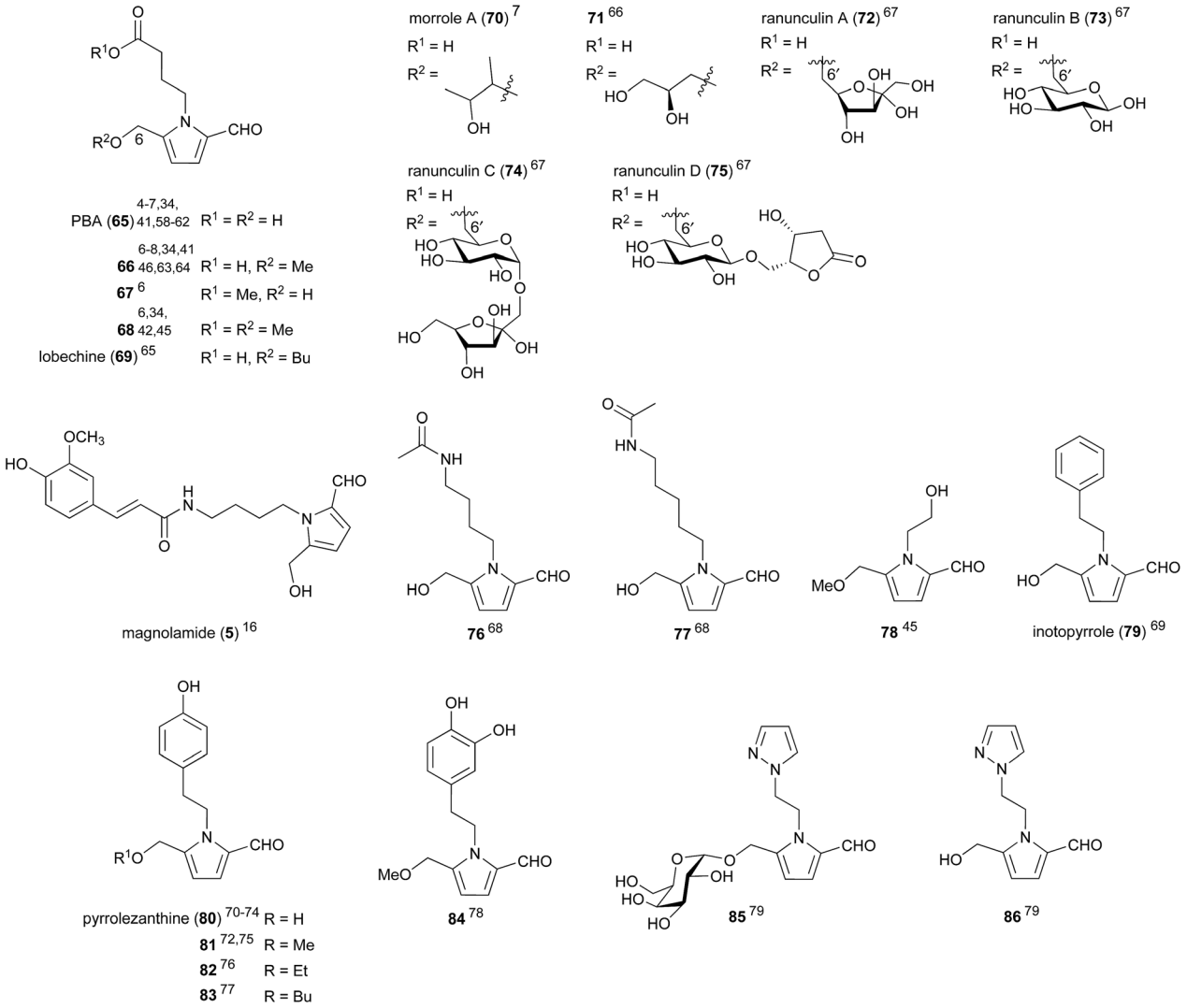


Fig. 4 2-Formylpyrroles derived from biogenic amines.

chemopreventative properties of PBA methyl ether 66 were investigated and it was found to exhibit hydroxyl radical scavenging activity.[46] PBA methyl ester **66** was also shown to induce quinone reductase (QR) with a concentration of 2.4 μM required to double QR activity.

Ranunculins A–D (**72–75**) were recently isolated from the roots of *Ranunculus ternatus* Thunb, a plant used in traditional Chinese medicine.[67] While no bioactivity was investigated for these four GABA-derived pyrroles, they contain an unprecedented 6-6′ ether link between the pyrrole hydroxymethyl substituent, putatively arising from C-6 of 3-DG (**19**), and the C-6 carbons of fructose (ranunculin A (**72**)) or glucose (ranunculins B–D (**73–75**)). This tail–tail ether connectivity has not been observed in any other natural products, whereas head–head (*e.g.* trehalose: 1,1 connected), head–tail (*e.g.* isomaltose: 1,6 connected) and head-body (*e.g.* sucrose: 1,2 connected) connectivities are all well-known. Attempts to synthesise these natural products by 6-6′ ether formation between PBA (**65**) and the appropriate sugar derivatives were unsuccessful.

Magnolamide (**5**), which contains *trans*-feruloyl and putrescine moieties, was shown to possess antioxidant activity, inhibiting Cu^{2+}/O_2-induced LDL lipid peroxidation with an IC_{50} of 9.7 ± 2.8 μM.[9] This was comparable to the positive control resveratrol (IC_{50} 13.1 ± 2.6 μM). Putrescine and cadaverine-derived pyrroles **76** and **77** showed weak activity against human cancer cell lines HeLa, K-562 and L-929, with IC_{50} values ranging between 8.9–20.2 μg mL^{-1}, but were inactive against the microbes *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* (IC_{50} > 10 μg mL^{-1}).[68]

Tyramine derivative pyrrolezanthine (**80**) was found to exhibit moderate cytotoxicity against lung cancer A-549 and human colon cancer SW480 cell lines with IC_{50} values of 38.3 and 33.7 μM respectively.[74] Pyrrolezanthine (**80**) was also demonstrated to possess anti-inflammatory activity, inhibiting NO production in RAW 264.7 macrophage cells with an IC_{50} of 58.8 μM.[73] Pyrrolezanthine butyl ether **83**, which was isolated from the butanol soluble fraction of *Reynoutria ciliinervis* (Nakai) Moldenke extract, was found to possess antifungal

activity against *Sclerotinia sclerotiorum* with a MIC of 31.2 μg mL^{-1}.[77]

Pyrroles **85** and **86** were isolated from watermelon (*Citrullus lanatus*) seeds in 2015.[79] They were the first compounds containing both pyrazole and pyrrole rings to be isolated from a natural source and are likely derived from β-(1-pyrazolyl) alanine, a non-proteinogenic amino acid produced in watermelon.

3.3. *N*-Unsubstituted 2-formylpyrroles derived from amino sugars

A small sub-class of 2-formylpyrroles exist with no *N*-substituents (Fig. 5). These compounds plausibly arise from the self-condensation of hexosamines. Interestingly, *O*-D-galactopyranoside **94** appears to arise either from a disaccharide precursor, or from the glycosylation of 2-formylpyrrole **88**. Of these *N*-unsubstituted 2-formylpyrroles, only ilanepyrrolal (**92**) was shown to exhibit biological activity. Ilanepyrrolal (**92**), which was isolated from rice fermented with the endophytic fungus *Annulohypoxylon ilanense* (Xylariaceae), was demonstrated to inhibit *Mycobacterium tuberculosis* growth with a MIC value of 76.8 mM.[80]

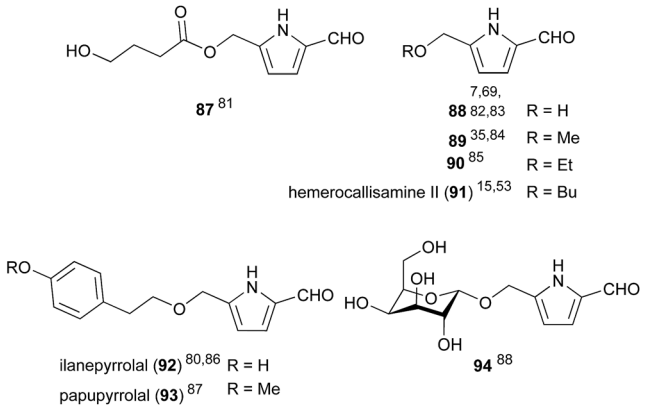


Fig. 5 *N*-Unsubstituted 2-formylpyrroles.

3.4. Pyrrolomorpholine spiroketals derived from amino sugars

Another small group of amino sugar derivatives, referred to as pyrrolomorpholine spiroketals (Fig. 6), are thought to arise from the intermolecular condensation of 3-DG (**19**) with 1-amino-1,3-dideoxy-D-fructose (**95**) (acortatarin A (**1**), pollenopyrroside A (**2**), shensongine B (**97**) and shensongine A (**98**)) or 1-amino-1-deoxy-D-fructose (**100**) (acortatarin B (**101**) and shensongine C (**102**)).[5] 3-DG (**19**) is a deamination product of Amadori compounds, while 1-amino-1-deoxyhexoses are the products of Strecker degradation. Both processes are associated with Maillard pathways. The generation of pyrrolomorpholine spiroketals by a Maillard pathway was proposed by Jiang and Peterson, who isolated acortatarin A (**1**) and a [6,6]-pyrrolomorpholine spiroketal, the stereochemistry of which was not determined, from bread.[4,5] These compounds were present in higher concentrations in the bread crust, which is exposed to the highest temperatures during baking, supporting this Maillard hypothesis.[4] There are regioisomeric [5,6]-spiroketals and [6,6]-spiroketals within this group of compounds depending on which hydroxy group of 1-amino-1,3-dideoxy-D-fructose (**95**) is engaged in spirocyclisation. For each regioisomer there are two possible configurations at the spiroketal center giving rise to pairs of spiroketal anomers.

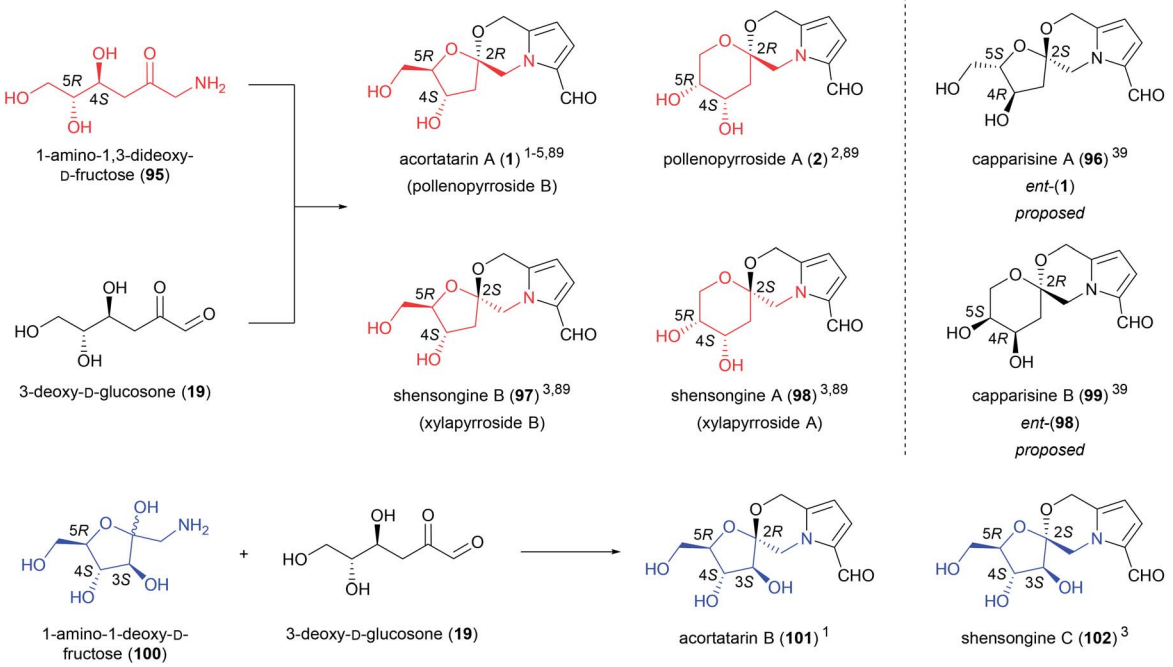


Fig. 6 Pyrrolomorpholine spiroketals.

Pyrrolomorpholine spiroketals first appeared in the literature in 2010 when three reports of their isolation emerged independently of each other.[1,2,39] Three different trivial naming systems were subsequently proposed in these reports, a problem which would later be compounded by the isolation of additional pyrrolomorpholine spiroketals. In addition to bread crust, these spiroketals have been isolated from the rhizomes of *Acorus tatarinowii*,[1] bee-collected *Brassica campestris* pollen,[2] fruits of *Capparis spinosa*,[39] the traditional Chinese medicine preparation Shensong Yangxin,[3] and the fermented mycelia of *Xylaria nigripes*.[89] All of these pyrrolomorpholine spiroketals are derived from D-sugars, with the exception of capparasines A (**96**) and B (**99**), the absolute stereochemistry of which was proposed from X-ray crystal structure.[39] While this enabled unambiguous assignment of the relative stereochemistry of capparisines A and B, insufficient evidence was provided for the assignment of the absolute stereochemistry of these two compounds, which are likely to be the misassigned structures of acortatarin A (**1**) and shensongine A (**98**), respectively.

Pyrrolomorpholine spiroketals inhibit the high glucose-induced production of reactive oxygen species (ROS) in mesangial cells. High glucose-induced ROS production is implicated in diabetic nephropathy, the leading cause of end-stage renal disease in the Western world.[90] ROS-inhibition was originally established for acortatarin A (**1**) and B (**101**),[1] however Verano and Tan later demonstrated that all members of the pyrrolomorpholine spiroketal family inhibit high glucose-induced ROS production.[91] Acortatarin A (**1**) and shensongine C (**102**) are the most active of the isolated compounds, with IC_{50} values of 4.6 and 4.8 μM respectively and a maximum inhibition of ROS production of 100%. The synthetic analogues **103** and **104** are the most potent pyrrolomorpholine spiroketals tested to date (Fig. 7), with IC_{50} values of 0.52 and 0.27 μM respectively, however they can only effect 80% and 60% maximum inhibition of ROS production.

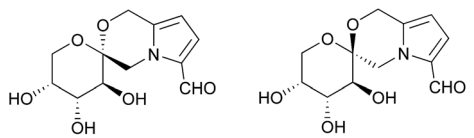


Fig. 7 Synthetic analogues of the pyrrolomorpholine spiroketals with improved inhibition of high glucose-induced ROS production.

A report by Nie and co-workers in 2013 elucidated the biological action of acortatarin A (**1**).[10] Pre-incubation of rat glomerular mesangial cells with acortatarin A (**1**) attenuates high-glucose phosphorylation of PKC isoforms PKCα and PKCβ1, PLCγ1 and the p85 regulatory subunit of PI3K. Inhibition of the PI3K–PLCγ1–PKC signalling pathway, which is an upstream regulator of NADPH oxidase activation, inhibits high glucose-induced ROS production. In turn, inhibition of high glucose-induced ROS production prevents overproduction of extracellular matrix proteins by mesangial cells, which has been closely correlated with deterioration of renal function.

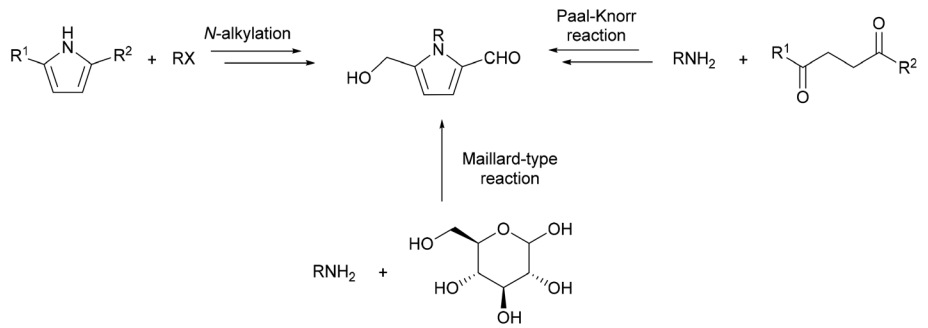
In addition to their effects on high glucose-induced ROS production, shensongine A (**98**) and C (**102**) were found to shorten action potential duration in rat myocardial cells, with noticeable effects at concentrations as low as 1 μM.[3] It was speculated that shensongine A (**98**) and C (**102**) might either inhibit L-type calcium channels, or facilitate the action of potassium channels.

4. Synthesis

Aside from the isolation of 2-formylpyrroles as minor products in amine–sugar reaction mixtures, efforts have been dedicated towards the selective synthesis of these compounds. Many of these syntheses employ the Paal–Knorr reaction to form pyrrole ring systems around readily available amines, while other approaches involve *N*-alkylation of a pyrrole substrate (Scheme 4). Both of these strategies often involve late stage modification of the pyrrole ring substituents in order to furnish the 5-hydroxymethylpyrrole-2-carbaldehyde system. More recently, Maillard chemistry-inspired methodologies have been developed to forge the 5-hydroxymethylpyrrole-2-carbaldehyde ring system cleanly in a single step from amines and sugars, or sugar surrogates. This section will focus on the total syntheses of 5-(hydroxymethyl)-1-[(*R*)-tetrahydro-2′-oxofur-3′-yl)-1*H*-pyrrole-2-carbaldehyde] (**64**), funebral (**5**) and the pyrrolomorpholine spiroketals, which best encompass the different synthetic strategies towards 2-formylpyrroles.

4.1. 5-(Hydroxymethyl)-1-[(*R*)-tetrahydro-2′-oxofur-3′-yl)-1*H*-pyrrole-2-carbaldehyde] (64)

The first total synthesis of a 2-formylpyrrole was reported in conjunction with the isolation and biological evaluation of 5-



Scheme 4 Different synthetic approaches to the 5-hydroxmethylpyrrole-2-carbaldehyde system.

(hydroxymethyl)-1-[(*R*)-tetrahydro-2′-oxofur-3′-yl)-1*H*-pyrrole-2-carbaldehyde] (**64**) by Lynn and co-workers in 1987 (Scheme 5).[52] The pyrrole ring system was constructed by the Paal–Knorr reaction of D-homoserine lactone (**105**) and 2,9-dimethyldeca-2,8-dien-4,7-dione (**106**), which proceeded with some racemisation of the α-stereocentre. Ozonolysis of bis(isobutenyl)pyrrole **107** and selective reduction of the resultant biscarbaldehyde with diborane afforded 2-formylpyrrole **64**. This Paal–Knorr strategy has since been employed in many syntheses of 2-formylpyrroles.

A racemic synthesis of 2-formylpyrrole **64** was reported by Neier and co-workers in 1993 (Scheme 6).[92] This synthesis also employed a Paal–Knorr condensation, using asymmetric dione equivalent **110** to enable a different end-game approach to the 5-hydroxymethylpyrrole-2-carbaldehyde system. Dione equivalent **110** was obtained by oxidation of 2-methylfuran (**108**) and subsequent hydrogenation of dihydrofuran **109** using RANEY® nickel. The Paal–Knorr condensation of dione equivalent **110** with *rac*-homoserine lactone (**105**) proceeded in excellent yield. Vilsmeier–Haack formylation and oxidation of the 5-methyl substituent with lead(IV) acetate afforded acetate **113**, hydrolysis of which furnished 2-formylpyrrole **64**.

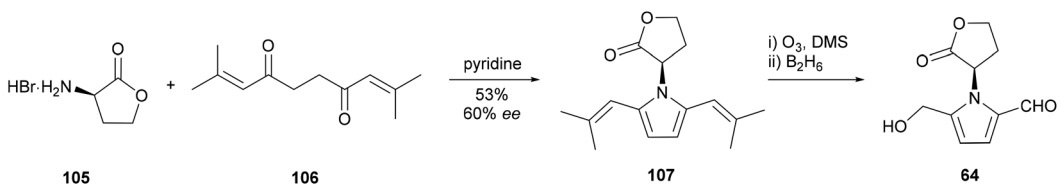
4.2. Funebral (3)

Funebral (**3**) has been the subject of four different total syntheses to date. While it shares a high degree of structural similarity to the cellular arrest inhibitor 5-(hydroxymethyl)-1-[(*R*)-tetrahydro-2′-oxofur-3′-yl)-1*H*-pyrrole-2-carbaldehyde] (**64**), funebral (**3**) has no known bioactivity. Interest in this compound has been driven largely by the synthetic challenge posed by the three contiguous stereocenters of its γ-butyrolactone ring and the sterically crowded pyrrole ring.

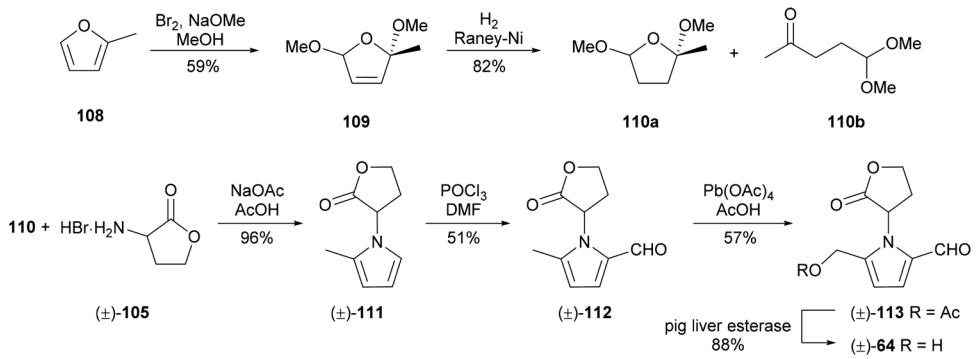
The first total synthesis of (±)-funebral (**3**) and (±)-funebrine **63** was reported by Le Quesne and co-workers in 1995,[93–95] which utilised 2,9-dimethyldeca-2,8-dien-4,7-dione (**106**) to construct the pyrrole ring from α-amino-γ-butyrolactone **120** (Scheme 7). Racemic α-amino-γ-butyrolactone **120** was afforded in 14% yield over eight steps, which included a diastereoselective Claisen rearrangement and iodolactonisation. Synthesis of the sterically crowded bis(isobutenyl)pyrrole **121** by Paal–Knorr condensation of α-amino-γ-butyrolactone **120** and dione **106** required titanium(IV) isopropoxide to proceed. (±)-Funebral (**3**) was afforded from bis(isobutenyl)pyrrole **121** by osmium-catalysed oxidative olefin cleavage and monoreduction. Treatment of (±)-funebral (**3**) with excess α-amino-γ-butyrolactone **120** provided (±)-funebrine **63**.

The first enantioselective synthesis of funebral (**3**) and funebrine (**63**) was reported by Ishibashi and co-workers in 2003 (Scheme 8).[96] Their preparation of (−)-α-amino-γ-lactone **120** involved a [2,3]-cycloaddition of (*E*)-crotyl alcohol (**115**) with nitrone **124**, which in turn was derived from methyl glyoxylate (**123**) and an oxime **122** bearing an L-gulose-based chiral auxiliary. Cleavage of the auxiliary and translactonisation provided lactone **126** in excellent yield, which was elaborated to α-amino-γ-lactone **120**. Funebral (**3**) and funebrine (**63**) were accessed *via* the same strategy employed by Le Quesne and co-workers[93] with further optimisation of reaction conditions. Interestingly, the Paal–Knorr conditions reported by Le Quesne and co-workers were not reproducible and titanium(IV) ethoxide was instead employed as a Lewis acid catalyst in this key step.

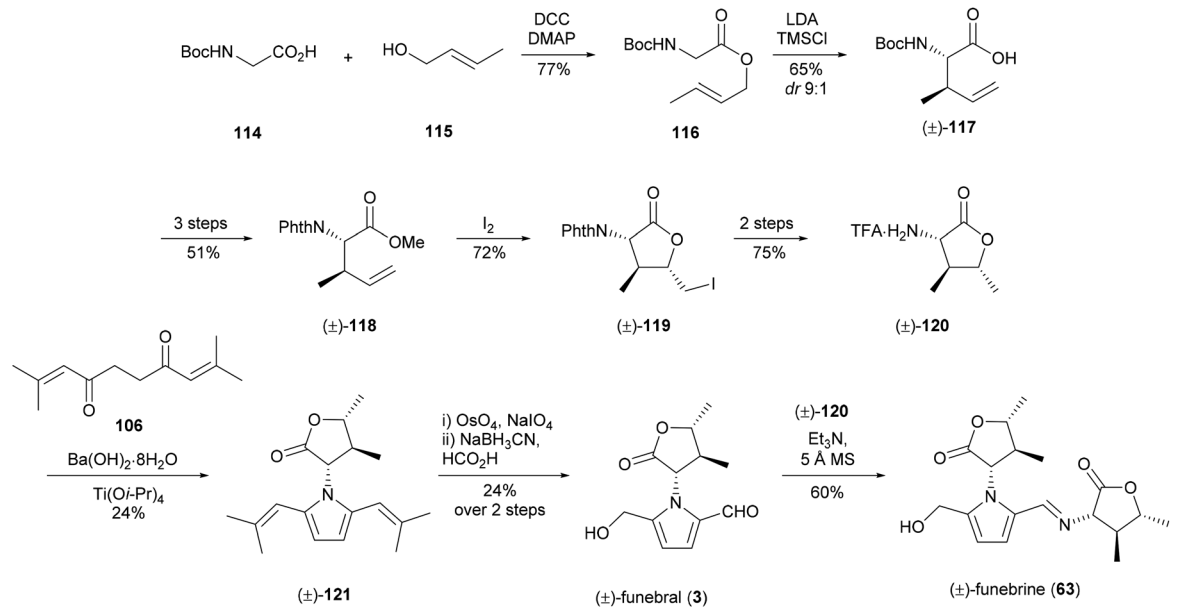
Sakaguchi and co-workers reported a synthesis of funebral (**3**) and funebrine (**63**) in 2011, utilising dione **129** for the Paal–Knorr reaction of α-amino-γ-lactone **120** (Scheme 9).[97] Dione **129** was prepared over five steps from hydroxymethylfurfural



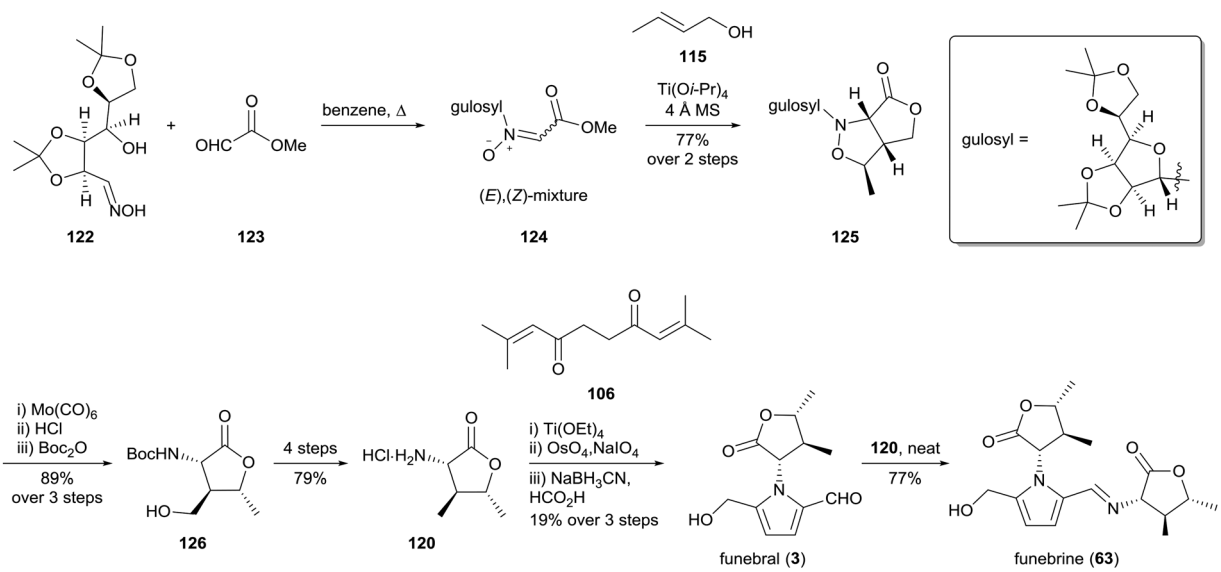
Scheme 5 Synthesis of 5-(hydroxymethyl)-1-[(*R*)-tetrahydro-2′-oxofur-3′-yl)-1*H*-pyrrole-2-carbaldehyde] (**64**) by Lynn and co-workers (yields omitted where not given).



Scheme 6 Synthesis of 5-(hydroxymethyl)-1-[(*R*)-tetrahydro-2′-oxofur-3′-yl)-1*H*-pyrrole-2-carbaldehyde] (**64**) by Neier and co-workers.



Scheme 7 Racemic synthesis of funebral (**3**) and funebrine (**63**) by Le Quesne and co-workers.



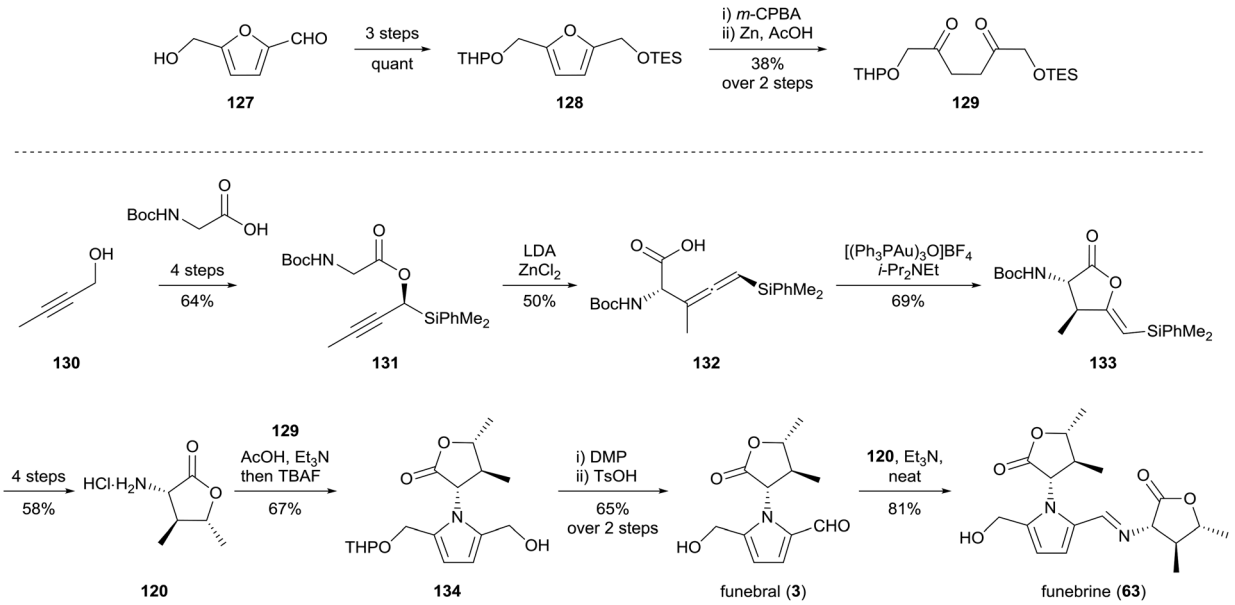
Scheme 8 Enantioselective synthesis of funebral (**3**) and funebrine (**63**) by Ishibashi and co-workers.

(**127**), while α-amino-γ-lactone **120** was prepared from 2-butyn-1-ol (**130**) and Boc-glycine over ten steps which included a diastereoselective Claisen rearrangement of propargyl ester **131** and gold(I)-catalysed cyclisation of the resultant allenylsilane **132**. The Paal–Knorr reaction of amine **120** with dione **129** provided pyrrole **134**, oxidation of which afforded access to funebral (**3**) and funebrine (**63**) in good yield.

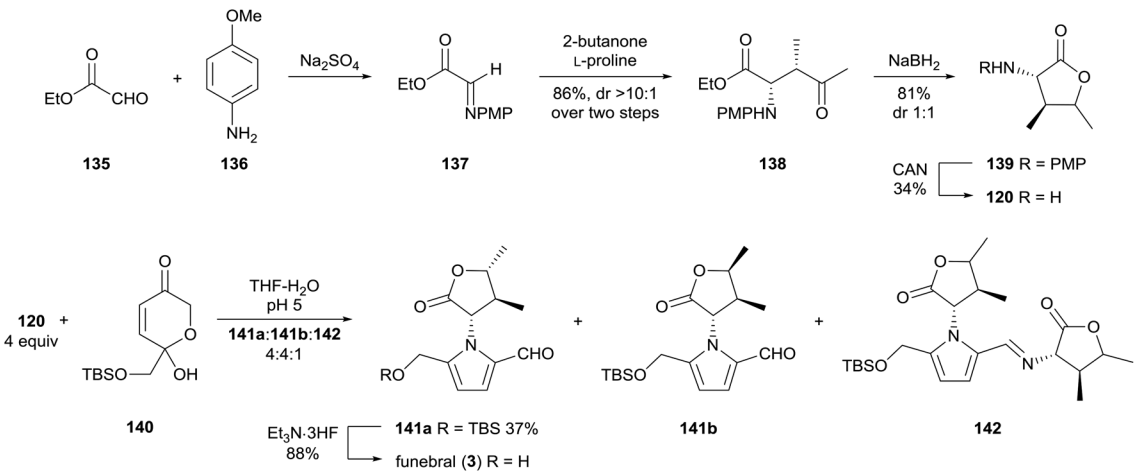
In 2014, Brimble and co-workers reported a concise synthesis of funebral (**3**) by a Maillard-type condensation approach, which forged the pyrrole substituents in the correct oxidation state (Scheme 10).[98] α-Amino-γ-butyrolactone **120** was prepared by an L-proline-catalysed Mannich reaction of ethyl glyoxal-derived imine **137** with 2-butanone. α-Amino-γ-butyrolactone **120** was afforded as a 1 : 1 mixture of diastereomers by sodium borohydride reduction. Dihydropyranone **140**, which had previously been prepared by the group,[99] underwent condensation with four equivalents of amine **120** to provide TBS-protected funebral **141a**, along with its diastereomer **141b** and funebrine-type adducts **142**. Desilylation of TBS-protected adduct **141a** afforded funebral (**3**) in a longest linear sequence of six steps.

4.3. Pyrrolomorpholine spiroketals

In 2011, Sudhakar and co-workers reported the first total synthesis of acortatarin A (**1**) and B (**101**) (Scheme 11).[100]



Scheme 9 Synthesis of funebral (3) and funebrine (63) by Sakaguchi and co-workers.

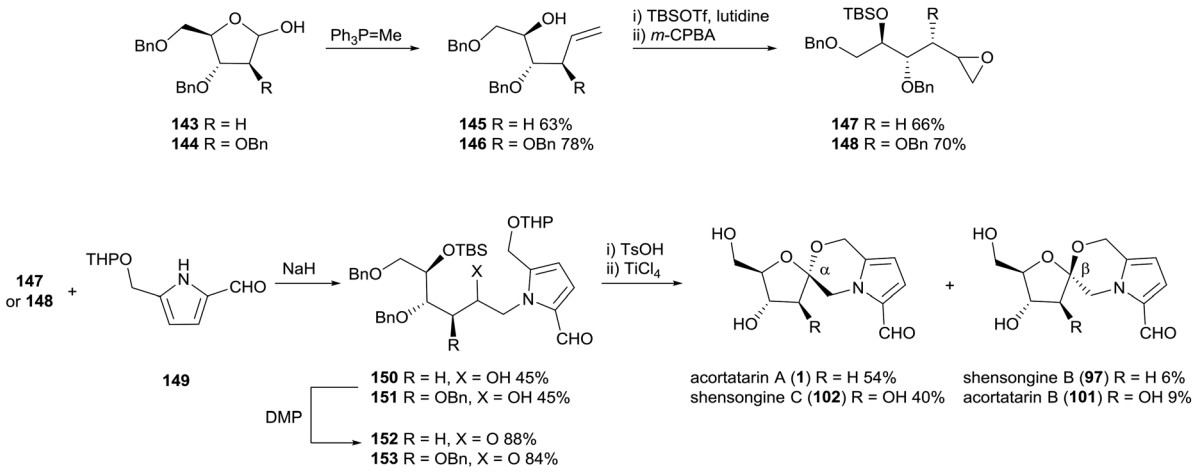


Scheme 10 Synthesis of funebral (3) by Brimble and co-workers.

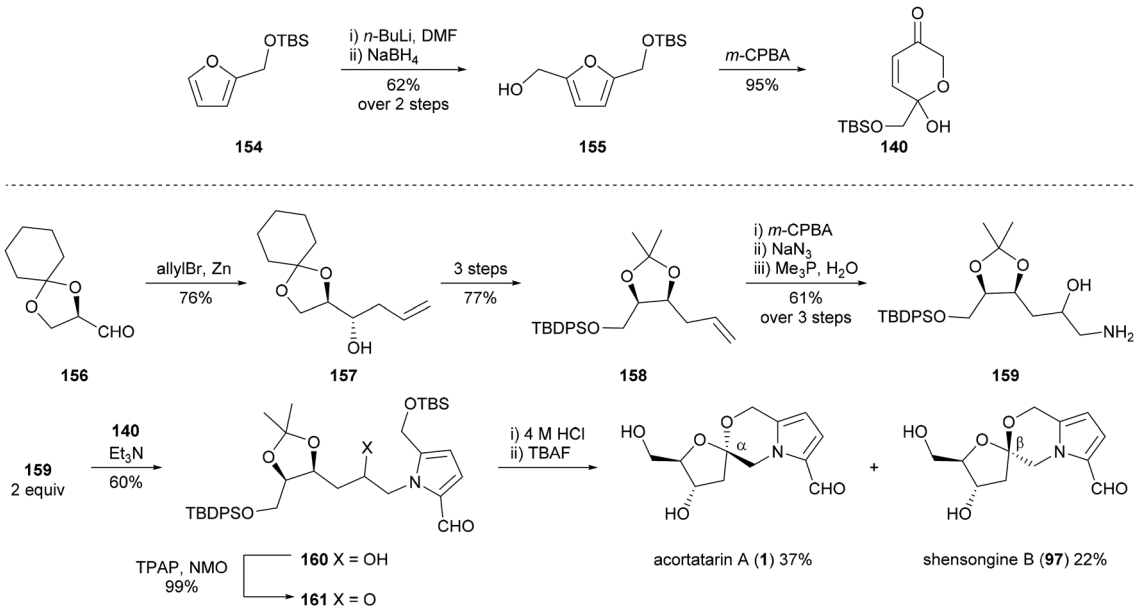
Incidentally, the acid-catalysed spiroketalisation conditions used also afforded the anomers of the acortatarins; shensongine B (**97**) and C (**102**), preceding their isolation from natural sources by three years. The synthesis strategy employed 2-deoxy-D-ribose and D-arabinose as chiral pool materials. Homologation and epoxidation of these sugars provided electrophiles for *N*-alkylation of pyrrole **149**, which had the requisite aldehyde and hydroxymethyl substituents already installed. Oxidation of secondary alcohols **150** and **151**, deprotection and acid-catalysed spirocyclisation afforded α-spiroketal anomers acortatarin A (**1**) and shensongine C (**102**) as major products, while β-spiroketal anomers shensongine B (**97**) acortatarin B (**101**) were afforded in minor quantities. The efficiency of this approach would inspire later syntheses of pyrrolomorpholine spiroketals by the groups of Kuwahara[101] and Hu,[89] which both used THP-protected pyrrole carbaldehyde **149**.

Brimble and co-workers utilised a Maillard-type approach to synthesise acortatarin A (**1**) in 2012 (Scheme 12).[99,102] Dihydropyranone **140**, which would be used to construct the pyrrole ring system of acortatarin A (**1**), was prepared by Achmatowicz rearrangement of furfuryl alcohol **155**, which in turn was prepared from furfuryl silyl ether **154**. Homoallylic alcohol **157** was obtained by the known allylation of (*R*)-glyceraldehyde derivative **156**. Subsequent protecting group manipulations and functional group interconversions provided aminohydrin **159**, which underwent condensation with dihydropyranone **140** to afford TBS-protected adduct **160**. Oxidation of alcohol **160**, acid-catalysed spirocyclisation and deprotection then furnished acortatarin A (**1**) as the major product along with β-anomer shensongine B (**97**) in a diastereomeric ratio of 3 : 2.

Brimble and co-workers employed the same synthetic strategy to access pollenopyrroside A (**2**) in 2016 (Scheme 13).[103]



Scheme 11 Synthesis of acortatarins A (**1**) and B (**101**) and shensongines B (**97**) and C (**102**) by Sudhakar and co-workers.

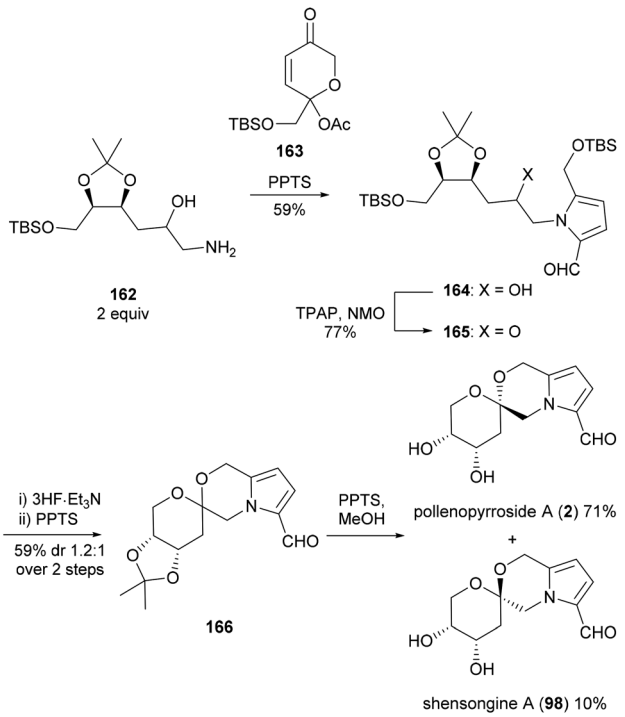


Scheme 12 Synthesis of acortatarin A (**1**) and shensongine B (**97**) by Brimble and co-workers.

The Maillard-type condensation of amine **162**, which was accessed in six steps from 2-deoxy-D-ribose, proved challenging and required the more reactive acetylated dihydropyranone **163** to proceed. Oxidation, silyl ether deprotection and spiroketalisation provided two [6,6]-spiroketal anomers with little diastereoselectivity. Deprotection of the acetonide protecting group with pyridinium *para*-toluenesulfonate in methanol resulted in concomitant epimerisation of the spiroketal ring, favouring pollenopyrroside A (**2**) over shensongine A (**98**) in a 7 : 1 ratio.

Tan and co-workers reported a synthesis of acortatarins A (**1**) and B (**101**), and shensongine B (**97**) in 2012, using D-thymidine (**167**) as a chiral pool starting material (Scheme 14).[104] The carbon skeleton of the natural products was forged by a high-yielding alkylation of pyrrole-2,5-dicarbaldehyde (**170**) with iodomethylglycal **169**. The [5,6]-spiroketal core of acortatarin A (**1**) was prepared diastereoselectively by mercury-mediated oxidative cyclisation of the hydroxymethyl pyrrole substituent onto the gycal, followed by borohydride reduction of the mercurial adduct. Deprotection of each anomer gave acortatarin A (**1**) and shensongine B (**97**), respectively. From the common glycal intermediate **171**, acortatarin B (**101**) was prepared by diastereoselective β-epoxidation using DMDO, followed by a one pot reduction of the pyrrole-2,5-dicarbaldehyde and spirocyclisation onto the epoxide.

Verano and Tan reported a follow-up synthesis of the [6,6]-pyrrolomorpholine spiroketals shensongine A (**98**) and pollenopyrroside A (**2**) in 2017 using a similar *N*-alkylation of pyrrole-2,5-dicarbaldehyde (**170**) (Scheme 15).[91] It was noted that biphasic conditions were required for the *N*-alkylation to prevent dimerization of pyrrole species. Monoreduction of dicarbaldehyde **174**, treatment with catalytic Brønsted acid and



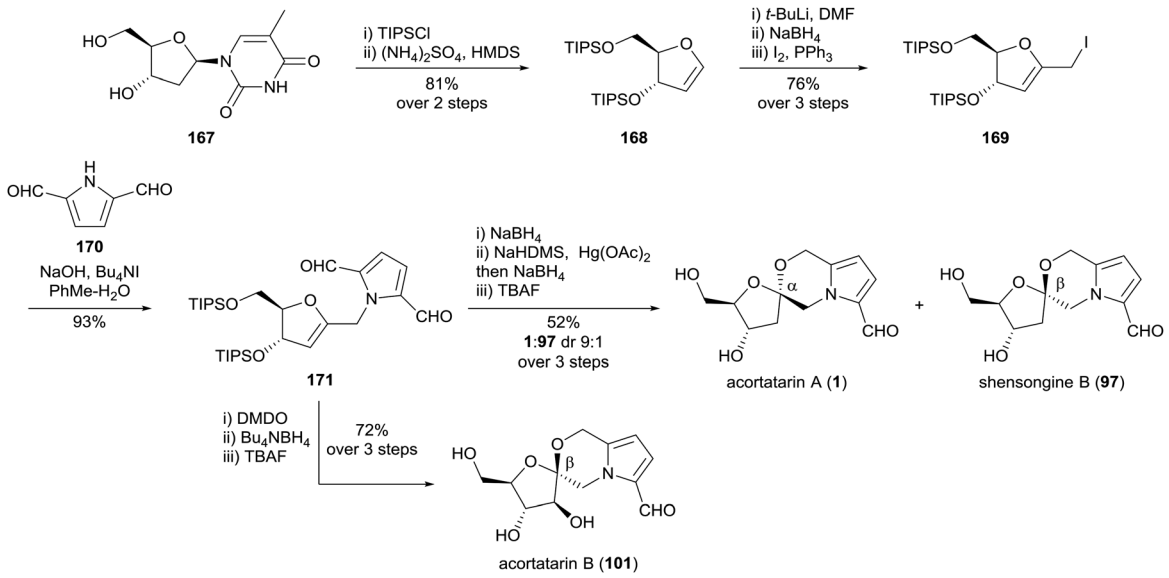
Scheme 13 Synthesis of pollenopyrroside A (**2**) and shensongine A (**98**) by Brimble and co-workers.

silyl deprotection afforded shensongine A (**98**) exclusively. Stereoselective synthesis of pollenopyrroside A (**2**) was achieved by *anti*-epoxidation and methanol-catalysed spirocyclisation of glycal epoxide **174**, affording the kinetic α-spiroketal anomer **175**. Barton–McCombie deoxygenation and desilylation provided pollenopyrroside A (**2**).

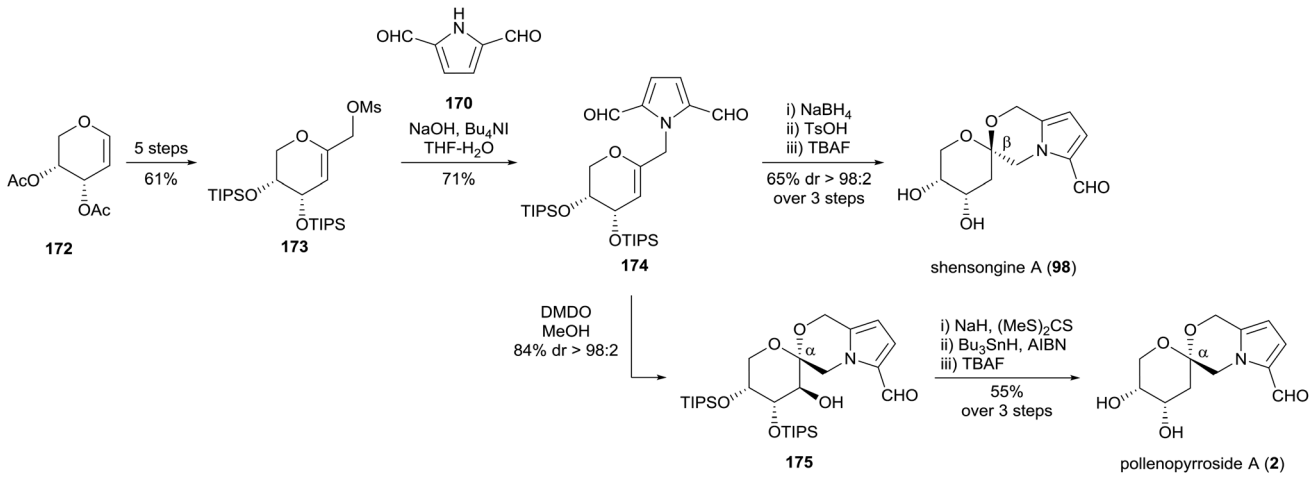
Borrero and Aponick reported a total synthesis of acortatarin A (**1**) and shensongine B (**97**) in 2012, featuring a palladium(II)-catalysed allylic transposition reaction developed within the group (Scheme 16).[105] Bromoketone **177** was synthesised over seven steps from known δ-hydroxyester **176**, which in turn was derived from L-tartrate. Union of 5-formylpyrrole-2-carboxamide **178** and bromoketone **177** proceeded best with caesium carbonate, which supressed competing elimination of the benzyloxy group. Reduction of pyrrole carbaldehyde **179** and treatment with bis(benzonitrile)palladium(II) chloride resulted in allylic transposition, forging the [5,6]-spiroketal system as a mixture of anomers **180** and **182**. The terminal olefins **180** and **182** were advanced separately, both affording acortatarin A (**1**) as the major product upon titanium(IV) chloride-catalysed benzyl cleavage.

Zhao and co-workers reported a synthesis of shensongine A (**98**) and pollenopyrroside A (**2**) in 2015 (Scheme 17).[106] The synthetic strategy involved functionalisation of pyrrole **184**, the synthesis of which had been described in an earlier publication by the group from pyrrole and D-fructose.[107] A microwave-accelerated protocol was developed to enable efficient bishydroxymethylation of pyrrole **184**, with subsequent MnO_2 oxidation affording the pyrrole-2,5-dicarbaldehyde **185**. Protecting group manipulations, followed by selective reduction of one carbaldehyde group gave 2-formylpyrrole **186**, which underwent acid-catalysed cyclisation to provide a 3 : 1 mixture of β-anomer **187** and α-anomer **188**. These two spiroketals were advanced separately to shensongine A (**98**) and pollenopyrroside A (**2**) by modified Barton–McCombie deoxygenation and benzyl deprotection.

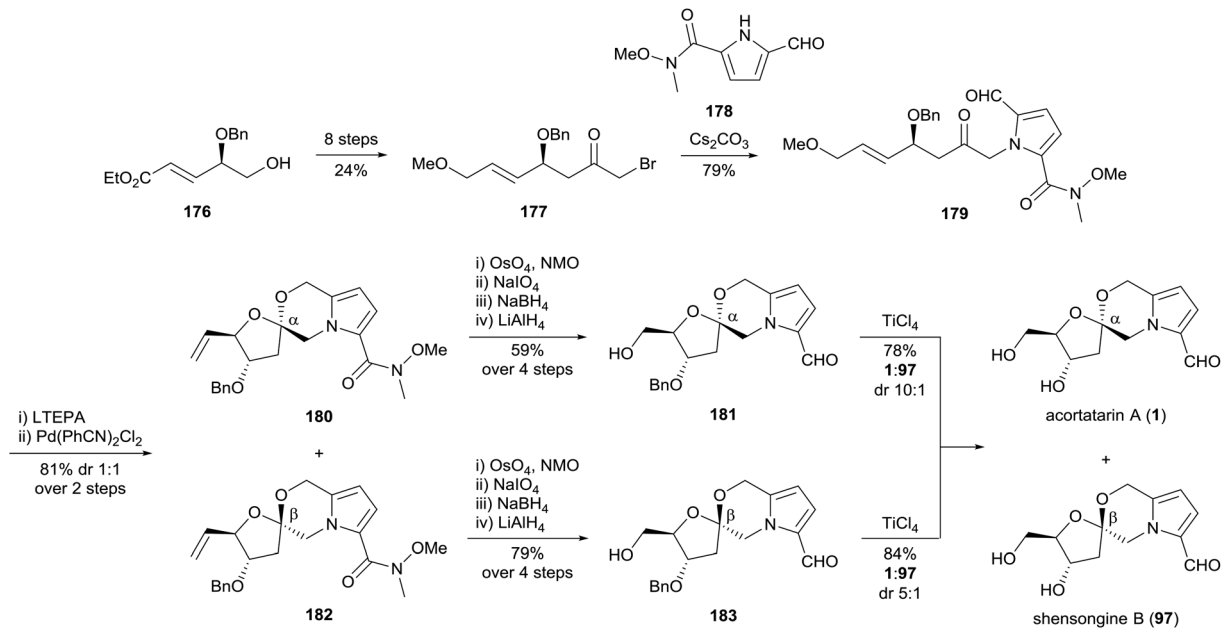
In 2017, Pale and co-workers reported a novel synthesis of acortatarin A (**1**) and shensongine B (**97**) which showcased the utility of zeolite-based organic synthesis (Scheme 18).[108] Five of the eleven steps in the synthesis were performed using native or metal-doped zeolite catalysts. The acortatarin skeleton was assembled by ynamide coupling of alkynyl bromide **192** and pyrrole **193**. This reaction was catalysed by copper(I)-doped



Scheme 14 Synthesis of acortatarins A (**1**) and B (**101**) and shensongine B (**97**) by Tan and co-workers.



Scheme 15 Synthesis of shensongine A (**98**) and pollenopyrroside A (**2**) by Verano and Tan.



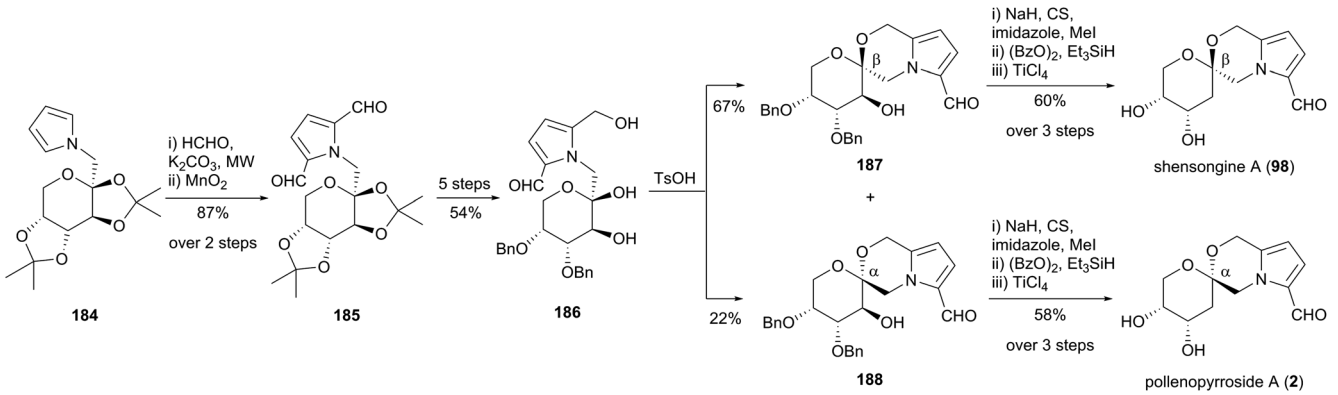
Scheme 16 Synthesis of acortatarin A (**1**) and shensongine B (**97**) by Borrero and Aponick.

zeolite, which performed better than both homogenous copper catalysts, and polystyrene and mesoporous silica-based heterogeneous copper catalysts. Sequential silver-catalysed alkyne hydroxylation and acid-catalysed cyclisation afforded spiroketal **196** as an anomeric mixture. The end-game synthesis-strategy involved redox manipulations to install the pyrrole carbaldehyde substituent and benzyl deprotection, providing acortatarin A (**1**) and shensongine B (**97**) as a 3 : 1 mixture of anomers.

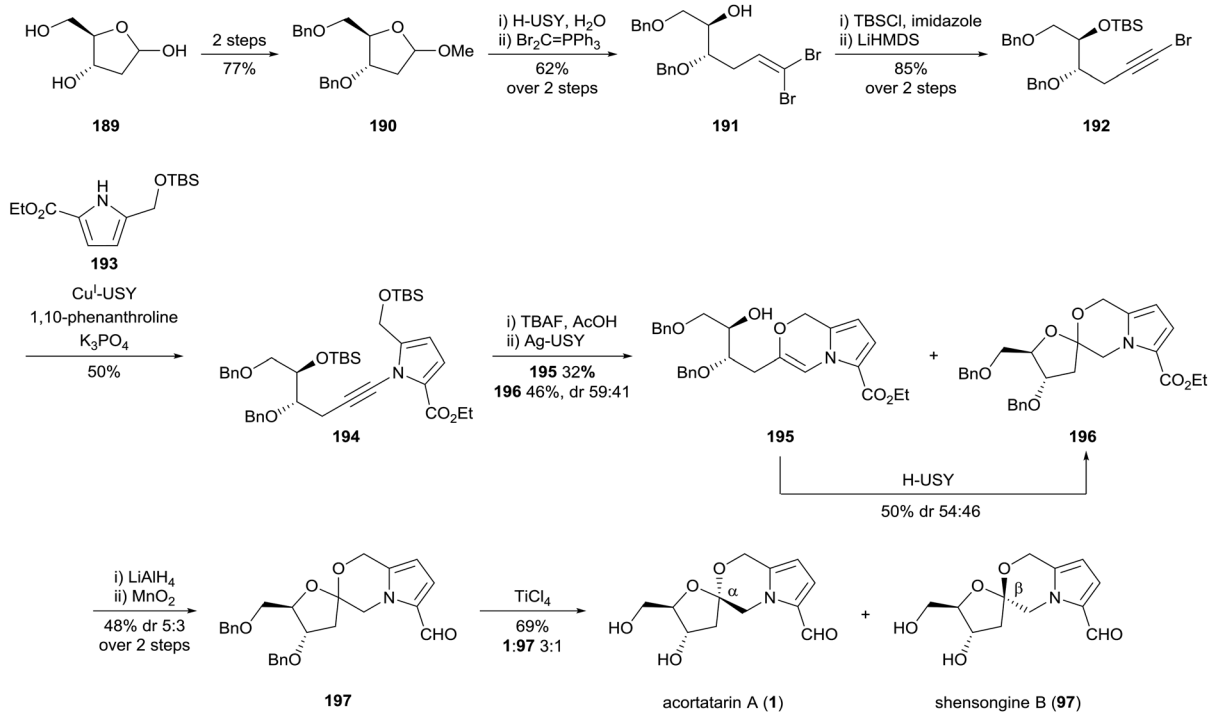
4.4. Methodologies for 2-formylpyrrole synthesis

In addition to the considerable efforts towards the total synthesis of complex 2-formylpyrroles, two recent methodology studies have explored the reaction of sugars with amines to deliver synthetically useful yields of 2-formylpyrroles. In 2015, Koo and co-workers reported conditions for the synthesis of 2-formylpyrroles directly from various hexose reducing sugars and amines (Scheme 19).[109] This Maillard-type reaction was performed in dimethylsulfoxide at 90 °C with one equivalent of oxalic acid to facilitate dehydration of D-glucose (**7**) in the presence of the basic amine substrates. These conditions were used to form the 2-formylpyrroles of a variety of amines as well as the lactonised pyrrole adducts **38** and **39** of L-phenylalanine methyl ester (**198**) and L-alanine methyl ester (**199**), respectively. The Maillard-type reaction of D-glucose (**7**) and γ-aminobutyric acid methyl ester (**200**) enabled access to lobechine (**69**) in three steps.

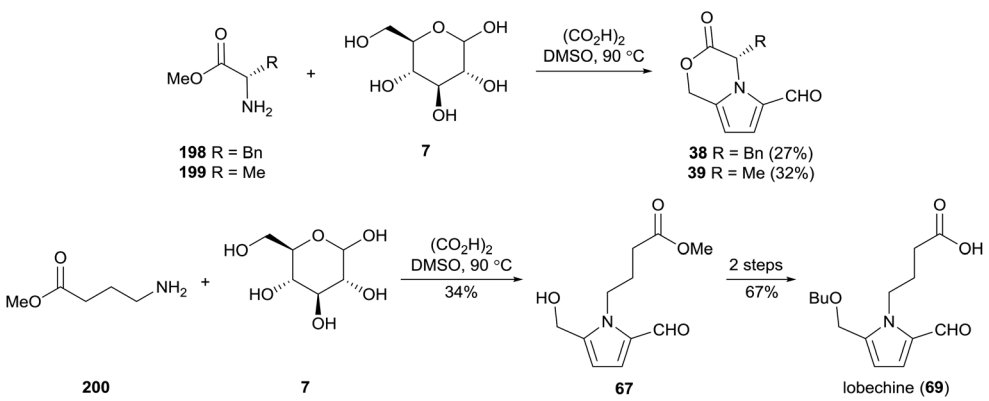
In 2016, Zhao and co-workers reported conditions for the synthesis of oxazine-fused pyrroles from amino acids and D-



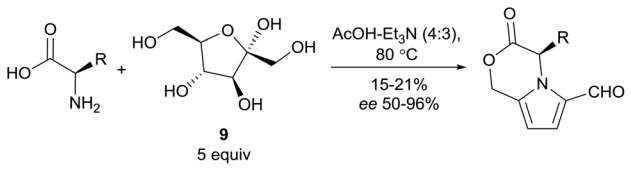
Scheme 17 Synthesis of shensongine A (**98**) and pollenopyrroside A (**2**) by Zhao and co-workers.



Scheme 18 Synthesis of acortatarin A (**1**) and shensongine B (**97**) by Pale and co-workers. USY = ultrastable Y-type zeolite.



Scheme 19 Maillard-type reaction developed by Koo and co-workers.



Scheme 20 Maillard-type reaction developed by Zhao and co-workers.

fructose (**9**) (Scheme 20).[110] Extensive optimisation led to the solvent mixture of acetic acid and triethylamine (4 : 3) and use of five equivalents of D-fructose (**9**) relative to the amino acid. Chiral HPLC analysis of the products indicated that partial racemisation of the α-stereocenter had occurred during the reaction. For substrates D-valine, D-isoleucine, D-phenylalanine and D-tyrosine, this racemisation was minimal, however substrates D-alanine and D-leucine suffered from 25% and 10% racemisation respectively.

5. Conclusions

Initially observed as trace products in amine–sugar reactions mixtures, 2-formylpyrroles have since been isolated from a broad range of natural sources. Derived from amines and reducing sugars by non-enzymatic Maillard pathways, these pyrroles are representative of amine metabolites present in the natural source, yet often possess unique biological activities. The most studied group of pyrrole-2-carbaldehydes — the pyrrolomorpholine spiroketals — may provide a basis for drug discovery directed towards therapeutic intervention of diabetic nephropathy and have therefore enjoyed sustained interest from the synthetic community, succumbing to eleven total syntheses from nine research groups. Inspired by the Maillard pathways responsible for 2-formylpyrroles, other research has realised the preparation of pyrroles from sugars and amines in synthetically useful yields. Such synthetic advances will aid ongoing investigations into the biological activity of 2-formylpyrroles and may even enable the use of this compound family as highly functionalised sustainable platform chemicals.

6. Conflicts of interest

There are no conflicts to declare.

7. Acknowledgements

We thank the University of Auckland for the award of a Doctoral Scholarship (JMW).

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