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Celastraceae sesquiterpene pyridyl ligands

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Celastraceae plant extracts have been widely used as traditional medicines and insecticides in China and South America. More recently, the extracts from *Celastraceae* plants have been studied at the molecular level and many of the interesting medicinal and agrochemical properties can be attributed to a large class of sesquiterpene alkaloids found in these extracts. These are generally based on highly oxygenated dihydroagarofuran cores with pyridyl diacid macrodilactone bridging ligands. Whereas previous reviews have focused on the dihydroagarofuran cores, in this article, the history, structure, and syntheses of the macrodilactone bridging ligands are reviewed.

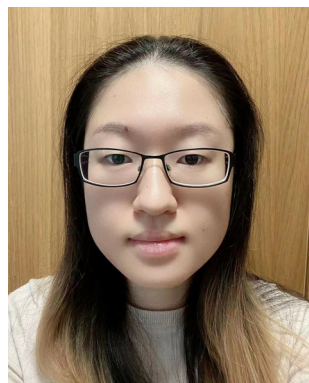
Introduction

Plant extracts have a long and venerable history of providing new lead compounds for drug discovery, and many drug candidates and approved therapeutics are derived from natural products.¹ The *Celastraceae* family has approximately 88 genera and 1300 individual species and is found in tropical and subtropical regions of the world, including North Africa, South America, and many parts of East Asia, especially China. In particular, the leaves and roots of the genera *Maytenus*, *Tripterygium* and *Celastrus* have been utilized in traditional medicine and agriculture for centuries and extracts of these

have been shown to exhibit *e.g.*, stimulant, appetite suppressive, sedative, emetic, purgative, memory restorative, male contraceptive, anti-tumour, anti-leukemic, anti-bacterial, insecticidal and insect repellent activities (Fig. 1).^{2–4}

Among all the bioactive natural products extracted from *Celastraceae* plants, a large set of sesquiterpenene alkaloids have proven to be predominantly responsible for their medicinal properties. These compounds are widely distributed in the *Celastraceae* and comprise a dihydroagarofuran core adorned with between two and nine esterified alcohol groups (Chart 1).^{2–4} These peripheral esterifying residues range from acetic and benzoic acids to the stereochemically unique pyridine-containing dicarboxylic acids which are characteristic of these natural products. The diacid ligands form macrodilactone bridges between C-3 and C-13 and/or C-8 and C-14, making these secondary metabolites topologically complex.²

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Chen Dai received an MSci in chemistry in 2022 from Imperial College London and is currently in the first year of research towards a PhD exploring approaches to the total synthesis of bioactive *Celastraceae* sesquiterpene alkaloids under the direction of Professor Alan Spivey at Imperial College London.



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Alan Spivey (<https://www.imperial.ac.uk/people/a.c.spivey>) has been professor of synthetic chemistry at Imperial College London since 2008. Previously, he was a lecturer then reader in the Department of Chemistry, University of Sheffield. His research encompasses the development of new reactions, synthesis of complex molecules of biomedical interest, including studies towards the synthesis of bioactive *Celastraceae* sesquiterpenoids, chemical biology and medicinal chemistry. For further details of his groups research activities see: <https://www.imperial.ac.uk/spiveygroup>.





Fig. 1 (a) The properties and uses of thunder god vine (*Tripterygium wilfordii*) as traditional Chinese medicine documented in *Addendum to Compendium of Materia Medica* (Xuemin Zhao, 1765, Qing dynasty of China); (b) a vintage chromolithograph of spindle tree (*Euonymus europaeus*).

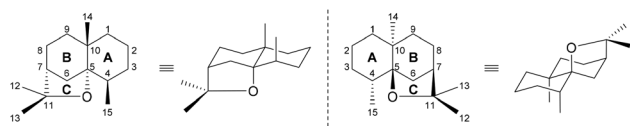


Chart 1 The dihydroagarofuran skeleton. Two different numbering systems are commonly used, and the left system will be used in this review.

The first reported isolation of a *Celastraceae* alkaloid was in 1887 when Katin was isolated from the root bark of *Catha edulis* Forskal. However, the sample obtained was impure and it was not until 14 years later that pure Katin was isolated and determined to have the molecular formula $C_{10}H_{18}N_2O$ (and a bitter taste!).⁵ This study was reported in *Die Alkaloide* in 1931, together with an account of the isolation of a few additional *Celastraceae* extracts, all of which were categorised as being 'alkaloide mit unbekannter stammsubstanz'.⁶ The presence of alkaloids in plants belonging to the *Euonymus* genus were first reported in 1934,⁷ and *Celastraceae* alkaloids have been investigated extensively since then.

Previous reviews of dihydroagarofuran sesquiterpenoids have mainly focused on the tricyclic polyol core, with less attention paid to the macro-dilactone bridging ligands. In this article, the history, structure, and syntheses of the bridging ligands are surveyed (Chart 2).

Discovery and classification of the macro-dilactone bridging ligands

The esterifying groups can be divided into two types in terms of their structures: nicotinic acid derivatives and 3-furoic acid derivatives. A monoterpene tricarboxylic acid has also been found with a bridging role. All the nicotinic acid derivatives have carboxylic acid-containing side chains at the 2- or 4-position of the pyridine ring; the wilfordates have butanoate side chains whereas evoninates have propanoate side chains. For the 3-furanoic acid derivatives, only the 2-position is substituted by a butanoate side chain. It is notable that each esterify-

ing bridge only appears on either the upper or lower rim of the natural product cores, never both.

Nicotinic acid derivatives

Among all macro-dilactone bridging ligands, the nicotinic acid derivatives are the most prevalent. This class includes wilfordates, evoninates and three other nicotinic acid derivatives. All these nicotinic acid derivatives with the exception of cathic acid, bridge between C-3 and C-13 across the lower rim of their dihydroagarofuran; cathic acid bridges on the upper rim between C-8 and C-14.

Wilfordic acid derivatives

Wilfordic acid derivatives **1** to **4** (Chart 3a) were named after the species *Tripterygium wilfordii*, from which wilfordic acid (**1**) and hydroxy wilfordic acid (**2a**) were first isolated and characterized.

In 1950, Acree extracted an alkaloid wilfordine from *Tripterygium wilfordii*. The extract was believed to be a pure compound, as the melting point did not change after several recrystallizations. The formula was deduced, and wilfordine was identified as an ester alkaloid containing eight equivalents of acid upon saponification (including two equivalents of 'steam non-volatile acid').⁸ However shortly afterwards, Beroza followed up Acree's work, and proved that Acree's wilfordine was in fact a mixture of two structurally similar alkaloids differing by the presence/absence of a hydroxy group in the bridging ligand:⁹ the alcohol-containing congener was named wilforine, while the *des*-hydroxy one assigned the name wilfordine (Chart 3c).¹⁰ The structures were elucidated based on evidence from UV-vis absorption spectra, elemental analysis, X-ray diffraction (XRD) data and degradative reactions of these diacids. These structures as assigned in 1953 (Chart 3b), were subsequently revised in 1963 following the advent of NMR techniques (Chart 3a).^{11–14} Later, Beroza extracted three more alkaloids (wilforine, wilfortrine, and wilforzine) from *Tripterygium wilfordii*, all of which had the same polyhydroxy core as wilforine and wilfordine. Several of these alkaloid were shown to possess significant insecticidal activity.¹⁵

Determination of the absolute configurations of these ligands was achieved only decades later. In the 1990s, Itokawa *et al.* studied some Amazonian medical plants belonging to the *Maytenus* genus, and isolated new sesquiterpenoids containing evoninate and wilfordate dilactone bridges.^{16–19} An XRD analysis on ebenifoline W-I (Chart 3c), a wilfordate type alkaloid from *Maytenus ebenifolia*, confirmed the structure of naturally occurring wilfordic acid **1** and revealed it to have an *S*-configuration.¹⁶ Hydroxy wilfordic acid (**2a**) as isolated from *Tripterygium wilfordii* Hook by Beroza in 1953, was determined to have an *R*-configuration in 2019 by both experimental and computational methods.^{20,21}

Other wilfordic derivatives have been less intensively studied. The ester derivatives of hydroxy wilfordic acid **2b** and **2c** (Chart 3a) were only identified as constituents of alkaloids extracted from *Tripterygium wilfordii* in 2014; their stereochemistry was determined as being identical to hydroxy wilfor-



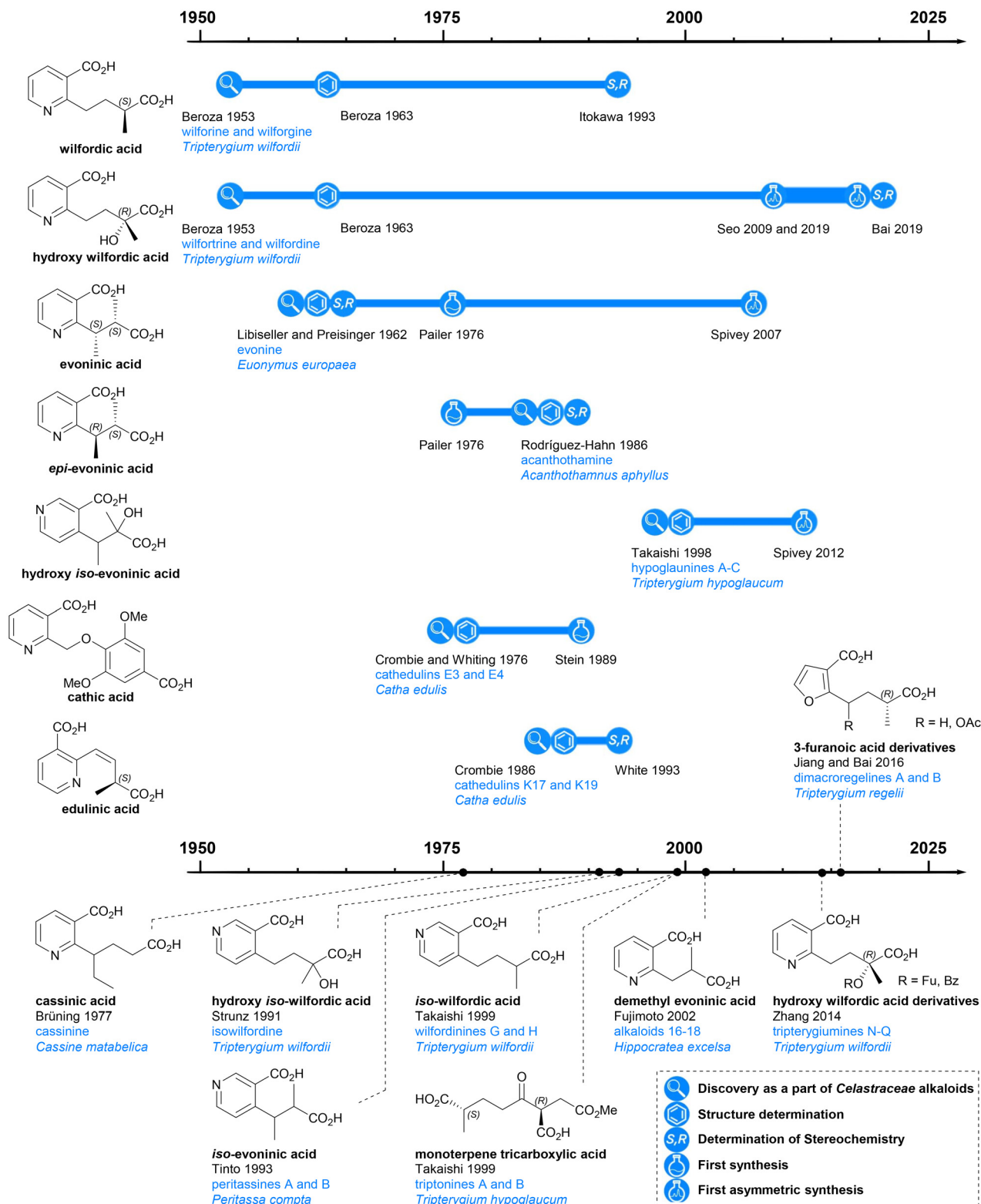


Chart 2 Discovery and further studies related to the macrodilactone bridging ligands of Celastraceae sesquiterpene alkaloids.

dic acid (Chart 3c). The alkaloid containing **2b**, named tripterygiumine Q, showed excellent immunosuppressive activity (IC_{50} 8.67 μ M against human peripheral mononuclear cells)

but no cytotoxicity even at a high dose, making it a promising lead for drug development.²² iso-wilfordic acid (**3**), in which the aliphatic acid-containing side chain is situated at the

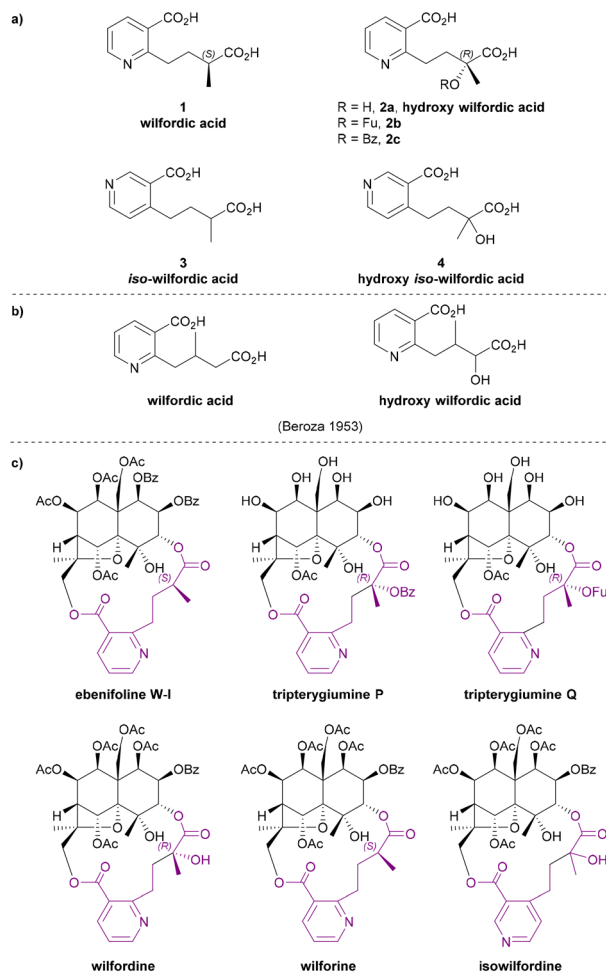


Chart 3 (a) Wilfordic acid derivatives as the macrodilactone bridging ligands, (b) the structures for wilfordic acid and hydroxy wilfordic acid suggested by Beroza in 1953,^{11,12} (c) examples for *Celastraceae* sesquiterpene alkaloids that contributed to the studies of their bridging ligands.

4- rather than 2-position of the nicotinic acid core, was first identified as a bridging ligand in three alkaloids (wilfordinines D-F) from the root xylem extract of *Tripterygium wilfordii* by Takaishi *et al.* in 1999.²³

Hydroxy iso-wilfordic acid (4) was found in an isowilfordine (Chart 3c) – which was extracted by Li *et al.* in 1991 while re-examining alkaloids from this genera.²⁴ The studies on both iso-wilfordic acid and hydroxy iso-wilfordic acid used NMR analysis for structure elucidation, and the absolute stereochemistry of the ligands were not determined.

Isotopic labelling studies relating to the biosynthesis of wilfordic and hydroxy wilfordic acids in *Tripterygium wilfordii* were reported in 1972²⁵ and in 2006, some structure activity relationships (SAR) studies established that the position of the carboxyalkyl chain in wilfordic *vs.* iso-wilfordic acids has negligible effect on their anti-HIV activity although the presence a hydroxy group in the carboxyalkyl side chain usually has a positive impact on activity.²⁶

Evoninic acid derivatives

Evoninic acid derivatives 5 to 9 (Chart 4a) were named after the species *Euonymus europaea*. Probably the most well-known dilactone bridging ligand of the *Celastraceae* sesquiterpene alkaloids, evoninic acid (5) was discovered in 1962 by Libiseller, Preisinger, and Pailer.^{27–29} Studying the alkaloids from *Euonymus europaea*, ‘bases A, B, and C’ from Doebel’s work in 1949³⁰ were identified as evorine, evozine, and evonine, respectively (Chart 4b). Upon the saponification of evonine, dimethyl evoninate was obtained. In 1976, Libiseller and Pailer suggested that evoninic acid (5) is a pyridine-containing dibasic acid with 2*S*,3*S* absolute configuration. They also determined that it is isomeric but not identical to wilfordic acid, as described by Beroza (Chart 6).^{28,29} Independently

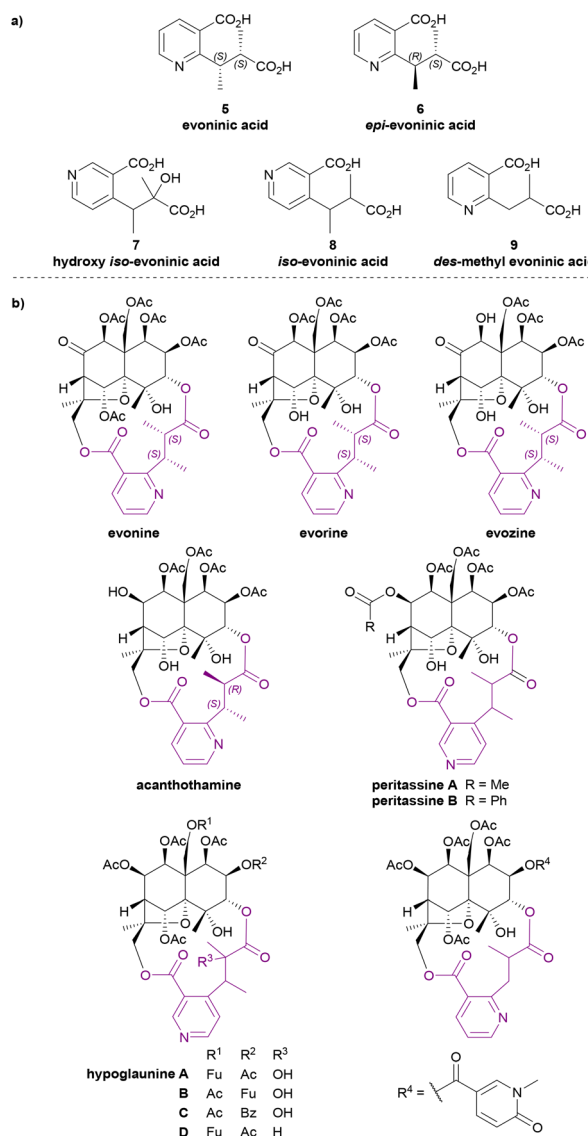


Chart 4 (a) Evoninic acid derivatives as the macrodilactone bridging ligands, (b) examples for *Celastraceae* sesquiterpene alkaloids that contributed to the studies of their bridging ligands.



in 1971, Klásek *et al.* confirmed the structures of bases A (evorine), B (evozine) and C (evonine).³¹

In 1986, Rodríguez-Hahn *et al.* isolated a new alkaloid acanthothamine from *Acanthothamnus aphyllus*, which was identified as the first, and to date only, *Celastraceae* sesquiterpene alkaloid with an *epi*-evoninic acid (6) dilactone bridging ligand (Chart 4b). Though initially reported as ‘an iso-evoninic acid residue’, the authors noted that the 2*R*,3*S* configuration of *epi*-evoninic acid (6) is epimeric to evoninic acid (5), as shown by XRD analysis.^{32,33}

In 1998, Takaishi *et al.* isolated four new sesquiterpene alkaloids hypoglaunines A, B, C and D (Chart 4b) from the root bark of *Tripterygium hypoglaucum*, and identified a novel bridging ligand, hydroxy iso-evoninic acid (7).³⁴ In the same year, Li *et al.* independently isolated and characterised hypoglaunine A from the same plant, although the work was published a year later.³⁵ More recently, a research group from Chongqing, China extracted hydroxy iso-evoninic acid (7) from the root bark of *Tripterygium hypoglaucum*. Their study found that this compound exhibits good immunosuppressive activity, anti-platelet aggregation activity and hypoglycaemic activity.³⁶

In 1993 McLean *et al.* reported the presence of iso-evoninic acid (8) as a bridging ligand in peritassines A and B isolated from *Peritassa compta* (Chart 4b).³⁷ In 2002, Fujimoto *et al.* reported *des*-methyl evoninic acid (9) (also named as *nor*-evoninic acid³⁸) as a bridging ligand in three new sesquiterpene alkaloids isolated from *Hippocratea excelsa*.³⁹ The absolute stereochemistries of neither 8 nor 9 were determined.

Other nicotinic acid derivatives

The three dilactone bridging ligands in this class (Chart 5a) are relatively rare compared to other *Celastraceae* sesquiterpene pyridine alkaloids: both cathic acid (10) and edulinic acid (11) were first found as bridging ligands in alkaloids from *Catha edulis* (khat), hence their names. Cassinic acid (12) has only been found as a bridging ligand in three *Celastraceae* plants, each belonging to different genera.

From the late 1970s to late 1980s, a series of bridged sesquiterpenoids from khat sourced from Kenya, Ethiopia, and Yemen, received significant attention. These compounds were named cathedulins.^{40–45} Whiting and Crombie *et al.* isolated cathedulins 3 to 6 (later named cathedulins E3–E6 to designate their Ethiopian origin, Chart 5b) from khat leaves in 1976 and used NMR analysis and treatment with LiAlH₄ to partially determine their structures. Cathedulins E3 and E4 were found to include a novel cathate ester unit, bridging between C-8 and C-14 of the core. Cathedulins E5 and E6 were shown to be congeners of cathedulins E3 and E4 but containing a gallate ester at C-8 and a nicotinate ester at C-14 – substituents that these authors speculated might undergo biosynthetic intramolecular radical macrocyclization to form the cathate dilactone bridge.^{41,46} In 1992, based on this hypothesis, Whiting *et al.* reported a radical process mimicking the proposed biosynthetic C–C bond formation.⁴⁷ Among all dilactone bridging ligands of *Celastraceae* sesquiterpene alkaloids, cathic acid (10) is the only one without a stereogenic centre. In 1989, Stein

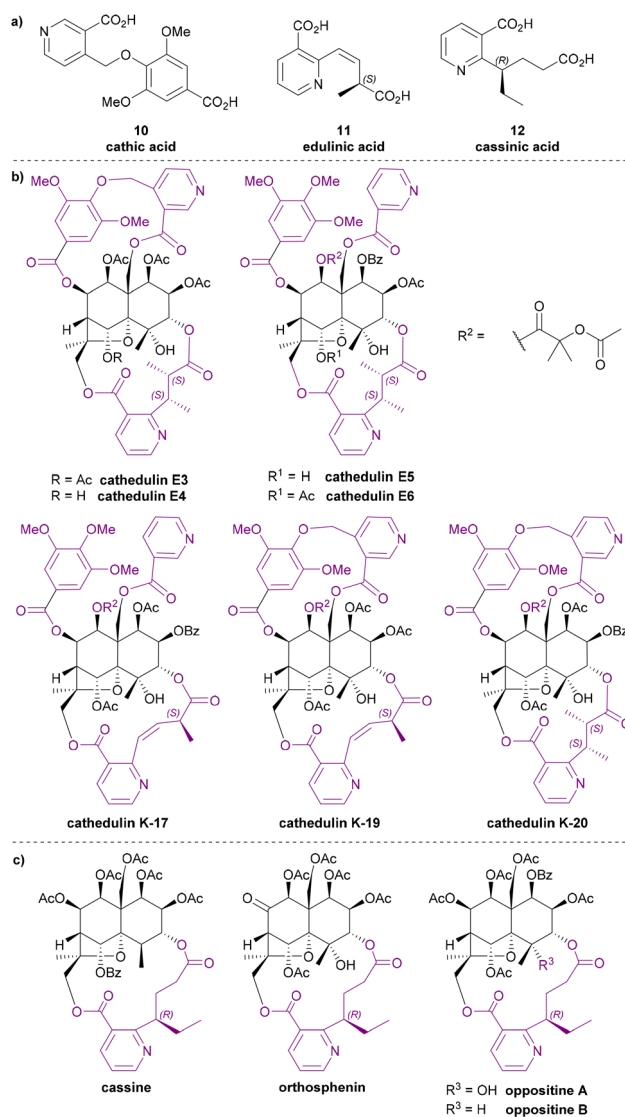


Chart 5 (a) Other nicotinic acid derivatives as the macrodilactone bridging ligands for *Celastraceae* sesquiterpene alkaloids, (b) representative cathedulins, (c) all known *Celastraceae* sesquiterpene alkaloids with cassinic acid as the bridging ligands.

and Nencini proposed a synthesis for dimethyl cathate (DMC) and performed the hydrolysis of DMC to obtain cathic acid (10). They also tested the bioactivity of DMC, showing that it appeared to protect mice from the convulsant effect of pentylenetetrazol.⁴⁸

Whiting and Crombie *et al.* also identified edulinic acid (11) in cathedulins K17, K19 and K20 found in Kenyan khat leaves (Chart 5b). This diacid is the only macrodilactone bridging ligand with an unsaturated alkenyl side chain. Both cathedulins K17 and K19 were found to have an edulinic acid bridging ligands between C-3 and C-13 of their dihydroagarofuran cores. Interestingly, cathedulin K19 also has a cathate bridge between C-8 and C-14, making it highly topologically complex. The structure of edulinic acid (11) was elucidated using *nOe* experiments, showing that the alkene has a



Z-configuration. The authors suggested edulinic acid (**11**) may have a similar biogenetic origin to evoninic acid (**5**), and therefore the stereogenic centre in edulinic acid (**11**) should be the same as found in evoninic acid (**5**).⁴² A synthesis (see later section) of (*S*)-edulinal was performed in 1993 by White *et al.*; this synthetic material was proven to be identical to the product obtained by reducing natural cathedulin K19. Hence, edulinic acid (**11**) was confirmed as having an *S*-configuration.⁴⁹

Cassinic acid (**12**) was found in sesquiterpene alkaloids from three Celastraceae plants: cassinine from *Cassine matabe-lica* (1977),^{50,51} orthosphenin from *Orthosphenia mexicana* (1989),⁵² and oppositines A and B from *Pleurostyliya opposita* (2006) (Chart 5c).⁵³ In a 1977 study, Brüning *et al.* reported the XRD structure of cassinine, revealing its structural similarity to evonine and wilfordine.⁵⁰

Monoterpene tricarboxylic acid

In 1999, Takaishi *et al.* extracted two novel sesquiterpene alkaloids, triptonines A and B (Chart 6b), from *Tripterygium hypoglaucum*.⁵⁴ Later, the same group also found triptonine A in *Tripterygium wilfordii*.⁵⁵ The structure elucidation of these two new alkaloids were completed using NMR and XRD analysis, which revealed a novel dilactone bridging ligand, the monoterpene tricarboxylic acid **13** (Chart 6a). The anti-HIV activity of triptonines A and B was tested: triptonine A exhibited potent anti-HIV activity (EC_{50} 2.54 $\mu\text{g mL}^{-1}$ for HIV replication in H9 lymphocytes) and relatively weak cell growth inhibition (IC_{50} >100 $\mu\text{g mL}^{-1}$ against uninfected H9 cell).^{54,55} Later, in 2014, Zhang *et al.* isolated a third *Celastraceae* sesquiterpene alkaloid featuring this monoterpene tricarboxylic acid bridge, tripterygiumine A (Chart 6b).²²

Monoterpene tricarboxylic acid **13** is the only tricarboxylic acid dilactone bridging ligand to be discovered as a part of *Celastraceae* sesquiterpene alkaloids, and it only features in these di-macrocylic derivatives on the bottom face of the dihydroagarofuran core, bridging between C-8 and C-14. Triacid **13** is the only known bridging ligand without an aromatic (*i.e.*, pyridyl or furanyl) component.

3-Furanoic acid derivatives

3-Furanoic acid derivatives **14** and **15** (Chart 6a) are the most recently discovered dilactone bridging ligands. Like monoterpene tricarboxylic acid **13**, they also bridge between C-8 and C-14 of the dihydroagarofuran core. Bai *et al.* extracted dimacoregelines A and B from *Tripterygium regelii* in 2016, and Kuang *et al.* extracted dimacoregelines C and D† from *Tripterygium wilfordii* in 2021 (Chart 6c).^{56,57}

†NB. the stereochemistry of these alkaloids have been corrected – see: link: <https://www.tandfonline.com/doi/epdf/10.1080/14786419.2021.1903460?needAccess=true&role=button>.

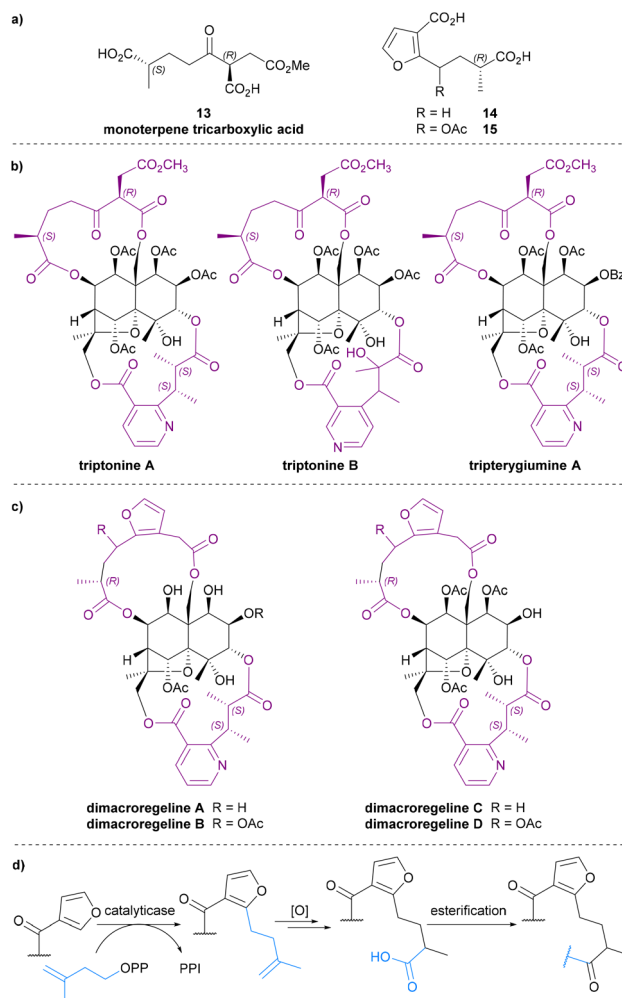


Chart 6 (a) Monoterpene tricarboxylic acid and 3-furanoic acid derivatives, (b) all known *Celastraceae* sesquiterpene alkaloids with monoterpene tricarboxylic acid bridge, (c) all known *Celastraceae* sesquiterpene alkaloids with 3-furanoic acid derivatives as bridging ligands, (d) a plausible biosynthetic pathway for the biosynthesis of the 3-furanoic acid derivatives.

By comparing NMR data, Bai *et al.* noticed the similarity in the structures of dimacoregelines A and B with triptonine A, which contains the monoterpene tricarboxylic acid **13**. The difference was the appearance of a furan ring, and with further analysis using correlation methods, the structure of dilactone bridging ligands **14** and **15** were elucidated and reported for the first time. Kuang *et al.* confirmed the structures of ligands **14** and **15** based on the study of Bai *et al.*, but the absolute configurations of these ligands were not established.^{56,57}

Bai *et al.* also proposed a biosynthetic pathway by which these unprecedented 3-furanoic acid derivatives might plausibly be formed – involving regiospecific prenylation of a 3-furyl ester by a plant flavonoid prenyltransferase (Chart 6d).⁵⁸ Due to their skeletal similarity, it is also possible that ligands **13** and **14** are biosynthetically related.



The synthesis of the macrodilactone bridging ligands and reactivities of *Celastraceae* sesquiterpene alkaloids

Compared to studies of dihydroagarofuran cores of *Celastraceae* sesquiterpene alkaloids and interest in their biological activity,^{59–62} studies directed at the structural elucidation and synthesis of their bridging ligands emerged later, reflecting advances in characterization techniques (e.g., NMR, XRD). The first synthesis of a bridging ligand was accomplished by Pailer in 1976,⁶³ Just two further syntheses were reported in 1989 and 1993,^{48,49} before the 21st century saw the first stereoselective approaches reported.^{20,64–66}

The syntheses of evoninic acid (5) and *epi*-evoninic acid (6)

As is evident from the forgoing section, (*S,S*)-evoninic acid (5) is the bridging ligand of many bioactive *Celastraceae* sesquiterpenoids. The first synthesis of racemic evoninic acid ($\pm$ -5), in 2% overall yield over 6 steps, was reported by Pailer and Pfeleger in 1976 (Chart 7a).⁶³

Bromination of ethyl 2-nicotinate **16** using *N*-bromosuccinimide in the presence of sub-stoichiometric benzoyl peroxide, yielded bromide **17**, to which was added the sodium salt of ethyl 2-cyanopropanoate prepared *in situ*. The resulting nitrile **19** was treated with conc. HCl under reflux to effect hydrolysis and decarboxylation, then neutralised and reacted with diazomethane in methanol/water to give a mix of stereoisomers of diester **20**.

The *syn* and *anti* isomers of ester **20** were separated using preparative TLC and their relative stereochemistries assigned by reference to literature spectroscopic (IR, NMR, MS) and GC data for the dimethyl esters of naturally occurring evoninic acid. The corresponding racemic acids were obtained by basic hydrolysis. The overall yield of the *syn*- or (*RS,RS*)-isomer corresponding to evoninic acid ($\pm$ -5) was just 2.3% from nicotinate **16** whereas the overall yield of the *anti*- or (*RS,SR*)-isomer corresponding to the (at that time, yet-to-be-isolated from a natural source) *epi*-evoninic acid ($\pm$ -6) was 3.0%. The overall yield of this synthetic route was primarily compromised by the moderate yield of the key C–C bond forming enolate alkylation reaction (**17** $\rightarrow$ **19**, 36%) and the poor diastereoselectivity of the decarboxylation step (**19** $\rightarrow$ **20**, dr ~29 : 45 *syn* : *anti*).

The first asymmetric total synthesis of evoninic acid (5), in 4 steps and 31% overall yield, was reported by Spivey *et al.* in 2007 (Chart 7b).⁶⁵ Their synthesis started with the conjugate addition of a 2-*pridinyl* Gilman homocuprate **21** to (*E*)-methyl crotonate giving racemic ester **22**. Subsequent diastereoselective methylation of the potassium enolate of this ester with MeI in toluene at low temperature gave the desired *syn* diastereoisomer **23s** in 98% yield and 96 : 4 dr.

The purified *syn*-isomer was then subject to hydrolytic kinetic resolution using *Pseudomonas fluorescens* lipase in phosphate buffer (pH 7, 37 °C), which afforded the corresponding *syn*-acid **24** with an er of 97 : 3 in 46% yield. Finally, treatment with KMnO₄ selectively oxidized the pyridine methyl

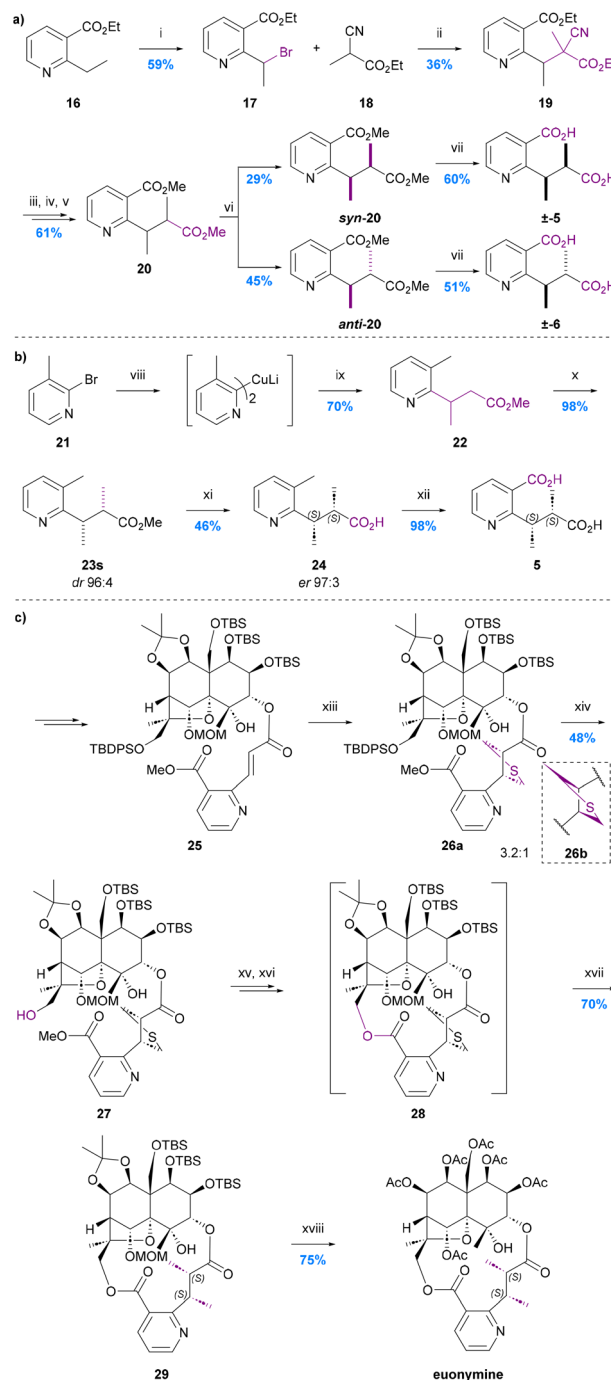


Chart 7 The syntheses of evoninic acid **5**. (a) Pailer and Pfeleger 1976,⁶³ i. *N*-Bromosuccinimide (1.9 eq.), benzoyl peroxide (0.04 eq.), CCl₄, heating; ii. Na (1.0 eq.), **18** (1.0 eq.), EtOH; iii. conc. HCl, reflux; iv. NaOH, Et₂O; v. CH₂N₂, MeOH/H₂O 9 : 1; vi. Prep-TLC (Pr₂O $\times$ 3); vii. 2 N KOH, reflux; (b) Spivey *et al.* 2007,⁶⁵ viii. ^{*n*}BuLi, Et₂O, –78 °C, then CuI, SBn₂, Et₂O, 0 °C; ix. methyl (*E*)-but-2-enoate, Et₂O, rt; x. KHMDS, MeI, toluene, –78 °C; xi. lipase *P. fluorescens*, pH 7.0 buffer; xii. KMnO₄, H₂O, reflux; (c) Inoue *et al.* 2021,⁶⁷ xiii. bis(trimethylsilylmethyl)sulfoxide (21 eq.), DMPU, 0 to 24 °C; xiv. ^{*n*}Bu₄NF, AcOH, DMF, 24 °C; xv. Me₃SnOH, PhCl, 100 °C; xvi. PyBOP, DMAP, DMF, 80 °C; xvii. RANEY®-Ni, EtOH, 24 °C; xviii. AcOH, H₂O, 100 °C, then Ac₂O, Et₃N, DMAP, CH₂Cl₂, 24 °C.



group of the acid **24**, to give (*S,S*)-evoninic acid **5** in almost quantitative yield. The absolute configuration was assigned by the conversion to the corresponding dimethyl ester and comparison with the literature data for the corresponding naturally derived material. Although both the diastereoselectivity and enantioselectivity obtained by this approach are good, the overall yield is compromised by the need for an enzymatic kinetic resolution step (**23s** → **24**), which although efficient, necessarily means that more than 50% of the material is not progressed into the final product. The development of an asymmetric variant of the key cuprate conjugate addition step (**21** → **22**) would significantly improve the approach.

In 2021, Inoue *et al.* reported the first total synthesis of the evoninic acid bridged macrodilactone-containing sesquiterpene alkaloid euonymine; their route featured an unusual *in situ* construction of the evoninic acid substructure (Chart 7c).⁶⁷ Thus, an aza-cinnamic acid precursor to the evoninate moiety was introduced at C-3 of an enantiopure advanced dihydroagarofuran intermediate *via* a standard esterification reaction giving ester **25** in 91% yield. The alkene therein was then heated with bis(trimethylsilylmethyl)sulfoxide (21 equiv.) and DBU to effect an intermolecular [3 + 2]-cycloaddition. This gave diastereomeric thiolanes **26a**:**26b** in a 3.2:1 ratio, the major isomer of which was subsequently shown to lead to the required (*S,S*)-product after macrocyclization and hydrogenolysis. Interestingly, when macrocyclization was carried out prior to the [3 + 2]-cycloaddition, a thiolane corresponding to the undesired (*R,R*)-diastereoisomer was obtained exclusively. Although **26a** and **26b** were inseparable, separation could be achieved once the C13 alcohol had been deprotected using TBAF (*i.e.*, compounds **27**). Methyl ester hydrolysis, and then macrolactonization on the required diastereoisomer set the stage for the final thioether hydrogenolysis to reveal the required (*S,S*)-dimethyl motif of the evoninate bridge in protected euonymine **29**.

Despite the large amount of bis(trimethylsilylmethyl)sulfoxide used and the high price of its commercially available precursor, the [3 + 2]-cycloaddition provided an elegant, albeit not very diastereoselective, way to introduce the two stereocentres of the evoninate bridge.

The synthesis of hydroxy iso-evoninic acid (**8**)

The first and only total synthesis of hydroxy iso-evoninic acid (**8**) was achieved *via* a benzylic ester rearrangement (BER) by Spivey and Warren in 2012 (Chart 8).⁶⁶ They prepared a mixture of racemic *syn* and *anti* diastereoisomers and then used chiral stationary phase (CSP) HPLC to separate all four stereoisomers. Neither the relative nor absolute stereochemistry of naturally occurring iso-evoninic acid (**8**) is known.

In the initial stage of the synthesis, *N*-carbamoylation of 3-picoline (**30**) and treatment with triethylphosphite gave the 1,4-dihydropyridine derivative **31** which was alkylated at the 4-position using *n*-BuLi (1 equiv.) and 2-bromopent-3-ene, and then re-aromatised to give 4-allyl-3-picoline **32** by treatment with *n*-BuLi (2 equiv.). This intermediate underwent epoxidation *via* a mixture of bromohydrins and subsequent hydro-

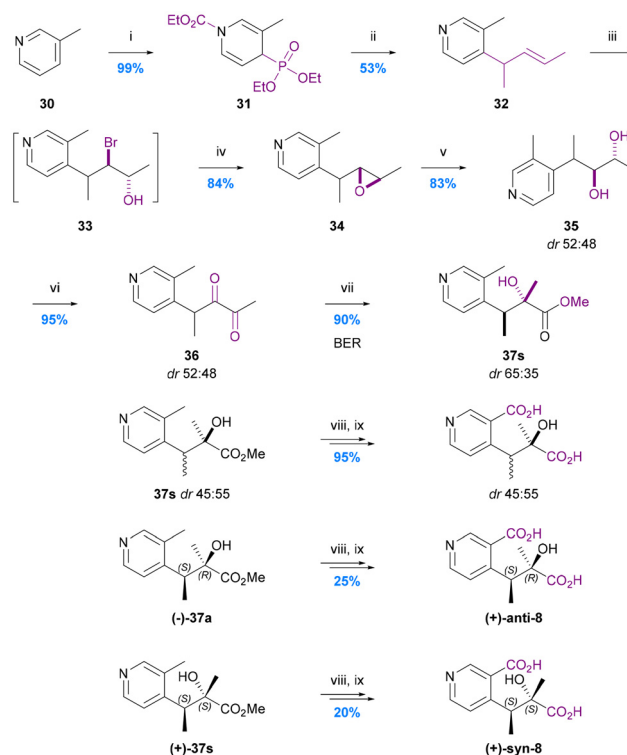


Chart 8 The synthesis of hydroxy iso-evoninic acid **8**. Spivey *et al.* 2012,⁶⁶ (i) EtOCOCl, MeCN, then P(OEt)₃, (ii) ⁿBuLi (1 eq.), THF, then 2-bromopent-3-ene, then ⁿBuLi (2 eq.), (iii) NBS, THF/H₂O, (iv) 1 M NaOH, MeCN, (v) 6% HClO₄ (aq.), MeCN, (vi) (COCl)₂, DMSO, CH₂Cl₂, then Et₃N, (vii) ZnCl₂ (1 eq.), MeOH, 40 °C, (viii) 2 M NaOH, MeOH, (ix) 1 M NaOH, KMnO₄.

lytic ring-opening to give diol **35** (in an inconsequential dr of 52:48) which was converted to the 1,2-diketone **36** *via* Swern oxidation. This labile 1,2-diketone was the substrate for the key BER which was promoted using zinc chloride in methanol at 40 °C. The BER afforded esters **37** in 90% yield with a dr of 35:65. A 76% yield of esters **37** with reverse diastereoselection (dr 66:34) could be obtained using 0.1 M NaOMe in methanol at 40 °C to promote the BER, but conditions that would deliver higher levels of diastereoselection favouring either diastereoisomer proved elusive. Consequently, all four stereoisomers were separated by CSP-HPLC and the dextro-rotatory *syn* and *anti* diastereoisomers progressed *via* saponification then benzylic oxidation using KMnO₄ to give (2*R*,3*S*)-hydroxy-iso-evoninic acid [(+)-*anti*-**8**] and (2*S*,3*S*)-hydroxy-iso-evoninic acid [(+)-*syn*-**8**]. Although this 9-step synthesis gives access to a racemic mix of *cis*- and *trans*-hydroxy iso-evoninic acids **8** with ~26% overall yield, the poor diastereoselectivity of the BER and need for CSP-HPLC separation of stereoisomers leaves much scope for improvement. In particular, the development of an asymmetric BER concomitant with dynamic kinetic resolution (DKR)⁶⁸ could constitute a very efficient 'second generation' approach.

The syntheses of (*S*)-hydroxy wilfordic acid ((*S*)-**2a**)

The total synthesis of hydroxy wilfordic acid has only been studied relatively recently. Seo *et al.* synthesized hydroxy wilfor-



dic acid employing an asymmetric cyanosilylation as the key step in 2009, and the same research group reported an improved synthesis in 2019.^{20,64} The 2019 disclosure also demonstrated that naturally occurring hydroxy wilfordic acid **2a** has the *R*-configuration, which is the antipode of their synthetic hydroxy wilfordic acid (*S*)-**2a**. The *R*-configuration of naturally occurring hydroxy wilfordic acid **2a** had been proposed by Bai *et al.* earlier in 2019, based on the comparison between simulated and experimental ECD spectra.²¹

In Seo's 2009 synthesis the methyl group in pyridine **21** was oxidised to aldehyde **38** and then a Horner–Wadsworth–Emmons (HWE) alkenylation was carried out to give enone **39** – the substrate for the key asymmetric cyanosilylation reaction (Chart 9a).⁶⁴ Use of Jacobsen's commercially available amino thiourea catalyst^{69,70} led to the highest yield and enantioselectivity for this process giving silylated cyanohydrin **40** in 82% yield and 75 : 25 er. The mixture of enantiomeric nitriles was hydrolysed/esterified with 6 M HCl in MeOH, the alkene hydrogenated, and the benzylic methyl group oxidized to the corresponding benzylic acid with concomitant ester hydrolysis using aqueous KMnO₄ to give hydroxy wilfordic acid (**2a**) as a crude mixture of enantiomers. This mixture was esterified and purified to give dimethyl hydroxy wilfordate **43** in 7 steps and

43% overall yield from bromopyridine **21**. The major enantiomer of this 75:25 er product was shown to have an *S*-configuration *via* derivatisation of the acid corresponding to cyanohydrin **40** as an amide with (*S*)- and (*R*)-phenylglycine methyl esters (PGMEs) followed by hydrogenation of the alkene. These amides were then separated by HPLC to facilitate stereochemical assignment by NMR.

Their second-generation 2019 route to hydroxy wilfordic acid, mirrored their initial route but started from methyl 2-chloronicotinate in order to avoid the late-stage benzylic oxidation (Chart 9b).²⁰ This tactic fortuitously resulted in a much improved asymmetric cyanosilylation step to give silylated cyanohydrin **46s** in 90% yield and 35 : 1 er using the same amino thiourea catalyst under unchanged conditions. Acid catalysed nitrile hydrolysis followed by hydrogenation gave the diester **47**, which was saponified to give (*S*)-hydroxy wilfordic acid (*S*)-**2a** ($[\alpha]^{20} = +20.4$; 93.3% ee) in 7 steps and 48% overall yield from methyl 2-chloronicotinate. A sample of the natural hydroxy wilfordic acid **2a** ($[\alpha]^{24} = -24.1$) was obtained by hydrolysing commercially available wilfortrine, thereby confirming natural hydroxy wilfordic acid as having an *R*-configuration.

The synthesis of cathic acid (10)

The only total synthesis of cathic acid (**10**) was reported in 1989 by Stein and Nencini (Chart 10a).⁴⁸ The synthesis commenced with regioselective methanolysis of 3,4-pyridinedicarboxylic acid anhydride **48**, to give mono-methyl ester **49**. LiAlH₄ reduction of this ester to the benzylic alcohol **50** followed directly by treatment with POCl₃/PCl₅ and quenching with methanol gave 4-chloromethyl methyl nicotinate (**51**).

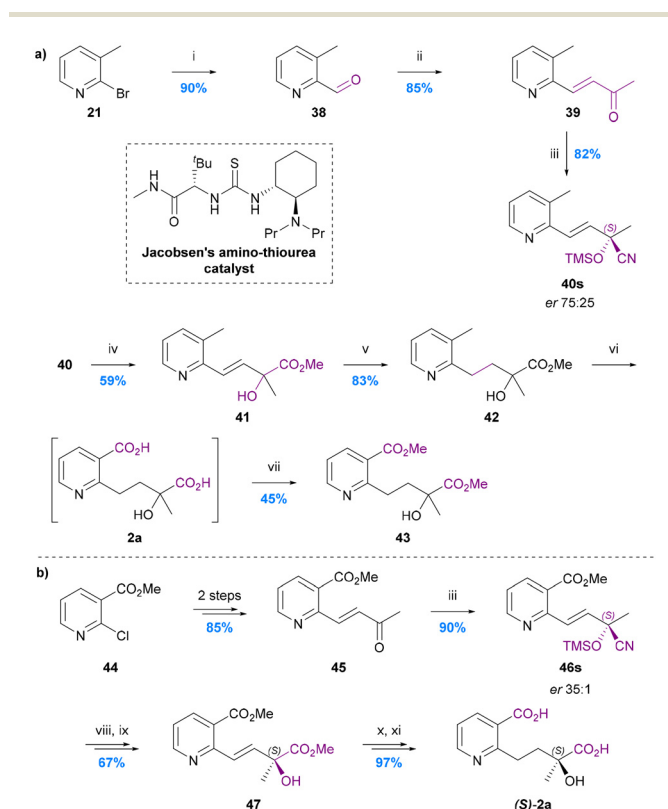


Chart 9 The synthesis of hydroxy wilfordic acid **2a**. (a) Seo *et al.* 2009.⁶⁴ (i) ^tBuLi, DMF, THF, (ii) MeCOCH₂P(O)(OMe)₂, NaH, THF, (iii) Jacobsen's amino-thiourea catalyst, TMSCN, CF₃CH₂OH, CH₂Cl₂, -78 °C, (iv) 6 M HCl, MeOH, reflux, (v) H₂, Pd/C, MeOH, (vi) KMnO₄, H₂O, reflux, (vii) HCl, MeOH; (b) Seo *et al.* 2019.²⁰ (viii) c. HCl, MeOH, 60 °C, (ix) TMSCHN₂, MeOH, (x) H₂, Pd/C, MeOH, (xi) LiOH·H₂O, MeOH/H₂O.

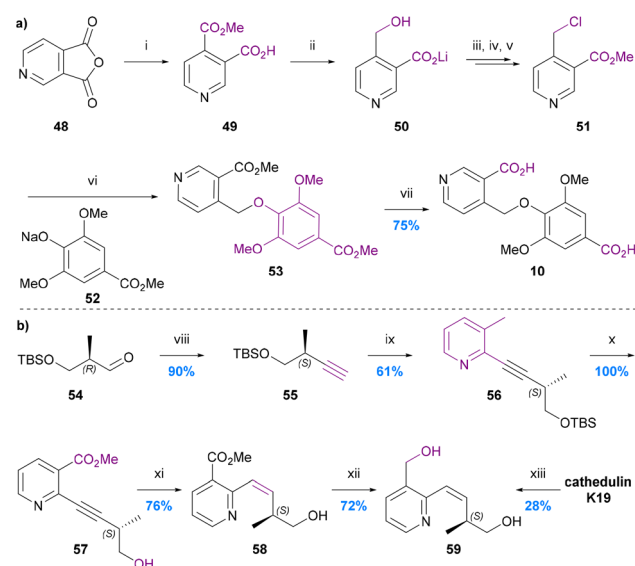


Chart 10 The synthesis of cathic acid **10** and edulinol **59**. (a) Stein and Nencini 1989.⁴⁸ (i) MeOH, (ii) LiAlH₄, THF, (iii) POCl₃, PCl₅, (iv) MeOH, (v) pH 7.4, (vi) MeOH, (vii) 4 N KOH, MeOH; (b) White *et al.* 1993.⁴⁹ (viii) (MeO)₂POCHN₂, ^tBuOK, THF, (ix) methyl 2-chloronicotinate, (Ph₃P)₂PdCl₂, Cul, Et₂NH, (x) 5% HF/MeCN, (xi) H₂, Lindlar cat., MeOH, (xii) LiAlH₄, THF, 0 °C, (xiii) LiAlH₄, THF/Et₂O, 0 to 25 °C.



Alkylation of sodium methyl syringate (**53**) with this nicotinate derivative gave dimethyl cathate (DMC) **53**. Saponification of the DMC gave cathic acid (**10**) in 75% yield, equating to an overall yield of ~4% over 6 steps from ester **49**. The yield and selectivity of the first step (**48** to **49**) was not reported, nor were any individual step yields up to DMC **53**, which was the first purified product. The authors noted however that the syringate alkylation step was particularly inefficient, presumably because of the steric hindrance of the di-*ortho*-substituted nature of this phenol. An alternative, more efficient etherification protocol for syngate will likely need to be developed for any efficient next generation synthesis of cathic acid.

The synthesis of edulinol (**59**)

No synthesis of edulinic acid **11** has been reported, but its reduced derivative edulinol **59** was synthesized by White in 1993 in order to establish the absolute configuration of edulinic acid from cathedulin K19 (Chart 10b).⁴⁹

The synthesis started with a Seyferth–Gilbert homologation of (2*R*)-3-siloxy-2-methylpropanaldehyde **54** to furnish terminal alkyne **55**. This alkyne then underwent Sonogashira coupling with methyl 2-chloronicotinate, deprotection and Lindlar's reduction to yield the *cis*-alkene **58**, which was reduced to give edulinol **59** ($[\alpha]^{22} = +126$) in 7 steps and 30% overall yield from aldehyde **54**. Edulinol was also obtained upon reduction of cathedulin K19 ($[\alpha]^{22} = +210$). The two edulinol samples had consistent IR, ¹H and ¹³C NMR spectra and so the significant difference between the optical rotation values was attributed to the partial racemization of alkyne **57** during its *syn*-hydrogenation. ¹H and ¹⁹F NMR spectroscopic analysis of its Mosher ester derivative indicated that alkene **58** had a 44% ee, suggesting that partial racemization also occurs during its isolation by reduction of cathedulin K19. There remains a need therefore for the future development of a synthesis of edulinic acid (**11**) that circumvents the racemisation-prone hydrogenation of an unsaturated C–C linkage between the stereogenic centre and the pyridine ring, either by introducing the stereogenic centre at a later stage of the synthesis or simply avoiding an unsaturated linkage.

Macrolactone formation using these diacid ligands

To date there have been only two studies addressing the incorporation of diacid ligands into the macrolactone structures of the *Celastraceae* alkaloids. In 1975 Yamada provided the first protocol for achieving this by the resynthesis of evonine from an evoninol core (obtained by degradation of natural evonine) and an evoninic acid derivative (Chart 11).⁶² Stepwise formation of the 14-membered dilactone ring with a modified core⁷¹ was accomplished by ester formation at the C-13 hydroxy group (**62** to **63**) followed by macrolactonization onto the C-3 hydroxy group (**64** to **65**). Remarkably, this remained the only report until the total syntheses of euonymine by Inoue *et al.* in 2021 (Chart 7c).⁶⁷ In contrast to Yamada's resynthesis, Inoue first performed ester formation at the C-3 hydroxy group, and elegantly constructed the stereo-

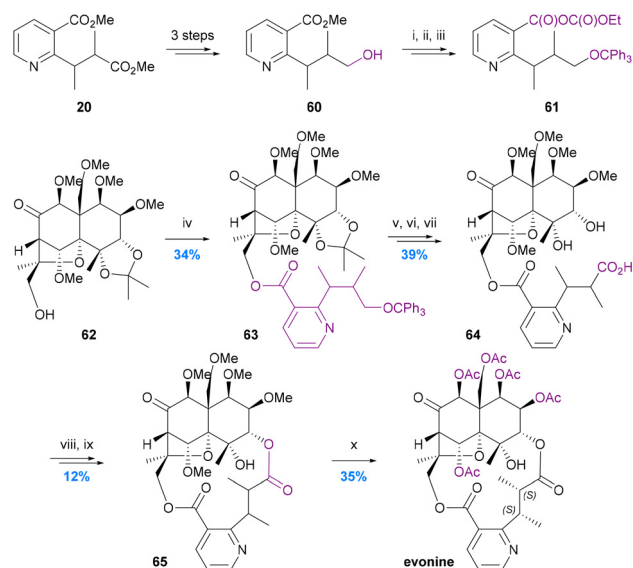


Chart 11 Yamada's resynthesis of evonine. Yamada *et al.* 1975,⁶² (i) Ph_3CCl -Py, 60 °C; (ii) 10% KOH–MeOH, 70 °C; (iii) ethyl chloroformate, Et_3N , DME, RT; (iv) crude **61**, DMAP, Et_3N , DME, 90 °C; (v) 80% AcOH, 50 °C; (vi) CrO_3 -Py, 65 °C; (vii) 50% AcOH, 85 °C; (viii) CH_2N_2 ; (ix) NaH, DMF, RT; (x) BCl_3 - CH_2Cl_2 , RT, and then AcO_2 -Py, 70 °C.

genic centres of the diacid ligand before forging the 14-membered macro-dilactone ring with C-13 ester formation.

Clearly, there is great scope for the development of creative new approaches to orchestrate the construction of the macrolactone rings found in the natural product alkaloids. It is notable that there has been no work published to date for forging the C-8/C14 linked structures. Although the lactonisation reactions themselves are likely not inherently difficult, involving as they do primary (C13 and C14) and secondary (C3 and C8) alcohols, the main challenge will be constructing the dihydroagarofuran cores such that these specific positions can be reacted/activated selectively. This is a formidable endeavour given the complexity of the most prevalent core polyols, but the Herzon group has made important recent progress by preparing a selectively protected derivative of the nonahydroxylated dihydroagarofuran core (–)-euonyminol,^{72,73} so we can probably expect exploration of this chemistry in the near future.

Conclusions

More than 50 years have elapsed since the structure of the first macrolactone containing sesquiterpene alkaloid was elucidated from a *Celastraceae* plant extract in 1971,⁷⁴ and despite the fact that hundreds more have now been characterised and many display exciting biological activity, these structures remain formidable targets for synthesis. Indeed just one successful total synthesis has been described to date – that of euonymine by the Inoue group in 2021 (see Chart 7c).⁶⁷ Whilst clearly the stereochemically rich polyhydroxylated dihydroagar-



Table 1 A summary of completed work for the stereochemistry determination and synthesis of macro-dilactone bridging ligands of *Celastraceae* sesquiterpene alkaloids

Bridging ligands	Stereochemistry	Synthesis
1, wilfordic acid		
2a, hydroxy wilfordic acid	✓	✓
2b, 2a derivative	✓	
2c, 2a derivative	✓	
3, iso-wilfordic acid		
4, hydroxy iso-wilfordic acid		
5, evoninic acid	✓	✓
6, <i>epi</i> -evoninic acid	✓	✓
7, hydroxy iso-evoninic acid		
8, iso-evoninic acid		
9, <i>des</i> -methyl evoninic acid		✓
10, cathic acid	N/A	✓
11, edulinic acid	✓	
12, cassinic acid		
13, monoterpene tricarboxylic acid	✓	
14, furanoic acid derivative	✓	
15, furanoic acid derivative		

ofuran cores constitute the primary challenge for synthesis and have consequently attracted significant attention (and this work has been reviewed previously^{2–4}), their elaboration to the bioactive natural products requires combination with the appropriate diacid bridging ligands that have been the focus of this review. Although progress has been made towards developing efficient methods to prepare these, there remain many ligands for which the relative and absolute stereochemistry remains unknown and for which no syntheses have been reported (Table 1). It is hoped that this review will spark interest in taking up the challenge of their synthesis, thereby paving the way for further total syntheses of the parent macrocyclic alkaloids and ultimately a better understanding of their biology and medicinal potential.

Author contributions

CD and ACS wrote this manuscript jointly.

Conflicts of interest

There are no conflicts to declare.

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